

Allergic rhinitis and the associated risk of nocturnal enuresis in children: a nationwide population-based cohort study

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Background: Despite controversy, an association between allergy and nocturnal enuresis (NE) has been reported for almost a century. Allergic rhinitis (AR)-associated sleep-disordered breathing frequently results in microarousals during sleep, decreased sleep efficiency, and change in sleep pattern and behavior. NE is a common sleep disorder in children. Hence, this study aimed to investigate the incidence and risk of NE in children with AR.

Methods: A population-based cohort study was conducted among 327,928 children with AR and 327,601 non-AR controls between 2000 and 2012 in Taiwan. By the end of 2012, the incidence of NE in both cohorts, and the AR-to-non-AR cohort hazard ratios (HRs) were measured.

Results: The adjusted HR of NE during the study period was 1.7-fold higher in the AR cohort compared to the non-AR cohort. The risk was greater for boys, children younger than 6 years old, those with comorbidities of asthma, atopic dermatitis, and attention deficit/hyperactivity disorder (ADHD), and those who had more than 5 AR-related medical visits per year. The risk of NE in the AR cohort decreased with follow-up time and was the highest within the first year after AR diagnosis.

Conclusion: Children with AR had a higher incidence and subsequent risk of NE. The risk of NE was greater for boys, younger children, and those with more frequent health utilization for AR symptoms. © 2018 ARS-AAOA, LLC.

Key Words:

allergic rhinitis; nocturnal enuresis; children; cohort study; hazard ratio

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Allergic rhinitis (AR) is a common disease affecting up to 10 to 20% of the population.¹ Despite its high prevalence, AR is frequently underestimated and undertreated in children. AR is classically characterized by sneezing, pruritus, rhinorrhea, and nasal congestion.^{1,2} Nasal congestion is thought to be a crucial cause of sleep-disordered breathing and sleep impairment in AR.^{3,4} AR-associated sleep-disordered breathing is characterized by periodic breathing, obstructive sleep apnea and hypopnea, which result in microarousals during sleep, decreased total sleep time, decreased sleep efficiency, and change in sleep pattern and behavior.^{5,6} Nocturnal enuresis (NE) is a frequent sleep disorder in children.^{7,8} Children with obstructive sleep apnea syndrome (OSAS) and adenotonsillar hypertrophy have shown an increased incidence of NE.⁸⁻¹⁰

According to the International Children's Continence Society (ICCS) definition, enuresis is an involuntary urination during sleep without organic causes with a minimum wetting frequency of once per month.¹¹ Previous studies reported a prevalence rate of 9% to 15% and prevalence decreases with age.¹² NE is a distressing disorder that is

associated with a significant psychological, social, and financial burden to the affected children and their families.¹³ Nocturnal polyuria, nocturnal detrusor overactivity, and high arousal thresholds are key pathogenic events of NE.¹¹ According to ICCS guidelines, bedwetting alarms and desmopressin are considered as an effective treatment for children with NE in combination with night time fluid restriction and motivation therapy.¹¹ Despite aggressive treatment, some children still experience suboptimal response, refractory NE, and relapse NE. These children show greater risk of psychological comorbidities, such as low perceived competence and self-esteem.¹³

Although NE is probably the most common developmental disorder in children, the pathogenesis and management remain unclear. Allergy is 1 of the proposed mechanisms for NE. In 1931, Bray¹⁴ stated that persistent enuresis in some children were allergic in origin. He noticed some children with NE along with allergic manifestations. It might be partly explained that nerve supply to the smooth muscle of bronchi and bladder derives from the parasympathetic system for the association between enuresis and asthma.¹⁴ Stimulation of the parasympathetic system may cause both bronchospasm and detrusor muscle contraction.¹⁴ In contrast, a small population study in 1976 by Siegel et al.¹⁵ showed that there is no relationship between respiratory allergy and enuresis. In 2005, Mugan et al.¹⁶ reported that 10 types of food and inhalant allergens were not significantly associated with NE, but soybean allergies were related to NE. In 2009, Sahin et al.¹⁷ found allergic symptoms and NE were significant and independent risk factors for habitual snoring. Moreover, increase in heart rate variability was reported in children with AR, which implies sympathetic withdrawal and parasympathetic predominance.¹⁸ The parasympathetic hyperfunction and abnormal circadian rhythm of autonomic nervous system functions have also been stated in enuretic children.¹¹

