

ORIGINAL ARTICLE

Epidemiology of pediatric nickel sensitivity: Retrospective review of North American Contact Dermatitis Group (NACDG) data 1994-2014

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Background: Nickel is a common allergen responsible for allergic contact dermatitis.

Objective: To characterize nickel sensitivity in children and compare pediatric cohorts (≤ 5 , 6-12, and 13-18 years).

Methods: Retrospective, cross-sectional analysis of 1894 pediatric patients patch tested by the North American Contact Dermatitis Group from 1994 to 2014. We evaluated demographics, rates of reaction to nickel, strength of nickel reactions, and nickel allergy sources.

Results: The frequency of nickel sensitivity was 23.7%. Children with nickel sensitivity were significantly less likely to be male ($P < .0001$; relative risk, 0.63; 95% confidence interval, 0.52-0.75) or have a history of allergic rhinitis ($P = .0017$; relative risk, 0.74; 95% confidence interval, 0.61-0.90) compared with those who were not nickel sensitive. In the nickel-sensitive cohort, the relative proportion of boys declined with age (44.8% for age ≤ 5 , 36.6% for age 6-12, and 22.6% for age 13-18 years). The most common body site distribution for all age groups sensitive to nickel was scattered/generalized, indicating widespread dermatitis. Jewelry was the most common source associated with nickel sensitivity (36.4%).

Limitations: As a cross-sectional study, no long-term follow-up was available.

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Conclusions: Nickel sensitivity in children was common; the frequency was significantly higher in girls than in boys. Overall, sensitivity decreased with age. The most common source of nickel was jewelry. (J Am Acad Dermatol <https://doi.org/10.1016/j.jaad.2018.02.071>.)

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

Worldwide, nickel is a common allergen associated with allergic contact dermatitis (ACD). This is also true for pediatric populations studied in various geographic regions.¹⁻¹⁵ Of 10 recent studies of contact allergy in children (Table 1),⁶⁻¹⁵ all but 1⁶ found that nickel was the most common allergen detected on patch testing. Frequencies of nickel sensitivity in pediatric populations reported in smaller studies by members of the North American Contact Dermatitis Group (NACDG) (Canadian and US data) over the past decade have ranged from 24% to 28%.^{9,11,15} Notably, 2 non-NACDG, United States-only studies found frequencies of 14% (N = 65)¹⁰ to 22% (N = 1142).¹⁴ In Europe, 5 studies^{6-8,12,13} reported frequencies from 17% (N = 6708)¹² to 33% (N = 500).⁷ Nickel release (not nickel content) is important for nickel ACD. Systemic contact dermatitis in children from nickel in food has also been described.¹⁶

Although nickel sensitivity is reported to be problematic in children, the pediatric population is often under-represented in large-scale epidemiologic studies.¹⁷ Few studies have provided detailed information regarding subgroup demographics or allergen source information in children. It is important to consider pediatric patients separately because potential nickel sources and presentations of nickel-associated ACD may differ from those for adult populations.¹⁸ This study characterizes the epidemiology of pediatric nickel sensitivity in a large referral patch test cohort in North America and compares pediatric cohorts (stratified by age) for sites of nickel dermatitis, clinical relevance of nickel allergy, and the most common sources of nickel allergy.

METHODS

Database

The study was approved by the Minneapolis Veterans Affairs Medical Center's Human Studies

CAPSULE SUMMARY

- Nickel is one of the most common allergens worldwide.
- The frequency of nickel sensitivity in children referred to tertiary referral patch test centers was 23.7%. Frequency was higher in girls and decreased with age; jewelry was the most frequently identified source.
- Nickel sensitivity in children is common and clinically relevant.

Subcommittee (R170802). Methods used by the NACDG for patch testing, evaluation of reactions, and data collection were described previously.¹⁹⁻²³ The screening allergen series comprised 50 to 70 allergens (Chemotechnique Diagnostics AB, Malmö, Sweden, and allergEAZE SmartPractice, Calgary, Canada); nickel (nickel sulfate hexahydrate, 2.5% petrolatum) was the only allergen analyzed for this study. Collected data included demo-

graphics (age, sex, and race), atopic history (allergic rhinitis, eczema, and asthma), dermatitis site(s) (3 maximum), final diagnosis/diagnoses (3 maximum), strength of reaction to nickel, clinical relevance of reaction, and nickel source. For the 1995-1996 data cycle, sources were not collected.

