

REVIEW

Work-related and personal risk factors for occupational contact dermatitis: A systematic review of the literature with meta-analysis

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Abstract

The objective of this review is to identify work-related and personal risk factors for contact dermatitis (CD), and assess their association with this frequently occurring occupational disease. A systematic review of the literature from 1990 to June 2, 2020, was conducted using Medline and Embase. Prospective cohort and case-control studies were included, and meta-analyses were conducted when feasible. Quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation. Twenty-nine studies were identified, comprising 26 study populations and with a total of 846 209 participants investigating 52 risk factors for CD. Meta-analyses were performed for five risk factors, all of them for irritant contact dermatitis (ICD). Moderate-quality evidence was found for associations between wet work and ICD (OR: 1.56, 95%CI: 1.21–2.01). High-quality evidence was found for the association between atopic dermatitis and ICD (OR: 2.44, 95%CI: 1.89–3.15). There was no evidence for an association between ICD and sex or history of hand dermatitis, respiratory and mucosal atopy. In conclusion, several work-related and personal risk factors associated with CD were identified. Our data emphasize the need for the assessment of both, work-related and personal, risk factors to prevent occupational CD.

KEYWORDS

contact dermatitis, occupational disease, occupational exposure, personal risk factors, prevention

1 | INTRODUCTION

Contact dermatitis (CD), also referred to as contact eczema is an eczematous local inflammatory skin reaction caused by direct and usually repeated exposures, to chemicals or physical factors, which, depending on location of contact, can occur anywhere on the body

(ESCD, 2020).¹ CD occurs in two forms, as allergic contact dermatitis (ACD) or irritant contact dermatitis (ICD),^{2,3} which differ in pathophysiology and risk factors. It is not possible to clinically distinguish an ACD from ICD, and diagnosis is based on confirmation or exclusion of ACD using allergy patch test. Diagnosing ACD, ICD, or a combination of both is important to undertake prevention measures.^{2,4} In

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epidemiological studies on CD, hand dermatitis (HD) is often assessed as clinical outcome as the hands are the most affected body part in the workplace. However, aetiology of HD is in many studies not well defined so it is not clear whether presented dermatitis symptoms can be classified as ICD, ACD, atopic dermatitis (AD) or a combination thereof. Therefore, some authors suggested that the case definition might be based on exposures to known irritants and the temporal relationship between exposure and the dermatitis. However, as the diagnostic criteria for ICD are based on known risk factors and not a valid test, a risk of missing ACD cases in occupational settings with high exposures to irritants might occur.^{5,6} A patch test should always be performed when there is a suspicion for ACD which pleads involvement of dermatologist in diagnostics and prevention.

CD has a tendency of becoming a chronic disease, thereby increasing the burden on affected individuals, organization, and society.^{7,8} A recent Danish study among workers younger than 35 years showed that 35% had changed their occupation since their diagnosis of occupational contact dermatitis (OCD), and 43% had lost their job because of OCD. In addition, it was found that allergic OCD increased job loss, change in work tasks, difficulties finding work, decrease in income, and more frequent and prolonged sick leave.⁹ In studies with a long-term follow-up, it was found that 34%–54% of patients changed their occupation within 7–15 years after diagnosis.^{7,10} Furthermore, 25% of patients left their job due to unemployment or retirement.^{7,10}

To prevent CD, various measures can be taken, depending on the work-related exposure and/or the type of CD (i.e., ACD or ICD).^{11–13} Next to work-related exposure, personal risk factors such as (a history of) atopic dermatitis (AD) or genetic factors may modify the risk for OCD.^{14–16}

Several systematic reviews on OCD have previously been done, focusing on the incidence of OCD or efficacy of preventive interventions.^{13,17,18,19} A recent systematic review assessed the occupational skin exposure in relation to ICD, in which several work-related risk factors showed an association with ICD.²⁰ However, to the best of our knowledge, there is no recent systematic review to date that has synthesized work-related and personal risk factors associated with CD. Evidence of these associations will aid in the development of strategies in the workplace to prevent (worsening of) OCD.⁷ In addition, evidence on the exposure dose-effect relationship might help (occupational) physicians in the assessment to what extent a patient's CD is work-related (i.e., OCD).

The objectives of this systematic review were: (1) to identify work-related and personal risk factors with corresponding risk estimates for CD, and (2) to pool comparable work-related and personal risk factors for CD in meta-analysis.

2 | METHODS

This review was conducted according to a protocol which was registered beforehand (June 19, 2020) in International prospective register of systematic reviews (PROSPERO) with registration number

CRD42020193241.²¹ We deviated from the protocol on the exposure, as in addition to work-related risk factors, personal factors and occupations were included in this review, as well. The personal risk factors were included, as personal susceptibility is an important factor in the development of CD.¹⁶ The risk estimates for occupational groups were included to obtain more information about (high) risk occupations. The Preferred Reporting Items for Systematic Reviews (PRISMA) were used for the reporting of this systematic review.²²

2.1 | Search methods

The systematic literature search was performed on the 2nd of June 2020 in the Ovid Medline and Embase database. The following (MESH) terms and initial key words in title and abstract were used to obtain the relevant literature: “contact dermatitis/eczema” or “allergic/irritant dermatitis” and “occupational” or “work” and “occupational exposure” or “risk assessment/factors” or “causality” (Supplement 1).

2.2 | Study eligibility

Articles were included when the following criteria were fulfilled: (1) written in English or Dutch; (2) publication between 1990 and June 2020; (3) study design was a prospective cohort or case-control; (4) publication in a peer-reviewed journal; (5) report of association of any work-related or personal risk factors for the development of (clinically assessed) CD among workers; (6) data provided on present or previous CD established by clinical examination or by a validated questionnaire; and (7) at least two levels of exposure reported, to retrieve or calculate a risk estimate.

Study eligibility was first assessed independently by two investigators based on title and abstract (M.G. Schütte, S.J. Tamminga, G.J. de Groene, S. Kezic, H.F. van der Molen) using Rayyan, a web and mobile app for systematic reviews.²³ If there was no abstract available, the decision was based on article title. The second assessment of eligibility was based on the full text of the articles and was done independently by two investigators (M.G. Schütte, S.J. Tamminga). During both assessments, disagreement (23%) was solved by discussion by the two of them; if needed, a third investigator was asked.

2.3 | Data extraction

Relevant data were extracted from all included articles by two independent investigators (M.G. Schütte, S.J. Tamminga) in a predetermined and piloted Excel-sheet. The following data were extracted and divided into the following six categories: publication (i.e., first author, publication year, study design, country, time period), study population (i.e., economic sector, occupations, number of participants and controls, mean age with standard deviation [SD], sex), reported confounding factors (i.e., smoking, a history of childhood eczema, present or

previous AD, allergic comorbidities), outcome assessment (i.e., type of assessment of CD, whether ACD or ICD was assessed, definition of CD, prevalence of CD per group), exposure assessment, and risk estimates (crude and/or adjusted risk estimates per investigated risk factor, exposure category, and reference category). The outcome is reported as stated in the study. For uniformity, diagnosis “hand eczema” was given in the tables as “hand dermatitis”. In addition, the type of CD was noted in the tables if this was reported or presumed in the study. If risk estimates of risk factors were not presented in an included article, relevant risk ratios with confidence intervals (CIs) were calculated by the investigators in Excel. If outcome data were only presented in figures of the article, Plotdigitizer²⁴ was used to estimate the values. These values were used and marked as such accordingly.

