

Prevalence of contact allergy to metals: nickel, palladium, and cobalt in Southern Sweden from 1995–2016

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Funding information

the Swedish Asthma and Allergy Association's Research Foundation

Abstract

Background: In 2001, the EU nickel directive was introduced to prevent contact allergy to nickel. Contact allergy to palladium and/or cobalt is often seen together with contact allergy to nickel.

Objectives: To compare the contact allergy prevalence of nickel, palladium, and cobalt allergy before and after the introduction of the EU nickel directive in consecutive patients with dermatitis.

Methods: A retrospective analysis of patch test results from 1995–2016 was performed (n = 18 264). Chi-square tests were used to examine trends for nickel, palladium, and cobalt across test years. Logistic regression was used for associations.

Results: The prevalence of nickel allergy decreased significantly in the youngest age group (6–30 years) for both female and male patients from 1995–1999 to 2012–2016: females: 33.4% to 19.1% ($P < .001$); males: 5.9% to 2.1% ($P < .05$). The concomitant reactions between nickel and palladium and nickel and cobalt among young females, respectively, also decreased significantly. Isolated palladium and cobalt allergy remained stable (1.4% and 2.3%, respectively) during the same time period for both men and women.

Conclusions: The prevalence of nickel has decreased among young females and males suspected of contact allergy in Southern Sweden after the introduction of the EU nickel directive. There has been no change in isolated palladium or cobalt allergy.

KEYWORDS

cobalt, delayed hypersensitivity, metal contact allergy, nickel, nickel directive, palladium, prevention

1 | INTRODUCTION

Metal allergy has for a long time been, and is still, the most frequent contact allergy. Among the metals, nickel is the most common contact allergen, with a prevalence of 10%–20% among women in the general population in Europe.¹ In 1990 the first National Nickel Regulation in Sweden came into force, regulating content of nickel in earrings or

piercing posts.² The first European nickel directive was later adopted in 1994 and came into force in 2001. The directive limited the rate of nickel release from products intended to come into direct and prolonged contact with the skin.³ In 2004, the directive was revised and the limit for post assemblies used in pierced holes was lowered.⁴ The directive is since 2009 part of the registration, evaluation, authorisation and restriction of chemicals (REACH) regulation.

Nickel sulfate hexahydrate (NiSO_4) is the most common nickel salt used when patch testing with nickel. In the European baseline series, NiSO_4 is tested at 5% w/w in pet. Positive patch test reactions to palladium salts are very often concomitant to positive patch test reactions to NiSO_4 . Nickel and palladium belong to the same group in the periodic table, and the concomitant reactions have mainly been explained by cross-reactivity.⁵⁻⁹

Today, palladium is used primarily for industrial catalysts in cars, dental appliances, and in jewelry. The main source from which the general population is sensitized to palladium is dental appliances (WHO 2002). Palladium is not routinely tested for in the European baseline series, but testing is often performed in dental series. Patch testing with palladium chloride (PdCl_2) has been the standard test for detecting palladium sensitization since the 1990s. In 2008, Muris et al showed that sodium tetrachloropalladate (Na_2PdCl_4) is a better test salt for detecting palladium sensitization.¹⁰ The prevalence of palladium allergy has increased since the 1990s,¹¹ but the prevalence of palladium sensitization might have been underestimated when using PdCl_2 as a test salt. In Malmö, the extended baseline series used for patch testing all patients included PdCl_2 since 1995 and Na_2PdCl_4 since 2009.

Not only are concomitant reactions between NiSO_4 and PdCl_2 common, but also concomitant patch test reactions of NiSO_4 and cobalt chloride (CoCl_2).¹² Cobalt does not belong to the same group as nickel and palladium in the periodic table but coexists with nickel in nature, which is why cobalt is present in many nickel alloys. Concomitant patch test reactions to CoCl_2 and NiSO_4 have thus more often been described as co-sensitivity rather than cross-sensitivity.¹³ Today cobalt without nickel is used in many different consumer articles such as electronic devices, jewelries, magnetic materials, dental alloys, and in pigments in cosmetics and leather.¹⁴⁻¹⁶

Because of the European nickel directive it has been suggested that metals such as cobalt and palladium could replace nickel in consumer items, and although the prevalence of nickel hopefully would decrease, it has been questioned whether the prevalence of palladium and cobalt allergy would increase.¹⁷⁻²⁰ The aim of this study was to determine the prevalence of sensitization among men and women to nickel, palladium, and cobalt in Southern Sweden from 1995–2016, the period when the European nickel directive came into force and was revised.

2 | METHODS

All patients patch tested with the extended baseline series as well as the Swedish baseline series because of suspected contact allergy at the Department of Occupational and Environmental Dermatology, Skåne University Hospital, Malmö, Sweden, between 1995 and 2016 (both years included) were included in this study.