Advancing our knowledge regarding the relation between AR and NE has the potential to uncover new mechanisms and risk factors for NE, thus opening new opportunities not only for novel treatments, but also for the development of preventative strategies. Therefore, we conducted a population-based retrospective cohort study to investigate the association between AR and NE, by analyzing data from the Taiwan National Health Insurance Research Database (NHIRD).

Materials and methods

Data sources

In this retrospective population-based cohort study, we used data from NHIRD (<http://www.nhi.gov.tw/english/index.aspx>). These claims data are derived from Taiwan's National Health Insurance, which is a government-run, single-payer, modest cost-sharing program that covers almost all citizens in Taiwan. We used the Children File,^{19,20} consisting of a randomly selected sample of one-half of all

insured children in Taiwan. Based on the Personal Information Protection Act, deidentification was performed before the release of the dataset to researchers; thus, informed consent was not required in this study. This study received approval from the institutional review board of the China Medical University Hospital (CRREC-103-048). The International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) was used for diagnosis.

Study design and participants

The AR cohort consisted of patients younger than 18 years old with newly diagnosed AR between 2000 and 2012. To improve diagnostic reliability and avoid overestimation of incidence, AR was defined as the presence of at least 3 records with ICD-9-CM code 477 in any diagnosis field of inpatient claims or ambulatory claims. The date of AR diagnosis was considered as the baseline. The residential areas of the study subjects, which covered 365 Taiwan townships, were classified into 7 levels of urbanization according to the method developed by Liu et al.²¹ Level 1 was referring to the "most urbanized" and level 7 was referring to the "least urbanized" communities. The variables used in developing the township stratification for urbanization level consisted of the population density (people/km²), population ratio of people with an educational level of college or above, population ratio of elder people over 65 years old, population ratio of agricultural workers, and the number of physicians per 100,000 people. As there were very small numbers of cases at levels 4, 5, 6, and 7, these 4 levels were combined into a single group (level 4). Therefore, the urbanization level was stratified into 4 levels, from the highest density (level 1) to the lowest density (level 4).^{21,22} In this study, we used the method of 1:1 matching to screen for healthy participants, as a control to potential confounders. Hence, we randomly selected 1 child without AR for each child with AR matched according to sex, age (in 1-year intervals), urbanization of residential area, and baseline year. NE was defined as children older than 5 years old, with at least 2 ICD-9-CM code 788.36 records in any diagnosis field of inpatient or ambulatory claims. Participants with a history of NE before baseline or missed demographic information were excluded. Children with neurogenic bladder (ICD-9-CM code 344.61), cauda equina syndrome with neurogenic bladder (ICD-9-CM code 330), cerebral degeneration disorders (ICD-9-CM code 330, 331), mental retardation (ICD-9-CM code 317–319), and congenital urinary tract anomaly (ICD-9-CM code 753) were also excluded. The comorbidities of AR and enuresis were identified and defined, including asthma (ICD-9-CM code 493), atopic dermatitis (ICD-9-CM code 691), obstructive sleep apnea (ICD-9-CM code 327.23), attention-deficit/hyperactivity disorder (ADHD) (ICD-9-CM code 314), obesity (ICD-9-CM code 278), and hypertrophy of tonsils and adenoids (ICD-9-CM code 474.1). All participants were followed until NE diagnosis, death, loss of follow-up, or withdrawal from the insurance system, until the end

