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Article Type: Original Article

Nickel allergy following EU regulation in Denmark, Germany, Italy and the United Kingdom

Running head: Nickel allergy following EU regulation

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Funding sources: None

Conflict of interests: None declared

What's already known about this topic?

- Nickel allergy affects 10-15% of women in the general population and is associated with hand eczema.
- Previous studies have shown a decrease in nickel allergy in young women in Denmark and Germany since regulations to control nickel release were implemented.

What does this study add?

- Post-regulation, a significant decrease in nickel allergy was seen in women with suspected dermatitis aged below 30 in all countries and in men below 30 in the UK and Germany, though an increase was seen in young Italian men.
- This study of 180 390 patients shows that the EU Nickel regulations are starting to reduce nickel allergy in young men and women, though allergy remains prevalent and more work needs to be done to improve compliance with the regulation.

Abstract

Background: Nickel allergy is common worldwide. It is associated with hand dermatitis and sensitization is often induced by nickel-releasing jewellery. The European Union introduced legislation to control nickel content and release from jewellery and other consumer items through the EU Nickel Directive 1994, which came in to force in 2001 and is now part of the REACH regulation.

Objective: To examine the effects of the EU Nickel regulations on the prevalence of nickel allergy in four European countries.

Methods: Nickel patch test data from 180 390 patients were collected from national databases in Denmark, Germany, Italy and the UK from between 1985 and 2002 to 2010. Patients with suspected allergic contact dermatitis who had been patch tested with nickel sulphate 5% in petrolatum were included in the analysis. The main outcomes studied were the percentage of positive results to nickel patch test and change in trends with time in an age- and sex-stratified analysis.

Results: A statistically significant decrease of nickel allergy was observed in Danish, German and Italian women below the age of 30 years. In British female patients, this was observed between 2004 and 2010. In young men, a statistically significant decrease of nickel allergy was observed in Germany and the UK, whereas a non-significant increase was observed in Italy.

Conclusion: There has been a reduction in the prevalence of nickel allergy in young women, contemporaneous with the introduction of the nickel regulation. A reduction is also suggested in German and British men. A causative effect of the regulatory intervention is the most likely explanation.

INTRODUCTION

Nickel allergy is common in Europe, affecting 15-30% of female dermatitis patients seen by specialists and 10-15% of women from the general population¹⁻³. Nickel allergic individuals may develop hand eczema leading to ill-health and time off work. Nickel allergy is considerably more frequent in women than men⁴ probably due to more frequent skin contact with nickel-releasing jewellery and accessories. To address this problem, the European Union (EU) introduced the Nickel Directive (Directive 94/27/EC) which was passed on the 30th June 1994 and came into full effect in June 2001. This Directive, the first of its kind, prohibited the sale of products intended to come into direct and prolonged contact with the skin, releasing nickel at rates greater than 0.5 $\mu\text{g}/\text{cm}^2/\text{week}$. All forms of jewellery, watches, buttons and zippers were included and recently mobile phones were added to the list^{5,6}. The maximum nickel release rate for piercing post assemblies is currently 0.2 $\mu\text{g}/\text{cm}^2/\text{week}$. For coated items, the rate should not exceed 0.5 $\mu\text{g}/\text{cm}^2/\text{week}$ after 2 years of normal use. Denmark, Germany and Sweden introduced legislation in 1990-91 to limit nickel allergy making the basis for the EU Nickel Directive^{6,7}. A similar legislation was later introduced in Korea and China⁸ whereas the US market remains unregulated despite current discussions about possible regulation of nickel exposure. Since June 2009 the EU Nickel Directive has been subsumed into the REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) regulation (item 27 of Annex XVII).

It is of interest and concern, whether the EU Nickel regulations have had an effect on the prevalence of nickel allergy in patients with suspected contact dermatitis. To this end, we have analysed data on nickel allergy prevalence in patch tested dermatitis patients in four European countries covered by the EU Nickel regulation over at least a 9- year period.

