

# Incidence Rate of Hand Eczema in Different Occupations: A Systematic Review and Meta-analysis

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**Hand eczema is a chronic disease that results in economic and psychosocial burdens. The aim of this study was to systematically review and assess the magnitude of the association between exposure related to occupations and the incidence rate of hand eczema. A systematic search in PubMed, EMBASE, CINAHL and Cochrane databases, from inception to September 2017, of full-text observational studies reporting incident cases of hand eczema during employment, and a supplementary search in PubMed to September 2020, were conducted. Among 2,417 screened abstracts, 15 studies fulfilled the inclusion criteria. Incidence rates were reported per 100 person-years. Based on the Newcastle-Ottawa Scale, 9 studies were good quality, 2 fair quality, and 4 poor quality. Hairdressers had a high incidence of hand eczema of 21.4 (95% confidence interval [CI] 15.3–27.4), as did nurses, 16.9 (95% CI 11.2–22.7), and metal workers, 12.4 (95% CI 3.5–21.3). Hairdressers were predominantly women, and metal worker were predominantly men. Office occupations had an incidence rate of hand eczema of 4.9 (95% CI 1.2–9.6). The high risk of hand eczema for hairdressers, nurses, and metal workers, should be considered by healthcare policymakers. Even occupations with low irritant profile, such as office workers, were at risk of developing hand eczema, and more occupations should be investigated regarding the related risk of developing hand eczema.**

*Key words:* hand eczema; epidemiology; occupation; incidence.

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Contact eczema is the most common occupational skin disease, accounting for up to 90% of all occupational skin diseases, and it predominantly affects the hands (1–4). Hand eczema (HE) is a chronic disease with a fluctuating course (5). Although occupational HE is not life-threatening, it has negative psychosocial effects on patients, reported as pain, anxiety, and depression, and it results in economic burdens, such as long-term sick leave, involuntary change of occupation, and cost of treatment (2, 6, 7).

## SIGNIFICANCE

Hand eczema is a chronic disease that results in economic and psychosocial burdens. A systematic review was performed to assess the association between occupations and incidence rate of hand eczema. The study found that hairdressers, nurses and metal workers had a high incidence of hand eczema. The high risk of hand eczema for hairdressers, nurses, and metal workers, should be considered by healthcare policymakers. The review also indicates a need for studies of other occupations with other occupational exposures, as it was found that even occupations with low irritant profile, such as office workers, were at risk of developing hand eczema.

HE is a multifactorial disease, in which endogenous and exogenous factors, mainly atopic dermatitis and wet exposure, respectively, are main risk factors (8–10). Recently, wet-work exposure, defined as having wet hands for 25–50% of the day, has been shown to result in a more than 2-fold increase in the odds of developing HE (9). The prevalence of HE in occupations with exposure to water, detergents, and metal fluids was reported to be up to approximately 30%, whereas, in the general population, the prevalence is estimated to be in the range 2–10% (11–14).

Previous meta-analyses of epidemiological studies have focused on the risk of atopic dermatitis and smoking with regard to HE (1, 8). To our best knowledge, no meta-analysis has been performed on the magnitude of the association between exposure related to occupations and the incidence rate (IR) of HE. The primary objective of the current study was to systematically review and determine the magnitude of the association between exposure related to occupations and the IR of HE, in order to test the hypothesis that the incidence of HE is high in certain occupations.

Data on the incident cases of HE, from the time that patients began working in the occupation, and exposure data from all accessible observational studies were analysed.

## MATERIALS AND METHODS

### Search strategy

A meta-analysis was conducted in accordance with the Meta-Analysis of Observational Studies in Epidemiology's (MOOSE)

checklist (15). The study was conducted in accordance with an *a priori* developed protocol registered in PROSPERO (the International Prospective Registry of Systematic Reviews; CRD: 42017056829).

A systematic electronic search was conducted from inception until 1 March 2020 in PubMed, EMBASE, CINAHL and Cochrane. The search terms used were: eczema, dermatitis, atopic eczema, hand, occupation, work, workplace, job, employment, employee, working, worker, occupational disease, occupation exposure, and work environment. These search terms were combined using conjunctions "AND" and "OR". The full search strategy is shown in Table SI.

#### *Inclusion criteria*

Studies were included if they were full-text observational studies, and they investigated incidence cases during employment. A study period of at least 3 months was required. The inclusion of articles was limited to those in which the number of participants was greater than 10. Regardless of the underlying assumed aetiology, incident cases of HE were acceptable if HE was diagnosed by a physician (clinical assessment), or self-reported via questionnaires. There were no restrictions regarding geographical region, language or publication period.

