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Association between atopic dermatitis and extracutaneous infections in US adults

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Dear Editor

Atopic dermatitis (AD or eczema) is a relapsing, inflammatory skin disorder characterized by impaired epidermal barrier function¹ and an abnormal cutaneous innate immune response.² It is firmly established that impaired epidermal function in AD predisposes towards cutaneous infections, including *Staphylococcus aureus* colonization, molluscum contagiosum and eczema herpeticum.^{3–5} More recently, studies have shown that AD is also associated with aberrant systemic immune function, including altered serum levels of immunomodulatory cytokines and increased systemic T-cell activation.^{6,7} Systemic immune dysregulation occurring in AD may increase the risk of extracutaneous infection, although the exact role remains unclear. We previously found increased risk of extracutaneous infections in childhood AD.^{8,9} In the present study, we sought to determine whether adult AD is associated with various aetiologies of extracutaneous infection.

We analysed data from the 2012 National Health Interview Survey (NHIS), a household survey of 34 613 adults aged ≥ 18 years. The survey was administered in person by 400 trained interviewers at households using a computer-based system. One adult per household was randomly selected to complete the survey. Sample weights were subsequently created using data from the US Census Bureau to allow for prevalence estimates that accurately represent the US population.

The questions used in this study are represented in Table 1. Several infectious aetiologies were assessed: influenza/pneumonia, strep throat, sinus infection, head or chest cold, fever, gastroenteritis, chickenpox, hepatitis, and a general category of other infectious diseases/immune problems. All infectious aetiologies assessed in NHIS 2012 were examined in this study. Associations between AD with and without additional atopic disease and number of infections were also examined.

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Conflicts of interest: none declared.

Data analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, U.S.A.). Bivariate and multivariate logistic regression models were constructed with infectious aetiologies as the dependent variable and AD as the independent variable. Multivariate models controlled for age, sex, race/ethnicity, household income, highest level of household education, birthplace, insurance coverage, number of healthcare visits, history of asthma, hay fever and food allergy, and vaccination for influenza, pneumonia, hepatitis A and hepatitis B. The control group included all adults in NHIS 2012 who responded 'no' to having AD in the past year, thus yielding a cross-sectional cohort of adults representative of the general US population. Complete data analysis was performed. Two-sided $P < 0.05$ were considered significant. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were determined.

In bivariate models, adult AD was significantly associated with increased odds of influenza/pneumonia (OR 2.37, 95% CI 1.96–2.88), strep throat (2.19, 1.74–2.76), head or chest cold (1.71, 1.54–1.91), sinus infection (2.36, 2.07–2.68), gastroenteritis (2.51, 2.06–3.07), chickenpox (1.61, 1.38–1.87), infectious diseases/immune problems (3.37, 2.78–4.08) and fever lasting more than 24 h (2.13, 1.87–2.44), but not hepatitis (1.12, 0.82–1.54) (Table 1). All significant bivariate associations remained significant in multivariate models.

Adult AD alone was significantly associated with one (OR 1.62, 95% CI 1.22–2.16), two (2.36, 1.78–3.13) and three (2.67, 1.93–3.69) infections, but was most strongly associated with four or more infections (2.78, 1.82–4.24) (Table 2). However, AD with additional atopic disease was associated with even higher risk of two (3.11, 1.99–4.87), three (6.96, 4.40–11.03) and four or more infections (17.34, 10.45–28.76) compared with AD alone. The associations remained significant in multivariate models.

These results suggest that AD and atopy are associated with higher risk for multiple extracutaneous infections. These associations remained significant in multivariate models that controlled for sociodemographics, comorbid allergic disease, healthcare utilization and vaccination history. Interestingly, adult AD was associated with increased risk of influenza/pneumonia, even though a previous analysis found adults with AD to have higher rates of both influenza and pneumonia vaccination than adults without.¹⁰ Previous studies found that children with AD had higher rates of recurrent ear infections,⁹ as well as influenza/pneumonia, sinus infections, head or chest colds and strep throat.⁸ Increased risk of infection is possibly related to systemic immune dysregulation occurring in AD and atopy.

