



# Increased Risk of Psychiatric Disorders in Allergic Diseases: A Nationwide, Population-Based, Cohort Study

Nian-Sheng Tzeng<sup>1,2</sup>, Hsin-An Chang<sup>1,2</sup>, Chi-Hsiang Chung<sup>3,4,5</sup>, Yu-Chen Kao<sup>1,6</sup>, Chuan-Chia Chang<sup>1</sup>, Hui-Wen Yeh<sup>1,7,8,9</sup>, Wei-Shan Chiang<sup>1</sup>, Yu-Ching Chou<sup>5</sup>, Shan-Yueh Chang<sup>10,11</sup> and Wu-Chien Chien<sup>3,4,12\*</sup>

<sup>1</sup> Department of Psychiatry, Tri-Service General Hospital, School of Medicine, National Defense Medical Center, Taipei, Taiwan, <sup>2</sup> Student Counseling Center, National Defense Medical Center, Taipei, Taiwan, <sup>3</sup> Department of Medical Research, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, <sup>4</sup> Taiwanese Injury Prevention and Safety Promotion Association, Taipei, Taiwan, <sup>5</sup> School of Public Health, National Defense Medical Center, Taipei, Taiwan, <sup>6</sup> Department of Psychiatry, Tri-Service General Hospital, Song-Shan Branch, National Defense Medical Center, Taipei, Taiwan, <sup>7</sup> Institute of Bioinformatics and Systems Biology, National Chiao Tung University, Hsin-Chu, Taiwan, <sup>8</sup> Department of Nursing, Tri-Service General Hospital, School of Nursing, National Defense Medical Center, Taipei, Taiwan, <sup>9</sup> Department of Nursing, Kang-Ning University (Taipei Campus), Taipei, Taiwan, <sup>10</sup> Division of Chest and Critical Medicine, Department of Medicine, Tri-Service General Hospital, School of Medicine, National Defense Medical Center, Taipei, Taiwan, <sup>11</sup> Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan, <sup>12</sup> Graduate Institute of Life Sciences, National Defense Medical Center, Taipei, Taiwan

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### \*Correspondence:

Wu-Chien Chien  
chienwu@ndmctsgh.edu.tw

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**Background/objective:** Allergic diseases, such as bronchial asthma, allergic rhinitis, atopic dermatitis, and psychiatric disorders, are major health issues. There have been reports that allergic diseases were associated with depression or anxiety disorders. This study aimed to investigate the association between these allergic diseases and the risk of developing overall psychiatric disorders in patients from Taiwan.

**Methods:** This cohort study used the database of the Taiwan National Health Insurance Program. A total of 186,588 enrolled patients, with 46,647 study subjects who had suffered from allergic diseases, and 139,941 controls matched for sex and age, from the Longitudinal Health Insurance Dataset of 2000–2015, were selected from a sub-dataset of the National Health Insurance Research Database. Fine and Gray's competing risk model analysis was used to explore the hazard ratio (HR), and 95% confidence interval, for the risk of allergic diseases being associated with the risk of developing psychiatric disorders during the 15 years of follow-up.

**Results:** Of the study subjects, 5,038 (10.8%) developed psychiatric disorders when compared to 9,376 (6.7%) in the control group, with significant difference ( $p < 0.001$ ). Fine and Gray's competing risk model analysis revealed that the adjusted HR was 1.659 (95% CI = 1.602–1.717,  $p < 0.001$ ). In this study, we found that the groups of atopic dermatitis alone and the allergic rhinitis + atopic dermatitis were associated with a lower risk of psychiatric disorders, but all the other four groups, such as bronchial asthma alone, allergic rhinitis alone, bronchial asthma + allergic rhinitis, bronchial asthma + atopic dermatitis, and the combination of all these three allergic diseases, were associated with a higher risk of psychiatric disorders.

**Conclusion:** Allergic diseases are therefore associated with a 1.66-fold increased hazard of psychiatric disorders in Taiwan.

**Keywords:** bronchial asthma, allergic rhinitis, atopic dermatitis, psychiatric disorders, risk factors, cohort study, Taiwan National Health Insurance Program, National Health Insurance Research Database

## INTRODUCTION

Child and adolescent allergic diseases, such as bronchial asthma, allergic rhinitis, and atopic dermatitis, are common and have made an impact on the patients' physical health (1–3). Furthermore, previous studies have shown the association between asthma and anxiety (4), depressive, bipolar, and overall mood disorders (5, 6), attention-deficit hyperactivity disorder (ADHD) (7, 8), schizophrenia (9), and even dementia (10). Some studies have also demonstrated the associations between allergic rhinitis and depressive disorder (11, 12) or bipolar disorder (13). The association between atopic dermatitis and depressive and anxiety disorders has also been reported (14). However, another study found that allergic diseases such as rhinitis or urticarial are associated with a lower risk of schizophrenia (15). Therefore, a study is needed for the overall consideration of the association between these three common allergic diseases and important psychiatric disorders.