#### *Primary and secondary outcomes*

IRs were pooled for every studied occupation with the same duration of exposure time since beginning work in the occupation, and exposure. Incident cases of HE were defined as the number of individuals without HE at study start who developed HE during follow-up. An IR was accepted if it was reported by studies, or if there were appropriate data to calculate an approximated IR.

For consistency, when studies reported IR per 100 or 1,000 person-years, the IR was scaled to a common denominator and reported in 100 person-years. Approximated IR was calculated if appropriate data were available, and the total number of person-years was not reported, in both closed cohorts with no loss to follow-up, and open cohorts with loss to follow-up (16, 17).

When available, the study aimed to report stratified IR, odds ratio (OR), and relative risk of any other risk factor for HE incidence; years in occupation, sex, age group, HE before occupation, previous or current atopy, previous or current smoking, contact allergy, medications, perceived stress at work, non-occupational exposure to skin irritants, and socioeconomic position.

#### *Primary and secondary exposures*

At every studied occupation, if data were available, risk factors for HE were studied: sex, age group, HE before occupation, childhood eczema, previous or current atopy, previous or current smoking, contact allergy, perceived stress at work, non-occupational exposure to skin irritants, and socioeconomic position. These were not systematically covered by the electronic search strategy of this study.

#### *Data extraction and evaluation of eligibility of studies*

Each title and abstract of the identified articles were independently screened for eligibility by 2 researchers (WJ and LK) to exclude irrelevant publications. In cases of disagreement, MG and AS were consulted to reach a consensus. The Covidence tool was used to organize and manage the screening process (<http://www.covidence.org/>).

Data extraction was performed by one researcher (WJ), using a pre-specified form to collect information decided upon by all authors, and a second author (ML) verified the data. Study and population characteristics are shown in Table SI.

#### *Qualitative assessment*

The methodological quality of the studies was assessed with the Newcastle-Ottawa Scale (NOS) for observational studies (18). Each study was judged for selection, comparability and outcome. Quality assessment was also performed by author WJ and verified by author ML. NOS yields a total score between 0 and 9 points, categorized into 3 levels of quality: (i) good quality (at least 3 stars in selection category, 1 or 2 stars in comparability category, and 2 or more stars in outcome category); (ii) fair quality (2 stars in selection category, 1 or more stars in comparability category, and 2 or more stars in outcome category); and (iii) poor quality (maximum of 1 star in selection category, or no stars in comparability category, or maximum of one star in outcome category) (18).

Whether the quality of the study affects the outcome was determined by comparing "good quality  $\geq 7$  points" with "fair and/or poor quality  $< 7$  points". Information regarding the NOS assessment is shown in Table SII.

#### *Statistical analysis*

A meta-analysis was conducted after at least 2 good-quality studies had been identified, according to NOS, which reported IRs for approximately the same length of time measured from the start of occupation and exposure (19). A random-effects model was used in the analysis to incorporate the expected heterogeneity in methodological quality to calculate the pooled IR with 95% CI for each occupation. When studies report IR for more than one occupation, we considered each occupation as contributing separately to this analysis. If studies compared the effect of intervention programmes on prevention of HE with a control group, only the control group data were considered. If studies reported IR for different time periods, this study reported the relationships for these time periods separately, and the overall IR for the whole studied period was recalculated if it was not reported.

When possible, a subgroup analysis was performed to compare pooled IR when 2 sets of quality assessment were reported. For subgroup analysis, a mixed effects model was applied. Statistical assessments of heterogeneity were used to provide a sense of dispersion in effect sizes across studies: (i) Q-statistic test (to assess whether the distribution of the observed effects was not due to chance but to a true heterogeneity). A heterogeneity in a Q-statistic test was considered significant if Q-statistic  $p < 0.05$ ; and (ii)  $I^2$ -statistics is the proportion of the variance in observed effects to the variation in true effects.  $I^2$  percentages were interpreted as low (0–25%), moderate (25–50%), substantial (50–75%) and high (75–100%) heterogeneity.

Prediction interval is another way to report heterogeneity, which has the advantage of showing the range of effects in the same metric of effect size. Reporting 95% prediction interval for an observed effect size in an occupation, tells us how widely the effect size varies in the populations that we expect would affect these results (20).

## RESULTS

### *Study selection*

The search strategy identified 3,300 records; 816 from PubMed, 2018 from EMBASE, 28 from CINAHL, and 438 from Cochrane. Following removal of duplicates, 2,417 records remained for screening by title and abstract. Of these, 40 potential studies were eligible for full-text review. A total of 28 full-text articles were excluded, for the following reasons; 16 studies reported prevalence, one study had a short follow-up of less than

3 weeks, one study reported IR without specifying an occupation, one study reported IR for occupational skin diseases, not specifying HE, and 9 studies concerned the same populations as the studies included in this meta-analysis.

