

Nickel allergy from adolescence to adulthood in the TOACS cohort

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Summary

Background. In 1995, we established a cohort of 1501 unselected eighth-grade schoolchildren to investigate the course of nickel allergy into adult life.

Objectives. To follow the course of nickel allergy and clinically relevant nickel dermatitis over 15 years from adolescence to adulthood, and the effect of ear piercing, atopic dermatitis and degree of nickel patch test reactivity.

Methods. One thousand two hundred and six young adults from the cohort were asked to complete a questionnaire and participate in a clinical examination including patch testing with TRUE Test® including a nickel dilution series.

Results. The questionnaire was answered by 899 (74.6%), and 442 (36.7%) had patch tests performed. The point prevalence of nickel allergy was 11.8% (clinical relevance 80.8%). The 15-year incidence rate was 6.7%. Most new sensitizations were clinically relevant with strong reactions, and many participants reacted to low concentrations. Only a few positive reactions were lost. Nickel allergy was more common among women with childhood atopic dermatitis, whereas no association with ear piercing was found. However, there was a significantly higher prevalence of nickel allergy among women ear pierced before implementation of the nickel regulation in Denmark.

Conclusion. This follow-up study in young adults 15 years after leaving primary school showed a high prevalence and a high incidence rate of nickel allergy, despite the nickel regulation. Most reactions from childhood could be reproduced and were clinically relevant. In women, childhood atopic dermatitis was associated with nickel allergy in adulthood, whereas only ear piercing before the Danish nickel regulation was associated with adult nickel allergy.

Key words: allergic contact dermatitis; atopic dermatitis; ear piercing; follow-up study; incidence; nickel allergy; nickel regulation; nickel sensitization; patch tests; prevalence.

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Nickel sensitization (allergy) is the most common contact allergy (1–5), and may lead to nickel allergic contact dermatitis if skin exposure exceeds the individual threshold dose in a nickel-sensitized individual. Epidemiological studies reporting the clinical relevance of a positive nickel patch test are sparse. A high rate of clinically relevant nickel patch test reactions was reported in individuals participating in The Odense Adolescents Cohort Study (TOACS) 15 years ago, where 8.6% had a positive patch test reaction to nickel sulfate, with clinical relevance in 69% (6). Nickel allergy was associated with ear piercing and the use of dental braces (6).

Patch testing is a biological assay with inherent pitfalls in performance, scoring and interpretation, according to the technique applied, variation between patients, and variation between investigators. Although nickel sulfate is regarded as one of the contact allergens with the highest frequency of reproducible positive patch test reactions (7), the level of sensitivity may vary considerably between serial test procedures in the same nickel-allergic individual over the course of a year (8). Furthermore, nickel is a peculiar contact allergen, as, besides the hapten-specific T cell response, it can also directly trigger an innate immune response through binding to Toll-like receptor 4 (9).

Ear piercing has been reported as the most common cause of sensitization (6, 10, 11). In 1990, the Danish government introduced regulations for nickel release from consumer products in contact with the skin, including jewellery (12). The adolescents in the TOACS cohort were born 9 years before the implementation of the Danish nickel regulation. The EU Nickel Directive came into full force in July 2001 (13, 14). Recent studies both in the general population and in selected patient groups have shown a decreasing prevalence of nickel allergy (15–19). However, a large proportion of inexpensive earrings still release nickel in concentrations that may result in nickel allergy and dermatitis (20). Another aspect is how atopic dermatitis is associated with the occurrence of nickel allergy. In a review from 2011, it was concluded that children with atopic dermatitis develop allergic contact dermatitis as frequently as children without atopic dermatitis (21). It has been suggested that filaggrin gene (*FLG*) null mutations may constitute a risk factor for the development of nickel sensitization (22).

This investigation was a follow-up study after 15 years to investigate the course of nickel allergy from adolescence to adulthood, performed by the same investigator team, using the same patch test technology, and including questionnaire and clinical examination.

Methods

Population and study design

A flowchart from phase 1 to 3 is given in Fig. 1. Phase 1 of the TOACS study was conducted in 1995–1996 as a cross-sectional study among 1501 eighth-grade schoolchildren in the municipality of Odense. It included questionnaires, interviews and clinical examinations, blood samples for IgE measurement, and patch tests. Phase 2 was conducted in 1996–1997 as a case–control study in selected groups of schoolchildren. The population and study design in phases 1 and 2 have been described elsewhere (1).