2.1 | Patch testing and patch test readings

During the study period, palladium has been patch tested as PdCl_2 2.0% pet. since 1995 and as Na_2PdCl_4 3.0% pet. since 2009. Nickel

has been patch tested as NiSO_4 5.0% pet. and cobalt as CoCl_2 0.5% pet. (Na_2PdCl_4 was obtained from Sigma Aldrich, Darmstadt, Germany, PdCl_2 , NiSO_4 and CoCl_2 from Chemotechnique Diagnostics, Vellinge, Sweden.) The patch test preparations were applied on the upper back of the patients with 20 mg in 8 mm Finn Chambers (Epitest, Tuusula, Finland or SmartPractice, Phoenix, Arizona) mounted on Scanpor tape (Norgeplaster, Oslo, Norway). The patch tests were removed on day (D) 2. During the years that are included in this study, standardization of the patch test technique has been performed, thus the doses used today are significantly better standardized than the doses used in 1995.

Patch test readings were performed by a dermatologist on D3/4 and on D7 according to the classification suggested by the International Contact Dermatitis Research Group.²¹ In Malmö all patch test data and basic characteristics of the patients are filed in our computer system DALUK. All irritant and doubtful reactions were classified as negative reactions. Positive reactions include +, ++, and +++ reactions.

2.2 | Ethics

The study was approved by the Regional Ethical Review Board, Lund, Sweden, Dnr 2015/491. When patients are patch tested, they are informed that data may be used for comparisons on a group level and approval is mandatory if the patients' data are stored in the computer system. To provide full information to the patients for this study and enable the possibility to opt out, an advertisement was published in the local newspaper that data from 1995–2016 would be used for a study of metal allergy in Southern Sweden. Nobody declined to participate.

2.3 | Definitions and statistics

We have only analyzed metal allergies; thus, individuals may possibly have had other contact allergies. In the following text and in the results "isolated" palladium- or cobalt allergy means palladium/cobalt allergy without concomitant nickel allergy and *not* considering any other allergy. Isolated nickel allergy means nickel allergy without palladium and/or cobalt allergy, not considering any other allergy. Palladium allergy "in total" means positive reactions to Na_2PdCl_4 and/or PdCl_2 with or without concomitant nickel reactions.

A chi-square test of linear-by-linear association was used to show significant trends of nickel, palladium, and cobalt allergy across test years. Fisher's exact test was used to examine the distribution of gender among the isolated patch test reactions to palladium, nickel, and cobalt. Two binary logistic regression models were performed to ascertain the effect on age and test year on the likelihood that women were allergic to nickel or palladium. Two different binary logistic regressions models were used, one with nickel as the dependent variable and age group, test year, and cobalt allergy as the independent variables; and one model with palladium allergy as the dependent variables and with age group, test year, and nickel allergy as the

independent variables. All results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). All analysis was performed in SPSS, version 22. A *P*-value <.05 was considered statistically significant.

3 | RESULTS

Eighteen thousand three hundred six patients were patch tested between 1995 and 2016 at the Department of Occupational and Environmental Dermatology, Skåne University Hospital, Malmö, Sweden. Eleven thousand seven hundred twenty-three women (W) and 6541 men (M) (Figure 1). (Forty-two individuals were not registered as either male or female and were excluded from the data.) Mean age for the study population was 44.3 years (range 6–99 years). Mean age among women was 44.3 years (range 8–99 years) and mean age among men was 44.1 years (range 6–92 years). The prevalence of contact allergy in women and men to the four metal salts during the study period is shown in Figure 2. A positive patch test reaction to nickel was observed in 20.5% of the study population; 89.8% of the positive reactions were seen in women and 10.2% in men. Among the females, 13.8% had an isolated nickel allergy, whereas 3.2% of the males had an isolated nickel allergy (Fisher's exact test, *P* < .001). A positive patch test reaction to either PdCl₂ or Na₂PdCl₄, or both, was seen in 9.8% of the study population. Women displayed 89.5% of the positive reactions and men displayed 10.5%. Regarding isolated palladium allergy, more females (1.6%) than males (1.0%) had an isolated palladium allergy (Fisher's exact test, *P* < .005). Positive reactions to cobalt were observed in 7.5% of the study population, 80.3% of the reactions in females and 19.7% in males. There was no association between gender and isolated cobalt allergy. An isolated cobalt allergy was found in 2.2% of the females and 2.6% of the males (Fisher's exact test, *P* > .3).

The overall prevalence of nickel allergy among women decreased from 29.6% in 1995–1999 and to 24.8% in 2012–2016 (*P* < .001) (Table 1). Regarding age groups, the difference was only significant among the youngest females (age 8–30). In 1995–1999, the prevalence among young females was 33.4% and in 2012–2016 it was 19.1%. For the older age groups (31–60 and 61–99) the prevalence was stable. The table 1 also visualizes that the youngest females had the highest nickel prevalence in the 1990s and the lowest nickel prevalence in 2012–2016. The prevalence of cobalt allergy together with nickel allergy decreased during the study period for the youngest and middle-aged women, but the tendency for women to have isolated cobalt allergy remained the same.

