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Children with allergic rhinitis and a risk of epilepsy: A nationwide cohort study

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ABSTRACT

Purpose: Little is known about whether allergic disease is associated with a subsequent increased risk of childhood-onset epilepsy. We used a large, population-based cohort study to examine whether children with antecedent allergic rhinitis (AR) were associated with a subsequent increased risk of epilepsy.

Methods: This retrospective population-based cohort study was conducted by using data from the 2000–2012 Taiwan's National Health Insurance Research Database. We enrolled 67,537 children aged 0–18 years diagnosed with AR and 67,537 age- and gender-matched children without the diagnosis of AR. The incidence rate (per 10,000 person-years) of epilepsy was calculated. We used Cox proportional hazards regression analysis to estimate hazard ratios (HRs) and 95 % confident interval (CI).

Results: Of the 135,074 children included in the analyses, those with AR had a higher incidence rate of epilepsy (6.84 versus 3.95 per 10,000 person-years, $p < 0.001$) and an earlier age at diagnosis of epilepsy than those without AR [8.54 (4.90) versus 9.33 (5.40) years, $p = 0.03$)]. The Kaplan-Meier survival analysis demonstrated that the children with AR had a higher likelihood of developing epilepsy than those without AR ($p < 0.001$). After adjusting for confounding factors in multivariate model, children with AR had a 76 % increased risk of epilepsy (HR 1.76, 95 % CI 1.51–2.04) than those without AR. Boys had a 21 % increased risk of epilepsy (HR 1.21, 95 % CI 1.05–1.40) than girls.

Conclusions: These results suggest that children with AR were associated with an increased subsequent risk of epilepsy.

1. Introduction

Primary epilepsy is the most common neurologic disorder of childhood, with the crude incidence rate ranging from 15 to 187 per 100,000 person-years depending on the population studied [1,2]. The incidence in boys and girls is almost identical [1]. Epilepsy-associated comorbidities and disabilities may cause neurobehavioral disorders, poor social and psychological function, and physical hazards, all of which are major public health concerns and place burdens on the patients, the families, societies and healthcare systems in general [3–5]. While the different causes of epilepsy can be identified in childhood, such as brain malformations, genetic factors, inborn errors of metabolism, infections, tumors, and brain injuries, recent growing evidence supports the notion that inflammation within the brain may play a key role in epileptogenesis [6,7].

Allergic diseases comprise the most common chronic disease among children that have a considerable negative impact on the quality of life and health [8,9]. Allergic diseases therefore represent a significant burden for the affected individuals and their families and for society [8,9]. Allergic rhinitis (AR) is a very common chronic illness affecting 10%–40% of children worldwide [8,9], and is usually associated with asthma, atopic dermatitis and allergic conjunctivitis in children [10]. A

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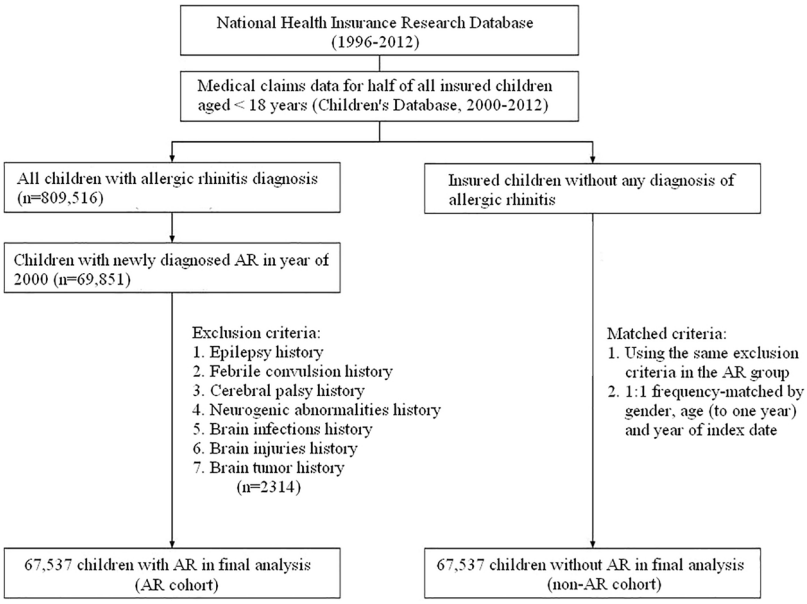

Fig. 1. Flowchart of the study population. AR, allergic rhinitis.

national study on epilepsy in the United States has examined patterns of comorbidities in children, and found that children with epilepsy were at an increased risk of physical comorbidities such as asthma and allergies [11]. Recently, one case-control and one cross-sectional large studies on children in the United States suggested that allergic diseases including asthma, atopic dermatitis/eczema, hay fever, and food allergies were associated with childhood epilepsy [12,13]. An increasing body of studies has explored mechanisms potentially involved for the development of childhood-onset epilepsy and suggested that mast cells degranulation by allergic triggers would release inflammatory and neurotoxic molecules, resulting in focal brain inflammation, and thus contributing to epileptogenesis [14–17].

