



Sensitization to nickel in the Triveneto region: Temporal trend after European Union regulations

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KEYWORDS: epidemiology, EU directive, nickel patch test

Nickel is the most common allergen among patients with dermatitis in Europe^{1,2} but also in the general population.³ Nickel sensitization is associated with a high frequency of contact with nickel releasing objects or work tools, and differences in prevalence are seen in different age groups, genders, and cultures etc.^{4,5} To prevent nickel sensitization and allergic nickel dermatitis, some countries adopted national limitations in 1989–1993⁶ and in 1994 the European Parliament and Council introduced the Nickel Directive 94/27/CE. In 2005, the Directive 2004/96/CE concerning piercing posts was amended. From 2009 the Directive was included in the European Union (EU) chemicals regulation REACH, Annex XVII. Italy accepted the Directive 94/27/CE on March 21, 2000 (entering gradually into force in July 2000 and fully in July 2001) and the amendment 2004/96/CE on October 18, 2005. The prevalence of nickel allergy in European countries decreased after the application of the EU restrictions, especially in the northern EU countries, while in Italy and Spain nickel sensitization remained common in patch tested patients^{7,8} and also in general population.³ The decrease in nickel sensitization caused an estimated positive economic effect in terms of saved costs of around 100 billion Euro over 20 years.⁹ The aim of this study was to investigate the trend of nickel sensitization in a population of consecutive patients with suspected allergic contact dermatitis before and after the introduction of the European Directives 94/27/CE and 2004/96/CE. This paper supplements the results of nickel sensitization studies in north-eastern Italy from 1996–2010,⁴ extending the analysis to 2016.

METHODS

From 1997 to 2016, 27 316 patients with suspected allergic contact dermatitis were patch tested in 8 Units of Dermatology or Occupational Medicine in north-eastern Italy, as already reported.¹⁰ All

patients were tested with European baseline series allergens from FIRMA (Firenze, Italy) including nickel sulfate 5% pet. Data analysis was performed with the software STATA v. 13.1 (Stata Corp., College Station, Texas). The associations between patch test results and patient age, year of patch testing, and birth years were investigated through multivariate logistic regression analysis. Statistical significance was set at $P < .05$.

RESULTS

The characteristics of the study population by gender are shown in Table S1. Women were more often sensitized to nickel than men, and men more often had occupational contact dermatitis when compared to non-sensitized women. Patients sensitized to nickel were younger and with more hand dermatitis than non-sensitized patients. Nickel sensitization significantly decreased only in young women (≤ 25 years) while nickel sensitization increased in the middle-aged category (36–65 years) (Table 1). Women born 1966–1975 had the highest percentages of nickel sensitization (47.5%) that gradually declined in women born thereafter. The minimum level of sensitization was seen in women and men born 1996–2005 (14.6% and 11.7%, respectively) (Figure 1). Table S2 reports nickel sensitization in some occupations in both genders compared to clerks. Women employed as metal workers or mechanics presented an increased risk of sensitization to nickel, while a small increase of risk was demonstrated for health care workers. In men, only farmers had an increased risk of nickel allergy.

DISCUSSION

In our study, nickel positivity decreased significantly only in the young female group (≤ 25 years) in patch tests performed after 2002 (compared with previous tests performed in 1997–2001), while the

TABLE 1 Sensitization to nickel in age classes and calendar years in females and males

