

The association between hand eczema and nickel allergy has weakened among young women in the general population following the Danish nickel regulation: results from two cross-sectional studies

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Background: An association between nickel contact allergy and hand eczema has previously been demonstrated. In 1990, Denmark regulated the extent of nickel release in the ear-piercing process as well as nickel release from consumer products.

Objectives: This study aimed to evaluate the effect of the Danish nickel regulation by comparing the prevalence of concomitant nickel allergy and hand eczema observed in two repeated cross-sectional studies performed in the same general population in Copenhagen.

Materials: In 1990 and 2006, 3881 18–69 year olds completed a postal questionnaire and were patch tested with nickel. Data were analysed by logistic regression analyses and associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

Results: The prevalence of concomitant nickel contact allergy and a history of hand eczema decreased among 18–35-year-old women from 9.0% in 1990 to 2.1% in 2006 ($P < 0.01$). The association between nickel contact allergy and a history of hand eczema decreased in this age group between 1990 (OR = 3.63; CI = 1.33–9.96) and 2006 (OR = 0.65; CI = 0.29–1.46). Among older women, no significant changes were observed in the association between nickel contact allergy and hand eczema.

Conclusions: Regulatory control of nickel exposure may have reduced the effect of nickel on hand eczema in the young female population.

Key words: general population; hand eczema; nickel allergy; public health; regulation; risk factor.
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Nickel contact allergy (nickel allergy) is prevalent in the general population as up to 3% of men and 17% of women are affected (1). Causative cutaneous nickel exposure may derive not only from long-term contact with inexpensive jewellery (2, 3), clothing fasteners (4, 5) and cell (mobile) phones (6) but also from occupational contact with, e.g. coins (7) and work tools (8). It has previously been debated

whether nickel allergy is a risk factor for hand eczema (9–16), a prevalent cutaneous disorder that may lead to decreased quality of life (17) and sick leave (18). Although the results from general population-based studies diverge, a cause–effect relationship between nickel allergy and hand eczema is indisputable. Thus, when nickel allergic subjects are repeatedly exposed on the hands to

nickel, allergic hand eczema is likely to develop at some point (19, 20). Besides direct cutaneous nickel exposure, other putative pathomechanisms of nickel induced hand eczema have been described. Firstly, a systemic allergic contact dermatitis reaction may develop following nickel ingestion (21). Secondly, transcutaneous absorption of nickel ions from, e.g. earrings may result in a hand eczema (22). Finally, the prognosis of hand eczema is significantly enhanced in nickel allergic patients who avoid cutaneous nickel exposure (23).

In 1990, the Danish nickel regulation dictated that nickel release from various consumer products should not exceed 0.5 µg nickel/cm²/week (24). In 1994, a similar but more detailed nickel regulation was passed in the European Union (EU) to protect European consumers from excessive nickel exposure and its allergic and cutaneous effects (25). So far, an effect from these regulatory interventions has been identified in terms of decreasing prevalences of nickel allergy among dermatitis patients (26–28) and among subjects in the general population (29, 30). In 1990 and 2006, two independent cross-sectional patch test studies were performed in the adult general population in Copenhagen, Denmark. Based on these data, the current study aimed to investigate whether the association between hand eczema and nickel allergy has changed following the Danish nickel regulation as a change would indicate that the regulation has decreased cutaneous morbidity associated with nickel contact.

Materials and Methods

Study populations

In 1990 and 2006, two consecutive cross-sectional population-based studies were organized by the same group of investigators (Menné and Nielsen in 1990; and Menné, Nielsen, Linneberg, Johansen, and Thyssen in 2006). Danish adults (with Danish citizenship and born in Denmark), living in one of the same 11 municipalities of the Copenhagen County, were invited to participate in a general health examination including patch testing. Study populations were random samples obtained from the Danish Central Personal Register. Participants completed a postal questionnaire using identical questions in 1990 and 2006. The questionnaire included a description of eczema: 'Eczema is an itching skin disorder showing redness, dryness, and possibly vesicles and exudation. Eczema is present at the same area for some time'. A history of self-reported hand eczema was defined as an affirmative answer to the question 'Have you ever had hand eczema?'. A diagnosis based on self-report of hand eczema generally has a low sensitivity and a high specificity (31–33). Atopic dermatitis was

defined as an affirmative answer to the question 'Has your doctor ever told you that you suffered from atopic dermatitis?'. Finally, the occurrence of nickel dermatitis was defined as an affirmative answer to the question 'Have you ever had eczema under the buckle of your watch strap, under the button of your jeans or from wearing ear pins or earrings?' together with a positive patch test reaction to nickel sulphate. The Ethical Committee of Copenhagen County approved the study (KA-20060011). A written informed consent form was obtained from all participants prior to the beginning of the study.