Although a number of studies have suggested an association between allergic diseases and a risk of epilepsy among children [12,13,18–20], these studies have recruited subjects either from a single center with small sample sizes [18–20], or from case-control and cross-sectional design studies using questionnaires to parents or guardians [12,13]. On the contrary, Castaneda et al. [21] reported that idiopathic epilepsy and asthma were not etiologically related or mutually predisposing conditions. Epilepsy and AR are both common chronic childhood illnesses; however, little is known about the relationship between children with AR and a risk of epilepsy. Epidemiologic data supporting the association are insufficient, especially in Asian ethnicity.

To verify an association between children with AR and the future risk of epilepsy, a study employed a large database of longitudinal claims data from the Taiwan's National Health Insurance Research Database (NHIRD) on this issue is necessary, because the NHIRD can provide a special opportunity for the long-term observation of the correlation between AR and epilepsy. Therefore, the present study aimed to examine an association between AR and a subsequent risk of childhood-onset epilepsy by using data from a large population-based cohort.

2. Methods

2.1. Data source

A universal compulsory national health insurance program, as a single-payer, social insurance plan was launched on 1 March 1995 in Taiwan. It is managed by the National Health Insurance Administration of Taiwan and covers over 99 % of the 23 million population of Taiwan. The NHIRD, a large-scale computerized medical claims database derived from the national health insurance program and maintained by the National Health Research Institute (NHRI), comprises comprehensive health care information and is provided to scientists for research purposes. All datasets for the relevant variables were linked using scrambled unique personal or medical institutional identification number, forming the original data files of the NHIRD. The files contain patients' data regarding personal medical history and demographic characteristics. To protect the personal privacy, only de-identified data are released by the NHRI.

In this study, health claims data were used from the children's database (2000–2012), a subset data of the NHIRD established by the NHRI. The children's database covered a cohort of a half of all children, which were recruited by randomly selected from half of all of the insured children (aged < 18 years) of the NHIRD (1996–2012). This database consisted of the same claims data as the NHIRD, including registry of beneficiary, codes for disease diagnoses (recorded as International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes), procedures and prescription records, and other medical services.

2.2. Study population

This study was a retrospective population-based longitudinal study, including a cohort of children with AR and a non-AR cohort. Fig. 1 shows the flowchart of the study population. The AR cohort included children with newly diagnosed AR (ICD-9-CM code 477) in 2000 with an age at diagnosis of 18 years or less. The index date for the AR group was the initial date of the diagnosis of AR. For each case, we randomly selected one matched control who did not have the diagnosis and coding of AR in the NHIRD datasets and was also matched on age and gender to the children with AR. The index date was the same as for the children with AR.

2.3. Definitions of epilepsy and comorbidities

In this study, children with epilepsy were defined according to the diagnostic criteria of the ICD-9-CM as ICD-9-CM code 345 for epilepsy. To improve diagnostic accuracy, the occurrence of epilepsy was defined as having at least three inpatient or outpatient visits with epilepsy as

Table 1
Characteristics of demographic data and comorbidity in children with and without allergic rhinitis.