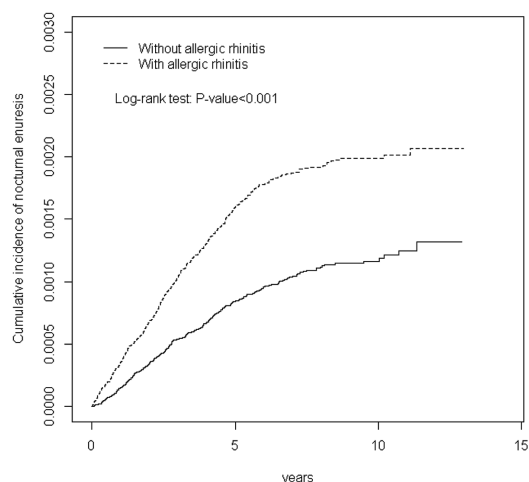


FIGURE 1. The Kaplan-Meier analysis of cumulative incidence of nocturnal enuresis for AR cohort compared to non-AR cohort. AR = allergic rhinitis.

of 2012. The selection flowchart of study participants is shown in Figure 1.

Statistical analysis

In this cohort study, we used person-years as the denominator to estimate the incidence rate for the individual follow-up duration in the study. The date of AR diagnosis was used as the index date for the calculation of follow-up person-years. The follow-up person-years were calculated starting from the index date until the date of NE diagnosis, or were censored due to lack of follow-up, death, or withdrawal from the insurance system, until the end of 2012. Follow-up person-years were used to estimate the incidence density rates (IRs) and hazard ratios (HRs) of NE for the AR cohort, which were compared with those of the non-AR cohort based on age, sex, urbanization, and comorbidities, including asthma, atopic dermatitis, obstructive sleep apnea, ADHD, obesity, and hypertrophy of tonsils and adenoid. HR was determined with the Cox proportional hazard regression model. The Cox model was also used to estimate the HR of NE associated with the mean annual number of medical visits for AR. Furthermore, we analyzed whether the association varied with the duration of the follow-up period after AR diagnosis. Kaplan-Meier plots showed the probability of enuresis-free survival, and log-rank test was used to test the difference between the AR and non-AR cohorts. We performed all data analyses with SAS statistical software, version 9.2, for Windows (SAS Institute Inc., Cary, NC). Kaplan-Meier survival curves were plotted with R software, version 2.14.1 (R Development Core Team, Vienna, Austria). A 2-sided $p < 0.05$ was considered statistically significant.

Results

In this study, 327,928 participants in the AR cohort and 327,601 in the non-AR cohort were enrolled (Table 1).

Most (80.2%) participants were younger than 12 years old. The majority of the AR cohort were boys (56%) and residents of highly urbanized areas (60%). The incidence rates of most comorbidities were significantly higher in the AR group compared to the non-AR group: asthma (17.5% vs 4.08%, respectively, $p < 0.001$), atopic dermatitis (6.93% vs 3.42%, $p < 0.001$), obstructive sleep apnea (0.56% vs 0.16%, $p < 0.001$), ADHD (1.68% vs 0.96%, $p < 0.001$), obesity (0.32% vs 0.18%, $p < 0.001$), hypertrophy of tonsils and adenoids (0.50% vs 0.19%, $p < 0.001$) (Table 1). NE incidence was 1.7-fold higher in the AR cohort compared to the non-AR cohort (2.49 vs 1.39 per 10,000 person-years, respectively; Table 2). Age-specific analysis showed that NE incidence significantly decreased with age in both cohorts. Sex-specific analysis showed that NE prevalence was higher in boys in both cohorts. The adjusted HR (1.23; 95% confidence interval [CI], 1.06 to 1.42) for NE was higher in boys of the AR to non-AR cohort than girls (reference group) (Table 2). The adjusted HR of the AR to non-AR cohort for NE was highest for children older than 12 years old (adjusted HR: 7.52; 95% CI, 4.91 to 11.5) than participants 6 years old or younger (reference group) (Table 2). Comorbidity-specific analyses showed that the adjusted HR for NE increased in patients with AR with certain comorbidities, including asthma (HR 1.21; 95% CI, 1.00 to 1.46), atopic dermatitis (HR 1.32; 95% CI, 1.02 to 1.72), and ADHD (HR 2.49; 95% CI, 1.67 to 3.72) than those without the comorbidity (reference group) (Table 2). Table 3 shows that the annual frequency of medical visits due to AR is associated with risk of NE. Compared with the non-AR cohort, the risk of NE in the AR cohort increased from 0.80 (95% CI, 0.67 to 0.97) for those with 3 visits or less to 15.1 (95% CI, 12.6 to 18.1) for those with more than 5 visits (trend test, $p < 0.0001$). This pattern was similar for both sexes (Table 3). Table 4 shows the risk of NE stratified according to median follow-up duration. The risk of NE increased since the first year of AR diagnosis (HR 2.19; 95% CI, 1.55 to 3.11) and decreased to the lowest level when patients were followed-up for more than 5 years (HR 1.28; 95% CI, 0.88 to 1.86). Based on the Kaplan-Meier survival analysis shown in Figure 1, the AR cohort was associated with a higher incidence of NE compared with the non-AR cohort.

