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Allergic disease is associated with childhood seizures: An analysis of the 1997-2013 National Health Interview Survey

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To the Editor

Epilepsy is a common neurologic disorder defined by recurrent seizures. Although the pathophysiology of epilepsy is yet to be fully elucidated, recent developments have implicated inflammatory processes and certain cytokines in the pathogenesis of epilepsy.^{1,2} Inflammation occurring in allergic disease might also contribute toward the development of epilepsy. Indeed, small studies have shown increased risk of allergic disease in children with epilepsy.³ However, epidemiologic studies on the association between allergic disease and epilepsy in adults and children have found conflicting results.⁴⁻⁶ In the present study, we examined the association between childhood allergic disease and seizures.

Data were assessed from the 1997-2013 National Health Interview Survey (NHIS). Briefly, the NHIS is the principle source of information on the health of noninstitutionalized children and adults in the United States. Household surveys were administered in both English and Spanish in-person by trained interviewers. Sample weights were created using data from the US Census Bureau to provide an accurate representation of the US population of children. The questions used in the study are presented in Table E1 in this article's Online Repository at www.jacionline.org. This study was approved by the institutional review board at Northwestern University.

A number of bivariate associations with caregiver-reported seizures and allergic disease were examined in pooled analyses including sex, age, race, household income, highest level of household education, US versus foreign birthplace, insurance coverage, and number of outpatient visits in the past year. Because of the low prevalence of seizures, the associations between seizures and allergic disease were examined in pooled analyses. The association between the number of allergic diseases (0, 1, 2, 3, and 4) and the history of seizures was

also examined. Pooled analyses were performed by merging the data sets and dividing the sampling weights by 17, the number of years of the NHIS analyzed. Weighted prevalence estimates are presented for pooled analyses.

Data analyses were performed using the SURVEY procedures in SAS version 9.4 (SAS Institute, Cary, NC). Bivariate and multivariate models were constructed with 1-year history of seizures as the dependent variable and history of allergic disease as the binary independent variable. Multivariate models also adjusted for age, sex, race, household income, highest level of household education, US versus foreign birthplace, insurance coverage, and outpatient health care utilization in the past year. Two-sided P values of less than or equal to .05 were considered significant. Adjusted odds ratios (aORs) and 95% CIs were determined.

Overall, data on 206,613 children aged 0 to 17 years were analyzed. The pooled prevalence of 1 or more allergic diseases was found to be 31.3% (95% CI, 31.0% to 31.5%), and the pooled prevalence of seizures was found to be 0.7% (0.7% to 0.8%) (see Table E2 in this article's Online Repository at www.jacionline.org). Allergic disease was significantly associated with male sex, adolescent age, black race, higher household income, higher levels of household education, US birthplace, and increased outpatient health care utilization in the past year. Seizures were significantly associated with early childhood, black race, low household income, lower levels of household education, US birthplace, and vastly increased levels of outpatient health care utilization (Table E2).

In bivariate models, seizures were significantly associated with 1-year history of eczema, hay fever, food allergy, and ever and current history of asthma (Table I). In multivariate models, seizures were significantly associated with eczema (aOR, 1.37; 95% CI, 1.13-1.67; $P = .002$), hay fever (aOR, 1.21; 95% CI, 1.02-1.44; $P = .03$), and food allergy (aOR, 1.49; 95% CI, 1.16-1.92; $P = .002$) but not ever ($P = .48$) or current ($P = .63$) history of asthma (Table I).

Childhood seizures were associated with 1 (OR, 1.42; 95% CI, 1.22-1.66), 2 (OR, 2.27; 95% CI, 1.86-2.78), and 3 (OR, 2.95; 95% CI, 2.16-4.01) comorbid allergic diseases but were most strongly associated with 4 comorbid allergic diseases (OR, 5.49; 95% CI, 3.0-10.03) in bivariate models ($P < .0001$ for trend). The trend remained significant in multivariate modeling ($P = .0069$) (Table II).

The results of this study confirm the results of previous studies that found a positive association between allergic disease and seizures. One study of data from the 2007 National Survey of Children's Health found that eczema, hay fever, asthma, and food allergy were associated with epilepsy in children. Furthermore, the risk of epilepsy was found to be more strongly associated with increased number of allergic diseases.⁵ Our present study did not find ever or current history of asthma to be significantly associated with seizures in the past year in multivariate models. In confounding analyses, performed by assessing each covariate separately with asthma as predictors of seizures, it was found that the major confounder in the association of asthma and seizures was outpatient health care visitation. In other words, the comorbidity of asthma and seizures in bivariate models was possibly related to increased

overall health care utilization and diagnosis. Two previous epidemiologic studies have found significant associations between asthma and epilepsy in adults.^{4,7} Of note, these studies did not control for confounding factors with multivariate models. In contrast, a study of the Taiwan National Health Insurance Research database found that atopic dermatitis and allergic rhinitis, but not asthma, were significantly associated with future development of epilepsy in children and adolescents.⁶