Study population

From January 1, 1994, to December 31, 2014, a total of 1934 pediatric patients were patch tested. Included patients were age 18 years or younger who had been patch tested to nickel (N = 1894).

Study design

Data were originally entered into Access (Access 2010, Microsoft Corp, Redmond, WA) and transferred to Excel (Excel 2010, Microsoft Corp) for analyses. Patients were subdivided according to age: 5 years or younger, 6 to 12 years, and 13 to 18 years. Nickel-sensitive patients were defined as those having a + (weak, nonvesicular erythema with papules, or infiltration), ++ (strong, edematous, or vesicular), +++ (extreme, spreading, bullous, or ulcerative), or doubtful (macular erythema) reaction to nickel on patch testing, regardless of clinical relevance, for which the final interpretation was coded as allergic. Non-nickel-sensitive patients were those who had (1) doubtful reactions not coded with a final interpretation of allergic, (2) irritant reactions, or (3) negative reactions. For clinical relevance analyses, 3 categories were used: *current*, *past*, and *unknown*. *Past* and

Abbreviations used:

ACD:	allergic contact dermatitis
CI:	confidence interval
NACDG:	North American Contact Dermatitis Group
RR:	relative risk

unknown were directly coded in the database. *Current* clinical relevance combined *definite* (result of use test with suspected item containing nickel was positive or result of patch test to the nickel-containing item was positive), *probable* (nickel was verified as present in known skin contactants and clinical presentation was consistent), and *possible* (patient was exposed to circumstances in which skin likely contacted materials known to contain nickel).¹⁹

Statistical analysis

Demographic information, reaction rates, and clinical relevance of reactions were presented as counts and proportions. Nickel-sensitive and non-nickel-sensitive populations were compared by using the Pearson χ^2 . Within the nickel-sensitive cohort, trends were assessed by using the χ^2 test of trends with 1 degree of freedom. Relative risk and confidence intervals were calculated with SAS software (version 9.2, SAS Inc, Cary, NC). In total, 19 comparisons were made and a cutoff of *P* less than .05 was used for statistical significance.

RESULTS

Study population

Of the 1894 pediatric patients patch tested to nickel, 448 were sensitive to nickel (23.7%); of this group, 6.5% (*n* = 29) were age 5 years or younger, 34.2% (*n* = 153) were 6 to 12 years old, and 59.4% (*n* = 266) were 13 to 18 years old (Fig 1).

Demographics

Nickel-sensitive versus non-nickel-sensitive children. Table II summarizes demographics of nickel-sensitive and non-nickel-sensitive children by age, including sex, race, and atopic history. Children with nickel sensitivity were significantly less likely to be male (*P* < .0001; relative risk [RR], 0.63; 95% confidence interval [CI], 0.52-0.75) or have a history of allergic rhinitis (*P* = .0017; RR, 0.74; 95% CI, 0.61-0.90) than those in the non-nickel-sensitive cohort. There was no statistical difference in the frequency of nickel sensitivity by race (white versus nonwhite) in the study population.

Age subgroups. Within the nickel-sensitive cohort, the proportion of boys relative to girls decreased with age (44.8% male for age ≤5, 36.6% for age 6-12, and 22.6% for age 13-18 years [*P* = .0003]). Frequency of eczema similarly decreased with age (*P* = .0005). The proportion of nickel-sensitive whites relative to nonwhites increased with age (*P* = .0007) (Table II). Within the nickel-sensitive group, there was no statistical trend for age or history of allergic rhinitis or asthma (*P* > .05).

Table III summarizes anatomic location(s) of dermatitis and final diagnoses. For all age groups with nickel sensitivity, the most common site was scattered/generalized. The next most common dermatitis sites by age were face, arm, hand, and leg for patients age 5 years or younger; face, trunk, and leg for patients 6 to 12 years old; and face, trunk, and arm for patients age 13 to 18 years. More than 75% of nickel-sensitive children had a final diagnosis of ACD, and ACD was the *primary* diagnosis for more than 58% of patients age 6 to 12 and 13 to 18 years (data not shown). For patients age 5 years or younger, atopic dermatitis was the most common *primary* diagnosis (44.8%), followed by ACD at 41.4% (data not shown).