MATERIALS AND METHODS

Nickel patch test data were collected from Denmark, Germany, Italy and the UK for a varying number of years, covering the period from between 1985 and 2002 to 2010. The patch test populations consisted of patients with suspected allergic contact dermatitis who had been patch tested routinely with nickel sulphate 5% in petrolatum. Readings were performed on day 3 in Germany and on day 4 in Denmark, Italy and the UK. Day 7 readings were also performed in Denmark.

The population was divided for analysis by sex and age, with age ranges: <30 yrs, 30-60 yrs and >60 yrs. These age groups were chosen to ensure that the differences in nickel exposure and allergy between the different generations (youngest, middle-aged and older) would be best reflected. The groups also roughly represent the different stages of working life i.e. pre/early working life, established work and late/post work.

Data were collected via databases from each country, namely the Information Network of Departments of Dermatology [IVKD] covering participating German contact dermatitis clinics, Italian departments from the North-East Italy Contact Dermatitis Group [NEICDG] and Genova (excluding the paediatric department in Padova), the Gentofte Allergy Database from Copenhagen, Denmark and the British Contact Dermatitis Society [BCDS, latterly the British Society of Cutaneous Allergy] for the UK, though only two centres contributed in 2002 and four in 2003. Statistical tests for trend in the single strata defined by country, gender and age group were performed with the statistical software package R (version 2.13, www.r-project.org/) in terms of linear regression analyses.

RESULTS

The demographics of the patch tested patients are shown in Table 1. The proportion of female dermatitis patients was similar in the four countries (62.2-67.1%) as was the proportion of ‘middle aged’ patients, aged 30-60 years (51.7-52.7%). However, the proportion of young patients (below 30 years of age) was slightly higher in the Italian population (28.5%) when compared to the other countries (18.9-26.7%). In line with this, the overall prevalence of nickel allergy was highest in Italian patients (25.0%) when compared to remaining populations (12.3-17.7%).

As expected there was a higher prevalence of nickel allergy in women compared to men in all age groups. A statistically significant (time trend $p < 0.05$) decrease in nickel allergy was observed in the youngest age group of Danish, German and Italian women whereas the decrease was only statistically significant in young British female patients between 2004-2010; a period with more comprehensive national coverage (Table 1 and Fig 1). Similarly, a statistically significant increase in nickel allergy was observed in middle-aged women (30-60 years) in all four populations (again only when considering the period 2004-10 for the UK population).

In German and British men aged below 30 a statistically significant decrease in nickel allergy was observed over the test periods, whereas an increase, albeit missing significance, was observed in Italian men. In middle-aged men, a statistically significant increase of nickel allergy was observed in Denmark, Italy and the UK.

DISCUSSION

This time series study, investigating a total of 180 390 patients with suspected allergic contact dermatitis, shows that the prevalence of nickel allergy has decreased significantly by at least 10% in young female dermatitis patients from four European countries following nickel regulation. In the UK this decrease was only significant between 2004 and 2010, probably due to under-representation of UK patients in 2002 and 2003. The increase of nickel allergy in middle-aged (and older) women is

well explained by a cohort effect. Once acquired nickel allergy usually persists life-long, accounting for the increased prevalence in the 'middle-aged' or older populations who have been widely exposed to high nickel concentrations in the 1960-80's⁹.

This data represents the hitherto largest combined attempt to investigate the effects of a pioneering public health regulation affecting approximately 500 million EU citizens. It demonstrates that the epidemiology of nickel allergy in women has changed in a very similar way in all four countries and indicates that the change may have been caused by the nickel regulations. In favour of this interpretation is the simultaneous increase of nickel allergy in the United States, a country without nickel regulation¹⁰ and in China, a country where the nickel regulation is not always followed and where inspection control visits are scarce¹¹. Several previous studies investigating nickel allergy following regulation have consistently shown that prevalence is decreasing in young European women¹²⁻¹⁹, while one study from Spain showed a similar prevalence in young and middle-aged women²⁰ as in our results from Italy. The higher nickel allergy prevalences in Southern Europe may be explained by insufficient or delayed implementation of the Nickel regulation as well as different patterns of referral for patch testing. Factors apart from the nickel regulation such as changes in fashion habits e.g. fewer piercings and less costume jewellery, better education of the public, the use of metal alloys with lower nickel content by the jewellery industry, changing work patterns and a decrease in referral of straight forward nickel allergy for patch testing may have also contributed to the apparent decrease of nickel allergy prevalence in Europe.