As seen in Table 1, the prevalence of PdCl₂ allergy followed the same trend as nickel allergy. The largest difference between test years was found among the youngest females. In this group the prevalence of PdCl₂ allergy was 16.0% in 1995–1999 and decreased to 9.1% in 2012–2016. Table 1 also shows that the prevalence of isolated PdCl₂ allergy was stable for all women during the entire study period. That means that only PdCl₂ allergy together with a nickel allergy (concomitant reactions) has decreased among young females. When exploring

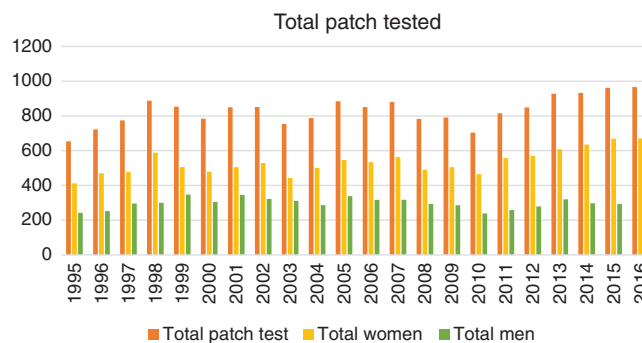


FIGURE 1 Total number of patients who were patch tested at the Department of Occupational and Environmental Dermatology, Skåne University Hospital, Malmö, Sweden. All patients were suspected to have contact allergy

the total prevalence of palladium, considering both PdCl₂ and Na₂PdCl₄, there was still a decrease of palladium allergy among young females from 1995–1999 to 2012–2016, but an increase in prevalence among the oldest women from 7.4% to 13.6% (*P* < .001) from 1995–1999 to 2012–2016.

The results for men are not shown in Table 1, but we did find a decrease in nickel prevalence among younger men age 6–30 years, from 5.9% in 1995–1999 to 2.1% in 2012–2016 (*P* = .027). For the other age groups the prevalence remained stable during the study period. Isolated cobalt allergy in men also remained stable during the study period (2%–4%). The prevalence of PdCl₂ positivity among men was stable for all age groups during the time period. For young men the prevalence in 1995–1999 was 2.3% and in 2012–2016, 1.5%, although the decrease was not statistically significant.

Addressing women, a logistic regressions analysis with nickel as the dependent variable and age group, test year, and cobalt allergy as independent variables (Table 2) showed that the prevalence of nickel allergy was not only dependent on age group but also dependent on test year. When adjusted for age, women in 2012–2016 were still significantly less likely (odds ratio [OR] 0.87, confidence interval [CI] 0.77–0.99) to have nickel allergy than in 1995–1999 (1.0, reference). The association between nickel and cobalt allergy remained the same after adjustment for age and test year. The odds to have nickel allergy if allergic to cobalt was approximately 10 times higher than if not allergic to cobalt.

A similar regression analysis with PdCl₂ as the dependent variable and age group, test year, and nickel allergy as independent variables (Table 2b) showed that the prevalence of palladium allergy was dependent on age group and nickel allergy. Individuals with nickel allergy were approximately 36 times more likely to have palladium allergy compared to individuals who were not allergic to nickel.

4 | DISCUSSION

We investigated the prevalence of nickel, palladium, and cobalt allergy before and after the EU nickel directive and the revision coming into

