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Allergic disease is associated with epilepsy in childhood: a US population-based study

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Abstract

Background: Previous studies using animal models suggest an association between allergic disease and epilepsy. We sought to determine whether allergic disease is associated with epilepsy in children.

Methods: We used the 2007–2008 National Survey of Children's Health, a US population-based study of 91 642 children aged 0–17 years to determine the association between the prevalence of epilepsy and allergic disease, including asthma, atopic dermatitis (AD)/eczema, hay fever, and food allergies. Multivariate logistic regression models were constructed that controlled for confounding variables.

Results: The US lifetime prevalence of childhood epilepsy was 1.03% and was significantly associated with older age, male sex, lower household income, family structure and history of brain injury or concussion. Children with ≥ 1 allergic disease had more epilepsy in their lifetime than nonallergic children (logistic regression, adjusted odds ratio [95% confidence interval] = 1.79 [1.37–2.33]). Lifetime prevalence (2.30 [1.50–3.52]) and one-year prevalence of asthma (2.00 [1.41–2.84]), AD/eczema (1.73 [1.17–2.56]), hay fever (1.93 [1.41–2.65]) and food allergies (2.69 [1.38–4.01]) were associated with increased odds of ever being diagnosed with epilepsy. Similar results were found for current history of epilepsy. Severe AD/eczema (23.89 [1.34–11.32]) and hay fever (2.46 [1.11–5.41]) were associated with even higher odds of epilepsy compared with mild/moderate disease. As the number of allergic diseases increased, so did the odds of lifetime history and current history of epilepsy.

Conclusions: The US prevalence of epilepsy is associated with allergic diseases in children. Further studies are needed to determine whether allergic inflammation contributes toward epileptogenesis.

Allergic diseases such as atopic dermatitis (AD) and asthma are associated with multiple neuropsychiatric and mental health disorders in children and adults, including depression, anxiety, attention deficit hyperactivity disorder, and autism (1–7). Despite the growing evidence of such an association, little is known about the relationship between allergic disease

and other neurologic disorders, including epilepsy. Previous studies from our laboratory found that a single tonic-clonic seizure in mice induced interleukin-4 (IL4) and immunoglobulin E (IgE)-negative T and B cells to infiltrate brain and switch to IL4+ and IgE+ cells (8, 9). These animal studies suggest that inflammatory pathways involved in allergic diseases may also be activated in brain and may contribute toward epilepsy.

Previous epidemiologic studies found associations between epilepsy and asthma in adults (10–12). Some of these studies suggested that obesity may play a role in this association,

Abbreviations

AD, atopic dermatitis; aOR, adjusted odds ratio; CI, confidence interval; NSCH, National Survey of Children's Health; OR, odds ratio.

although the mechanism for this interaction is not known. However, there have been no studies of the association between epilepsy and other allergic diseases. Moreover, little is known about the relationship between epilepsy and allergic disease in childhood. Taken together with previous clinical and epidemiological studies of other neuropsychiatric disorders in children (1–7) and epilepsy in adults (10–12), we hypothesized that childhood epilepsy is associated with allergic disease, including eczema, asthma, hay fever, and food allergy.

Methods

National Survey of Children's Health (NSCH)

We used data from the 2007 NSCH, which was designed to estimate the prevalence of various child health issues. The NSCH was sponsored by the Maternal and Child Health Bureau and the US Department of Health and Human Services. The National Center for Health Statistics was conducted using the State and Local Area Integrated Telephone Survey program with a goal of >1700 households per state. The telephone numbers were chosen at random, followed by identification of the households with one or more children under the age of 18. Subsequently, one child per household was randomly selected as the subject for interview. Questionnaires were completed by parents or guardians of the child. Interviews were conducted in English, Spanish, Korean, Mandarin, Cantonese and Vietnamese. The survey results were weighted to represent the population of noninstitutionalized children nationally and in each state. 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 <18 years of age. The National Center for Health Statistics of the Center for Disease Control and Prevention oversaw sampling and telephone interviews. Verbal-informed consent was obtained before interview. All NSCH procedures and modifications were approved by the National Center for Health Statistics Research Ethics Review Board and the NORC Institutional Review Board. Approval by the local institutional review board was waived.