The mechanisms of the relationship between allergic disease and seizures remain undetermined. Perhaps inflammation caused by allergic disease predisposes children to seizures. Conversely, it could be that an underlying proinflammatory state manifests as both allergic disease and epilepsy. We were also unable to determine whether therapeutic control of either allergy or seizures could affect clinical manifestations of the other. Our present study is a cross-sectional analysis and as such precludes any conclusions from being made on causality. All exposures and outcomes in the study were assessed by caregiver report and not verified by physical examination and may be subject to misclassification. However, we recently performed a multicenter validation study of the eczema question used in the NHIS and found very good sensitivity, specificity, and positive and negative predictive values.⁸ Moreover, self-report of asthma has been previously validated.⁹ Thus, we believe that the case definitions for allergic disease are sufficiently valid for epidemiological study. Nevertheless, confirmation of these findings using objective measures in prospective cohorts is warranted.

In conclusion, hay fever, eczema, and food allergy, but not asthma, are associated with history of seizures in children. Risk of seizures was more strongly associated with increased number of comorbid allergic diseases. Future studies are needed to characterize the mechanism of this relationship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Association between allergic disease and seizures

Variable	1-y history of seizures					
	No (n = 204,619)			Yes (n = 1,494)		
	Frequency	% Prev (95% CI)	Frequency	% Prev (95% CI)	Crude OR (95% CI)	P value
Eczema						
No	185,054	99.3 (99.3-99.4)	1,229	0.7 (0.6-0.7)	1.00	—
Yes	19,384	98.6 (98.4-98.9)	263	1.4 (1.1-1.6)	2.09 (1.75-2.50)	<.0001
Hay fever						
No	169,500	99.4 (99.3-99.4)	1,094	0.6 (0.6-0.7)	1.00	—
Yes	34,482	98.9 (98.9-99.0)	395	1.1 (1.0-1.2)	1.72 (1.48-2.00)	<.0001
Food allergy						
No	195,760	99.3 (99.3-99.4)	1,349	0.7 (0.6-0.7)	1.00	—
Yes	8,569	98.4 (98.1-98.7)	141	1.6 (1.2-1.9)	2.29 (1.83-2.86)	<.0001
Ever asthma						
No	177,938	99.3 (99.3-99.4)	1,183	0.7 (0.6-0.7)	1.00	—
Yes	26,409	98.9 (98.8-99.1)	307	1.1 (0.9-1.2)	1.62 (1.38-1.90)	<.0001
Current asthma						
No	193,356	99.3 (99.3-99.4)	1,315	0.7 (0.6-0.7)	1.00	—
Yes	10,943	98.6 (98.3-98.8)	174	1.5 (1.2-1.7)	2.17 (1.77-2.65)	<.0001

Binary logistic regression models were constructed with 1-year history of seizures as the dependent variable and eczema, hay fever, food allergy, and ever or current history of asthma as the independent variable. Multivariate models included sex, age, race, household income, highest level of household education, US versus foreign birthplace, insurance coverage, and outpatient health care utilization over the past year. aORs and 95% CIs were estimated. Boldface indicates statistical significance. *Prev*, Prevalence.

Table II

Association between number of allergic diseases and seizures

No. of allergic diseases	1-y history of seizures					
	No (n = 204,619)			Yes (n = 1,494)		
	Frequency	% Prev (95% CI)	Frequency	% Prev (95% CI)	Crude OR (95% CI)	aOR (95% CI)
0	140,341	99.4 (99.4-99.5)	802	0.6 (0.5-0.6)	1.00	1.00
1	43,455	99.1 (99.1-99.3)	393	0.8 (0.7-0.9)	1.42 (1.22-1.66)	1.02 (0.86-1.22)
2	14,915	98.7 (98.4-98.9)	189	1.3 (1.1-1.6)	2.27 (1.86-2.78)	1.22 (0.97-1.53)
3	3,929	98.3 (97.8-98.8)	73	1.9 (1.4-2.4)	2.95 (2.16-4.01)	1.48 (1.04-2.11)
4	765	96.9 (95.1-98.7)	26	3.1 (1.3-4.9)	5.49 (3.00-10.03)	1.98 (0.98-3.96)
<i>P</i> value for trend					<.0001	.0069

Binary logistic regression models were constructed with 1-year history of seizures as the dependent variable and number of allergic diseases as the ordinal independent variable (eczema, hay fever, food allergy, or ever history of asthma). Multivariate models included sex, age, race, household income, highest level of household education, US versus foreign birthplace, insurance coverage, and outpatient health care utilization over the past year. aORs and 95% CIs were estimated. Boldface indicates statistical significance. *Prev*, Prevalence.