Determinants of current hand eczema: results from case–control studies nested in the PACO follow-up study (PACO II)

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Background: Hand eczema is often a result of the interplay of exogenous and endogenous risk factors. Epidemiological studies demonstrating the interrelationship between these factors are lacking.

Objective: To analyse risk factors associated with current hand eczema and current irritant hand eczema in two case–control studies nested in a long-term follow-up study in the car industry.

Patients/Materials/Methods: Eligible participants were individuals who had been followed until the end of their apprenticeship in the original cohort study (1990–1998, N = 1909). Participants were interviewed and underwent dermatological examination. Two case–control studies were nested within the cohort, one using current hand eczema cases (n = 110) and one using current irritant hand eczema cases (n = 57). Multivariable modelling was performed.

Results: The only significant finding was a positive association of atopic skin diathesis with hand eczema in both studies. Wet work ≥2 hr/day was positively related to current irritant hand eczema. Age and having an office job were inversely related to hand eczema.

Conclusions: Atopic skin diathesis was the most important determinant of hand eczema. Constitution seems to play a dominant role compared with environmental and occupational hazards in a setting where skin protection measures are well established.

Key words: atopy; case–control study; epidemiology; hand eczema.

Conflict of interests: The authors have declared no conflicts.

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Hand eczema is a common skin disease with varying aetiology, severity and morphology (1). A Swedish study reported a point prevalence in the background population of 9.7% in 1996 (2). The incidence rate has been reported to be 5.5–8.8 per 1000 persons per year (3). Besides costs to society and the private sector when jobs are lost because of hand eczema, individuals experience considerable impairment of their quality of life (4).

Often a combination of exogenous (irritant and allergic) and endogenous factors is involved in the pathogenesis of hand eczema (1) and studies have been performed to analyse the role of these factors (3, 5–7).

We previously reported incidence figures of hand eczema in the car industry from the PACO (Prospective Audi Cohort) study. The study took place between 1990 and 1998 (baseline and two follow-ups) (8) and a follow-up was again performed in 2005/2006 (9). The period prevalence of hand eczema in the follow-up period of 10 years was 21.0% (95% CI 19.0–23.1%), yielding a cumulative incidence of 29.3% (95% CI 26.9–31.6%) in the entire study period of 13 years. Here, we give an estimate of factors associated with current hand eczema according to dermatological investigation and experiences in exploratory analyses.

In order to gain more insight into the role of exogenous and endogenous factors associated with current hand eczema, we performed two nested case–control studies. In the first study, the outcome variable was current hand eczema at the time of dermatological examination. In the second study, we focused on current irritant hand eczema.
In addition to work-related exposures, we paid specific attention to atopic skin diathesis among all participants of the cohort.

**Patients and Methods**

*Study design*

Two case–control studies were nested within the cohort to simultaneously assess a number of exogenous and endogenous factors. The origin and the composition of cases and controls for both studies are illustrated in Fig. 1. Eligible participants were individuals who had been examined in the context of the original PACO study (1990–1998) and had been followed through until the end of their apprenticeship \((N = 1909)\) (8). Examinations and interviews took place in 2005/2006 in the cities of Ingolstadt and Neckarsulm, Germany.

The population we analysed for the purpose of the analysis presented here consists of those individuals that we were actually able to examine and interview \((N = 1170)\). Methodological aspects of the study have been described previously (9). Briefly, participants were examined and interviewed in detail if they had current hand eczema or had hand eczema during the follow-up period, if they were classified as belonging to a risk group in the original PACO study (PACO I) or if there was evidence of an atopic skin diathesis. Participants were considered at risk in the original PACO study if there was evidence of hand eczema before or during apprenticeship, dyshidrosis, flexural eczema or white dermographism. In addition, it was intended to obtain exposure information from every 10th participant with healthy skin. We finally obtained

![Fig. 1. Origin of cases and controls for the case–control studies.](image-url)
full dermatological and exposure information from 11.2% of the healthy individuals (n = 84).

The assessment of hand eczema was performed by a dermatologist (M. R.) and hand eczema was recorded if at least one of the following combinations were seen (9):

1. Erythema and vesicles
2. Erythema and scaling
3. Erythema and papules
4. Erythema and erosions/fissures
5. Erythema and lichenification

Whenever hand eczema was seen, a diagnosis was recorded by the study dermatologist. Current irritant hand eczema was thus a subgroup of all cases of hand eczema.

