Epidemiology of nickel sensitivity: Retrospective cross-sectional analysis of North American Contact Dermatitis Group data 1994-2014

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Background: Nickel is a common allergen.

Objective: To examine the epidemiology of nickel sensitivity in North America.

Methods: Retrospective, cross-sectional analysis of 44,097 patients patch tested by the North American Contact Dermatitis Group from 1994 to 2014. Nickel sensitivity was defined as a positive patch test for nickel. We evaluated the frequency of nickel sensitivity and patient demographics. For each positive reaction to nickel, we tabulated clinical relevance, occupational relatedness, and exposure sources.

Results: The average frequency of nickel sensitivity was 17.5% (1994-2014). Nickel sensitivity significantly increased over time (from 14.3% in 1994-1996 to 20.1% in 2013-2014 [$P < .0001$]). Nickel-sensitive patients were significantly more likely to be female, young, nonwhite, and atopic (have eczema and asthma) and/or have dermatitis affecting the face, scalp, ears, neck, arm, or trunk (P values $\leq .0474$). Overall, 55.5% of reactions were currently clinically relevant; this percentage significantly increased over time (from 44.1% in 1994-1996 to 51.6% in 2013-2014 [$P < .0001$]). The rate of occupational relatedness was 3.7% overall, with a significant decrease over time (from 7.9% in 1994-1996 to 1.9% in 2013-2014 [$P < .0001$]). Jewelry was the most common source of nickel contact.

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Limitations: Tertiary referral population.

Conclusions: Nickel allergy is of substantial public health importance in North America. The frequency of nickel sensitivity in patients referred for patch testing has significantly increased over a 20-year period. (J Am Acad Dermatol 2019;80:701-13.)

Key words: allergic contact dermatitis; nickel; North American Contact Dermatitis Group.

CAPSULE SUMMARY

- Detailed analyses of trends in nickel sensitivity in North America are lacking.
- Clinicians should be aware of a significant increase in nickel sensitivity over time (from 14.3% to 20.1% from 1994 to 2014) and a significant increase in the clinical relevance of reactions over time (from 44.1% to 51.6% from 1994 to 2014).

Claims data indicate that contact dermatitis affected 4.2% of Americans in 2013,[1] and nickel is the most commonly detected allergen in patients patch tested worldwide.[2,3] Cutaneous nickel sensitivity is associated with poor quality of life and occupational difficulties.[3] In 2008, the American Contact Dermatitis Society named nickel the contact allergen of the year to raise awareness regarding new sources of nickel and the increasing frequency of positive reactions.[2] Many large studies have examined the frequency of positive patch tests for sensitivity to nickel (Table I).[4-31]

Although the North American Contact Dermatitis Group (NACDG) publishes patch test results in 2-year cycles,[32-36] detailed analyses of trends and associations have not been reported for nickel sensitivity. This study examined the epidemiology of nickel allergy in North America over 2 decades and evaluated trends in nickel sensitivity in a large cohort of patch-tested patients.

METHODS

Database

The Minneapolis Veterans Affairs Medical Center's Human Studies Subcommittee approved this study. Methods for patch testing, evaluation of reactions, and data recording by the NACDG have been described previously.[32-36] Allergens (Chemotechnique Diagnostics AB, Malmö, Sweden, and allergEAZE SmartPractice, Calgary, Canada) were applied by using Finn chambers (SmartPractice, Phoenix, AZ) and Scanpor tape (Norgesplaster Alpharma AS, Vennesla, Norway). Nickel was tested as nickel sulfate hexahydrate 2.5% petrolatum. The data collected included sex, age, race, atopy (hay fever, eczema, asthma), dermatitis site(s) (maximum of 3), final diagnosis/diagnoses (maximum of 3), clinical relevance, occupational relatedness, and source. Only 1 source was entered per allergen; if multiple sources were present, the most clinically relevant source was recorded. Sources were not collected for the 1994-1996 data cycle. In 1996-1998, 8 possible sources were available for coding. In 1998-2000, 9 sources were available. Starting in 2001, the source list was expanded to more than 100 sources.

Study population

From January 1, 1994, to December 31, 2014, a total of 44,908 patients were patch tested for sensitivity to the NACDG screening series. Occasionally, specific allergens were not tested (usually on account of strong reactions in previous testing); 811 patients (1.8%) were not tested to nickel and were excluded from the analysis.

Study design

Data were entered in Access software (Access 2010; Microsoft Corporation, Redmond, WA) and analyzed in Excel (Excel 2010, Microsoft Corporation). Nickel sensitivity was defined as having a mild (+ [nonvesicular, erythematous, infiltrated, or possible papules]), strong (++ [edematous or vesicular]), or extreme (+++ [spreading, bullous, or ulcerative]) reaction to nickel at the second reading. Doubtful (macular erythema), irritant, and negative reactions were excluded. For clinical relevance analyses, "current" clinical relevance comprised "definite" (a positive patch test or use test for sensitivity to a skin contactant was demonstrated to release nickel or verified to contain nickel), "probable" (a skin contactant was demonstrated to release nickel or verified to contain nickel with a consistent clinical presentation), and "possible" (likely exposure to skin contactants known to release nickel or verified to contain nickel).[32]

Statistical analysis

Nickel sensitivity, demographics, clinical relevance, and occupational relatedness were presented

Abbreviations used:

ACD:	allergic contact dermatitis
CI:	confidence interval
EU:	European Union
NACDG:	North American Contact Dermatitis Group
NOS:	not otherwise specified
RR:	relative risk
SANR:	statistical analysis not reported

as counts and proportions. Nickel-sensitive and non–nickel-sensitive populations were compared by using chi-square tests. Because of the exploratory nature of this analysis, no correction for multiple tests was used; a P value less than .05 indicated statistical significance. Relative risk (RR) and confidence intervals (CIs) were calculated by using SAS software (version 9.2; SAS Inc, Cary, NC). The chi-square test of trend was used to analyze variables over time.