Despite the substantial decrease of nickel allergy it remains very common. There are several explanations that were recently discussed in detail^{6,9}. Important ones include:

- i) Inconsistency of the EN 1811 reference test method which is used to test whether items comply with the Nickel regulation. The adjustment factor used to correct this increases the acceptable nickel release rate, allowing more items to pass.²¹
- ii) Non-compliance with the Nickel regulation as indicated by the observation that 10-20% of earrings and other jewellery for sale in European countries still release nickel in amounts that cause nickel allergy and dermatitis.^{19, 22-25}

iii) Continued introduction of new consumer sources of nickel exposure, e.g. mobile phones and laptop computers.²⁶

iv) The maximum permissible rate of nickel liberation set by the regulation was not in the first place expected to completely remove nickel allergy, but to strongly limit the problem.²⁷

The development of nickel allergy in male patients differed largely between the four countries. In Germany and the UK, a statistically significant decrease in nickel allergy was observed in young men whereas an increase was observed in Italy. In middle-aged men, a significant increase was observed in all countries except Germany. These results are difficult to interpret and correlate however they suggest that despite some reductions in prevalence, nickel allergy remains a problem in men referred for patch testing in all the European countries studied, more so in Italy. Nickel allergy in men is often caused by occupational nickel exposure however piercings are also popular and must be considered. Future studies are required to monitor this aspect of nickel allergy.

This study included patients referred for patch testing with a suspected allergic contact dermatitis. There may therefore be an increased rate of nickel allergy in this population, though conversely uncomplicated nickel allergy may not be referred to secondary care for patch testing. The other limiting factor is the variability in time periods available for study which limited analysis especially for the UK data.

Taken together, there is strong evidence to suggest that nickel allergy has decreased in young European women following nickel regulation however nickel allergy is still prevalent and warrants continuous attention from dermatologists and public health regulators to ensure the prevalence continues to decrease in both sexes. Public information campaigns explaining nickel allergy, its sources and implications may be beneficial to the general public but also to more targeted areas including manufacturing facilities and their occupational health teams. Dermatologists need to ensure that those patients who are found to be patch test positive to nickel are aware of the significance of nickel allergy and how to avoid contact. Ensuring compliance with the nickel regulations and therefore decreasing the amount of nickel the general public comes into contact with, is the most

important factor in the controlling the development of nickel allergy. Random inspection control visits of shops and stores followed by fines for manufacturers, wholesalers, importers and retailers who are not compliant with the nickel regulations should be enforced. The Nickel regulation may serve as inspiration for the regulation of other chemicals and metals causing significant morbidity.

Fig. 1: The temporal development of nickel allergy in male and female dermatitis patients (% positive, lines in blue and red, respectively) from four European countries in three age strata: < 30 (solid lines), 30-60 (dashed lines) and > 60 (dotted lines). The vertical lines represent important dates in nickel regulation (1990 – Introduction of the Danish regulation; 1994 – EU Nickel Directive passed; 2001 – EU Nickel Directive came into full effect; 2009 – Nickel regulation became part of REACH regulation)

Table 1. Characteristics of patients patch tested with nickel sulphate 5% in petrolatum in the four countries, with gender and age-stratified results. The ‘slope’ indicates the average annual increase or decrease in percentage points during the respective study periods.