Atopic skin diathesis was assessed according to Diepgen et al. (10, 11), based on the evaluation of clinical and cutaneous signs and symptoms of atopic eczema. Each sign or symptom is given between one and three points by the examining physician. An atopic skin diathesis was assumed to be present if the summary score was above 10 points.

The prevalences of various exposure variables describing exposure at the current workplace in those with current hand eczema and in controls were compared. In the first case–control study (study I), all 110 cases with current hand eczema were included. In the second case–control study (study II), only those cases with a diagnosis of irritant hand eczema were included.

The control group included all healthy controls, enriched by 11.2% of all participants with hand eczema in history, evidence of atopic skin diathesis and those who were classified as belonging to a risk group in PACO I (Fig. 1). This was carried out to make the control group representative of the population from which the cases originated. Added up, the control group consisted of 120 individuals.

The study was approved by the works committee of AUDI AG. In addition, there had been a data protection agreement between the company and the University of Erlangen, where the study was initiated (8).

**Exposure assessment**

The exposure assessment was conducted as a structured interview by a health scientist (C. J. A.) and information on occupational and domestic exposure for each workplace since the end of apprenticeship was obtained retrospectively. The interviews were standardized and had been piloted at the beginning of the PACO follow-up study (9).

Duration of occupational exposure was measured as average hours/day for wet skin soiling, direct contact with water, dry skin soiling, wearing of gloves with/without lining, wearing of leather gloves and wearing of moist cotton gloves. Direct skin contact with water-based metalworking fluids, oil/oil-based metalworking fluids, solvents, epoxide and metal dust was assessed by a yes/no dichotomy. The use of cleaning pastes/abrasive cleaners and the application of creams after work/in leisure time and cleaning pastes/abrasive cleaners (average frequency per day) were used for the analyses.

**Statistical analysis**

Data entry and storage was carried out using Microsoft Office Access 2003. Data analysis was performed using SAS® for Windows 9.1.

Associations between exposure variables and current hand eczema were tested using the chi-squared test or the Fisher exact test where cell counts were below 5. The mean age of cases and controls was compared using the t-test.

A variable for wet work was created according to the following formula: total time of wearing occlusive gloves (gloves with/without lining) + time of wearing moist gloves + time of wet skin soiling + time of direct contact with water + time of domestic wet work. The variable was transformed into a dichotomous variable with a cut off point of ≥2 hr. This cut off was chosen according to the German legislation TRGS 401 (12). For dry skin soiling, a cut off ≥3 hr was chosen.

Occupational and domestic application of creams was analysed as one variable. Occupational and domestic use of abrasive cleaners was also analysed as one variable. Both variables were transformed into a dichotomous variable with a cut off more than once/day. All other variables were analysed as binary variables: male sex, hand eczema during apprenticeship, office job, atopic skin diathesis, flexural eczema, contact to water-based metalworking fluids, contact to oil/oil-based metalworking fluids, contact to solvents, contact to epoxy and contact to metal dust.

Logistic regression was performed to obtain adjusted odds ratios (ORs) and 95% confidence intervals (CI). Clinically/biologically meaningful models were fitted including age as a continuous variable and all variables univariately associated with current hand eczema or current irritant hand eczema (P < 0.1). Use of creams was not included in these models, because their application is a consequence of rather than a risk factor for hand eczema. Furthermore, flexural eczema was not
entered into the models, because of collinearity with atopic skin diathesis.

In addition, prevalence estimates together with their 95% CIs of a history of flexural eczema and atopic skin diathesis were calculated for the whole study population and separately for those with hand eczema in the study period and those without. Prevalences were compared using the chi-squared test.

Results

The cases had a mean age of 28.9 years (SD ± 1.52), which was significantly lower compared with the mean age of the controls (29.3 years, SD ± 1.67; \( P = 0.04 \)). In both studies, contact to oil/oil-based metalworking fluids, wet work \( \geq 2 \) hr and use of abrasive cleaners more than once/day were the most frequent exposures. The prevalence of applied skin protection/skin care products more than once daily was higher than the prevalence of any single occupational exposure.

Univariate associations of the exposure variables with hand eczema obtained in study I are shown in Table 1. Working in an office job was significantly more prevalent in controls, whereas hand eczema during apprenticeship, atopic skin diathesis, flexural eczema and the application of skin protection/skin care products more than once/day were significantly more prevalent in cases.