Phase 3 was a 15-year follow-up study in the same population (28–30 years of age). It included questionnaires, interviews, clinical examinations, blood samples for IgE measurement, prick tests, and patch tests. One thousand two hundred and seventy-one persons had given consent to be contacted later. Details of the follow-up study are reported elsewhere (23).

Questionnaire

The responders completed the questionnaire with questions on atopic dermatitis, asthma, allergic rhinoconjunctivitis, hand eczema, urticaria/angioedema, and type I and IV allergy. The questionnaire consisted of the same questions as in phase 1, supplemented with new questions including occupational aspects (1, 24–26). In this article, only questions about nickel exposure and self-reported contact dermatitis, smoking and education are included, together with basic information on atopic dermatitis and hand eczema from phase 1. The question on ear piercing was: 'Have you ever had your ears pierced or had any other piercing of your skin?' The lifetime prevalence of self-reported eczema caused by metal skin contact was evaluated with the question: 'Do you get eczema (rash) when metals comes into contact with your skin such as jeans buttons, metal fasteners, metal costume jewellery (e.g. earrings) or other metal parts of clothes next to your skin (excluding under the finger ring)?'

Patch tests

Nickel sulfate from TRUE Test® was used, supplemented with a nickel sulfate dilution series consisting of nickel sulfate (NiSO_4) in three concentrations (66, 33 and 11 $\mu\text{g}/\text{cm}^2$). The dilution series was made similar to TRUE Test®. The patch tests were applied to the upper back for 2 days, and reading took place at D3/D4 according to the International Contact Dermatitis Research Group criteria (27, 28). Positive reactions of grades +, ++ and +++ were considered to be positive. The clinical relevance of a positive patch test result was evaluated in relation to the history of exposure, and dermatitis pattern. Pregnant women were not allowed to participate in patch testing.

Ethics

The Regional Scientific Ethical Committee for Southern Denmark approved the study (S-VF-19950022).

Data handling and statistics

The questionnaire was answered electronically by 743 participants, and 156 answered a paper version; the

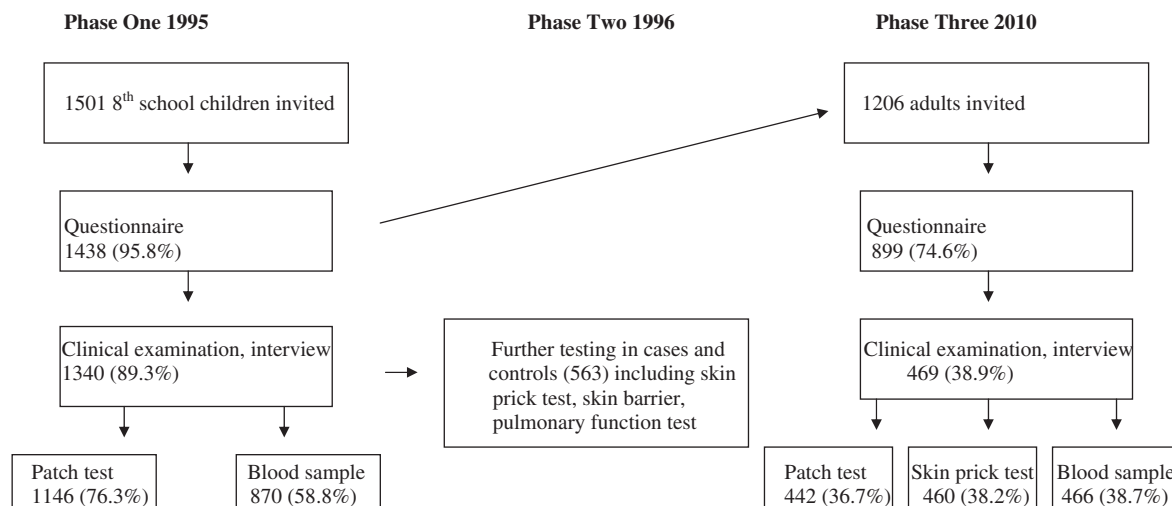


Fig. 1. Flowchart and participation proportions in phases 1–3.

responses were subsequently entered into the database by the first author (C.G.M.). All clinical data were entered twice; when differences were found, a comparison with raw input forms was made, and corrections were made accordingly. Statistical analysis was performed with STATA™/SE 11.0 (Stata Corporation, College Station, TX, USA).