Discussion

NE is a common condition. The overall NE prevalence in children in Taiwan was 5.5%,²³ which is compatible with the NE prevalence in 7-year old children in the United States (5-10%).²⁴ The incidence of NE was 9.2% in France in 2000.²⁵ Our study showed that the incidence of childhood NE was 1.39 in 10,000 person-years in the non-AR cohort and 2.49 in 10,000 person-years in the AR cohort. Our data were retrieved only from Taiwan's National Health Insurance Administration and covered over 99% of the population. Disease was recorded only during medical visits. Therefore, NE may be underestimated, because the

TABLE 1. Demographics between children with and without AR

	Non-AR (N = 327601)	AR (N = 327928)	<i>p</i> ^a
Age (years), mean ± SD	9.05 ± 3.30	9.05 ± 3.32	
Stratified age (years), n (%)			0.01
<6	69490 (21.2)	69490 (21.2)	
6–12	194063 (59.2)	192744 (58.8)	
> 12	64048 (19.6)	65694 (20.0)	
Sex			0.72
Girl	144297 (44.1)	144297 (44.0)	
Boy	183304 (56.0)	183631 (56.0)	
Urbanization, n (%) ^b			0.95
1 (highest)	100864 (30.8)	101181 (30.9)	
2	101300 (30.9)	101310 (30.9)	
3	62805 (19.2)	62805 (19.2)	
4 (lowest)	62632 (19.1)	62632 (19.1)	
Comorbidity, n (%)			
Asthma	13375 (4.08)	57230 (17.5)	<0.001
Atopic dermatitis	11193 (3.42)	22740 (6.93)	<0.001
Obstructive sleep apnea	515 (0.16)	1842 (0.56)	<0.001
ADHD	3143 (0.96)	5524 (1.68)	<0.001
Obesity	602 (0.18)	1036 (0.32)	<0.001
Hypertrophy of tonsils and adenoids	633 (0.19)	1638 (0.50)	<0.001

^aThe t test or chi-square test was used to quantify differences in means or prevalence between the patients with AR and without AR for continuous and categorical matching variables.

^bThe urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized. ADHD = attention-deficit/hyperactivity disorder; AR = allergic rhinitis; SD = standard deviation.

parental concern level was not high. Most parents thought that NE will spontaneously improve with age and did not seek medical help.