	Allergic rhinitis		Non-Allergic rhinitis		
	n = 67,537		n = 67,537		p value
Variable	n	%	n	%	
Gender					> 0.99
Girls	27,693	41.0	27,693	41.0	
Boys	39,844	59.0	39,844	59.0	
Age at diagnosis for allergic rhinitis, year					> 0.99
0–5	45,962	68.1	45,962	68.1	
6–12	19,678	29.1	19,678	29.1	
13–18	1,897	2.81	1,897	2.81	
Mean (SD)	4.97 (3.51)		4.95 (3.52)		0.18
Epilepsy event no. (incidence rate per 10,000 person-years)	517 (6.84)		297 (3.95)		< **0.001**
Age at diagnosis for epilepsy, years, mean (SD)	8.54 (4.90)		9.33 (5.40)		**0.03**
Parental occupational status					< **0.001**
White-collar workers	44,858	66.4	37,823	56.0	
Blue-collar workers	15,105	22.4	18,266	27.1	
Other	7,574	11.2	11,448	16.9	
Urbanization					< **0.001**
Level 1 (highest)	22,351	33.1	18,115	26.8	
Level 2	21,673	32.1	20,111	29.8	
Level 3	12,396	18.4	13,861	20.5	
Level 4 (lowest)	11,117	16.5	15,450	22.9	
Comorbidity					
Asthma	10,417	15.4	1,093	1.62	< **0.001**
Atopic dermatitis	1,359	2.01	255	0.38	< **0.001**
Allergic conjunctivitis	4,639	6.87	1,406	2.08	< **0.001**
Attention deficit hyperactivity disorder	90	0.13	266	0.39	< **0.001**
Autism spectrum disorder	20	0.03	41	0.06	**0.01**
Developmental delay	149	0.22	81	0.12	< **0.001**
Psychomotor retardation	157	0.23	107	0.16	**0.003**
Follow-up years, mean (SD)	11.2 (2.43)		11.1 (2.44)		**0.004**

Bold data show statistical significance < 0.05.
Abbreviations: SD, standard deviation.

the primary diagnosis and once receiving at least one of the anti-epileptic drugs after the diagnosis of epilepsy. The diagnosis of epilepsy was made by pediatricians or neurologists based on patient's neurological manifestations, electroencephalographic and imaging findings, and the physician-diagnosed epilepsy (ICD-9-CM code 345) was recorded in the NHIRD. In order to ensure that AR had occurred before epilepsy, we excluded the children with a diagnosis of epilepsy before the diagnosis of AR. It was excluded that diseases or conditions might be associated with the development of later epilepsy, including febrile convulsions (ICD-9-CM code 780.31), cerebral palsy (ICD-9-CM codes 343.9 and 344.9), neurogenic abnormalities (ICD-9-CM code 742), brain infections (ICD-9-CM codes 320–324), brain injuries (ICD-9-CM codes 854.0 and 959.01), and brain tumors (ICD-9-CM codes 191 and 239.6). All study subjects were followed from the entry date to a diagnosis of epilepsy, withdrawal from the National Health Insurance program, an age over 18 years, or the end of 2012.

Associated comorbidities in children with AR were defined as the presence of other conditions after the diagnosis of AR, including asthma (ICD-9-CM code 493), atopic dermatitis (ICD-9-CM code 691.8), allergic conjunctivitis (ICD-9-CM codes 372.05, 372.10, and 372.14), attention deficit hyperactivity disorder (ADHD, ICD-9-CM code 314), autism spectrum disorder (ASD, ICD-9-CM code 299), developmental delay (DD, ICD-9-CM codes 315 and 783.4), and psychomotor retardation (PR, ICD-9-CM codes 317–319). All comorbidities were defined as at least three corresponding diagnostic files in inpatients and outpatients to improve diagnostic accuracy and avoid an overestimation of the incidence.

2.4. Statistical analyses

Data were reported as mean (standard deviation) for the continuous variable (age), and number and percentage for categorical variables (gender, age group, parental occupation status, urbanization and comorbidities). The Student's *t* test was used to assess the difference in age between the AR group and the non-AR group, and the chi-square test was used to evaluate differences in categorical variables. Incidence rate (per 10,000 person-years) of epilepsy were calculated by dividing the number of epilepsy with follow-up person time, and the cumulative incidence curves of epilepsy for each group were evaluated using the Kaplan-Meier analysis. The log-rank test was used to test differences in curves between the two groups. To determine the risk of epilepsy between the two groups, hazard ratios (HRs) and corresponding 95 % confidence intervals (CIs) were estimated using univariate and multivariate Cox proportional hazard models.

We retrieved information on parental occupation and urbanization from the NHIRD and adjusted for sociodemographic covariates based on previous Taiwanese studies [22]. The parental occupation was divided into three groups according to working status: white collar, long indoor working hours; blue collar, long outdoor working hours; and other retirees, low-income people [22]. Based on the number of residents and area for each of the 359 townships in Taiwan, the population density (people/km^2) of each township was calculated and was categorized into four groups. Level 1 expressed the most urbanized region and level 4 indicated the least urbanized region [22].

SAS software version 9.4 (SAS Institute, Cary, NC, USA) was used to manage the data and to compute the statistical analyses, and R software (R Foundation for Statistical Computing, Vienna, Austria) was used to draw the incidence curves. All statistical tests were two-sided and a value of $p < 0.05$ was considered statistically significant.