RESULTS

Frequency of nickel sensitivity

The overall frequency of nickel sensitivity was 17.5% (7729 of 44,097 [in 1994-2014]). Nickel sensitivity increased significantly over time, from 14.3% (in 1994-1996) to 20.1% (in 2013-2014) ($P < .0001$, Table II).

Demographics

Table III compares the demographics of nickel-sensitive and non–nickel-sensitive patients. Nickel-sensitive patients were significantly more likely to be female (RR, 3.13 [95% CI, 2.94-3.33]), less than 18 years old (RR, 1.49 [95% CI, 1.39-1.61]), nonwhite (RR, 1.19 [95% CI, 1.14,-1.27]), and/or atopic (RR, 1.09 [95% CI, 1.05-1.14]). Eczema (RR, 1.10 [95% CI, 1.05-1.15]) and asthma (RR, 1.11 [95% CI, 1.05-1.17]), but not hay fever, were significantly associated with nickel sensitivity. Nickel sensitivity was significantly associated with dermatitis involving the face (RR, 1.27 [95% CI, 1.22-1.32]); scalp, ears, and/or neck (RR, 1.34 [95% CI, 1.27-1.41]); arm (RR 1.06, [95% CI, 1.00-1.12]); trunk (RR, 1.08 [95% CI, 1.02-1.15]); and other sites (RR, 1.09 [95% CI, 1.01-1.18]). Individuals with nickel sensitivity were significantly more likely to have a final diagnosis of allergic contact dermatitis (ACD) (RR, 2.31 [95% CI, 2.20-2.43]).

Clinical relevance and occupational relatedness

Overall, the clinical relevance of positive reactions to nickel was deemed current in 55.5% of cases (2.1% definite, 18.0% probable, and 35.4% possible [Table IV]). Approximately one-third of reactions (29.7%) were deemed to be of past relevance. Current clinical relevance increased significantly over time (from 44.1% in 1994-1996 to 51.6% in 2013-2014 [$P < .0001$]). Overall, 3.7% of positive reactions to nickel were related to occupation. Occupational relatedness decreased significantly over time, from 7.9% in 1994-1996 to 1.9% in 2013-2014 ($P < .0001$ [Table IV]).

Nickel sources

For the first 3 cycles (1994-2000), source code options were limited. Between 1996 and 1998, the most commonly identified source of nickel dermatitis was other/jewelry (44.4% [216 of 486]), followed by occupational (6.2% [30 of 486]), medication plus cosmetic (2.9% [14 of 486]), and cosmetic (2.7% [13 of 486]). Between 1998 and 2000, the most commonly identified source was jewelry/glasses (37.9% [358 of 944]), followed by shoes/clothing (1.6% [15 of 944]), cosmetic (0.6% [6 of 944]), and medication/cosmetic (0.1% [1 of 944]).

For the period 2001-2014, more than 100 source codes were utilized; Table V lists the top 25 nickel sources from 2001 to 2014. Jewelry, food, and consumer items not otherwise specified (NOS) were the top sources. Jewelry was the most common source of nickel for each 2-year cycle (Table VI).

When sources were stratified by age and sex, jewelry remained the most common source of nickel in all categories, except males 18 years and younger (Table VII). Belts were within the top 4 most common sources in all male age groups. Food and consumer items NOS were notable sources for both males and females of all ages. Sources of nickel dermatitis present within the top 5 for males but not for females included watches; shirts, pants, or dresses; and minerals (ores, clay, earth, dirt, rocks, stone, sand, or gravel). Sources present within the top 5 female subgroups but not male subgroups included equipment and instruments (medical or surgical; audio or video; photographic; recreational or athletic; musical; and writing, drawing, or art), personal grooming devices, dentistry materials (especially for those age 40 years and older), cosmetics, and glasses and contact lenses.

DISCUSSION

Several key findings arose from this study. First, the frequency of nickel sensitivity increased significantly over the 20-year study period (from 14.3% to 20.1% [$P < .0001$]). Second, nickel-sensitive patients were significantly more likely to be female, young, nonwhite, and atopic ($P \leq .0003$) and/or have dermatitis affecting the face; scalp, ears, and/or

Table I. Previous studies of nickel sensitivity

Study	Country	Sites, n	Study period	Population size	Frequency of nickel sensitivity, %	Nickel sulfate concentration, %
North America						
Davis et al, 2011[4]	United States	3 (Mayo)	2000-2009	7083	16.7	2.5
Wentworth et al, 2014[5]	United States	3 (Mayo)	2006-2010	3087	16.5	2.5
Wetter et al, 2005[6]	United States	3 (Mayo)	1998-2000	1317	14.1	2.5
Europe						
Kuljanac et al,. 2006[7]	Croatia	1	1994-2003	1102	33.4	5
Rui et al, 2013[8]	Italy	8	1996-2010	19,088	25.4	5
Garcia-Rabasco et al, 2014[9]	Spain	1	2000-2010	3404	24.2	5
Fall et al, 2015[10]	Sweden	14	1991-1993	3680	21.4	5
			1999-2001	3825	19.8	
			2008-2010	3112	17.6	
ESSCA Writing Group, 2008[11]	11 European countries	31 (ESSCA)	2004	9871	20.1 (20.7*)	5
Uter et al, 2016[12]	12 European countries	53 (ESSCA)	2009-2012	56,761	19.7 (19.0*)	5
Uter et al, 2017[13]	12 European countries	46 (ESSCA)	2013-2014	28,109	18.7 (18.1*)	5
Bangha and Elsner, 1996[14]	Switzerland	1	1990-1994	5565	18.5	5
Uter et al, 2005[15]	9 European countries	17 (ESSCA)	2002-2003	9520	18.0 (17.3*)	
Schnuch et al, 1997[16]	Germany and Austria	24 (IVDK)	1990-1995	36,720	15.7 (12.9*)	5
Uter et al, 2003[17]	Germany and Austria	33 (IVDK)	1992-2000	74,940	15.5	5
Tichy and Karlova, 2015[18]	Czech Republic	1	2008-2012	1941	15.4	5
Mahler et al, 2014[19]	Germany, Austria, and Switzerland	56 (IVDK)	2010	13,117	14.9	5
			2011	13,320	15.6	
			2012	12,529	15.3	
Hegewald et al, 2005[20]	Germany and Austria	30 (IVDK)	1995-2002	57,341	14.6	5
Machovcova et al, 2005[21]	Czech Republic	9	1997-2001	12,058	13.8	5
Johansen et al, 1999[22]	Denmark	7	1985-1986	1232	13.8,	5
			1997-1998	1267	15.0	
Other						
Yin et al, 2011[23]	China	1	2004-2009	2758	39.5	5
Dou et al, 2011[24]	China	1	1990-2009	1858	25.7	5
Lam et al, 2008[25]	China	9	1995-1999	2585	24.4	5
Almutairi and Almutawa, 2017[26]	Kuwait	2	2014-2015	2461	23.9	200 μg/cm^2
Goon and Goh, 2005[27]	Singapore	1	2001-2003	3047	19.9	5
Cheng et al, 2008[28]	Taiwan	1	1978-2003	3559	17.7	5
Lim et al, 1992[29]	Singapore	1	1986-1990	5557	17.7	5
Lazarov 2006[30]	Israel	1	1998-2004	2156	13.9	5
Bajaj et al, 2007[31]	India	1	1997-2006	1000	12.9	5

Analyses of North American Contact Dermatitis Group data have been excluded from this table.
ESSCA, European Surveillance System on Contact Allergies; *IVDK*, Information Network of Dermatology Departments; Mayo, Mayo Clinic.
*Standardized for age and sex.

Table II. Study population

Patient	1994-1996	1996-1998	1998-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012	2013-2014	Total
All patients tested for sensitivity to nickel, n	2029	3434	5823	4901	5128	4428	5045	4294	4164	4851	44,097
Nickel-sensitive patients, n (%)	290 (14.3)	486 (14.2)	944 (16.2)	818 (16.7)	953 (18.6)	842 (19.0)	985 (19.5)	666 (15.5)	769 (18.5)	976 (20.1)	7729 (17.5)
Non–nickel-sensitive patients, n (%)	1739 (85.7)	2948 (85.8)	4879 (83.8)	4083 (83.3)	4175 (81.4)	3586 (81.0)	4060 (80.5)	3628 (84.5)	3395 (81.5)	3875 (79.9)	36,368 (82.5)

A statistically significant increase in nickel-positive reactions over time was observed ($P < .0001$).

neck; arm; or trunk ($P \leq .0474$). Third, 55.5% of reactions were currently clinically relevant and relevance significantly increased over time (from 44.1% to 51.6% [$P < .0001$]) whereas a decrease was seen in nickel reactions related to occupation (from 7.9% to 1.9% [$P < .0001$]). Finally, jewelry was overwhelmingly the most common source of nickel dermatitis.

Frequency of nickel sensitivity

The overall frequency of nickel sensitivity was 17.5%. This was similar to the frequencies in recent large US studies from the Mayo Clinic (16.7%, 16.5%, and 14.1%).[4,5] Although our study is difficult to directly compare with non–US and/or Canadian studies (which commonly test with 5% nickel sulfate), our frequency was similar to that reported by the European Surveillance System on Contact Allergies (unadjusted frequencies of 20.1%, 19.7%, 18.7%, and 18.0%),[11-13,15] Singapore (19.9% and 17.7%),[27,29] Switzerland (18.5%),[14] and Taiwan (17.7%).[28] Countries reporting high frequencies included China (39.5%, 25.7%, and 24.4%),[23-25] Croatia (33.4%),[7] Italy (25.4%),[8] Spain (24.2%),[9] and Kuwait (23.9%).[26] Our frequency was higher than that reported by the Information Network of Dermatology Departments (unadjusted frequencies of 15.7%, 15.6%, 15.5%, 15.3%, 14.9%, and 14.6%),[16,17,19,20] Czech Republic (15.4% and 13.8%),[18,21] Denmark (15.0% and 13.8%),[22] Israel (13.9%),[30] and India (12.9%).[31]

We found that the frequency of nickel sensitivity significantly increased over time (from 14.3% in 1994-1996 to 20.1% in 2013-2014 [$P < .0001$]). Other non-European countries have also documented increased nickel sensitivity; these include Taiwan (from 14.3% in 1978-1990 to 23.0% in 1991-2003 [statistical analysis not reported (SANR)]),[28] Singapore (from 13.9% in 1984-1985 to 19.9% in 2001-2003 [SANR]),[27] and China (from 15.4% in 1990-1993 to 31.6% in 2006-2009 [$P < .001$]).[24]

The Danish Nickel Regulation, which was implemented in Denmark in 1990, limited nickel release from jewelry, watches, glasses, and metal in clothing to no more than 0.5 $\mu g/cm^2/wk$. Following implementation of the Danish Nickel Regulation, there was decreased frequency of nickel sensitivity in Danish children age 18 years and younger (from 24.8% in 1985-1986 to 9.2% in 1997-1998 [$P = .0008$])[22] and Danish females age 5 to 30 years (from 27.6% in 1985 to 16.8% in 2007 [$P < .02$]),[37] although the overall frequency in patch-tested patients increased (from 13.8% in 1985-1986 to 15.0% in 1997-1998 [$P > .05$]).[22] In 2001, the European Union (EU) introduced the Nickel

Table III. Patient demographics: all, nickel-sensitive, and non–nickel-sensitive patients

	Overall, n (%)	Nickel-sensitive,* n (%)	Non–nickel-sensitive,† n (%)	Nickel-sensitive vs non–nickel-sensitive	
Characteristic	**N = 44,097**	**n = 7729**	**n = 36,368**	**RR (95% CI)**	***P* value**
Sex					
Male‡	15,211 (34.5)	1117 (14.5)	14,094 (38.8)	0.32 (0.30-0.34)	<.0001§
Age, y					
Mean	48.0	43.9	48.9		
>40‡	29,474 (66.9)	4554 (58.9)	24,920 (68.6)	0.71 (0.68-0.74)	<.0001§
>18	42,183 (95.7)	7240 (93.7)	34,943 (96.1)	0.67 (0.62-0.72)	<.0001§
19-29	4734 (10.7)	1152 (14.9)	3582 (9.9)		
30-39	7109 (16.1)	1374 (17.8)	5735 (15.8)		
40-49	9377 (21.3)	1740 (22.5)	7637 (21.0)		
50-59	9654 (21.9)	1677 (21.7)	7977 (21.9)		
≥60	11,309 (25.7)	1297 (16.8)	10,012 (27.5)		
Race					
White	38,023 (86.5)	6494 (84.3)	31,529 (87.0)	0.84 (0.79-0.88)	<.0001§
Nonwhite					
Black	2809 (6.4)	515 (6.7)	2294 (6.3)		
Asian	1692 (3.9)	378 (4.9)	1314 (3.6)		
Hispanic	831 (1.9)	176 (2.3)	655 (1.8)		
Other	584 (1.3)	141 (1.8)	443 (1.2)		
Atopy					
Hay fever	12,044 (27.3)	2170 (28.1)	9874 (27.2)	1.04 (0.99-1.09)	.0963
Eczema	9129 (20.8)	1724 (22.4)	7405 (20.4)	1.10 (1.05-1.15)	.0001§
Asthma	6232 (14.1)	1194 (15.5)	5038 (13.9)	1.11 (1.05-1.17)	.0003§
Any of the 3 aforementioned‡	17,909 (40.8)	3307 (42.9)	14,602 (40.3)	1.09 (1.05-1.14)	<.0001§
Site‖					
Scattered generalized	9265 (21.0)	1431 (18.5)	7834 (21.6)	0.85 (0.81-0.90)	<.0001§
Hand‡	12,532 (28.4)	2123 (27.5)	10,409 (28.6)	0.95 (0.91-1.00)	.0394§
Foot	3170 (7.2)	444 (5.7)	2726 (7.5)	0.79 (0.72-0.86)	<.0001§
Face‡	15,719 (35.7)	3194 (41.3)	12,525 (34.5)	1.27 (1.22-1.32)	<.0001§
Face NOS	9386 (21.3)	1897 (24.6)	7489 (20.6)		
Lips	1643 (3.7)	323 (4.2)	1320 (3.6)		
Nose	53 (0.1)	10 (0.1)	43 (0.1)		
Eyelids	4211 (9.6)	903 (11.7)	3308 (9.1)		
Eyes	426 (1.0)	61 (0.8)	365 (1.0)		
Scalp, ears, neck	6470 (14.7)	1446 (18.7)	5024 (13.8)	1.34 (1.27-1.41)	<.0001§
Arm	6865 (15.6)	1261 (16.3)	5604 (15.4)	1.06 (1.00-1.12)	.0474§
Leg‡	4796 (10.9)	768 (9.9)	4028 (11.1)	0.90 (0.84-0.97)	.0034§
Trunk	5231 (11.9)	985 (12.8)	4246 (11.7)	1.08 (1.02-1.15)	.0086§
Anal/genital	1233 (2.8)	182 (2.4)	1051 (2.9)	0.84 (0.73-0.96)	.0094§
Other	2973 (6.7)	565 (7.3)	2408 (6.6)	1.09 (1.01-1.18)	.0288§
Most exposed areas	781 (1.8)	150 (1.9)	631 (1.7)		
Only under clothing	660 (1.5)	102 (1.3)	558 (1.5)		
Erythroderma	70 (0.2)	6 (0.1)	64 (0.2)		
Other NOS	1462 (3.3)	307 (4.0)	1155 (3.2)		
Final diagnosis¶					
Allergic contact dermatitis	25,286 (57.5)	5842 (75.8)	19,444 (53.6)	2.31 (2.20-2.43)	<.0001§
Irritant contact dermatitis	8048 (18.3)	1244 (16.1)	6804 (18.8)	0.86 (0.81-0.91)	<.0001§
Atopic dermatitis	6190 (14.1)	1123 (14.6)	5067 (14.0)	1.04 (0.98-1.10)	.1741
Psoriasis	1928 (4.4)	263 (3.4)	1665 (4.6)	0.77 (0.69-0.86)	<.0001§
Stasis dermatitis	396 (0.9)	35 (0.5)	361 (1.0)	0.50 (0.37-0.69)	<.0001§
Nummular eczema	847 (1.9)	92 (1.2)	755 (2.1)	0.61 (0.51-0.75)	<.0001§
Photo dermatitis	608 (1.4)	113 (1.5)	495 (1.4)	1.06 (0.90-1.25)	.4648
Other dermatitis	7348 (16.7)	829 (10.7)	6519 (18.0)	0.60 (0.56-0.64)	<.0001§
Other dermatoses	4988 (11.3)	715 (9.3)	4273 (11.8)	0.80 (0.74-0.86)	<.0001§

Continued

Table III. Cont'd

Characteristic	Overall, n (%) N = 44,097	Nickel-sensitive,* n (%) n = 7729	Non–nickel-sensitive,† n (%) n = 36,368	Nickel-sensitive vs non–nickel-sensitive RR (95% CI)	*P* value
Seborrheic dermatitis	998 (2.3)	138 (1.8)	860 (2.4)	0.78 (0.67-0.92)	.0018§
Pompholyx	351 (0.8)	43 (0.6)	308 (0.8)	0.70 (0.53-0.92)	.0090§
Contact urticaria	362 (0.8)	60 (0.8)	302 (0.8)	0.94 (0.75-1.19)	.6300
Occupationally related‡#	6252 (14.2)	1042 (13.5)	5210 (14.3)	0.94 (0.89-1.00)	.0553

CI, Confidence interval; *MOAHLFA*, male, occupational dermatitis, atopic dermatitis, hand, leg, face, age older than 40; *NOS*, not otherwise specified; *RR*, relative risk.

*Nickel-sensitive patients: sex missing for 1 patient, age missing for 2 patients, race missing for 25 patients, hay fever status missing for 11 patients, eczema status missing for 20 patients, asthma status missing for 7 patients, site missing for 3 patients, final diagnosis missing for 17 patients, and occupational relevance missing for 11 patients. Denominators adjusted accordingly.

†Non–nickel-sensitive patients: sex missing for 4 patients, age missing for 19 patients, race missing for 133 patients, hay fever status missing for 49 patients, eczema status missing for 89 patients, asthma status missing for 42 patients, site missing for 26 patients, final diagnosis missing for 75 patients, and occupational relevance missing for 34 patients. Denominators adjusted accordingly.

‡MOAHLFA index.

§Indicates statistical significance.

‖Total number of affected sites, with up to 3 sites per patient.

¶Total number of final diagnoses, with up to 3 diagnoses per patient.

#Refers to overall skin disease being occupationally related.

Directive, which limited nickel release to no more than 0.5 $\mu g/cm^2/wk$ in consumer products with prolonged skin contact. In 2005, the regulation of piercing posts was changed from content limit to release limit of no more than 0.2 $\mu g/cm^2/wk$.[38] Following implementation of the EU Nickel Directive, several populations documented decreased nickel sensitivity, particularly in children and women, including individuals in Sweden (overall, from 21.4% in 1992 to 17.6% in 2009, and in women younger than 40 years, from 33.8% in 1992 to 23.3% in 2009 [SANR]),[10] women in Italy age 26 years and younger (from 38.3% in 1996-1998 to 29.0% in 2008-2010 [$P < .05$]),[8] women in Germany and Austria age 30 years and younger (from 36.7% in 1992 to 25.8% in 2001 [$P < .0001$]),[39] and individuals in Poland age 20 years or younger (from 15.9% in 1995 to 10.0% in 2004 [SANR]).[40] Whereas the frequency of nickel sensitivity has decreased in European populations since implementation of the EU Nickel Directive, nickel release remains unregulated in North America and the frequency of nickel sensitivity has significantly increased.

Demographics

Nickel-sensitive patients were significantly more likely to be female, young, nonwhite, atopic (eczema and asthma), and/or have dermatitis affecting the face, scalp, ears, neck, arm, or trunk. Other studies have also noted an association between increased nickel sensitivity and the following characteristics: female sex[4,12,17,20,28,41-43]; young age[12,17,20,41,42]; history of eczema[43]; and involvement of the head,[17] neck,[17] face,[28,43] arms,[26,28] and hands.[26,28] Dickel et al also found that black patients had a higher rate of nickel sensitivity than white patients (10.6% vs 8.0%), but this difference was not statistically significant.[44] The increased sensitivity in females versus in males is not surprising given increased the opportunities for nickel exposure through jewelry and piercings.[3,45] Additionally, the involved locations are not surprising given that jewelry and watches are typically worn on the face, ears, neck, and arms, whereas other nickel-releasing objects such as belts contact the trunk.

Clinical relevance and occupational relatedness

Overall, 55.5% of reactions were currently clinically relevant and 3.7% were related to occupation. Few studies have evaluated clinical relevance and occupational relatedness. Studies of 3559 patients in Taiwan[28] and 1060 patients in the United States[4] showed current clinical relevance rates of 76.6% and 73.2%, respectively. On the other hand, a study of 3404 patients patch tested in Spain showed clinical relevance in only 6.9% of positive reactions to nickel, and of those clinically relevant reactions, 15.8% were related to occupation.[9] A study of 1190 cases of occupational contact dermatitis in the United Kingdom found that 36% of positive reactions to nickel were related to occupation.[46] Lastly, a study of 1187 patients in Kansas (these patients are also included in the current NACDG analysis) showed

Table IV. Clinical relevance and occupational relatedness in nickel-sensitive patients

Clinical relevance/occupational relatedness	1994-1996 n = 290	1996-1998 n = 486	1998-2000 n = 944	2001-2002 n = 818	2003-2004 n = 953	2005-2006 n = 842	2007-2008 n = 985	2009-2010 n = 666	2011-2012 n = 769	2013-2014 n = 976	Total* n = 7729
Clinical relevance, n (%)†											
Definite	7 (2.4)	26 (5.3)	10 (1.1)	13 (1.6)	11 (1.2)	12 (1.4)	24 (2.4)	29 (4.4)	19 (2.5)	10 (1.0)	161 (2.1)
Probable	56 (19.3)	77 (15.8)	141 (14.9)	84 (10.3)	140 (14.7)	171 (20.3)	242 (24.6)	129 (19.4)	154 (20.0)	197 (20.2)	1391 (18.0)
Possible	65 (22.4)	136 (28.0)	403 (42.7)	307 (37.5)	290 (30.4)	295 (35.0)	329 (33.4)	291 (43.7)	324 (42.1)	297 (30.4)	2737 (35.4)
Past	113 (39.0)	178 (36.6)	230 (24.4)	270 (33.0)	363 (38.1)	238 (28.3)	248 (25.2)	122 (18.3)	191 (24.8)	339 (34.7)	2292 (29.7)
Unknown or not applicable	49 (16.9)	69 (14.2)	160 (16.9)	144 (17.6)	149 (15.6)	126 (15.0)	142 (14.4)	95 (14.3)	81 (10.5)	133 (13.6)	1148 (14.9)
Occupational relatedness, n (%)†											
Yes	23 (7.9)	30 (6.2)	53 (5.6)	26 (3.2)	24 (2.5)	27 (3.2)	48 (4.9)	21 (3.2)	29 (3.8)	19 (1.9)	300 (3.9)
No	224 (77.2)	-	837 (88.7)	759 (92.8)	903 (94.8)	795 (94.4)	918 (93.2)	637 (95.6)	736 (95.7)	945 (96.8)	6754 (93.2)
Unsure	43 (14.8)	-	54 (5.7)	33 (4.0)	26 (2.7)	20 (2.4)	19 (1.9)	8 (1.2)	4 (0.5)	12 (1.2)	219 (3.0)

Statistically significant increase in current clinical relevance (definite, probably, and possible) over time ($P < .0001$). Statistically significant decrease in occupational relevance over time ($P < .0001$).
*No and unsure parameters for occupational relevance were not collected in the 1996-1998 cycle; denominators have been adjusted accordingly.
†Denominator is the total number of allergic reactions to nickel in the corresponding 2- year cycle.

Table V. Top 25 nickel sources, 2001-2014

Order	Nickel source	%	n = 6009
1.	Jewelry	59.1	3550
2.	Food	5.8	351
3.	Consumer items NOS*	4.6	274
4.	Belts	2.4	143
5.	Clothing NOS†	1.1	65
6.	Tools	1.0	62
7.	Machinery and vehicles	0.9	57
8.	Watches	0.9	55
9.	Cosmetics	0.8	48
10.	Dentistry materials	0.8	48
11.	Equipment and instruments	0.7	42
12.	Glasses and contact lenses	0.6	38
13.	Personal grooming devices	0.6	34
14.	Shirts, pants, and dresses	0.5	33
15.	Essential oils, massage oils, and medical devices	0.5	29
16.	Minerals	0.4	27
17.	Building materials	0.3	16
18.	Accessories (eg, ties, wallets, purses)	0.2	15
19.	Undergarments and swimwear	0.2	14
20.	Soaps and cleansers	0.2	14
21.	Furniture and fixtures	0.2	12
22.	Medical and surgical instruments	0.2	11
23.	Coins	0.2	10
24.	Orthopedic implants and prostheses	0.2	10
25.	Shoes	0.2	10

No source data collected in the 1994-1996 cycle. The 1996-1998 and 1998-2000 cycles are described in the text. Only specified sources are reported here. Unknown and not applicable were excluded.
NOS, Not otherwise specified.
*Excludes coins, keys, and personal grooming devices.
†Excludes specific categories, including gloves, shoes, shirts, pants, dresses, socks, suits, coats, hats, belts, accessories, undergarments, and swimwear.

occupational relatedness in 23.7% of positive reactions to nickel.[43] Previous studies have found hairdressers, jewelers, cashiers, metal furnace operators, metal finishers, and jobs related to packing and transporting to be more commonly associated with occupational nickel ACD,[3,17,26] which likely accounts for the much higher percentage of occupational relatedness in the Kansas study than other NACDG sites. Differences in clinical relevance and occupational relatedness rates may be explained in part by variations in clinicians (operator dependence) and, as already noted, demographics.

