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Title: Prevalence and Trend of Allergen Sensitization in Patients with Nummular (Discoid) Eczema Referred for Patch Testing, North American Contact Dermatitis Group Data, 2001-2016

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Funding sources: none

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/cod.13824](https://doi.org/10.1111/cod.13824)

Conflicts of interest:

Denis Sasseville receives royalties from UpToDate (Wolters Kluwer Health)

James S. Taylor owns non-controlling common stock in Cigna, Merck, Johnson and Johnson, Astra Zeneca and Opko Health; is a member of the Cosmetic Ingredient Review Steering Committee; and a non-dependent child is employed by Pfizer.

Erin M. Warshaw has served as a consultant for Wen by Chaz Dean and Noven Pharmaceuticals as well as a grant funded by Wen by Chaz Dean.

Manuscript word count: 2693

Abstract word count: 194

References: 40

Figures: 1

Tables: 5

Supplemental Table: 2

Supplemental Figures: 2

Supplemental Methods: 1 (for Mendeley)

Supplemental Results: 1 (for Mendeley)

Keywords: *epidemiology, nummular eczema, discoid, coin-shaped, allergic contact dermatitis, patch test, dermatitis, rash, pruritus, itch, health*

Abstract:

Background: Few studies examined the relationship between nummular (discoid) eczema (NE) and allergic contact dermatitis (ACD).

Objective: To examine the trends, associations, and clinical relevance of ACD in NE patients referred for patch testing.

Methods: Retrospective analysis of 38,723 patients from the North American Contact Dermatitis Group.

Results: Overall, 748 (1.9%) patients were diagnosed with NE; 23.9% had a concomitant diagnosis of ACD. The prevalence of NE fluctuated over time between 2001-2016, with no overall change in prevalence in diagnosed NE. In multivariable logistic regression models, NE steadily increased with age and was associated with male sex, Asian and other race/ethnicity, and inversely associated with a history of AD and hay fever. Patients with NE had lower proportions of ≥ 1 positive allergic reaction and lower odds of a positive reaction in multiple, individual allergens. The most commonly relevant allergens in patients with NE were formaldehyde 2.0% aq., methylisothiazolinone, quaternium-15, fragrance mix I, and propylene glycol.

Conclusion: NE is a heterogeneous disorder with distinct subsets of lesional distribution and profile of relevant allergens, especially formaldehyde and formaldehyde releasers. Nearly 1 in 4 NE patients had ACD, supporting the role of patch testing in NE patients.

1. Introduction

Nummular eczema (NE) lesions are coin-shaped, erythematous, eczematous, and highly pruritic. They can be idiopathic, a manifestation of atopic dermatitis (AD), particularly in adult and adult-onset AD(1-5), and/or related to underlying allergic contact dermatitis (ACD)(6-9). NE has also been associated with several underlying factors and/or triggers, including xerosis(7, 10), *Staphylococcus aureus* colonization(11), alcohol consumption(12), and specific allergen exposures(7, 11, 13). The pathological and clinical features are usually indistinguishable between the various etiologies(14). As such, patch testing is often indicated to identify ACD as a potential etiology.

Few studies examined the relationship between NE and ACD or the most common allergens associated with NE(8, 10, 13). Given regional differences and shifting trends in personal care products (PCP) and environmental exposures, it is unclear whether the results of previous studies are generalizable to North America (or elsewhere). Moreover, there is a need to understand the profile of allergens that are most relevant in NE patients. Using a large, North American cohort of patients referred for patch testing, this retrospective study examined temporal trends, demographic associations, and the frequency and clinical relevance of the allergens among patients with a final diagnosis of NE.

2. Methods

North American Contact Dermatitis Group (NACDG) Database

This study analyzed de-identified data from 38,723 individuals who were patch tested by the NACDG from 2001 to 2016 using standardized methods (Supplemental Methods)(15-18). Data were entered at a centralized location (Access 2010 and Excel 2019; Microsoft). This study was approved by the Institutional Review Board at Northwestern University.

NE Subsets

Subsets were grouped by the presence or absence of a final diagnosis (1 of 3 final diagnoses) of NE. A sensitivity analysis was also performed based on NE as the primary final diagnosis with the exclusion of patients with NE as the secondary or tertiary diagnosis.

Statistical Analysis

Data were analyzed using SAS version 9.4 software (SAS Institute, Cary, NC). The frequency and proportion of patients with any (of 3) and/or a primary diagnosis of NE were estimated. The proportion and frequency of the dermatitis sites were estimated for and compared between patients with and without NE using Chi-square tests.

Summary statistics were estimated for patient age, sex, race/ethnicity, employment, and history of AD, asthma, and hay fever in patients with and without NE. Multivariable models were created with any diagnosis of NE or a primary diagnosis of NE vs. no NE as the dependent variable, and the aforementioned demographic characteristics as the independent variables. Additional models were constructed with ≥ 1 positive allergic reaction (yes/no) or relevant

allergic reaction (yes/no) as the dependent variable among patients with a diagnosis of NE.

Adjusted OR (aOR) and 95% confidence intervals (95% CI) were estimated.

Proportions of patients with any and a primary diagnosis of NE were estimated by 2-year cycle (2001-2002/2003-2004/2005-2006/-2007-2008/2009-2010/2011-2012/2013-2014/2015-2016) and were plotted.

The proportion of allergens with a positive patch reaction and relevant patch test results were determined in those with and without a final diagnosis of NE, sorted in descending order, and analyzed using Chi-square analysis. The mean number $\pm$ standard deviation (SD) of positive allergens was estimated and compared using t-test analysis. To determine the association between each specific allergen with NE, multivariable logistic regression models were constructed with any diagnosis or a primary diagnosis of NE (yes/no) as the dependent variable, and the top 25 most common (yes/no) or most relevant (definite, probable, or possible/negative [past relevance excluded]) as the independent variable, and age, sex, race/ethnicity, and history of AD, asthma, and hay fever as the covariates.

The significance-prevalence index number (SPIN) was estimated using a weighted calculation incorporating the allergen's prevalence and relevance to determine the relative importance of each allergen ($[\text{proportion of population allergic}] * [1 * \text{percentage with definite relevance} + 0.66 * \text{percentage with probable relevance} + 0.33 * \text{percentage with possible relevance}] * 100$)(19). Among patients with a final diagnosis of NE, SPIN scores for each allergen were estimated biennially, averaged, and sorted in descending order. The top 10 allergens based on SPIN were also compared between different demographics and clinical characteristics.

The frequency and proportion of those with an occupationally relevant allergen were estimated in patients with and without NE and compared using Chi-square analysis.

Complete case analysis was performed. Post-hoc correction was performed for multiple testing using the Benjamini-Hochberg method and yielded a critical P-value of 0.0148.

3. Results

Population Characteristics

The cohort consisted of 38,723 individuals (mean±SD age: 48±17 years), of which 32.8% were male, 86.3% white, 61.6% employed, and 23.8%, 15.2%, and 29.3% had a self-reported history of AD, asthma, and hay fever, respectively (Table 1).

Overall, 748 (1.9%) patients had NE as one of three final diagnoses, and 616 (1.5%) had NE as the primary diagnosis. The prevalence of NE fluctuated over time between 2001-2002 and 2015-2016, with no overall change in prevalence in any diagnosis or primary diagnosis of NE (Supplemental Figure 1).

Characteristics of NE patients

Patients with vs. without NE had higher proportions of dermatitis in a generalized distribution (54.7% vs. 21.7%), as well as a dermatitis affecting the trunk (18.9% vs. 12.3%) and legs (24.1% vs. 10.7%) (Chi-square, $P<0.0001$ for all) (Figure 1). NE patients were less likely to have any involvement of the face, eyelids, neck, lips, ears, anogenital, exposed and other regions ($P\leq 0.0117$). There were no associations of NE with dermatitis of the nose, foot, arm, or clothing-covered sites (i.e. multiple sites but not hands, feet, head or neck) ($P\geq 0.0353$).

Among patients diagnosed with NE, 68.9% had NE alone, while 23.9%, 3.5%, and 3.7% had a concomitant diagnosis of ACD, irritant contact dermatitis, and AD, respectively. In multivariable logistic regression models, NE steadily increased with age, peaking at age >70 years, and was associated with male sex, Asian and other race/ethnicity, and inversely associated with self-reported history of AD and hay fever, but not associated with employment or history of asthma.

Positive allergic reactions in patients with a final diagnosis of NE

Patients with any NE or primary NE had significantly lower proportions of ≥ 1 positive allergic patch test reactions (49.5% and 44.8% vs. 65.0%) and a lower mean $\pm$ std. dev. number (1.1 ± 1.7 and 0.9 ± 1.4 vs. 1.8 ± 2.2) of allergic patch test reactions compared to those without NE ($P < 0.0001$ for all). Likewise, patients with any diagnosis or a primary diagnosis of NE had lower proportions of ≥ 1 positive patch test reactions to non-NACDG allergens than those without NE (7.9% and 6.2% vs. 22.3%, $P < 0.0001$).