2.5. Ethics approval

The retrospective study was approved by the Institutional Review Board of the Chung Shan Medical University Hospital, Taichung,

Taiwan (CSMUH No: CS14019) and informed consent was waived because of the retrospective nature of the study.

3. Results

3.1. Characteristics of the study population

This study cohort included 67,537 children with AR and 67,537 gender- and age-matched children without AR. Children with AR were more likely to have parents with a high socio-economic status and to reside in more urbanized regions (Table 1). During an average observational period of 11 years, the children with AR had a higher incidence rate of developing epilepsy (6.84 versus 3.95 per 10,000 person-years, $p < 0.001$) and an earlier age at diagnosis of epilepsy [8.54 (4.90) versus 9.33 (5.40) years, $p = 0.03$] than those without AR. In addition, the children with AR had a higher prevalence rate of associated comorbidities, including asthma, atopic dermatitis, allergic conjunctivitis, ADHD, ASD, DD, and PR than those without AR (all of $p < 0.001$, except for ASD, $p = 0.01$ and for PR, $p = 0.003$, respectively).

3.2. Univariate and multivariate analyses of outcomes and comorbidities

Fig. 2 shows the 12-year cumulative incidence curves of epilepsy by AR status. The Kaplan-Meier survival analysis with the log-rank test demonstrated that the children with AR had a higher estimated cumulative incidence of developing epilepsy than those without AR ($p < 0.001$). Table 2 shows the association between children with AR and the risk of epilepsy. The univariate analyses revealed that children who had AR, asthma, DD and PR were more likely to develop epilepsy than those without diseases. Boys had a higher risk of developing epilepsy than girls (HR 1.21, 95 % CI 1.05–1.39). Additionally, children aged 6–12 years (HR 0.83; 95 % CI 0.70–0.98) appeared to have a lower risk of epilepsy when compared with those aged 0–5 years.

After adjusting for sociodemographic data and comorbidities, the multivariate analyses revealed that the children with AR had a 76 % increased risk of developing epilepsy (HR 1.76, 95 % CI 1.51–2.04) than those without AR. Boys had a 1.21-fold higher risk of epilepsy (HR 1.21, 95 % CI 1.05–1.41) than girls. The children with AR aged 6–12 years (HR 0.81, 95 % CI 0.69–0.96) seemed to have a lower risk of developing epilepsy when compared with those aged 0–5 years. In addition, the children with DD (HR 2.59, 95 % CI 1.06–6.33) and PR (HR 7.55, 95 % CI 4.22–13.5) were associated with an increased risk of epilepsy compared with their counterparts.

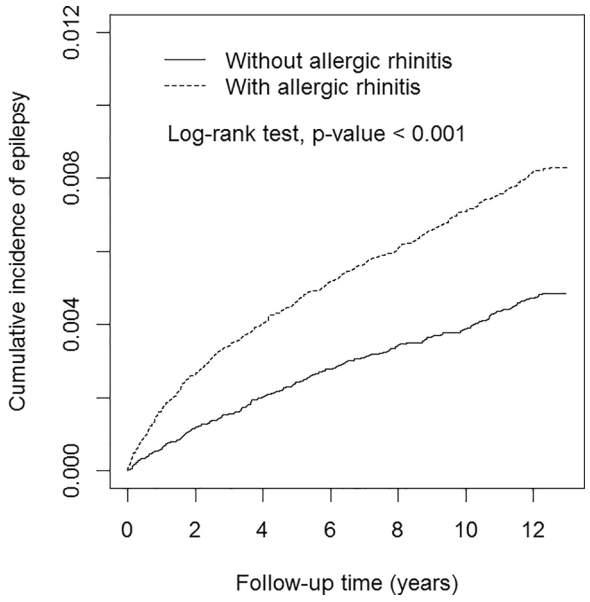

Fig. 2. Cumulative incidence curves of epilepsy for children with and without allergic rhinitis. Kaplan-Meier survival analysis with the log-rank test showed that the children with allergic rhinitis had a higher likelihood of developing epilepsy than those without allergic rhinitis ($p < 0.001$).