Psychiatric, or mental, disorders are defined as clinically significant behavioral or psychological syndromes, which are associated with present distress, disability, or an increased risk of suffering death, pain, or disability, and subsequent behavioral, psychological, or biological dysfunctions (16, 17). Previous studies have found that some psychiatric disorders are associated with several inflammatory diseases (18, 19), such as multiple sclerosis (20, 21), fibromyalgia (22, 23), or inflammatory bowel diseases (24). Psychological stressors related to these diseases might also contribute to both psychiatric and physical morbidity (25, 26).

Recent studies have been increasing on the interactions between allergy-related inflammatory or immunological factors and psychiatric disorders, such as depression (27), anxiety (28), bipolar disorder, and schizophrenia (29). However, further study is still needed to clarify the mechanisms underlying the association between allergic diseases and psychiatric disorders. Nevertheless, the association between allergic diseases and psychiatric disorders has not, as yet, been studied. Therefore, a nationwide, population-based study is necessary for the association between allergic diseases and the risk of psychiatric disorders for the clinicians who actually care for these patients.

## MATERIALS AND METHODS

### Data Sources

The National Health Insurance (NHI) Program was launched in Taiwan in 1995, and as of June 2009, included contracts with 97% of the medical providers with approximately 23 million beneficiaries or more than 99% of the entire population (30, 31). The National Health Insurance Research Database (NHIRD), which contains all the claims data of the beneficiaries, uses the International Classification of Diseases, 9th Revision, Clinical

Modification (ICD-9-CM) codes to record diagnoses (32). The details of the program have been documented in previous studies (22, 33–42).

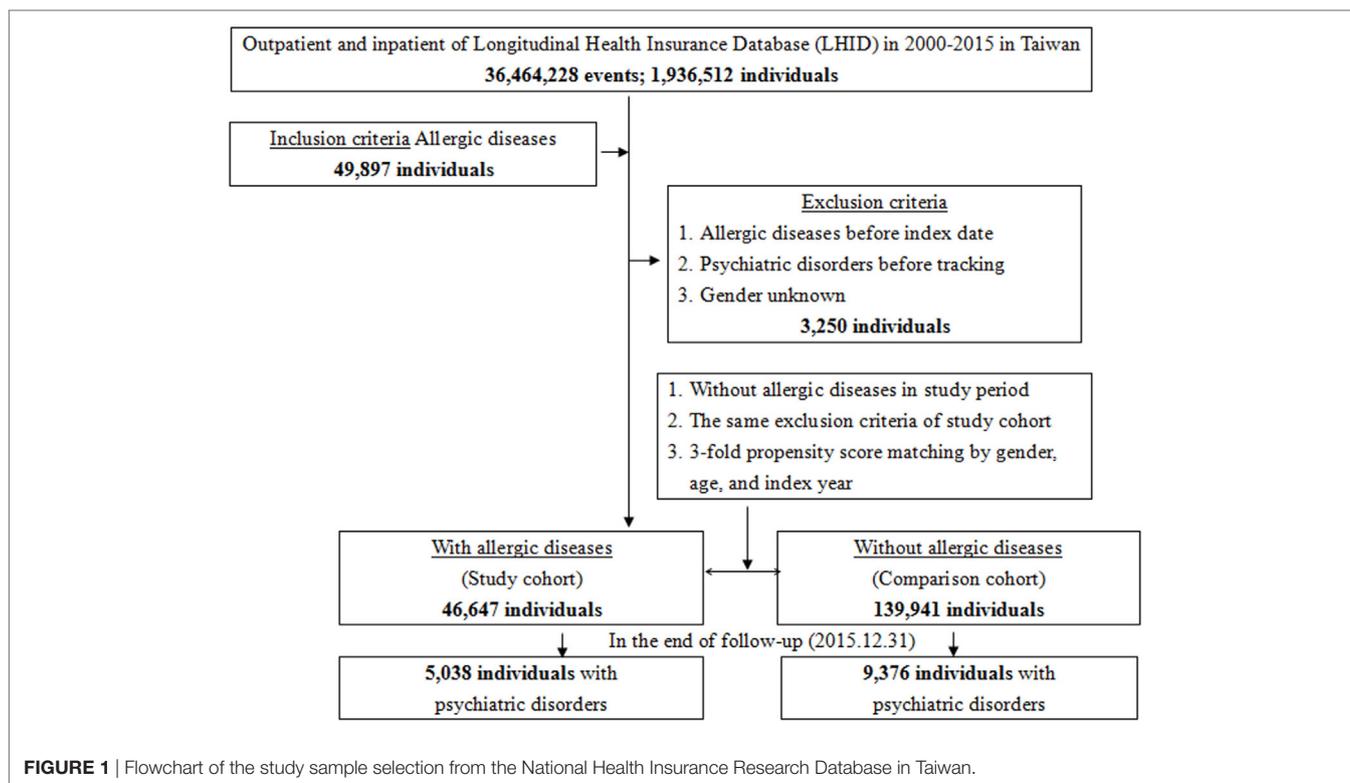
A subset of the NHIRD, Longitudinal Health Insurance Database of a two million randomized sampled population in 2000–2015, was used to study the association between allergic diseases and the risk of psychiatric disorders. The present study used the NHIRD to identify patients with the diagnosis of allergic diseases, based on the ICD-9-CM codes, such as bronchial asthma (ICD-9-CM: 493.x), allergic rhinitis (ICD-9 CM code 477.X), and atopic dermatitis (ICD-9-CM code 691.X) during this period. The Institutional Review Board of the Tri-Service General Hospital approved this study and waived the need for individual written informed consent (IRB No. 2-105-05-040 and IRB No. 2-105-05-082).