Prevalence of allergic disorders

One-year prevalence of AD/eczema, asthma, hay fever, and food allergy was determined by parental response to the NSCH questions, '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?', '...asthma?', '...hay fever or any kind of respiratory allergy?' and '...any kind of food or digestive allergy?' History of ever having asthma was also determined by the question 'Have you ever been told by a doctor or other health professional that (child) had asthma?' Ever history of other allergic diseases was not assessed. A composite binary variable was created for any

allergic disorders using responses to the above four questions. Number of allergic disorders was created, which represent the sum of all the above-mentioned allergic disorders.

Severity of allergic disease

Severity of AD/eczema was determined using the NSCH question, 'Would you describe (child's) eczema or skin allergy as mild, moderate, or severe?' Severity of asthma was determined by 'Would you describe (child's) asthma as mild, moderate, or severe?' Severity of hay fever was determined by 'Would you describe (child's) hay fever or respiratory allergies as mild, moderate, or severe?' Severity of food allergy was determined by 'Would you describe (child's) food or digestive allergy as mild, moderate, or severe?' Responses were encoded as an ordinal variable, where 1 = mild, 2 = moderate, and 3 = severe.

Epilepsy

Lifetime and point prevalence of epilepsy were determined by the questions, 'Has a doctor or other health care provider ever told you that (child) had epilepsy or seizure disorder?' and 'Does (child) currently have epilepsy or seizure disorder?', respectively.

Body mass index (BMI)

BMI-for-age classification of adolescents aged 10–17 years was determined using a combination of questions, 'How much does (child) weigh now?' (pounds) and 'How tall is (child) now?' (inches). The question about weight was asked of all parents. However, the question about height was only asked of parents of adolescents aged 10–17 years owing to concerns about parental underestimation of height and resultant overestimation of overweight/obesity prevalence among preschool and elementary school-aged children (13). To protect the identity of children with extreme height or weight measurements, these values were top coded to 95th percentile or bottom coded to 5th percentile accordingly. BMI was calculated by: $(\text{weight} \times 703)/\text{height}^2$. BMI-for-age percentiles were determined using Centers for Disease Control standards.

Data processing and statistical methods

All data processing and statistical analyses were performed in SAS, version 9.2 (SAS Institute, Cary, NC, USA). Analyses of survey responses were performed using SURVEY procedures. Univariate associations were tested by Rao–Scott chi-square tests. Analysis of eczema severity was performed by dichotomizing responses into mild/moderate versus severe eczema. This approach was used over ordinal logistic regressions because the data did not meet the proportional odds assumption (Score test, $P < 0.01$). Multivariate logistic regression models were constructed that included age, sex, household income, family structure, healthcare interaction in the past year, and history of brain injury or concussion,

which were selected based on univariate models. Complete data analysis was performed, that is, subjects with missing data were excluded. Linear interactions were tested and only included in final models if P -value < 0.05 and modification of estimates by $>10\%$; no significant statistical interactions were found.

A two-sided P -value < 0.05 was taken to indicate statistical significance for all estimates. However, the multiple-dependent tests performed in this study increase the risk of falsely rejecting the null hypothesis. Therefore, P -values near 0.05 should be interpreted with caution.

Results

Epilepsy prevalence

Data were collected on a total of 91 642 children. The US lifetime prevalence of childhood epilepsy was 1.03%. There was no significant statewide variation of the prevalence of epilepsy ($P = 0.63$). Lifetime prevalence of epilepsy was significantly associated with older age, male sex, lower household income, family structure, and history of brain injury or concussion, but not race/ethnicity, highest level of education in the household, healthcare interaction in the past year, residence in a metropolitan area, or smoking in the home (Table 1).