Years	Females			Total			Males			Total		
	≤25	26-35	36-45	46-55	56-65	>65	≤25	26-35	36-45	46-55	56-65	>65
	(n = 3270)	(n = 3996)	(n = 3495)	(n = 2947)	(n = 2432)	(n = 2349)	(n = 18489)	(n = 1556)	(n = 1881)	(n = 1624)	(n = 1446)	(n = 1106)
1997-2001	%	39.97	48.44	36.38	19.17	13.61	33.7	9.67	11.65	11.68	7.55	8.99
	(n = 586)	(n = 945)	(n = 501)	(n = 292)	(n = 166)	(n = 132)	(n = 2622)	(n = 64)	(n = 105)	(n = 75)	(n = 45)	(n = 41)
OR	1	1	1	1	1	1	1	1	1	1	1	1
2002-2006	%	29.09	45.74	43.35	34.3	23.56	33.6	10.92	15.18	13.25	12.34	10.85
	(n = 210)	(n = 397)	(n = 336)	(n = 202)	(n = 135)	(n = 69)	(n = 1349)	(n = 39)	(n = 70)	(n = 55)	(n = 39)	(n = 23)
OR	0.62	0.9	1.34	1.53	1.3	1.04	1.15	1.36	1.15	1.72	1.5	1.09
95% CI	0.51-0.75	0.76-1.05	1.12-1.60	1.24-1.90	1.01-1.7	0.76-1.42	0.75-1.74	0.98-1.88	0.8-1.68	1.09-2.71	0.90-2.50	0.64-1.88
2007-2011	%	28.59	43.55	48.32	37.3	21.4	34.62	10.12	13.14	12.22	11.68	10.71
	(n = 187)	(n = 331)	(n = 388)	(n = 251)	(n = 125)	(n = 74)	(n = 1356)	(n = 34)	(n = 46)	(n = 43)	(n = 34)	(n = 24)
OR	0.6	0.82	1.63	1.75	1.15	1.27	1.05	1.15	1.05	1.22	1.22	1.21
95% CI	0.49-0.73	0.69-0.97	1.37-1.95	1.42-2.15	0.88-1.49	0.93-1.74	0.68-1.63	0.79-1.66	0.70-1.57	1.01-2.59	0.71-2.1	0.71-2.07
2012-2016	%	23.36	45.8	44.44	44.01	25.67	34.14	10.45	10.06	15.81	12.76	12.94
	(n = 100)	(n = 191)	(n = 240)	(n = 235)	(n = 105)	(n = 76)	(n = 947)	(n = 21)	(n = 17)	(n = 34)	(n = 31)	(n = 26)
OR	0.46	0.9	1.4	2.31	1.46	1.3	1.09	0.85	1.42	1.79	1.83	1.18
95% CI	0.36-0.59	0.72-1.11	1.14-1.71	1.86-2.87	1.10-1.92	0.96-1.77	0.64-1.83	0.49-1.46	0.92-2.2	1.10-2.90	1.06-3.16	0.67-2.08
Average							33.93%					11.06%

Note: Odds ratios (OR) and 95% confidence Intervals (95% CI) are calculated with the years 1997-2001 as reference category. Significant values are in bold.

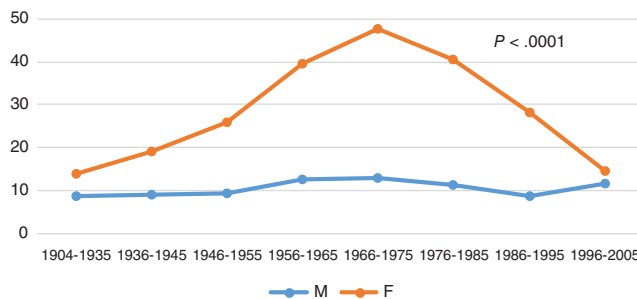


FIGURE 1 Percentage of sensitization to nickel sulfate by birth years

prevalence remained high in older women. This confirms results from other countries where the national directives came in to force during the 1990s.¹¹⁻¹⁴ Persistence of nickel sensitivity in older women was also seen by Garg et al in 2013 and Thyssen in 2011.^{7,14}

The analysis of nickel sensitization in women according to birth years can better illustrate the effect of EU legislation. We found a progressive increase in nickel sensitization in women born after 1935, reaching a peak in those born between 1966 and 1975, probably in relation to higher nickel exposure before 2000. Women born after 1975 showed a decrease in nickel sensitization reaching values (14.6%) similar to men (11.7%) in the last birth years considered (1996–2005). The low prevalence of sensitization to nickel can be considered as the first noticeable effect of the EU directive, reducing nickel exposure and subsequent sensitization in young women.

Moreover, the higher percentages of nickel sensitization in middle-aged Italian women is possibly related to higher nickel exposure due to the late implementation of the EU directive 94/27/CE. In fact, countries where nickel in jewellery was limited or labelled previously nowadays have a lower sensitization prevalence in both genders, both in patients with dermatitis and in the general population.^{2,14,15}

Nickel sensitization in Italian men was quite stable, but with a higher prevalence compared to men in other EU countries.⁷ This sensitization can be due to contact with metal objects, such as belt buckles and wrist watches, which were the principal causes in men of nickel sensitization.¹² It is possible that in Italy, the warm climate can increase sweating with a possible higher release of nickel ions from nickel containing objects in contact with the skin.¹⁶ Moreover, the main reason for the continuing high prevalence of nickel allergy, especially in southern Europe, may be related to cultural aspects (ie, piercing of babies), but also to a lack of control, surveillance, and information campaigns.¹⁷