Next to work-related risk factors such as exposure to substances, work-related risk estimates for occupational groups based on International Standard Classification of Occupations-08 (ISCO-08) were extracted as sub-category.²⁵

2.4 | Risk of bias

The risk of bias (RoB) for individual included studies was assessed using two different methods depending on the study design. The RoB for the prospective cohort studies was analysed using the Quality In Prognosis Studies (QUIPS) tool for prospective cohort studies.²⁶ This checklist contains six items: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and presentation; each item could be rated as high, moderate, or low RoB. For case-control studies, a selection of questions of the Critical Appraisal Skills Program (CASP) checklist²⁷ was used, as some of the questions were inherent to the inclusion and exclusion criteria used in this systematic review and would not show any differences between the included studies. The selection included: focus on the topic, methods for aim of study, recruitment of cases and controls, exposure bias, equal treatment of different groups, and study confounding. The questions from this checklist could be answered with yes, no, or cannot tell.

2.5 | Meta-analysis

Meta-analysis was conducted for risk factors that were eligible according to the following criteria: two or more risk estimates were available for one risk factor. When more than two adjusted or crude risk estimates were available, the preference was to use the adjusted risk estimates in case the confounding factors were similar. The results from cohort and case-controls studies were pooled together as subgroups. The pooling was performed for the studies reporting the same type of CD (i.e., ICD or ACD). Crude and adjusted risk estimates were not pooled together. If multiple exposure categories were available from one study, the highest exposure level was used for meta-analysis (e.g., in the case of several categories for the frequency

of hand-washing, the risk estimate for the highest frequency was taken).

If different risk estimates were available (odds ratio (OR) and risk ratio (RR)), the OR was transformed to RR by taking the square root of the OR.²⁸ Hazard ratio (HR) was converted to OR or RR accordingly, if data was available to perform this calculation; in this way, it was possible to include more data for meta-analyses. Review Manager (RevMan 5)²⁹ was used for the meta-analysis and generating forest plots. The effect was set to random, and the CI of the risk estimates was transformed to standard errors (SE) by hand.

The risk estimates for occupational groups were not pooled, as the exposure for the occupational groups was not described and most likely differed considerably.

2.6 | Strength of evidence

The overall quality of evidence of the pooled risk factors was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).³⁰ Strength of evidence was scored into four quality categories: very low, low, moderate, and high, based on the criteria described in Huguette et al. (2013).³¹ The starting point of the quality of evidence was high and downgraded if the RoB of $\geq 50\%$ of the included studies was high, inconsistency was substantial ($I^2 > 50\%$), indirectness was present (no clear outcome definition of CD), imprecision was present (confidence interval effect size was <1 and >2), and publication bias was present (sample of studies is unrepresentative for risk factor, not detected when <10 studies were included in meta-analysis).

3 | RESULTS

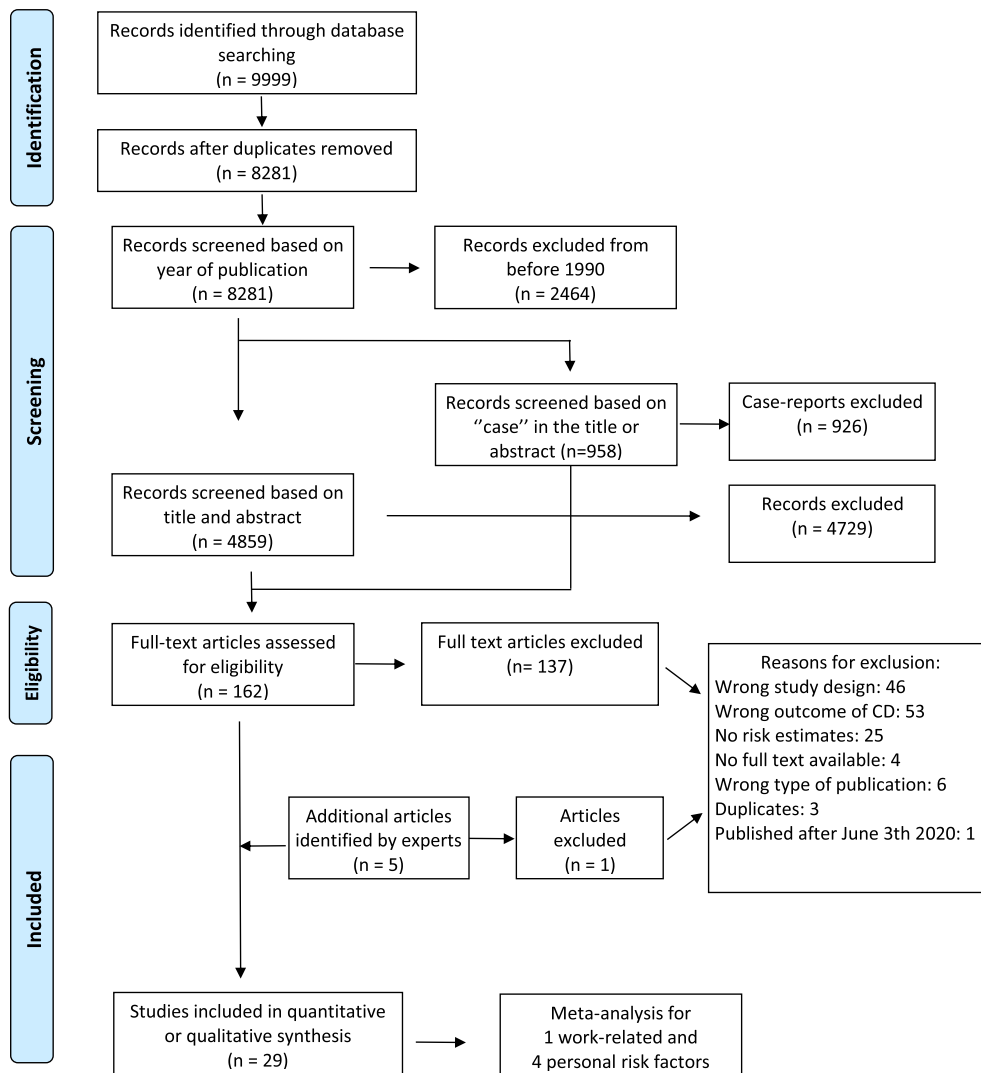
3.1 | Study selection

After removing duplicates, 8281 records were eligible for screening (Figure 1). Based on year of publication, type of study, title and abstract screening, 8119 records were excluded, leaving 162 articles eligible for full text screening, of which 137 were excluded mainly due to wrong outcome or wrong study design (Supplement 2). Five additional articles were identified by an expert (SK), of which four were included. Thus, in total, 29 articles were included for data extraction and analyses, of which 15 were articles with a prospective cohort design and 14 articles with a case-control design (for study characteristics see Table 1 and Supplements 3 and 4).

3.2 | Study characteristics

The majority of the included articles were from Germany ($n = 13$, 45%)^{32–44} and the minority from outside of Europe ($n = 4$, 14%).^{45–48} Eleven articles studied various occupations

FIGURE 1 PRISMA flow diagram adapted from Page et al.²²



($n = 11$, 38%),^{32,35–37,41,42,44,48–51} whereas in other articles, a specific occupation was studied, that is, metal workers ($n = 8$, 28%),^{38,39,45–47,52–54} hairdressers ($n = 6$, 21%),^{40,43,55–58} health care workers ($n = 3$, 10%),^{58–60} and bakers ($n = 2$, 7%).^{33,34}

The outcome CD was not uniform in the included articles and therefore was categorized in six main descriptions: hand dermatitis (HD) or hand eczema (HE)^{32,49,50,55,56,33,34,40,42,43,47,52,53,58–60} ($n = 16$, 55%), ICD^{36–39,41,44,46} ($n = 7$, 24%), ACD^{51,54,57} ($n = 3$, 10%), CD⁴⁸ ($n = 1$, 3%), airborne CD³⁵ ($n = 1$, 3%), and hypersensitivity dermatitis⁴⁵ ($n = 1$, 3%).