Nickel sources

Jewelry is a well-recognized source of nickel dermatitis,[2,3] and it was consistently the source most commonly associated with nickel reactions in our study; this is likely due to both the ease of

Table VI. Top 5 nickel sources from 2001-2014, in 2-year cycles

2-year cycle	Nickel source	%	n
2001-2002	Jewelry	59.8	489
(n = 818)	Tools	1.7	14
	Clothing NOS*	1.6	13
	Machinery and vehicles	1.5	12
	Dentistry materials	1.2	10
2003-2004	Jewelry	60.8	579
(n = 953)	Food	3.1	30
	Watches	1.9	18
	Tools	1.4	13
	Belts	1.3	12
2005-2006	Jewelry	62.2	524
(n = 842)	Food	7.6	64
	Cosmetics	1.8	15
	Clothing NOS*	1.7	14
	Belts	1.5	13
2007-2008	Jewelry	48.5	478
(n = 985)	Consumer items NOS†	10.8	106
	Food	9.4	93
	Belts	3.2	32
	Clothing NOS*	1.8	18
2009-2010	Jewelry	55.7	371
(n = 666)	Consumer items NOS†	8.3	55
	Food	7.5	50
	Belts	2.6	17
	Equipment and instruments‡	1.8	12
	Personal grooming devices‡	1.8	12
2011-2012	Jewelry	64.1	493
(n = 769)	Consumer items NOS†	6.4	49
	Food	6.1	47
	Belts	4.0	31
	Glasses and contact lenses‡	0.9	7
	Machinery and vehicles‡	0.9	7
2013-2014	Jewelry	63.1	616
(n = 976)	Consumer items NOS†	6.6	64
	Food	6.0	59
	Belts	3.4	33
	Personal grooming devices	1.1	11

No source data collected in the 1994-1996 cycle. The 1996-1998 and 1998-2000 cycles are described in the text. Only specified sources are reported here. Unknown and not applicable were excluded.

NOS, Not otherwise specified.

*Excludes specific categories, including gloves, shoes, shirts, pants, dresses, socks, suits, coats, hats, belts, accessories, undergarments, and swimwear.

†Excludes coins, keys, and personal grooming devices.

‡Sources with equal prevalence; thus, more than 5 sources have been reported.

identifying jewelry in a patient's environment and accessibility of testing jewelry items for nickel release in clinic. A recent study demonstrated nickel release in 82.3% of earrings purchased in California (79 of 96), with amounts ranging from 0.01 to 598 $\mu g/cm^2/wk$, as determined by using the plasma optical emission spectroscopy method.[47]

In this study, food was coded as a source for nickel dermatitis, although it was a very distant second to jewelry. Additional analyses (data not shown) found that 1 NACDG member coded 96.0% of all food sources. This reflects the current state of expert disagreement and controversy surrounding nickel systemic contact dermatitis secondary to nickel in food. In a double-blind randomized control study of 131 nickel-sensitive patients, Veien et al reported dermatitis flares in 42.0% of patients receiving oral challenge with 2.5 mg of nickel (55 of 131), compared with 17.6% of controls (23 of 131) ($P < .00002$).[48] In another double-blind randomized control study, Jensen et al demonstrated widespread cutaneous reactions in 6 of 10 nickel-sensitive patients following oral intake of 4 mg of nickel. A lower dose, 0.3 mg (the amount contained in a normal daily diet), resulted in localized reactions in 4 of 10 patients and widespread reactions in 0 of 10 patients.[49] Convincing case reports of systemic contact dermatitis to nickel have been reported[50-52]; however, oral challenge tests were generally not performed in these reports or in the NACDG patients included in this study.

Another commonly identified source was consumer items NOS. Although not specified in the database, an informal survey of NACDG members indicated coding of miscellaneous items used in daily life, such as perfume caps, cigarette lighters, and smart phone accessories (Fig 1). Recently, electronic cigarettes have also been implicated.[53] Although these items may sometimes have only brief skin contact, there are situations in which prolonged contact occurs (eg, carrying lipstick and cigarette lighters in pockets or using a smart phone). Coins, keys, and personal grooming devices were coded separately.

Other sources in our study included belts, eye glasses, watches, clothing, personal grooming devices, machinery and vehicles, tools, and dentistry materials, which is consistent with previous reports. In a study of 3047 patients in Singapore, the most common nickel sources were costume jewelry, belt buckles, watches, and eye glasses.[27] In a study of 2985 patients in Kuwait, the most common nickel sources were metal buttons, earrings, and watches.[26] Other studies have also reported jewelry, belt buckles, and eye glasses to be common sources.[9,28] Dentistry materials such as braces,[54] crowns,[55] and retainer wires[56] have also been implicated as sources of nickel dermatitis.

Table VII. Top 5 nickel sources by age and sex from 2001-2014

	Males			Females		
Age	Nickel source	%	n/N	Nickel source	%	n/N
All ages	Jewelry	23.5	203/864	Jewelry	65.1	3346/5142
	Belts	11.1	96/864	Food	5.9	301/5142
	Food	5.8	50/864	Consumer items NOS*	4.6	236/5142
	Consumer items NOS*	4.4	38/864	Belts	0.9	46/5142
	Watches	3.9	34/864	Clothing NOS†	0.9	45/5142
≤18 y	Belts	22.1	23/104	Jewelry	52.3	161/308
	Jewelry	14.4	15/104	Food	12.3	38/308
	Food	14.4	15/104	Consumer items NOS*	4.5	14/308
	Clothing NOS†	7.7	8/104	Clothing NOS†	4.5	14/308
	Shirts, pants, and dresses	5.8	6/104	Belts	4.2	13/308
19-29 y	Jewelry	19.7	26/132	Jewelry	65.3	545/834
	Belts	17.4	23/132	Food	6.5	54/834
	Consumer items NOS*	4.5	6/132	Consumer items NOS*	4.1	34/834
	Food	3.8	5/132	Belts	1.9	16/834
	Machinery and vehicles	3.0	4/132	Equipment and instruments‡	1.1	9/834
				Personal grooming devices‡	1.1	9/834
30-39 y	Jewelry	29.3	41/140	Jewelry	66.7	598/896
	Belts	13.6	19/140	Food	5.5	49/896
	Food	4.3	6/140	Consumer items NOS*	4.0	36/896
	Machinery and vehicles	4.3	6/140	Tools	1.5	13/896
	Tools	4.3	6/140	Belts‡	1.0	9/896
				Clothing NOS†‡	1.0	9/896
				Equipment and instruments‡	1.0	9/896
				Machinery and vehicles‡	1.0	9/896
				Personal grooming devices‡	1.0	9/896
40-49 y	Jewelry	21.3	29/136	Jewelry	65.2	750/1150
	Machines and vehicles	8.8	12/136	Food	5.0	57/1150
	Belts	6.6	9/136	Consumer items NOS*	4.9	56/1150
	Food*	4.4	6/136	Dentistry materials	1.0	12/1150
	Consumer items NOS*‡	4.4	6/136	Cosmetics	1.0	12/1150
	Minerals‡	4.4	6/136			
50-59 y	Jewelry	25.0	40/160	Jewelry	67.0	772/1152
	Belts	7.5	12/160	Food	5.3	61/1152
	Watches	5.6	9/160	Consumer items NOS*	4.6	53/1152
	Machinery and vehicles	5.0	8/160	Dentistry materials	1.0	12/1152
	Minerals	5.0	8/160	Cosmetics	1.0	12/1152
≥60 y	Jewelry	27.1	52/192	Jewelry	64.8	520/802
	Food	6.8	13/192	Consumer items NOS*	5.4	43/802
	Consumer items NOS*	6.8	13/192	Food	5.2	42/802
	Belts	5.2	10/192	Glasses and contact lenses	1.2	10/802
	Watches	4.7	9/192	Dentistry materials	1.1	9/802