The strengths of this study include the use of a large population-based survey of US adults of all socioeconomic and racial backgrounds, acquired with minimal selection bias, and the use of multivariate regression modelling to control for factors that impact the diagnosis of both AD and infection.

The study also has several limitations. While AD was not assessed by physician diagnosis, we used a validated question for self-report,¹¹ in which the sensitivity, specificity and positive predictive value (PPV) of the question used to assess for AD were 0.70, 0.95 and 0.87, respectively. The high PPV is ideal for studying comorbidities of AD, as the subjects who reported AD very likely had AD. However, the lower sensitivity may result in

misclassification in which some patients who reported not having AD actually had the disease. Additionally, the infections assessed in this study were also based on self-report and have not been fully validated. However, one previous study of varicella self-report in pregnant women found high PPV but low negative predictive value in determining varicella zoster antibodies.¹²

Furthermore, we were unable to determine which respondents used systemic immunosuppressive medications. The use of such medications could increase the risk of extracutaneous infection, unrelated to the underlying disease process. Finally, the cross-sectional nature of this study precludes us from determining causation or direction of association. It is possible that aberrant inflammation in AD predisposes towards infection, but it is also possible that there are unknown factors underlying the development of both infection and AD. Future prospective clinical studies are warranted to confirm and determine the mechanism of these associations.

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Table 1
Association between atopic dermatitis and infection in US adults (n = 34 613)

Atopic dermatitis						
No (n = 32 100)			Yes (n = 2488)			
Variable	n	% prevalence (95% CI)	n	% prevalence (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI) P-value
Influenza/pneumonia (past year)						
No	30 863	96.4 (96.1–96.6)	2255	91.8 (90.5–93.1)	1.00	1.00 –
Yes	1201	3.6 (3.4–3.9)	226	8.2 (6.9–9.5)	2.37 (1.96–2.88)	< 0.001 1.68 (1.34–2.11) < 0.001
Strep throat (past year)						
No	31 054	97.0 (96.7–97.2)	2255	93.6 (92.3–94.9)	1.00	1.00 –
Yes	971	3.0 (2.8–3.3)	226	6.4 (5.1–7.7)	2.19 (1.74–2.76)	< 0.001 1.73 (1.31–2.28) < 0.001
Head or chest cold (past year)						
No	19 243	58.0 (57.3–58.7)	1103	44.6 (42.1–47.2)	1.00	1.00 –
Yes	12 821	42.0 (41.3–42.7)	1382	55.4 (52.8–57.9)	1.71 (1.54–1.91)	< 0.001 1.40 (1.24–1.60) < 0.001
Sinus infection (past year)						
No	28 446	88.7 (88.2–89.1)	1876	76.9 (74.7–79.1)	1.00	1.00 –
Yes	3637	11.3 (10.9–11.8)	609	23.1 (20.9–25.3)	2.36 (2.07–2.68)	< 0.001 1.52 (1.29–1.80) < 0.001
Gastroenteritis (past 2 weeks)						
No	30 803	96.1 (95.8–96.3)	2240	90.7 (89.1–92.3)	1.00	1.00 –
Yes	1290	3.9 (3.7–4.2)	246	9.3 (7.7–10.9)	2.51 (2.06–3.07)	< 0.001 1.58 (1.26–1.99) < 0.001
Chickenpox (ever)						
No	6598	20.7 (20.1–21.2)	365	13.9 (12.2–15.7)	1.00	1.00 –
Yes	23 652	79.3 (78.9–79.9)	1975	86.1 (84.3–87.8)	1.61 (1.38–1.87)	< 0.001 1.31 (1.11–1.56) 0.002
Hepatitis (ever)						
No	30 400	97.4 (97.2–97.6)	2346	97.1 (96.2–97.9)	1.00	1.00 –
Yes	960	2.6 (2.4–2.8)	87	2.9 (2.1–3.8)	1.12 (0.82–1.54)	0.48 0.86 (0.58–1.27) 0.44
Infectious diseases/immune problem (past year)						
No	31 184	97.2 (97.0–97.4)	2257	91.2 (89.8–92.6)	1.00	1.00 –
Yes	892	2.8 (2.6–3.0)	221	8.8 (7.4–10.2)	3.37 (2.784.08)	< 0.001 2.09 (1.63–2.66) < 0.001
Fever > 24 h (past year)						