Finally, 12 studies (2, 21–31), of 11 studied populations met all eligibility criteria from the electronic search. An additional 2 studies (32, 33) were identified by hand-searching, and an another study (34) from supplementary searches in PubMed from September 2017 to March 2020, yielding a total of 15 (2, 21–34) studies included in this meta-analysis (**Fig. 1**).

#### Qualitative assessment of included articles

Methodological assessment with NOS, and the characteristics of included studies are shown in Tables SII and SIII. A total of 9 studies were rated as being of good quality (2, 21, 23–25, 27, 32–34), 2 as fair quality (26, 29), and 4 as poor quality (22, 28, 30, 31).

#### Summary of results by occupation

**Hairdressers.** Two studies evaluated the same population (23, 25), and were thus considered as a single study, as both of them contributed to the analysis. A total of 6 studies reported IR (21, 23, 25, 27, 28, 30, 31). Of these, 3 studies evaluated IR in cohorts of apprentice hairdressers (21, 23, 25, 27), and another 3 in graduated hairdressers (28, 30, 31). Two studies were from Denmark (30, 31), 2 from Germany (23, 25, 27), 1 from Sweden (28) and 1 from the Netherlands (21). The studies were conducted between 1970 to 2016, and included 4,330 participants, for a total of 43,983 person-years of follow-up.

Four studies evaluated IR at different times from the start of an occupation and exposure (21, 23, 25, 28, 30). The studied time periods ranged from 0.7 to 13.5 years. Only 2 studies (27, 31) reported IR at a total of 3 years since the start of an occupation, but a pooled IR was not conducted because of differences in methodological qualities regarding design, definition of HE, and response rate.

Study quality was assessed using the NOS scale. Of 6 studies, 3 were rated as "good quality" (21, 23, 25, 27). This set of studies had a prospective design, and the HE diagnosis was based on clinical assessment. The 3 studies of good quality had a follow-up of 2.6–3 years. Another 3 studies (28, 30, 31) were rated "poor quality". This set of studies had a retrospective design, and HE diagnosis was based on a questionnaire. In the 3 "good quality" studies, the pooled IR was 21.4 (95% CI 15.3–27.4) with a substantial heterogeneity ( $\chi^2 = 6.457.0$ ,  $df=2$ ,  $p=0.04$ ;  $i^2=69.025$ , 95% prediction interval 2.6–73.1 per 100 person-years). The 3 "poor quality" studies yielded a pooled IR of 3.8 (95% CI 0.0–7.5) with no evidence of heterogeneity ( $\chi^2=2.179$ ,  $df=2$ ,  $p=3.336$ ;  $i^2=8.234$ , 95% prediction interval 0.04–80.7 per 100 person-years). A significant difference was noted for pooled IRs between studies of "good quality" and "poor quality" ( $\chi^2=23.562$ ,  $df=1$ ,  $p<0.01$ ); the IR in good quality studies was 5.6 times higher than the reported IR of poor quality studies (**Fig. 2**).

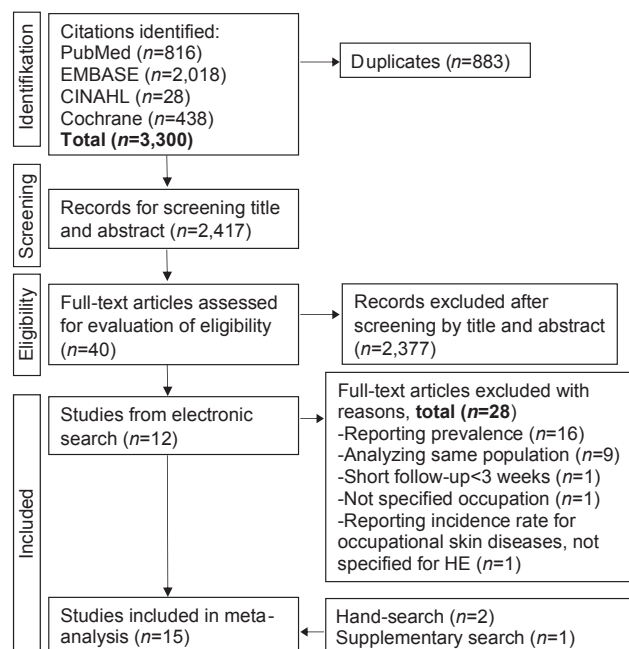
Lind et al. (28) reported IRs of HE stratified with regard to age, showing the highest IR in the youngest age group. IR for age <25 years was 3.71, 1.38 for ages 25–34 years, and 0.66 for ages >34 years. A stratified IR in those with a history of childhood eczema was evaluated in the same study. Patients with previous childhood eczema had an IR of 4.39, compared with 2.13 for those without childhood eczema.