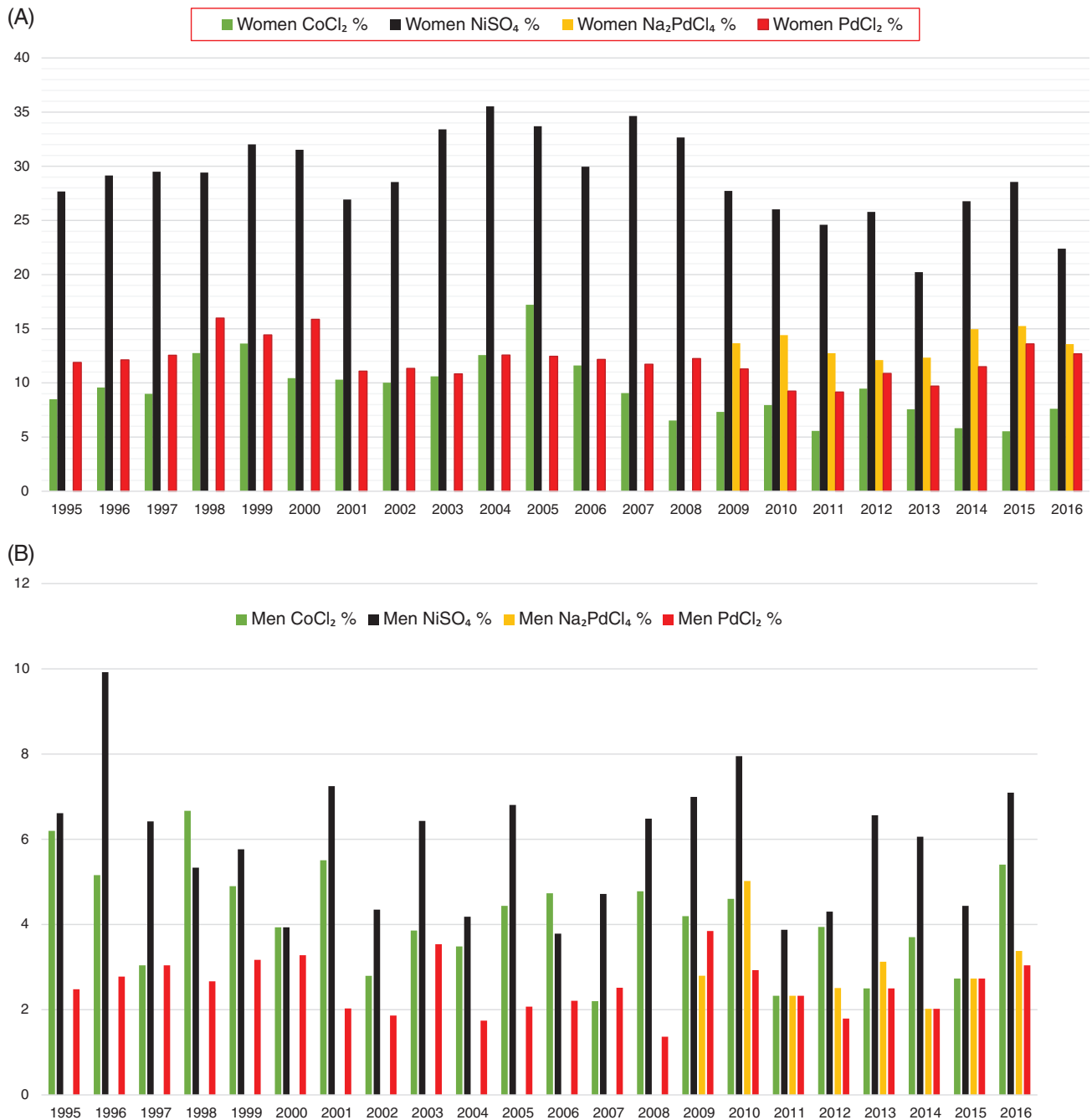


FIGURE 2 The prevalence of contact allergy to nickel, palladium, and cobalt among 11 723 female patients (A) and 6541 male patients (B). All patients were suspected to have contact allergy and were patch tested between 1995 and 2016 at the Department of Occupational and Environmental Dermatology, Skåne University Hospital, Malmö, Sweden

force in 2001 and 2004, respectively. Before the EU nickel directive came into force, there had been a Swedish nickel affecting nickel concentrations in consumer items on the Swedish market already in the 1990s. The highest prevalence of nickel contact allergy in 1995–1999 was found among young females (age 8–30 years). They had been exposed to nickel during 1970–1990, a period when nickel was a common metal in many consumers items that were in repeated or prolonged contact with the skin, such as wrist watches, belt buckles, and jewelries. During 1995–2015 the

general population increased from 1 111 731 persons in 1995 to 1 303 627 in 2015 in Skåne (Regionsfakta.com) and the number of patients referred for patch testing for suspected contact allergy was also increasing (Figure 1). However, we found a significant decrease in the nickel prevalence in the youngest female age group from 33.4% in 1995–1999 to 19.4% in 2012–2016. The prevalence in the older age groups remained stable, probably due to exposure and sensitization to nickel prior to when the nickel directive came into force. Our regression analysis confirmed these findings by showing that the likelihood

TABLE 1 Patch test results to nickel and cobalt among 11 723 female patients suspected to have contact allergy at the Department of Occupational and Environmental Dermatology, Skåne University Hospital, Malmö, Sweden, stratified by test year and age group