Pediatric nickel sensitivity

More than two-thirds of positive patch test results were of current clinical relevance (69.4%), and this was consistent for all age subgroups (65.5% currently clinically relevant for ≤5 years, 69.3% for 6-12 years, and 69.9% for 13-18 years) (Table IV). Nickel sensitivity was modestly more prevalent in younger age groups (27.9% for ≤5 years and 25.5% for 6-12 years) than in older children (22.4% for 13-18 years) (Table IV). When the most recent 10 years of the data set were compared with the data from the 10 years before that, the prevalence of nickel sensitivity significantly increased for the oldest age group (13-18 years [*P* = .0009; RR, 1.47; 95% CI, 1.17-1.86]), as well as for the overall pediatric cohort (≤18 years [*P* = .0001; RR, 1.40; 95% CI, 1.17-1.66]). There was no statistically significant change in nickel positivity for the 5 years and younger or 6-12 years age groups (data not shown). The strength of patch test reactions to nickel varied by age (Table V); pairwise comparisons found no statistically significant differences (*P* > .05) in strength of reaction (+++ or ++ versus +/?) and age group (data not shown). Doubtful reactions (macular erythema) comprised very few of the reactions with a final interpretation of allergic (2.2%).

Table I. Recent pediatric studies of nickel sensitivity

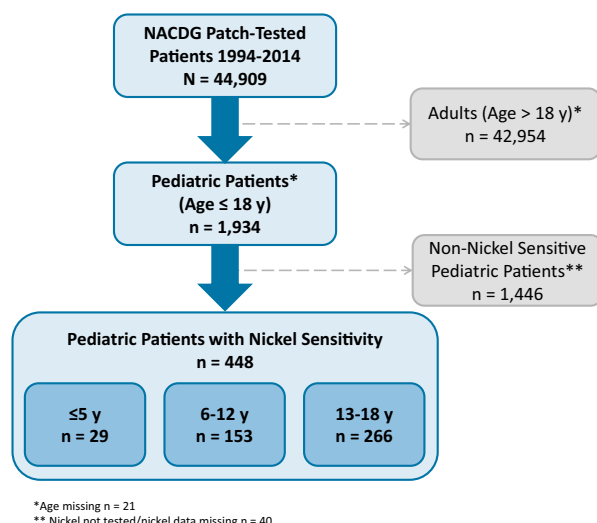
Study	Country/region	Study period	Age range	Population size	Nickel	
					Reaction frequency	Most common allergen?
North America						
Zug et al, 2008 ^{11*†}	United States and Canada	2001-2004	0-18	391	28%	Yes
Hogeling and Pratt 2008 ^{9*†}	Canada	1996-2006	4-18	100	26%	Yes
Ascha et al, 2016 ^{15*†}	Ohio	2005-2015	3-18	157	24%	Yes
Goldenberg et al, 2016 ^{14‡}	United States	2015-2016	0-18	1142	22%	Yes
Jacob et al, 2008 ^{10†}	Florida	2001-2006	1-18	65	14%	Yes
Europe						
Clayton et al, 2006 ^{7†}	United Kingdom	1995-2004	0-16	500	33%	Yes
Beattie et al, 2007 ^{8†}	United Kingdom	1999-2002	3-15	114	20%	Yes
Fernández Vozmediano and Armario Hita, 2005 ^{6†}	Spain	1990-2000	0-15	96	18%	No [§]
Smith et al, 2016 ^{13†}	United Kingdom	2005-2014	0-17	500	18%	Yes
Belloni Fortina et al, 2015 ^{12†}	Europe	2002-2010	1-16	6708	17%	Yes

*Author is a member of the North American Contact Dermatitis Group; children in this study may overlap with those in the current study.

†Study conducted in dermatology clinics.

‡Study conducted in multidisciplinary clinics (dermatology, allergy, primary care).

§Thimerosal and mercury were more common than nickel.

**Fig 1.** Study population. *NACDG*, North American Contact Dermatitis Group.

Sources of nickel sensitivity

Among all pediatric patients, jewelry was the most common source of nickel sensitivity (36.4%) (Table VI). Jewelry was also the most common source for children 6-12 years (28.3%) and 13-18 years (42.9%). In the youngest cohort (≤ 5 years), the most common source was miscellaneous items unspecified (27.6%), with jewelry the second most common (20.7%). The frequency of jewelry as the source of nickel sensitivity increased with age (≤ 5 years, 20.7%; 6-12 years, 28.3%; and 13-18 years, 42.9% [$P = .0006$]).