Smit et al. (21) reported IRs at different time intervals, showing a steady decline in IR 26 weeks after the start of apprenticeship and exposure. For weeks 0–33, IR was 33.5, for weeks 14–26, IR was 57.2, for weeks 27–39, IR was 14.6, and for weeks 40–52, it was 0.

Uter et al. reported IR for a softer definition of "any skin changes", meaning the presence of any irritation on the hands (23, 25). The IR of any skin changes was 34.3, compared with an IR of HE 15.2. Stratified IR with regard to previous history of HE was also reported by Uter et al., concluding that there was no difference in IR between participants who never had HE in their lifetime (IR 15.1) and participants who were free of HE symptoms at the start of their training (IR 15.2).

Smit et al. reported an IR in hairdresser apprentices of 32.8, and an IR of 1.2 in a comparable population of office worker apprentices (21). Hairdressers had an excess in IR of 31.6 per 100 person-years compared with office workers.

John et al. (27) reported a higher OR for developing HE among hairdressers with previous flexural eczema



**Fig. 1.** Flow chart of the study inclusion process.

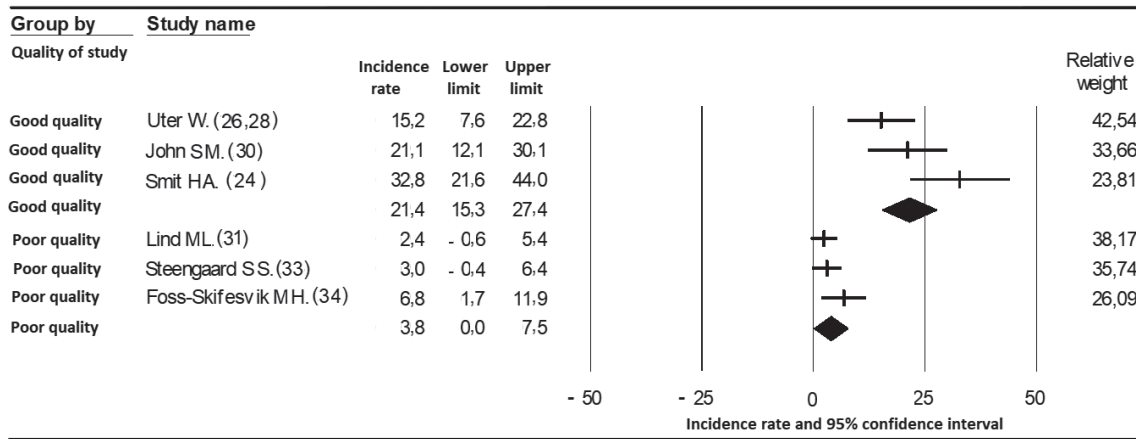


Fig. 2. Forest plot of mixed-effects meta-analysis of the incidence rates of hairdressers reported in 100 per-son-years grouped by study quality according to Newcastle-Ottawa Scale (high quality corresponds to  $\geq 7$  and poor quality  $\leq 3$ ).

OR 22.51 (95% CI 2.90–481.47), while finding that past HE was not significantly associated with developing HE 4.88 (95% CI 0.52–56.65).

**Nurses.** Four studies reported the IR for nurses (21, 29, 32, 33), 3 for nurse apprentices (21, 29, 33), and one for newly hired nurses at a hospital (32). Three studies were from the Netherlands (21, 29, 32) and one from Germany (33). Of these, one study had a retrospective design, and based HE diagnosis on a questionnaire (32), whereas the others had a prospective design and based HE diagnosis on clinical assessment and/or a questionnaire (21, 29, 33). The studies were conducted between 1987 and 2011, and included 1,234 participants for a total 2,294 person-years of follow-up.

Three studies (21, 32, 33) were rated as “good quality”, and one as “fair quality” (29). The 3 “good quality” studies reported the IR after 1 year working in the occupation, giving a pooled IR of 16.2 (95% CI 8.8–23.5). However, there was evidence of considerable heterogeneity ( $\chi^2 = 5.24$ ,  $df=2$ ,  $p=0.073$ ;  $i^2 = 61.82$ ; 95% prediction interval 0.9–80.8). A summary analysis of all 4 studies reporting IR at 1 year, including the “fair quality” study (29), offers a similar pooled IR of 16.9 (95% CI 11.2–22.7) (Fig. 3).

Schmid et al. (33) reported the IR of severe HE, defined as when symptoms last for 3 weeks or occurred more than once. After 1 year in the occupation, the IR of severe HE was 3.85 (vs an IR of HE of 25.0), whereas after 3 years, it was 1.6 (vs an IR of HE of 10.3).