	Test years, % (positive/total tested)			
Women	1995–1999	2000–2011	2012–2016	P-value
Nickel allergy				
All age groups	29.6 (727/2454)	30.4 (1861/6117)	24.8 (781/3152)	<.001
6–30 years	33.4 (213/637)	29.0 (452/1561)	19.1 (141/738)	<.001
31–60 years	30.7 (442/1438)	33.8 (1190/3525)	29.0 (498/1717)	.21
61–99 years	19.0 (72/379)	21.2 (219/1031)	20.3 (142/697)	.72
Cobalt allergy				
All age groups	10.9 (267/2454)	10.0 (609/6117)	7.1 (225/3152)	<.0001
6–30 years	11.9 (76/637)	9.2 (144/1561)	5.3 (39/738)	<.0001
31–60 years	10.6 (152/1438)	11.1 (393/3525)	8.0% (138/1717)	.01
61–99 years	10.3 (39/379)	7.0 (72/1031)	6.9 (48/697)	.08
Concomitant nickel and cobalt allergy				
All age groups	8.6 (210/2454)	7.9 (481/6117)	4.8 (152/3152)	<.001
6–30 years	10.4 (66/637)	7.6 (118/1561)	3.4 (25/738)	<.001
31–60 years	8.0 (115/1438)	9.0 (319/3525)	6.0 (103/1717)	.02
61–99 years	7.7 (29/379)	4.3 (44/1031)	3.4 (24/697)	.003
Isolated cobalt allergy				
All age groups	2.3 (57/2454)	2.1 (128/6117)	2.3 (73/3152)	.95
6–30 years	1.6 (10/637)	1.7 (26/1561)	1.9 (14/738)	.63
31–60 years	2.6 (37/1438)	2.1 (74/3525)	2.0 (35/1717)	.32
61–99 years	2.6 (10/379)	2.7 (28/1031)	3.4 (24/697)	.39
Palladium chloride allergy				
All age groups	13.6 (333/2454)	11.7 (713/6117)	11.7 (370/3152)	.05
6–30 years	16 (102/637)	11.2 (175/1561)	9.1 (867/738)	<.001
31–60 years	14.1 (203/1438)	13.1 (462/3525)	13.7 (236/1717)	.81
61–99 years	7.4 (28/379)	7.4 (76/1031)	9.6 (67/697)	.13
Concomitant nickel and palladium chloride allergy				
All age groups	12.5 (306/2454)	10.5 (643/6117)	10.3 (326/3152)	.02
6–30 years	14.8 (94/637)	10.3 (161/1561)	8.0 (59/738)	<.001
31–60 years	13.2 (190/1438)	12.0 (422/3525)	12.5 (215/1717)	.61
61–99 years	5.8 (22/379)	5.8 (60/1031)	7.5 (52/697)	.21
Isolated palladium chloride allergy				
All age groups	1.1 (27/2454)	1.1 (70/6117)	1.4 (44/3152)	.29
6–30 years	1.3 (8/637)	0.9 (14/1561)	1.1 (8/738)	.78
31–60 years	0.9 (13/1438)	1.1 (40/3525)	1.2 (21/1717)	.4
61–99 years	1.6 (6/379)	1.6 (16/1031)	2.2 (15/697)	.42
Palladium allergy incl. Na ₂ PdCl ₄ and PdCl ₂				
All age groups	13.6 (333/2454)	13.1 (799/6117)	15.0 (472/3152)	.09
6–30 years	16.0 (102/637)	12.6 (196/1561)	11.0 (81/738)	.006
31–60 years	14.1 (203/1438)	14.5 (512/3525)	17.2 (296/1717)	.012
61–99 years	7.4 (28/379)	8.8 (91/1031)	13.6 (95/697)	<.001

of having nickel allergy depends not only on age but also on test year. The likelihood was higher in 1995–1999 than in 2012–2016, which most certainly depends on the nickel directive.

Other European studies demonstrate similar data. In Denmark, two similar studies have been performed: one shows a decreasing nickel prevalence among young females (5–30 year) from 25.1% in 1985–1990 to 18.3% in 2002–2007¹² and the other from Odense shows decreasing nickel prevalence among young females (2–30 years) from 29.8% in 1992–1997 to 19.6% in 2004–2009.²² In Germany, results from the Information Network of Departments of Dermatology (IVDK) showed that the nickel allergy among females 1–44 years had decreased significantly from 2005–2012.²³ Data from the UK and Italy show similar results.²⁴

Our results are very much in line with the observed reduced nickel release from consumer items on the Swedish market. In 1999, 25% of consumer items had nickel release that was too high according to the EU nickel directive.²⁵ This was reduced to 9% in 2010.²⁶ The limit for

items in prolonged contact with the skin is 0.5 $\mu\text{g}/\text{cm}^2/\text{week}$ and for post assemblies 0.2 $\mu\text{g}/\text{cm}^2/\text{week}$. Investigated items were all items meant to be in prolonged contact with the skin such as cheap watches and jewelries, sewing material, zippers, and buttons on the Swedish market.²⁶ It is most likely that the Swedish nickel regulation and the EU nickel directive have had an effect on the decrease in nickel allergy among young people with dermatitis, but owing to the fact that there are still items on the market that release too much nickel, the prevalence is still high, 19.1%, among young females. Daily living habits have changed over the past 20 years and what needed to be controlled in the 1990s was especially nickel in ear piercings, whereas today the source of nickel exposure may have changed.²⁷ The REACH regulation is still only controlling items that are meant to be in prolonged contact with the skin, where “prolonged contact” is defined as 10 minutes on three or more occasions within 2 weeks, or 30 minutes on one or more occasions within 2 weeks.²⁸ This means that the regulation does not control the amount of released nickel from items meant to have short

TABLE 2 Prevalence of positive patch test results to nickel (A) and palladium (B) among 11 723 female patients tested at the Department of Occupational and Environmental Dermatology, Skåne University Hospital, Malmö, Sweden from 1995 to 2016. The results are stratified by age group