The pathophysiology of NE is still unclear and most people believe that NE is a multifactorial problem. Several pathogenic mechanisms are supported by sufficient evidence. Snoring is a common symptom of AR. Sans Capdevila et al.²⁶ reported that a mild increase in sleep pressure, such as snoring, may lead to slightly elevated hypercapnic arousal threshold. Researchers consider that complete or partial nasal obstruction may cause chronic, intermittent hypercapnia, which results in secondary blunting of arousal responses.²⁷ In addition, brain natriuretic peptide increases in children with enuresis and obstructive sleep apnea. Complete or partial obstructions of the upper airway caused negative intrathoracic pressure swings and increased peripheral vascular resistance thus increasing venous return, while pressure may release brain natriuretic peptide from ventricular myocytes.²⁸ Brain natriuretic peptide (BNP) is a neurohormone that induces vasodilation and natriuresis. Therefore, the risk of enuresis increases with ex-

cessive urination volume. In addition, it has been suggested that the bladder may be as sensitive to allergy as other end-organs, such as the nose, the lungs, and the skin, that may cause some renal-uretero-bladder diseases.²⁹ After exposure to allergen, immunoglobulin E (IgE) molecules attach to mast cells. Increasing numbers of IgE-coated mast cells recognize the allergen in the target organ, and degranulate. Chemicals, such as histamine, tryptase, chymase, kininogenase, heparin, and other enzymes are released. Moreover, mast cells secrete several inflammatory mediators such as prostaglandin D₂ and sulfidopeptidyl leukotrienes (LTC₄, LTD₄, and LTE₄)³⁰; these proinflammatory mediators may cause blood vessel leakage and inflammation.³⁰ Subsequently, inflammation produces local edema with mucus production and smooth muscle contraction. Therefore, AR and NE symptoms may be presented.³⁰ On the basis of this hypothesis, Mungan et al.¹⁶ reported that NE is associated significantly with certain food types. The research results showed that total IgE concentration was 2-fold to 3-fold higher and eosinophil cationic protein (ECP) was also significantly higher in the NE group. In this study,

TABLE 2. The risk of nocturnal enuresis compared to children without AR stratified by demographics in Cox proportional hazard regression

	Non-AR			AR			Adjusted HR (95% CI) ^a	Adjusted HR (95% CI) ^a
	Event	Person-years	IR	Event	Person-years	IR		
All	287	2060457	1.39	514	2066156	2.49	1.70 (1.46–1.97)**	1.70 (1.46–1.97)**
Stratified age								
<6	108	530851	2.03	213	532543	4.00	1.92 (1.51–2.44)**	7.52 (4.91–11.5)**
6–11	171	1327795	1.29	286	1324127	2.16	1.55 (1.28–1.89)**	3.97 (2.61–6.05)**
≥12	8	201812	0.40	15	209485	0.72	1.87 (0.79–4.42)	1.00 (Reference)
Sex								
Girl	113	878968	1.29	186	880920	2.11	1.63 (1.28–2.08)**	1.00 (Reference)
Boy	174	1181489	1.47	328	1185236	2.77	1.74 (1.44–2.10)**	1.23 (1.06–1.42)**
Asthma								
No	267	1986244	1.34	395	1684760	2.34	1.76 (1.51–2.06)**	1.00 (Reference)
Yes	20	74213	2.69	119	381396	3.12	1.25 (0.78–2.01)	1.21 (1.00–1.46)*
Atopic dermatitis								
No	277	2008305	1.38	463	1946361	2.38	1.68 (1.44–1.96)**	1.00 (Reference)
Yes	10	52152	1.92	51	119795	4.26	2.14 (1.07–4.28)*	1.32 (1.02–1.72)*
Obstructive sleep apnea								
No	287	2058447	1.39	509	2058402	2.47	1.69 (1.46–1.96)**	1.00 (Reference)
Yes	0	2010	0.00	5	7754	6.45	–	2.29 (0.95–5.55)
ADHDr								
No	278	2044826	1.36	498	2036688	2.45	1.73 (1.49–2.02)**	1.00 (Reference)
Yes	9	15631	5.76	16	29467	5.43	0.87 (0.38–2.01)	2.49(1.67–3.72)**
Obesity								
No	287	2057668	1.39	513	2061176	2.49	1.69 (1.46–1.97)**	1.00 (Reference)
Yes	0	2789	0.00	1	4979	2.01	–	0.70 (0.10–4.99)
Hypertrophy of tonsils and adenoids								
No	287	2056724	1.40	512	2056265	2.49	1.69 (1.46–1.97)**	1.00 (Reference)
Yes	0	3733	0.00	2	9891	2.02	–	0.59 (0.15–2.38)