Between February 1990 and January 1991, 567 (71.5%) of 793 invited 15–69 year olds were patch tested with nickel sulphate. In order to compare the results with those from the 2006 study, participants aged 15–17 years were excluded. Thus, 543 participants aged 18–69 years were patch tested with nickel. Between June 2006 and May 2008, 3338 (42.1%) of 7931 invited subjects aged 18–69 years were patch tested with nickel. For practical reasons, persons below the age of 18 years were not invited for the 2006 study, as an informed, written consent from the parents is now mandatory in Denmark.

Patch tests

In all studies, patch testing was performed by using the standardized ready to apply TRUE-test® (suppliers were ALK-Abelló A/S, Hørsholm, Denmark in 1990 and Mekos Laboratories, Hillerød, Denmark in 2006). The TRUE-test® contains prevalent contact allergens, including nickel sulphate in a concentration of 0.16 mg per patch. Directions to apply the patch test panels to the upper back 2 days before examination were mailed together with the patch tests. They were read and photographed 1–1½ hour after removal by Nielsen in 1990 and by trained health care personnel in 2006 (supervised by Thyssen and Linneberg). The photographs were reviewed in a blinded manner by Nielsen and Menné in 1990 and by Nielsen, Menné, Linneberg and Thyssen in 2008. This was done to secure that the International Contact Dermatitis Research Group (ICRDG) criteria were used consistently over time (34). Nickel allergy was defined as a positive (at least grade 1+ according to ICRDG) patch test to nickel. It has been estimated that approximately 18–29% of positive patch test reactions to nickel are missed when patch test readings are only performed on day 2 and not also on day 4 (35). In case the patch had no skin contact upon removal, or if the subject had removed it prior to testing as a result of known nickel allergy, it was regarded as missing data.

Statistical analysis

Characteristics of participants who were nickel patch tested in 1990 and 2006 were compared using the chi-squared (χ^2) test and where appropriate the Fisher's exact test. The Fisher's exact test was used when the expected values were less than 5. Due to a well-known marked sex difference in the prevalence of nickel allergy, atopic dermatitis, and hand eczema, the analyses were stratified by sex. Three identical logistic regression analyses, with hand eczema as the dependent variable and with study year ('1990' versus '2006'), atopic dermatitis and nickel allergy as the explanatory variables, were performed among women in different age groups (i.e. women aged 18–35 years, 36–55 years, and 56–69 years). In these models, a test for interaction between study year and nickel allergy was performed by using a log-likelihood ratio test. Associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Data analyses were performed by using the Statistical Products and Service Solutions package (SPSS Inc., Chicago, IL, USA) for windows (release 15.0).

RESULTS

A comparison of participation rates in 1990 and 2006 showed that participation rates decreased significantly for all age groups (36). The smallest decline was observed among women in the oldest age group (56–69 years).

The overall prevalence of a self-reported history of hand eczema (i.e. an affirmative answer to the question 'Have you ever had hand eczema?') and atopic dermatitis (i.e. an affirmative answer to the question 'Has your doctor ever told you that you suffered from atopic dermatitis?') was 21.4% (men = 16.7% and women = 25.8%) and 4.9% (men = 3.3% and women = 6.5%), respectively, when data from the 1990 and 2006 studies were analysed together. The overall prevalence of hand eczema increased slightly from 20.6% in 1990 to 21.8% in 2006, whereas the overall prevalence of atopic dermatitis increased from 2.8% in 1990 to 5.5% in 2006.

Table 1 shows gender-specific characteristics of participants. Hand eczema tended to increase in all age groups during the two study periods except among 56–69-year-old men and among 36–55-year-old women where slight decreases were observed. The prevalence of atopic dermatitis increased in all age groups between 1990 and 2006 and was generally higher among women than men. A decrease in the prevalence of nickel allergy was observed among male age groups and among 18–35-year-old women, whereas increasing prevalences were observed among women older than

35 years (Table 1). The prevalence of combined nickel allergy and hand eczema (i.e. participants who reported hand eczema and also had a positive patch test reaction to nickel) decreased from 9.4% (10/106) in 1990 to 2.2% (8/363) in 2006 among women in the youngest age group (18–35 years) ($p < 0.002$) (Fig. 1 and Table 1) but increased from 1.6% (2/124) in 1990 to 4.2% (38/897) in 2006 among women aged 36–55 years ($P = 0.22$) and from 0% in 1990 to 1.0% (6/559) in 2006 among 56–69-year-old women ($P = 1.00$). Among 18–35-year-old nickel allergic women, the prevalence of hand eczema decreased from 47.6% (10/21) in 1990 to 19.0% (8/42) in 2006 ($P < 0.02$). In comparison, the prevalence of hand eczema increased among nickel allergic women aged 36–55 years from 25.0% (2/8) in 1990 to 32.5% (38/117) in 2006 ($P = 0.66$).

