

Childhood atopic dermatitis and warts are associated with increased risk of infection: A US population-based study

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Background: Previous studies suggested that atopic dermatitis (AD) is associated with aberrant immune responses, which might predispose toward both cutaneous and extracutaneous infections. The goal of this study was to determine whether childhood AD is associated with increased risk of warts, extracutaneous infections, and other atopic diseases and how these disorders cosegregate.

Methods: The 2007 National Health Interview Survey from a nationally representative sample of 9417 children age 0 to 17 years was used.

Results: Children with AD and other atopic disease had higher odds of warts. In contrast, children with AD with or without other atopic disease had higher odds of extracutaneous infections, including strep throat, other sore throat, head or chest cold, influenza/pneumonia, sinus infections, recurrent ear infections, chickenpox, and urinary tract infections ($P < .0001$). Children with AD and other atopic disease had a higher number of infections than those with either disorder by itself ($P < .0001$). Warts were also associated with increased odds of all extracutaneous infections ($P < .0001$), except recurrent ear infections. Children with warts and AD had a higher number of infections than those with either disorder alone ($P < .0001$). Finally, children with AD and warts had higher odds of ever receiving a diagnosis of asthma, current asthma, asthma exacerbation in the past year, hay fever, and food allergy. Children with AD with warts had even higher odds of asthma, hay fever, and food allergies than those with AD and no warts.

Conclusions: The associations between childhood AD, atopic disease, warts, and extracutaneous infections suggest that barrier disruption, immune disruption, or both contribute to susceptibility to warts and extracutaneous infections in children. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: Atopic dermatitis, eczema, asthma, allergic disease-rhinoconjunctivitis, hay fever, food allergies, respiratory allergies, warts, verruca vulgaris, age, race, ethnicity, Hispanic, infections, strep throat, influenza, head cold, pneumonia, sinusitis, ear infection, urinary tract infection

Abbreviations used

AD: Atopic dermatitis
aOR: Adjusted odds ratio
HPV: Human papilloma virus

Susceptibility to cutaneous infections, such as *Staphylococcus aureus* and warts (cutaneous infection with human papilloma virus [HPV]), has been linked to atopic dermatitis (AD), and a tendency toward skin infection is one of the minor criteria of Hanifin and Rajka.¹ It is well established that barrier disruption related to AD is associated with increased cutaneous viral infections, including eczema herpeticum and molluscum contagiosum.²⁻⁵ However, there are conflicting reports about the risk for acquisition of warts in patients with AD. Several well-designed international studies have challenged this dogma with reports of lower prevalence of warts in children with AD.^{6,7}

Recent studies demonstrated aberrant Toll-like receptor signaling and innate immunity in patients with AD^{8,9}; increased thymic stromal lymphopoietin,^{10,11} T_H2 and T_H22 cytokine,¹² and serum IgE levels and sensitization to cutaneous exposure to allergens¹³; and increased expression of FcεRI on Langerhans cells.¹⁴ Silverberg and Simpson¹⁵ recently found that childhood AD is associated with recurrent ear infections and multiple dental health comorbidities. This suggests that children with AD might be at higher risk for both cutaneous and extracutaneous infections.

Finally, little is known about how warts caused by HPV infection cosegregate with other infections. HPV is ubiquitous and commonly found on the skin of healthy children and adults without any history of warts.¹⁶⁻¹⁸

We hypothesized that there are specific subsets of patients with AD with increased risk for warts and extracutaneous infections. We hypothesize that certain host factors, such as impaired barrier or immune responses, contribute to susceptibility to warts. Thus children infected with warts might also be at greater risk for extracutaneous infections. We aim to study these associations in a representative cohort of the US population.

METHODS

National Health Interview Survey

This study was approved by the institutional review board at St Luke's-Roosevelt Hospital Center in New York City. We used the 2007 National Health Interview Survey (NHIS), which is collected by the National Center for Health Statistics and is the principal source of information on the health of the civilian noninstitutionalized population of the United States. A waiver of informed consent was obtained by the National Center for Health Statistics because the survey posed minimal risk and respondents were not identifiable by the recorded data. The survey included a separate questionnaire about children's health based on parental response to estimate the prevalence of various child health issues, including physical, emotional, and behavioral factors. The survey was administered in person to selected households by the Bureau of the Census using approximately 400 trained interviewers with

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Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Presented in part at the 2013 International Investigative Dermatology meeting in Edinburgh, Scotland.

Received for publication May 5, 2013; revised August 9, 2013; accepted for publication August 13, 2013.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2013.08.012>

computer-assisted personal interviewing. Subsequently, one child was randomly selected for the sample-child questionnaire. Interviews were conducted in English and Spanish. Using data from the US Bureau of the Census, weights were adjusted for age, sex, race, ethnicity, household size, and educational attainment of the most educated household member to provide a data set that was more representative of each state's population of noninstitutionalized children less than 18 years of age. All prevalence estimates presented reflect this complex weighting.