The results are given as prevalence proportions and 95% confidence intervals (CIs). Comparisons between sexes were made by χ^2 -based table analysis. For small samples, Fisher's exact test was used. Incidence rate was calculated from 1995 to 2010 based on those with negative nickel patch tests in 1995. Odds ratios (ORs) are given as Mantel–Haenszel ORs, with associated 95% CIs in parentheses. A logistic regression model was performed among women. Nickel allergy was the dependent variable (binary outcome), and atopic dermatitis and ear piercing were the independent variables.

Statistical significance was defined as $p < 0.05$.

Results

A total of 1206 of the 1271 adults were retrieved in Denmark through the national central person register; 4 had died, 1 was missing, and 60 had emigrated to other countries. After four reminders, the response rate for answering the questionnaire was 74.6% (899/1206). Four hundred and sixty-nine of 1206 (38.9%) of those invited (52.2% of those who responded by questionnaire) participated in the clinical examination, and 36.7% (442/1206) were patch tested (Fig. 1).

Information about skin exposure to metals, and associated self-reported contact dermatitis, was obtained

from 889 respondents in the questionnaire. A total of 11.4% (15.0% women, 5.4% men, $p < 0.0001$) reported eczema caused by metal skin contact (such as with metal buttons, belt buckles, jewellery as earrings but not finger rings, or other metal parts in the clothes). In this population, 67.5% had ever had ear piercing (93.2% women, 34.3% men, $p < 0.0001$).

The patch test population in 2010 comprised 442 adults (274 women, 168 men, $p < 0.001$), including 403 tested in 1995 and 39 from the population not patch tested in 1995 but who participated in other parts of the 1995 study. More than 97% had a patch test reading at D3/D4. In 3 persons, the reading was performed after 2 days, and in 1 after 5 days; in 6 persons, readings were performed at home after instruction and, if possible, photo documentation (all negative). Reaction to the test tape was seen in only 1 case. No irritant reactions were recorded.

A positive patch test reaction to nickel sulfate 200 $\mu\text{g}/\text{cm}^2$ was found in 11.8% (Table 1). On testing with the nickel dilution series, 7.5% of the population reacted to nickel sulfate 66 $\mu\text{g}/\text{cm}^2$, 8.1% to nickel sulfate 22 $\mu\text{g}/\text{cm}^2$, and 6.5% to nickel sulfate 11 $\mu\text{g}/\text{cm}^2$. Significantly more women than men reacted to nickel sulfate at all concentrations (Table 1). Clinical relevance was found for 80.8% of the reactions to nickel 200 $\mu\text{g}/\text{cm}^2$, and for 90–91% of the reactions in the nickel dilution series.

A total of 403 participants were patch tested with nickel sulfate 200 $\mu\text{g}/\text{cm}^2$ in TRUE Test® both in 1995 and in 2010, and the 15-year incidence of nickel contact allergy was 7.0% (26/372) calculated as the development of contact allergy in those who had a negative nickel patch

Table 1. Point prevalence of nickel allergy (positive patch test result with TRUE Test®, and nickel dilution series) and associated relevance in 2010

	Contact allergy (%)			Relevance (%) (number positive with relevance/number positive)
	Women (n = 274)	Men (n = 183)	Total population (n = 442)	
Nickel sulfate 200 µg/cm ²	18.3*	1.2	11.8	80.8 (42/52)
Nickel sulfate 66 µg/cm ²	11.7*	0.6	7.5	90.9 (30/33)
Nickel sulfate 22 µg/cm ²	12.8*	0.6	8.1	91.2 (33/36)
Nickel sulfate 11 µg/cm ²	10.2*	0.6	6.5	89.7 (26/29)

* $p < 0.0001$ for sex difference.

test result in 1995 in TRUE Test®. When results from the nickel sulfate dilution series in 1995 were included, the incidence was 6.7% (25/371), as 1 adolescent reacted to nickel sulfate 200 µg/cm² in the dilution series without reacting to nickel sulfate 200 µg/cm² in TRUE Test®.

The reproducibility of nickel allergy in TRUE Test® in the 403 young adults is shown in Table 2. Contact allergy to nickel was reproduced in 77.4% (24/31) of the adults with a positive reaction to nickel in TRUE Test® in adolescence, 7 positive reactions from 1995 were lost, and 26 new positive reactions were found. All of the lost reactions were previously mild positive reactions (+), whereas new sensitizations were scored from + to ++++. Among the 24 persons with a reproducible reaction to nickel, all except 1 had the same score in 2010 as in 1995, or a higher score.