Allergic disease prevalence

The US prevalence of ≥ 1 childhood allergic disease was 32.9%. There was significant statewide variation of the prevalence of ≥ 1 allergic disease ($P < 0.0001$), with the highest prevalence in Washington, DC (41.8%), and the lowest in California (27.1%). Prevalence of allergic disease was significantly associated with older age, African-American race, male sex, healthcare interaction in the past year, and history of brain injury or concussion, but not household income, highest level of education in the household, residence in a metropolitan area, or smoking in the home (Table 1).

Association between prevalence of allergic disease and epilepsy

Overall, children with ≥ 1 allergic disease had a higher odds of epilepsy compared with nonallergic children (OR [95% CI], P -value: 1.79 [1.37–2.33], $P < 0.0001$) (Table 2). Lifetime prevalence of asthma (2.30 [1.50–3.52], $P = 0.0007$) and one-year prevalence of asthma (2.00 [1.41–2.84], $P = 0.0001$), eczema (1.73 [1.17–2.56], $P = 0.0006$), hay fever (1.93 [1.41–2.65], $P < 0.0001$), and food allergies (2.69 [1.38–4.01], $P < 0.0001$) were all associated with increased odds of ever being diagnosed with epilepsy. These associations remained significant in multivariate models that included age, sex, household income, family structure, healthcare interaction in the past year, and history of brain injury or concussion ($P \leq 0.02$).

Similarly, allergic disease was associated with 1-year history of epilepsy in univariate and multivariate models (Table 2).

Association between number of allergic diseases and epilepsy

The total number of allergic diseases was associated with increased epilepsy. That is, as the number of comorbid allergic diseases increased, so did the odds of both lifetime and point prevalence of epilepsy (Table 3). These associations remained significant in multivariate models.

Association between severity of allergic diseases and epilepsy

The severity of some allergic diseases was associated with increased epilepsy. That is, severe AD/eczema (3.89 [1.34–11.32], $P = 0.01$) and hay fever (2.46 [1.11–5.41], $P = 0.03$) were associated with higher point prevalence of epilepsy (Table 4). These associations remained significant in multivariate models. However, severity of asthma and food allergy was not associated with epilepsy.

Association between allergic diseases and epilepsy is not related to obesity

Lifetime and point prevalence of epilepsy were not associated with obesity (lifetime: 1.23 [0.82–1.85], $P = 0.32$; point: 0.99 [0.58–1.71], $P = 0.98$) (Table 5). Further, the association between multiple allergic diseases and epilepsy remained significant even when body mass index classification was included in multivariate models ($P = 0.02$). There were no significant interactions between obesity and history of allergic disease in models of lifetime or point prevalence of epilepsy ($P \geq 0.40$).

Discussion

Using a population-based parental survey, we demonstrate that children with allergic disease, including asthma, AD/eczema, hay fever, and food allergies, have a higher lifetime and point prevalence of healthcare-provider-diagnosed epilepsy. Further, severe AD/eczema and hay fever were associated with even higher odds of epilepsy than mild/moderate disease. These results are consistent with previous studies that found associations between epilepsy and asthma in children and adults (10, 12, 14–17). A questionnaire-based single-center study of 406 children found that asthma was associated with significantly more neurological problems, including epilepsy, hearing impairment, and developmental delay (14). A previous study of data from the 2002 National Health Interview Survey found that adults with seizures had a two-fold higher odds of asthma, as well as cancer, arthritis, heart disease, stroke, severe headaches, lower back, and neck pain (10). Similarly, studies from the 2002 and 2006 Behavioral Risk Factor Surveillance System found that adults with epilepsy had a higher prevalence of asthma (12, 15). A study of 50 adults with generalized and 75 patients with partial convulsive epilepsy found high prevalences of atopy in both groups (56% and 65%, respectively), although signs of allergy *per se* were only present to a lesser extent (16). A study of 250 adults with epilepsy and 250 age-matched healthy controls found that epilepsy was associated with a

Table 1 Subject characteristics (*n* = 91 642)

Variable	Ever history of epilepsy		<i>P</i> -value*	≥ 1 allergic disease		
	No (<i>n</i> = 90 628)	Yes (<i>n</i> = 977)		No (<i>n</i> = 60 199)	Yes (<i>n</i> = 30 963)	<i>P</i> -value*
Age (years)						
Mean (95% CI)	8.6 (8.5–8.9)	10.4 (10.1–10.7)	<0.0001	8.4 (8.3–8.4)	8.6 (8.5–8.7)	<0.0001
Freq – no. (%)						
0–5	27 351 (99.4)	204 (0.6)	<0.0001	19 193 (71.3)	8190 (28.7)	<0.0001
6–10	22 862 (99.0)	247 (1.0)		14 745 (64.7)	8260 (35.3)	
11–17	40 415 (98.6)	526 (1.4)		26 261 (65.3)	14 513 (34.7)	
Race/ethnicity – no. (%)						
African-American	8761 (98.9)	108 (1.1)	0.60	5088 (59.4)	3732 (40.6)	<0.0001
Hispanic	11 399 (99.1)	121 (0.9)		8059 (73.9)	3393 (26.1)	
White	60 819 (98.9)	633 (1.1)		40 739 (66.7)	20 360 (33.3)	
Other/mixed	8225 (99.2)	95 (0.8)		5250 (66.1)	3010 (33.9)	
Sex – no. (%)						
Male	47 005 (98.8)	508 (1.2)	0.03	30 512 (65.4)	16 773 (34.6)	<0.0001
Female	43 514 (99.1)	469 (0.9)		29 613 (68.9)	14 157 (31.1)	
Household income (Poverty level) [†] – no. (%)						
0–99%	10 787 (98.7)	176 (1.3)	0.02	7182 (68.9)	3698 (31.1)	0.12
100–199%	15 361 (98.7)	222 (1.3)		10 287 (67.5)	5211 (32.5)	
200–399%	30 482 (99.1)	300 (0.9)		20 333 (66.3)	10 314 (33.7)	
≥400%	33 998 (99.3)	279 (0.7)		22 397 (66.6)	11 740 (33.4)	
Family structure – no. (%)						
Two parents – Biological or adopted	63 505 (99.2)	570 (0.8)	0.03	43 201 (69.5)	20 588 (30.5)	<0.0001
Two parents – Step family	6421 (98.4)	99 (1.6)		4102 (63.7)	2387 (36.3)	
Single mother/no father present	14 505 (98.6)	217 (1.4)		8788 (60.7)	5849 (39.3)	
Other family type	5655 (98.6)	86 (1.4)		3721 (64.5)	1965 (35.5)	
Highest level of parental education – no. (%)						
<High-school graduate	2515 (98.6)	39 (1.4)	0.64	1706 (69.0)	831 (40.0)	0.06
High-school graduate or GED	6996 (98.6)	110 (1.4)		4582 (66.0)	2484 (34.0)	
>High-school	24 999 (98.9)	298 (1.1)		16 079 (63.7)	9087 (36.6)	
Healthcare interaction in past year – no. (%)						
No	11 879 (99.1)	89 (0.9)	0.72	8789 (74.3)	3119 (25.7)	<0.0001
Yes	78 749 (99.0)	888 (1.0)		51 399 (66.1)	27 832 (33.9)	
Residence in metropolitan area – no. (%)						
No	48 836 (99.0)	521 (1.0)	0.40	32 006 (67.3)	17 090 (32.6)	0.43
Yes	13 620 (98.8)	154 (1.2)		8934 (66.6)	4771 (33.4)	
Smoking in home – no. (%)						
No	15 738 (98.9)	195 (1.1)	0.21	10 129 (64.2)	5692 (35.8)	0.30
Yes	6322 (98.5)	105 (1.5)		3979 (62.6)	2418 (37.4)	
Ever history of brain injury or concussion – no. (%)						
No	88 730 (99.2)	807 (0.8)	<0.0001	59 111 (67.4)	29 977 (36.6)	<0.0001
Yes	1867 (88.3)	165 (11.7)		1065 (53.8)	954 (46.2)	

*Rao–Scott chi-square tests were used for categorical variables. Survey-weighted t-tests were used for continuous variables.

[†]The family poverty level in 2007 for the 48 contiguous states and District of Columbia was \$17 170 for a family with 3 people, \$20 650 with 4 people, \$24 130 with 5 people, \$27 610 with 6 people, \$31 090 with 7 people, \$34 570 with 8 people, and \$3480 for each additional person in the family (Federal Register, Vol. 72, No. 15, January 24, 2007, pp. 3147–3148).

Parental refusal to answer a particular question or response of 'don't know' occurred for the questions pertaining to ever history of epilepsy in 40 (0.02%), current history of eczema in 79 (0.06%), ever history of asthma in 104 (0.1%), current history of asthma in 107 (0.2%), current history of hay fever in 154 (0.2%) and current history of food allergy in 120 (0.2%), age in 0 (0.0%), race/ethnicity in 1313 (1.6%), sex in 92 (0.2%), family structure in 547 (0.6%), highest level of parental education in 612 (1.4%), household income in 0 (0.0%), healthcare interaction in 0 (0.0%), insurance coverage in 183 (0.2%), residence in a metropolitan area in 28 485 (31.1%), smoking in home in 8 (0.1%), and ever history of brain injury or concussion in 36 (0.1%), respectively.

small but significantly increased prevalence of asthma, as well as hypertension, diabetes, osteoarthritis, hypothyroidism, and acid-peptic disease (17). Finally, a study of 24 children

diagnosed with asthma and 24 age- and sex-matched healthy controls found that asthmatics were more likely to exhibit epileptiform activity on electroencephalogram (EEG) (18).

Table 2 Association between allergic disorders and epilepsy

Allergic disease	No epilepsy (<i>n</i> = 90 628)		Ever history of epilepsy (<i>n</i> = 977)					
	Freq	Percent (95% CI)	Freq	Percent (95% CI)	OR (95% CI)	<i>P</i> -value	aOR (95% CI)	<i>P</i> -value
≥ 1 allergic disease		0.77 (0.63–0.91)	439	1.37 (1.10–1.63)	1.79 (1.37–2.33)	<0.0001	1.56 (1.20–2.02)	0.0009
AD/Eczema	807	0.94 (0.78–1.10)	168	1.62 (1.06–2.18)	1.73 (1.17–2.56)	0.006	1.63 (1.12–2.38)	0.01
Asthma								
Ever asthma	754	0.87 (0.74–1.01)	220	1.99 (1.21–2.76)	2.30 (1.50–3.52)	0.0001	1.77 (1.27–2.45)	0.0007
Current asthma	817	0.94 (0.78–1.10)	154	1.86 (1.31–2.41)	2.00 (1.41–2.84)	0.0001	1.54 (1.07–2.21)	0.02
Hay fever	718	0.89 (0.72–1.06)	256	1.71 (1.29–2.13)	1.93 (1.41–2.65)	<0.0001	1.61 (1.16–2.24)	0.005
Food allergies	874	0.88 (0.77–0.99)	96	2.69 (1.38–4.01)	3.12 (1.86–5.25)	<0.0001	2.85 (1.74–4.68)	<0.0001
	No epilepsy (<i>n</i> = 91 068)		Current history of epilepsy (<i>n</i> = 526)					
≥ 1 allergic disease	276	0.44 (0.32–0.55)	243	0.89 (0.65–1.14)	2.06 (1.41–3.01)	0.0002	1.78 (1.23–2.58)	0.002
AD/Eczema	439	0.58 (0.43–0.73)	87	1.04 (0.43–0.73)	1.81 (1.04–3.14)	0.03	1.81 (1.06–3.06)	0.03
Asthma								
Ever asthma	398	0.51 (0.39–0.62)	126	1.43 (0.68–2.19)	2.86 (1.60–5.10)	0.0004	2.12 (1.38–3.24)	0.0006
Current asthma	427	0.57 (0.42–0.72)	96	1.27 (0.77–1.77)	2.25 (1.39–3.63)	0.0009	1.67 (1.03–2.72)	0.04
Hay fever	386	0.54 (0.38–0.69)	138	1.13 (0.74–1.52)	2.12 (1.35–3.33)	0.001	1.68 (1.05–2.69)	0.03
Food allergies	464	0.52 (0.42–0.62)	58	1.91 (0.64–3.18)	3.73 (1.85–7.53)	0.0002	3.37 (1.73–6.56)	0.0004