History of atopic disease and infectious comorbidities

AD was determined by asking the following question: "During the past 12 months, have you been told by a doctor or other health professional that (child) had eczema or any kind of skin allergy?" History of ever receiving a diagnosis of asthma was determined by asking the following question: "Has a doctor or other health professional ever told you that (child) had asthma?" Current history of asthma was determined by asking the following question: "Does (child) still have asthma?" One-year history of asthma exacerbations was determined by asking the following question: "During the past 12 months, has (child) had an episode of asthma or an asthma attack?" Hay fever was determined by asking the following question: "During the past 12 months, have you been told by a doctor or other health professional that (child) had hay fever or any kind of respiratory allergy?" Food allergy was determined by asking the following question: "During the past 12 months, have you been told by a doctor or other health professional that (child) had any kind of food or digestive allergy?" A composite binary variable was created for atopic diseases by using responses to the above 4 questions.

History of warts was determined by using the following NHIS question: "During the past 12 months, has (child) had warts?" History of episodes of other infections was determined by asking the following question: "During the past 12 months, has a doctor or other health professional told you that (child) had..." "strep throat or tonsillitis?," "sore throat other than strep or tonsillitis?," "influenza or pneumonia?," "sinusitis?," "three or more ear infections?," and "urinary tract infections?" History of an episode of chickenpox was determined by asking the following question: "Has (child) ever had chickenpox?" History of colds was determined by asking the following question: "Did (child) have a head cold or chest cold during those two weeks (of missed school days from illness)?"

Data processing and statistical methods

All data processing and statistical analyses were performed with SAS version 9.2 software (SAS Institute, Cary, NC). Bivariate and multivariate analyses of survey responses were performed with SURVEY procedures. Bivariate associations were tested by using Rao-Scott χ^2 tests. Significant predictors from bivariate analyses were included as covariates in multivariate logistic regression models. Adjusted odds ratios (aORs) and 95% CIs were determined. Complete data analysis was performed (ie, subjects with missing data were excluded). Our *a priori* hypothesis was that children with AD and other atopic disease might have more infections than those with AD alone. Therefore models were constructed that tested interaction terms between AD and other atopic disease. Similarly, models were constructed that tested interaction terms between AD and warts. Two- and 3-way interaction terms between other covariates were also tested. Interactions were only included in final models in cases of *P* values of less than .01 and modification of estimates by greater than 20%. In models of binary outcomes with significant statistical interactions, we constructed generalized linear models using a logit link function in PROC GLIMMIX. Similarly, in models of continuous outcomes, we constructed generalized linear models using a normal link function. *Post hoc* analyses were conducted of differences among the levels of one factor at a fixed level of the other factor. Least-squares means and aORs (95% CIs) were estimated for each combination of factors included in the interaction effects. The best model was selected by using the Bayesian information criterion, which penalizes for extra parameters and takes into account the large sample size.

Correction for multiple tests ($k = 59$) was performed by using the Bonferroni method and yielded a critical *P* value of .0008.

RESULTS

Population characteristics

Data were collected on a total of 9417 children. Overall, the prevalence of AD was 8.9% (95% CI, 8.2% to 9.6%) in US children. The prevalence of AD was significantly associated with age, African American race, non-Hispanic origin, higher household income and level of education, health care interaction in the past year, health insurance coverage, and birthplace in the United States (Table I).

Nine infectious causes were assessed, including warts (percentage prevalence, 3.3%; 95% CI, 2.8% to 3.8%), strep throat (percentage prevalence, 12.0%; 95% CI, 11.2% to 12.9%), other sore throat (percentage prevalence, 32.2%; 95% CI, 31.0% to 33.4%), head or chest cold (percentage prevalence, 14.1%; 95% CI, 13.2% to 15.0%), influenza/pneumonia (percentage prevalence, 6.4%; 95% CI, 5.7% to 7.0%), sinus infections (percentage prevalence, 7.2%; 95% CI, 6.6% to 7.9%), recurrent ear infections (percentage prevalence, 5.1%; 95% CI, 4.5% to 5.6%), chickenpox (percentage prevalence, 28.3%; 95% CI, 27.1% to 29.5%), and urinary tract infection (percentage prevalence, 1.4%; 95% CI, 1.1% to 1.6%). Of the subjects, 62.8% (95% CI, 61.6% to 64.0%) reported 1 or more of these 9 disorders. History of 1 or more infections was associated with older age, race, non-Hispanic origin, higher household income and level of education, family structure, and health care interaction in the past year (Table I). All significant associations from the bivariate analyses were considered potential confounding variables and included in multivariate models.

Association between AD and infections

There were significant interactions between AD and other atopic disease as predictors of infections (logistic regression, $P < .01$). Therefore generalized linear models with binary distributions were constructed, which tested pairwise differences of rows from the coefficient matrix. This approach allowed comparison of the effects of AD with or without other atopic disease with not having AD for each infectious outcome (Table II).

AD with or without other atopic disease was associated with higher odds of strep throat (aOR, 1.47 [95% CI, 1.46-1.47] and 1.56 [95% CI, 1.54-1.57]), other sore throat (aOR, 1.61 [95% CI, 1.61-1.62] and 1.91 [95% CI, 1.91-1.92]), head or chest cold (aOR, 1.47 [95% CI, 1.46-1.47] and 1.48 [95% CI, 1.47-1.48]), influenza/pneumonia (1.24 [95% CI, 1.23-1.24] and 1.67 [95% CI, 1.66-1.67]), sinus infections (2.18 [95% CI, 2.18-2.19] and 2.59 [95% CI, 2.58-2.60]), recurrent ear infections (1.41 [95% CI, 1.40-1.42] and 1.33 [95% CI, 1.32-1.34]), chickenpox (1.33 [95% CI, 1.32-1.33] and 1.19 [95% CI, 1.19-1.20]), and urinary tract infections (1.72 [95% CI, 1.70-1.73] and 3.12 [95% CI, 3.10-3.14]; Table II).

AD without other atopic disease was associated with a slightly lower odds of warts compared with no AD (0.91 [95% CI, 0.90-0.92]). In contrast, AD with other atopic disease was associated with higher odds of warts (1.83 [95% CI, 1.82-1.84]). We constructed additional logistic regression models to determine whether the increased odds of warts was due to atopic disease in general. Children who had atopic disease without AD had higher odds of warts (1.44 [95% CI, 1.43-1.44]), whereas children with atopic disease and AD had even higher odds (2.81 [95% CI, 2.79-2.84]).

TABLE I. Determinants of AD and infectious disease in children (n = 9417)

Variable, no. (%)	AD (n = 856)			Infections (n = 5723)		
	Frequency	% Prevalence (95% CI)	P value	Frequency	% Prevalence (95% CI)	P value
Age (y)			<.0001			<.0001
<1	38	6.2 (4.3-8.2)		153	25.1 (21.6-28.5)	
1-5	311	11.6 (10.4-12.9)		1342	50.2 (48.3-52.1)	
6-10	215	9.2 (8.0-10.4)		1367	58.6 (56.6-60.6)	
11-17	292	7.7 (6.8-8.5)		2861	75.3 (73.9-76.7)	
Sex			.13			.98
Male	421	8.7 (7.9-9.5)		2956	60.8 (59.4-62.1)	
Female	435	9.6 (8.7-10.4)		2767	60.8 (59.4-62.2)	
Race			.0009			<.0001
White	523	8.9 (8.1-9.6)		3834	64.9 (63.7-66.1)	
African American	191	11.3 (9.8-12.8)		879	51.9 (49.5-54.3)	
American Indian	17	12.8 (7.1-18.5)		85	63.9 (55.7-72.1)	
Asian	28	8.6 (5.5-11.6)		147	45.0 (39.6-50.3)	
Multiracial/other	97	7.2 (5.8-8.5)		778	57.4 (54.8-60.1)	
Hispanic origin			<.0001			<.0001
No	648	9.9 (9.2-10.6)		4120	62.9 (61.8-64.1)	
Yes	208	7.2 (6.3-8.2)		1603	55.9 (54.0-57.7)	
Household income (× \$1000)			.01			<.0001
0-34	286	9.2 (8.2-10.3)		1801	58.1 (56.4-59.8)	
35-49	93	7.3 (5.8-8.7)		747	58.4 (55.7-61.1)	
50-74	149	9.8 (8.3-11.3)		952	62.5 (60.0-64.9)	
75-99	92	8.8 (7.1-10.5)		701	66.8 (64.0-69.7)	
≥100	170	10.7 (9.2-12.2)		1077	67.9 (65.6-70.2)	
Children in household			.21			.61
Single	364	9.5 (8.6-10.5)		2308	60.5 (58.9-62.0)	
Multiple	492	8.8 (8.0-9.5)		3415	61.0 (59.7-62.3)	
Highest level of household education			<.0001			<.0001
Less than high school	68	5.4 (4.2-6.7)		674	54.0 (51.2-56.8)	
High school or GED	173	7.9 (6.8-9.0)		1253	57.1 (55.0-59.1)	
Greater than high school	490	10.4 (9.5-11.3)		3011	63.8 (62.4-65.2)	
Family structure			.34			.0002
Both parents	412	8.9 (8.1-9.7)		2713	58.7 (57.3-60.1)	
Single parent	397	9.1 (8.2-10.0)		2739	62.7 (61.3-64.2)	
Other adult, no parents	47	11.1 (8.1-14.0)		269	63.3 (58.7-67.9)	
Health care interaction in past year			<.0001			<.0001
No	44	4.0 (2.8-5.2)		557	50.7 (47.8-53.7)	
Yes	800	9.8 (9.2-10.4)		5093	62.4 (61.3-63.4)	
Health insurance coverage			.003			.92
No	60	6.4 (4.8-8.0)		568	60.7 (57.6-63.9)	
Yes	793	9.4 (8.8-10.0)		5140	60.9 (59.9-62.0)	
Birthplace in the US			<.0001			.33
No	22	4.1 (2.4-5.8)		314	58.8 (54.6-63.0)	
Yes	834	9.4 (8.8-10.0)		5409	60.9 (59.9-61.9)	