(A)			
	Nickel allergy % (positive/ total number tested)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age groups			
6–30 years	27.5 (806/2936)	0.81 (0.73–0.89)	0.82 (0.74–0.91)
31–60 years	31.9 (2130/6680)	1.0 (reference)	1.0 (reference)
61–99 years	20.6 (433/2107)	0.55 (0.49–0.62)	0.56 (0.50–0.64)
Test year			
1995–1999	29.6 (727/2454)	1.0 (reference)	1.0 (reference)
2000–2011	30.4 (1861/6117)	1.04 (0.94–1.15)	1.08 (0.97–1.21)
2012–2016	24.8 (781/3152)	0.78 (0.70–0.88)	0.87 (0.77–0.99)
Cobalt allergy			
Negative	21.5 (2526/10622)	1.0 (reference)	1.0 (reference)
Positive	76.6 (843/1101)	10.47 (9.05–12.12)	10.37 (8.95–12.01)
(B)			
	Palladium (PdCl ₂) allergy % (positive/ total number tested)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age groups			
6–30 years	11.7 (344/2936)	0.85 (0.75–0.97)	0.98 (0.84–1.15)
31–60 years	13.5 (901/6680)	1.0 (reference)	1.0 (reference)
61–99 years	8.1 (171/2107)	0.57 (0.48–0.67)	0.81 (0.66–0.98)
Test year			
1995–1999	13.6 (333/2454)	1.0 (reference)	1.0 (reference)
2000–2011	11.7 (713/6117)	0.84 (0.73–0.97)	0.77 (0.65–0.90)
2012–2016	11.7 (370/3152)	0.85 (0.72–0.99)	1.03 (0.85–1.24)
Nickel allergy			
Negative	141/8354	1.0 (reference)	1.0 (reference)
Positive	1275/3369	35.47 (29.61–42.48)	35.7 (29.78–42.80)

contact with the skin such as coins or tools in the home environment, including laptop computers. Such items have shown to release nickel ions to the skin surface by one single touch and can lead to accumulated nickel doses on the skin.^{29,30} Today, every household most likely has at least one tablet or laptop, and new regulations might therefore be needed. Furthermore, the REACH Regulation only controls items imported to and bought in Europe, which means that items bought privately outside Europe can be a problem. In the general population in Sweden there is a high number of immigrants from all over the world, which means that some patients might have been sensitized to nickel outside Europe, before they immigrated to Sweden. The above-mentioned limitations in the REACH Regulation could, together with the still high amount of nickel-containing cheap jewelries, hair clips, and so on, on the Swedish market, explain why the prevalence of nickel allergy among young females with dermatitis still is as high as 19.1%. In this study, hand dermatitis and atopy were not included as a variable in the regression analysis because the data were not retrievable from the database during the entire time period investigated.

Concerning palladium, this is the first study where the prevalence of Na_2PdCl_4 sensitization over time in a patch-tested dermatitis population is studied. We found the prevalence to be approximately 10% and stable over 8 years (2009–2016). The prevalence of PdCl_2 sensitization was investigated during a longer period, in which the nickel directive came into force. As the concomitant reaction between NiSO_4 and PdCl_2 had been an ongoing debate, we found it interesting to look at the prevalence of PdCl_2 together with the prevalence of NiSO_4 . We found that the prevalence of PdCl_2 sensitization had decreased among the youngest females, hence following the prevalence of nickel sensitization. We also found that there was an increased likelihood of palladium allergy if a person was nickel allergic. When looking at the prevalence of Na_2PdCl_4 and PdCl_2 together we saw that the prevalence of palladium allergy increased among the older females from 1995–1999 to 2012–2016. We think this increase is due to the introduction of Na_2PdCl_4 as test salt for palladium in 2009, and not a result of increased palladium allergy. In previous European studies in patients with dermatitis, the patch test substance has been 1% PdCl_2 pet., while we used 2% in pet. Still we do not find a higher prevalence of PdCl_2 sensitization. The prevalence of PdCl_2 sensitization in different European populations has been reported to be 5.3%–13%.^{20,31–35} In the United States, the sensitization to PdCl_2 2% in pet. was 12.1% in the period from 1997–2006.³⁶

The prevalence of nickel and PdCl_2 allergy in Southern Sweden follows the prevalence seen in many other European countries. In contrast, the prevalence of positive reaction to Na_2PdCl_4 is more divergent among the European countries. The prevalence of positive reactions to Na_2PdCl_4 3% pet. was investigated in patients undergoing routine diagnostic testing in European clinics (including Malmö) in 2011–2012,³⁷ and large differences in the prevalence between the clinics were found. Basel and Amsterdam had a prevalence of more than 30%, whereas Leuven and Barcelona had a prevalence of 16% and 20%, respectively. Malmö had the lowest prevalence, 11%, together with Odense at 12%.³⁷ In the aforementioned study, isolated palladium allergy was associated with dental alloys.³⁷ Palladium is

used in different dental alloys and the use varies between countries as to whether it is used and to what extent. In Sweden the most common dental alloy is chrome-cobalt alloys³⁸ which could explain why we have much lower prevalence of palladium sensitization in Sweden. However, it does not explain why Swedish women are more sensitized to palladium than Swedish men, compared to the findings in other European countries, where the prevalence of isolated palladium allergy was the same among genders.³⁷ From earlier studies we know that the intensity of patch test reactions to NiSO_4 varies over time. This means that a person with a reaction to nickel by a later test occasion only gets a weak reaction or no reaction at all and then again later at another test occasion gets a positive reaction again.^{39,40} The individuals who show an isolated palladium allergy could therefore actually have nickel allergy with a false-negative nickel reaction on a particular test occasion and the positive reaction to palladium could thus still reflect cross-sensitization. New results have suggested that isolated reactions to Na_2PdCl_4 can be false positive in aluminium-sensitized persons due to contaminating aluminium from aluminium patch test chambers. (Y. Hedberg, personal communication 2019).