In multivariable analysis, inverse associations of age and office job and positive associations of atopic skin diathesis and wet work \( \geq 2 \) hr with hand eczema were observed (Table 2). Atopic skin diathesis with hand eczema during apprenticeship were positively associated with hand eczema. Atopic skin diathesis was the only variable that was significantly associated with hand eczema.

Like study I, study II showed having an office job as significantly more prevalent in controls and atopic skin diathesis, and the application of skin protection/skin care products more than once/day as significantly more prevalent in cases (Table 3). Hand eczema during apprenticeship and a history of flexural eczema were no longer associated, but wet work \( \geq 2 \) hr was associated and significantly more prevalent in cases (\( P = 0.02 \)).

Logistic regression showed inverse associations of age and office job and positive associations of atopic skin diathesis and wet work \( \geq 2 \) hr with hand eczema (Table 4). Atopic skin diathesis was the only variable significantly associated with hand eczema.

A more detailed investigation of atopic skin diathesis in all participants \((N = 1170)\) of the study showed the following: overall, atopic skin diathesis (atopy score \( \geq 10 \)) was found in 12.9% (95% CI 11.0–14.8%) and a history of flexural eczema in 6.2% (95% CI 4.8–7.6%) \((N = 1162)\) of the participants. Atopic skin diathesis was unclear in 6.2% (95% CI 4.9–7.6%). Atopic skin diathesis occurred in 37.2% (95% CI 31.3–43.0%) of those with hand eczema during the follow-up period \((N = 261)\), compared with 5.9% (95% CI 4.4–7.5%) of those without hand eczema during the follow-up period \((N = 909)\) \( (P < 0.0001) \). A history of flexural eczema occurred in 17.7% (95% CI 13.0–22.4%) of those with hand eczema during the follow-up period \((N = 254)\), compared with 3.0% (95% CI 1.9–4.1%) of those with no hand eczema during the follow-up period \((N = 908)\) \( (P < 0.0001) \). The differences are illustrated in Fig. 2.

Table 1. Univariate associations of various exposure variables with hand eczema (study I)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>( N )</th>
<th>Prevalence in cases (%)</th>
<th>( N )</th>
<th>Prevalence in controls (%)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>110</td>
<td>86.4</td>
<td>120</td>
<td>84.2</td>
<td>0.64</td>
</tr>
<tr>
<td>Hand eczema during apprenticeship</td>
<td>110</td>
<td>20.9</td>
<td>120</td>
<td>12.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Office job</td>
<td>109</td>
<td>19.3</td>
<td>120</td>
<td>32.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Atopic skin diathesis</td>
<td>109</td>
<td>38.5</td>
<td>119</td>
<td>10.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Flexural eczema</td>
<td>110</td>
<td>11.8</td>
<td>120</td>
<td>2.5</td>
<td>0.006</td>
</tr>
<tr>
<td>Wet work ( \geq 2 ) hr (occupational + domestic)</td>
<td>110</td>
<td>37.3</td>
<td>120</td>
<td>31.7</td>
<td>0.37</td>
</tr>
<tr>
<td>Dry skin soiling ( \geq 3 ) hr</td>
<td>109</td>
<td>17.4</td>
<td>120</td>
<td>11.7</td>
<td>0.21</td>
</tr>
<tr>
<td>Contact to water-based metalworking fluids</td>
<td>109</td>
<td>14.7</td>
<td>120</td>
<td>10.0</td>
<td>0.28</td>
</tr>
<tr>
<td>Contact to oil/oil-based metalworking fluids</td>
<td>109</td>
<td>41.3</td>
<td>120</td>
<td>33.3</td>
<td>0.21</td>
</tr>
<tr>
<td>Contact to solvents</td>
<td>109</td>
<td>15.6</td>
<td>120</td>
<td>15.0</td>
<td>0.90</td>
</tr>
<tr>
<td>Contact to epoxy (epoxy resin)</td>
<td>109</td>
<td>8.3</td>
<td>120</td>
<td>4.2</td>
<td>0.20</td>
</tr>
<tr>
<td>Contact to metal dust</td>
<td>109</td>
<td>10.1</td>
<td>120</td>
<td>9.2</td>
<td>0.81</td>
</tr>
<tr>
<td>Use of abrasive cleaners (occupational + domestic)</td>
<td>109</td>
<td>22.0</td>
<td>120</td>
<td>26.7</td>
<td>0.41</td>
</tr>
<tr>
<td>Application of creams (occupational + domestic) more than once/day</td>
<td>110</td>
<td>67.3</td>
<td>120</td>
<td>51.7</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Table 2. Odds ratios from logistic regression in study I (108 hand eczema cases, 119 controls)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.85 (0.71–1.03)</td>
</tr>
<tr>
<td>Hand eczema during apprenticeship</td>
<td>1.14 (0.51–2.54)</td>
</tr>
<tr>
<td>Office job</td>
<td>0.59 (0.29–1.18)</td>
</tr>
<tr>
<td>Atopic skin diathesis</td>
<td>2.47 (1.71–3.55)</td>
</tr>
</tbody>
</table>

Discussion

We consistently found positive associations of atopic skin diathesis as well as inverse associations of age and having an office job with hand eczema. The OR for atopic skin diathesis was the only significant estimate and was somewhat lower when only hand eczema cases with current irritant hand eczema were included.

Age and sex

The inverse association of age with hand eczema could perhaps reflect an independent protective effect known as hardening effect. Although not clearly defined, ‘hardening effect’ refers to a possible adaptation of the skin to exogenous agents (13). A process is conceivable by which irritant contact dermatitis develops but subsequently heals resulting not only in the restitution of normal skin tolerance but also in a particular insensitivity (14). An inverse relationship between age and irritant hand eczema has also been observed in the Prevention of Occupational Skin Diseases in Hairdressers (POSH) study (15).

Table 3. Univariate associations of various exposure variables and hand eczema cases with current irritant hand eczema (study II)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>N</th>
<th>Prevalence in cases (%)</th>
<th>N</th>
<th>Prevalence in controls (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>57</td>
<td>86.0</td>
<td>120</td>
<td>84.2</td>
<td>0.76</td>
</tr>
<tr>
<td>Hand eczema during apprenticeship</td>
<td>57</td>
<td>19.3</td>
<td>120</td>
<td>12.5</td>
<td>0.23</td>
</tr>
<tr>
<td>Office job</td>
<td>57</td>
<td>15.8</td>
<td>120</td>
<td>32.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Atopic skin diathesis</td>
<td>57</td>
<td>26.3</td>
<td>119</td>
<td>10.9</td>
<td>0.009</td>
</tr>
<tr>
<td>Flexural eczema</td>
<td>57</td>
<td>3.5</td>
<td>120</td>
<td>2.5</td>
<td>0.66*</td>
</tr>
<tr>
<td>Wet work ≥2 hr (occupational + domestic)</td>
<td>57</td>
<td>49.1</td>
<td>120</td>
<td>31.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Dry skin soiling ≥3 hr</td>
<td>57</td>
<td>17.5</td>
<td>120</td>
<td>11.7</td>
<td>0.29</td>
</tr>
<tr>
<td>Contact to water-based metalworking fluids</td>
<td>57</td>
<td>15.8</td>
<td>120</td>
<td>10.0</td>
<td>0.27</td>
</tr>
<tr>
<td>Contact to oil/oil-based metalworking fluids</td>
<td>57</td>
<td>43.9</td>
<td>120</td>
<td>33.3</td>
<td>0.17</td>
</tr>
<tr>
<td>Contact to solvents</td>
<td>57</td>
<td>21.1</td>
<td>120</td>
<td>15.0</td>
<td>0.32</td>
</tr>
<tr>
<td>Contact to epoxy (epoxy resin)</td>
<td>57</td>
<td>10.5</td>
<td>120</td>
<td>4.2</td>
<td>0.18*</td>
</tr>
<tr>
<td>Contact to metal dust</td>
<td>57</td>
<td>12.3</td>
<td>120</td>
<td>9.2</td>
<td>0.52</td>
</tr>
<tr>
<td>Use of abrasive cleaners (occupational + domestic) more than once/day</td>
<td>57</td>
<td>29.8</td>
<td>120</td>
<td>26.7</td>
<td>0.66</td>
</tr>
<tr>
<td>Application of creams (occupational + domestic) more than once/day</td>
<td>57</td>
<td>71.9</td>
<td>120</td>
<td>51.7</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Fisher’s exact test.
risk of hand eczema in employees with past or present eczema concludes that a history of skin atopy without exposure at least doubles the risk for hand eczema and that occupational exposure doubles this risk again (17). The strength of the odds ratios of atopic skin diathesis in our studies is concordant with this finding—roughly a doubling in the odds of hand eczema. Comparing our estimates with ‘history of skin atopy without exposure’ is appropriate, because occupational exposure parameters were controlled for in the multivariable models. It must, however, be acknowledged that the Swiss Prospective Metal Worker Eczema Study (PROMETES) found a significant association of flexural eczema but not of atopic skin diathesis with incident hand eczema (18).