Parental refusal to answer a particular question or response of “don’t know” occurred for the questions pertaining to AD in 5 (0.04%), warts in 5 (0.08%), strep throat in 13 (0.2%), other sore throat in 22 (0.2%), head or chest cold in 27 (0.3%), influenza/pneumonia in 6 (0.07%), sinus infection in 3 (0.04%), recurrent ear infections in 7 (0.07%), chickenpox in 120 (1.4%), urinary tract infection in 1 (0.003%), age in 0 (0.0%), race in 0 (0.0%), Hispanic/Spanish origin in 0 (0.0%), household income in 551 (5.3%), number of children in household in 0 (0.0%), family structure in 3 (0.03%), health care interaction in the past year in 152 (1.6%), health insurance coverage in 44 (0.5%), and birthplace in the United States in 6 (0.06%) cases, respectively.

Association between AD, other atopic disease, and number of infections

Children who had AD without other atopic disease or atopic disease without AD had a higher number of infections compared with those with no AD or atopic disease (general linear model, least-squares means, 1.05 [95% CI, 0.94-1.16] and 1.14 [95% CI, 1.07-1.20] vs 0.67 [95% CI, 0.62-0.72], respectively; $P < .0001$; [Fig 1, A](#)). Furthermore, children with AD and other atopic disease had an even higher number of infections (1.61 [95% CI, 1.49-1.73], $P < .0001$).

Association between history of warts and other infections

Warts were associated with increased odds of strep throat (logistic regression, 1.93 [95% CI, 1.92-1.93]), other sore throat (1.91 [95% CI, 1.90-1.91]), head or chest cold (1.61 [95% CI, 1.61-1.62]), influenza or pneumonia (1.77 [95% CI, 1.76-1.78]), sinus infections (1.97 [95% CI, 1.96-1.98]), chickenpox (1.16 [95% CI, 1.15-1.16]), and urinary tract infections (1.76 [95% CI, 1.75-1.78]) but less recurrent ear infections (0.87 [95% CI, 0.86-0.88], [Table III](#)).

TABLE II. Infectious comorbidities of AD and other atopic disease (n = 9417)