The 10 NACDG screening allergens with highest proportions of positive reactions in patients with any diagnosis of NE were thimerosal 0.1% petrolatum (pet.) (13.3%), formaldehyde 2.0% aqueous (aq.) (9.9%), nickel sulfate hexahydrate 2.5% pet. (9.5%), *Myroxylon pereirae* resin 25.0% pet. (6.0%), bacitracin 20.0% pet. (5.9%), fragrance mix I 8.0% pet. (5.9%), propylene glycol 100% (5.4%), benzalkonium chloride 0.1% aq. (5.3%), cobalt (ii) chloride hexahydrate 1.0% pet. (5.1%), and quaternium 15 2.0% pet. (5.1%) (Table 2). Results were similar in patients with a primary diagnosis of NE, with the addition of sodium gold thiosulfate 0.5% pet. (5.2%) and the exclusion of quaternium 15 2.0% pet. (Supplemental Table 1).

Those with any diagnosis of NE had lower odds of a positive reaction to nickel sulfate hexahydrate 2.5% pet., *Myroxylon pereirae* resin 25.0% pet., fragrance mix I 8.0% pet., neomycin sulfate 20.0% pet., formaldehyde 1.0% aq., and methylisothiazolinone 0.1% aq. (1000 ppm) (Table 2). A primary diagnosis of NE was similarly associated with lower odds of these allergens, as well as quaternium 15 2.0% pet., carba mix 3.0% pet., and iodopropynyl butylcarbamate 0.5% pet. (Supplemental Table 1).

Allergen relevance in patients with NE

The 5 allergens with the highest proportions of current relevance in patients with any diagnosis of NE were formaldehyde 2.0% aq., methylisothiazolinone 0.1% aq. (1000 ppm), quaternium 15 2.0% pet., fragrance mix I 8.0% pet., and propylene glycol 100% (Table 3). Results were similar in patients with a primary diagnosis of NE (Supplemental Table 2).

Patients with any diagnosis of NE were less likely to have the following relevant positive allergens: fragrance mix I 8.0% pet., fragrance mix II 14.0% pet., *Myroxylon pereirae* resin 25.0% pet., formaldehyde 1.0% aq., carba mix 3.0% pet., nickel sulfate hexahydrate 2.5% pet., iodopropynyl butylcarbamate 0.5% pet., methyldibromoglutaronitrile/phenoxyethanol 2.0% pet., or thiuram mix 1.0% pet. (Table 3). Results were similar in a primary diagnosis of NE with lower likelihood of relevance from methylisothiazolinone 0.1% aq. (1000 ppm), quaternium 15 2.0% pet., and diazolidinyl urea 1.0% pet. (Supplemental Table 2).

There were no significant differences of demographics, atopic history, or dermatitis distribution with positive and/or relevant patch test reactions (Table 4).

SPIN

In patients with any diagnosis or a primary diagnosis of NE, the allergens with the highest mean SPIN score included formaldehyde 2.0% aq., methylisothiazolinone 0.1% aq. (1000 ppm), quaternium-15 2.0% pet., bacitracin 20.0% pet., fragrance mix I 8.0% pet. and propylene glycol 100%. (Supplemental Figure 2A-B). Additional allergens with high mean SPIN scores are also included in these figures. These allergens and/or their co-reactors (neomycin sulfate 20.0% pet. with bacitracin 20.0% pet.) or cross-reactors (*Myroxylon pereirae* resin 25.0%

pet. with fragrance mix I 8.0% pet.; diazolidinyl urea 1.0% pet. and 2-bromo-2-nitropropane - 1,3-diol 0.5% pet. with formaldehyde 1.0 and 2.0% aq. and quaternium 15 2.0% pet.) had the highest SPIN scores in those with any dermatitis involving a generalized distribution, trunk or legs (Table 5). However, there were some notable differences. Methylisothiazolinone 0.1% aq. (1000 ppm) had the highest SPIN for the trunk. Methylidibromoglutaronitrile/phenoxyethanol 0.4% pet. constituted the top two SPIN scores for lesions affecting the trunk and legs, but not generalized distribution. In contrast, methylidibromoglutaronitrile/phenoxyethanol 0.4% pet. had much lower SPIN overall, being ranked only number 20 among those with any NE diagnosis.

Occupationally relevant allergens in NE patients

Patients with any diagnosis of NE had lower proportions of ≥ 1 occupationally relevant allergen (3.6% vs. 11.7%; Chi-square, $P < 0.0001$).

4. Discussion

This study found that approximately one-quarter of patients referred for patch testing with a final diagnosis of NE also had a final diagnosis of ACD. NE patients were less likely to have any positive patch tests and had fewer patch test reactions compared to those without NE. There were no significant differences in patient characteristics associated with ≥ 1 positive and/or relevant patch test. That is, all patient subsets had similar likelihood of having a final diagnosis of ACD. However, the most impactful allergens in those with NE as determined by SPIN, a measure of allergen prevalence and relevance, varied by the site of dermatitis. Of note, the highest SPIN observed in NE patients are considerably lower than the highest SPIN observed in patients referred for patch testing overall(16) and with hand eczema(20). This further indicates that NE patients are less likely to have a positive and/or relevant allergic reaction. Together, these results indicate that NE is a heterogeneous disorder with variable etiologies. An Italian study including 1022 patients with a final diagnosis of NE evaluated between 1982 and 2009 found a lower prevalence of ≥ 1 positive patch test reaction (32.5%)(8). However, the prevalence of contact positivity in NE patients widely varied across studies that had disparate study sampling, methodology, and quality (32.5-77.9%)(8, 10, 13, 21, 22). Nonetheless, the results suggest that patch testing may play a role in the assessment of NE patients.

We found that many common allergens in North America were frequently positive in NE patients, including thimerosal 0.1% pet., nickel sulfate hexahydrate 2.5% pet., cobalt (ii) chloride hexahydrate 1.0% pet. and para-phenylenediamine 1.0% pet. However, these allergens were often not relevant in NE patients. There was a distinct profile of relevant allergens in NE patients, with formaldehyde 2.0% aq., methylisothiazolinone 0.1% aq. (1000 ppm), quaternium 15 2.0% pet., fragrance mix I 8.0% pet., and propylene glycol 100% being most relevant. These

results differ from the abovementioned Italian study that found sensitization most commonly to nickel sulfate, potassium dichromate, cobalt chloride, and para-phenylenediamine (8). The differences might be attributable to different allergen exposures by region. However, that study did not examine specific allergen relevance (8) and may have overestimated clinical relevance for some often irrelevant allergens.

Formaldehyde and formaldehyde releasing preservatives were among the most commonly positive and clinically relevant allergens in patients with NE, although still at lower proportions than those without NE. Formaldehyde exposure can occur from PCP, household cleaners, occupations involving fabrics, building materials, and paint, medications, and sources of smoke, and can potentially even cause systemic contact dermatitis(23-26).

Methylisothiazolinone is a preservative that can be found in every class of PCP and variety of industrial exposures(27-29). Proportions of positive reactions to methylisothiazolinone were lower in patients with NE. Fragrance mix I is a combination of 8 chemical fragrances that is commonly used in PCP, perfumes, lotions, and detergents, as well as the workplace(30, 31). Propylene glycol is a ubiquitous allergen found in PCP, medications, and foods as an emollient and an emulsifier(32, 33). Positive reactions to propylene glycol were found in similar proportions in those with and without NE. It is unknown how these allergens, particularly formaldehyde and formaldehyde releasers, specifically relate to NE. We speculate that these allergens may induce a T-helper (Th-)17 and/or Th2 response in skin(34), which have both been shown to be upregulated in NE(35). Alternatively, NE patients may have developed secondary ACD through application of emollients and topical medications to their NE lesions.

These results provide important context for clinicians who are considering patch testing in patients with NE. First, approximately 25% of patients referred for patch testing with a final

diagnosis of NE also had a final diagnosis of ACD. However, clinicians and patients should have a realistic understanding that there is a lower likelihood of testing positive in NE compared to other patients referred for patch testing. The Thin-Layer Rapid-Use Epicutaneous test (T.R.U.E.) includes most of the most common relevant allergens that we observed with a final diagnosis of NE(36). However, clinicians should consider supplementing with additional allergens common in NE, such as propylene glycol. Additionally, a small subset of NE patients had a positive reaction to non-NACDG allergens and occupationally relevant allergens, indicating the need for supplemental testing in patients with NE.

NE was associated with older age, male sex, employment, Asian and other race, but inversely associated with a history of AD or hay fever. Less than 1% of NE patients referred for patch testing were children, consistent with previous findings that NE is rare in children(8, 37). Our results also confirm the predilection of NE for males(8, 10). Previous studies found conflicting results about the association of NE with AD and atopic disease. Some studies found low or normal rates of personal ($\leq 11\%$) or family history ($\leq 15\%$) of atopy in NE patients(38, 39). One study found high rates of personal (50%) and family history (38%) of atopy in NE(10). A study of 26 NE patients found lower serum immunoglobulin E levels compared to AD(40). It may be that clinicians were more inclined to assign a final diagnosis of AD if the patient had a history of atopy and a final diagnosis NE if not. Further research is needed to elucidate the relationship between NE and atopy.

There are several limitations to this study. Since there are no formal diagnostic criteria for NE, there may be variability or misclassification in how NE was defined. Some consider NE as a diagnosis of exclusion in the setting of negative patch test results, which may partially explain the lower proportions of allergen sensitization observed in NE patients. Whereas, others

interpret NE as dermatitis with a predominant nummular morphology. Additional limitations include a lack of data on NE onset and phenotype and on patient follow-up encounters, precluding analysis of improvement after allergen avoidance to confirm relevance. Clinical relevance was assessed at the time of final patch reading and not at follow-up. We did not analyze allergen sources in this study. Also, the NACDG cohort consists of patients who were referred for patch testing and results may not be generalizable to the overall population.