DISCUSSION

This study resulted in several key findings. First, almost one-fourth (23.7%) of patch tested children were sensitive to nickel; this frequency was higher in younger cohorts. Second, boys were significantly less likely to have nickel sensitivity than girls, and the proportion of boys in the nickel-sensitive cohort decreased with age. Third, more than two-thirds of positive patch test reactions to nickel were +++ or ++ reactions. Finally, jewelry was the most common source of nickel sensitivity overall, and the relative frequency of jewelry compared with other sources was positively correlated with age.

Pediatric nickel sensitivity

The frequency of nickel sensitivity in the pediatric population was 23.7%. This is higher than the frequencies reported in predominantly adult populations (15.5%-20.1%)¹⁹⁻²³ but similar to the US study by Goldenberg et al,¹⁴ who found a positivity frequency of 22% in 1142 children age 0 to 18 years who were patch tested not only in tertiary referral contact dermatitis clinics but also in general dermatology, allergy, and pediatric practices. Frequency of nickel positivity in North American children is much higher than in more recent European studies; a large multicenter European study of 6708 children found that 17% tested positive to nickel.¹² This is possibly due to nickel regulation in Europe and increased public awareness of nickel allergy. Under the European Union Nickel Directive and the Registration, Evaluation, Authorization, and

Table II. Demographics of nickel-sensitive pediatric population by age, sex, race, and atopic history

Demographic characteristic	Nickel-sensitive			Entire nickel-sensitive pediatric (≤ 18 y) population, n (%) [†]	Entire non-nickel-sensitive pediatric (≤ 18 y) population, n (%) [‡]	Sensitive vs non-nickel-sensitive, RR (95% CI), <i>P</i> value
	Age ≤ 5 y, n (%)	Age 6-12 y, n (%) [*]	Age 13-18 y, n (%) [†]			
	n = 29	n = 153	n = 266	n = 448	n = 1446	
Sex						
Male [§]	13 (44.8)	56 (36.6)	60 (22.6)	129 (28.8)	614 (42.5)	0.63 (0.52-0.75), <.0001
Race						
White	21 (72.4)	110 (73.3)	229 (86.1)	360 (80.9)	1,200 (83.4)	0.88 (0.72-1.08), .2123
Nonwhite						
Black	6 (20.7)	17 (11.3)	16 (6.0)	39 (8.8)	97 (6.7)	
Asian	1 (3.4)	11 (7.3)	13 (4.9)	25 (5.6)	70 (4.9)	
Hispanic	0 (0.0)	10 (6.7)	1 (0.4)	11 (2.5)	39 (2.7)	
Other	1 (3.4)	2 (1.3)	7 (2.6)	10 (2.2)	32 (2.2)	
Atopy						
Allergic rhinitis	6 (20.7)	40 (26.1)	66 (24.9)	112 (25.1)	475 (32.9)	0.74 (0.61-0.90), .0017
Eczema [§]	19 (65.5)	82 (53.6)	106 (40.3)	207 (46.5)	675 (46.8)	0.99 (0.84-1.17), .9232
Asthma	11 (37.9)	29 (19.0)	53 (19.9)	93 (20.8)	328 (22.8)	0.91 (0.75-1.12), .3736
Any of aforementioned 3	19 (65.5)	98 (64.1)	144 (54.1)	261 (58.3)	884 (61.2)	0.91 (0.77-1.07), .2698

CI, Confidence interval; RR, relative risk.

*Of nickel-sensitive patients age 6-12 y, race was missing for 3 patients. Denominators adjusted accordingly.

†Of nickel-sensitive patients age 13-18 y, allergic rhinitis status was missing for 1 patient and eczema status was missing for 3 patients. Denominators adjusted accordingly.

‡Of pediatric non-nickel-sensitive patients, race was missing for 8 patients, allergic rhinitis status was missing for 2 patients, eczema status was missing for 3 patients, asthma status was missing for 5 patients, and all atopic history was missing for 1 patient. Denominators adjusted accordingly.

§Male, occupational dermatitis, atopic dermatitis, hand, leg, face, age older than 40 index.

||Signifies a statistically significant value ($P < .05$).