Variable	No AD (n = 8556)		AD (n = 856)							
	Frequency	% Prevalence (95% CI)	With no other atopic disease (n = 460)				With other atopic disease (n = 396)			
			Frequency	% Prevalence (95% CI)	aOR (95% CI)	P value	Frequency	% Prevalence (95% CI)	aOR (95% CI)	P value
Warts										
No	8347	96.8 (96.3-97.3)	447	97.4 (95.6-99.2)	1.00 (reference)	—	370	92.3 (89.0-95.6)	1.00 (reference)	—
Yes	205	3.2 (2.7-3.7)	13	2.6 (0.8-4.4)	0.91 (0.90-0.92)	<.0001	26	7.7 (4.4-11.0)	1.83 (1.82-1.84)	<.0001
Strep throat										
No	7690	88.6 (87.7-89.4)	395	85.8 (81.8-89.4)	1.00 (reference)	—	314	77.3 (71.7-82.8)	1.00 (reference)	—
Yes	855	11.4 (10.5-12.3)	65	14.2 (10.6-18.2)	1.56 (1.54-1.57)	<.0001	81	22.7 (17.2-28.3)	1.47 (1.46-1.47)	<.0001
Other sore throat										
No	6106	69.3 (68.0-70.5)	285	58.6 (52.9-64.3)	1.00 (reference)	—	193	47.2 (41.2-53.2)	1.00 (reference)	—
Yes	2435	30.7 (29.5-32.0)	171	41.4 (35.7-47.1)	1.91 (1.91-1.92)	<.0001	201	52.8 (46.8-58.8)	1.61 (1.61-1.62)	<.0001
Head or chest cold										
No	7341	86.5 (85.7-87.4)	367	81.1 (76.8-85.3)	1.00 (reference)	—	303	77.7 (72.8-82.6)	1.00 (reference)	—
Yes	1193	13.5 (12.6-14.3)	90	18.9 (14.7-23.2)	1.48 (1.47-1.48)	<.0001	92	22.3 (17.4-27.2)	1.47 (1.46-1.47)	<.0001
Influenza/pneumonia										
No	8064	93.9 (93.3-94.6)	423	92.4 (89.5-95.2)	1.00 (reference)	—	349	88.0 (84.1-91.8)	1.00 (reference)	—
Yes	487	6.1 (5.4-6.7)	37	7.6 (4.8-10.5)	1.67 (1.66-1.67)	<.0001	47	12.0 (8.2-15.9)	1.24 (1.23-1.24)	<.0001
Sinus infections										
No	8028	93.7 (93.1-94.3)	420	91.5 (88.4-94.7)	1.00 (reference)	—	299	73.7 (68.0-79.3)	1.00 (reference)	—
Yes	526	6.3 (5.7-6.9)	40	8.5 (5.3-11.6)	2.59 (2.58-2.60)	<.0001	97	26.3 (20.7-32.0)	2.18 (2.18-2.19)	<.0001
Recurrent ear infections										
No	8139	95.2 (94.6-95.8)	426	93.7 (91.2-96.2)	1.00 (reference)	—	358	90.5 (87.0-93.9)	1.00 (reference)	—
Yes	412	4.8 (4.2-5.4)	34	6.3 (3.8-8.8)	1.33 (1.32-1.34)	<.0001	38	9.5 (6.1-13.0)	1.41 (1.40-1.41)	<.0001
Chickenpox infections										
No	6132	71.6 (70.3-72.8)	348	77.2 (72.5-82.0)	1.00 (reference)	—	274	67.7 (61.8-73.6)	1.00 (reference)	—
Yes	2318	28.4 (27.2-29.7)	104	22.8 (18.0-27.5)	1.19 (1.19-1.20)	<.0001	118	32.3 (26.4-38.2)	1.33 (1.32-1.33)	<.0001
Urinary tract infections										
No	8454	98.8 (98.5-99.1)	449	97.2 (95.3-99.1)	1.00 (reference)	—	384	97.1 (95.3-98.9)	1.00 (reference)	—
Yes	102	1.2 (0.9-1.5)	11	2.8 (0.9-4.7)	3.12 (3.10-3.14)	<.0001	12	2.9 (1.1-4.7)	1.72 (1.70-1.73)	<.0001

Binary survey logistic regression models were constructed with infectious causes as the dependent variable (warts, strep throat, other sore throat, head or chest cold, influenza/pneumonia, sinus infections, recurrent ear infections, chickenpox infection, and urinary tract infections). The independent variables were a 1-year history of AD and a history of other atopic disease (binary composite of asthma, hay fever, respiratory allergy, and/or food/digestive allergy) and an interaction term between them. Multivariate logistic regression models were constructed that included age, race, Hispanic/Spanish origin, household income, highest level of education in the household, health insurance coverage, health care interaction in the past year, and US birthplace. Parental refusal to answer a particular question or response of “don’t know” occurred for the questions pertaining to AD in 5 (0.04%), warts in 5 (0.08%), strep throat in 13 (0.2%), other sore throat in 22 (0.2%), head or chest cold in 27 (0.3%), influenza/pneumonia in 6 (0.07%), sinus infection in 3 (0.04%), recurrent ear infections in 7 (0.07%), chickenpox in 120 (1.4%), urinary tract infection in 1 (0.003%), age in 0 (0.0%), race in 0 (0.0%), Hispanic/Spanish origin in 0 (0.0%), household income in 551 (5.3%), number of children in household in 0 (0.0%), family structure in 3 (0.03%), health care interaction in the past year in 152 (1.6%), health insurance coverage in 44 (0.5%), and birthplace in the United States in 6 (0.06%) cases, respectively.

Association between warts and number of infections

Children who had either warts or AD had a similar number of infections compared with those without warts or AD (general linear models, least-squares means, 0.29 [95% CI, 0.29-0.29] and 0.28 [95% CI, 0.28-0.28] vs 0.30 [95% CI, 0.30-0.31], respectively; Fig 1, B). However, children with warts and AD had a greater number of infections (0.47 [95% CI, 0.46-0.47], $P < .0001$). Similar results were also found with the Wilcoxon rank sum test and Poisson regression models (data not shown). Furthermore, similar results were found in models of warts and atopic disease in general (data not shown).

Association between AD, warts, and atopic disease

There were significant interactions between AD and history of warts as predictors of atopic disease (logistic regression, $P < .01$). Therefore generalized linear models with binary distributions were constructed, which tested pairwise differences of rows from the coefficient matrix. This approach allowed for comparison of the effects of AD with or without

a history of warts with not having AD for each atopic outcome (Table IV).

AD without warts was associated with increased odds of ever receiving a diagnosis of asthma (aOR, 1.95 [95% CI, 1.94-1.95]), current asthma (aOR, 1.62 [95% CI, 1.61-1.62]), asthma exacerbation in the past year (aOR, 1.96 [95% CI, 1.95-1.97]), hay fever (aOR, 2.60 [95% CI, 2.60-2.61]), and food allergy (aOR, 3.87 [95% CI, 3.86-3.89], Table IV). However, AD with warts had even higher odds of asthma, hay fever, and food allergies.

DISCUSSION

In the present study AD, even in the absence of other atopic disease, was associated with a higher number of infections, including strep throat, other sore throat, head or chest cold, influenza/pneumonia, sinus infections, recurrent ear infections, chickenpox, and urinary tract infections. AD with other atopic disease was associated with higher odds of warts and even higher numbers of infections. Warts were associated with increased odds of all of the above infections, but only children with warts in the

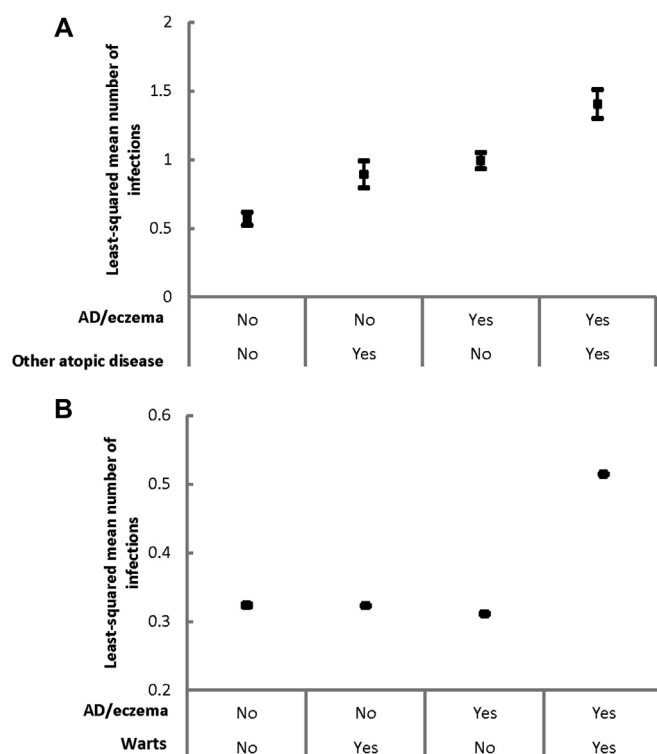


FIG 1. Association between AD/eczema and number of infections. Generalized linear models were constructed with the number of infections as the dependent variable. The independent variables were history of AD/eczema and history of other atopic disease (**A**) and warts (**B**) and an interaction between them. Race, ethnicity, age, household income, and highest level of education in the household were included as covariates. Least-squares means and 95% CIs were estimated for subgroups of children with AD/eczema and/or atopic disease (Fig 1, **A**) or warts (Fig 1, **B**).

setting of AD had a higher number of infections. Furthermore, children with AD and warts versus those with AD alone had even higher odds of ever receiving a diagnosis of asthma, current asthma, asthma exacerbations, hay fever, and food allergy.

The conventional dogma is that barrier disruption associated with AD predisposes toward more skin infections, such as *Staphylococcus aureus*, molluscum contagiosum, and eczema herpeticum.¹⁻⁵ Therefore one would expect a tendency toward cutaneous warts in patients with AD. However, a British birth cohort study actually found a lower prevalence of warts in children with visible eczema at ages 11 and 16 years compared with those without.⁶ Similarly, a Swedish cohort found that teenagers age 12 to 16 years with active AD had a lower prevalence of warts than those without AD.⁷ The present study found a higher prevalence of warts in children with AD and other atopic disorders but a slightly lower prevalence of warts in patients with AD alone. The results of the present study suggest that AD with other atopic disease, in particular, is associated with warts.

It is intriguing that children with AD and warts have even higher risk for asthma, hay fever, and food allergy than those with AD alone. It is unlikely that HPV is involved in the pathogenesis of atopic disease. Rather, the presence of warts is likely a sign of either greater barrier impairment secondary to AD or aberrant immune responses that might play a role in susceptibility to warts and development of atopic disease. Thus children with AD and

warts might represent a distinct subset of patients with AD who are at higher risk for a variety of infections.

The strong association between AD (with or without other atopic disease) and various infectious causes supports a potential role of immune dysfunction in the development of AD. Several *in vitro*, animal model, and human genetic studies found aberrant Toll-like receptor signaling and innate immunity in patients with AD.⁹ Furthermore, AD has been associated with a host of other abnormalities of both the innate and adaptive immune pathways.¹⁰⁻¹⁴ Such aberrancies would likely predispose to both cutaneous and extracutaneous infections. Silverberg and Simpson¹⁵ previously found that AD is associated with recurrent ear infections. Furthermore, AD was associated with multiple dental problems, including toothache, broken teeth, bleeding gums, and tooth decay. The authors suggested that these dental comorbidities might be related to increased oral infections secondary to impaired innate or cellular immunity in patients with AD. The results of the present study further suggest that AD is associated with increased susceptibility to a wide array of extracutaneous infections.