In contrast to nickel and palladium, the prevalence of isolated cobalt allergy was similar among genders in our study, which might reflect that dental alloys can be a cause of exposure for cobalt and thus a reason for isolated cobalt allergy in Southern Sweden. Concomitant reaction to either palladium or cobalt is common in persons who patch tested positive to nickel. Cross-reaction between nickel and palladium has been the general explanation to the concomitant reaction between nickel and palladium.^{5–9} The fact that cobalt is often found in nickel alloys makes it possible to be sensitized to nickel and cobalt simultaneously.¹³ Especially nickel can activate T cells through different immunological pathways, which means that a small amount of nickel in a cobalt alloy can enhance the response to cobalt,⁴¹ and that some other nickel-recognizing T cells react when stimulated with palladium.⁸ This is a synergistic effect of metal allergens, and reflects what we saw in our results, namely, that the overall reactions to PdCl_2 and CoCl_2 decreased together with the decreasing prevalence of nickel allergy. The fact that isolated allergy to palladium and cobalt remained stable during the same time period is interesting, since this might indicate different sensitization routes. That there might be interference with patch test technique does, however, underscore the importance of further studies.

In conclusion, contact allergy to nickel has decreased in Southern Sweden from 1995 to 2016 among young patients, both men and women, age 6–30 years, suspected to have contact dermatitis. Today the prevalence of nickel allergy among younger female is 19.1%, which still makes it the most common contact allergy. The REACH regulation seems to have had an impact on the decrease in nickel allergy. The enigma of a continued high prevalence of contact allergy, especially in females, emphasizes the need for further studies on the impact of nickel allergy. The prevalence of concomitant reactions between nickel and palladium and nickel and cobalt followed the prevalence of nickel allergy among women, whereas the isolated allergies to palladium and to cobalt remained stable during the same time period. In Southern Sweden, women are still more often allergic to

nickel and to palladium, whereas isolated cobalt allergy seems to be equally distributed among genders.

CONFLICTS OF INTEREST

None relevant to declare.

ACKNOWLEDGEMENTS

The authors would like to thank Cecilia Tillman, MD and Malin Engfeldt, Ass. Professor, for their help in the initiation of this project. The study was supported from grants from the Swedish Asthma and Allergy Association's Research Foundation.

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REFERENCES

- Diepgen TL, Ofenloch RF, Bruze M, et al. Prevalence of contact allergy in the general population in different European regions. *Br J Dermatol*. 2016;174:319-329.
- General advice regarding ear piercing. National Board of Health and Welfare SOSFS. 1989; 40 (in Swedish).
- European Parliament and Council Directive 94/27/EC. *Off J Eur Union*. 1994;L-188:1-2.
- Commission Directive 2004/96/EC of September 27, 2004 amending Council Directive 76/769/EEC as regards restrictions on the marketing and use of nickel for piercing post assemblies for the purpose of Adapting its Annex I to technical progress. *Off J Eur Union*. 2004.
- Wahlberg JE, Boman AS. Cross-reactivity to palladium and nickel studied in the Guinea pig. *Acta Derm Venereol*. 1992;72:95-97.
- Hindsén M, Spirén A, Bruze M. Cross-reactivity between nickel and palladium demonstrated by systemic administration of nickel. *Contact Dermatitis*. 2005;53:2-8.
- Pistoors FH, Kapsenberg ML, Bos JD, Meinardi MM, von Blomberg ME, Scheper RJ. Cross-reactivity of human nickel-reactive T-lymphocyte clones with copper and palladium. *J Invest Dermatol*. 1995;105:92-95.
- Moulon C, Vollmer J, Weltzien HU. Characterization of processing requirements and metal cross-reactivities in T cell clones from patients with allergic contact dermatitis to nickel. *Eur J Immunol*. 1995;25:3308-3315.
- Bordignon V, Palamara F, Cordiali-Fei P, et al. Nickel, palladium and rhodium induced IFN-gamma and IL-10 production as assessed by in vitro ELISpot-analysis in contact dermatitis patients. *BMC Immunol*. 2008;9:19.
- Muris J, Kleverlaan CJ, Rustemeyer T, et al. Sodium tetrachloropalladate for diagnosing palladium sensitization. *Contact Dermatitis*. 2012;67:94-100.
- Faurschou AMT, Johansen JD, Thyssen JP. Metal allergen of the 21st century—a review on exposure, epidemiology and clinical manifestations of palladium allergy. *Contact Dermatitis*. 2011;64:185-195.
- Thyssen JP, Johansen JD, Carlsen BC, Menné 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;61:799-805.
- Wahlberg JE, Lidén C. Cross-reactivity patterns of cobalt and nickel studied with repeated open applications (ROATS) to the skin of Guinea pigs. *Am J Contact Dermat*. 2000;11:42-48.
- Thyssen JP. Cobalt sensitization and dermatitis: considerations for the clinician. *Dermatitis*. 2012;23:203-209.
- Uter W, Gefeller O, Geier J, Schnuch A. Contact sensitization to cobalt—multifactorial analysis of risk factors based on long-term data of the Information Network of Departments of Dermatology. *Contact Dermatitis*. 2014;71:326-337.
- Lidén C, Bruze M, Thyssen JC, Menné T. Metals. *Contact Dermatitis*. Vol 2011. 5th ed. Springer; 2011:642-680.
- Lidén C. Nickel in jewellery and associated products. *Contact Dermatitis*. 1992;26:73-75.
- Hindsén M, Persson L, Gruvberger B. Allergic contact dermatitis from cobalt in jewellery. *Contact Dermatitis*. 2005;53:350-351.
- Cristaudo A, Bordignon V, Petrucci F, et al. Release of palladium from biomechanical prostheses in body fluids can induce or support PD-specific IFN-gamma T cell responses and the clinical setting of a palladium hypersensitivity. *Int J Immunopathol Pharmacol*. 2009;22:605-614.
- Finch TM, Prais L, Foulds IS. Palladium allergy in a British patch test clinic population. *Contact Dermatitis*. 1999;41:351-352.
- Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. *Contact Dermatitis*. 2015;73:195-221.
- Carøe C, Andersen KE, Mortz CG. Fluctuations in the prevalence of nickel and cobalt allergy in eczema patients patch tested after implementation of the nickel regulation in Denmark. *Contact Dermatitis*. 2011;64:126-131.
- Schnuch A, Schwitulla J. Decrease in nickel allergy in women after the second EU nickel directive. *Contact Dermatitis*. 2013;69:253-256.
- Garg S, Thyssen JP, Uter W, et al. Nickel allergy following European Union regulation in Denmark, Germany, Italy and the U.K. *Br J Dermatol*. 2013;169:854-858.
- Lidén C, Johnsson S. Nickel on the Swedish market before the Nickel Directive. *Contact Dermatitis*. 2001;44:7-12.
- Biesterbos J, Yazar K, Lidén C. Nickel on the Swedish market: follow-up 10 years after entry into force of the EU Nickel Directive. *Contact Dermatitis*. 2010;63:333-339.
- Ahlström MG, Thyssen JP, Wennervaldt M, Menné T, Johansen JD. Nickel allergy and allergic contact dermatitis: a clinical review of immunology, epidemiology, exposure, and treatment. *Contact Dermatitis*. 2019;81:227-241.
- Prolonged contact with the skin - definition building for nickel. Definition of "prolonged contact with the skin" in relation to nickel restriction (Entry 27 of Annex XVII to REACH). *Eur Chem Agency*. 2014;797:1-16.
- Erfani B, Lidén C, Midander K. Short and frequent skin contact with nickel. *Contact Dermatitis*. 2015;73:222-230.
- Midander K, Hurtig A, Borg Tornberg A, Julander A. Allergy risks with laptop computers - nickel and cobalt release. *Contact Dermatitis*. 2016;74:353-359.
- Bordel-Gomez MT, Miranda-Romero A. Palladium allergy: a frequent sensitization. *Allergol Immunopathol (Madr)*. 2008;36:306-307.
- Akasya-Hillenbrand E, Özkaya-Bayazit E. Patch test results in 542 patients with suspected contact dermatitis in Turkey. *Contact Dermatitis*. 2002;46:17-23.
- Larese Filon F, Uderzo D, Bagnato E. Sensitization to palladium chloride: a 10-year evaluation. *Am J Contact Dermat*. 2003;14:78-81.
- Kränke B, Aberer W. Multiple sensitivities to metals. *Contact Dermatitis*. 1996;34:225.
- Vincenzi C, Tosti A, Guerra L, et al. Contact Dermatitis to Palladium: a study of 2,300 patients. *Am J Contact Dermat*. 1995;6:110-112.
- Durosaro O, el-Azhary RA. A 10-year retrospective study on palladium sensitivity. *Dermatitis*. 2009;20:208-213.
- Muris J, Goossens A, Gonçalves M, et al. Sensitization to palladium in Europe. *Contact Dermatitis*. 2015;72:11-19.
- Oädlalegeringar för metallkeramik: basmetallegeringar. Kunskapscenter för Dentalmaterial, Swedish National Board of Health and Welfare; 2007.

39. Rosholm Comstedt L, Engfeldt M, Svedman C, Akesson A, Hindsen M, Bruze M. Variation and covariation in patch test reactivity to palladium and nickel salts. *Eur J Dermatol*. 2018;28:668-676.
40. Hindsén M, Bruze M, Christensen OB. Individual variation in nickel patch test reactivity. *Am J Contact Dermat*. 1999;10:62-67.
41. Bonefeld CM, Geisler C, Giménez-Arnau E, Lepoittevin JP, Uter W, Johansen JD. Immunological, chemical and clinical aspects of exposure to mixtures of contact allergens. *Contact Dermatitis*. 2017;77: 133-142.

How to cite this article: Rosholm Comstedt L, Dahlin J, Bruze M, et al. Prevalence of contact allergy to metals: nickel, palladium, and cobalt in Southern Sweden from 1995–2016. *Contact Dermatitis*. 2020;82:218–226. <https://doi.org/10.1111/cod.13422>