Twenty-eight work-related risk factors were extracted from eight articles (Supplement 5),^{32–34,47,48,50,59,60} reporting exposure to compounds and wet work. Twenty articles described 24 personal risk factors (Supplement 6),^{32–34,36–41,44,45,47,51–53,56,58–61} such as AD, childhood eczema, exposure at home, or genetic factors. Occupational groups associated with CD were extracted from 15 articles (Supplement 7).^{32,33,35,38,39,42,43,46–49,54–57}

The population size in included studies varied largely (Table 1). The largest study included 597 401 workers, in which 23 843 cases of new-onset dermatitis were identified.⁴⁸ This cohort study, based on

the national registries is comprised of different occupations and did not distinguish different types of CD.

3.3 | RoB

The RoB within the included cohort studies varied between low, moderate, and high on the six domains (Supplement 8). If the RoB of one or more domains was high, the study was rated as high RoB. The risk of study attrition was rated low for one article, for the other articles ($n = 14$) this was rated moderate or high, which means that the lost to follow-up is not well documented. Statistical analysis and presentation was rated low RoB for 10 studies, meaning that overall the statistical analysis was well-defined and adequately described.

For the case-control studies, the RoB varied between the seven domains (Supplement 9). If RoB was present on one or more domains, the study was rated as high RoB. In general, the RoB was low for the study objective ($n = 13$) and method used to reach the objective ($n = 14$). However, the assessment of confounding factors was regarded as not taken into account in four case-control studies.

TABLE 1 Summary of the study characteristics of the included studies

Reference	Country	Study design	Outcome	Study period	Occupation of exposed and controls				Sample size	
					Economic sector(s) (NACE)	Occupation(s) (ISCO-08)	Occupation controls (ISCO-08)	Exposure	Cases (n)	Controls (n)
Anveden et al., 2006 ⁴⁹	Sweden	Case-Control	HD	1996	NR	NR	NR	High risk occupations with more frequent exposure to water, chemicals, foodstuffs, glove wearing and hand washings.	129	132
Apfelbacher et al., 2010 ³²	Germany	Case-Control	HD	2005–2006	C29 – Manufacture of motor vehicles, trailers and semi-trailers	Various	Various	Occupation or personal and work-related exposure	110	120
Bauer et al., 1998 ³⁴	Germany	Prospective cohort	HD, mainly ICD (70%–74%).	1996–1997	C10.7 – Manufacture of bakery and farinaceous products	7512 – Bakers, pastry-cooks and confectionery makers	NA	Occupation of baker and confectionary apprentices	91	NA
Bauer et al., 2001 ³³	Germany	Prospective cohort	HD. Mainly ICD (79%), atopic HD (16%), dyshydrotic HD (1.5%).	1996–1999	C10.7 – Manufacture of bakery and farinaceous products	7512 – Bakers, Pastry-cooks and confectionery Makers	NA	Occupation of baker and confectionary apprentices	63	NA
Berndt et al., 1999 ⁵²	Switzerland	Prospective cohort	HD, not further defined	1994–1997	C24 – Manufacture of basic metals	72 – metal workers, mechanics, etc.	NA	Occupation of metal workers apprentices	201	NA
Breuer et al., 2015 ³⁵	Germany	Case-control	Occupational airborne CD	1994–2013	Various	Various	Various	Various occupations	241	200 141
Dai et al., 2009 ⁴⁵	China	Case-control	Hypersensitivity dermatitis	1999–2007	C24 – Manufacture of basic metals C27 – Manufacture of electrical equipment	72 – metal workers, mechanics, etc.	72 – metal workers, mechanics, etc. Exposed to TCE >3 months	Exposed to Trichloroethylene (TCE) <3 months	111	154
de Jongh et al., 2008a ³⁷	Germany	Case-control	Chronic ICD	2005–2007	Various	Various	Various participants without chronic ICD	Genetic mutations	296	217
De Jongh et al., 2008b ³⁶	Germany	Case-control	Chronic ICD	2005–2007	Various	Various	Various Participants without chronic ICD	Genetic mutations	197	217

(Continues)

TABLE 1 (Continued)

Occupation of exposed and controls										Sample size	
Reference	Country	Study design	Outcome	Study period	Economic sector(s) (NACE)	Occupation(s) (ISCO-08)	Occupation controls (ISCO-08)	Exposure	Cases (n)	Controls (n)	
Foss-Skiftesvik et al., 2017 ⁵⁵	Denmark	Case-control	HD, not further defined	2013-2016	S96.0.2 – Hairdressing and other beauty treatment	5141 – Hairdresser	Other than hairdresser	Occupation as hairdresser apprentice	248	816	
Funke et al., 1995 ³⁸	Germany	Prospective cohort	ICD	1990 – NR	C29 – Manufacture of motor vehicles, trailers and semi-trailers	72 – metal workers, mechanics, etc.	NA	Occupation as metal worker apprentice	2054	NA	
Funke et al., 2001 ³⁹	Germany	Prospective cohort	ICD (93%)	1990-1994	C29 – Manufacture of motor vehicles, trailers and semi-trailers	72 – metal workers, mechanics, etc.	Other blue collar workers White collar workers	Occupation as metal worker apprentice	1110	800	
Goh and Gan, 1994 ⁴⁶	Singapore	Prospective cohort	ICD	1986-1989	O84.2.2 – Defence activities	72 – metal workers, mechanics, etc. 35 – Health Associate Professionals	2240 – Paramedical Practitioners	Daily exposure to mineral oils	24	27	
John et al., 2000 ⁴⁰	Germany	Prospective cohort	HD (referred to as ICD)	1992-1995	S96.0.2 – Hairdressing and other beauty treatment	5141 – Hairdresser	NA	Occupation as hairdresser apprentice	66	NA	
Kristensen, 1992 ⁵³	Sweden	Prospective cohort	HD (mainly ICD)	1985-1988	C29 – Manufacture of motor vehicles, trailers and semi-trailers	Various within industry	NA	Occupation of apprentice in metal working industry	1564	NA	
Landeck et al., 2013 ⁴¹	Germany	Case-control	Chronic ICD	1996-1998	Various	Various	Various	Genetic mutation	478	393	
Lind et al., 2007 ⁵⁶	Sweden	Retrospective cohort	HD	1996	S96.0.2 – Hairdressing and other beauty treatment	5141 – Hairdresser	Various	Occupation as hairdresser	3665	5034	
Lund et al., 2020 ⁵⁰	Denmark	Case control	HD	2003-2015	Various	Various	Various, Patients with facial eczema.	Wet work	11 706	5499	
Radon et al., 2006 ⁴²	Germany	Prospective cohort	Doctors' diagnosed dermatitis: eczema, skin allergy, or	1995/ 1996-2002	Various	Various	Various	Working more than 8 hours/week longer than 1 month	964	1302	

TABLE 1 (Continued)

Reference	Country	Study design	Outcome	Study period	Occupation of exposed and controls			Sample size	
					Economic sector(s) (NACE)	Occupation(s) (ISCO-08)	Occupation controls (ISCO-08)	Cases (n)	Controls (n)
Sakhvidi et al., 2019 ⁴⁷	Iran	Case-control	atopic dermatitis HD, not further defined	NR	C29 – Manufacture of motor vehicles, trailers and semi-trailers	72 – metal workers, mechanics, etc.	Office workers	153	140
Schwensen et al., 2014a ⁵⁷	Denmark	Case-control	ACD	2002–2011	S96.0.2 – Hairdressing and other beauty treatment	5141 – Hairdresser	Other than hairdresser	399	1995
Schwensen et al., 2014b ⁵⁴	Denmark	Case-control	ACD	2003–2012	Various	7 – Craft and Related Trades Workers 8 – Plant and Machine Operators and Assemblers 93 – Laborers in Mining, Construction Manufacturing and Transport	Other than blue collar workers	1471	1471
Shakik et al., 2019 ⁴⁸	Canada	Prospective cohort	CD, not further defined	1983–2014	Various	Various	NA	597 401	NA
Smit et al., 1994 ⁵⁸	The Netherlands	Prospective cohort	HD, not further defined	1990–1992	Q86 – Human health activities S96.0.2 – Hairdressing and other beauty treatment	35 – Health Associate Professionals 5141 – Hairdresser	NA	74	NA
Spee et al., 2016 ⁵¹	The Netherlands	Case-control	ACD	2004–2007	Various	Various	Various	179	151
Uter et al., 1999 ⁴³	Germany	Prospective cohort	HD (referred to as ICD)	1992–1994	S96.0.2 – Hairdressing and other beauty treatment	5141 – Hairdresser	Office workers	1134	68

(Continues)

TABLE 1 (Continued)

Reference	Country	Study design	Outcome	Study period	Occupation of exposed and controls			Sample size	
					Economic sector(s) (NACE)	Occupation(s) (ISCO-08)	Occupation controls (ISCO-08)	Cases (n)	Controls (n)
Visser et al., 2013 ⁴⁴	Germany	Case-control	ICD	2005–2011	Various	Various trainees	Apprentices, for example, hairdressing, nursing, metalworking, food and catering, or floristry	634	393
Visser et al., 2014a ⁶⁰	The Netherlands	Prospective cohort	HD, (referred to as ICD)	2008–2011	Q86 – Human health activities	35 – Health Associate Professionals	NA	721	NA
Visser et al., 2014b ⁵⁹	The Netherlands	Prospective cohort	HD, (referred to as ICD)	2008–2011	Q86 – Human health activities	35 – Health Associate Professionals	Occupation of nurse Exposure to wet work as nurse	721	383
							Occupation of nurse Genetic mutations	721	NA
								446	

Abbreviations: ACD, allergic contact dermatitis; CD, contact dermatitis; HD, hand dermatitis; NA, not applicable; NR, not recorded; ICD, irritant contact dermatitis; TCE, trichloroethylene.

3.4 | Work-related factors and CD and strength of evidence

The studies reporting association between work-related factors and CD are summarized in Table 2 and Supplement 5. The large majority of studies, with exception those related to wet-work did not specify the type of CD (ICD or ACD). Therefore, a meta-analysis could only be performed for wet work for which three studies were identified, all of them reported ICD as the outcome (Figure 2). In the analysis, two cohort and a case-control studies were included. In the cohort study of Uter et al. (1999)⁴³ apprentices hairdressers ($n = 1202$) were included and in the study of Visser et al. (2014) apprentices nurses ($n = 553$).⁶⁰ The case-control study of Apfelbacher et al. (2010) comprised 176 apprentices in car industry and 119 controls.³² All three studies reported adjusted risk estimates. Wet work showed moderate quality evidence for an increased risk for ICD (OR: 1.56, 95% CI: 1.21–2.01) (Figure 2).

When assessing single risk estimate(s), five risk factors showed a significant increase of risk for CD based on a low-quality cohort study⁴⁸: bleach (HR: 1.2, 95%CI 1.1–1.4), aliphatic amines (HR: 1.1, 95%CI: 1.0–1.3), isocyanates (HR: 1.3, 95%CI: 1.1–1.7), acrylates (HR: 1.1, 95%CI 1.0–1.3), and persulfate and henna (HR: 1.5, 95%CI: 1.0–2.2). Eight work-related factors showed significant decrease of risk for CD within the same study⁴⁸: herbicides (HR: 0.7, 95%CI: 0.6–0.8), insecticides (HR: 0.8, 95%CI 0.8–0.9), fungicides (HR: 0.9, 95%CI: 0.8–0.9), exhaust fumes (HR: 0.8, CI95%: 0.8–0.9), latex (HR: 0.8, 95%CI: 0.7–0.9), textile dust (HR: 0.9, 95%CI: 0.8–0.9), moulds/fungi (HR: 0.9, 95%CI: 0.8–0.9), and endotoxins (HR: 0.8, 95% CI: 0.8–0.9).

Of the 28 work-related risk factors found, nine did not show a significant risk for CD: disinfectants,^{48,60} wood dusts,⁴⁸ pharmaceutical drugs,⁴⁸ animals,⁴⁸ food,^{33,48} plants,⁴⁸ mites and insects,⁴⁸ enzymes,⁴⁸ and dry skin soiling.³²

3.5 | Personal factors and CD and strength of evidence

The studies reporting association between personal factors and CD are summarized in Table 2 and Supplement 6. Meta-analysis was performed for four personal risk factors, all of them concerned ICD: history of HD, AD, respiratory and mucosal atopy, and sex (female vs. male) (Table 2, Figures 3–6). For the individual risk factors history of HD and AD, the adjusted risk estimates were used while for sex and respiratory atopy only studies with crude risk estimates were available.

High quality of evidence was found for the personal risk factors AD (OR: 2.44, 95%CI: 1.89–3.15) (Figure 5). Three studies were included, one cohort study in apprentices nurses ($n = 446$),⁵⁹ one nested case-control in apprentices in car industry ($n = 57$ cases and 119 controls)³² and another case-control study in various occupations (634 cases and 393 controls).⁴⁴ All studies reported adjusted risk estimates.

TABLE 2 Summary of findings table and grading of recommendations assessment development and evaluation (GRADE) framework for pooled work-related and personal risk factors for contact dermatitis (CD)