3.3. Stratified analyses by gender, age and associated comorbidities

Stratified analyses were performed to elucidate further the role of gender, age and associated comorbidities on the relationship between AR and epilepsy. Table 3 summarizes the risk of epilepsy between the AR and non-AR cohorts stratified by gender, age and comorbidities. The girls with AR had a 1.32-fold higher risk of epilepsy (HR 1.32, 95 % CI 1.03–1.68) than those without AR, while the boys with AR had a 2-fold higher risk of epilepsy (HR 2.08, 95 % CI 1.72–2.51) compared with those without AR. When compared with those without AR, children with AR aged 0–5 years, 6–12 years, and 13–18 years had 1.79-fold (HR 1.79, 95 % CI 1.51–2.13), 1.73-fold (HR 1.72, 95 % CI 1.27–2.37), and 2.96-fold (HR 2.06, 95 % CI 0.57–15.4) higher risks of epilepsy, respectively. Sub-analysis stratified by children with or without associated comorbidities further delineated that children with AR had 1.72-fold (HR 1.72, 95 % CI 1.47–2.80) higher risk of developing epilepsy than those without AR. These findings indicated that among children without associated comorbidities, only the children with AR exhibited a higher risk of developing epilepsy compared with those without AR, suggesting that AR alone is a risk factor of epilepsy.

4. Discussion

In this large, retrospective, population-based cohort study, the children with AR had a 76 % increase in subsequent risk of developing epilepsy and were significantly younger at diagnosis of epilepsy compared with those without AR. Our findings on the association implied that AR was an independent risk factor for childhood-onset epilepsy.

Our results showed that the children with AR were associated with higher prevalence rates of allergic comorbidities, including asthma, atopic dermatitis and allergic conjunctivitis, which are similar to previous reports [9,10]. Previous studies have reported the associations between allergic diseases, including asthma, atopic dermatitis/eczema, hay fever and food allergies and an increased risk of childhood-onset epilepsy [12,13,18–20]. Our results present supporting finding for the relationship between children with AR and a subsequent risk of epilepsy. We observed that asthma was associated with an increased risk of epilepsy in children in the bivariate models but not in the multivariate models, which is similar to previous studies that asthma and epilepsy was not related [13,21], but in contrast to several previous reports [12,18–20]. We also observed that the children with AR appeared to be younger at diagnosis of epilepsy than those without AR (8.54 versus 9.33 years). This finding has not yet been reported. It is suggested that some are vulnerable children who have experienced focal brain inflammation triggered by allergic response during AR episodes and that this could predispose them to develop childhood-onset epilepsy at an earlier age. A number of studies reported that epilepsy was significantly associated with early childhood (2–6 years) [13,19,20], several reports indicated that their patients whose age average was 10 years [18,21], but other studies reported a higher prevalence rate of epilepsy in older children (12–17 years) [11,12]. Details of studies of the associations between allergic diseases and childhood-onset epilepsy are outlined in Table 4. The possible explanations for these inconsistent results across ours and previous studies included the differences in study designs, comparison groups, study sample sizes (a single, multi, local or nationwide institutes), diagnostic criteria (parent/caregiver-recalled epilepsy or board-certified physician-diagnosed epilepsy), cohort ages as well as lack of control for potential confounding factors in statistical analyses.

The underlying mechanisms and causal relationship between AR

Table 2
Crude and adjusted HRs for epilepsy compared children with and without AR and other associated comorbidities.