Age is missing for 2 patients and sex is missing for 1 patient; denominators have been adjusted accordingly. Only specified sources are reported here. Unknown and not applicable were excluded.

NOS, Not otherwise specified.

*Excludes coins, keys, and personal grooming devices.

†Excludes specific categories, including gloves, shoes, shirts, pants, dresses, socks, suits, coats, hats, belts, accessories, undergarments, and swimwear.

‡Sources with equal prevalence; thus, more than 5 sources have been reported.

Limitations

This study is retrospective and cross-sectional; therefore, follow-up is lacking. Additionally, patients with strongly positive reactions to nickel in previous patch testing were likely not retested for sensitivity to nickel. In this study, 1.8% of patients

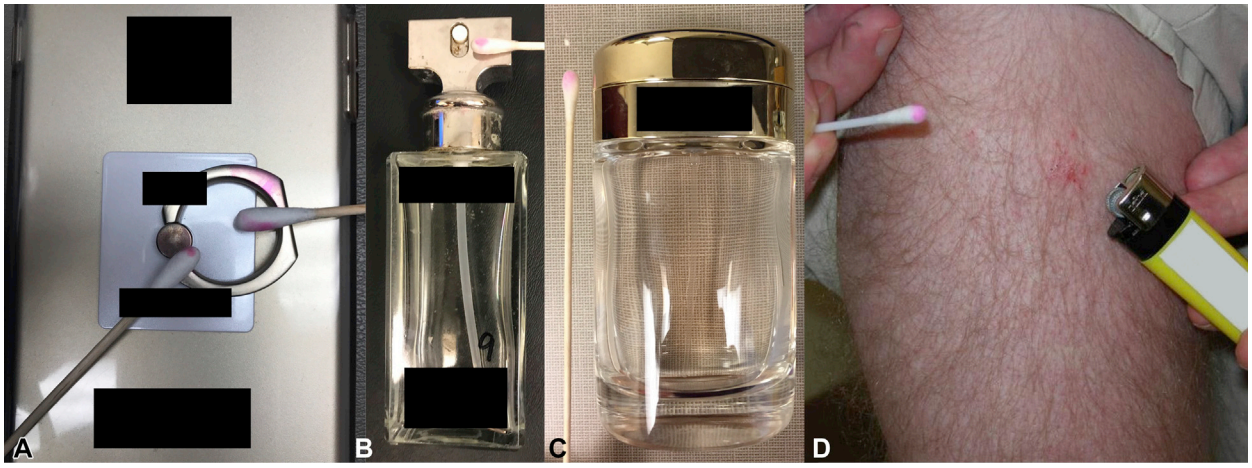

Fig 1. Consumer items not otherwise specified as sources of nickel dermatitis. A smart phone ring accessory **(A)**, perfume caps **(B** and **C)**, and cigarette lighter kept in front pants pocket **(D)** were all demonstrated to release nickel in a dimethylglyoxime spot test.

(811 of 44,908) were not tested for sensitivity to nickel. The composition of the NACDG (members and clinic locations) has varied over time. Sources are limited to those with codes; for example, toys and games[57] are not included in the NACDG source list.

Lastly, these patients represent a tertiary referral population. Previous studies have shown that the frequency of nickel sensitivity in patch-tested patients is higher than that in the general population.[58] Similarly, individuals referred specifically for implant testing may not have been tested for sensitivity to the screening series.

SUMMARY

Nickel contact allergy has tremendous clinical and public health importance. This study documents the significant increase in frequency of nickel sensitivity (14.3% to 20.1%) over 2 decades in North America, compared with a decrease in frequency of nickel sensitivity in several European populations. Nickel-sensitive patients were significantly more likely to be female, young, nonwhite, atopic, and/or have dermatitis affecting the face; scalp, ears, and/or neck; arm; or trunk. In all, 55.5% of reactions were currently clinically relevant, with a significant increase over time (44.1% to 51.6%). Only 3.7% of reactions were occupationally related with a significant decrease over time (from 7.9 to 1.9%). Jewelry was the most common source of nickel ACD.

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