Exposure	N studies (n population)	Study design	Confounding	Outcome	RoB ^c	Incons. ^d	Indirect. ^e	Impre. ^f	Pub. Bias ^g	Risk estimate ^h [95%CI]	Grad. ⁱ	GRADE
Work-related exposure												
Organic solvents	2 (520020)	Case-control ^{32,48}	Crude	HD						Min: 1.0 [0.5–2.2] Max: 1.1 [1.0–1.3]		
Disinfectants	2 (597934)	Cohort ^{48,60}	Adjusted ⁶⁰ and crude ⁴⁸	CD ⁴⁸ , HD(ICD) ⁶⁰						Min: 0.9 [0.7–0.9] Max: 1.1 [0.9–1.8] ^b		
Herbicides	1 (589563)	Cohort ⁴⁸	Crude	CD						0.7[0.6–0.8]		
Insecticides	1 (595177)	Cohort ⁴⁸	Crude	CD						0.8 [0.8–0.9]		
Fungicides	1 (585827)	Cohort ⁴⁸	Crude	CD						0.8 [0.8–0.9]		
Indoor cleaning products	2 (525699)	Cohort ⁴⁸ and case-control ³²	Crude	CD ⁴⁸ , HD ³²						Min.: 0.8 [0.4–0.9] Max.: 1.0 [1.1–1.5]		
Bleach	1 (559923)	Cohort ⁴⁸	Crude	CD						1.2 [1.1–1.4]		
Exhaust fumes	1 (539177)	Cohort ⁴⁸	Crude	CD						0.8 [0.8–0.9]		
Metal working fluids	2 (595935)	Cohort ⁴⁸ and case-control ³²	Crude	CD ⁴⁸ , HD ³²						Min.: 1.0 [0.9–1.1] Max.: 1.4 [1.1–1.5]		
Aliphatic amines	1 (591275)	Cohort ⁴⁸	Crude	CD						1.1 [1.0–1.3]		
Isocyanates	1 (592322)	Cohort ⁴⁸	Crude	CD						1.3 [1.1–1.7]		
Acrylates	1 (597401)	Cohort ⁴⁸	Crude	CD						1.1 [1.0–1.3]		
Epoxy resins	2 (587253)	Cohort ⁴⁸ and case-control ³²	Crude	CD ⁴⁸ , HD ³²						Min.: 0.8 [0.5–0.7] Max.: 2.1 [0.8–8.5]		
Persulfate and henna	1 (597401)	Cohort ⁴⁸	Crude	CD						1.5 [1.0–2.2]		
Wood dust	1 (587741)	Cohort ⁴⁸	Crude	CD						1.0 [0.8–1.1]		
Metal and metal fumes	2 (521465)	Cohort ⁴⁸ and case-control ³²	Crude	CD ⁴⁸ , HD ³²						Min.: 0.8 [0.4–0.7] Max.: 4.1 [0.9–3.1]		
Wet work –adjusted only	3 (2030)	Cohort ^{48,60} and case-control ³²	Adjusted	HD(ICD)	Yes	No	No	No	ND	1.6 [1.21–2.01]	No	Moderate (Figure 2)
Pharmaceutical drugs	1 (597401)	Cohort ⁴⁸	Crude	CD						1.1 [0.7–1.3]		
Animals	1 (597401)	Cohort ⁴⁸	Crude	CD						Min: 0.7 [0.6–0.9] Max: 1.0 [0.8–1.1]		
Food	2 (597355)	Cohort ^{33,48}	Crude	HD (mainly ICD) ³³ , CD ⁴⁸						Min: 1.0 [0.7–0.8] Max: 1.2 [1.1–1.6]		
Plants	1 (591787)	Cohort ⁴⁸	Crude	CD						1.0 [0.9–1.1]		
	1 (591813)	Cohort ⁴⁸	Crude	CD						Min: 0.8 [0.7–0.9]		

(Continues)

TABLE 2 (Continued)

Exposure	N studies (n population)	Study design	Confounding	Outcome	RoB ^c	Incons. ^d	Indirect. ^e	Impr. ^f	Pub. Bias ^g	Risk estimate ^h [95%CI]	Grad. ⁱ	GRADE
Mites and insects (2 risk estimates)										Max: 1.0 [0.9–1.1]		
Enzymes	1 (597401)	Cohort ⁴⁸	Crude	CD						1.0 [0.9–1.1]		
Latex	1 (570451)	Cohort ⁴⁸	Crude	CD						0.8 [0.7–0.9]		
Textile dusts	1 (594974)	Cohort ⁴⁸	Crude	CD						0.9 [0.8–0.9]		
Moulds/Fungi	1 (597401)	Cohort ⁴⁸	Crude	CD						0.9 [0.8–0.9]		
Endotoxins	1 (585179)	Cohort ⁴⁸	Crude	CD						0.8 [0.8–0.9]		
Dry skin soiling	1 (229)	Case-control ³²	Crude	HD						1.6 [0.7–3.9]		
Personal risk factors												
Previous skin conditions (5 different conditions)	1 (736)	Cohort ³⁹	Crude	ICD						Min: 2.0 [1.0–1.8] Max: 5.1 [3.6–14.4]		
History of HD	2 (1648)	cohort ^{43,59}	Adjusted	HD(ICD) ^{43,59}	Yes	85% Yes	No	Yes	ND	1.8 [0.68, 4.54]	No	Very low (Figure 3)
Childhood dermatitis	2 (248)	Cohort ^{33,58}	Crude ³³ and adjusted ⁵⁸	HD						Min: 0.4 [0.1–5.0] Max: 41.1 [6.8–339]		
Atopic dermatitis	3 (1649)	Cohort ⁶⁰ and case-control ^{32,44}	Adjusted	HD(ICD) ⁶⁰ ; HD(ICD) ³² ; HD(ICD) ⁴⁴	No	28% No	No	No	ND	2.4 [1.89, 3.15]	No	High (Figure 5)
Respiratory and mucosal atopy	2 (2799)	Cohort ^{33,38}	Crude	HD(ICD) ³³ ; ICD ³⁸	No	65% Yes	No	Yes	ND	1.7 [0.80, 3.44]	No	Low (Figure 6)
Metal sensitization	2 (799)	Cohort ^{33,38}	Crude	HD(ICD) ³³ ; ICD ³⁸						Min: 0.5 [0.3] ^a Max: 1.1 [4.4] ^a		
Metal reactivity	1 (201)	Cohort ⁵²	Crude	CD						7.0 [1.3–38.3]		
Nickel sensitization	1 (185)	Cohort ⁵⁸	Adjusted	CD						Min: 1.1 [0.3–0.5] Max: 1.7 [4.0–5.5]		
Sensitization to allergens	1 (185)	Cohort ⁵⁸	Adjusted	CD						Min: 1.5 [0.5–0.6] Max: 1.8 [4.6–5.0]		
Sensitization to epoxy	1 (330)	Case-control ⁵¹	Crude	ACD						94.3 [63.1–140.9]		
Sex (female vs. male)	3 (1328)	Cohort ^{33,38,53}	Crude	HD(ICD)	No	0% No	No	No	ND	1.2 [0.97, 1.42]	No	High (Figure 4)
Age (mean age cases vs. controls)	1 (230)	Case-control ³²	Adjusted	CD						0.9 [0.7–1.0]		
Skin type (dry vs. oily skin)	1 (185)	Cohort ⁵⁸	Adjusted	CD						Min: 1.7 [0.5–2.2] Max: 7.3 [6.4–24.3]		
NAT polymorphisms	1 (264)	Case-control ⁴⁵	Crude	Hypersensitivity dermatitis						2.0 [1.1–3.5]		
Filaggrin loss-of-function mutations	3 (1988)		Crude ³⁷ and adjusted ^{44,59}	HD(ICD) ⁵⁹ ; ICD ³⁷ ; HD ⁴⁴						Min: 0.7 [0.3–1.3] Max: 1.9 [1.7–3.6]		

TABLE 2 (Continued)

Exposure	N studies (n population)	Study design	Confounding	Outcome	RoB ^c	Incons. ^d	Indirect ^e	Impre. ^f	Pub. Bias ^g	Risk estimate ^h [95%CI]	Grad. ⁱ	GRADE
		Cohort ⁵⁹ and case- control ^{37,44}										
Interleukin SNPs	2 (1285)	Case- control ^{36,41}	Crude	ICD						Min: 0.8 [0.5–0.8] Max: 1.1 [1.0–1.4]		
TNF α SNPs	1 (414)	Case-control ³⁶	Crude	ICD						Min: 0.7 [0.4–0.9] Max: 1.3 [1.4–1.9]		
Trans-epidermal water loss hands	2 (251)	Cohort ^{40,58}	Adjusted	CD						Min: 0.5 [0.1–0.5] Max: 1.6 [1.7–6.4]		
Relative skin moisture	1 (66)	Cohort ⁴⁰	Adjusted	CD						0.6 [0.2–10.9]		
Serum IgE	1 (63)	Cohort ³³	Crude	CD						0.4 [0.1–2.1]		
Smoking	1 (3646)	Cohort ⁵⁶	Crude	CD						1.2 [1.0–1.3]		
Construction work at home	1 (63)	Cohort ³³	Crude	CD						5.4 [1.1–27.8]		
Frequent hand washing at home >10/day	1 (446)	Cohort ⁵⁹	Adjusted	CD						1.9 [0.9–4.2] ^b		
Working in a side job involving wet work for >8 h/week	1 (446)	Cohort ⁵⁹	Adjusted	CD						1.2 [0.6–2.1] ^b		

Abbreviations: 95%CI, 95% confidence interval; ACD, allergic contact dermatitis; CD, contact dermatitis; ICD, irritant contact dermatitis; NAT, N-acetyltransferase; SNP, single nucleotide polymorphism; TNF, tumour necrosis factor.