Variable	Event no.	Person-years	IR	HR (95 % CI)			
				Crude	p value	Adjusted[a]	p value
AR							
No	297	752,743	3.95	1 (Reference)		1 (Reference)	
Yes	517	755,318	6.84	1.74 (1.51–2.01)	< **0.001**	1.76 (1.51–2.04)	< **0.001**
Gender							
Girls	298	620,471	4.80	1 ([Reference]		1 (Reference)	
Boys	516	887,589	5.81	1.21 (1.05–1.39)	**0.009**	1.21 (1.05–1.40)	**0.009**
Age, years							
0–5	622	1,131,951	5.49	1 (Reference)		1 (Reference)	
6–12	179	362,545	4.94	0.83 (0.70-0.98)	**0.02**	0.81 (0.69-0.96)	**0.01**
13–18	13	13,564	9.58	1.19 (0.69–2.07)	0.53	1.19 (0.69–2.08)	0.53
Parental Occupational status							
White-collar workers	501	927,681	5.40	1 (Reference)		1 (Reference)	
Blue-collar workers	198	368,393	5.37	0.99 (0.84–1.17)	0.91	1.05 (0.88–1.24)	0.60
Other	115	211,987	5.42	1.00 (0.82–1.23)	0.96	1.09 (0.88–1.33)	0.44
Urbanization							
Level 1 (highest)	261	451,095	5.79	1 (Reference)		1 (Reference)	
Level 2	232	466,683	4.97	0.86 (0.72–1.03)	0.09	0.86 (0.72–1.03)	0.10
Level 3	156	292,409	5.33	0.92 (0.76–1.13)	0.42	0.96 (0.78–1.17)	0.66
Level 4 (lowest)	165	297,874	5.54	0.96 (0.79–1.17)	0.67	1.01 (0.82–1.23)	0.96
Comorbidity							
Asthma							
No	722	1,372,920	5.26	1 (Reference)		1 ([Reference]	
Yes	92	135,141	6.81	1.31 (1.06–1.63)	**0.01**	1.04 (0.83–1.30)	0.75
Atopic dermatitis							
No	806	1,489,131	5.41	1 (Reference)		1 (Reference)	
Yes	8	18,930	4.23	0.79 (0.39–1.58)	0.50	0.65 (0.32–1.31)	0.23
Allergic conjunctivitis							
No	778	1,443,005	5.39	1 (Reference)		1 (Reference)	
Yes	36	65,056	5.53	1.01 (0.73–1.42)	0.93	0.89 (0.64–1.25)	0.49
ADHD							
No	810	1504386	5.38	1 (Reference)		1 (Reference)	
Yes	4	3674	10.9	1.98 (0.74–5.28)	0.32	1.56 (0.62–4.21)	0.23
Autism spectrum disorder							
No	813	1507373	5.39	1 (Reference)		1 (Reference)	
Yes	1	687	14.6	2.70 (0.38–19.2)	0.29	2.35 (0.31–17.35)	0.18
Developmental delay							
No	809	1,505,515	5.37	1 (Reference)		1 (Reference)	
Yes	5	2,545	19.7	3.65 (1.52–8.80)	**0.003**	2.59 (1.06–6.33)	**0.03**
Psychomotor retardation							
No	802	1,505,353	5.33	1 (Reference)		1 (Reference)	
Yes	12	2,708	44.3	8.15 (4.61–14.4)	< **0.001**	7.55 (4.22–13.5)	< **0.001**

Bold data show statistical significance < 0.05.
Abbreviations: AR allergic rhinitis; IR incidence rate per 10,000 person-years; HR hazard ratio; CI confidence interval; ADHD attention deficit hyperactivity disorder.
[a] Models adjusting for gender, age (categorical), parental occupational status, urbanization, asthma, atopic dermatitis, allergic conjunctivitis, ADHD, autism spectrum disorder, developmental delay, and psychomotor retardation.

Table 3
The HRs of epilepsy in children with allergic rhinitis stratified by gender, age, and comorbidities.

	Allergic rhinitis group			Non- Allergic rhinitis group			HR (95 % CI)			
Variable	Event no.	Person-years	IR	Event no.	Person-years	IR	Crude	p value	Adjusted[a]	p value
Gender										
Girls	174	310,985	5.60	124	309,486	4.01	1.40 (1.11–1.76)	**0.004**	1.32 (1.03–1.68)	**0.02**
Boys	343	444,333	7.72	173	443,257	3.90	1.98 (1.65–2.38)	< **0.001**	2.08 (1.72–2.51)	< **0.001**
Age, years										
0–5	399	567,449	7.03	223	564,502	3.95	1.79 (1.52–2.10)	< **0.001**	1.79 (1.51–2.13)	< **0.001**
6–12	111	181,118	6.13	68	181,427	3.75	1.66 (1.23–2.25)	**0.001**	1.73 (1.27–2.37)	< **0.001**
13–18	7	6,750	10.4	6	6,814	8.81	1.58 (0.49–5.09)	0.44	2.96 (0.57–15.4)	0.19
Comorbidities[b]										
No	387	579,622	6.68	284	720,516	3.94	1.70 (1.45–1.98)	< **0.001**	1.72 (1.47–2.00)	< **0.001**
Yes	130	175,696	7.40	13	32,227	4.03	1.85 (1.05–3.28)	**0.03**	1.81 (1.02–3.20)	**0.04**

Bold data show statistical significance < 0.05.
Abbreviations: IR, incidence rate, per 10,000 person-years; HR, hazard ratio; CI, confidence interval.
[a] Models mutually adjusting for gender, age (categorical), asthma, atopic dermatitis, allergic conjunctivitis, attention deficit hyperactivity disorder, autism spectrum disorder, developmental delay and psychomotor retardation.
[b] Children with any one of asthma, atopic dermatitis, allergic conjunctivitis, attention deficit hyperactivity disorder, autism spectrum disorder, developmental delay, and psychomotor retardation were classified as the comorbidities group.

Table 4
Details of studies involved with regard to the associations between allergic diseases and childhood-onset epilepsy, ordered by the reference number.