Eighteen of the 26 new nickel-allergic adults (69.2%) had associated clinical relevance, and the scores of the new reactions were + in 7, ++ in 10, and +++ in 9. All of those with +++ reactions had clinical relevance, in contrast to only 2 of 7 with + reactions.

Table 2. The reproducibility of nickel allergy (TRUE Test®) in the 403 young adults patch tested both in 1995 and 2010 illustrated in relation to patch test score

		Nickel patch test reactions 1995				
		+1	+2	+3	Negative	Total
Nickel patch test reactions 2010	+1	4	1	0	7	12
	+2	5	4	0	10	19
	+3	2	7	1	9	19
	Negative	7	0	0	346	353
	Total	18	12	1	372	403

The nickel dilution series showed that 14 of 26 reacted to a concentration of 11 µg/cm². Eight (30.8%) of the 26 new nickel-allergic adults reported eczema caused by metal skin contact in 1995, but then had negative nickel patch test results in TRUE Test®. The nickel dilution series in 1995 comprised nickel sulfate 200, 10 and 1 mg/cm², and in 2010 it comprised nickel sulfate 66, 22 and 11 mg/cm². All individuals with reactions to the low nickel concentrations in 1995 (1 or 10 mg/cm²) had a positive nickel patch test reaction in 2010, although not all reacted to the lowest concentrations (6 of 8 with reactions to 10 mg/cm² in 1995 reacted to 11 mg/cm² in 2010, and 1 of 2 with reactions to 1 mg/cm² in 1995 reacted to 11 mg/cm² in 2010).

Table 3 shows the relationship between history of eczema caused by skin contact with metals (questionnaire) and the patch test reaction to nickel sulfate. In the questionnaire, 11% (49/442) of the adults patch tested in 2010 reported eczema caused by skin contact with metals (Table 3), and 27 of the 49 (55%) had a positive nickel patch test reaction. Among the 393 without a history of eczema caused by metal skin contact, 25 had a positive patch test reaction to nickel sulfate. However, by repeated interview after patch testing, 15 of the 25 with no history in the questionnaire recalled a history of eczema caused by metals. The sensitivity and specificity of questionnaire-based metal dermatitis as compared with nickel sulfate patch test sensitivity were 55% and 94%, respectively.

The relationship between ear piercing and nickel allergy could not be evaluated in men, owing to the low number with nickel allergy (n = 2). In women, nickel allergy was not significantly associated with ear piercing at school age (OR 2.39, 95% CI 0.89–6.41) or ear piercing ever (OR 1.85, 95% CI 0.41–8.34). In 1995, the children and parents were asked to give the year of ear piercing. The relationship between time of ear piercing and nickel

Table 3. Distribution of results for patch testing with nickel sulfate (TRUE Test®) in 2010 in relation to self-reported eczema caused by metal contact reported in the questionnaire in 2010; results of calculations of sensitivity and specificity

		History of eczema caused by metals			
		Yes	No	Total	
Nickel sulfate	Positive reaction	27	25	52	Sensitivity* 55.1%
	Negative reaction	22	368	390	Specificity* 93.6%
	Total	49	393	442	

*The sensitivity was calculated as 27/(27 + 22) and the specificity as 368/(368 + 25).

allergy in 2010 is shown in Table 4, together with self-reported eczema caused by metals. Among those with ear piercing before the nickel regulation in Denmark in 1990, 29% had nickel allergy (14% reacted down to 11 µg/cm²), as compared with 14% in those ear pierced after 1990 (9% reacted down to 11 µg/cm²), and 6% in those without ear piercing. The difference in frequency of nickel allergy between those ear pierced before 1990 and those ear pierced after 1990 is significant ($p < 0.005$). The same trend was found for self-reported nickel dermatitis ($p < 0.05$).

The association between the degree of nickel allergy and childhood atopic dermatitis in women is shown in Table 5. A significant association was found between having atopic dermatitis in childhood and having nickel allergy as an adult. This association was not dose-dependent.