^aAdjusted for age, sex, and comorbidity of asthma, atopic dermatitis, obstructive sleep apnea, and attention-deficit/hyperactivity disorder, obesity, and hypertrophy of tonsils and adenoids.

* $p < 0.01$.

** $p < 0.001$.

ADHD = attention-deficit/hyperactivity disorder; AR = allergic rhinitis; CI = confidence interval; HR = hazard ratio; IR = incidence rate (per 1000 person-years).

only soybean and hazelnut food allergens were found to be related to NE. Water-soluble allergens such as isoflavone from soybean excreted in urine and deposited in the bladder mucosa was considered as the cause of overactive bladder.¹⁵ Upon allergy diagnosis, allergen avoidance is suggested to reduce the risk of NE. Because NE is multifactorial, it is not possible to completely treat NE, despite elimination of allergens. In addition, Tascilar et al.¹⁸ reported that heart rate variability (HRV) is increased in patients with AR. HRV is widely used to assess sympathetic and parasymp-

athetic activity, especially in the cardiological research field.¹⁷ The study by Tascilar et al.¹⁸ implied both sympathetic withdrawal and parasympathetic predominance in AR children. To our knowledge, sympathetic stimulation is predominant during bladder filling, and parasympathetic stimulation causes bladder emptying. Therefore, overactivation of the sympathetic nervous system in AR patients may cause detrusor contraction, which increases the risk of NE. Similarly, our study results showed an association between high childhood NE prevalence and AR. Based on

TABLE 3. The risk of nocturnal enuresis among average frequency of medical visits for AR in Cox proportional hazard regression

Average frequency of medical visit, per year	Event	Person-years	IR	Adjusted HR (95% CI) ^a
All				
None	287	2060457	1.39	1.00 (Reference)
≤3	200	1788908	1.12	0.80 (0.67–0.97)*
4–5	90	174352	5.16	3.55 (2.79–4.52)**
>5	224	102896	21.8	15.1 (12.6–18.1)**
<i>p</i> for trend				<0.001
Girls				
None	113	878968	1.29	1.00 (Reference)
≤3	76	771665	0.98	0.79 (0.59–1.06)
4–5	31	68530	4.52	3.69 (2.47–5.54)**
>5	79	40725	19.4	16.1 (12.0–21.8)**
<i>p</i> for trend				<0.001
Boys				
None	174	1181489	1.47	1.00 (Reference)
≤3	124	1017243	1.22	0.81 (0.64–1.03)*
4–5	59	105823	5.58	3.48 (2.58–4.71)**
>5	145	62170	23.3	14.5 (11.5–18.3)**
<i>p</i> for trend				<0.001

^aAdjusted for age, sex, and comorbidity of asthma, atopic dermatitis, obstructive sleep apnea, and attention-deficit/hyperactivity disorder, obesity, and hypertrophy of tonsils and adenoids.

**p* < 0.01.

***p* < 0.001.

AR = allergic rhinitis; CI = confidence interval; HR = hazard ratio; IR = incidence rate (per 1000 person-years).