Author [Reference], published year	Study design	Methods of diagnosis	No. of participants		Results	Time period
			Cases	Controls		
Silverberg [12], 2014	Case-control design	Questionnaires to parents or guardians	977	90,628	Epilepsy was associated with allergic diseases in children, including atopic dermatitis/eczema, asthma, hay fever, food allergies. Children with more number of allergic diseases were associated with increased epilepsy. A higher prevalence of epilepsy was noted among older children (11–17 years).	2007–2008
Strom [13], 2016	Cross-sectional design	Questionnaires to parents or guardians	1494	204,619	Epilepsy was associated with eczema, hay fever and food allergy. Asthma was associated with epilepsy in bivariate model, not in multivariate model. Risk of epilepsy was more strongly associated with increased number of comorbid allergic diseases. Aged 2–6 years had a higher risk of developing epilepsy compared with aged 0–1 year.	1997–2013.
Barr [18], 1998	Case-control design	Electroencephalographic studies	24	24	The cases studied had a mean age of 9.6 (3.5) years at diagnosis. A sub-group of children with asthma was associated with epilepsy.	Non-available
Frediani [19], 2001	Case-control design	Neurologic manifestations, electroencephalograms, computed tomographic or magnetic resonance imaging findings	72	202	The cases studied had a mean age of 6 years (6 months to 13 years). A higher incidence of allergy was noted in the children with epilepsy and their immediate families, including eczema, rhinitis, asthma, conjunctivitis, cow's milk protein allergy, urticaria, food intolerance, and drug allergy.	Non-available
Bilan [20], 2010	Cross-sectional and analytical design	Not specified the surveillance for seizure disorders	26	774	The study children had a mean age of 6 (2.1) years. The prevalence rate of epilepsy in asthmatic children (3.25 %) was significantly higher than those in general population (1 %).	2004–2008
Castaneda [21] 1998	Case-control design	Neurologic manifestations, electroencephalographic, computed tomographic or magnetic resonance imaging findings	201	400	The median age of the study group was 10 years (range, 1–17 years). Epilepsy and asthma were not etiologically related or mutually predisposing conditions.	Non-available
The current study 2019	Retrospective cohort study design	ICD-9-CM codes in the NHIRD	67,537[a]	67,537[a]	Allergic rhinitis was independently associated with an increased subsequent risk of childhood-onset epilepsy. Children with allergic rhinitis were significantly younger at diagnosis of epilepsy than those without (8.54 versus 9.33 years). Asthma was associated with epilepsy in bivariate model, not in multivariate model. Children with allergic rhinitis were also associated with the higher prevalence rates of neurodevelopmental disorders, including attention deficit hyperactivity disorder, autism spectrum disorder, developmental delay, and psychomotor retardation.	2000–2012

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NHIRD, The National Health Insurance Research Database.

[a] Children with allergic rhinitis had an age at diagnosis of 18 years or less and the control group did not have any diagnosis of allergic rhinitis with age- and gender- matched to the children with allergic rhinitis.

and epilepsy are not completely understood. It has been recently suggested that mast cells activation by peripheral allergic triggers is a mechanism specially implicated in AR and epilepsy [23–28]. Mast cells are thought to function primarily as effector and sensor cells in allergic diseases like AR, asthma, atopic dermatitis, acute conjunctivitis and food allergies [23]. They are first responders and are regarded as the immune gate to the brain [24,25], acting as catalyst and recruiters to initiate, magnify, and prolong immune and nervous responses in the brain upon activation [14–17,24–29]. Mast cells produce a plethora of vasodilatory and proinflammatory mediators upon stimulation by allergic triggers, including histamine, serotonin, and cytokines, thereby eliciting a cascade of inflammatory events within the brain, and thus focal brain inflammation could then contribute to or exacerbate seizures [14–17,24–29]. It is suggested that mast cells are present in the brain as resident cells or migratory cells from the periphery [27–29], resident mast cells of the brain therefore become activated and/or peripheral mast cells become recruited into the brain upon allergic responses, resulting in focal brain inflammation and that this could become an epileptogenic site [24–27].

The current and previous studies have suggested the relationships between AR, asthma, atopic dermatitis/eczema and food allergies and the risk of epilepsy among children [12,13,18–20]. Recently, emerging epidemiological evidence further supports this interaction, with inflammatory diseases, and especially allergies, being more prevalent in subjects with epilepsy [30]. It is believed that the brain may function as an allergic target organ like the nose, eye, airway, gastrointestinal tract, and skin following ingested or inhaled allergens [19,20,23,31], suggested that epilepsy can be triggered by allergen sensitization. On the basis of this hypothesis, a number of studies have demonstrated that an elimination diet or environmental controls could lead to a decrease in both frequency and intensity of epilepsy in children with a history of food and respiratory allergies, suggesting a real relationship between allergy and epilepsy [19,20,31–36]. These findings have presented supporting evidence for the involvement of mast cells in allergen-triggered brain inflammation that increase the likelihood of epileptogenesis, at least in a subgroup of children.