### Study Design and Sampled Participants

This study was of a population-based, matched-cohort design. Patients with newly diagnosed bronchial asthma, allergic rhinitis, or atopic dermatitis were selected from the Longitudinal Health Insurance Database from January 1, 2000, to December 31, 2015. The patients with asthma, allergic rhinitis, or atopic dermatitis before 2000 were excluded. This method could be viewed as a wash-out period to make sure all the allergic diseases were recent onset with references from other studies for the association between allergic diseases and psychiatric morbidity, using the NHIRD (6, 7, 11, 15). This wash out period method could avoid the carry-over bias from exposure to the pre-existing allergic diseases. In addition, the patients diagnosed with dementia, depressive disorders, anxiety disorders, eating disorders, bipolar disorders, sleep disorders, and psychotic disorders, before 2000, or before their first visit for asthma, allergic rhinitis, or atopic dermatitis were also excluded. Each enrolled patient was required to have made at least three outpatient visits within the 1-year study period for allergic diseases according to these ICD-9-CM codes. A total of the patients who were enrolled, including 46,647 subjects with allergic diseases and 139,941 controls without allergic diseases, were matched for age, sex, and index date (**Figure 1**).

### Covariates

The covariates included sex, age groups (<20, 20–49, ≥50 years), geographical area of residence (north, center, south, and east of Taiwan), urbanization level of residence (levels 1–4), and monthly income (in New Taiwan Dollars; <18,000, 18,000–34,999, and ≥35,000). The urbanization level of residence was defined according to the population and various indicators of the level of development. Level 1 was defined as a population of >1,250,000, and a specific designation as political, economic, cultural, and metropolitan development. Level 2 was defined as a population between 500,000 and 1,249,999 and as playing an important role



in the politics, economy, and culture. Urbanization levels 3 and 4 were defined as a population between 149,999 and 499,999, and <149,999, respectively (43).

## Comorbidities

Comorbidities were assessed using the Charlson Comorbidity Index (CCI), which categorizes the comorbidities using the ICD-9-CM codes, scores each comorbidity category (44–49), and combines all scores to calculate a single comorbidity score. A score of zero indicates that no comorbidities were found, and higher scores indicate higher comorbidity burdens (31).

## Major Outcome

All of the study participants were followed from the index date until the onset of dementia (ICD-9-CM codes: 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.41, 290.42, 290.43, 290.8, 290.9, and 331.0), anxiety disorders (ICD-9-CM 300), depressive disorders (ICD-9-CM 296.2–296.3, 300.4, and 311), eating disorders (anorexia nervosa 307.1, bulimia nervosa 307.51, and other disorders of eating 307.59), bipolar disorders (ICD-9-CM 296.0, and 296.4–296.8), sleep disorders (ICD-9-CM 307.4 and 780.5), and psychotic disorders (ICD-9-CM 295 and 297–298), withdrawal from the NHI program, or the end of 2015. In addition, each psychiatric diagnosis was required to have made at least three outpatient visits within the 1-year study period for psychiatric disorders according to these ICD-9-CM codes.

## Statistical Analyses

All statistical analyses were performed using the SPSS for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).  $\chi^2$  and

*t* tests were used to evaluate the distributions of the categorical and continuous variables, respectively, with a Fisher's exact examination. Fine and Gray's competing risk analysis was used to determine the risk of psychiatric disorders since death can act as a competing risk factor for psychiatric disorders (40, 50, 51). The results were presented as hazard ratio (HR) with a 95% confidence interval (CI). Differences in the risk of psychiatric disorders between the study and control groups were estimated using the Kaplan–Meier method with the log-rank test. A two-tailed *p* value < 0.05 was considered to indicate the statistical significance.

## RESULTS

### Baseline Characteristics of the Study Population

The baseline characteristics of the study population are depicted in **Table 1**. There were 46,647 subjects in the allergic diseases group and 139,941 non-allergic diseases in the control group, with a similar distribution of sex, age, marital status, education years, and monthly insured premiums. The mean CCR (SD) for the subjects was 1.32 (1.10) and 0.67 (1.68) for the allergic diseases and control group, respectively. The subjects had more medical visits in the spring and winter, with residence in the south, east, and offshore islands of Taiwan, living in levels 3 and 4 in urbanization, or seeking help in local hospitals than the control group (*p* < 0.001 for all). In the subjects with allergic diseases, 40,405 have asthma, 1,809, allergic rhinitis, and 4,433, atopic dermatitis.

**TABLE 1** | Characteristics of study at the baseline.

Allergic diseases Variables	With		Without		<i>p</i>
	<i>n</i>	%	<i>n</i>	%	
<b>Total</b>	46,647	25.00	139,941	75.00	
<b>Gender</b>					0.999
Male	27,162	58.23	81,486	58.23	
Female	19,485	41.77	58,455	41.77	
<b>Age (years)</b>	44.82 ± 30.58		44.83 ± 27.77		0.948
<b>Age group (years)</b>					0.999
<20	14,766	31.65	44,298	31.65	
20–49	6,174	13.24	18,522	13.24	
≥50	25,707	55.11	77,121	55.11	
<b>Married</b>					0.147
Without	20,526	44.00	61,476	43.62	
With	26,121	56.00	79,465	56.38	
<b>Education (years)</b>					0.421
<12	13,757	29.49	40,997	29.30	
≥12	32,890	70.51	98,944	70.70	
<b>Insured premium (New Taiwan Dollars)</b>					0.437
<18,000	37,275	79.91	111,495	79.67	
18,000–34,999	5,520	11.83	16,642	11.89	
≥35,000	3,852	8.26	11,804	8.43	
<b>CCI_R</b>	1.32 ± 1.10		0.67 ± 1.68		<0.001
<b>Season</b>					<0.001
Spring (March–May)	12,770	27.38	37,326	26.67	
Summer (June–August)	11,376	24.39	35,204	25.16	
Autumn (September–November)	10,095	21.64	30,807	22.01	
Winter (December–February)	12,406	26.60	36,604	26.16	
<b>Location</b>					<0.001
Northern Taiwan	16,460	35.29	56,914	40.67	
Middle Taiwan	12,150	26.05	38,437	27.47	
Southern Taiwan	13,324	28.56	35,541	25.40	
Eastern Taiwan	4,398	9.43	8,117	5.80	
Outlets islands	315	0.68	932	0.67	
<b>Urbanization level</b>					<0.001
1 (the highest)	12,504	26.81	50,018	35.74	
2	18,131	38.87	59,219	42.32	
3	4,319	9.26	9,957	7.12	
4 (the lowest)	11,693	25.07	20,747	14.83	
<b>Level of care</b>					<0.001
Hospital center	8,046	17.25	45,001	32.16	
Regional hospital	13,379	28.68	43,677	31.21	
Local hospital	25,222	54.07	51,263	36.63	

*p*: Chi-square/Fisher's exact test on category variables and *t*-test on continue variables.  
 Without married: un-married, divorce, spouse death, and unknown.  
 CCI\_R, Charlson comorbidity index removed dementia.

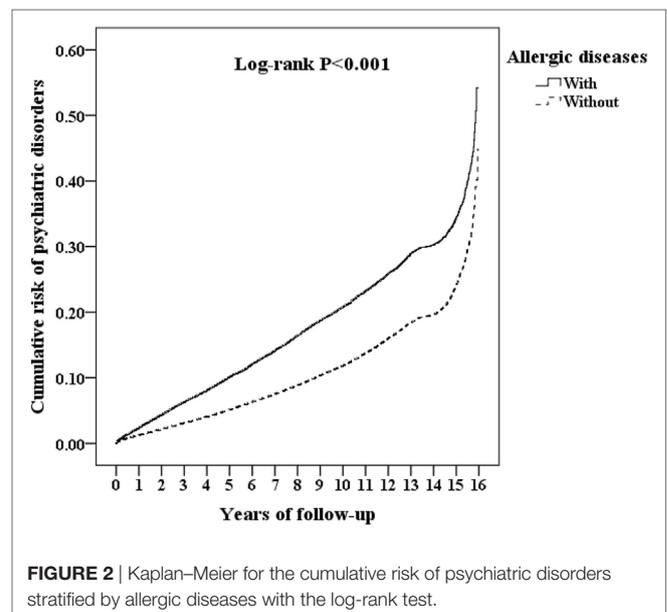
## Allergic Diseases Associated With Psychiatric Disorders

Of the study subjects, 5,038 (10.8%) developed psychiatric disorders when compared to 9,376 (6.7%) in the control group, in the 15-year follow-up. We have also examined the risk of psychiatric disorders associated with allergic diseases. After adjusting for age, sex, CCI scores, and all the covariates, the Fine and Gray's survival analysis revealed that the adjusted HR for psychiatric disorders was 1.659 for the subjects (95% CI = 1.602–1.717,  $p < 0.001$ )

**TABLE 2** | Factors of psychiatric disorders by using Fine and Gray's competing risk model.

Model Variables	Competing risk in the model			
	Adjusted HR	95% CI	95% CI	<i>p</i>
<b>Allergic diseases</b>				
Without	Reference			
With	1.659	1.602	1.717	<0.001
<b>Gender</b>				
Male	1.108	1.072	1.146	<0.001
Female	Reference			
<b>Age group (years)</b>				
<20	Reference			
20–49	3.807	3.375	4.293	<0.001
≥50	8.747	7.819	9.784	<0.001

HR, hazard ratio; CI, confidence interval; adjusted HR, adjusted variables listed in Table 1.

**FIGURE 2** | Kaplan–Meier for the cumulative risk of psychiatric disorders stratified by allergic diseases with the log-rank test.

when compared with the control group. With reference to the female subjects, the male subjects were associated with a higher risk of psychiatric disorders. With reference to the younger group (aged < 20 years), older age groups (aged 20–49 years and aged ≥ 50 years) were associated with a higher risk of psychiatric disorders ( $p < 0.001$ ) (Table 2). Figure 2 shows the Kaplan–Meier analysis for the cumulative incidence of psychiatric disorders in the study subjects and the control groups (log-rank test,  $p < 0.001$ ).

Furthermore, each single increased score of CCI was associated with a 2% increased risk of psychiatric disorders, and study subjects who sought medical help in the summer (adjusted HR 0.914,  $p < 0.001$ ), autumn (adjusted HR 0.748,  $p < 0.001$ ), and winter (adjusted HR 0.921,  $p < 0.001$ ) were associated with a lower risk of psychiatric disorders (data not shown). Study subjects who live in urbanization level 3 were associated with a lower risk of psychiatric disorders than those in level 4 (adjusted HR 0.817,  $p < 0.001$ ). Study subjects who sought medical help in

the medical centers (adjusted HR 0.504,  $p < 0.001$ ) and regional hospitals (adjusted HR 0.635,  $p < 0.001$ ) were associated with a lower risk of psychiatric disorders than those in the local hospitals (data not shown).

## Association Between Different Allergic Diseases and Risk of Psychiatric Disorders

**Table 3** reveals that the association between each group of allergic diseases and the individual psychiatric disorders using Fine and Gray's competing risk model. The subjects with atopic dermatitis were associated with a decreased risk of overall and individual psychiatric disorders.

In addition, the patients with allergic diseases who live in the middle (adjusted HR: 1.118,  $p < 0.001$ ), southern (adjusted HR: 1.055,  $p = 0.003$ ), and eastern Taiwan (adjusted HR: 1.596,  $p < 0.001$ ) showed slightly higher risk of psychiatric disorders, with reference of those who live in northern Taiwan. The patients who live in area of urbanization level 3 (adjusted HR: 0.763,  $p < 0.001$ ) showed lower risk of psychiatric disorders, with reference of those who live in the urbanization level 4. The patients who sought for medical help in the hospital centers (adjusted HR: 0.504,  $p < 0.001$ ) and regional hospitals (adjusted HR: 0.635,  $p < 0.001$ ) showed lower risk of psychiatric disorders with the reference of local hospitals (Data not shown).

**Table 4** reveals the adjusted HR of affective disorders (adjusted HR: 1.385,  $p = 0.001$ , in which depression with adjusted HR: 1.412,  $p = 0.001$ , and bipolar disorders with adjusted HR: 1.124,  $p = 0.001$ ), anxiety disorders (adjusted HR: 2.397,  $p = 0.009$ ), psychotic disorders (adjusted HR: 1.192,  $p = 0.003$ ), and dementia (adjusted HR: 1.193,  $p < 0.001$ ) in patients with allergic diseases, when compared to the patients those without allergic diseases.

We divided the subjects with allergic diseases into six groups: bronchial asthma alone, allergic rhinitis alone, atopic dermatitis alone, bronchial asthma + allergic rhinitis, bronchial asthma + atopic dermatitis, allergic rhinitis + atopic dermatitis, and a combination of all these three allergic diseases. In this study, we found that the groups of atopic dermatitis alone and allergic rhinitis + atopic dermatitis were associated with a lower risk of psychiatric disorders, but the other four groups were associated with a higher risk of psychiatric disorders (**Table 5**).

## Risk of Psychiatric Disorders Stratified by Covariates

We analyzed the data by the stratification of the factors such as sex, age, marital status, education levels, urbanization level, geographic areas of residence, seasons of medical visits, monthly insured premiums, and levels of care from medical services providers. We found that the subjects, who were either male or female, married or not married, and in different educational years, urbanization levels, residence areas, seasons of visits, insured premiums, and levels of care, were associated with an increased risk of psychiatric disorders. In the different age groups, subjects aged  $< 20$  years were associated with a lower risk of psychiatric disorder, while subjects in other age groups ( $\geq 20$  years) were associated with a higher risk (**Table 6**).

**TABLE 3** | Factors of psychiatric disorders subgroup stratified by allergic diseases subgroup by using Fine and Gray's competing risk model.

Psychiatric disorders subgroup	Adjusted HR	95% CI	95% CI	<i>p</i>
Overall	1.659	1.602	1.717	<0.001
Dementia	1.193	1.152	1.234	<0.001
Anxiety	2.397	2.315	2.481	0.009
Eating disorders	2.646	2.555	2.739	<0.001
Anorexia nervosa	2.573	2.485	2.663	0.003
Bulimia nervosa	–	–	–	–
Other disorders of eating	3.087	2.981	3.195	0.003
Depression	1.412	1.364	1.461	<0.001
Bipolar disorders	1.124	1.086	1.163	0.001
Sleep disorders	2.302	2.223	2.383	0.007
Psychotic disorders	1.192	1.151	1.234	0.003
Asthma	1.780	1.719	1.842	<0.001
Dementia	1.293	1.249	1.339	0.007
Anxiety	2.579	2.491	2.669	<0.001
Eating disorders	2.943	2.842	3.046	0.010
Anorexia nervosa	2.861	2.763	2.961	0.003
Bulimia nervosa	–	–	–	–
Other disorders of eating	3.434	3.316	3.554	<0.001
Depression	1.482	1.431	1.533	0.004
Bipolar disorders	1.180	1.139	1.221	<0.001
Sleep disorders	2.483	2.398	2.570	<0.001
Psychotic disorders	1.260	1.217	1.304	0.001
Allergic rhinitis	1.156	1.117	1.197	<0.001
Dementia	0.329	0.317	0.340	0.027
Anxiety	1.806	1.744	1.870	0.001
Eating disorders	0.000	–	–	0.989
Anorexia nervosa	0.000	–	–	0.976
Bulimia nervosa	–	–	–	–
Other disorders of eating	0.000	–	–	0.992
Depression	1.818	1.756	1.882	<0.001
Bipolar disorders	1.303	1.258	1.349	<0.001
Sleep disorders	1.342	1.296	1.389	<0.001
Psychotic disorders	1.331	1.285	1.377	<0.001
Allergic dermatitis	0.256	0.247	0.265	0.031
Dementia	0.272	0.263	0.282	0.030
Anxiety	0.190	0.183	0.196	0.025
Eating disorders	0.000	–	–	0.986
Anorexia nervosa	0.000	–	–	0.977
Bulimia nervosa	–	–	–	–
Other disorders of eating	0.000	–	–	0.993
Depression	0.211	0.204	0.219	0.028
Bipolar disorders	0.246	0.238	0.255	0.034
Sleep disorders	0.317	0.306	0.328	0.006
Psychotic disorders	0.162	0.156	0.167	0.005

*P*Ys, person-years; adjusted HR, adjusted hazard ratio; adjusted for the variables listed in **Table 1**; CI, confidence interval.

## HR Analysis of Psychiatric Disorders in Patients With Different Medications for the Treatment of Asthma

The different medications of treatment durations more than 30 days for the treatment of bronchial asthma were grouped into four classes by the number of subjects who had used these medications: oral prednisolone, inhaled steroids, beta-agonist, aminophylline, leukotriene receptor antagonists, and anti-IgE

**TABLE 4** | Hazard ratio (HR) of affective, anxiety, psychotic disorders, and dementia in patients with vs. without allergic diseases.

Allergic diseases (with vs. without)	Competing risk in the model			
	Adjusted HR	95% confidence interval (CI)	95% CI	p
<b>Psychiatric disorders subgroup</b>				
Affective disorders	1.385	1.337	1.434	0.001
Depression	1.412	1.364	1.461	<0.001
Bipolar disorders	1.124	1.086	1.163	0.001
Anxiety disorders	2.397	2.315	2.481	0.009
Psychotic disorders	1.192	1.151	1.234	0.003
Dementia	1.193	1.152	1.234	<0.001

**TABLE 5** | Factors of psychiatric disorders by using Cox regression and Fine and Gray's competing risk model.

Allergic diseases	Competing risk in the model			
	Reference	95% CI	95% CI	p
Without	Reference			
Asthma	1.780	1.719	1.842	<0.001
Allergic rhinitis	1.156	1.117	1.197	<0.001
Atopic dermatitis	0.256	0.247	0.265	0.031
Asthma + allergic rhinitis	1.770	1.713	1.896	<0.001
Asthma + atopic dermatitis	1.723	1.673	1.852	<0.001
Allergic rhinitis + atopic dermatitis	0.554	0.213	0.966	0.018
Asthma + allergic rhinitis + atopic dermatitis	3.702	1.613	24.978	0.027

antibody (omalizumab). Oral prednisolone usage was associated with a lower risk of developing psychiatric disorders in bronchial asthma patients. Besides, usage of beta-agonist, aminophylline, and leukotriene receptor antagonists was also associated with a lower risk of developing psychiatric disorders while adjusted with all the covariates and comorbidities, either with or without prednisolone usage (Table 7).

## DISCUSSION

In this study, we examined the association between the overall allergic diseases and the risk of psychiatric disorders. After adjusting the covariates, the adjusted HR was 1.659 for the subjects (95% CI = 1.602–1.717,  $p < 0.001$ ) when compared with the control group. In other words, the adult patients with allergic diseases had a 1.66-fold increased risk of developing psychiatric disorders. The Kaplan–Meier analysis revealed that the study subjects had a significantly higher 15-year psychiatric disorders-free survival rate than the controls.

Bronchial asthma and allergic rhinitis were associated with the risk of overall psychiatric disorders, but atopic dermatitis was associated with a lower risk of psychiatric disorders. Bronchial asthma was associated with the risk of individual psychiatric disorders, such as dementia, anxiety disorders, depressive disorders, eating disorders, bipolar disorders, sleep disorders, and psychotic disorders, but allergic rhinitis was associated with a lower risk of dementia and an increased risk of other psychiatric

**TABLE 6** | Factors of psychiatric disorders stratified by variables listed in the table by using Fine and Gray's competing risk model.

Allergic diseases (with vs. without)	Competing risk in the model			
	Adjusted HR	95% CI	95% CI	p
<b>Stratified</b>				
<b>Total</b>	1.659	1.602	1.717	<0.001
<b>Gender</b>				
Male	1.705	1.646	1.765	<0.001
Female	1.604	1.549	1.660	<0.001
<b>Age group (years)</b>				
<20	0.832	0.804	0.861	0.027
20–49	2.752	2.658	2.849	0.007
≥50	1.651	1.595	1.709	0.001
<b>Married</b>				
Without	1.631	1.575	1.688	0.004
With	1.660	1.603	1.718	0.001
<b>Education (years)</b>				
<12	3.140	3.032	3.250	<0.001
≥12	1.266	1.222	1.310	0.011
<b>Insured premium (New Taiwan Dollars)</b>				
<18,000	1.651	1.595	1.709	0.007
18,000–34,999	2.543	2.455	2.632	<0.001
≥35,000	1.457	1.407	1.508	0.015
<b>Season</b>				
Spring	1.599	1.545	1.655	<0.001
Summer	1.677	1.620	1.736	<0.001
Autumn	1.645	1.589	1.703	0.002
Winter	1.708	1.649	1.768	<0.001
<b>Urbanization level</b>				
1 (the highest)	1.326	1.280	1.372	<0.001
2	1.634	1.578	1.691	<0.001
3	1.757	1.697	1.818	0.001
4 (the lowest)	1.883	1.818	1.949	<0.001
<b>Level of care</b>				
Hospital center	1.402	1.354	1.451	<0.001
Regional hospital	1.315	1.270	1.361	0.017
Local hospital	2.023	1.954	2.094	<0.001

PYS, person-years; adjusted HR, adjusted hazard ratio; adjusted for the variables listed in Table 1; CI, confidence interval.

disorders. However, the increasing number of allergic diseases was associated with an increased risk of psychiatric disorders. In comparison to the previous studies for individual allergic diseases in several psychiatric disorders, such as anxiety disorders, depressive disorders, bipolar disorders, schizophrenia, and ADHD (4, 6–8, 10–15, 43), this is the first study on the topic of the association of allergic diseases and the broader spectrum of psychiatric disorders. Atopic dermatitis seems to be an exception in these allergic diseases, by being associated with a lower risk of psychiatric disorders, even though previous reports found that atopic dermatitis are associated with ADHD and autism spectrum disorders (52–55). Further study is needed to clarify the association between atopic dermatitis and the risk of psychiatric disorders.