In a logistic regression model (in women, $n = 274$) with nickel allergy as the binary outcome and atopic dermatitis and ear piercing in childhood as the explanatory variables, the association between nickel allergy and atopic dermatitis in childhood was verified (OR 2.2, 95% CI 1.15–4.29, $p < 0.02$), whereas no association between ear piercing in childhood and nickel allergy was found. It was not possible to include data on the year of ear piercing in the model, because of the small population size.

Possible selection biases in 1995 and 2010 were investigated. Those with atopic dermatitis and hand eczema in 1995 were more prone to participate in patch testing than those without atopic dermatitis and hand

eczema both in 1995 [OR 3.18 (95% CI 2.05–4.94) and OR 2.40 (95% CI 1.30–4.44), respectively] and in 2010 [OR 2.35 (95% CI 1.51–3.66) and OR 1.93 (95% CI 1.08–3.44), respectively]. The 403 tested in 2010 constituted a representative part of the 1995 patch test population, except that more women than men participated in the follow-up patch testing (Table 6).

Lifestyle factors in 2010 and participation in patch testing were evaluated for smoking and educational level. Medium-duration (3–4 years) to long-duration (more than 4 years) vocational training was reported by 475 of 899 in the questionnaire. Among those participating in patch testing, 55.7% (246/442) had medium-duration to long-duration vocational training, whereas 50.1% (229/457) of those only answering the questionnaire had this vocational level (not significant). Nickel allergy was found among 10.2% (25/246) of those with medium-duration to long-duration vocational training, as compared with 13.8% (27/196) of those with no vocational training, short-duration vocational training, or craftsman/other practical education (not significant). Smoking was reported by 431 of 889 (ever smoked regularly) in the questionnaire. Among those who participated in patch testing, 44.3% (196/442) were smokers, whereas 52.6% of those answering the questionnaire but not participating in patch testing were smokers ($p < 0.02$). Nickel allergy was found among 17.4% (34/196) of the smokers as compared with 7.3% (18/246) of the non-smokers ($p < 0.001$).

Discussion

The prevalence of nickel allergy among adolescents in 1995 was 8.6% (29), and 15 years later the prevalence had increased to 11.8%. The prevalence increased in women (13.7% to 18.3%), and decreased in men (2.5% to 1.2%). Most of the reactions were clinically relevant (80.8%), and 56% (29/52) of the nickel-allergic individuals were positive to low concentrations of nickel sulfate (11 µg/cm²). A 15-year incidence rate of nickel allergy of 6.7% was found among the 442 individuals patch tested both in 1995 and 2010.

Both in 1995 and in 2010, more individuals with atopic dermatitis and hand eczema participated in patch testing, which could lead to an overestimation of the prevalence of contact allergy and allergic contact dermatitis (23). With the exception of sex, the comparison of baseline characteristics between participants and non-participants in the follow-up did not show significant differences (Table 6). Data were analysed separately for women and men. Therefore, non-participants seemed unlikely to bias the results substantially (23). Furthermore, although

Table 4. Prevalence of nickel allergy (TRUETest®) and self-reported nickel dermatitis among women with ear piercing before 1990, among those with ear piercing between 1990 and 2010, and among those newer pierced

	Ear pierced before 1990, n (%)	Ear pierced between 1990 and 2010, n (%)	Ears never pierced [†] , n (%)	<i>p</i> - value*
Nickel allergy 2010 [‡]	25/86 (29.1)	24/172 (14.0)	1/16 (6.3)	< 0.005
Nickel dermatitis 2010 (self-reported)	37/175 (21.4)	42/299 (14.0)	1/27 (3.7)	< 0.05

**p*-value for comparison of the prevalence of nickel allergy and nickel dermatitis among those pierced before 1990 and those pierced after 1990.

[†]There was no significant association between those ear pierced after 1990 and those never pierced ($p = 0.7$, Fisher's exact test).

[‡]Of those ear pierced before 1990, 14.0% (12/86) reacted down to 11 µg/cm², as compared with 9.3% (16/172) of those ear pierced between 1990 and 2010. None of those never pierced reacted down to 11 µg/cm².