While this study did not prove that the underlying mechanisms of an association between AR and epilepsy, this observational data suggest that children with AR are at increased subsequent risk of developing epilepsy. It is possible that AR is associated with an increased risk of certain types of epilepsy among the susceptible children. Age appears to influence the risk of developing epilepsy. Epilepsy in younger children differs significantly from those in older children and adults. It has been reported that the most frequent type of epilepsy in one month to three years old is generalized simple motor seizures and hypomotor seizures; in three to six years old is generalized myoclonic and tonic seizures; and in six to ten years old is dialeptic seizures (mostly with a generalized epileptogenic zone) and focal seizure [37]. In contrast to younger children, focal epilepsy become more frequent in patients aged 10–18 years old, which is similar to that in the adult population [37]. However, the NHIRD did not provide claims data on related neurological manifestations, electroencephalographic and imaging findings, and thus, we could only identify the study subjects by ICD-9-CM code 345 for epilepsy, and limited the ability to determine a subtype of epilepsy for further analysis. Future prospective studies are needed to explore whether allergic immune response involved in epileptogenesis and to identify a subpopulation of epileptic children who may benefit from early screening and management of AR.

The current study also confirms the previous reports that allergic disorders in early childhood were associated with the increased prevalence rates of neurodevelopmental disorders and psychological and behavioral problems, including ADHD ASD, DD, and PR [38–42]. It has been suggested that mast cells can promote deleterious outcomes in brain function [24,43,44]. Allergen-activated mast cells may serve as mediators by releasing inflammatory factors during allergy episodes that could interfere with maturation of the cortex and the transmitter systems and adversely affect brain function, thus contributing to the development of ASD, ADHD, and other neurodevelopmental disorders [24,41,43–47]. In this study, in confounding analyses performed by assessing each covariate separately with AR as predictors of epilepsy, it was found that only children with DD and PR, not ADHD or ASD, showed an increased risk of epilepsy. Probably, there was an insufficient case number of ADHD and ASD involved in this study and that this could not provide enough power to reach a statistical significance.

This study has several strengths. Data were retrieved from the NHIRD, a comprehensive and reliable database that is highly representative of the general population, and a large population-based sample size increased a statistical power to demonstrate associations. This was a population-based cohort study with an observational period of 12 years; therefore the long observational period and the large sample size were enough to yield reliable risk estimates. Several reports have shown that a large study can demonstrate consistent and sometimes novel results, even when the associations are relatively weak [12,13,48]. The study subjects enrolled in the current study were based on board-certified physicians' diagnoses, yielding better diagnostic accuracy relative to the bias evoked by questionnaires recall.

The study also has several limitations. First, although the diagnosis of epilepsy was made by board-certified physicians and therefore the diagnostic accuracy should be high in the present study, the incidence rate of epilepsy may have been underestimated because only patients who sought medical help were enrolled in the study. Second, the NHIRD does not provide detailed information on relevant clinical variables such as neurological manifestations, neurological assessments and disease severity, electroencephalographic and imaging findings, family history of systemic diseases, environmental and genetic factors, and we therefore were unable to determine their influence. Finally, unmeasured unknown factors and residual cofounding might have been associated with the risk of epilepsy and the inability to adjust for these potential confounders might have affected the results. In addition, it is possible that someone in the non-AR cohort was later diagnosed with AR, such as their age at the onset of AR over 18 years old or after the year of 2012. Because the exploration of this issue is beyond the spectrum of this study, we have no data regarding this issue.

5. Conclusions

This large study suggests that the children with AR are independently associated with an increased subsequent risk of epilepsy, at least in a subgroup of epilepsy subjects. Epilepsy in a proportion of children with AR confirms the assumption that mast cells activation-derived focal brain inflammation is involved in this disorder. Pediatricians should be aware of the possible coexistence of these disorders in children. Epilepsy may be a comorbidity of severe AR, which may require multidisciplinary management by pediatricians, neurologists and allergists/immunologists alike. Long-term surveillance is needed for those at-risk children.

Declaration of Competing Interest

None of the authors have any conflict of interest to disclose.

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