Atopic dermatitis						
Yes (n = 2488)						
No (n = 32 100)						
Variable	n	% prevalence (95% CI)	n	% prevalence (95% CI)	Crude OR (95% CI)	P-value
No	28 676	89.2 (88.7–89.6)	1962	79.4 (77.4–81.4)	1.00	–
Yes	3386	10.8 (10.4–11.3)	520	20.6 (18.6–22.8)	2.13 (1.87–2.44)	< 0.001

Binary logistic regression models were constructed with different infectious aetiologies as the dependent (outcome) variable and atopic dermatitis as the independent variable. Multivariate models included sex, age, race, household income, highest level of household education, US vs. foreign birthplace, insurance coverage, number of healthcare visits, ever history of asthma, 1-year history of hay fever and digestive allergy, and vaccination for influenza, pneumonia, hepatitis A and hepatitis B as independent variables. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. The questions used in the study are as follows. Atopic dermatitis, 'During the past 12 months have you had eczema or any kind of skin allergy?' (missing values 25, 0.06%). Influenza/pneumonia, 'During the past 12 months have you had influenza or pneumonia?' (missing values 49, 0.15%). Strep throat, 'During the past 12 months have you had strep throat or tonsillitis?' (missing values 92, 0.32%). Sinusitis, 'During the past 12 months, have you been told by a doctor or other health professional that you had sinusitis?' (missing values 47, 0.13%). Head or chest cold, 'During the past 12 months, have you had a head or chest cold?' (missing values 29, 0.09%). Chickenpox, 'Have you ever had chickenpox?' (missing values 2105, 5.8%). Gastroenteritis, 'Did you have a stomach or intestinal illness with vomiting or diarrhoea that started during the past 2 weeks?' (missing values 13, 0.03%). Hepatitis, 'Have you EVER had hepatitis?' (missing values 801, 2.3%). Infectious diseases/immune problem, 'During the past 12 months, have you had a infectious diseases or problems of the immune system?' (missing values 43, 0.10%). Fever, 'During the past 12 months, have you had fever more than 1 day?' (missing values 52, 0.14%).

Table 2

Association between atopic dermatitis and number of infections

Atopic dermatitis															
No		Yes, without additional atopic disease						Yes, with additional atopic disease (asthma, hay fever or food allergy)							
		n	n	Crude OR	(95% CI)	P-value	Adjusted OR	(95% CI)	P-value	n	Crude OR	(95% CI)	Adjusted OR	(95% CI)	P-value
number of infections	0	3975	108	1.00		–	1.00		–	35	1.00		1.00		–
	1	13 222	505	1.62 (1.22–2.16)		<0.001	1.54 (1.11–2.12)		0.009	227	1.68 (1.22–2.26)		0.03	1.50 (0.91–2.47)	0.11
	2	9304	532	2.36 (1.78–3.13)		<0.001	2.10 (1.51–2.92)		<0.001	310	3.11 (1.99–4.87)		<0.001	2.41 (1.47–3.97)	<0.001
	3	2773	186	2.67 (1.93–3.69)		<0.001	2.37 (1.63–3.46)		<0.001	214	6.96 (4.40–11.03)		<0.001	4.56 (2.74–7.59)	<0.001
	4–7	710	57	2.78 (1.82–4.24)		<0.001	2.52 (1.57–4.05)		<0.001	142	17.34 (10.45–28.76)		<0.001	8.44 (4.89–14.56)	<0.001

Binary logistic regression models were constructed with number of infections as the dependent (outcome) variable (sum of influenza/pneumonia, strep throat, head or chest cold, sinus infection, chickenpox, hepatitis and/or gastroenteritis). The independent variable was atopic dermatitis [no / yes, without additional atopic disease / yes, with additional atopic disease (asthma, hay fever, or food allergy)]. Multivariate models included sex, age, race, household income, highest level of household education, US vs. foreign birthplace, insurance coverage, number of healthcare visits and vaccination for influenza, pneumonia, hepatitis A and hepatitis B as independent variables. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated.