

Research paper

Allergic rhinitis increases the risk of incident panic disorder among young individuals: A nationwide population-based cohort study in Taiwan



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ABSTRACT

Background: Studies have reported an association between allergy and panic disorder. However, few studies have explored the relationship between allergic rhinitis and panic disorder. Previous studies were limited by cross-sectional study designs, self-reported symptoms, absence of matched controls, and lack of consideration of the influence of steroid and comorbidities. This study aimed to explore the longitudinal association between allergic rhinitis and panic disorder in a large population-based cohort of young people.

Methods: In this study, 79,917 new cases of allergic rhinitis between 1998 and 2012 in individuals younger than 20 years were identified from Taiwan's National Health Insurance Research Database. One control (nonallergic rhinitis) per case (allergic rhinitis) was randomly selected from the remaining sample, matching for age, sex, residence, and insurance premium. Both groups were followed until the end of 2013 for incidence of panic disorder. Cox regression analysis was performed, adjusting for sex, age, residence, insurance premium, systemic steroids, asthma, atopic dermatitis, allergic conjunctivitis, attention deficit hyperactivity disorder, depression, and Charlson index.

Results: Allergic rhinitis was associated with a 2-fold increase in risk for panic disorder after adjustment for other variables. Additional independent risk factor of panic disorders were female sex, older age group, and depression.

Limitations: Lifestyle, substance use, smoking by the patient or family members, and psychosocial stressors were not evaluated.

Conclusions: Allergic rhinitis was associated with increased risk of panic disorder. Assessment and intervention of allergy rhinitis among young people with panic disorder are critical.

1. Introduction

Allergic rhinitis (AR) is a common allergic disorder, which manifests as sneezing, nasal congestion, and rhinorrhea in children and

adolescents, and potentially leads to not only physical but also mental distress. Physical and mental stress may significantly impair activities and relationships in patients and their families (Schatz, 2007). Common physical complications include otitis media with effusion, sinusitis, and

Abbreviations: AR, allergic rhinitis; NHIRD, National Health Insurance Research Database; NHRI, National Health Research Institutes; NHI, National Health Insurance; LHID, Longitudinal Health Insurance Database; ICD-9, International Classification of Disease Ninth revision; DDD, defined daily dose; AD, atopic dermatitis; AC, allergic conjunctivitis; ADHD, attention deficit hyperactivity disorder; NTD, New Taiwan Dollar; HR, Hazard ratio; HPA, hypothalamic-pituitary-adrenal; CRH, corticotropin-releasing hormone; CI, confidence interval; OR, odds ratio; IRR, incidence rate ratio

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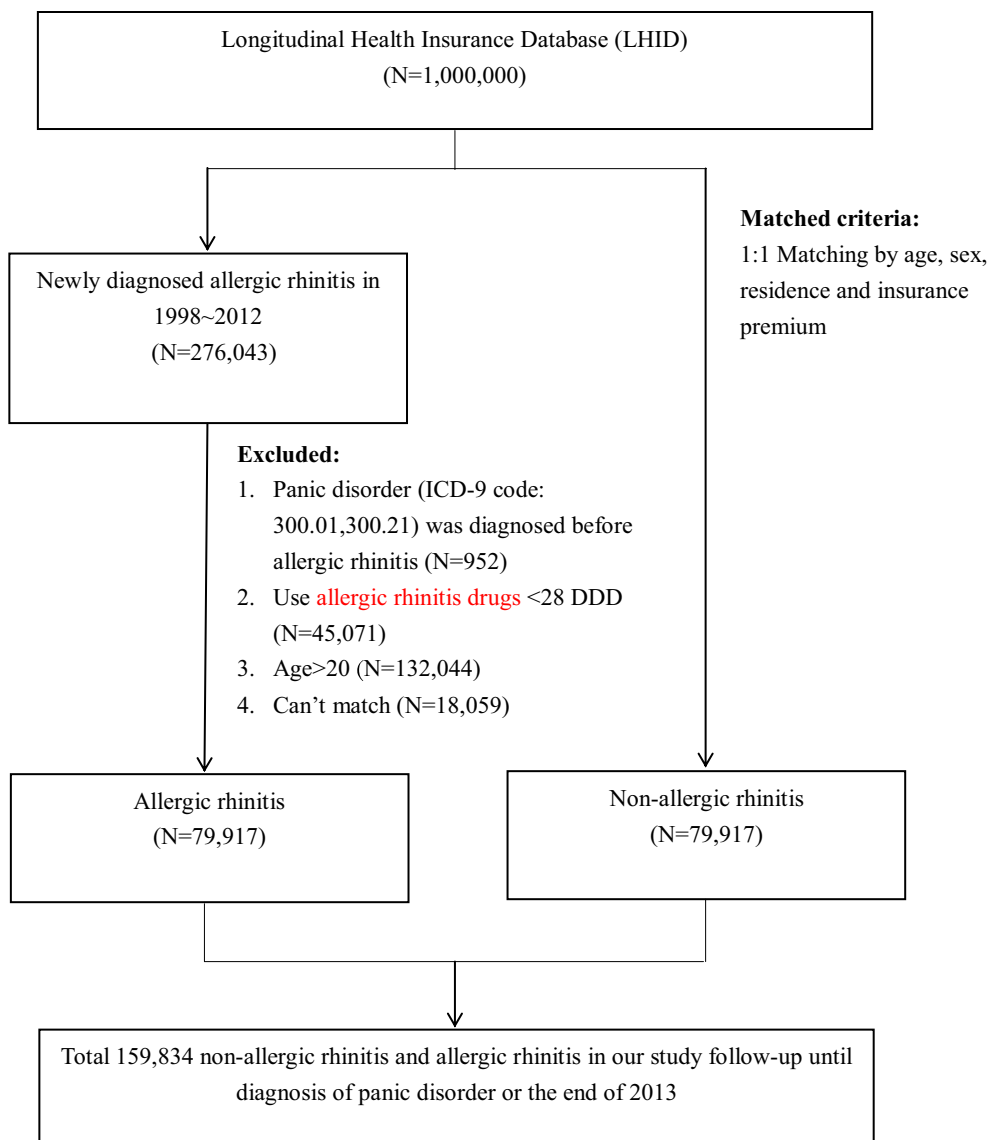


Fig. 1. Flowchart of data collection.

asthma. Associated mental-health related complications include sleep problems, poor school performance, and hyperactivity (van Cauwenberge et al., 2000). The prevalence rate of AR ranges from 2.9% to 54.1% in regions around the world (Lee et al., 2016). In Taiwan, the prevalence of physician-diagnosed AR has been reported to be 28.6% and 19.5% in male and female middle-school students, respectively (Hasler et al., 2005). The increasing prevalence of AR in Taiwan has been attributed to increasing industrialization, urbanization, higher nonsummer temperatures, and traffic-related air pollutants (Goodwin, 2003; Hasler et al., 2005).

Studies have demonstrated associations between atopic disorders and psychiatric symptoms, especially anxiety disorder (Bedolla-Barajas et al., 2017; Goodwin, 2003). However, these studies have focused on asthma and reported substantial association between asthma and anxiety disorder (Hasler et al., 2005; Lee et al., 2016). Potential mechanisms driving the relationships could be the association with recurrent respiratory inflammation and sensitization to fear of dyspnea (Goodwin, 2003).

Results of studies examining the association between AR and anxiety disorder have been inconsistent. Some studies have reported a positive association between AR and anxiety symptoms or disorders (Bedolla-Barajas et al., 2017; Sansone and Sansone, 2011; Slattery and

Essex, 2011; Xi et al., 2016) while others such as Kennedy et al. (2002) have reported a negative association. In addition, few studies have explored the relationship between AR and panic disorder (Goodwin, 2002; Patten and Williams, 2007). Goodwin (2002) determined that self-reported hay fever increased the odds of panic attacks (OR = 1.8) in an adult population in a community in the United States. Moreover, Patten and Williams (2007) reported that allergic individuals had greater chances of experiencing panic disorders (OR = 1.7) in a population in a Canadian community.

Previous studies have had several limitations, including the use of cross-sectional study designs, the use self-reported assessments for the diagnosis of AR and panic disorder, and not taking into account the influences of steroid medications and comorbidities of other allergic disorders or psychiatric disorders. Therefore, the aim of this study was to investigate the association between AR and panic disorder by using a national population-based cohort study design.

2. Methods

2.1. Sample

We designed a cohort study using data from the Taiwan National

Health Insurance Research Database (NHIRD). The National Health Insurance (NHI) Program, implemented in 1995, is a compulsory health insurance program that covers approximately 98% of the population in Taiwan. Information on hospitals, outpatient clinics, and dental services are included in the NHIRD. In addition, the Longitudinal Health Insurance Database (LHID) contains representative data on approximately 1,000,000 individuals, randomly sampled from all NHI beneficiaries. The distributions of age, sex, or health care costs are not significantly different between LHID samples and all beneficiaries (Institutes, 2013).

AR was recognized according to International Classification of Disease, Ninth revision (ICD-9) code 477. All medical claims made under this diagnostic code between January 1, 1998 and December 31, 2012 were obtained from the NHIRD for analysis. AR cases in the present study required at least two ambulatory claims within one year or at least one inpatient claim with a diagnosis. We identified newly diagnosed AR cases by excluding individuals that had received an AR diagnosis before January 1, 1998. Individuals diagnosed with panic disorder before AR ($N = 952$), individuals using less than 28 defined daily doses (DDD) of allergic rhinitis drugs ($N = 45,071$), individuals aged above 20 years ($N = 132,044$), and individuals who could not be matched ($N = 18,059$) were all excluded. Allergic rhinitis drugs included Fexofenadine, Cyproheptadine, Levocetirizine, Desloratadine, Azelastine, Loratadine, and Pseudoephedrine. In this manner, 79,917 cases of AR in individuals aged less than 20 years were defined. To assess the relationship between AR and risk of panic disorder, one control (nonallergic rhinitis) per case (allergic rhinitis) was randomly selected from the remaining sample, matching for age within 1 year, sex, residence, and insurance premium. We monitored both AR cases and non-AR controls until incident panic disorders or the end of 2013.

Patients with a diagnosis of panic disorder without agoraphobia (ICD-9-CM code 300.01) and agoraphobia with panic disorder (ICD-9-CM code 300.21) were extracted from the NHIRD. The definition of panic disorder also required at least two ambulatory claims within one year or at least one inpatient claim with a diagnosis. Patients who received both a diagnosis of panic disorder without agoraphobia and a diagnosis of agoraphobia with panic disorder before allergic rhinitis were excluded. A flow chart of our data collection activity is presented in Fig. 1.

Covariates in the present study included sex, age group, residence, insurance premium, usage of prednisone, asthma (ICD-9-CM code 493, 493.0, 493.1, or 493.9), atopic dermatitis (ICD-9-CM code: 691 or 691.8), allergic conjunctivitis (ICD-9-CM code: 372.05, 372.10), attention deficit hyperactivity disorder (ICD-9-CM code: 314.0), depression (ICD-9-CM codes: 296.2, 296.3, 300.4, and 311) and general physical health condition (the Charlson comorbidity index). The definition of the aforementioned physical illness and psychiatric disorders required at least two ambulatory claims within one year or at least one inpatient claim with a diagnosis. The Charlson comorbidity index consisted of a weighted score of comorbid diseases based on the relative risk of mortality (D'Hoore et al., 1993).

The insurance premium has three categories: (i) fixed premium and dependent, (ii) less than New Taiwan Dollars (NTD) 20,000 (income per month), and (iii) NTD 20,000 or more (1US \$ = 32.1 NTD in 2008). Citizens requiring social welfare support, such as citizens with low income and veterans, were classified in the group of fixed premium. Citizens without a fixed salary or income were classified in the dependent group.

Usage of systematic prednisone was regarded as a covariate only if patients used systemic prednisone at least one year. The annual average cumulative defined daily dose (DDD) of prednisone was classified into two groups (0–99, ≥ 100). DDD is a standardized measure for medication consumption, defined by the WHO. Cumulative DDD is the sum of DDDs of a drug within a certain period. The present study was reviewed and approved by the Institutional Review Board of Tsaotun Psychiatric Center, Ministry of Health and Welfare.

2.2. Statistical analysis

Death prior to panic disorder was considered a competing risk event. Death date was obtained from the national mortality database. The Fine and Gray method was used to estimate death-adjusted cumulative incidences of panic disorder (Zhang et al., 2011). A survival analysis was performed to calculate the risk of panic disorder during the follow-up period, with the time function calculated as the number of years from the index date of AR diagnosis to December 31, 2013 (end of follow-up) or until the date of death. The index date, defined as the first diagnosis date of AR, was also applied to the matched controls. Competing risk adjusted Cox regression models (Zhang et al., 2011) were performed to evaluate the association between AR and incident panic disorder after adjusting the covariates. Hazard ratios and 95% confidence intervals were calculated. The model was tested first with all the sample cases included. R package “cmprsk” was used to estimate cumulative incidences and Cox models in the competing risk analysis (Gray, 2010). Analyses were conducted using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Sample characteristics

The demographic characteristics of AR cases and their matched controls are listed in Table 1. The two cohorts in the present study comprised 79,917 cases with newly diagnosed AR and 79,917 matched controls retrieved from the NHIRD, covering the period from 1998 to 2012. The two cohorts did not differ significantly in gender, age at entry, residence, and insurance premium. In the AR cohort, sex ratio was nearly even (49.5% female and 50.5% male). Younger ages at entry (0–10 years old, 61.2%) and rural residence (71.3% of cases lived in rural areas) were dominant among the AR group. Most cases had a fixed premium and a dependent insurance ($n = 73,889$, 92.5%). In the sample, 5.6% ($n = 4432$) of cases had less than a NTD 20,000 insurance premium, while 2.0% ($n = 1596$) of cases had a more than NTD 20,000 insurance premium. Of the 159,834 subjects, 230 cases had a panic disorder diagnosis during the period of our survey. Among the 230 cases that had a panic disorder, 158 cases (0.2%) were within the AR cohort while 72 cases were within the non-AR cohort (0.1%, $p < .001$). There were 13,833 subjects among the AR cohort (17.3%) and 3409 subjects among the non-AR cohort (4.3%) who used prednisone for more than 30 annual cumulative DDDs. The mean duration of usage of systemic steroids was longer in the AR cohort than in the non-AR cohort (21.1 ± 112.1 days, 6.2 ± 41.9 days, $p < .001$).

More subjects were comorbid with asthma, atopic dermatitis, allergic conjunctivitis, attention deficit hyperactivity disorder, and depression in the AR group than in the non-AR group (all $p < .001$). Moreover, the AR group scored higher on the Charlson index compared with the non-AR group ($p < .001$).

3.2. Association between allergic rhinitis and risk of panic disorder

The results of the analysis of the association between AR and panic disorder are presented in Table 2 and Fig. 2. AR was associated with increased risk of panic disorder in the Cox regression model (HR: 2.42, 95% CI: 1.68–3.49) after adjustment for sex, age, residence, insurance amount, prednisone, asthma, atopic dermatitis, allergic conjunctivitis, ADHD, depression, and Charlson comorbidity index. Additional factors associated with panic disorders were female sex, age (between 11 and 20 years old), and depression.

The results of the Cox regression analysis of disease combination risk for panic disorder are summarized in Table 3. After adjustment for either physical illness (asthma, atopic dermatitis, or allergic conjunctivitis) or mental illness (depression and ADHD), or a combination of physical illness and mental illness, the results showed that allergic

Table 1
Characteristics of allergic rhinitis cases and their matched controls.

Characteristic	Panic disorder N	Allergic rhinitis N	%	Non-Allergic rhinitis N	%	Chi-square test p value
<i>Sex</i>						
Girl	131	39,563	49.5	39,563	49.5	1.000
Boy	99	40,354	50.5	40,354	50.5	
<i>Age at entry (years)</i>						
0–10	54	48,930	61.2	48,930	61.2	1.000
11–20	176	30,987	38.8	30,987	38.8	
<i>Residence</i>						
Urban	67	22,938	28.7	22,938	28.7	1.000
Rural	163	56,979	71.3	56,979	71.3	
<i>Insurance premium</i>						
Fixed premium and dependent	169	73,889	92.5	73,889	92.5	1.000
Less than NTD ^a 20,000	40	4432	5.6	4432	5.6	
NTD 20,000 or more	21	1596	2.0	1596	2.0	
<i>Prednisone* (DDD^b)</i>						
0–99	222	77,269	96.7	79,437	99.4	<.001
≥ 100	8	2648	3.3	480	0.6	
Median (IQR ^d)		4.5 (19.5)	0.0 (4.5)	<.001 ^e		
<i>Asthma</i>						
No	187	51,077	63.9	74,762	93.6	<.001
Yes	43	28,840	36.1	5155	6.5	
<i>Atopic dermatitis</i>						
No	211	66,925	83.7	74,130	92.8	<.001
Yes	19	12,992	16.3	5787	7.2	
<i>Allergic conjunctivitis</i>						
No	164	45,694	57.2	60,975	76.3	<.001
Yes	66	34,223	42.8	18,942	23.7	
<i>ADHD^c</i>						
No	222	76,347	95.5	78,000	97.6	<.001
Yes	8	3570	4.5	1917	2.4	
<i>Depression</i>						
No	159	78,055	97.7	78,869	98.7	<.001
Yes	71	1862	2.3	1048	1.3	
<i>Charlson index*</i>						
Mean ± SD		0.1 ± 0.3	0.03 ± 0.2	<.001		
<i>Panic disorder</i>						
No		79,759	99.8	79,845	99.9	<.001
Yes		158	0.2	72	0.1	

* Past of index date.

^a 1US \$ = 32.1 NTD in 2008.

^b DDD: Defined daily dose (mg).

^c ADHD: Attention deficit hyperactivity disorder.

^d IQR: Interquartile range.

^e Wilcoxon-Mann-Whitney (rank-sum) test.

rhinitis was still associated with increased risk of panic disorder (HR: 2.02, 95% CI: 1.50–2.71).

4. Discussion

This nationwide cohort study is the first to show that newly-diagnosed AR, which occurred in one's early life, is associated with a two-fold increased risk in panic disorder after adjustment for other variables (i.e., sex, age, residence, insurance premium, asthma, AD, AC, ADHD, and depression). This finding is consistent with those of previous studies in the United States (Goodwin, 2002) and Canada (Patten and Williams, 2007). However, the previous studies were limited to cross-sectional study designs, the use of self-reported questionnaires to diagnose AR or panic symptoms, and the absence of matched control groups.

The prevalence of panic disorder in the AR cohort was 20.2/100,000 person-years and in the non-AR cohort was 9.2/100,000 person-years (incidence rate ratio [IRR]: 2.19, 95% CI: 1.66–2.90) in NHIRD in Taiwan (Appendix A). The risk of developing panic disorder among AR cases in the present study (HR: 2.02, 95% CI: 1.50–2.71) was higher than the risk observed in cross-sectional community studies in the United States (OR = 1.8, 95% CI: 1.2–2.6) (Goodwin, 2002) and Canada (OR = 1.7, 95% CI: 1.5–2.3) (Patten and Williams, 2007). A

possible reason for the difference is that AR cases in the present study were recruited from the medical service system and were formally diagnosed by physicians. In addition, the individuals examined in the present study could have more severe symptoms than those recruited from community settings, as is the case in previous studies. Moreover, our study recruited young people aged less than 20 years, while previous studies have recruited older people. Furthermore, we recruited newly-diagnosed AR patients and investigated the risk of later development of incident panic disorder. Previous studies have not explored the longitudinal sequence of AR and later panic disorder. In addition, potential confounding factors (i.e., sex, age, residence, insurance premium, prednisone, asthma, AD, AC, ADHD, and depression) were controlled for in this study but were not taken into account in previous studies.

In this study, we focused on the risk of panic disorder in AR young patients. However, some patients with less severe symptoms might be diagnosed as anxiety disorder, unspecified. We performed the sensitivity analysis and found that AR was also associated with increased risk of anxiety disorder, unspecified (ICD-9: 300.00) in the Cox regression model (adjusted HR: 1.75, 95% CI: 1.62–1.88, *p*-value: <.0001) after adjustment for sex, age, residence, insurance amount, prednisone, asthma, atopic dermatitis, allergic conjunctivitis, ADHD, depression, and Charlson comorbidity index (Appendix B). This result was

Table 2
Adjusted Cox regression analysis of incident panic disorder.

Unadjusted hazard ratio Variables	Sample sizes	Person-time	No. of patients	Hazard ratio	95% CI ^b	P value	Adjusted hazard ratio ^a Hazard ratio	95% CI	P value
<i>Allergic rhinitis</i>									
No(reference)	79,917	781,947.30	72	1.00			1.00		
Yes	79,917	781,897.02	158	2.19	1.66–2.90	<.0001	2.42	1.68–3.49	<.0001
<i>Sex</i>									
Girl(reference)	79,126	753,454.74	131	1.00			1.00		
Boy	80,708	810,389.62	99	0.68	0.52–0.88	0.0038	0.70	0.53–0.94	0.0173
<i>Age at entry (years)</i>									
0–10(reference)	97,860	981,173.71	54	1.00			1.00		
11–20	61,974	582,670.65	176	5.67	4.18–7.69	<.0001	3.56	2.48–5.12	<.0001
<i>Residence</i>									
Urban	45,876	463,478.67	67	0.95	0.71–1.26	0.7104	0.89	0.65–1.21	0.4385
Rural(reference)	113,958	1,100,365.69	163	1.00			1.00		
<i>Insurance premium</i>									
Fixed premium and dependent(reference)	147,778	1,422,691.72	169	1.00			1.00		
Less than NTD ^c 20,000	8864	99,323.36	40	3.11	2.20–4.39	<.0001	1.34	0.91–1.98	0.1369
NTD 20,000 or more	3192	41,829.28	21	3.53	2.23–5.56	<.0001	1.52	0.92–2.51	0.1021
<i>Prednisone * (DDD^d)</i>									
0–99(reference)	156,706	1,528,548.90	222	1.00			1.00		
≥ 100	3128	35,295.46	8	1.41	0.70–2.85	0.3425	1.01	0.49–2.09	0.9747
<i>Asthma</i>									
No(reference)	125,839	1,225,225.81	187	1.00			1.00		
Yes	33,995	338,618.55	43	0.82	0.59–1.14	0.234	0.93	0.64–1.34	0.6886
<i>Atopic dermatitis</i>									
No (reference)	141,055	1,396,274.69	211	1.00			1.00		
Yes	18,779	167,569.67	19	0.81	0.50–1.29	0.3711	0.84	0.49–1.43	0.5171
<i>Allergic conjunctivitis</i>									
No (reference)	106,669	1,049,908.38	164	1.00			1.00		
Yes	53,165	513,935.98	66	0.84	0.63–1.11	0.217	0.86	0.63–1.17	0.3342
<i>ADHD^e</i>									
No (reference)	154,347	1,513,851.67	222	1.00			1.00		
Yes	5487	49,992.69	8	1.15	0.57–2.33	0.6983	1.23	0.57–2.66	0.6014
<i>Depression</i>									
No (reference)	156,924	1,531,493	159	1.00			1.00		
Yes	2910	32,351.35	71	19.72	14.90–26.11	<.0001	11.65	8.50–15.97	<.0001
<i>Charlson index*</i>	159,834	1,563,844.36	230	1.18	0.78–1.81	0.4367	0.99	0.64–1.53	0.9679

* Past of index date.

^a Adjusted Cox regression analysis controlling for sex, age, residence, insurance amount, prednisone, asthma, atopic dermatitis, allergic conjunctivitis, attention deficit hyperactivity (ADHD), depression, and Charlson comorbidity index.

^b CI: Confidence interval.

^c 1 US \$ = 32.1 NTD in 2008.

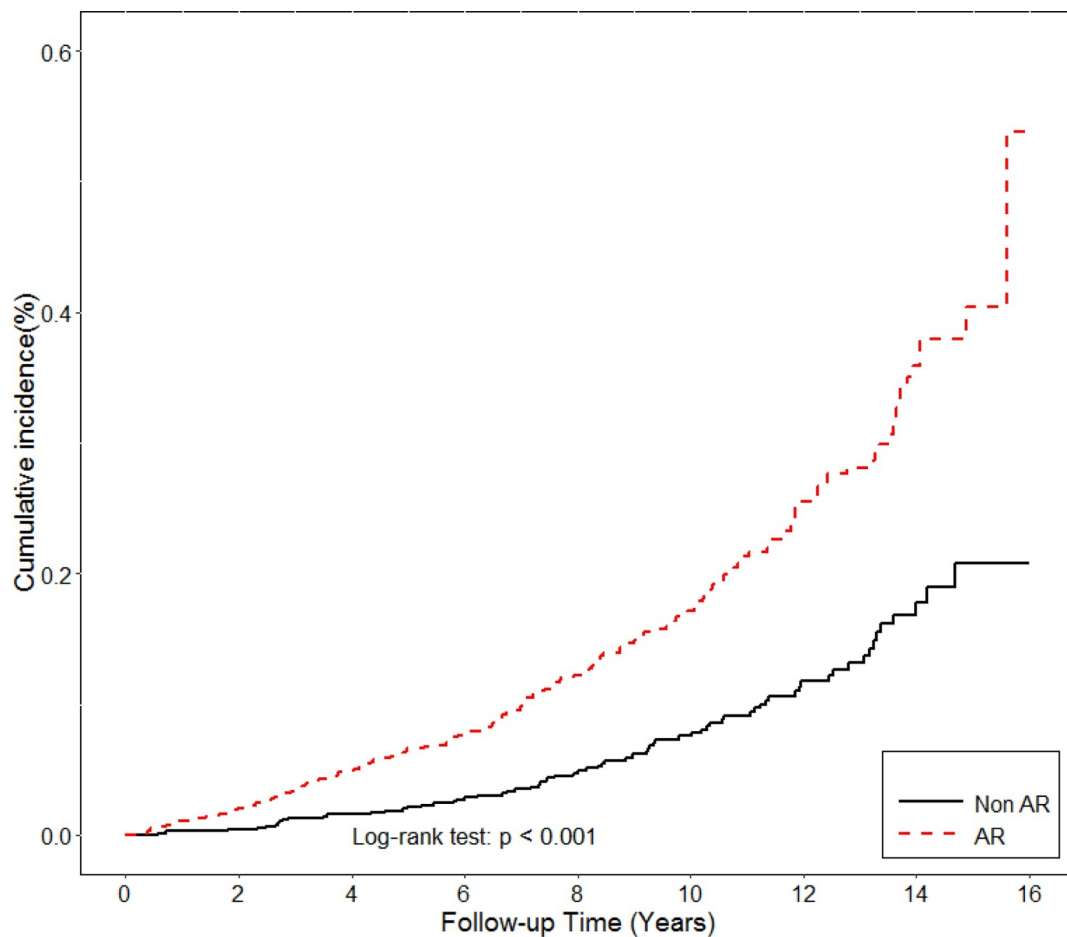
^d DDD: Defined daily dose (mg).

^e ADHD: Attention deficit hyperactivity disorder.

consistent with previous studies (Bedolla-Barajas et al., 2017; Munoz-Cano et al., 2018; Sansone and Sansone, 2011; Slatery and Essex, 2011) which also indicated an association between AR and anxiety.

This study observed that AR was associated with increased risk of panic disorder. Research has indicated that perceived dyspnea or abnormalities of carbon dioxide sensitivity could trigger fear networks or alarm systems in patients with panic disorder (Martinez et al., 2001; Nardi et al., 2009). Moreover, a diminished sense of smell accompanied by chronic nasal inflammation was associated with anxiety and depression (Katotomichelakis et al., 2014), while sleep impairment caused by nasal obstruction could aggravate anxiety symptoms in patients with AR (Fang et al., 2010; Leger et al., 2006). Furthermore, allergy could activate the immune system and cytokines, which have been reported to be related to anxiety (Muller and Ackenheil, 1998). Another common mechanism for AR and panic disorder association may involve the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, a neuroendocrine stress system, which has been reported to be involved in the etiology of anxiety, depression, and sleep disorder (Hammen, 2005; Han et al., 2012; Reul and Holsboer, 2002). An activated HPA axis plays a key role in modulating plasma cytokines, IgE, and subsequent inflammatory responses in AR (Eskandari and Sternberg, 2002; Hashimoto et al., 2010), while HPA axis hyperactivity and enhanced corticotropin-releasing hormone (CRH) and glucocorticoid secretion are associated with panic disorder (Abelson et al., 2007).

The present study also found depression and female sex to be independent risk factors of panic disorder. Panic disorder has frequently been observed to be comorbid with depression and associated with increased severity of depression and suicide risk (Amami et al., 2010; Batinic et al., 2017). Shared mechanisms for both conditions include genetic and biological vulnerability, behavioral inhibition, anxiety sensitivity, increased stress reaction, and dysregulation of the HPA axis (Amami et al., 2010; Batinic et al., 2017; Limmer et al., 2015; Reul and Holsboer, 2002; Zorn et al., 2017). Our result was consistent with previous studies, which reported that women were at a greater risk of developing panic disorders (Kinrys and Wygant, 2005; McLean and Anderson, 2009; Sheikh et al., 2002). Genetic factors, serotonin function, female reproductive hormones, increased social stress, and greater phobic avoidance for women may play a role in the association between female sex and panic disorder (Kinrys and Wygant, 2005; Maron et al., 2011; McLean and Anderson, 2009; Rose and Rudolph, 2006; Weber et al., 2012). The present study also observed that individuals aged 11–20 years had a greater risk of developing panic disorder than those aged less than 10 years. Previous studies have reported similar results, which suggests that late adolescence or early adulthood are more likely to be associated with the age-of-onset of panic disorder (Kessler et al., 2007a, 2007b). Additional studies that explore the underlying mechanisms between the above risk factors and panic disorder are required. Furthermore, assessments and interventions for panic disorder



Number at risk									
Non AR	79917	78497	73536	65629	55221	41520	26002	10447	0
AR	79917	78495	73542	65636	55219	41510	25971	10448	0

Fig. 2. Cumulative incidence of panic disorder by study groups (allergic rhinitis vs. nonallergic rhinitis).

Table 3

Adjusted Cox regression analysis of disease combination risk for incident panic disorder.

	Adjusted hazard ratio		P value
	Hazard ratio	95% CI	
Main model*	2.20	1.66–2.90	<.001
Main model + Asthma	2.22	1.66–2.97	<.001
Main model + Atopic dermatitis	2.20	1.66–2.91	<.001
Main model + Allergic conjunctivitis	2.25	1.69–2.99	<.001
Main model + Attention-deficit/hyperactivity	2.17	1.64–2.87	<.001
Main model + Depression	1.90	1.43–2.51	<.001
Main model + Allergic diseases**	2.27	1.69–3.05	<.001
Main model + Mental illness***	1.89	1.43–2.51	<.001
Main model + Allergic diseases + Mental illness	2.02	1.50–2.71	<.001

* Allergic rhinitis, sex, age at entry, residence, insurance premium.