In conclusion, a final diagnosis of NE in patients referred for patch testing was associated with a distinct profile of relevant allergens, especially formaldehyde and formaldehyde releasers. Approximately 25% of patients with a final diagnosis of NE were also diagnosed with ACD, supporting the role of patch testing in select NE patients.

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Figures

Figure 1. Distribution of sites of dermatitis in patients with (light grey) and without (dark grey)

NE. P-values refer to Chi Square analysis.

Table 1. Association of nummular eczema with demographics and atopic history.

Variable	Overall (n=38613)	Nummular Eczema							
		Nummular Eczema coded as the Primary/Secondary Diagnosis (n=748)				Nummular Eczema coded as the Primary Diagnosis (n=616)			
		No	Yes	Adjusted OR	P	No	Yes	Adjusted OR	P
	Freq (%)	Freq (%)	Freq (%)	(95% CI)		Freq (%)	Freq (%)	(95% CI)	
Age (yr)									
0-17	1631 (4.2%)	1618 (99.2%)	13 (0.8%)	1.000 [ref]	-	1621 (99.4%)	9 (0.6%)	1.000 [ref]	-
18-30	4932 (12.7%)	4883 (99.0%)	49 (1.0%)	1.198 (0.626-2.293)	0.5863	4893 (99.2%)	38 (0.8%)	1.281 (0.608-2.698)	0.5144
31-40	6107 (15.8%)	6010 (98.4%)	97 (1.6%)	1.733 (0.928-3.236)	0.0846	6027 (98.8%)	76 (1.2%)	1.870 (0.914-3.828)	0.0867
41-50	8033 (20.8%)	7899 (98.3%)	134 (1.7%)	1.846 (0.997-3.419)	0.0512	7920 (98.7%)	107 (1.3%)	2.041 (1.007-4.135)	0.0478
51-60	8539 (22.1%)	8367 (98%)	172 (2.0%)	2.243 (1.221-4.122)	0.0093	8382 (98.3%)	146 (1.7%)	2.625 (1.308-5.269)	0.0066
61-70	5772 (14.9%)	5621 (97.4%)	151 (2.6%)	3.116 (1.708-5.683)	0.0002	5640 (97.8%)	128 (2.2%)	3.591 (1.803-7.151)	0.0003
>70	3686 (9.5%)	3554 (96.4%)	132 (3.6%)	4.343 (2.381-7.925)	<0.0001	3566 (96.8%)	116 (3.2%)	5.105 (2.565-10.16)	<0.0001
Sex									
Female	26030 (67.2%)	25700 (98.7%)	330 (1.3%)	0.406 (0.350-0.472)	<0.0001	25737 (99.0%)	270 (1.0%)	0.397 (0.337-0.468)	<0.0001
Male	12689 (32.8%)	12271 (96.7%)	418 (3.3%)	1.000 [ref]	-	12331 (97.2%)	350 (2.8%)	1.000 [ref]	-
Race/ethnicity									
White	33230 (86.3%)	32609 (98.1%)	621 (1.9%)	1.000 [ref]	-	32695 (98.5%)	510 (1.5%)	1.000 [ref]	-
Black	1941 (5.0%)	1910 (98.4%)	31 (1.6%)	0.926 (0.635-1.351)	0.6904	1915 (98.8%)	24 (1.2%)	0.858 (0.558-1.322)	0.4883
Hispanic	749 (1.9%)	731 (97.6%)	18 (2.4%)	1.476 (0.915-2.382)	0.1107	732 (97.9%)	16 (2.1%)	1.607 (0.967-2.669)	0.0670
Asian	1909 (5.0%)	1850 (96.9%)	59 (3.1%)	2.137 (1.622-2.816)	<0.0001	1854 (97.3%)	52 (2.7%)	2.350 (1.751-3.154)	<0.0001
Other	659 (1.7%)	640 (97.1%)	19 (2.9%)	1.752 (1.084-2.83)	0.0220	641 (97.3%)	18 (2.7%)	2.164 (1.337-3.504)	0.0017
Occupation									
Unemployed	14365 (38.4%)	14087 (98.1%)	278 (1.9%)	1.000 [ref]	-	14113 (98.3%)	242 (1.7%)	1.000 [ref]	-
Employed	23071 (61.6%)	22609 (98.0%)	462 (2.0%)	1.279 (1.061-1.542)	0.0098	22677 (98.4%)	373 (1.6%)	1.204 (0.983-1.474)	0.0733
Atopic disease									
Atopic dermatitis									
No	29385 (76.2%)	28751 (97.8%)	634 (2.2%)	1.000 [ref]	-	28826 (98.2%)	533 (1.8%)	1.000 [ref]	-
Yes	9183 (23.8%)	9069 (98.8%)	114 (1.2%)	0.757 (0.609-0.941)	0.0121	9091 (99.1%)	87 (0.9%)	0.725 (0.568-0.926)	0.0101
Asthma									
No	32745 (84.8%)	32076 (98.0%)	669 (2.0%)	1.000 [ref]	-	32158 (98.3%)	560 (1.7%)	1.000 [ref]	-
Yes	5873 (15.2%)	5795 (98.7%)	78 (1.3%)	0.829 (0.642-1.071)	0.1513	5809 (99.0%)	60 (1.0%)	0.824 (0.619-1.097)	0.1852
Hay fever									
No	27283 (70.7%)	26698 (97.9%)	585 (2.1%)	1.000 [ref]	-	26763 (98.2%)	497 (1.8%)	1.000 [ref]	-
Yes	11330 (29.3%)	11169 (98.6%)	161 (1.4%)	0.826 (0.683-1.001)	0.0506	11200 (98.9%)	122 (1.1%)	0.756 (0.610-0.938)	0.0109

Missing values were encountered in 23 (0.06%) for age, 4 (0.01%) for sex, 235 (0.61%) for race/ethnicity, 1287 (3.3%) for occupation, 155 (0.40%) for history of eczema, 105 (0.27%) for history of asthma and 110 (0.28%) for history of hay fever.

Table 2. Most common positive allergic reactions in patients with a primary or secondary diagnosis of nummular eczema.

Allergen	No Diagnosis of Nummular Eczema			Primary/Secondary Nummular Eczema			Adjusted OR (95% CI)	P-value
	No. of pts tested	Allergic reaction, n (%)	Rank order	No. of pts tested	Allergic reaction, n (%)	Rank order		
Thinolone 0.1% pet.	4823	493 (10.2%)	3	75	10 (13.3%)	1	1.584 (0.801-3.131)	0.18578
Formaldehyde, 2.0% aq.	5499	503 (9.1%)	6	81	8 (9.9%)	2	0.930 (0.442-1.957)	0.84737
Nickel sulfate hexahydrate, 2.5% pet.	37828	6772 (17.9%)	1	748	71 (9.5%)	3	0.662 (0.513-0.854)	0.00147
Shirley's Resin (Balsam of Peru), 25.0% pet.	37949	3176 (8.4%)	8	748	45 (6.0%)	4	0.617 (0.454-0.838)	0.00198
Bacitracin, 20.0% pet.	37917	2855 (7.5%)	9	748	44 (5.9%)	5	0.762 (0.559-1.037)	0.08418
Emulphor mix I, 8.0% pet.	37910	3770 (9.9%)	4	748	44 (5.9%)	5	0.511 (0.374-0.699)	<0.0001
Propylene glycol, 100%	10432	347 (3.3%)	21	167	9 (5.4%)	7	1.369 (0.688-2.724)	0.37037
Benzalkonium Chloride, 0.1% aq.	4816	226 (4.7%)	14	75	4 (5.3%)	8	1.029 (0.368-2.871)	0.95704
Cobalt (ii) chloride hexahydrate, 1.0% pet.	37907	2819 (7.4%)	10	748	38 (5.1%)	9	0.843 (0.605-1.174)	0.31209
Quaternium 15, 2.0% pet.	37937	2564 (6.8%)	12	748	38 (5.1%)	9	0.674 (0.484-0.938)	0.01943
Sodium gold thiosulfate, 0.5% pet.	9810	968 (9.9%)	4	197	9 (4.6%)	11	0.553 (0.28-1.092)	0.08802
Chlorhexidine sulfate, 20.0% pet.	37902	3357 (8.9%)	7	748	34 (4.5%)	12	0.507 (0.357-0.721)	0.00016
Formaldehyde, 1.0% aq.	37942	2654 (7.0%)	11	748	33 (4.4%)	13	0.520 (0.363-0.744)	0.00035
Diphenylguanidine, 1% pet.	10431	318 (3.0%)	24	167	7 (4.2%)	14	1.020 (0.471-2.212)	0.95956
Methylisothiazolinone, 0.1% aq. (1000 ppm)	10428	1211 (11.6%)	2	167	7 (4.2%)	14	0.313 (0.146-0.67)	0.00277
Methyldibromoglutaronitrile/Phenoxyethanol,(Euxyl K 400), 2.0% pet.	37915	1719 (4.5%)	15	747	29 (3.9%)	16	0.695 (0.476-1.014)	0.05877
4-phenylenediamine, 1.0% pet.	37882	2062 (5.4%)	13	748	28 (3.7%)	17	0.665 (0.451-0.982)	0.04006
Color mix, 3.0% pet.	37940	1595 (4.2%)	17	748	28 (3.7%)	17	0.679 (0.46-1.004)	0.05217
Carmin, 2.5% pet.	4152	139 (3.3%)	21	82	3 (3.7%)	17	1.434 (0.441-4.661)	0.54908
Diazolidinyl urea (Germall II), 1.0% aq.	19143	405 (2.1%)	37	400	11 (2.8%)	20	1.033 (0.559-1.909)	0.91705
Methyldibromoglutaronitrile/Phenoxyethanol,(Euxyl K 400), 0.4% pet.	4821	114 (2.4%)	31	75	2 (2.7%)	21	1.027 (0.246-4.294)	0.97098
Ammonium Persulfate, 2.5% pet.	5503	103 (1.9%)	40	81	2 (2.5%)	22	1.268 (0.302-5.314)	0.74551
Propylene glycol, 30.0% aq.	37925	978 (2.6%)	28	748	19 (2.5%)	22	0.825 (0.52-1.311)	0.41632
2-bromo-2-nitropropane -1,3-diol (Bronopol), 0.5% pet.	33761	763 (2.3%)	34	666	16 (2.4%)	24	1.021 (0.617-1.69)	0.93532
Amidazolidinyl urea, 2.0% pet.	37920	734 (1.9%)	40	748	17 (2.3%)	25	0.868 (0.531-1.419)	0.57269

Table 3. Most common relevant allergens in adults with a primary or secondary diagnosis of nummular eczema.

Allergen	Rank order of allergen relevance in primary or secondary diagnosis of nummular eczema	Primary or secondary diagnosis of nummular eczema	Relevance of allergens - freq. (%)					Adjusted OR (95% CI)*	P-value
			Not relevant allergen	Definite	Probable	Possible	Past		
Formaldehyde, 2.0% aq.	1	No	5015 (93.0%)	5 (0.1%)	108 (2.0%)	255 (4.7%)	8 (0.1%)	1.00[ref]	-
		Yes	73 (92.4%)	0 (0%)	0 (0%)	5 (6.3%)	1 (1.3%)	0.777 (0.309-1.954)	0.59184
Methylisothiazolinone, 0.1% aq. (1000 ppm)	2	No	9135 (88.3%)	90 (0.9%)	622 (6.0%)	468 (4.5%)	28 (0.3%)	1.00[ref]	-
		Yes	157 (94.0%)	0 (0%)	4 (2.4%)	6 (3.6%)	0 (0%)	0.457 (0.24-0.871)	0.01727
Quaternium 15, 2.0% pet.	3	No	35173 (93.3%)	74 (0.2%)	788 (2.1%)	1540 (4.1%)	107 (0.3%)	1.00[ref]	-
		Yes	708 (95.0%)	0 (0%)	2 (0.3%)	34 (4.6%)	1 (0.1%)	0.686 (0.489-0.963)	0.02957
Fragrance mix I, 8.0% pet.	4	No	33794 (90.2%)	85 (0.2%)	1144 (3.1%)	2264 (6.0%)	164 (0.4%)	1.00[ref]	-
		Yes	704 (95.1%)	0 (0%)	5 (0.7%)	28 (3.8%)	3 (0.4%)	0.423 (0.297-0.601)	<0.0001
Polyethylene glycol, 100%	5	No	10054 (96.8%)	24 (0.2%)	193 (1.9%)	110 (1.1%)	4 (0%)	1.00[ref]	-
		Yes	158 (95.8%)	0 (0%)	2 (1.2%)	5 (3.0%)	0 (0%)	1.162 (0.537-2.513)	0.70343
Myroxylon Pereirae Resin (Balsam of Peru), 25.0% pet.	6	No	34311 (91.5%)	46 (0.1%)	1016 (2.7%)	2002 (5.3%)	121 (0.3%)	1.00[ref]	-
		Yes	701 (95.8%)	0 (0%)	3 (0.4%)	26 (3.6%)	2 (0.3%)	0.405 (0.278-0.589)	<0.0001
Formaldehyde, 1.0% aq.	7	No	35096 (93.6%)	31 (0.1%)	710 (1.9%)	1595 (4.3%)	66 (0.2%)	1.00[ref]	-
		Yes	713 (95.8%)	0 (0%)	3 (0.4%)	26 (3.5%)	2 (0.3%)	0.527 (0.362-0.768)	0.00084
Diazolidinyl urea (Germall II), 1.0% aq.	8	No	18674 (97.8%)	23 (0.1%)	162 (0.8%)	234 (1.2%)	7 (0%)	1.00[ref]	-
		Yes	386 (97.0%)	2 (0.5%)	3 (0.8%)	7 (1.8%)	0 (0%)	1.092 (0.607-1.966)	0.76839
Diphenylguanidine, 1% pet.	9	No	10082 (97.6%)	16 (0.2%)	49 (0.5%)	157 (1.5%)	21 (0.2%)	1.00[ref]	-
		Yes	159 (96.4%)	1 (0.6%)	1 (0.6%)	3 (1.8%)	1 (0.6%)	1.060 (0.427-2.631)	0.89943
Bacitracin, 20.0% pet.	10	No	34971 (93.6%)	198 (0.5%)	618 (1.7%)	436 (1.2%)	1148 (3.1%)	1.00[ref]	-
		Yes	702 (94.9%)	2 (0.3%)	14 (1.9%)	5 (0.7%)	17 (2.3%)	0.792 (0.511-1.23)	0.29943
Polyethylene glycol, 30.0% aq.	11	No	36727 (97.3%)	140 (0.4%)	444 (1.2%)	421 (1.1%)	16 (0%)	1.00[ref]	-
		Yes	726 (97.3%)	4 (0.5%)	3 (0.4%)	13 (1.7%)	0 (0%)	0.857 (0.545-1.345)	0.50181
Carba mix, 3.0% pet.	12	No	36159 (96.0%)	107 (0.3%)	490 (1.3%)	793 (2.1%)	111 (0.3%)	1.00[ref]	-
		Yes	716 (97.5%)	0 (0%)	2 (0.3%)	15 (2.0%)	1 (0.1%)	0.514 (0.316-0.835)	0.00719
Neomycin sulfate, 20.0% pet.	13	No	34345 (92.4%)	141 (0.4%)	484 (1.3%)	438 (1.2%)	1762 (4.7%)	1.00[ref]	-
		Yes	711 (96.6%)	2 (0.3%)	9 (1.2%)	5 (0.7%)	9 (1.2%)	0.679 (0.412-1.121)	0.13045
Nickel sulfate hexahydrate, 2.5% pet.	14	No	30975 (83.8%)	131 (0.4%)	129 (3.5%)	2485 (6.7%)	2103 (5.7%)	1.00[ref]	-
		Yes	668 (92.3%)	0 (0%)	3 (0.4%)	13 (1.8%)	40 (5.5%)	0.269 (0.163-0.444)	<0.0001

Imidazolidinyl urea, 2.0% pet.	15	No	37084 (97.9%)	28 (0.1%)	239 (0.6%)	490 (1.3%)	27 (0.1%)	1.00[ref]	-
		Yes	730 (98.0%)	0 (0%)	3 (0.4%)	12 (1.6%)	0 (0%)	0.760 (0.452-1.278)	0.30062
Isopropyl propenyl butylcarbamate, 0.5% pet.	16	No	26870 (96.6%)	30 (0.1%)	358 (1.3%)	525 (1.9%)	22 (0.1%)	1.00[ref]	-
		Yes	535 (98.2%)	0 (0%)	1 (0.2%)	9 (1.7%)	0 (0%)	0.456 (0.242-0.857)	0.01481
Decyl glucoside, 5.0% pet.	17	No	18412 (98.4%)	25 (0.1%)	85 (0.5%)	165 (0.9%)	16 (0.1%)	1.00[ref]	-
		Yes	339 (98.3%)	0 (0%)	2 (0.6%)	4 (1.2%)	0 (0%)	1.011 (0.413-2.48)	0.98011
DMDM hydantoin (Germall 115), 1.0% pet.	18	No	37206 (98.2%)	39 (0.1%)	225 (0.6%)	392 (1%)	17 (0%)	1.00[ref]	-
		Yes	734 (98.3%)	0 (0%)	3 (0.4%)	10 (1.3%)	0 (0%)	0.877 (0.503-1.531)	0.64494
Diazolidinyl urea (Germall II), 1.0% pet.	19	No	36959 (97.6%)	56 (0.1%)	286 (0.8%)	530 (1.4%)	28 (0.1%)	1.00[ref]	-
		Yes	733 (98.3%)	1 (0.1%)	2 (0.3%)	10 (1.3%)	0 (0%)	0.576 (0.331-1.004)	0.05171
Methyldibromoglutaronitrile/Phenoxyethanol,(Euxyl K 400), 2.0% pet.	20	No	35983 (96.3%)	40 (0.1%)	416 (1.1%)	849 (2.3%)	82 (0.2%)	1.00[ref]	-
		Yes	719 (97.7%)	0 (0%)	1 (0.1%)	12 (1.6%)	4 (0.5%)	0.404 (0.233-0.703)	0.00135
Fragrance mix II, 14.0% pet.	21	No	22521 (95.3%)	27 (0.1%)	435 (1.8%)	612 (2.6%)	34 (0.1%)	1.00[ref]	-
		Yes	451 (98.3%)	0 (0%)	1 (0.2%)	7 (1.5%)	0 (0%)	0.386 (0.191-0.779)	0.00793
Imidazolidinyl urea, 2.0% aq.	22	No	18870 (98.6%)	10 (0.1%)	96 (0.5%)	155 (0.8%)	7 (0%)	1.00[ref]	-
		Yes	393 (98.5%)	0 (0%)	1 (0.3%)	5 (1.3%)	0 (0%)	0.823 (0.362-1.872)	0.64294
Thiuram mix, 1.0% pet.	23	No	36526 (96.7%)	101 (0.3%)	430 (1.1%)	572 (1.5%)	137 (0.4%)	1.00[ref]	-
		Yes	732 (98.4%)	0 (0%)	2 (0.3%)	8 (1.1%)	2 (0.3%)	0.439 (0.235-0.824)	0.0103
2,2-Dibromo-2-nitropropane -1,3-diol (Bronopol), 0.5% pet.	24	No	32942 (98.2%)	13 (0%)	110 (0.3%)	459 (1.4%)	27 (0.1%)	1.00[ref]	-
		Yes	649 (98.5%)	0 (0%)	0 (0%)	9 (1.4%)	1 (0.2%)	0.765 (0.393-1.488)	0.42951
Methyldibromoglutaronitrile/Phenoxyethanol,(Euxyl K 400), 0.4% pet.	25	No	4678 (98.0%)	9 (0.2%)	21 (0.4%)	65 (1.4%)	1 (0%)	1.00[ref]	-
		Yes	73 (98.6%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0.663 (0.09-4.874)	0.68666

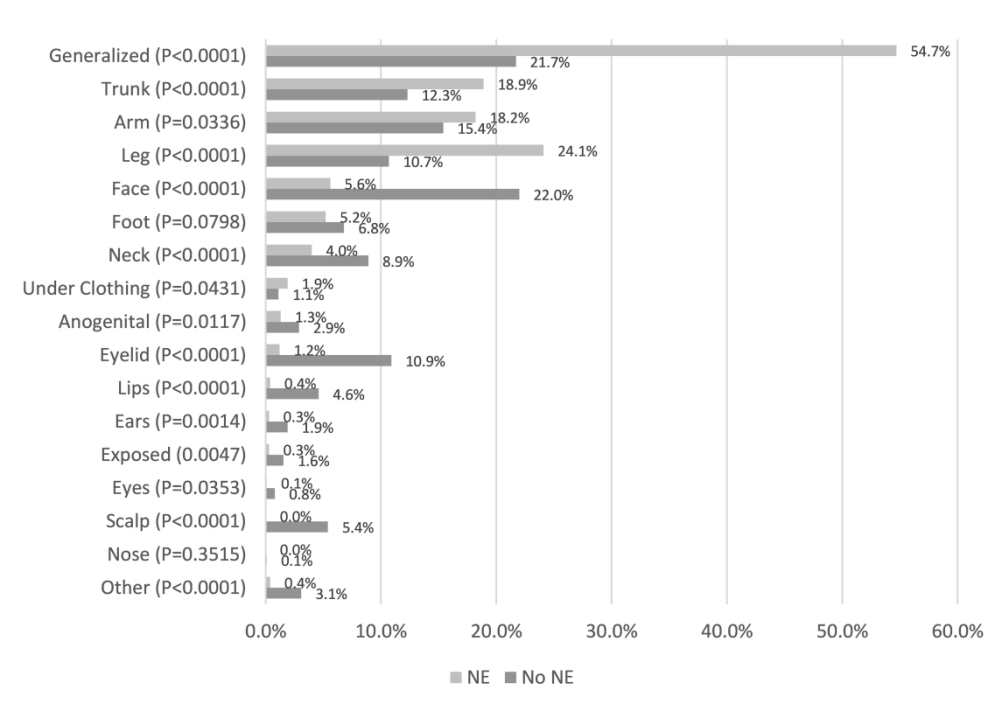
* Multivariable logistic regression models were constructed with specific allergen relevance (definite/probable/possible vs. not relevant; excluding past or unknown relevance) as the dependent variable and primary or secondary diagnosis of nummular eczema (yes vs. no) as the independent variable, and age (continuous), race/ethnicity (white, non-Hispanic/black/Hispanic/Asian/other), sex, employment, and history of eczema, asthma, and hay fever.

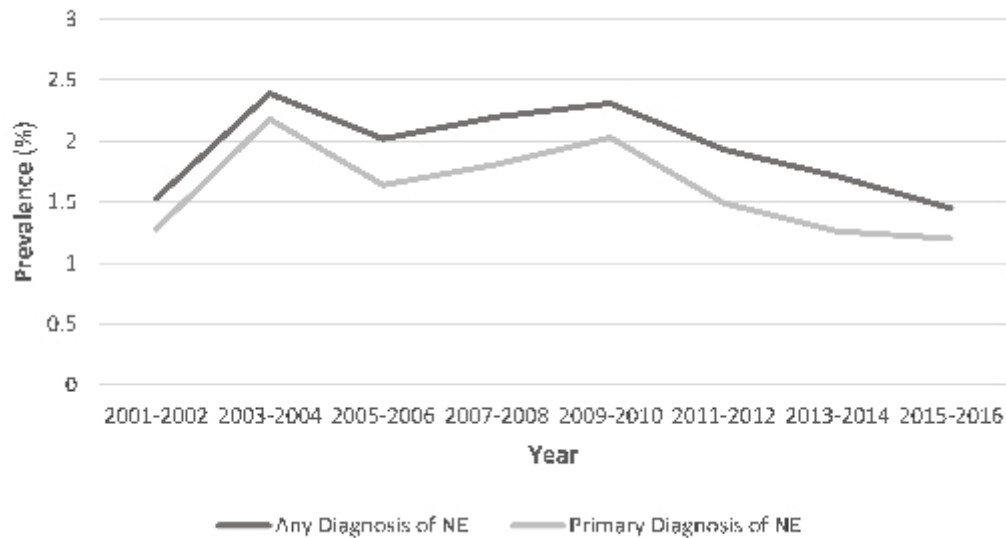
Table 4. Association of one or more positive and relevant allergic reactions with demographics, atopic history, and most common distributions of dermatitis in patients with nummular eczema.

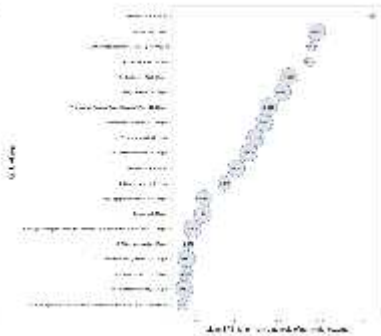
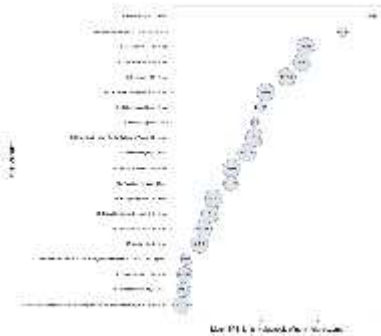
Variable	Overall (n=748)	Nummular Eczema							
		One or more Positive Allergic Reaction (n=370)				One or more Relevant Allergic Reaction (n=201)			
		No	Yes	Adjusted OR	P	No	Yes	Adjusted OR	P
	Freq (%)	Freq (%)	Freq (%)	(95% CI)		Freq (%)	Freq (%)	(95% CI)	
<i>Age (yr)</i>									
0-7	2 (0.3%)	2 (100%)	0 (0%)	1.000 [ref]	-	2 (100%)	0 (0%)	1.000 [ref]	-
8-30	11 (1.5%)	1 (9.1%)	10 (90.9%)	0.330 (0.076-1.429)	0.1381	6 (54.5%)	5 (45.5%)	1.173 (0.288-4.789)	0.8237
31-40	49 (6.6%)	27 (55.1%)	22 (44.9%)	0.530 (0.128-2.191)	0.3807	34 (69.4%)	15 (30.6%)	0.969 (0.250-3.753)	0.9637
41-50	97 (13.0)	42 (43.3%)	55 (56.7%)	0.492 (0.121-2.001)	0.3213	72 (74.2%)	25 (25.8%)	1.246 (0.329-4.711)	0.7463
51-60	134 (17.9%)	62 (46.3%)	72 (53.7%)	0.435 (0.109-1.73)	0.2372	94 (70.1%)	40 (29.9%)	0.884 (0.24-3.258)	0.8534
61-70	172 (23.0%)	84 (48.8%)	88 (51.2%)	0.308 (0.078-1.217)	0.093	129 (75.0%)	43 (25.0%)	0.914 (0.251-3.328)	0.8917
>70	151 (20.2%)	85 (56.3%)	66 (43.7%)	0.283 (0.0710-1.129)	0.0738	111 (73.5%)	40 (26.5%)	0.775 (0.209-2.868)	0.7025
<i>Sex</i>									
Female	330 (44.1%)	154 (46.7%)	176 (53.3%)	1.135 (0.834-1.545)	0.4201	238 (72.1%)	92 (27.9%)	1.012 (0.715-1.432)	0.9456
Male	418 (55.9%)	224 (53.6%)	194 (46.4%)	1.000 [ref]	-	309 (73.9%)	109 (26.1%)	1.000 [ref]	-
<i>Race/ethnicity</i>									
White	621 (83%)	323 (52.0%)	298 (48.0%)	1.000 [ref]	-	458 (73.8%)	163 (26.2%)	1.000 [ref]	-
Black	31 (4.1%)	15 (48.4%)	16 (51.6%)	0.874 (0.404-1.893)	0.7333	21 (67.7%)	10 (32.3%)	1.318 (0.574-3.027)	0.5157
Hispanic	18 (2.4%)	8 (44.4%)	10 (55.6%)	1.207 (0.459-3.172)	0.7031	13 (72.2%)	5 (27.8%)	1.065 (0.366-3.102)	0.9080
Asian	59 (7.9%)	21 (35.6%)	38 (64.4%)	1.801 (1.02-3.179)	0.0426	38 (64.4%)	21 (35.6%)	1.490 (0.837-2.651)	0.1750
Other	19 (2.5%)	11 (57.9%)	8 (42.1%)	0.643 (0.24-1.721)	0.3791	17 (89.5%)	2 (10.5%)	0.164 (0.0210-1.26)	0.0823
<i>Occupation</i>									
Unemployed	278 (37.6%)	143 (51.4%)	135 (48.6%)	1.000 [ref]	-	200 (71.9%)	78 (28.1%)	1.000 [ref]	-
Employed	462 (62.4%)	231 (50.0%)	231 (50.0%)	0.837 (0.571-1.225)	0.3598	342 (74.0%)	120 (26.0%)	0.783 (0.510-1.202)	0.2629
<i>Atopic disease</i>									
<i>Atopic dermatitis</i>									
No	634 (84.8%)	332 (52.4%)	302 (47.6%)	1.000 [ref]	-	470 (74.1%)	164 (25.9%)	1.000 [ref]	-
Yes	114 (15.2%)	46 (40.4%)	68 (59.6%)	1.361 (0.874-2.121)	0.1726	77 (67.5%)	37 (32.5%)	1.148 (0.709-1.859)	0.5737
<i>Asthma</i>									
No	669 (89.6%)	345 (51.6%)	324 (48.4%)	1.000 [ref]	-	496 (74.1%)	173 (25.9%)	1.000 [ref]	-
Yes	78 (10.4%)	33 (42.3%)	45 (57.7%)	1.129 (0.659-1.932)	0.6593	51 (65.4%)	27 (34.6%)	1.14 (0.638-2.037)	0.6574
<i>Hay fever</i>									
No	585 (78.4%)	304 (52.0%)	281 (48.0%)	1.000 [ref]	-	438 (74.9%)	147 (25.1%)	1.000 [ref]	-
Yes	161 (21.6%)	74 (46.0%)	87 (54.0%)	1.088 (0.740-1.599)	0.668	108 (67.1%)	53 (32.9%)	1.295 (0.852-1.968)	0.2258
<i>Distribution</i>									
<i>Generalized</i>									
No	339 (45.3%)	166 (49.0%)	173 (51.0%)	1.000 [ref]	-	251 (74.0%)	88 (26.0%)	1.000 [ref]	-
Yes	409 (54.7%)	212 (51.8%)	197 (48.2%)	0.875 (0.589-1.299)	0.5065	296 (72.4%)	113 (27.6%)	1.351 (0.859-2.125)	0.1930
<i>Trunk</i>									
No	607 (81.1%)	306 (50.4%)	301 (49.6%)	1.000 [ref]	-	441 (72.7%)	166 (27.3%)	1.000 [ref]	-
Yes	141 (18.9%)	72 (51.1%)	69 (48.9%)	0.936 (0.603-1.452)	0.7669	106 (75.2%)	35 (24.8%)	0.913 (0.552-1.507)	0.7207
<i>Leg</i>									
No	568 (75.9%)	288 (50.7%)	280 (49.3%)	1.000 [ref]	-	422 (74.3%)	146 (25.7%)	1.000 [ref]	-
Yes	180 (24.1%)	90 (50.0%)	90 (50.0%)	0.946 (0.626-1.43)	0.7921	125 (69.4%)	55 (30.6%)	1.592 (0.999-2.536)	0.0505

Table 5. Top 4 mean SPIN scores among patients with a diagnosis of nummular eczema by common distributions of dermatitis

Rank	Generalized (n=409)		Trunk (n=141)		Leg (n=180)	
	Allergen	Mean SPIN	Allergen	Mean SPIN	Allergen	Mean SPIN
1	Formaldehyde, 2.0% aq.	27.2	Methylisothiazolinone, 0.1% aq. (1000 ppm)	51.6	Methyldibromoglutaronitrile/Phenoxyethanol, (Euxyl K 400), 0.4% pet.	45.7
2	Methylisothiazolinone, 0.1% aq. (1000 ppm)	22.3	Methyldibromoglutaronitrile/Phenoxyethanol, (Euxyl K 400), 0.4% pet.	39.1	Formaldehyde, 1.0% aq.	31.1
3	Fragrance mix I, 8.0% pet.	17.9	Fragrance mix I, 8.0% pet.	33.5	Nickel sulfate hexahydrate, 2.5% pet.	28.9
4	<i>Myroxylon pereirae</i> Resin (Balsam of Peru), 25.0% pet.	17.7	2-Bromo-2-nitropropane -1,3-diol (Bronopol), 0.5% pet.	29.6	Quaternium 15, 2.0% pet.	25.9







Supplemental Material

Supplemental Methods

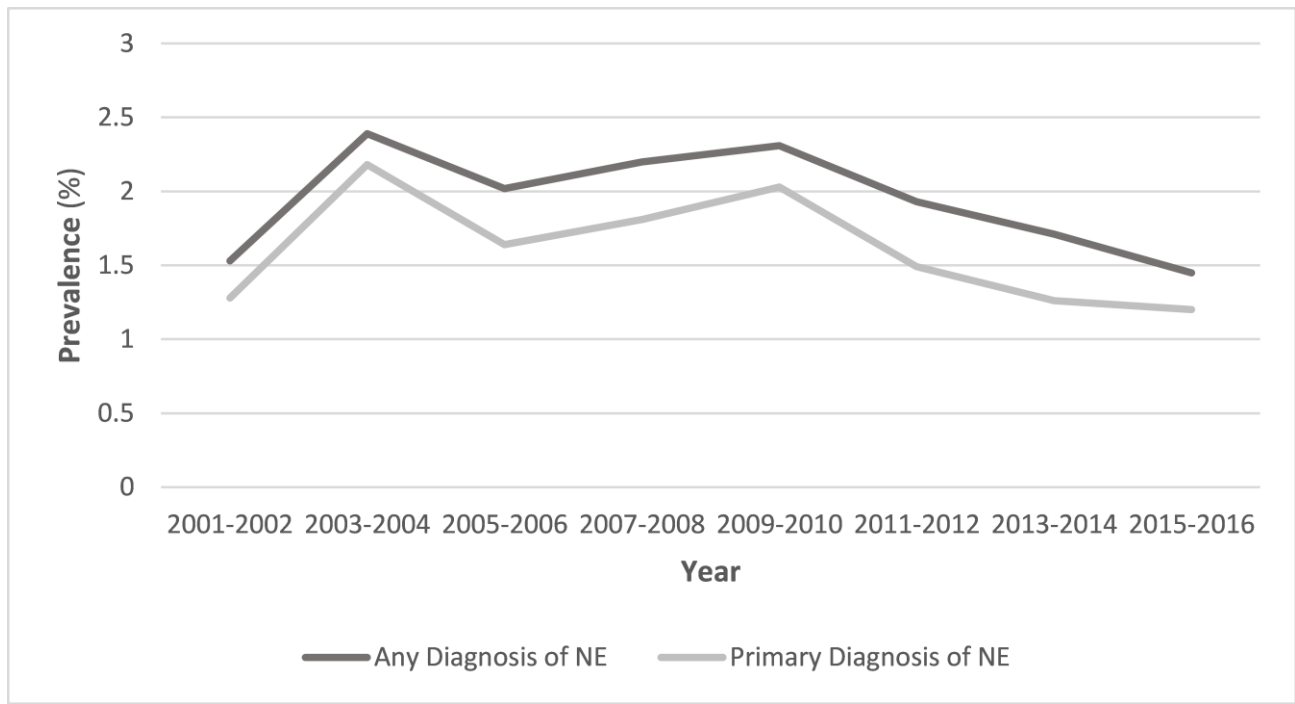
Data elements

Patients were patch tested using the NACDG screening series for each 2-year cycle. Data were collected in 2-year cycles that included information on patient demographics (age, sex, race/ethnicity, and employment), history of atopy (atopic dermatitis, asthma, and hay fever), dermatitis sites (up to 3 coded), and patch test results including strength of reaction to each allergen (allergen tested varied for each 2-year cycle), clinical and occupational relevance of each allergen, and final diagnosis (up to 3 coded). Final diagnoses were determined by the temporal pattern of the clinician's patch test reading at 48 and 72-168 hours after allergen application. The patch test reading was assessed as negative (-), indeterminate (+/-), weak (+), strong (++), and extreme (+++). In addition, a final interpretation was coded as "allergic" or "not allergic." Thus, indeterminant reactions could be coded as allergic or not allergic based on temporal pattern, other patch test reactions, and clinical judgement. Clinical relevance was determined at the time of final patch reading by a combination of patient history and patch test results, and assessed as definite (positive patch test with suspected allergen), probable (known antigen exposure with consistent clinical presentation), possible (contact with substance that may have contained the allergen), or past relevance (positive patch test with a past exposure).

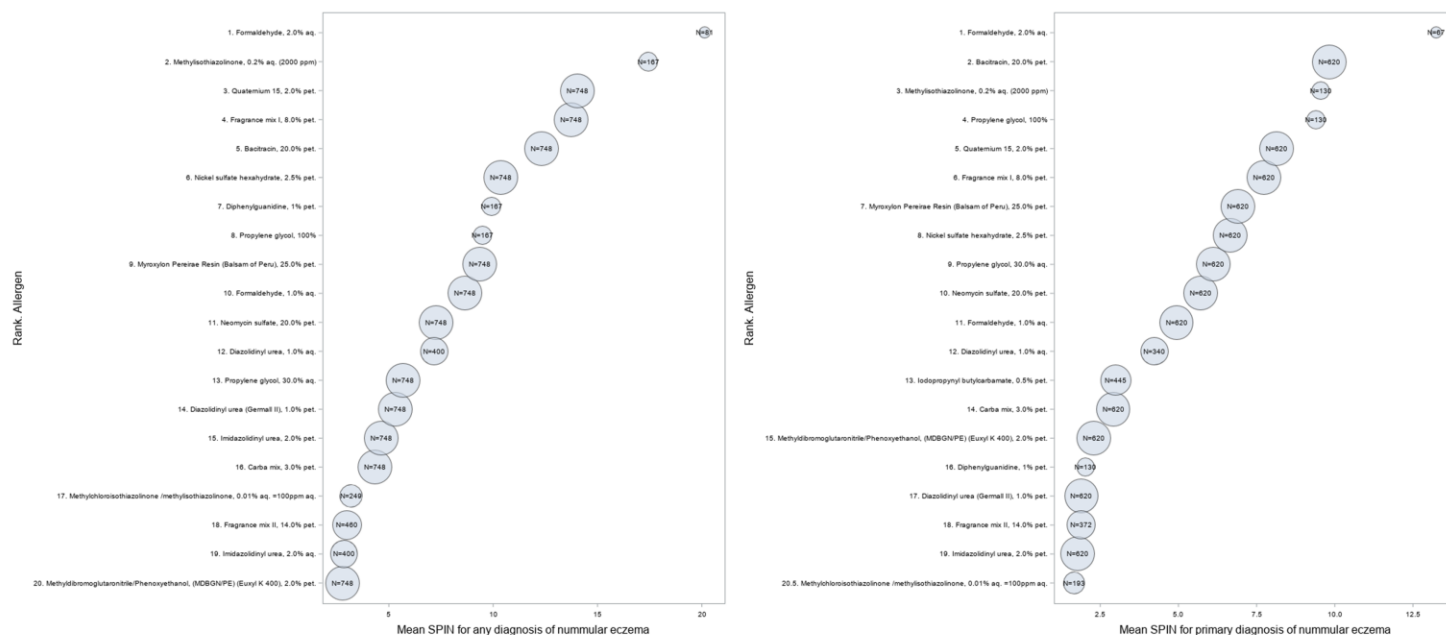
Supplemental Results

Occupationally relevant allergens

Occupationally relevant allergens included carba mix 3.0% pet. (n=3; sources: clothing; occupations: health aide, janitor, machine operator), colophonium 20.0% pet. (n=2; animals /infectious agents/plants/minerals and personal care products; millright and other), glutaral 1.0% pet. (n=1; chemicals; mechanic), bacitracin 20.0% pet. (n=1; drugs/medications; financial officer), bisphenol A epoxy resin 1.0% pet. (n=1; chemicals; machinery repairer), chloroxylonol 1.0% pet. (n=1; source/occupation missing), formaldehyde 1.0% aq. (n=1; chemicals; health aide), fragrance mix I 8.0% pet. (n=1; personal care products; mechanic), neomycin sulfate 20.0% pet. (n=1; drugs/medications; financial officer), nickel sulfate hexahydrate 2.5% pet. (n=1; furniture/structures/surfaces; production coordinator), quaternium 15 2.0% pet. (n=1; personal care products; health aides), and thiuram mix 1.0% pet. (n=1; gloves; health aide).



Supplemental Figure 1. Temporal trends of patients with any diagnosis of NE (dark grey) and a primary diagnosis of NE (light grey). Prevalence of NE were estimated by 2 year cycles (2001-2002/2003-2004/2005-2006/2007-2008/2009-2010/2011-2012/2013-2014/2015-2016).



Supplemental Figure 2. Highest mean significance-prevalence index number (SPIN) of NACDG allergens in patients with (A) any diagnosis and (B) a primary diagnosis of NE. SPIN was calculated by 2 –year intervals using the calculation: (proportion of population allergic) * (1*percentage with definite relevance + 0.66*percentage with probable relevance + 0.33*percentage with possible relevance) * 100.

Supplemental Table 1. Most common positive allergic reactions in patients with a primary diagnosis of nummular eczema.								
Allergen	No Diagnosis of Nummular Eczema			Primary Nummular Eczema			Adjusted OR (95% CI)	P-value
	No. of pts tested	Allergic reaction, n (%)	Rank order	No. of pts tested	Allergic reaction, n (%)	Rank order		
Thimerosal 0.1% pet.	4834	496 (10.3%)	3	63	7 (11.1%)	1	1.305 (0.586-2.909)	0.51443
Nickel sulfate hexahydrate, 2.5% pet.	37925	6783 (17.9%)	1	620	56 (9.0%)	2	0.631 (0.474-0.84)	0.00159
Formaldehyde, 2.0% aq.	5509	505 (9.2%)	6	67	6 (9.0%)	2	0.828 (0.353-1.943)	0.66368
Myroxylon Pereirae Resin (Balsam of Peru), 25.0% pet.	38047	3184 (8.4%)	8	620	36 (5.8%)	4	0.583 (0.415-0.82)	0.00193
Bacitracin, 20.0% pet.	38014	2863 (7.5%)	9	620	34 (5.5%)	5	0.700 (0.494-0.994)	0.04599
Propylene glycol, 100%	10448	349 (3.3%)	22	130	7 (5.4%)	6	1.327 (0.61-2.888)	0.47527
Sodium gold thiosulfate, 0.5% pet.	9831	967 (9.8%)	5	174	9 (5.2%)	7	0.646 (0.326-1.281)	0.21098
Benzalkonium Chloride, 0.1% aq.	4827	227 (4.7%)	14	63	3 (4.8%)	8	0.892 (0.274-2.9)	0.84917
Fragrance mix I, 8.0% pet.	38007	3782 (10.0%)	4	620	29 (4.7%)	9	0.387 (0.264-0.567)	<0.0001
Cobalt (ii) chloride hexahydrate, 1.0% pet.	38004	2826 (7.4%)	10	620	29 (4.7%)	9	0.783 (0.536-1.143)	0.20529
Quaternium 15, 2.0% pet.	38034	2577 (6.8%)	12	620	23 (3.7%)	11	0.477 (0.313-0.726)	0.00055
Neomycin sulfate, 20.0% pet.	37999	3366 (8.9%)	7	620	23 (3.7%)	11	0.421 (0.277-0.64)	<0.0001
4-phenylenediamine, 1.0% pet.	37979	2064 (5.4%)	13	620	23 (3.7%)	11	0.677 (0.444-1.033)	0.07025
Methyldibromoglutaronitrile/Phenoxyethanol,(Euxyl K 400), 2.0% pet.	38012	1725 (4.5%)	15	619	21 (3.4%)	14	0.590 (0.38-0.917)	0.01906
Formaldehyde, 1.0% aq.	38039	2668 (7.0%)	11	620	18 (2.9%)	15	0.341 (0.212-0.546)	<0.0001
Carba mix, 3.0% pet.	38037	1606 (4.2%)	17	620	17 (2.7%)	16	0.500 (0.307-0.814)	0.00532
Propylene glycol, 30.0% aq.	38022	982 (2.6%)	28	620	15 (2.4%)	17	0.772 (0.459-1.298)	0.3289
Methylisothiazolinone, 0.1% aq. (1000 ppm)	10444	1215 (11.6%)	2	130	3 (2.3%)	18	0.169 (0.054-0.532)	0.00238
Diphenylguanidine, 1% pet.	10447	322 (3.1%)	24	130	3 (2.3%)	18	0.530 (0.167-1.688)	0.28288
2-Bromo-2-nitropropane -1,3-diol (Bronopol), 0.5% pet.	33843	767 (2.3%)	34	557	12 (2.2%)	20	0.898 (0.503-1.603)	0.71605
Iodopropynyl butylcarbamate, 0.5% pet.	28152	981 (3.5%)	19	445	9 (2.0%)	21	0.392 (0.194-0.795)	0.00939
Colophonium (rosin), 20.0% pet.	38046	907 (2.4%)	31	620	12 (1.9%)	22	0.838 (0.471-1.494)	0.54985
Oleamidopropyl dimethylamine, 0.1% aq.	18808	536 (2.8%)	26	280	5 (1.8%)	23	0.602 (0.246-1.47)	0.26500
Diazolidinyl urea (Germall II), 1.0% aq.	19199	410 (2.1%)	37	340	6 (1.8%)	23	0.630 (0.278-1.43)	0.26948
Methyldibromoglutaronitrile/Phenoxyethanol,(Euxyl K 400), 0.4% pet.	4832	115 (2.4%)	31	63	1 (1.6%)	25	0.601 (0.082-4.431)	0.61733

Supplemental Table 2. Most common relevant allergens in patients with a primary diagnosis of nummular eczema									
Allergen	Rank order of allergen relevance in primary diagnosis of nummular eczema	Primary diagnosis of nummular eczema	Relevance of allergens - freq. (%)					Adjusted OR (95% CI)*	P-value
			Not relevant allergen	Definite	Probable	Possible	Past		
Formaldehyde, 2.0% aq.	1	No	5023 (93.0%)	5 (0.1%)	108 (2%)	257 (4.8%)	8 (0.1%)	1.00[ref]	-
		Yes	61 (93.8%)	0 (0%)	0 (0%)	3 (4.6%)	1 (1.5%)	0.554 (0.171-1.791)	0.32361
Methylisothiazolinone, 0.1% aq. (1000 ppm)	2	No	9147 (88.3%)	90 (0.9%)	624 (6.0%)	470 (4.5%)	28 (0.3%)	1.00[ref]	-
		Yes	124 (95.4%)	0 (0%)	2 (1.5%)	4 (3.1%)	0 (0%)	0.346 (0.152-0.787)	0.01145
Propylene glycol, 100%	3	No	10068 (96.8%)	24 (0.2%)	193 (1.9%)	112 (1.1%)	4 (0%)	1.00[ref]	-
		Yes	123 (96.1%)	0 (0%)	2 (1.6%)	3 (2.3%)	0 (0%)	1.043 (0.421-2.586)	0.92784
Quaternium 15, 2.0% pet.	4	No	35256 (93.3%)	74 (0.2%)	788 (2.1%)	1555 (4.1%)	107 (0.3%)	1.00[ref]	-
		Yes	596 (96.6%)	0 (0%)	1 (0.2%)	19 (3.1%)	1 (0.2%)	0.447 (0.285-0.7)	0.00044
Fragrance mix I, 8.0% pet.	5	No	33879 (90.2%)	85 (0.2%)	1145 (3.0%)	2274 (6.1%)	164 (0.4%)	1.00[ref]	-
		Yes	591 (96.3%)	0 (0%)	3 (0.5%)	17 (2.8%)	3 (0.5%)	0.300 (0.191-0.47)	<0.0001
Myroxylon Pereirae Resin (Balsam of Peru), 25.0% pet.	6	No	34398 (91.5%)	46 (0.1%)	1016 (2.7%)	2011 (5.3%)	121 (0.3%)	1.00[ref]	-
		Yes	585 (96.5%)	0 (0%)	2 (0.3%)	17 (2.8%)	2 (0.3%)	0.313 (0.197-0.496)	<0.0001
Bacitracin, 20.0% pet.	7	No	35059 (93.6%)	199 (0.5%)	620 (1.7%)	437 (1.2%)	1154 (3.1%)	1.00[ref]	-
		Yes	585 (95.6%)	1 (0.2%)	11 (1.8%)	4 (0.7%)	11 (1.8%)	0.720 (0.436-1.188)	0.19859
Propylene glycol, 30.0% aq.	8	No	36820 (97.3%)	140 (0.4%)	444 (1.2%)	425 (1.1%)	16 (0%)	1.00[ref]	-
		Yes	602 (97.4%)	4 (0.6%)	3 (0.5%)	9 (1.5%)	0 (0%)	0.819 (0.495-1.354)	0.43551
Formaldehyde, 1.0% aq.	9	No	35180 (93.6%)	31 (0.1%)	712 (1.9%)	1608 (4.3%)	66 (0.2%)	1.00[ref]	-
		Yes	600 (97.4%)	0 (0%)	1 (0.2%)	13 (2.1%)	2 (0.3%)	0.297 (0.174-0.505)	<0.0001
Diazolidinyl urea (Germall II), 1.0% aq.	10	No	18724 (97.7%)	24 (0.1%)	164 (0.9%)	237 (1.2%)	7 (0%)	1.00[ref]	-
		Yes	332 (98.2%)	1 (0.3%)	1 (0.3%)	4 (1.2%)	0 (0%)	0.612 (0.27-1.386)	0.23876
Neomycin sulfate, 20.0% pet.	11	No	34433 (92.4%)	143 (0.4%)	487 (1.3%)	439 (1.2%)	1764 (4.7%)	1.00[ref]	-
		Yes	594 (97.5%)	0 (0%)	6 (1%)	4 (0.7%)	5 (0.8%)	0.504 (0.268-0.946)	0.03286
Diphenylguanidine, 1% pet.	12	No	10093 (97.6%)	17 (0.2%)	49 (0.5%)	159 (1.5%)	22 (0.2%)	1.00[ref]	-
		Yes	127 (98.4%)	0 (0%)	1 (0.8%)	1 (0.8%)	0 (0%)	0.506 (0.123-2.071)	0.34317
Methyldibromoglutaronitrile/Phenoxyethanol,(Euxyl K 400), 2.0% pet.	13	No	36073 (96.3%)	40 (0.1%)	417 (1.1%)	851 (2.3%)	84 (0.2%)	1.00[ref]	-
		Yes	598 (98.0%)	0 (0%)	0 (0%)	10 (1.6%)	2 (0.3%)	0.368 (0.196-0.69)	0.00184
Ammonium Persulfate, 2.5% pet.	14	No	5412 (98.7%)	1 (0%)	25 (0.5%)	27 (0.5%)	18 (0.3%)	1.00[ref]	-
		Yes	66 (98.5%)	0 (0%)	0(0%)	1 (1.5%)	0 (0%)	1.692 (0.225-12.712)	0.60929
Carba mix, 3.0% pet.	15	No	36245 (96.0%)	107 (0.3%)	492 (1.3%)	799 (2.1%)	112 (0.3%)	1.00[ref]	-

		Yes	599 (98.5%)	0 (0%)	0(0%)	9 (1.5%)	0 (0%)	0.321 (0.165-0.621)	0.00075
Nickel sulfate hexahydrate, 2.5% pet.	16	No	31060 (83.8%)	131 (0.4%)	1291 (3.5%)	2489 (6.7%)	2107 (5.7%)	1.00[ref]	-
		Yes	556 (92.7%)	0 (0%)	1 (0.2%)	8 (1.3%)	35 (5.8%)	0.186 (0.096-0.36)	<0.0001
Iodopropynyl butylcarbamate, 0.5% pet.	17	No	26941 (96.6%)	30 (0.1%)	359 (1.3%)	528 (1.9%)	22 (0.1%)	1.00[ref]	-
		Yes	435 (98.6%)	0 (0%)	0 (0%)	6 (1.4%)	0 (0%)	0.326 (0.145-0.734)	0.00681
Imidazolidinyl urea, 2.0% pet.	18	No	37173 (97.9%)	28 (0.1%)	241 (0.6%)	496 (1.3%)	27 (0.1%)	1.00[ref]	-
		Yes	610 (98.9%)	0 (0%)	1 (0.2%)	6 (1.0%)	0 (0%)	0.410 (0.193-0.87)	0.02011
Fragrance mix II, 14.0% pet.	19	No	22579 (95.3%)	27 (0.1%)	435 (1.8%)	615 (2.6%)	34 (0.1%)	1.00[ref]	-
		Yes	367 (98.9%)	0 (0%)	1 (0.3%)	3 (0.8%)	0 (0%)	0.236 (0.088-0.634)	0.00418
DMDM hydantoin (Germall 115), 1.0% pet.	20	No	37296 (98.2%)	39 (0.1%)	225 (0.6%)	399 (1.1%)	17 (0%)	1.00[ref]	-
		Yes	613 (99%)	0 (0%)	3 (0.5%)	3 (0.5%)	0 (0%)	0.474 (0.211-1.066)	0.07098
Imidazolidinyl urea, 2.0% aq.	21	No	18923 (98.6%)	10 (0.1%)	96 (0.5%)	158 (0.8%)	7 (0%)	1.00[ref]	-
		Yes	336 (99.1%)	0 (0%)	1 (0.3%)	2 (0.6%)	0 (0%)	0.465 (0.148-1.465)	0.19104
Colophonium (rosin), 20.0% pet.	22	No	37087 (98.1%)	39 (0.1%)	141 (0.4%)	315 (0.8%)	241 (0.6%)	1.00[ref]	-
		Yes	610 (98.5%)	0 (0%)	2 (0.3%)	3 (0.5%)	4 (0.6%)	0.638 (0.263-1.549)	0.32082
2-Bromo-2-nitropropane -1,3-diol (Bronopol), 0.5% pet.	23	No	33019 (98.2%)	13 (0%)	110 (0.3%)	464 (1.4%)	27 (0.1%)	1.00[ref]	-
		Yes	545 (99.1%)	0 (0%)	0 (0%)	4 (0.7%)	1 (0.2%)	0.399 (0.148-1.071)	0.06828
Diazolidinyl urea (Germall II), 1.0% pet.	24	No	37047 (97.6%)	56 (0.1%)	287 (0.8%)	538 (1.4%)	28 (0.1%)	1.00[ref]	-
		Yes	614 (99.4%)	1 (0.2%)	1 (0.2%)	2 (0.3%)	0 (0%)	0.205 (0.076-0.55)	0.00165
Oleamidopropyl dimethylamine, 0.1% aq.	25	No	18210 (97.5%)	10 (0.1%)	102 (0.5%)	347 (1.9%)	10 (0.1%)	1.00[ref]	-
		Yes	275 (99.3%)	0(0%)	0 (0%)	2 (0.7%)	0 (0%)	0.300 (0.074-1.212)	0.09106

* Multivariable logistic regression models were constructed with specific allergen relevance (definite/probable/possible vs. not relevant; excluding past or unknown relevance) as the dependent variable and primary diagnosis of nummular eczema (yes vs. no) as the independent variable, and age (continuous), race/ethnicity (white, non-Hispanic/black/Hispanic/Asian/other), sex, employment, and history of eczema, asthma, and hay fever.