^aCI not given for one of the risk estimates.

^b90% CI.

^cLimitation: downgraded if $\geq 50\%$ of the studies had a high RoB.

^dInconsistency: downgrade if $I^2 \geq 50\%$.

^eIndirectness: downgrade if indirectness is present.

^fImprecision: downgrade if the 95% confidence interval is <1 and >2 .

^gPublication bias: downgraded if publication bias is present; ND = not detected if <10 risk estimates were available for meta-analyses.

^hEffect size: upgrade if the lower limit of the 95% confidence interval is >2.0 .

ⁱGradient: upgraded if there is a dose-response gradient available.

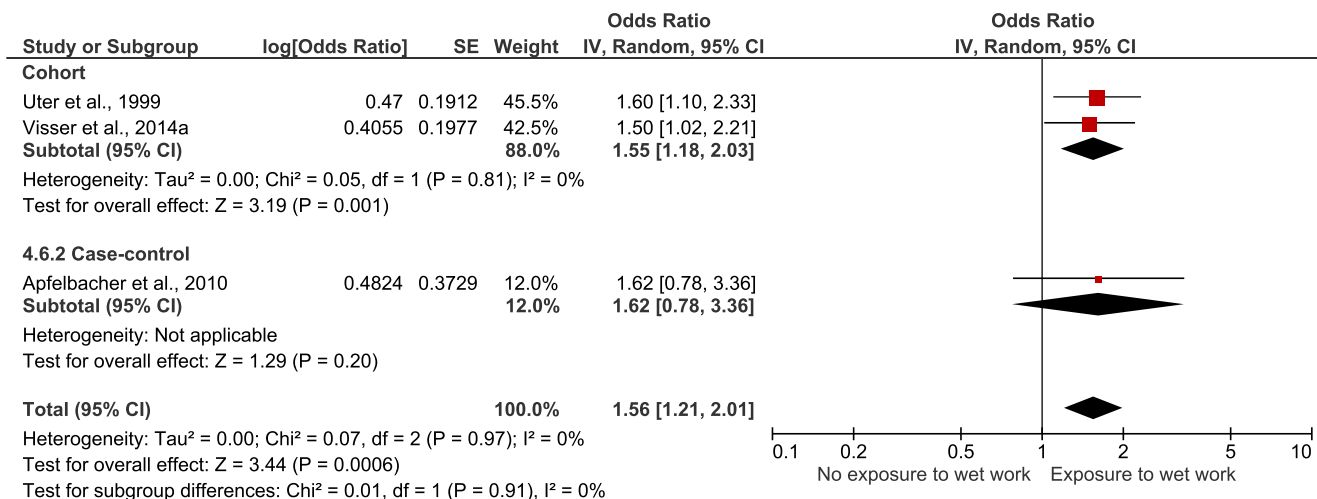


FIGURE 2 Forest plot of the meta-analysis of wet work in association with irritant contact dermatitis (ICD)

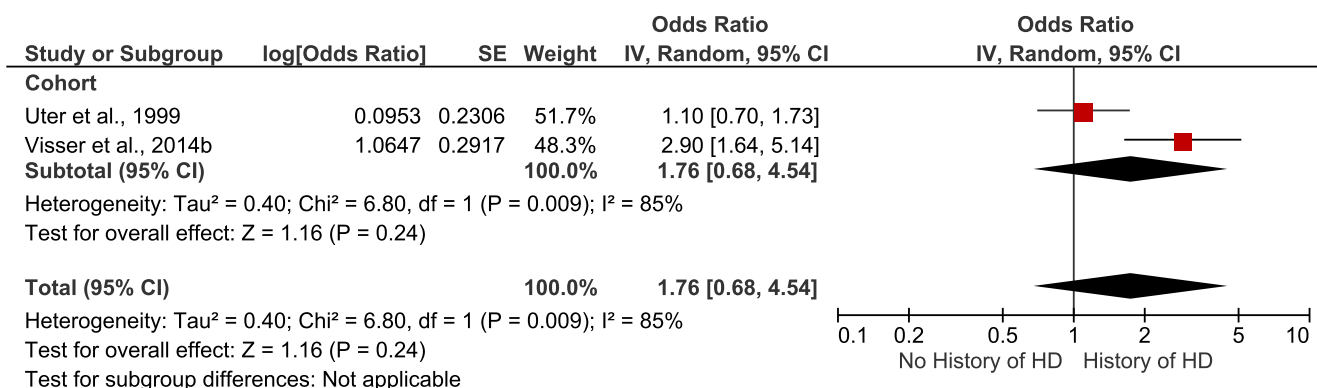


FIGURE 3 Forest plot of the meta-analysis of history of hand dermatitis (HD) in association with irritant contact dermatitis (ICD)

Sex (female vs. male) did not show a significant risk with CD (RR: 1.17, 95%CI: 0.97–1.42; high quality evidence) (Figure 4). Three studies were included, all of them investigated risk for ICD, and reported crude risk estimates. One study was performed in apprentices bakers ($n = 36$ male and 27 female),³³ and two studies in apprentices in car industry (940 male and 256 female)³⁹ and (35 male and 34 female).⁵³

Previous HD did not show a significant risk with CD (OR: 1.76, 95%CI: 0.68–4.54; very low quality evidence) (Figure 3). Two cohort studies were included and both reported adjusted risk estimates for ICD. One study was performed in apprentices hairdressers ($n = 1202$)⁴³ and another in apprentices nurses ($n = 446$).⁵⁹

In meta-analysis for respiratory and mucosal atopy two cohort studies were included (Figure 6). One study was performed in apprentices bakers ($n = 63$)³³ and another in apprentices in car industry ($n = 736$).³⁸ Respiratory and mucosal atopy did not show a significant risk with CD (RR: 1.66, 95%CI: 0.80–3.44) with low quality of evidence. The other personal risk factors that showed a significant increased risk for CD in separate studies were as follows: previous skin conditions³⁸ (RR: 2.0–5.1), metal reactivity⁵² (OR: 7.0, 95%CI:

1.3–38.3), sensitization to epoxy⁵¹ (OR: 94.3, 95%CI: 63.1–140.9), NAT polymorphisms⁴⁵ (OR: 2.0, 95%CI: 1.1–3.5), smoking⁵⁶ (RR: 1.2, 95%CI: 1.0–1.3), and construction work at home³³ (OR: 5.4, 95%CI: 1.1–27.8). A personal risk factor that showed a significant decreased risk for CD based on risk estimate from one article was tumour necrosis factor (TNF)- α single nucleotide polymorphisms (SNPs) (OR: 0.7, 95%CI: 0.4–0.9).³⁶

Of the 24 personal risk factors, 13 did not show a significant risk with CD: childhood (hand) dermatitis,^{33,58} metal sensitization,^{33,38} nickel sensitization,⁵⁸ sensitization to allergens,⁵⁸ age,³² skin type (dry vs. oily skin),⁵⁸ filaggrin loss-of-function mutation,^{37,44,59} interleukin SNPs,^{36,41} trans-epidermal water loss,^{40,58} relative skin moisture,⁴⁰ serum IgE,³³ frequent hand washing at home,⁵⁹ and working in a side job involving wet work >8 h/week.⁵⁹

3.6 | Occupation and CD

Risk estimates of twenty-four ISCO-08 occupational groups were extracted from the included articles. The following occupational

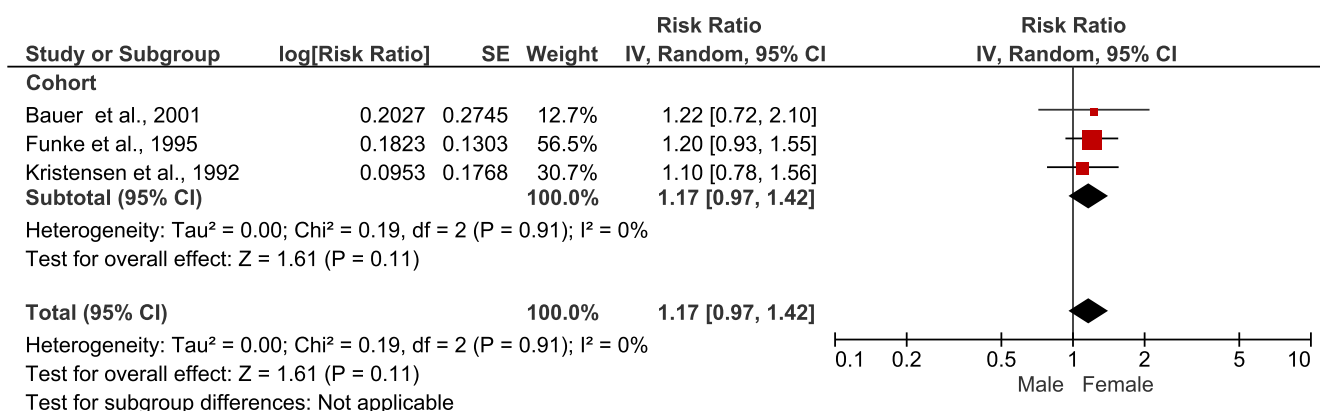


FIGURE 4 Forest plot of the meta-analysis of sex in association with irritant contact dermatitis (ICD)

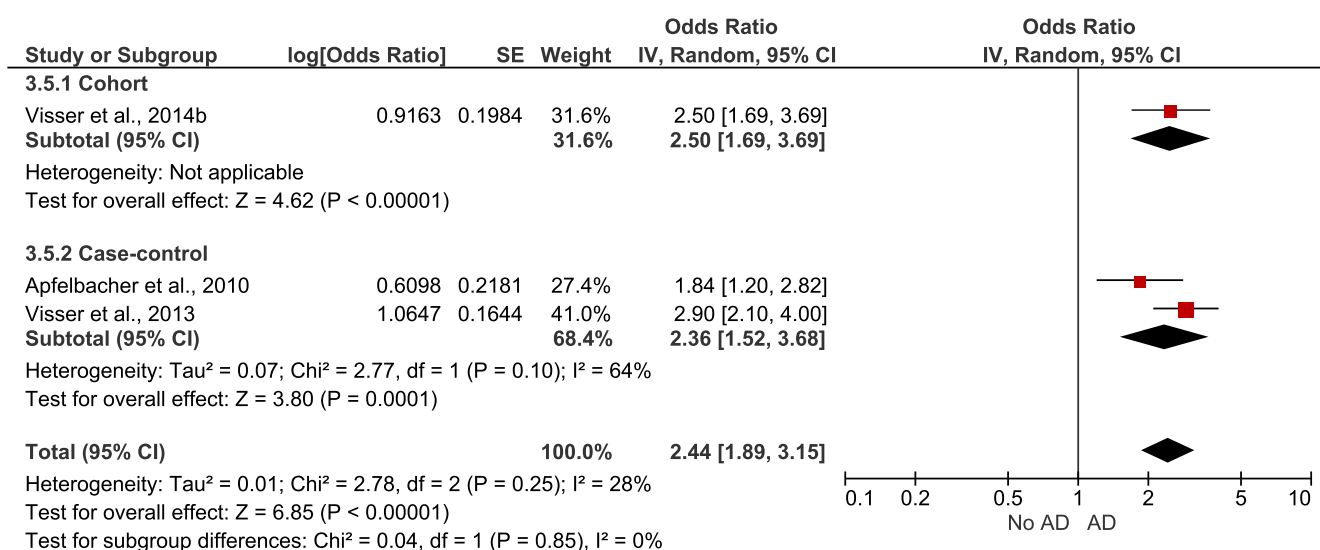


FIGURE 5 Forest plot of the meta-analysis of atopic dermatitis (AD) in association with irritant contact dermatitis (ICD)

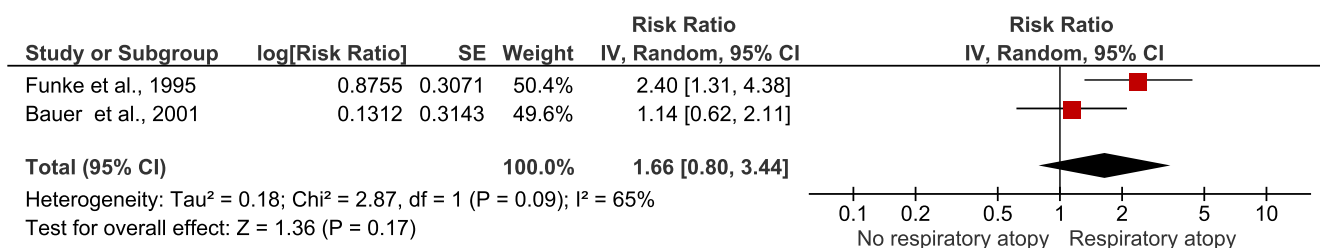


FIGURE 6 Forest plot of the meta-analysis of respiratory and mucosal atopy in association with irritant contact dermatitis (ICD)

groups showed a significantly increased risk of CD in two or more studies (range of risk estimates showed significant increased effect): health care workers^{35,42} (OR: 2.0–7.8; 95%CI: 1.2–38.7), hair-dressers^{40,43,55–57} (OR/RR/HR: 1.5–9.2; 95%CI: 1.0–11.9), blue collar workers^{38,54} (OR/RR: 1.9–2.0; 95%BI: 1.1–3.6), painters^{35,48} (OR/HR: 1.3–13.6; 95%CI: 1.1–19.5), metal workers^{35,39,46–48} (OR/RR/HR: 1.1–30.2; 95%CI: 1.0–482.9), and cleaners^{35,42} (OR: 2.0–11.4; 95%CI: 1.2–45.9) (Supplement 7).

4 | DISCUSSION

4.1 | Summary of evidence

In this systematic review, 29 articles were identified comprising 26 study populations that included 846 209 participants and investigated 52 risk factors for CD in an occupational setting. In the meta-analysis, exposure to wet work indicated an increased risk of

developing ICD. Meta-analysis revealed that persons with (a history of) AD, had a higher risk of ICD. Personal risk factors that were not included in the meta-analysis that had a significant association with CD were: previous skin conditions, metal reactivity, higher age, sensitization to epoxy, NAT polymorphisms, smoking, and construction work at home. The associations between occupational ISCO-08 group and CD revealed significant increased risk estimates for health care workers, hairdressers, blue collar workers, painters, metal workers, and cleaners.

4.2 | Strengths and limitations

A strength of this review was inclusion of only case-control and prospective cohort studies, as these study designs allow for controlling for the time sequence between exposure and the development of CD.⁶² Moreover, cross-sectional studies are subject to selection bias, as workers with severe CD often leave the high-risk occupation which might lead to missing or underestimating risk factors.⁶³ On the other hand, the exclusive selection of case-control and prospective cohort studies in the present systematic review could also be seen as a limitation because relevant risk factors investigated in cross-sectional studies might have been missed. This is in particular relevant for risk factors associated with ACD, which are often investigated in cross-sectional studies based on registry of patch tests.^{2,64,65} Hence, the association between the risk factors and development of CD found in this review are based on a higher quality studies, but some well-known or less well-known risk factors are not included in this evidence synthesis.

Another strength of this review was the well-defined inclusion criteria, assuring that the included articles were comparable in terms of outcome and risk estimates to combine studies in a meta-analysis. An important exclusion criterion was the lack of the definition of CD or the description of the method used to diagnose CD. For example, studies were excluded when the definition of CD was based on a single question in a questionnaire ("Have you had CD?"), or on a single symptom of CD. Although these criteria resulted in a considerable reduction of studies selected for analysis, their exclusion increased the overall quality of evidence.

Major challenge and limitation of this systematic review was low number of studies that reported the type of CD which limited data synthesis. A meta-analysis could only be done for ICD for which sufficient number of studies were identified for several risk factors. As ICD and ACD have different pathophysiology these results could not be generalized for all types of CD.

A further limitation of the studies was that exposure was often assessed retrospectively by using self-reporting questionnaires, or by using Job Exposure Matrices (JEMs). With self-reporting questionnaires there is a chance of recall bias, which means participants do not recall events or exposure that occurred in the past.⁶⁶ JEMs could cause bias in results as one standardized exposure matrix is used for all workers in a specific occupation.⁶⁷ Both might result in an inaccurate exposure estimation, that could affect the risk estimates found in

this review. This problem was in particular relevant in the study of Shakik et al. who used JEMs for asthma, which, however, has not been evaluated for CD.⁴⁸ Another limitation regarding exposure estimates was the definition of wet work which varied between studies. The criteria of wet work are not well defined, however having wet hands for ≥ 2 hours per working day, hand washing ≥ 20 times per working day, or wearing occlusive gloves for ≥ 2 hours per working day is widely accepted.⁵⁰

4.3 | Interpretation of findings

Both ICD and ACD may occur in the workplace and often the workers are exposed to both contact allergens and skin irritants. Both forms of CD share similar clinical features but their disease pathophysiology is different. ICD is mediated by innate immune response triggered by skin barrier damage, while ACD is a T-cell mediated delayed-type hypersensitivity occurring after skin contact with an allergen in a previously sensitised individual.^{68,69} ICD is more frequent and constitutes up to 80% of all occupational CDs.⁷⁰ In the present review, most studies that were included did not specify whether their outcome involved ICD or ACD, and the outcome of CD was given in more general terms such as hand eczema (HE), hand dermatitis (HD), or contact dermatitis (CD). In most of the studies, the patch test necessary for the diagnosis or exclusion of ACD was not performed and it was not possible to relate a risk factor specifically to ICD or ACD. Though, in a number of studies the authors stated that despite of objective confirmation of the type of CD, the nature of exposure (mainly wet work activities) allowed assumption that majority of cases concerned ICD. It should be noted that next to ICD and ACD, atopic dermatitis manifests often on the hands which furthermore makes the correct classification even more complex. Therefore, generalization of results for all types of CD is difficult. As previously addressed in the introduction, differentiation of ICD and ACD is of importance because it determines disease management and preventive measures. Furthermore, individual risk factors might differ for ICD and ACD. Therefore, it is recommended for further research that a distinction is made between ICD and ACD.

High-quality evidence showed that individuals with (a history of) AD have 2.4-fold increased risk for ICD. AD is associated with impaired skin barrier function even in non-lesional skin. It may therefore be expected that reduced skin barrier in AD will facilitate penetration of skin irritants and allergens into the skin leading to an immune and inflammation reaction.⁷¹ Furthermore, AD is associated with aberrant levels of Interleukin-1 innate cytokines even in the non-lesional skin, which might contribute to a stronger immune response.⁷²

The meta-analysis comprised of three studies revealed a 1.6-fold increased risk for ICD due to wet work. Included studies were carried out in apprentices nurses,⁶⁰ hairdressers,⁴³ and workers in car industry.³² Wet work is primarily a risk factor for ICD, as water can work as an irritant that easily penetrates into the skin leading to barrier damage. In agreement with the findings of the present review, in a recent systematic review of Jacobsen et al. evidence was found for strong association between ICD and wet work exposure.²⁰

During data extraction and quality assessment of the individual studies, older studies (>10 years old) often showed publication bias as result of incompleteness of results. Often, if no significant effect for a certain risk factor was found, the result was not shown or only the p-value, making extraction of the risk estimates for all investigated risk factors within these studies impossible. As a consequence, some risk factors, such as smoking or exposure to disinfectants, could not be interpreted, as often they were not reported. It will be important for future studies to report all the investigated risk factors, for example in the supplements, to be able to compare and make a synthesis of the results from multiple studies.

4.4 | Implications for practice

This systematic review showed that wet work increases the risk for ICD 1.6-fold. Although wet-work is largely responsible for ICD, skin barrier damage and activated innate immune response in ICD will likely increase the risk for ACD. Therefore, maintenance of the skin barrier is a crucial step in the prevention of both ICD and ACD. In 2018, Bauer et al.¹³ conducted a systematic review investigating intervention studies for the prevention of ICD, concluding that moisturizers alone or in combination with barrier creams were most effective for the prevention of ICD. Rising awareness of the work-related risk factors for CD among health professionals, safety managers as well as workers in general, should lead to prevention measures aiming reduction of exposure.²

Next to exposures to irritants and allergens, personal susceptibility factors, in particular a history of atopic dermatitis should be considered in prevention programs. Prevention measures regarding atopic dermatitis are included in Dutch and German guidelines on contact dermatitis for occupational physicians.^{73–75} However, it is also important that workers in high-risk occupations, including those identified in the present review, are informed on individual risk for CD during education, apprenticeships, or during the start of their career. With this knowledge, they could make an informed decision about their career or the preventive measures they should take to avoid developing CD.^{59,60,76} Actively providing this information seems necessary, as the studies by Visser et al.^{59,60} showed that young people do not consider their individual susceptibility and potential health risks when choosing a professional training.

4.5 | Follow-up research

Considering continuous changes in exposures for example, due to new technologies, materials, and regulations, prospective cohort studies or high-quality case-control studies would be of importance in detecting current and emerging risks. A further advantage of prospective studies would be identification of early adverse effects for example, those associated with skin barrier damage or immune local response. Harmonization and validation of the criteria used for the diagnostics of CD and exposure assessment would improve the

quality and synthesis of data from various studies. Furthermore, when possible quantitative exposure assessment should be preferred above retrospective self-administered questionnaires.

5 | CONCLUSION

In conclusion, several work-related and personal risk factors associated with CD were identified. Our data emphasize the need for including both, work-related and personal, risk factors in the prevention of occupational CD.

AUTHOR CONTRIBUTIONS

M.G. Schütte: Conceptualization; writing – original draft; methodology; formal analysis; project administration. **S.J. Tamminga:** Conceptualization; data curation; supervision. **G.J. de Groene:** Writing – review & editing. **S. Kezic:** Conceptualization; validation; supervision; project administration. **H.F. van der Molen:** Conceptualization; funding acquisition; methodology; data curation; supervision.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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