Visser et al. (29) and Smit et al. (32) reported separate IRs of HE while receiving practical training during follow-up. In the Visser et al. study (29), the IR was higher at the time of practical training compared with the total study period. For the first year, the IR during practical training was 36.7 (vs 20.0 for the total first year follow-up period), while after 3 years, it was 13.7 during practical training time (vs 8.5 for the total 3 years’ follow-up period). Smit et al. (21) reported a higher IR during practical training, compared with other classes at different time intervals, and also showed a declining IR over time after beginning an apprenticeship. IR during practical training between weeks 0 and 13 was 23.4 (vs 10.4 during classes between weeks 14–20), 22.4 during practical training between weeks 20 and 32, (vs 4.2 during other classes between weeks 33 and 66).

Smit et al. (32) reported IRs at different time intervals, showing rapidly declining IRs over time after start of employment. At 0–3 months, IR was 18.9, at 4–6 months, 1.5, at 7–12 months, 1.56, at 13–18 months, 1.1, and >19 months, 1.32.

Smit et al. (21) reported an IR in nurse apprentices of 11.28, and an IR of 1.2 in a comparable population of office worker apprentices. Nurses had an excess in IR of 10.08 per 100 person-years compared with office workers.

Visser et al. (29) found a trend for developing HE when in contact with soap/detergents  $\geq 4$  times per shift, an OR of 1.5 (95% CI 0.97–2.30), whereas contact with disin-

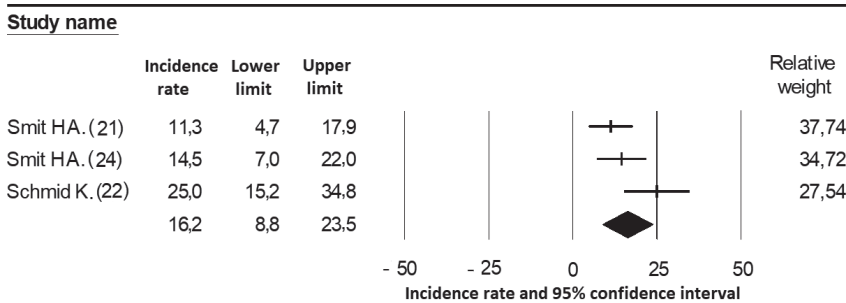


Fig. 3. Forest plot of random-effects meta-analysis of the incidence rate of nurses reported in 100 person-years.

fectants  $\geq 2$  times per shift did not lead to a significantly increased risk, the OR was 1.1 (95% CI 0.69–1.79).

**Metal workers.** All 3 included studies reported the IR of HE in metal worker apprentices (2, 26, 34), 2 studies (2, 34) were from Germany, and 1 was from Switzerland (26). All studies based HE diagnosis on clinical assessment, and were of "good quality", according to NOS. The studies were conducted between 1997 and 2014, and included 1,483 participants for a total 4,233 person-years of follow-up.

All 3 studies evaluated IR after 1 year in the occupation (2, 26, 34), and 2 studies reported IR at 3 years (2, 34). Subgroup analysis based on length of time in the occupation was conducted, yielding a pooled IR at 1 year of 7.2 per 100 (95% CI –0.4–14.0). There was no statistical evidence of heterogeneity ( $\chi^2 = 1.24$ ,  $df = 2$ ,  $p = 0.538$ ;  $i^2 = 0$ ; 95% prediction interval 0.0–90.5 per 100 person-years). Pooled IR at 3 years was 12.4 per 100 (95% CI 3.5–21.3), but the heterogeneity was high ( $\chi^2 = 12.1$ ,  $df = 2$ ,  $p < 0.001$ ;  $i^2 = 91.7$ ). No significant difference was noted for pooled IRs between the sets of studies at 1 and 3 years in the occupation ( $\chi^2 = 0.842$ ,  $df = 1$ ,  $p = 0.359$ ) (Fig. 4).

Berndt et al. (26) also reported IRs at different time intervals, showing a rapidly declining IR over time after starting in the occupation. IRs were reported in 100 person-years. At 0.5 year, the IR was 18.5, at 1 year, 5.1, at 1.5 years, 3.4, at 2 years, 1.3, and at 2.5 years, 0.5.

Reich et al. (34) and Funke et al. (2) reported IRs in metal worker apprentices of 23.7 and 31.9 per 100 person-years, respectively, and 12.2 and 2.3, respectively, per 100 person-years, in a comparable population of office worker apprentices. Metal workers thus had an excess in IR of 29.6 and 11.5 per 100 person-years, compared with office workers.

One study evaluated other risk factors for developing HE due to occupational exposure. Berndt et al. (26) reported a higher OR for developing HE for metal workers with previous flexural eczema (OR 11.97 (95% CI 1.12–127.97)) and for those who had  $\leq 1.5$  h/day of theoretical classes, OR 2.81 (95% CI 1.20–6.56), and there was also a trend for developing HE after contact with solvent, OR 1.44 (95% CI 0.99–2.08).

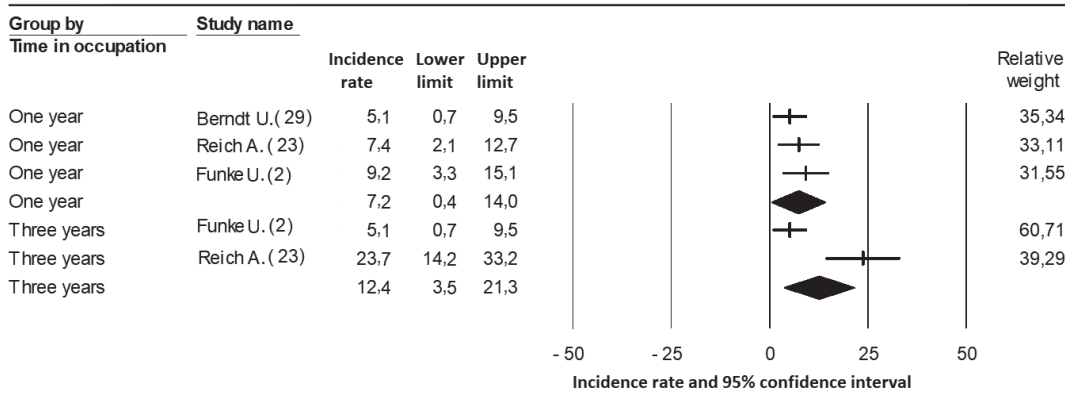
**Office workers.** Four studies reporting the IR of HE in office workers were identified (2, 24, 32, 34), 3 for office worker apprentices (2, 24, 32), and 1 for newly hired office workers. (34) Three studies were from Germany (2, 24, 34), and 1 was from the Netherlands (32). Of these, only 1 study based HE diagnosis on a questionnaire (32), whereas the others used clinical assessment (2, 24, 34). The studies were conducted between 1987 and 2014, and included 504 participants for a total 1,227 person-years of follow-up.

In 2 studies (2, 34), IR was evaluated after 1 year after starting the occupation, while it was evaluated at 3 years by 3 studies (2, 24, 34). Subgroup analysis, based on the length of time in the occupation, was conducted. After 1 year in the occupation, the pooled IR was 4.1 (95% CI –0.3–8.4), with no statistical evidence of heterogeneity ( $\chi^2 = 0.122$   $df = 1$ ,  $p = 0.727$ ;  $i^2 = 0$ ). The Z-value for the test of the null hypothesis was 1.832, with a corresponding  $p$ -value of 0.067. We conclude that the pooled IR after 1 year at an office occupation showed no statistically significant increase in IR for HE. After 3 years in occupation, the pooled IR was 4.9 for HE (95% CI 1.2–9.6), but the heterogeneity was high ( $\chi^2 = 6.768$ ,  $df = 2$ ,  $p = 0.034$ ;  $i^2 = 70.45$ ). No significant difference was noted for pooled IRs between office workers after 1 and 3 years in the occupation ( $\chi^2 = 0.083$ ,  $df = 1$ ,  $p = 0.774$ ). All studies employed for the meta-analysis's calculation were rated as "good quality", according to NOS (2, 24, 34) (Fig. 5).

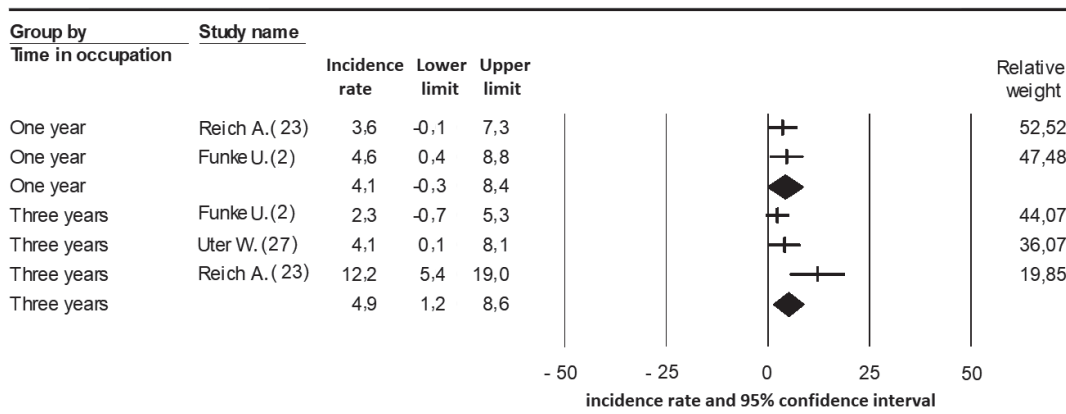
Smit et al. (32) studied the IR for office workers from 0.75 to 2.75 years in the occupation, without reporting IR at 1 year. Of 101 office workers, 2 developed HE, giving an IR of 1.2 per 100 person-years.