Parental refusal to answer a particular question or a response of 'don't know' occurred for the questions pertaining to ever history of epilepsy in 40 (0.02%), current history of epilepsy in 11 (0.01%), current history of eczema in 79 (0.06%), ever history of asthma in 104 (0.1%), current history of asthma in 107 (0.2%), current history of hay fever in 154 (0.2%), and current history of food allergy in 120 (0.2%), respectively.

Logistic regression models were constructed with ever or current history of epilepsy as the dependent variables. The independent variable was the specific etiologies of allergic disease, including current history of AD/eczema, ever and current history of asthma, current history of hay fever, current history of food allergy, and a composite variable for any of the abovementioned allergic disorders (all binary). OR and 95% CI were estimated. Multivariate logistic regression models were constructed that included age, sex, household income, family structure, healthcare interaction in the past year, and history of brain injury or concussion (selected from univariate models).

Table 3 Association between number of allergic diseases and epilepsy

Number of allergic diseases*	No epilepsy (<i>n</i> = 90 628)		Ever history of epilepsy (<i>n</i> = 977)					
	Freq	Percent (95% CI)	Freq	Percent (95% CI)	OR (95% CI)	<i>P</i> -value	aOR (95% CI)	<i>P</i> -value
0	59 924	99.2 (99.1–99.4)	527	0.77 (0.63–0.91)	1.00	–	1.00	–
1	20 825	98.7 (98.3–99.2)	254	1.25 (0.77–1.74)	1.64 (1.07–2.51)	0.02	1.36 (0.94–1.96)	0.10
2	7232	98.5 (98.0–98.9)	121	1.52 (1.09–1.95)	2.00 (1.42–1.80)	<0.0001	1.59 (1.11–2.28)	0.01
3	2162	96.4 (94.4–98.4)	56	3.60 (1.61–5.60)	4.82 (2.64–8.79)	<0.0001	3.80 (2.13–6.76)	<0.0001
4	485	95.5 (90.4–100.0)	19	4.51 (0.00–9.61)	6.09 (1.84–20.17)	0.003	4.36 (1.74–10.89)	0.002
	No epilepsy (<i>n</i> = 91 068)		Current history of epilepsy (<i>n</i> = 526)					
0	60 167	99.6 (99.5–99.7)	276	0.4 (0.3–0.5)	1.00	–	1.00	–
1	20 934	99.2 (98.7–99.6)	143	0.8 (0.4–1.3)	1.96 (1.06–3.60)	0.03	1.65 (0.99–2.73)	0.05
2	7287	99.1 (98.7–99.4)	65	0.9 (0.6–1.3)	2.13 (1.32–3.43)	0.002	1.63 (0.99–2.70)	0.06
3	2186	97.3 (95.4–99.2)	32	2.7 (0.8–4.6)	6.33 (2.90–13.81)	<0.0001	4.91 (2.36–10.22)	<0.0001
4	494	96.7 (91.7–100.0)	10	3.3 (0.0–8.3)	7.74 (1.56–38.50)	0.01	5.38 (1.52–19.00)	0.009

*Number of allergic disease = eczema ± asthma ± hay fever ± food allergy.

Logistic regression models were constructed with ever or current history of epilepsy as the dependent variables. The independent variable was the number of allergic diseases (ordinal from 0–4). OR and 95% CI were estimated for each number of allergic diseases. Multivariate logistic regression models were constructed that included age, sex, household income, family structure, healthcare interaction in the past year, and history of brain injury or concussion (selected from univariate models).