Similarly, the strong association between warts and various infectious causes supports a potential role of immune dysfunction in the development of childhood warts. These children might have impaired immunity, which predisposes to a variety of infections. Previous studies demonstrated the importance of CD4⁺ T cells in the control of HPV infections and that absent or aberrant cell-mediated immunity results in increased severity and oncogenicity of the virus.¹⁹ We deemed the role of poor hygiene less likely because (1) wart-related HPV and strep throat, non-strep sore throat, influenza or pneumonia, and sinusitis have different modes of transmission and (2) we found that warts were more associated with higher education level and socioeconomic status.²⁰

It is interesting that AD was associated with birthplace in the United States. In a recent study of 91,462 children and adolescents, Silverberg et al²¹ demonstrated that foreign-born American children have significantly lower prevalence of allergic disease (AD, asthma, hay fever, and food allergy) than US-born American children. Furthermore, the prevalence of atopic disease increased with prolonged residence in the United States. The results of the present study likewise support this conclusion. The mechanism of this association is likely multifactorial, including the hygiene hypothesis²² and different climate exposures,²³ for example. In contrast, the present study found no association between warts and other infections and US birthplace. This suggests that cumulative environmental exposures do not play a major role in susceptibility to warts. Rather, short-term exposure and host susceptibility to HPV appear to be the dominant factors.

The strengths of this study include being a large-scale, US population-based survey with minimal selection bias and controlling for confounding demographic variables in multivariate models. However, the study also has some limitations. AD, warts, and other infections were assessed based on self-reports, which have not been fully validated. Future studies are needed to validate the accuracy of self-reporting. One concern about self-reports or parental reports of warts in this study is potential reporting bias, such that subjects with higher socioeconomic status might have better overall health and be more motivated to seek out care for warts. To address this point, we controlled for age, race, Hispanic origin,

TABLE III. Infectious comorbidities of warts (n = 9417)

Variable	No warts (n = 9168)		Warts (n = 244)		
	Frequency	Frequency	% Prevalence (95% CI)	aOR (95% CI)	P value
Strep throat					
No	8214	168	2.84 (2.34-3.33)	1.00 (reference)	—
Yes	943	58	7.05 (5.04-9.06)	1.93 (1.92-1.93)	<.0001
Other sore throat					
No	6479	108	2.20 (1.69-2.71)	1.00 (reference)	—
Yes	2670	136	5.76 (4.66-6.86)	1.91 (1.90-1.91)	<.0001
Head or chest cold					
No	7819	29	19.2 (11.8-26.7)	1.00 (reference)	—
Yes	1326	21	20.3 (11.4-29.3)	1.61 (1.61-1.62)	<.0001
Influenza/pneumonia					
No	8619	218	3.15 (2.65-3.64)	1.00 (reference)	—
Yes	545	26	6.18 (3.58-8.78)	1.77 (1.76-1.78)	<.0001
Sinus infections					
No	8546	202	2.99 (2.50-3.48)	1.00 (reference)	—
Yes	621	42	7.80 (5.14-10.46)	1.97 (1.96-1.98)	<.0001
Recurrent ear infections					
No	8688	235	3.40 (2.88-3.91)	1.00 (reference)	—
Yes	475	9	2.23 (0.55-3.91)	0.87 (0.86-0.88)	<.0001
Chickenpox infections					
No	6617	138	2.72 (2.20-3.25)	1.00 (reference)	—
Yes	2436	104	4.87 (3.74-5.99)	1.16 (1.15-1.16)	<.0001
Urinary tract infections					
No	9050	236	3.28 (2.79-3.78)	1.00 (reference)	—
Yes	117	8	7.15 (1.61-12.68)	1.76 (1.75-1.78)	<.0001

Binary survey logistic regression models were constructed with infectious causes as the dependent variable (strep throat, other sore throat, influenza/pneumonia, sinus infections, recurrent ear infections, chickenpox infection, and urinary tract infections). The independent variable was history of warts. Multivariate logistic regression models were constructed that included age, race, Hispanic/Spanish origin, household income, highest level of education in the household, health insurance coverage, health care interaction in the past year, and US birthplace. Parental refusal to answer a particular question or response of “don’t know” occurred for the questions pertaining to warts in 5 (0.08%), strep throat in 13 (0.2%), other sore throat in 22 (0.2%), head or chest cold in 27 (0.3%), influenza/pneumonia in 6 (0.07%), sinus infection in 3 (0.04%), recurrent ear infections in 7 (0.07%), chickenpox in 120 (1.4%), urinary tract infection in 1 (0.003%), age in 0 (0.0%), race in 0 (0.0%), Hispanic/Spanish origin in 0 (0.0%), household income in 551 (5.3%), number of children in household in 0 (0.0%), family structure in 3 (0.03%), health care interaction in the past year in 152 (1.6%), health insurance coverage in 44 (0.5%), and birthplace in the United States in 6 (0.06%) cases, respectively.