Patient characteristics	Age (years)	Denmark (n=19 828) %		Germany (n=104 933) %		Italy (n=20 231) %		United Kingdom (n=35 398) %	
		1985-2010		1995-2010		1997-2010		2002-2010	
Nickel tested:									
Women		64.6		62.2		67.1		67.1	
Overall Age Distribution	<30	21.2		18.9		28.5		26.7	
	30-60	52.7		52.4		52.4		51.7	
	>60	26.1		28.7		19.0		21.5	
Nickel Allergic:									
Overall		12.3		13.6		25.0		17.7	
	<30	14.2		18.8		27.2		16.1	
	30-60	14.5		15.8		27.9		21.2	
	>60	6.5		6.2		13.7		11.3	
Men		3.1		5.1		10.8		6.2	
	<30	3.0		5.9		10.6		6.0	
	30-60	3.4		5.4		11.4		7.3	
	>60	2.6		3.9		9.4		3.9	
Women		17.4		18.9		31.9		23.4	
	<30	18.9		26.0		35.2		20.4	
	30-60	20.7		23.1		35.9		28.4	
	>60	8.9		7.6		15.8		15.6	
Time Trend:		Slope	p-value	Slope	p-value	Slope	p-value	Slope [§]	p-value [§]
Men	<30	0	0.96	-0.18	0.004	+0.46	0.08	-0.34 (-0.41)	0.04 (0.06)
	30-60	+0.09	0.01	-0.01	0.7	+0.89	< 0.0001	+0.31 (+0.34)	0.04 (0.009)
	>60	+0.12	0.046	-0.04	0.5	+0.32	0.27	-0.07 (+0.03)	0.7 (0.9)
Women	<30	-0.38	< 0.0001	-1.14	< 0.0001	-0.97	0.01	-0.62 (-1.23)	0.2 (0.007)

	30-60	+0.54	< 0.0001	+0.15	0.05	+1.08	0.009	+0.07 (-0.66)	0.9 (0.003)
	>60	+0.19	0.01	+0.05	0.5	+0.75	0.03	+0.18 (-0.15)	0.6 (0.6)

§ The results in brackets shows analysis of the data from 2004-2010 (excluding 2002-3) for the UK.

REFERENCES

- (1) Schafer T, Bohler E, Ruhdorfer S, Weigl L, Wessner D, Filipiak B et al. Epidemiology of contact allergy in adults. *Allergy* 2001; 56(12):1192-1196.
- (2) Thyssen JP, Linneberg A, Menne T, Nielsen NH, Johansen JD. Contact allergy to allergens of the TRUE-test (panels 1 and 2) has decreased modestly in the general population. *Br J Dermatol* 2009; 161(5):1124-1129.
- (3) Uter W, Ramsch C, Aberer W, Ayala F, Balato A, Beliauskienė A et al. The European baseline series in 10 European countries, 2005/2006 - Results of the European Surveillance System of Contact Allergies (ESSCA). *Contact Dermatitis* 2009; 61:31-38.
- (4) Uter W, Pfahlerberg A, Gefeller O, Geier J, Schnuch A. Risk factors for contact allergy to nickel - results of a multifactorial analysis. *Contact Dermatitis* 2003; 48(1):33-38.
- (5) Thyssen JP, Johansen JD. Mobile phones are now covered by the European Union Nickel Directive. *Contact Dermatitis* 2009; 61(1):57.
- (6) Thyssen JP, Uter W, McFadden J, Menne T, Spiewak R, Vigan M et al. The EU Nickel Directive revisited - future steps towards better protection against nickel allergy. *Contact Dermatitis* 2011; 64(3):121-125.
- (7) Liden C. Nickel in jewellery and associated products. *Contact Dermatitis* 1992; 26(2):73-75.
- (8) Hamann CR, Hamann DJ, Hamann QJ, Hamann CP, Boonchai W, Li LF et al. Assessment of nickel release from earrings randomly purchased in China and Thailand using the dimethylglyoxime test. *Contact Dermatitis* 2010; 62(4):232-240.
- (9) Thyssen JP. Nickel and cobalt allergy before and after nickel regulation - evaluation of a public health intervention. *Contact Dermatitis* 2011; 65 Suppl 1:1-68.
- (10) Rietschel RL, Fowler JF, Warshaw EM, Belsito D, DeLeo VA, Maibach HI et al. Detection of nickel sensitivity has increased in North American patch-test patients. *Dermatitis* 2008; 19(1):16-19.
- (11) Hamann D, Hamann C, Li L-F., Maibach HI, Hamann K, Taylor J et al. The Sino-American Belt Study: Nickel and Cobalt Exposure, Epidemiology and Clinical Considerations. *Dermatitis*. In press 2012.
- (12) Jensen CS, Lisby S, Baadsgaard O, Volund A, Menne T. Decrease in nickel sensitization in a Danish schoolgirl population with ears pierced after implementation of a nickel-exposure regulation. *Br J Dermatol* 2002; 146(4):636-642.
- (13) Lindberg M, Edman B, Fischer T, Stenberg B. Time trends in Swedish patch test data from 1992 to 2000. A multi-centre study based on age- and sex-adjusted results of the Swedish standard series. *Contact Dermatitis* 2007; 56(4):205-210.