Table 2 shows unadjusted associations between nickel allergy and hand eczema among female participants. This approach was justified as the proportion of self-reported atopic dermatitis did not differ significantly among female age groups in the two study years. Among women aged 18–35 years, the association was markedly stronger in 1990 (OR = 3.63; CI 95% = 1.33–9.96) than in 2006 (OR = 0.65; CI 95% = 0.29–1.46), whereas this was not the case among women in older age groups (Table 2). Three identical logistic regression analyses with hand eczema as the dependent variable and with atopic dermatitis, nickel allergy and study year ('1990' versus '2006') as the explanatory variables were performed among women aged 18–35 years, 36–55 years, and 56–69 years, respectively, including both the 1990 and 2006 study. In these models, an interaction term between nickel allergy and study year was inserted to investigate whether the association between nickel allergy and hand eczema was dependent on the study year. This interaction term was found to be statistically significant among women aged 18–35 years ($P = 0.017$) whereas it was not significant among women aged 36–55 years ($P = 0.44$) and among women aged 56–69 years ($P = 1.00$).

DISCUSSION

This study showed that the prevalence of concomitant nickel allergy and hand eczema decreased significantly among Danish women aged 18–35 years between 1990 and 2006 (Fig. 1). Furthermore, the association between nickel allergy and hand eczema was weakened in this age group during the study period (Table 2). *A priori*, we expected to observe a decreasing prevalence of concomitant nickel allergy and hand eczema first among women in the youngest age group for several reasons: the prevalence of

Table 1. Characteristics of male and female participants tested in 1990 and 2006.

Age group (years)		Test year					
		Men			Women		
		1990 % (n/n _{total})	2006 % (n/n _{total})	P-value [†]	1990 % (n/n _{total})	2006 % (n/n _{total})	P-value [†]
18–35 n = 852	Nickel allergy	3.6 (3/84)	1.2 (3/253)	0.17	19.8 (21/106)	11.4 (42/369)	0.02
	History of hand eczema	10.6 (10/94)	14.2 (37/260)	0.38	24.3 (27/111)	26.3 (99/376)	0.67
	Atopic dermatitis*	0 (0/94)	5.5 (14/253)	0.01	8.1 (9/111)	10.5 (39/371)	0.46
	Nickel allergy and a history of hand eczema	0 (0/84)	0.8 (2/248)	1.00	9.4 (10/106)	2.2 (8/363)	0.002
	Nickel allergy	1.7 (2/121)	1.4 (10/718)	0.68	6.5 (8/124)	13.0 (118/907)	0.03
36–55 n = 1937	History of hand eczema	14.8 (19/128)	18.3 (134/732)	0.35	32.6 (42/129)	27.9 (259/928)	0.27
	Atopic dermatitis*	1.6 (2/128)	5.0 (36/721)	0.08	3.9 (5/129)	7.5 (69/916)	0.13
	Nickel allergy and a history of hand eczema	0.4 (1/121)	0.3 (2/708)	0.37	1.6 (2/124)	4.2 (38/897)	0.22
	Nickel allergy	1.6 (1/64)	0.4 (2/524)	0.29	2.3 (1/44)	5.1 (29/567)	0.4
	History of hand eczema	21.5 (14/65)	16.6 (90/543)	0.32	13.0 (6/46)	21.9 (129/590)	0.16
56–69 n = 1255	Atopic dermatitis*	0 (0/65)	1.5 (8/537)	1.00	0 (0/46)	3.1 (18/576)	0.39
	Nickel allergy and a history of hand eczema	0 (0/64)	0 (0/521)	—	0 (0/44)	1.0 (6/559)	1.00
	Nickel allergy	2.2 (6/263)	1.0 (15/1495)	0.12	10.9 (30/274)	10.3 (189/1843)	0.72
	History of hand eczema	15.0 (43/287)	17.0 (261/1535)	0.40	26.2 (75/286)	25.7 (487/1894)	0.85
	Atopic dermatitis*	1.0 (2/287)	3.8 (58/1511)	0.007	5.3 (14/286)	6.8 (126/1863)	0.23
All ages n = 4044	Nickel allergy and a history of hand eczema	0.4 (1/269)	0.3 (4/1477)	0.57	4.4 (12/274)	2.9 (52/1819)	0.17
	History of hand eczema	15.0 (43/287)	17.0 (261/1535)	0.40	26.2 (75/286)	25.7 (487/1894)	0.85
	Atopic dermatitis*	1.0 (2/287)	3.8 (58/1511)	0.007	5.3 (14/286)	6.8 (126/1863)	0.23
	Nickel allergy and a history of hand eczema	0.4 (1/269)	0.3 (4/1477)	0.57	4.4 (12/274)	2.9 (52/1819)	0.17
	History of hand eczema	15.0 (43/287)	17.0 (261/1535)	0.40	26.2 (75/286)	25.7 (487/1894)	0.85