However, this is the first study to demonstrate an association between epilepsy and other allergic diseases, such as AD/eczema, hay fever, and food allergies. An intriguing finding

of this study is that the risk of epilepsy increases with the number of comorbid allergic disorders. Despite the study having a very large sample size, only 1.03% of children had

Table 4 Association between severity of allergic disease and epilepsy

Severity of allergic diseases	No epilepsy		Ever history of epilepsy					
	Freq	Percent (95% CI)	Freq	Percent (95% CI)	OR (95% CI)	P-value	aOR (95% CI)	P-value
AD/eczema								
Mild/Moderate	10 522	98.6 (98.2–99.1)	143	1.4 (0.9–1.8)	1.00	–	1.00	–
Severe	611	94.9 (90.1–99.8)	24	5.1 (0.2–9.9)	3.89 (1.34–11.32)	0.01	2.71 (1.11–6.62)	0.03
Asthma								
Mild/Moderate	7430	98.3 (97.7–98.8)	319	1.7 (1.2–2.3)	1.00	–	1.00	–
Severe	133	96.0 (92.6–99.4)	21	4.0 (0.6–7.4)	2.38 (0.93–6.08)	0.07	2.10 (0.84–5.25)	0.11
Hay fever								
Mild/Moderate	15 585	98.4 (97.9–98.8)	229	1.6 (1.2–2.1)	1.00	–	1.00	–
Severe	562	1.6 (1.2–2.1)	26	3.9 (1.1–6.7)	2.46 (1.11–5.41)	0.03	2.25 (1.01–5.02)	0.04
Food allergy								
Mild/Moderate	3603	97.2 (95.6–98.8)	68	2.8 (1.2–4.4)	1.00	–	1.00	–
Severe	917	97.7 (96.4–99.0)	28	2.3 (1.0–3.6)	0.82 (0.36–1.89)	0.64	0.94 (0.41–2.15)	0.88

Logistic regression models were constructed with ever history of epilepsy as the dependent variables. The independent variable was the severity of allergic diseases (severe vs. mild/moderate), including AD/eczema, asthma, hay fever and food allergy. OR and 95% CI were estimated for moderate-severe allergic diseases. Multivariate logistic regression models were constructed that included age, sex, household income, family structure, healthcare interaction in the past year, and history of brain injury or concussion (selected from univariate models).

Table 5 Association between allergic disease and epilepsy in adolescents age 10–17 years is not related to body mass index

BMI-for-age percentile	Lifetime prevalence of epilepsy (<i>n</i> = 977)			Point prevalence of epilepsy (<i>n</i> = 526)		
	Freq (%)	OR (95% CI)	P-value	Freq (%)	OR (95% CI)	P-value
<5	31 (1.5)	1.07 (0.29–3.93)	0.91	19 (1.3)	1.40 (0.30–6.44)	0.67
6–84	320 (1.4)	1.00	–	172 (0.9)	1.00	–
85–94	95 (1.3)	0.92 (0.53–1.60)	0.77	42 (0.7)	0.79 (0.33–1.85)	0.58
≥ 95	118 (1.7)	1.22 (0.78–1.90)	0.38	66 (0.9)	0.98 (0.54–1.78)	0.94

Parental refusal to answer a particular question or response of 'don't know' occurred for the questions pertaining to ever history of epilepsy in 40 (0.02%), current history of epilepsy in 11 (0.01%) and body mass index in 1796 (3.9%), respectively.

Logistic regression models were constructed with lifetime and point prevalence of epilepsy as the dependent variables. The independent variable was BMI-for-age percentiles (<5, 6–84, 85–94, ≥95). OR and 95% CI were estimated.

epilepsy and 32.9% had allergic disease. Thus, we were unable to determine the effects of all 15 combinations of allergic disease.

In this study, there was significant statewide variation of the prevalence of allergic disease. This is consistent with a previous US population-based study that found significant statewide variation for eczema prevalence (19). Regional differences of allergic disease prevalence is likely related a host of environmental factors. This raises an important question of whether regional differences of allergic disease prevalence might contribute toward regional differences of epilepsy. However, there was no significant statewide variation of epilepsy prevalence observed. This suggests that environmental factors may not play a major role in the association between epilepsy and allergic disease.