Restriction of Chemicals Regulation, The European Union has implemented restrictions regarding acceptable nickel content of products contacting the skin (eg, jewelry). Following such regulations, significant reductions in the risk of nickel sensitivity after piercing have been reported.²⁴⁻²⁶

Demographics

Girls were significantly more likely to be nickel sensitive than boys. This is likely the result of trends and social norms. A recent NACDG study on the association between piercing and nickel sensitivity in all ages revealed that females were significantly more likely to be pierced than males.²⁷ Piercings are just 1 common mode for exposure to nickel through jewelry. With age, girls may be more likely to encounter high nickel release through piercing jewelry, bracelets, necklaces, hair clips, etc, resulting in higher proportions of girls than boys with nickel allergy with increasing age.

Nickel sources

Nickel release, not nickel content, is important for nickel ACD. Direct (without a barrier) and prolonged (not transient) skin contact with nickel-containing materials is also needed for nickel release to occur.

The European Chemicals Agency defines this as more than 10 minutes on 3 or more occasions within 2 weeks or more than 30 minutes on 1 or more occasions within 2 weeks.²⁸ For all children, as well as for most subgroups, jewelry was the most common source of nickel allergy. However, in the youngest cohort (0-5 years), there were more varied sources of nickel allergy, including miscellaneous items unspecified, shirts, pants, blouses, dresses, skirts, shoes, and other clothing items. The clothing items likely represent sensitization from snaps and buttons.²⁹ Although the term *miscellaneous items unspecified* is not further characterized, it likely represents a wider range of nickel exposures in young children. In this study, some of these sources included cigarette lighters, toys, metal containers (such as makeup containers—children often play with these items from their mother's purse) and metal tops of perfume bottles. Case reports have also highlighted diverse nickel sources in children with nickel allergy, such as a swallowed coin in a 6-year-old,³⁰ metal studs on school chairs in a 10-year-old,³¹ and electronic devices such as cell phones³² and iPads³³ in those 11 to 18 years. Additionally, musical instruments, metal parts in children's toys,³⁴ and food products¹⁶ may also be

Table III. Demographics of nickel-sensitive pediatric patients by age, body location of dermatitis, and final diagnoses

Demographic	Nickel-sensitive			Entire nickel-sensitive pediatric (≤ 18 y) population, n (%) [*]
	Age ≤ 5 y, n (%) n = 29	Age 6-12 y, n (%) n = 153	Age 13-18 y, n (%) n = 266	
Sites[†]				
Scattered/generalized	14 (48.3)	58 (37.9)	81 (30.5)	153 (34.2)
Face ^{‡§}	8 (27.6)	35 (22.9)	80 (30.1)	123 (27.5)
Trunk	2 (6.9)	32 (20.9)	68 (25.6)	102 (22.8)
Arm	3 (10.3)	21 (13.7)	49 (18.4)	73 (16.3)
Leg [‡]	3 (10.3)	32 (20.9)	35 (13.2)	70 (15.6)
Scalp, ears, neck	0 (0.0)	13 (8.5)	47 (17.7)	60 (13.4)
Hand [‡]	3 (10.3)	12 (7.8)	34 (12.8)	49 (10.9)
Foot	1 (3.4)	21 (13.7)	25 (9.4)	47 (10.5)
Other	0 (0.0)	9 (5.9)	10 (3.8)	19 (4.2)
Anal/genital	1 (3.4)	5 (3.3)	1 (0.4)	7 (1.6)
Most exposed areas	1 (3.4)	3 (2.0)	3 (1.1)	7 (1.6)
Only under clothing	0 (0.0)	1 (0.7)	5 (1.9)	6 (1.3)
Final diagnoses[†]				
ACD	22 (75.9)	118 (77.1)	202 (75.9)	342 (76.3)
Atopic dermatitis	15 (51.7)	61 (39.9)	91 (34.2)	167 (37.3)
ICD	1 (3.4)	11 (7.2)	28 (10.5)	40 (8.9)
Other dermatitis	2 (6.9)	11 (7.2)	16 (6.0)	29 (6.5)
Other dermatoses	1 (3.4)	8 (5.2)	15 (5.6)	24 (5.4)
Psoriasis	1 (3.4)	3 (2.0)	6 (2.3)	10 (2.2)
Photo dermatitis	0 (0.0)	3 (2.0)	2 (0.8)	5 (1.1)
Seborrheic dermatitis	0 (0.0)	2 (1.3)	1 (0.4)	3 (0.7)
Pompholyx	0 (0.0)	0 (0.0)	2 (0.8)	2 (0.4)
Stasis dermatitis	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)
Contact urticaria [*]	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)

ACD, Allergic contact dermatitis; ICD, irritant contact dermatitis.

^{*}Diagnosis code unavailable in data from 1994 and 1996 data cycles. Denominators adjusted accordingly.[†]Percentages may sum to greater than 100 because up to 3 sites or final diagnoses could be recorded per patient.[‡]Male, occupational dermatitis, atopic dermatitis, hand, leg, face, age older than 40 index.[§]Face includes face, lips, nose, eyelids, and eyes.^{||}Diagnosis code unavailable in data from 1994 data cycle. Denominators adjusted accordingly.**Table IV.** Frequency of nickel sensitivity and clinical relevance by age

Age group	Total nickel-positive reactions, n (%) [†]	Clinical relevance, n (%) [*]					
		Current				Past, n (%)	Unknown, n (%)
		Definite	Probable	Possible	Total current, n (%) [‡]		
All pediatric (≤ 18 y)	448/1894 (23.7)	12	157	142	311 (69.4)	82 (18.3)	47 (10.5)
≤ 5 y	29/104 (27.9)	0	9	10	19 (65.5)	4 (13.8)	6 (20.7)
6-12 y	153/601 (25.5)	5	48	53	106 (69.3)	23 (15.0)	20 (13.1)
13-18 y	266/1189 (22.4)	7	100	79	186 (69.9)	55 (20.7)	21 (7.9)

^{*}Denominator is the total allergic reactions to nickel in the corresponding age bracket.[†]Denominator is the number of patients tested to nickel, by age bracket.[‡]Includes definite, probable, and possible relevance.

relevant sources of exposure that could be easily overlooked. A recent study by Parker et al³⁵ has further investigated the frequency of nickel release from items in community facilities frequented by children, such as pencil sharpeners (100%), lockers (84%), and plastic bag racks at grocery stores (100%).

Limitations

There were several limitations associated with this study. First, because it was a cross-sectional study, no long-term follow-up was collected. Second, the concentration of nickel used for patch testing in this study was 2.5%, whereas many European clinics

Table V. Strength of nickel reactions in pediatric patients by age

Age group	Strength of nickel reaction, n (%) [*]			
	Extreme (+++)	Strong (++)	Weak (+)	Doubtful
All pediatric (≤18 y)	148 (33.0)	164 (36.6)	126 (28.1)	10 (2.2)
≤5 y	5 (17.2)	11 (37.9)	12 (41.4)	1 (3.4)
6-12 y	63 (41.2)	41 (26.8)	47 (30.7)	2 (1.3)
13-18 y	80 (30.1)	112 (42.1)	67 (25.2)	7 (2.6)

*Denominator is the total allergic reactions to nickel in the corresponding age bracket.

Table VI. Top 3 nickel sources by age

Age group	Top nickel sources
All pediatric (≤18 y)	Jewelry (161/442) Food products (50/442) Belts (29/442)
≤5 y	Miscellaneous items unspecified (8/29) Jewelry (6/29) Shirts, pants, blouses, dresses, skirts* (2/29) Shoes/clothing* (2/29)
6-12 y	Jewelry (43/152) Food products (14/152) Belts (10/152)
13-18 y	Jewelry (112/261) Food products (35/261) Belts (18/261)

No source data collected from the 1994 data cycle (1 nickel-sensitive patient 6-12 years old and 5 nickel-sensitive patients 13-18 years old). Denominators adjusted accordingly. Only specified sources are reported here. If unknown or not applicable was in the top 3 sources, it was excluded. For jewelry, source codes 930 and 931 were combined. No other source codes were combined.

*Designates sources with equal prevalence; thus, more than 3 sources are reported.

utilize a 5% nickel concentration, making direct comparisons difficult. Finally, the study population was a tertiary referral population. Nickel ACD is often diagnosed clinically without patch testing when the source is obvious; when confirmation is needed, often a single patch or a more limited set of allergens is tested. Thus, children in this cohort referred for extensive testing are likely to have severe or resistant disease.

SUMMARY/CONCLUSION

This study was consistent with other recent investigations reflecting high frequencies of nickel allergy in children. Boys were significantly less likely

to have nickel allergy than girls. The most common source of nickel allergy for all children was jewelry, with miscellaneous items most common in the youngest age cohort.

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