*Affirmative answer to the question 'Have your doctor ever told you that you suffered from atopic dermatitis?'.

[†]Univariate analysis with χ^2 -test and Fisher's exact test (when the expected values were less than 5) were used to test for statistical differences between study year 1990 and 2006.

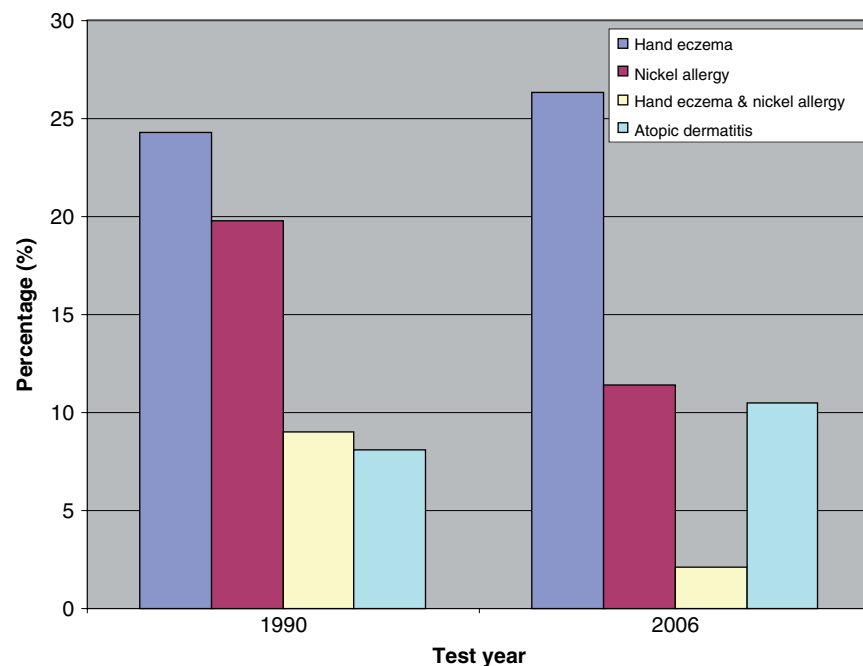


Fig. 1. Changes in the prevalence of hand eczema (i.e. a history of hand eczema), nickel allergy and atopic dermatitis among female participants aged 18–35 years.

nickel allergy decreased among young women who ear pierced after the 1990 nickel regulation (30); women in this age group were theoretically less exposed to nickel in 2006 when compared with those tested in 1990; the association between nickel

allergy and hand eczema showed a decrease among young Danes tested in 1998 when compared with those tested in 1990, although this was not statistically significant (14). As the prevalence of nickel allergy decreased significantly among women aged

Table 2. Nickel allergy stratified by a history of hand eczema among female participants

Age group (years)		Test year					
		1990			2006		
		Nickel allergy		Crude OR	Nickel allergy		Crude OR
		Yes	No		Yes	No	
18–35	History of hand eczema: Yes	9.4 (10)	16.0 (17)	3.63 (1.33–9.96)	2.2 (8)	23.4 (85)	0.65 (0.29–1.46)
	No	10.4 (11)	64.2 (68)		9.4 (34)	65.0 (236)	
36–55	History of hand eczema: Yes	1.6 (2)	32.3 (40)	0.63 (0.12–3.28)	4.2 (38)	23.4 (210)	1.36 (0.86–1.98)
	No	4.8 (6)	61.3 (76)		8.8 (79)	63.5 (570)	
56–69	History of hand eczema: Yes	0 (0)	13.6 (6)	0.97 (0.92–1.03)	1.1 (6)	19.3 (108)	1.12 (0.44–2.85)
	No	2.3 (1)	84.1 (37)		3.8 (21)	75.8 (424)	

OR, odds ratio.

