

The association between contact allergy and hand eczema in 2 cross-sectional surveys 8 years apart

The Copenhagen Allergy Study

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Hand eczema is a recurrent chronic skin disease related to contact allergy and atopic dermatitis. When possible, efforts should be redoubled to eliminate provoking factors. Our objective was to assess changes in the prevalence of self-reported hand eczema and to evaluate the association between contact allergy and hand eczema among adult Danes before and after nickel exposure regulation in Denmark. In 1990 and 1998, random samples of 15–41-year-old persons were examined in 2 cross-sectional studies of the general population in Copenhagen, Denmark. The studies included questionnaires, patch and prick testing. From 1990 to 1998 the prevalence of a history of hand eczema increased significantly. This increase did not appear to be fully explained by changes in the prevalence of flexural eczema, prick test reactivity, patch test reactivity, and nickel allergy. In 1990, nickel allergy and allergic nickel contact dermatitis were significantly associated with a history of hand eczema among women. In 1998, these associations were not found. It can be concluded that, from 1990 to 1998, the prevalence of a history of hand eczema rose significantly. It was indicated that it might be possible to prevent the hand eczema related to nickel allergy by exposure regulation, public education or both.

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Hand eczema is a common skin disease in the general population as well as among patients treated by dermatologists. The consequences for the individual may be prolonged sick-leaves. The risk factors for hand eczema include both the exogenous, such as irritants and allergens, and the endogenous, such as atopic dermatitis and other genetic factors (1–3). During recent decades the prevalence of atopic dermatitis has increased in many European countries (4, 5). This increase is likely to influence the frequency of hand eczema.

In the 1980s, 2 studies demonstrated that nickel allergy was a risk factor for hand eczema among Danish eczema patients (6, 7). Prevention of hand eczema related to contact allergy could be obtained by prevention of primary sensitization as well as prevention of eliciting exposures. Since the introduction of the Danish nickel exposure regulation (8) in the early 1990s, nickel allergy has become less frequent among patients treated by der-

matologists (9). However, over the same period of time, the frequency of allergy to cosmetic-related allergens has increased (9, 10). These changes may also influence the frequency of hand eczema and the associations between hand eczema, contact allergy and atopic dermatitis.

In 1990, a cross-sectional study on allergic contact sensitization was performed in a random sample of the general Danish population (11). In 1998, a second population study was conducted using the same sampling method and frame, and employing the same questionnaires and patch test technology (the TRUE Test). The data sets were utilized to evaluate the associations between contact allergy and a self-reported history of hand eczema.

Materials and Methods

This study is based on 2 cross-sectional surveys conducted in 1990 and 1998 at the Centre for Pre-

ventive Medicine (former Glostrup Population Studies). Both surveys were preceded by a screening of a random sample of the population in the western part of Copenhagen County (Denmark) performed via a mailed questionnaire about respiratory symptoms. The random samples were obtained from the Danish Central Personal Register (Ministry of Internal Affairs). The 1990 sample was a non-stratified sample of 15–41-year-olds, whereas the 1998 sample was stratified on 2 age groups: 15–22-year-olds and 23–41-year-olds. Citizenship (Danish) and birthplace (Denmark) further restricted the samples. Random samples of the responders to the screening questionnaire were invited to a health examination focusing on allergy. Sample sizes in 1998 were calculated to demonstrate a possible increase in type-I allergy from 1990 to 1998 of 33% (from 30% to 40%) ($2\alpha = 0.05$, $\beta = 0.2$) (12). Pregnant women were excluded. The Ethical Committee for Copenhagen County approved the studies.

1990 survey

Of a total of 3603 responders to the screening questionnaire (response rate 86.1%), a random sample of 418 subjects were invited to the health examination. 312 subjects (participation rate 74.6%) were examined between February 1990 and January 1991. These subjects were the 15–41-year-old participants in The Glostrup Allergy Study, Denmark (11).

1998 survey

A total of 592 15–22-year-old subjects and 546 23–41-year-old subjects responded to the screening questionnaire (response rates 72.0% and 78.0%, respectively). Among the 15–22-year-old responders, a random sample of 369 subjects were invited to the health examination, and 186 subjects were examined (participation rate 50.4%). Among the 23–41-year-old responders, a random sample of 533 subjects were invited to the health examination, and 296 subjects were examined (participation rate 55.5%). The participants were examined between January 1998 and November 1998.

Patch testing

The patch tests used were the ready to apply TRUE Test (ALK-Abelló, Hørsholm, Denmark) (13–15). The haptens and mixtures of haptens in this test series comprise widely used environmental chemicals, such as metals, preserv-

atives and substances in cosmetics, glues, rubber and medicaments. In 1990, formaldehyde was not included. The haptens further differed from the European standard series (Hermal, Reinbeck, Germany) by including thimerosal and excluding primin. Directions to apply the patch tests to the upper back 2 days before the examination were mailed with the patch test. The patch tests were read $1/2$ – $1 1/2$ h after removal. Reactions were classified according to the guidelines of the International Contact Dermatitis Research Group (16). A positive reaction (+) was defined as at least homogeneous redness and palpable infiltration in the test area. Reactions not fulfilling these criteria were classified as nonallergic reactions, whether these were follicular reactions, faint erythema, or typical irritant reactions. If the tests were not applied 2 days before attending, or if the contact with the skin was poor, a new appointment was made when possible. In 1990 and 1998 all reactions were read by Nielsen and Linneberg, respectively. In both studies, Menné revised photos of the test sites, and in case of disagreement consensus was reached by discussion.

Prick testing

The prick tests, performed with a standard panel of 10 inhalation allergens (Phazet (Pharmacia, Uppsala, Sweden) and Soluprick (ALK-Abelló) in 1990 and 1998, respectively), have been described earlier (12). A 3-mm mean wheal diameter to at least 1 allergen was used as an objective marker of prick test reactivity.

Questionnaire before examination

In both surveys a questionnaire including questions about eczema was sent with the standard invitation letter. The questionnaire described eczema as follows: 'Eczema is an itching skin disease showing redness, dryness, and eventually vesicles and exudation. Eczema is present in the same skin area for some time'. The questions were the following:

'Have you ever had eczema from wearing earpins or earrings, under the buckle (tightener) of your watch strap, or under the button of your jeans?', 'Have you ever had hand eczema?' and 'Have you ever had eczema in the flexures of your arms or legs?'.

Definitions of metal contact dermatitis and allergic nickel contact dermatitis

Persons with a history of eczema from wearing earpins or earrings, under the buckle of one's

Table 1. Participation in patch testing by sex and age

	Males				Females			
	1990		1998		1990		1998	
Age (years)	15-22	23-41	15-22	23-41	15-22	23-41	15-22	23-41
Participants (n)	28	108	76	117	48	106	102	174
Participation rate (%)	56.0	66.7	41.1	49.8	75.0	72.1	55.4	56.1

Table 2. Prevalence of a history of hand eczema and flexural eczema among men and women in 1990 and 1998

	Men				Women				Total			
	1990	1998	1998 vs 1990	1990	1990	1998	1998 vs 1990	1990	1990	1998	1998 vs 1990	1990
	%	%	Odds ratio* (95% CI)	%	%	Odds ratio* (95% CI)	%	%	%	%	Odds ratio* (95% CI)	%
History of hand eczema	10.1	18.4	2.19 (1.14-4.22)	23.3	32.4	1.61 (1.04-2.51)	17.0	26.6	1.78 (1.23-2.56)			
History of flexural eczema	4.7	10.4	1.99 (0.88-4.90)	12.3	22.1	1.96 (1.13-3.39)	8.7	17.2	1.98 (1.24-3.16)			

*Age (and sex) adjusted odds ratio comparing the prevalence in 1998 to that in 1990.

watch strap or under the button of one's jeans were defined as cases of metal contact dermatitis. Persons with metal contact dermatitis and a positive patch test to nickel were defined as cases of allergic nickel contact dermatitis.

Statistical analysis

The associations between a history of hand eczema and different risk factors were expressed as odds ratios. Changes in the prevalence of a history of eczema were expressed by odds ratios comparing the prevalence in 1998 to that in 1990. Test for a change between 1990 and 1998 in the odds ratio reflecting the association between the explanatory variable and a history of hand eczema (dependent variable) was done by testing for interaction between study year and the explanatory variable in a logistic regression model. The odds ratios were adjusted for sex and age in logistic regression models as indicated. Because formaldehyde was not included in 1990 this hapten has been excluded when reporting prevalence of more than 1 sensitivity. All data were analysed with SPSS for Windows (Release 8.5). 95% confidence intervals were used.

Results

Participation by sex and age in 1990 and in 1998 is shown in Table 1.

Table 2 shows the distribution in 1990 and 1998 of a history of hand eczema and a history of flexural eczema among men and women, respectively. The prevalence of both a history of hand eczema and flexural eczema increased significantly.

Table 3 shows the prevalence of a history of hand eczema among women in 1990 and in 1998, with and without the explanatory variables. In

1990, nickel allergy and allergic nickel contact dermatitis (nickel allergy and a history of metal contact dermatitis) were significantly associated with a history of hand eczema among women, whereas these associations were not found in 1998. The changes in association were not statistically significant. In both studies there was a positive association between a history of hand eczema and a history of flexural eczema among women, although this was significant only in 1998.

Table 4 shows the prevalence of a history of hand eczema among men in 1990 and in 1998, with and without the explanatory variables. Among men the association between a history of hand eczema and a history of flexural eczema was significant in 1998.

Table 5 shows that the frequencies of a history of hand eczema increased from 1990 and 1998 among those with a history of flexural eczema (29.6% and 50.6%, respectively ($p = 0.05$)) as well as among those without a history of flexural eczema (15.8% and 21.6%, respectively ($p = 0.05$)). There was no significant interaction between flexural eczema and study year.

The increase in the frequency of hand eczema remained significant in a logistic regression model with history of hand eczema as the dependent variable and age, sex, study year, history of flexural eczema, prick test reactivity, patch test reactivity, and nickel allergy as independent variables. This suggests that the increase in prevalence of a history of hand eczema is not fully explained by changes in the prevalence of flexural eczema or contact allergy.

Discussion

From 1990 to 1998 the frequency of a history of hand eczema rose significantly among men and

Table 3. Prevalence of a history of hand eczema among women with and without explanatory variables in 1990 and 1998. The association in 1990 and 1998 among women expressed by age-adjusted odds ratio

Explanatory variables	History of hand eczema 1990		History of hand eczema 1998		1998 vs 1990*
	% (n)	Odds ratio (95% CI)	% (n)	Odds ratio (95% CI)	
1 or more positive patch tests					
Yes	38.2 (13)	2.33 (1.00-5.43)	32.9 (24)	1.02 (0.57-1.82)	$p = 0.10$
No	20.8 (25)		32.5 (65)		
Nickel allergy	42.3 (11)	2.95 (1.17-7.44)	31.9 (15)	0.95 (0.48-1.88)	$p = 0.06$
Yes					
No	21.1 (27)		32.6 (74)		
Allergic nickel contact dermatitis**					
Yes	43.5 (10)	2.99 (1.15-7.80)	32.5 (13)	0.99 (0.48-2.03)	$p = 0.07$
No	21.4 (28)		32.6 (76)		
1 or more positive patch tests other than nickel					
Yes	42.9 (6)	2.04 (0.65-6.44)	31.6 (12)	0.94 (0.45-1.98)	$p = 0.16$
No	22.9 (32)		32.8 (78)		
1 or more positive prick tests					
Yes	20 (8)	0.81 (0.33-1.98)	40.5 (30)	1.64 (0.94-2.85)	$p = 0.17$
No	24.4 (30)		29.6 (61)		
History of flexural eczema					
Yes	35.0 (7)	2.61 (0.90-7.61)	50.0 (31)	2.72 (1.52-4.89)	$p = 0.65$
No	21.7 (31)		27.4 (60)		

*Test for a change between 1990 and 1998 in the odds ratio reflecting the association between the explanatory variable and a history of hand eczema.

**Metal contact dermatitis and nickel allergy.

women in our study population. In 1990, significant associations were found between a history of hand eczema and both nickel allergy and allergic nickel contact dermatitis among women. These associations were not found 8 years later.

The increased frequency of reported symptoms of eczematous skin diseases might be seen as a sign of increased focus on allergic symptoms in general. This critique has also been applied regarding symptoms of allergic airway disease. However, other studies of the present populations have demonstrated that an increased frequency of allergic rhinitis was accompanied by increases in prick test reactivity and increases in levels of specific IgE (12, 17).

A history of flexural eczema was associated with a history of hand eczema in both studies. We also found an increased frequency of hand eczema among those with and those without a history of flexural eczema. Thus, the increasing prevalence of flexural eczema does not seem fully to explain the increase in prevalence of hand eczema. Increased exposure to irritants may be part of an explanation of the increased frequency of hand eczema but was not evaluated in our study. The increased frequency of a history of flexural dermatitis is consistent with another study of a sample of the Danish general population (5). In the present study

the associations between a history of hand eczema and the explanatory variables were essentially similar among subjects with and without a history of flexural eczema (data not shown). Increased exposure to irritants may be part of an explanation of the increased frequency of hand eczema but was not evaluated in our study.

In 1990 among women, a history of hand eczema was non-significantly associated with 1 or more positive patch tests other than nickel (Table 3). Although the change from 1990 to 1998 in this association was not statistically significant, the odds ratio was 2 in 1990 as compared to 1 in 1998. There may be several reasons for this change in association. One possible explanation could be that the pattern of allergen exposure has changed from 1990 to 1998. Of note is that the reporting of hand eczema increased only among those without contact allergy (Table 3). Among women with, for example, nickel allergy there even appeared to be a decrease in the reporting of hand eczema.

In 1990 the Danish nickel legislation was introduced (8). The borderline-significant reduction of the risk of having a history of hand eczema related to nickel allergy among women might be related to lower nickel exposure in 1998. The results may therefore support a reduction of exposures to ubiquitous allergens preventing elicitation of con-

Table 4. Prevalence of a history of hand eczema among men with and without explanatory variables in 1990 and 1998. The association in 1990 and 1998 among men expressed by age-adjusted odds ratio

Explanatory variables	History of hand eczema 1990		History of hand eczema 1998		History of hand eczema 1998 _{vs} 1990*
	% (n)	Odds ratio (95% CI)	% (n)	Odds ratio (95% CI)	
1 or more positive patch tests					
Yes	0	**	21.4 (3)	1.26 (0.33–4.81)	**
No	10.5 (13)		17.9 (32)		
Nickel allergy					
Yes	0	**	0	**	**
No	9.8 (13)		18.5 (35)		
Allergic nickel contact dermatitis***					
Yes	0	**	0	**	**
No	9.7 (13)		18.3 (35)		
1 or more positive patch tests other than nickel					
Yes	0	**	30.0 (3)	2.06 (0.50–8.45)	**
No	10.2 (13)		17.5 (32)		
1 or more positive prick tests					
Yes	7.0 (4)	0.56 (0.17–1.87)	18.8 (16)	1.13 (0.54–2.35)	<i>p</i> = 0.33
No	12.0 (11)		18.1 (21)		
History of flexural eczema					
Yes	14.3 (1)	1.51 (0.16–14.0)	52.5 (11)	8.29 (2.99–22.98)	<i>p</i> = 0.19
No	9.9 (14)		14.4 (26)		

*Test for a change between 1990 and 1998 in the odds ratio reflecting the association between the explanatory variable and a history of hand eczema.

**Metal contact dermatitis and nickel allergy.

***Not applicable due to empty cell in two-by-two table.

Table 5. Prevalence of a history of hand eczema among subjects with and without a history of flexural eczema in 1990 and 1998

	Flexural eczema 'yes'			Flexural eczema 'no'		
	1990 %	1998 %	1998 _{vs} 1990 Odds ratio* (95% CI)	1990 %	1998 %	1998 _{vs} 1990 Odds ratio* (95% CI)
History of hand eczema	29.6	50.6	2.56 (1.00–6.59)	15.8	21.6	1.50 (1.00–2.25)

*Age- and sex-adjusted odds ratio comparing the prevalence in 1998 to that in 1990.

tact dermatitis. A number of studies have supported the fact that nickel exposure has been reduced. In Denmark, over a 10-year period from the mid-1980s to the mid-1990s the frequency of primary sensitization to nickel was significantly reduced among 0–18-year-old eczema patients, as shown by Johansen et al. (9). Of the nickel-sensitive subjects, 33.2% were judged to have current non-occupational exposure to nickel in 1997–98 as opposed to 73.5% in 1985–86 (9). In 1999–2000, Jensen performed dimethylglyoxime testing to show nickel exposure among Danish teenage schoolgirls. More than 250 metal items worn in direct and prolonged contact with the skin tested negative and only cheap hairpins and old wrist-watches where the plating had been worn off were positive (18). These results are contrasted by findings in Sweden where the EU Nickel Directive

came into force by July 2001. In 1999, Lidén & Johnson found a positive dimethylglyoxime test in 25% out of 725 items intended for direct and prolonged contact with the skin (19).

The mechanism of hand eczema associated with nickel allergy may be direct exposure of the hands as well as vesicular hand eczema as part of a systemic contact dermatitis caused by transcutaneous absorption, or both. As early as 1956, Calnan reported that active allergic nickel contact jewellery dermatitis was associated with active vesicular hand eczema (20). Elimination of cutaneous nickel exposure was a predictor of prognosis of hand eczema in patients with nickel allergy, as Kalimo et al. showed (21). They demonstrated that the prognosis of hand eczema among patients with nickel allergy was better among those who avoided nickel contact than among those who did not.

The definition of hand eczema was based on the subject's recognition of a clinical description of eczema, the same definition being employed in both surveys. There is no 'gold standard' that defines hand eczema. Typically, the severity of hand eczema varies. General population samples were examined, and point prevalence on the day of examination was not used because this would give only part of the disease spectrum.

The relatively low participation rate in the 1998 survey may have influenced the results. The invitation procedures were kept the same, and it is therefore unlikely that the difference in participation rate was due to methodological differences between the surveys. However, the effect of possible selection bias may be enhanced by the lower participation rate in the second survey. The screening questionnaire did not include questions on skin symptoms, and consequently the possibility of selection bias cannot be specifically evaluated. Both surveys employed the same explanation of eczema, the same patch test technology (the TRUE Test), and standard classification system of reactions. Assuming that the prevalence of hand eczema among invited non-participating subjects was 50% lower than among those who participated (Table 2), the estimated prevalence of hand eczema would be 14.8% and 20.4% in 1990 and 1998, respectively (Chi-square test: p -value = 0.02). This assumption of the distribution of hand eczema among participants and non-participants is more extreme than the observed distribution of allergic rhinitis symptoms reported in the screening questionnaire among participants and non-participants as previously described (12). Using the same assumption for self-reported flexural eczema, the estimated prevalence of flexural eczema would be 7.6% and 13.2% in 1990 and 1998, respectively (Chi-square test: p -value = 0.004). The possible influence of this hypothesized prevalence of eczema among non-participants did not appear substantially to influence the results of our study. The frequencies of patch test reactions were read at day 2 only, and frequencies of sensitization were probably underestimated in both surveys. This possible systematic bias was not likely to affect the changes in the associations between contact allergy and hand eczema.

Risk factors for hand eczema can be investigated case by case, in occupational groups with uniform exposure pattern, or in the general population, depending on their frequency. Avnstorp has evaluated the impact of ferrous sulphate addition to cement, and shown a decrease in hand eczema related to chromate allergy over time in a specific occupationally exposed group (22). Such an effect could not have been illustrated in a population

study, because of the rarity of chromate dermatitis outside specifically exposed occupational groups. Atopic dermatitis, with a population frequency of 5–10%, and nickel allergy, with a prevalence of 10% in females, are risk factors that occur so frequently that investigations based on the general population are realistic.

It can be concluded that, from 1990 to 1998, the prevalence of a history of hand eczema rose significantly in both sexes. Over the same period of time the association between a history of hand eczema and nickel allergy decreased among women, which may be related to reduced nickel exposure of the skin due to nickel exposure regulation. Because the group of persons at risk of developing hand eczema as well as the group reporting a history of hand eczema increased, efforts should be redoubled to create environments that will reduce exposure to allergens and irritants able to elicit hand eczema.

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