TABLE 4. The risk of nocturnal enuresis in children with AR compared those without AR stratified by follow-up years after AR diagnosed in Cox proportional hazard regression

Follow-up time	Non-AR			AR			Adjusted HR (95% CI) ^a
	Event	Person-years	IR	Event	Person-years	IR	
≤1 years	48	321288	1.49	114	322310	3.54	2.19 (1.55–3.11)*
2–3 years	114	906588	1.26	201	909024	2.21	1.66 (1.31–2.11)*
4–5 years	72	1383875	0.52	133	1387446	0.96	1.73 (1.29–2.33)*
>5 years	53	676582	0.78	66	678710	0.97	1.28 (0.88–1.86)

^aAdjusted for age, sex, and comorbidity of asthma, atopic dermatitis, obstructive sleep apnea, and attention-deficit/hyperactivity disorder, obesity, and hypertrophy of tonsils and adenoids.

**p* < 0.001.

AR = allergic rhinitis; CI = confidence interval; HR = hazard ratio; IR = incidence rate (per 1000 person-years).

the aforementioned studies, we hypothesized that AR may potentially influence the onset of NE and we determined the possible link between AR and NE.

Based on a review of the literature, several studies demonstrated the association between NE and allergic diseases.^{14,15,18} Most previous studies were single-center case studies, with limited number of cases and mainly fo-

cused on allergic diseases other than AR, and psychiatric disorders. This is the first population-based cohort study in Taiwan that examines the association between AR and the risk of childhood enuresis. Previously, several diseases have been proved to be associated with NE. NE prevalence was 2.1 times higher in the ADHD group compared to the normal control group.³¹ Children with asthma were 2.33 times

more likely to have enuresis than healthy children.³² Therefore, this association was independent of other risk factors such as age, sex, urbanization, and comorbidity. Our study suggests a significant relationship between AR and NE. Boys have higher risk of NE than girls within the AR group, which is consistent with the results of sex distribution of all NE children in a previous statistical analysis.^{23,24} Our results revealed that the HR for NE decreased with age within the AR cohort in comparison with the non-AR cohort. The HRs were greater for AR children with comorbidities of asthma, atopic dermatitis, and ADHD in comparison those without comorbidity. Children with AR who had frequent AR-related medical visits showed a relatively higher risk of NE. It is hypothesized that children visited hospitals more frequently due to poor AR control. Serious nasal obstruction may cause elevated arousal threshold, increased BNP, and parasympathetic predominance; thus, NE prevalence may be higher in the AR with poor control group.

This is the first population-based cohort study to precisely quantify the subsequent risk of NE in children with AR compared with the non-AR controls. Most previous studies were cross-sectional case-control studies with limited numbers of patients that described the occurrence of NE in AR with obstructive sleep apnea or adenoid hypertrophy.^{8–10} The current study is a cohort study. Cohort studies have the merit of no temporal ambiguity between the exposure and outcome and may minimize the selection bias in case-control studies. Nonetheless, our study still has some inevitable limitations. First, most children with AR may have not undergone polysomnography to confirm the diagnosis

of OSAS, which may be underestimated in this study.³³ Second, there might be some residential confounders that might be associated with the cause of AR and NE. In the current study, we identified the possible confounders between AR and NE according to the literature, including asthma, atopic dermatitis, OSAS, ADHD, obesity, and hypertrophy of tonsils and adenoids.^{7–10,34} After adjusting for all these confounders, the association between AR and increased subsequent risk of NE still existed. Third, genetic and behavioral factors, and severity of NE were not captured in administrative claims databases. Fourth, the diagnosis of the current study was based on ICD-9-CM coding. The hypertrophy of tonsil and adenoids may be underdiagnosed and may not be coded if mild degree and without disturbing symptoms. Fifth, skin-prick test and serum IgE test were not performed. Some participants may have AR without symptoms. Last, the research population of this study is Chinese and hence, our results may not be representative of other populations.

Conclusion

In summary, children with AR had higher incidence and risk of NE. NE resolved spontaneously with age increase. The high comorbidity between NE, sleep, and neuropsychological functioning is probably due to a common pathogenic pathway, emphasizing the importance of a multidisciplinary focus regarding screening and treatment of children with NE. Further research in human patients is necessary to fully elucidate the pathophysiological features of this disorder. 4

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