Uter et al. (24) also reported IR for a softer definition of "any skin changes", meaning the presence of any irritation on the hands. The IR of any skin changes was 18.4 per 100 person-years, compared with IR of HE of 4.1 per 100 person-years

**Bakers.** Only one study, of retrospective design, reported the IR among bakers (22). Brisman et al. (22) studied a cohort of 1,644 Swedish graduated bakers and followed them up for a range of 3–31 years after graduation. The



**Fig. 4. Forest plot of mixed-effects meta-analysis of the incidence rate of metal workers reported in 100 person-years grouped by one and 3 years in occupation.**



**Fig. 5. Forest plot of mixed-effects meta-analysis of the incidence rate of office workers reported in 100 person-years grouped by one and 3 years in occupation.**

assessment of HE was based on a questionnaire, and the study was rated "poor quality" according to NOS.

Brisman et al. (22) reported a higher IR for: (i) women 3.44 (vs men 1.67); (ii) bakers with family history of atopic dermatitis (for women, 7.57 (vs no family history 2.79) and for men, 2.32 (vs no family history 1.64)); (iii) bakers with previous childhood eczema (for women, 7.17 (vs no previous childhood eczema 2.90) and for men, 4.71 (vs no previous childhood eczema 1.43)); and (iv) first year of employment (for women, 4.35 (vs  $\geq 6$  years 2.0) and for men, 2.34 (vs  $\geq 6$  years 1.05)).

**Cooks.** Only one study reported the IR for cooks (2). Funke et al. (2) studied a cohort of 13 cook apprentices. The diagnosis of HE in this prospective study was based on clinical assessment (presence of any symptoms on hands and/or forearms, without any restriction as to the morphological pattern, except for mere dryness, which was accepted if it was combined with redness or scaling). After a total of 3 years of follow-up, IR was 31.9 cases per 100 person-years. No further stratification was reported. The study was of "good quality".

## DISCUSSION

Among the studied occupations, hairdressers had an IR  $> 20$  for developing HE, nurses an IR of nearly 20, and metal workers an IR  $> 10$ . Hairdresser apprentices were predominantly women, whereas metalworker apprentices were mostly men. Interestingly, the risk of HE decreased with time spent working in the occupation. Office occupations, which are usually not dominated by wet exposure, had no risk of developing HE at 1-year exposure. After a longer exposure period, however, 3 years in an office occupation, had an IR for the development of HE of 4.9 (95% CI 1.2–9.6).

This meta-analysis also highlights that, in the same occupation, incident cases of HE were reported higher when assessed by clinical examination, compared with self-reported questionnaires. This could indicate that symptoms on hands were not considered by patients to be HE. These skin changes could be precursors of later,

more severe, HE (35, 36). Another important finding was that the risk of confounding factors for developing HE in all occupations was sparsely studied. Only 2 studies (22, 28) of poor quality reported stratified IRs by age, sex, atopic dermatitis and childhood eczema for baking (22) and hairdressing (28) occupations. The most studied OR for developing HE was for previous flexural eczema, which was reported in only 2 studies (26, 27).

The highest risk of HE for apprentices was observed to be shortly after starting an occupation, and the risk declined in proportion to the length of time spent in the occupation. This could be explained by excessive exposure at the start of the apprenticeship, as individuals with increased susceptibility develop HE at an early stage of exposure (22, 27).

### Strengths and limitations

This is the first meta-analysis on the magnitude of the association between risk occupations and the risk of developing HE. This meta-analysis used broad terms in 4 databases, with no restrictions as to language and country, which allowed us to analyse the risk of HE in different populations, working conditions and health-care systems. A final strength to consider is that using the person-time approach when measuring incidence, considering the time that each participant was at risk in the occupation, was an appropriate approach when a significant proportion of the participants are at the beginning of exposure, beginning the occupation, and will not be at risk throughout the study (37). On the other hand, the person-time approach does not differentiate between studies evaluating IR for a small number of participants exposed for a long time, and large number of participants exposed for a short time (38). Drop-out rates can be different between short and long study periods, which can alter its effect size. Therefore, pooled IRs were calculated when studies reported IRs of approximately the same length of time since the start of the occupation and exposure.