Table 5. Association between the degree of nickel sensitivity (TRUE Test®) in adulthood (phase 3, 2010) and atopic dermatitis in childhood (0–14 years, evaluated in phase 1, 1995) among women. Odds ratios (ORs) are given as Mantel–Haenszel ORs

		Atopic dermatitis in childhood				
		Yes (%)	No (%)	OR	95% CI	p-value
Positive patch test reaction 2010	Nickel 200 µg/cm ²	26.7	15.1	2.05	1.07–3.92	< 0.03
	Nickel 66 µg/cm ²	20.0	8.5	2.91	1.25–5.75	< 0.009
	Nickel 22 µg/cm ²	20.0	10.1	2.24	1.07–4.68	< 0.03
	Nickel 11 µg/cm ²	17.3	7.5	2.58	1.15–6.76	< 0.02

CI, confidence interval.

Table 6. Comparison of baseline characteristics (1995) between those participating and those not participating in patch testing in the follow-up study (2010); in 1995, 1146 schoolchildren were patch tested, and of these, 403 were retested in 2010 as adults (reproduced from reference 23)

Baseline characteristics 1995	Participants in follow-up patch testing 2010		Non-participants in follow-up patch testing 2010		p-value
	Prevalence (%)	n = 403	Prevalence (%)	n = 743	
Sex					< 0.001
Female	63.5	256	49.0	364	
Male	36.5	147	51.0	379	
One or more positive patch test reactions	14.9	60	15.3	114	0.84
Nickel allergy	7.7	31	8.2	61	0.76
History of metal contact eczema	20.1	81	16.7	124	0.76
Present or past atopic dermatitis	26.3	106	23.6	175	0.30
Present or past hand eczema	11.4	46	10.1	75	0.49

only 36.8% of those invited participated in patch testing, the questionnaire data for 74.6% of those invited showed that the educational level in those participating in patch testing was the same as in those not participating in patch testing. There were fewer smokers among those patch tested than among those not patch tested, which could lead to an underestimation of the prevalence, as nickel allergy seems to be higher among smokers than among non-smokers (30).

The Danish nickel regulation of 1990 limits nickel release to 0.5 µg/cm²/week from jewellery and other consumer products in contact with the skin (12). Recent studies have shown a significant decrease in nickel allergy in the younger population when comparing the time periods before and after the implementation of the nickel regulation in Denmark (3, 15). The TOACS cohort was investigated for the first time 5 years after the implementation in Denmark (6), and we therefore expected that the 1995 study would not reflect an effect of the nickel regulation. However, after another 15 years, only a few new positive reactions to nickel were expected. The high incidence of nickel allergy over the 15-year period was unexpected, and suggests that the effect of the nickel regulation is limited. However, this study is based on incidence data in the same population, and it can be difficult to compare with studies performed in different

populations over time. Another Danish study has recently shown that, in spite of the EU Nickel Directive entering into full force in the EU in July 2001, a large proportion of inexpensive earrings still release nickel in concentrations that may result in nickel allergy and dermatitis (20), and one-fifth of inexpensive jewellery items and hair clasps released nickel in concentrations that may lead to nickel allergy (31). This is in accordance with reports from other countries, and may lead to the conclusion that persistent exposure to nickel at a level sufficiently high to sensitize may contribute to the occurrence of new nickel sensitizations in the population (16). In a recent review from Thyssen et al., possible explanations for the persistence of nickel allergy and dermatitis are discussed. Patterns of consumer nickel exposure include jewellery and hair clasps sold mainly in street markets, but occupational nickel exposure, such as from tools and coins, may also contribute (14). The history of eczema in the cohort caused by skin contact with metals decreased from 15.5% in 1995 to 11.4% in 2010 (6). This decrease may be explained by recall bias or reduced exposure to nickel-containing metal parts in contact with the skin. In accordance with other studies, the association between a history of eczema caused by metals and a positive patch test reaction was poor, and overestimated the true prevalence of nickel allergy (32, 33). In 1995,

only 31% of adolescents with self-reported metal-related eczema reacted positively in a nickel patch test, and the frequency increased to 55.1% in those participating in 2010. Interview after patch testing in 2010 showed that recall bias plays a significant role in questionnaire-based studies.

The combination of questionnaire, interview and clinical examination performed by the same investigator team supports the reliability of our data on nickel contact allergy and allergic nickel dermatitis.

The application of TRUE Test® has achieved complete technical uniformity, as dosages and bioavailabilities of the allergens are standardized. Readings were performed at D3 or D4, both in 1995 and in 2010; a D7 reading was not included in the protocol, owing to logistic difficulties in having an extra visit. The omission of a D7 reading could lead to the true prevalence of nickel allergy being underestimated (19, 34). A retrospective study comprising nearly 10 000 dermatitis patient patch tested with TRUE Test® panels showed that ~10% of negative or doubtful positive nickel sulfate test results became positive at the late reading on D6 or D7 (28). The participants in this study were asked to report delayed reactions, but none were reported.