In this study, epilepsy was not associated with obesity. In contrast, a previous study of data from the 2006 Behavioral Risk Factor Surveillance System found a higher prevalence of obesity in adults with epilepsy (12). Epilepsy is a chronic disorder associated with impaired physical activity and

perhaps sedentary lifestyle, which might predispose toward obesity. On the other hand, obesity has been found to be a risk factor for developing AD (20–22), asthma (23–30), and atopy (31–34). Thus, our *a priori* hypothesis was that immune changes secondary to obesity (35–39) might contribute toward the pathogenesis of epilepsy. However, the results of the present study found that the association between allergic disease and epilepsy was not related to obesity and appear to refute this hypothesis.

The mechanism(s) of association between allergic disease and epilepsy is unknown. Further studies are warranted to determine the mechanism of association between allergic disorders and epilepsy.

The strengths of this study include being large-scale, US population-based, survey of multiple allergic disorders, minimization of selection bias, and controlling for confounding demographic variables in multivariate models. The case-control study design is appropriate for initial investigation into a disease (epilepsy) with a low prevalence (~1%). Nevertheless, the study also has some limitations. The very large sample

size may result in associations with small effect sizes that may not be clinically relevant. However, the significant associations in this study had adjusted odds ratios ranging from 1.59 to 5.38, which would likely be detected in smaller cohorts. The study is cross-sectional and does not allow for determination of the direction of association between allergic disease and epilepsy. That is, chronic allergic disease might provoke epilepsy or *vice versa* or there may be a common pathway that triggers both. Future longitudinal studies are necessary to demonstrate the direction of these associations. Allergic diseases were assessed by parental report of physician diagnosed disease. This methodology has been previously validated in the International Study of Asthma and Allergies in Childhood (ISAAC) and other studies and is a standard approach in the epidemiologic study of allergic disease. Moreover, the preponderant form of skin and airway disease in children is AD/eczema and asthma, respectively. Severity of allergic disease was also assessed by parental report. There are numerous validated clinical and self-reported scales of allergic disease severity and control, such as Asthma Control Test (ACT) and Asthma Therapy Assessment Questionnaire (ATAQ), each with their pros and cons. Self- and parental report of allergic disease severity using a scale of mild, moderate, and severe disease and other self-reported scales have been validated and found to have moderate to high correlation with physician assessment (40–44) and standardized diagnostic testing (45, 46). Epilepsy was also assessed by parental report using a question that asked about healthcare-provider-diagnosed epilepsy or recurrent seizures. This approach has also been validated and used in previous studies (10, 12, 15, 47). Based on previous studies that validated self- and parental report of epilepsy and allergic, parental report of these disorders was considered to be a valid approach. Nevertheless, future clinical studies with objective measurements of epilepsy and allergic disease are warranted to verify these findings and to determine the etiologies of epilepsy associated with allergic disease. It is important to note that epilepsy is a spectrum of seizure disorders with heterogeneous etiologies. It may be that a specific subtype(s) of epilepsy is associated with allergic disease. However, the use of parental report of epilepsy limited our ability to determine this. Future studies with neurologic assessment and objective measures of epilepsy are indicated to answer this question. In summary, this study generates some early hypotheses to be further tested in studies specifically designed to investigate the study question. Future

confirmatory studies should be longitudinal, with neurologic assessment and clinical of epilepsy and objective measures of both allergic disorders and epilepsy.

This study raises several important issues. First, it highlights a possible link between the two disorders that begs confirmation and future basic science and translational research studies. Second, it suggests that epilepsy may be a comorbidity of severe childhood allergic disease, which may require addressing by allergists, dermatologists, and primary care providers alike. History of epilepsy might have prognostic value in predicting which children will have more severe allergic disease or *vice versa*. As the prevalence of epilepsy is relatively low (~1%), routine screening of all children with allergic disease would likely be low yield. On the other hand, children with epilepsy were found to have a high prevalence of allergic disease (~46%) and would benefit from routine screening for allergic disease by history and physical. Future longitudinal studies are necessary to determine the time course and direction of association between allergic disease and epilepsy and the impact of treatment for allergic disease on comorbid epilepsy.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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