18–35 years at the same time as the prevalence of hand eczema remained stable (or slightly increased), this development would inevitably tend to dilute the proportion of concomitant nickel allergy and hand eczema in 2006 and lead to a decreasing prevalence (Fig. 1). Nevertheless, logistic regression analyses performed with hand eczema as the dependent variable revealed a significant interaction term between nickel allergy and study year among 18–35-year-old women but not among older women. Thus, the effect of nickel allergy on the prevalence of hand eczema depended significantly on study year and age group. However, it should be noted that no information on wet exposure was included in our analysis, a risk factor known to be independently associated with hand eczema (37). Furthermore, the definition of atopic dermatitis has never been validated but it seemed fairly reliable as it revealed essentially similar results to those of the UK working group criteria on atopic dermatitis (38) when used in an logistic regression analysis in a previous population-based study (36).

The increasing prevalence of hand eczema among 18–35-year-old women could be explained by coincidence (the *P*-value was 0.67); or by an increased focus on skin diseases in the general population which may lead to increased reporting; or by an increased prevalence of atopic dermatitis in this age group leading to a higher prevalence of hand eczema; or finally, it may add support to the validity of the main study finding, i.e., the prevalence of concomitant nickel allergy and hand eczema is decreasing among young women as a consequence of reduced nickel exposure in the environment. Thus, the Danish nickel regulation may possibly have resulted in a decreased ‘negative effect’ or decreased ‘burden’ of nickel exposure and nickel allergy in the pathogenesis of hand eczema. However, it should be acknowledged that nickel is only one of many possible pathogenic factors of hand eczema and that e.g. irritant hand eczema is far more prevalent.

A non-significant increase of concomitant nickel allergy and hand eczema was observed among

middle-aged women and older women between 1990 and 2006. This increase may be explained by a cohort effect as women in this age group were highly exposed to nickel prior to the Danish nickel regulation and as nickel allergy is considered a persistent condition (39). Of note, the increase of concomitant nickel allergy and hand eczema replicated the increase of nickel allergy between 1990 and 2006 (Table 1). However, the increase of nickel allergy during the study period was statistically significant, whereas the increase of concomitant nickel allergy and hand eczema was not statistically significant. This may either be coincidental, or be a result of low power in the analysis of concomitant nickel allergy and hand eczema, or be a weak indication of a reduced burden of nickel exposure in the pathogenesis of hand eczema. Furthermore, it should be recognized that we obtained information only about the life-time prevalence of hand eczema and not about e.g. the 1-year prevalence of hand eczema. Thus, we were not able to determine whether hand eczema in these participants occurred to a higher degree before the Danish nickel regulation was introduced than after its introduction.

A weakness of our study was the significantly decreasing rate of participation in all age groups from 1990 to 2006. This decrease was in line with a general trend of decreasing participation rates in Danish general population studies (40). To minimize the influence of differences in the distribution of age and sex between the studies, our analyses were stratified by these variables. Furthermore, participants in both studies were informed in the invitation letter that testing for nickel allergy was part of the health examination. This may have caused an overrepresentation of nickel allergic participants and thus led to an overestimation of the prevalence of allergy. Assuming that a lower participation rate results in a stronger selection of nickel allergic persons (i.e. a larger difference in prevalence of nickel sensitization between participants and non-participants), this would tend to underestimate the decrease in nickel allergy in the youngest age group.

We submit that reduced cutaneous exposure to nickel in the Danish society following the nickel regulation has limited its pathogenic potential to induce hand eczema in adult young women. Josefson et al. recently examined the association between nickel allergy and hand eczema in a cohort of school girls who were questioned and nickel patch tested in 1982–1983 and again in 2006–2007 (10;16). They concluded that the risk of hand eczema in nickel allergic women may previously have been overestimated as they could not identify any increased risk of hand eczema among nickel allergic women in comparison to women without nickel allergy (16). Furthermore, they found that the risk of hand eczema was doubled in nickel allergic women without a history of childhood eczema (16). This follow-up study is interesting but like our study, it does not measure the burden of nickel exposure in the environment. Thus, as nickel exposure has decreased significantly in Sweden following the EU Nickel Directive (2, 41), we speculate that the burden of nickel in the pathogenesis of hand eczema in the Swedish cohort also has been reduced to a level where it only influences the prevalence of hand eczema to a small degree.

Conclusion

Although the study design makes it impossible to determine the cause and effect, the study suggested that the prevalence of concomitant nickel allergy and hand eczema as well as the association between nickel allergy and hand eczema were reduced among young adult women following the Danish nickel regulation. Thus, we submit that these findings may be explained by reduced exposure to nickel in the environment, and that today, nickel mainly affects the risk of hand eczema in women with occupational nickel exposure or accidental high nickel exposure from consumer products.

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