The reproducibility of positive nickel sulfate patch test reactions (TRUE Test®) from 1995 to 2010 was 77.4%. A similarly high reproducibility (66%) was found in selected patients from our department tested twice in the period 1991–2002 with the same test system (TRUE Test®) (35). This is in accordance with previous publications showing that nickel sulfate is one of the contact allergens with the highest frequency of reproducible positive patch test reactions (7). However, the level of sensitivity may vary considerably between serial test procedures in the same nickel-allergic individual over the course of a year (8). As expected, those with positive reactions to nickel sulfate down to low concentrations and those with high patch test scores in 1995 (++, +++) had a higher degree of persistence over the 15-year period. Only seven reactions could not be reproduced, and they were all weak positive reactions (+) in 1995. In contrast, 19 of the 26 individuals who developed sensitization to nickel sulfate in TRUE Test® from 1995 to 2010 had strong positive reactions (++, +++) and reacted to low concentrations of nickel sulfate, and most reactions were clinically relevant. The clinical value of the application of a nickel sulfate patch test dilution series is limited.

There are no previous reports on incidence rates of nickel allergy from adolescence to adulthood, either in selected patient groups or in the general population. Nielsen and co-workers reported an incidence rate of

6% for nickel allergy in adults over an 8-year time period (36). The study was performed in 1990–1998, which is 12 years before our study, and it showed the same incidence of nickel allergy. However, the time period for follow-up was different (8 years versus 15 years), and our study included a younger age group.

A total of 67.5% had ever had ear piercing (93.2% women, 34.3% men, $p < 0.0001$). In women, nickel allergy was not significantly associated with ear piercing (OR 1.85, 95% CI 0.41–8.34, $p > 0.05$), in contrast to our results from 1995 (OR 5.12, 95% CI 1.82–14.44, $p < 0.002$) (6).

A weakness of the follow-up study is the decreasing rate of participation, making associations more difficult to obtain. However, on examination of ear piercing before and after the nickel regulation in Denmark, a trend was apparent. There was a significantly higher prevalence of nickel allergy among those ear pierced before 1990 than among those ear pierced after 1990 (29.1% versus 14.0%). However, the association between ear piercing before 1990 and nickel allergy could also be explained by the long duration of exposure to nickel-containing metal objects in those with early ear piercing as compared with those ear pierced later. There was no significant difference in the occurrence of nickel allergy between those ear pierced between 1990 and 2010 and those who had never been ear pierced. The results are in agreement with another cohort study examining two different populations 16 years apart in Denmark (15).

The association between contact allergy and atopic dermatitis has been controversial. The general opinion today is that children with atopic dermatitis are sensitized as frequently as children without atopic dermatitis (21). A significantly higher prevalence of nickel allergy was found among women with atopic dermatitis in childhood (0–14 years) than among women without atopic dermatitis in childhood (19.4% versus 9.1%). The same tendency was found for women reacting to low nickel concentrations (12.5% versus 4.6%) (Table 5). Recently, it has been suggested that *FLG* null mutations may constitute a risk factor for the development of nickel sensitization (22). However, in a recent cross-sectional study, nickel allergy was not associated with atopic dermatitis unless those with ear piercing were excluded. The authors suggested that inclusion of individuals with ear piercing in the analyses of data on nickel sensitization could introduce a bias, because ear piercing 'bypasses' the cutaneous route of sensitization (37). Only 16 women in this study had no ear piercing, so we could not evaluate this further.

This follow-up study showed a high incidence rate of nickel allergy in young adults followed up 15 years

after leaving primary school; most reactions were strong reactions with clinical relevance, and many individuals reacted to low concentrations of nickel sulfate. Only a few reactions were lost, all with a low score (+1). The validity of self-reporting of eczema caused by metal contact is low, and it overestimates the prevalence of nickel allergy. Women with atopic dermatitis in childhood seemed to have a higher risk of nickel allergy. In 2010, we could not find an association between ear piercing and nickel allergy. However, when women were divided according to ear piercing before and after the Danish nickel regulation, a significant association between nickel allergy and ear

piercing was found among those pierced before the nickel regulation in Denmark as compared with those with ear piercing after.

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