**Exogenous exposure**

Single exposure variables representing known skin hazards did not show significant associations with hand eczema in either study. Wet work ≥2 hr appeared in the model of study II only. This seems to be due to the exclusion of hand eczema cases which were suspected to be of the atopic, endogenous type. Wet work is generally a well-known risk factor for irritant contact dermatitis (19). The finding is in line with the observation made in the POSH study, where unprotected wet work ≥2 hr was shown to be the major risk factor for irritant hand eczema (15).

Overall, exogeneous factors seemed to play a minor role in this setting. It is important to bear in mind that these results are not directly generalizable to the metalworking industry. As mentioned above, the company has a well-established health and skin hazard management and the application of adequate skin protection and skin care has been continuously emphasized since the beginning of the original PACO study. Working conditions completely free from hazards (office environment) seemed to confer some protection. This finding seems to be more generalizable to other settings because office environments share the characteristic of being free from known skin hazards. The non-significant association of having an office job with hand eczema in both studies is in line with the non-significant difference in cumulative incidences between white- and blue-collar jobs which we reported previously (9). If the manifestation of hand eczema in this setting is predominantly endogenously determined, incidences in environments with different exposure cannot be expected to be very different.

A study in a different occupation (bakers, confectioners and bakery shop assistants) did also not find exogenous irritant factors to be strongly associated with an increased risk of hand eczema (20). In this study, endogenous factors such as atopic skin diathesis, previous hand eczema and flexural dermatitis proved to be predictive of hand eczema over a 3-year apprenticeship period.

The most similar study to our study was performed in Sweden, comparing self-reported skin exposure in 182 hand eczema cases and 182 controls (21). The study did not find significant differences in occupational exposure to water, hand washing or chemicals in individuals with or without hand eczema. Although cases and controls were drawn from the population, the evidence from this Swedish study is very much in line with what we found.

**Strengths and limitations**

A particular strength of the study is that we tried to measure a wide range of exposure variables related to both the occupational and the domestic environment. We cannot, however, rule out that others factors play a significant role. For instance, we did not measure climate parameters like temperature or humidity nor did we measure mechanical irritation, or interacting factors such as stress.

The sample size of this study may not have provided enough power to allow the observation of moderate associations, particularly relating to the exogenous exposure variables.

Moreover, in a case–control study using prevalent cases, it is not easily possible to disentangle the time sequence of cause and effect. As a consequence, in our studies, the application of creams appeared to be associated with an increased odds of hand eczema in multivariable analysis (data not shown). This is most probably explained by the fact that people affected by hand eczema might start creaming their hands after the local hand inflammation becomes visible to them. Hence, the application of creams should be thought of as a consequence of hand eczema which is why a decision was taken not to include this variable in the final multivariable models.
Information on exposure from questionnaires might yield biased results. For instance, a study performed in the Netherlands compared information on duration and frequency of wet work activities from questionnaires with information obtained from observation (22). The data from observation showed less than half the duration of wet work and almost double the frequency, compared with questionnaire reported data. The questionnaire reports hence overestimated duration of wet work and underestimated frequency. We did, however, use standardized, structured interviews and did not rely on questionnaire data. This method has presumably yielded a more accurate assessment. Difficulty in recalling exposure (recall bias) can never be ruled out in interviews either. Participants might also recall exposure differentially, according to whether they had hand eczema or not. However, this form of bias seems to be minimal in the study presented here, as only current exposure was taken into account.

Generally, it would have been of value to additionally assess frequency of wet work in our study. Malten’s original thoughts on irritant contact dermatitis suggested that disease manifestation occurs when through repetition of the same stimulus or a combination of varying stimuli the degree of impairment surpasses a critical level (23).

Conclusion

In conclusion, atopic skin diathesis was found to be the single most important determinant of current and current irritant contact dermatitis, suggesting that constitution plays a dominant role compared with (single) environmental hazards. Overall, it seems that given an established skin hazard management policy, hand eczema does present as a disease largely determined by endogenous factors.

Further analyses must make full use of the longitudinal study design and hence focus on the relationship between early risk factors (before and during apprenticeship) and incident hand eczema. Additionally, analyses must clarify the relationship between different exposure levels over time (corresponding to different workplaces over time) and hand eczema risk.

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