- (14) Schnuch A, Uter W. Decrease in nickel allergy in Germany and regulatory interventions. *Contact Dermatitis* 2003; 49(2):107-108.
- (15) Thyssen JP, Johansen JD, Carlsen BC, Menne T. Prevalence of nickel and cobalt allergy among female patients with dermatitis before and after Danish government regulation: a 23-year retrospective study. *J Am Acad Dermatol* 2009; 61(5):799-805.
- (16) Thyssen JP, Johansen JD, Menne T, Nielsen NH, Linneberg A. Nickel Allergy in Danish Women before and after Nickel Regulation. *N Engl J Med* 2009; 360(21):2259-2260.
- (17) Thyssen JP, Hald M, Avnstorpe C, Veien NK, Lauerberg G, Nielsen NH et al. Characteristics of Nickel-allergic Dermatitis Patients Seen in Private Dermatology Clinics in Denmark: A Questionnaire Study. *Acta Dermato-Venereologica* 2009; 89(4):384-388.
- (18) Rui F, Bovenzi M, Prodi A, Fortina AB, Romano I, Peserico A et al. Nickel, cobalt and chromate sensitization and occupation. *Contact Dermatitis* 2010; 62(4):225-231.
- (19) Schnuch A, Wolter J, Geier J, Uter W. Nickel allergy is still frequent in young German females - probably because of insufficient protection from nickel-releasing objects. *Contact Dermatitis* 2011; 64(3):142-150.
- (20) Garcia-Gavin J, Armario-Hita JC, Fernandez-Redondo V, Fernandez-Vozmediano JM, Sanchez-Perez J, Silvestre JF et al. Nickel allergy in Spain needs active intervention. *Contact Dermatitis* 2011; 64(5):289-291.
- (21) Thyssen JP, Uter W, Menne T, Liden C. Revision of the European standard for control of the EU nickel restriction - a probable improvement for European citizens. *Contact Dermatitis* 2011; 65(1):60-61.
- (22) Biesterbos J, Yazar K, Liden C. Nickel on the Swedish market: follow-up 10 years after entry into force of the EU Nickel Directive. *Contact Dermatitis* 2010; 63(6):333-339.
- (23) Thyssen J, Menne T, Liden C, White I, White J, Spiewak R et al. Excessive nickel release from earrings purchased from independent shops and street markets - a field study from Warsaw and London. *J Eur Acad Dermatol Venereol* 2010.
- (24) Thyssen JP, Menne T, Johansen JD. Nickel release from inexpensive jewelry and hair clasps purchased in an EU country - Are consumers sufficiently protected from nickel exposure? *Sci Total Environ* 2009; 407(20):5315-5318.
- (25) Biesterbos J, Liden C, van d, V. Nickel on the Dutch market: 10 years after entry into force of the EU Nickel Directive. *Contact Dermatitis* 2011; 65(2):115-117.
- (26) Jensen P, Johansen JD, Zachariae C, Menne T, Thyssen JP. Excessive nickel release from mobile phones- a persistent cause of nickel allergy and dermatitis. *Contact Dermatitis* 2011; 65(6):354-358.
- (27) Gawkrödger DJ. Nickel dermatitis: How much nickel is safe? *Contact Dermatitis* 1996; 35(5):267-271.