** Asthma, atopic dermatitis, allergic conjunctivitis.

*** Attention deficit hyperactivity disorder, depression.

are warranted, especially for people with AR and the above risk factors.

4.1. Strengths and limitations

To the best of knowledge, this study is the first to explore the longitudinal association between AR during early life and later incident

panic disorder from a nationally representative sample.

Previous studies have been limited to cross-sectional study designs, while we have explored the longitudinal sequence of the onset of AR and panic disorder. Additionally, we recruited newly-diagnosed AR patients and investigated the risk of later development of incident panic disorder by excluding diagnoses of panic disorder before AR. Unlike our study, most previous studies have identified AR mostly through self-reported questionnaires. In the present study, our cases were identified by well-trained physicians. In addition, only patients with at least two ambulatory claims within one year or at least one inpatient claim with a diagnosis were included in the present study. Furthermore, most previous studies have not accounted for the influence of potential confounding variables, whereas we controlled for sex, age, residence, insurance premium, prednisone, asthma, AD, AC, ADHD, depression, and the Charlson comorbidity index when estimating the risk of AR and later panic disorder.

Nevertheless, our study has some limitations. Data on subjects' body weights, personal lifestyles, exercise habits, substance use, cigarette smoking by the patient and their family members, psychosocial stressors, seasonal pollution, and other environmental factors as well as the severity of the AR symptoms and panic disorder could not be obtained from the NHIIRD. Another limitation was lack of information on medication compliance for prednisone. To counteract the limitation associated with lack of information on prednisone compliance, DDD was used to estimate the dose-effects of prednisone. In addition, the

diagnosis of AR was performed by not only specialists but also general practitioners. Consequently, stricter criteria were set for AR cases (required at least two ambulatory claims within one year or at least one inpatient claim with a diagnosis) to enhance the validity of the AR diagnosis. The present study also included only participants that were aged less than 20 years old, and the results cannot be generalized for older age groups.

5. Conclusion

AR was associated with an approximate two-fold increase in risk of incident panic disorder among young people after adjusting for confounding factors, including epidemiology, and physical and mental illness. Therefore, screening, assessment, and intervention of previous allergy rhinitis among patients with panic disorder are critical.

Additional studies exploring the relationship between AR and panic disorder from a large community sample, with longer follow-up duration, while considering other confounding factors (i.e., personal life-style, substance use, cigarette smoking by the patient or their family members, psychosocial stressors, seasonal pollution, and other environmental factors) are required.

Declarations

Ethics approval and consent to participate.

All participants provided written informed consent before participation, were informed of their right to discontinue participation at any time and were assured of confidentiality. The study was reviewed and approved by the Institutional Review Board of the TsaoTun Psychiatric Center, Ministry of Health and Welfare, Taiwan.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jad.2019.04.037](https://doi.org/10.1016/j.jad.2019.04.037).

Appendix A

Table A1.

Table A1

The prevalence and incidence rate ratio of panic disorder.

	Allergic rhinitis		Non- allergic rhinitis		IRR (95%CI)	P value
	No.	No./10 ⁵ person year	No.	No./10 ⁵ person year		
Panic disorder	158	20.2(17.1–23.4)	72	9.2(7.1–11.3)	2.1946 (1.6608 - 2.8999)	<.0001

Appendix B

Table B1.

Table B1

Adjusted Cox regression analysis of incident anxiety disorder.

Unadjusted hazard ratio						Adjusted hazard ratio ^a			
	Sample sizes	Person-time	No. of patients	Hazardratio	95% CI ^b	P value	Hazard ratio	95% CI	P value
Allergic rhinitis									
No (reference)	79,268	771,445.17	1249	1.00			1.00		
Yes	79,268	766,931.85	2283	1.84	1.72–1.97	<.0001	1.75	1.62–1.88	<.0001

^a Adjusted Cox regression analysis controlling for sex, age, residence, insurance amount, prednisone, asthma, atopic dermatitis, allergic conjunctivitis, attention deficit hyperactivity (ADHD), depression, and Charlson comorbidity index.

^b CI: Confidence interval.

Authors' contributions

Authors M.T.H. and S.H.Y.L. are joint first authors, and they contributed equally to the work. Authors M.T.H., M.H.W., and V.C.H.C. designed the study and wrote the protocol. Author Y.H.Y., T.Y.K., and T.Y.L. collected the data. Authors M.T.H. and M.H.W. drafted the initial manuscript. Authors V.C.H.C., S.H.Y.L., and M.H.W. revised and edited the manuscript. All authors made significant contributions to the conception and design of the study, and analysis and interpretation of the data. All authors read and approved the final manuscript.

Conflict of interest

No conflict declared.

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