Some authors analysed nickel sensitization in relation to occupational exposures, piercings, and smoking habits.^{4,5,8,9} Our analysis did not confirm an occupational role, except for male farmers, who are probably exposed to metal tools used during different work tasks, and for females who work in health care and women involved in mechanical tasks. Shum et al in 2003¹⁸ analysed occupational contact dermatitis to nickel in the UK, finding some categories in which sensitization to nickel was believed to be job related (eg., hairdressers, bartenders, cooks, etc.);

however, they did not compare nickel sensitization in these professions with a reference category, neither they did look at the presence of nickel-releasing items at work. The authors concluded that the clinical relevance of occupational exposure to nickel can only be assessed if workplace measurements are possible. More recently, Wennervaldt et al¹⁹ demonstrated the presence of nickel in metallic items in the workplace and in nurse's hands after 30 minutes of normal work using the dimethylglyoxime test. Our study confirmed a significant increase in nickel sensitization in female nurses compared to clerks.

The lack of association between male workers highly exposed to nickel (mechanics, manufactures of metals and metal machinery) and sensitization to this metal could suggest a protective role of high exposure in inducing immunological tolerance to this metal,^{20,21} while women, probably already sensitized to nickel, can develop symptoms when exposed to metals during work. However, this is only a hypothesis that needs confirmation by additional studies.

In conclusion, EU regulatory intervention introduced in Italy since 2000 produced a significant reduction in nickel sensitization only in young female born after 1995. This age group needs to be followed-up to verify the downward trend in nickel sensitization trend. Nickel allergy remains a problem in older women due to the persistence of allergy, but also in men who are more often sensitized compared to other countries. More efforts are needed to improve metal objects and tools to avoid nickel release and to reduce nickel sensitization in the Italian population.

CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Basso P, Mauro M, Miani A, Belloni Fortina A, Corradin MT, Larese Filon F. Sensitization to nickel in the Triveneto region: Temporal trend after European Union regulations. *Contact Dermatitis.* 2020;82:247-250. <https://doi.org/10.1111/cod.13450>

Systemic allergic dermatitis presenting as acute generalized exanthematous pustulosis due to betamethasone sodium phosphate

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KEYWORDS: acute generalized exanthematous pustulosis, betamethasone disodium phosphate, case report, corticosteroids, dexamethasone-21-phosphate disodium, patch test, severe cutaneous adverse drug reaction

Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse drug reaction characterized by generalized erythematous eruption with small, non-follicular, sterile pustules associated with fever and neutrophilia. The reaction is caused by drugs, mainly

beta-lactam and macrolide antibiotics, in at least 90% of cases.¹ We report a case of AGEP following systemic administration of betamethasone sodium phosphate in a patient contact sensitized to dexamethasone-21-phosphate disodium contained in eye drops.

Online supplemental Table 1. Population characteristics. All values are expressed as a percentage (%). Values in bold are statistically significant ($P < .05$).

	Male (32,3)		Female (67,7)	
	+	-	+	-
Patch test for nickel sulfate 5.0%	11.1	88.9	33.9	66.1
Occupational	10.5	9.2	7.9	6.2
Age (mean $\pm$ SD)	41.9 $\pm$ 16.9	43.3 $\pm$ 17.7	39.0 $\pm$ 14.4	45.1 $\pm$ 18.4
Atopic dermatitis	7.2	6.7	6.4	7.6
Hand	35.0	33.7	31.1	29.0
Leg	7.4	8.1	5.3	5.8
Face	11.2	10.3	18.7	18.9
Age > 40 years	48.5	53.2	43.2	58.0

Online supplemental Table 2. Prevalence of nickel sensitization (number and %) in the occupational groups and association between nickel sensitization and occupation by gender. The odds ratios (OR) and 95% confidence intervals (CI) are adjusted by age and personal and family history of atopy, with office workers as reference category. Statistically significant results are highlighted in bold.

Occupation	Women			Men		
	N (%)	OR	95%CI	N (%)	OR	95%CI
Office workers	1844 (38.1)	1		237 (11.3)	1	
Health care workers	883 (40.4)	1.1	1.0-1.23	71 (12.6)	1.15	0.9-1.5
Metal & mechanical workers	203 (47.9)	1.5	1.2-1.83	77 (9.1)	0.89	0.60-1.04
Agriculture	32 (32.0)	0.81	0.53-1.24	23 (17.3)	1.68	1.1-2.7