The pooled IRs for the same times after starting an occupation and exposure should be interpreted with caution,

given that the studies varied in methodological quality, were conducted in countries with differing regulations on occupational diseases, and included participants with different background risk factors for HE, other than the studied occupational exposure. Our approach was to use a random-effects model, which allowed us to not only calculate the pooled IR, so that the large studies did not dominate in the results, but also to assess its accuracy with a wider CI (39). It was found that, despite the variation in the included studies, the 95% CI of all reported pooled IRs of the studied occupation in this meta-analysis were larger than 0. This confirms the high IR for developing HE in all of the studied occupations. Another advantage of the random-effects model was the ability to assess heterogeneity, and generalize the study results to a universe of comparable populations (39). What is clear from measuring heterogeneity using the prediction interval method is that, in any given population, the IR could be substantially higher and lower than the calculated pooled IR in each studied occupation. Thus, further studies are needed to identify which populations in each occupation have a higher or lower risk of developing HE.

There are a number of other factors that can influence the study results; the calculated IR of each study could be affected by selection bias at the level of the included participants of each study. A higher rate of participation of those with previous skin diseases can lead to an overestimation of IRs. On the other hand, the IRs could be also affected by a higher rate of drop-out among participants who developed HE at occupations, before they could be registered as cases by clinical examination, thereby biasing the results towards the null value. Also, information bias related to assessing the prevalence and incidence of HE might occur, and an underestimation might occur for self-reported HE, possibly underestimating the effect size of the occupation/HE relationship. Self-reported HE could lead to false-negative answers, partly because patients were unfamiliar with HE symptoms, and partly because participants with minor skin changes considered them normal for their occupation (40). These minor skin changes could be precursors of more severe HE (36). However, in the current meta-analysis, there were 4 studies using a self-reported questionnaire to diagnose HE (22, 28, 30, 31). All 4 studies were assessed as "poor quality" according to NOS and were not included in calculations of pooled IR; in all included studies, participants were free of HE at inclusion. However, it should be noted that some studies evaluated whether some participants had worked in the same occupation prior to inclusion. These participants who had previously experienced occupational exposure without developing HE may represent a less susceptible group. This can lead to an underestimate of the reported IR in risk occupations; even though only good-quality studies were used for the calculation of pooled IRs, and all studies (2, 21, 23–25, 27, 33, 34) except one (32) had a prospective design, this cannot exclude the

underestimation of study results. The relatively long intervals between examinations in prospective studies could mean that several incident HE cases occurred and were resolved at follow-up examination, which may underestimate the results. In the current study, there were 6 included prospective studies (21, 23–25, 33, 34) in which the diagnosis of HE was based on both clinical examination and a questionnaire, which is considered to capture the incident cases of HE between clinical examinations.

One way to be able to trust the findings of this meta-analysis, when faced with the above-mentioned bias factors, was to assess study quality against NOS criteria in order to conduct subgroup-analysis between good quality vs fair/poor quality. The hairdressing occupation was the subject of more studies than any other occupation. Therefore, there were enough studies to conduct a subgroup-analysis based on study quality, which concluded that there was a significant difference between pooled IRs between studies of poor and good quality. Good-quality studies gave a 5.6-times higher IR than poor-quality studies. For hairdressers, epidemiological data of good quality was crucial to better understanding the risk of HE. For metal and office workers, all included studies were rated as "good quality". For nurses, 3 of the 4 included studies were rated as "good quality".

Assessment of publication bias was not applicable, as the studies reported IR, because the studies did not test whether it was significantly different from any specific value (39). Assessment of the incidence of HE in different occupations and in the general population, as well as systematic assessment of potential confounding factors would have been beneficial. The main body of studies investigated occupations that have an already known relationship with HE, such as hairdressers, nurses, metal workers; the only additional occupation that was investigated was office workers. Only a few studies investigated bakers, butchers, cleaners and other occupations, who might have an increased risk of HE, possibly due to contact allergic dermatitis or irritant dermatitis. For healthcare decision-making, it is highly important to gain evidence regarding a broad spectrum of occupations and their relationship with HE, since there may be a hidden problem in uninvestigated professions.

### Conclusion

Among the occupations studied there was a high risk of HE for hairdressers, nurses and metal workers. There was also a risk of HE in office occupations, which are characterized by a low irritant profile. High-quality studies with prospective design and clinical assessment of HE are needed to gain a better understanding of the risk of developing HE. The confounding factors of developing HE in an occupation were not sufficiently researched. These results, along with the fact that HE is a chronic disease with negative impacts on patients' quality of life, and a cause of economic burden on society, should

be considered by healthcare policymakers, who should provide additional support aiming to reduce the development of HE in occupations.

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