TABLE IV. Association between AD, warts, and atopic disease (n = 9417)

Variable	No AD (n = 8556)		AD (n = 856)							
	Frequency	% Prevalence (95% CI)	With no warts (n = 817)				With warts (n = 39)			
			Frequency	% Prevalence (95% CI)	aOR (95% CI)	P value	Frequency	% Prevalence (95% CI)	aOR (95% CI)	P value
Ever asthma										
No	7512	87.8 (86.9-88.7)	644	79.0 (75.4-82.5)	1.00 (reference)	—	27	61.7 (42.8-80.6)	1.00 (reference)	—
Yes	1033	22.2 (11.3-13.1)	171	21.0 (17.5-24.6)	1.95 (1.94-1.95)	<.0001	12	29.3 (19.4-57.2)	3.20 (3.17-3.23)	<.0001
Current asthma										
No	319	31.2 (27.6-34.9)	37	20.5 (13.2-27.8)	1.00 (reference)	—	4	16.2 (0.0-33.7)	1.00 (reference)	—
Yes	706	68.8 (65.1-72.4)	133	79.5 (72.2-86.8)	1.62 (1.61-1.62)	<.0001	7	83.8 (66.3-100.0)	2.37 (2.33-2.42)	<.0001
Asthma exacerbation in past year										
No	642	62.8 (59.0-66.7)	79	43.9 (34.5-53.3)	1.00 (reference)	—	8	49.1 (15.9-82.3)	1.00 (reference)	—
Yes	389	37.2 (33.3-41.0)	92	56.1 (46.7-65.5)	1.96 (1.95-1.97)	<.0001	4	50.1 (17.7-84.1)	2.40 (2.37-2.43)	<.0001
Hay fever										
No	7771	90.9 (90.1-91.6)	665	81.3 (78.0-84.5)	1.00 (reference)	—	23	50.4 (31.6-69.2)	1.00 (reference)	—
Yes	767	9.1 (8.4-9.9)	148	18.7 (15.5-22.0)	2.60 (2.60-2.61)	<.0001	16	49.6 (30.8-68.4)	5.17 (5.13-5.21)	<.0001
Food allergy										
No	8291	96.8 (96.3-97.3)	706	88.2 (85.8-90.7)	1.00 (reference)	—	33	82.6 (69.0-96.3)	1.00 (reference)	—
Yes	262	3.2 (2.7-3.7)	110	11.8 (9.3-14.2)	3.87 (3.86-3.89)	<.0001	6	17.4 (3.7-31.0)	8.07 (7.97-8.17)	<.0001

Binary survey logistic regression models were constructed with atopic diseases/disease outcomes as the dependent variable (ever history of asthma, current history of asthma, 1-year history of asthma exacerbations, or 1-year history of hay fever and food allergy). The independent variables were 1-year history of AD, warts, and an interaction term between them. Multivariate logistic regression models were constructed that included age, race, Hispanic/Spanish origin, household income, highest level of education in the household, and health insurance coverage. Parental refusal to answer a particular question or response of “don’t know” occurred for the questions pertaining to AD in 5 (0.04%), warts in 5 (0.08%), age in 0 (0.0%), race in 0 (0.0%), Hispanic/Spanish origin in 0 (0.0%), household income in 551 (5.3%), number of children in household in 0 (0.0%), family structure in 3 (0.03%), and health care interaction in the past year in 152 (1.6%) cases, respectively.

household income, highest level of education in the household, health care interaction in the past year, health insurance coverage, and birthplace in the United States. All associations remained significant without a dramatic reduction in effect size. This suggests that the associations between warts and comorbid infections are not due to confounding socioeconomic issues.

Taken together, the results of this study suggest that immune dysfunction plays an important role in the development of AD and warts and their association with increased risk for other infections. Further studies are necessary to verify these points and identify the mechanism of association between AD and susceptibility to warts and extracutaneous infections.

Key messages

- This study found that children with AD had higher rates of extracutaneous infections, whereas children with AD and atopic disease had higher rates of warts.
- Children with a history of warts and AD had a higher number of extracutaneous infections than those with either disorder alone.
- Children with AD and warts had higher rates of ever receiving a diagnosis of asthma and currently having asthma, asthma exacerbation in the past year, hay fever, and food allergy.

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