The results of this study showed the association between overall allergic diseases and the risk of psychiatric disorders, which echoed the findings of other studies on the association between the overall allergic or atopic diseases and the risk of psychiatric

**TABLE 7** | HRs of patients with psychiatric disorders by medication use compared with patients with oral prednisolone use.

Medications use	Psychiatric disorders n(%)	Crude HR (95% CI)	Adjusted HR (95% CI)	Without prednisolone Adjusted HR (95% CI)	With prednisolone Adjusted HR (95% CI)
<b>Prednisolone</b>					
Yes (n = 20,202)	2,011 (9.95)	0.706 (0.465–0.801)**	0.713 (0.472–0.813)**	N/A	N/A
No (n = 20,203)	2,849 (14.10)	Reference	Reference		
<b>Inhaled steroids</b>					
Yes (n = 8,612)	988 (11.47)	0.942 (0.802–1.051)	0.970 (0.834–1.167)	0.982 (0.857–1.266)	0.912 (0.818–1.109)
No (n = 31,793)	3,872 (12.18)	Reference	Reference	Reference	Reference
<b>Beta-agonist</b>					
Yes (n = 21,720)	2,041 (9.40)	0.623 (0.511–0.729)***	0.684 (0.522–0.800)**	0.697 (0.529–0.824)*	0.662 (0.513–0.789)**
No (n = 18,685)	2,819 (15.09)	Reference	Reference	Reference	Reference
<b>Aminophylline</b>					
Yes (n = 21,898)	2,020 (9.22)	0.601 (0.499–0.714)***	0.654 (0.513–0.824)**	0.632 (0.492–0.810)**	0.678 (0.527–0.883)*
No (n = 18,507)	2,840 (15.35)	Reference	Reference	Reference	Reference
<b>Leukotriene receptor antagonists</b>					
Yes (n = 3,345)	291 (8.70)	0.706 (0.459–0.816)**	0.710 (0.469–0.826)**	0.709 (0.468–0.825)**	0.712 (0.472–0.829)**
No (n = 37,060)	4,569 (12.33)	Reference	Reference	Reference	Reference
<b>Anti-IgE antibody</b>					
Yes (n = 27)	1 (3.70)	0.308 (0.007–0.995)*	0.420 (0.010–1.097)	0.683 (0.145–2.894)	No patients
No (n = 40,378)	4,859 (12.03)	Reference	Reference	Reference	Reference

Adjusted HR, adjusted hazard ratio; adjusted for the variables listed in Table 1; CI, confidence interval.

\* $p < 0.05$ .

\*\* $p < 0.01$ .

\*\*\* $p < 0.001$ .

disorders: for example, children with eczema, asthma, or hay fever had more emotional, conduct, and hyperactivity problems in a cross-sectional study in Denmark (56), and atopic diseases might be associated with an elevated risk of developing depression in a birth cohort study in Finland (57). Several studies have reported the associations between bronchial asthma or other atopic diseases and psychiatric disorders, such as affective disorders, anxiety disorders, schizophrenia, substance-related disorders, autism-spectrum disorders, or ADHDs (9, 58–62). Some researchers have also reported the associations between atopic dermatitis and attention-deficit/hyperactivity disorder, or speech disorders in childhood (63), and the association between allergic rhinitis and the risk of suicides and depression (64). Furthermore, parental exposure to occupational asthmagens might also be associated with children autism-spectrum disorders (65). Previous studies have also reported the associations between other immune or inflammation-related diseases, such as periodontitis (66), gluten-related illnesses (67), amyotrophic lateral sclerosis (68), psoriasis (69), food or other allergies (70), and idiopathic environmental intolerance (71) and the risk of psychiatric disorders. Conversely, psychiatric disorders might also affect the immune systems (72). In this study, the overall allergic diseases were associated with affective disorders, anxiety disorders, psychotic disorders, and dementia, respectively. The interplay between allergic diseases and psychiatric disorders, therefore, warrant further study.

The underlying mechanism of the association between allergic diseases and psychiatric disorders remains unclear. The “orchestration” of the pro-inflammatory cytokines plays an important role in the pathogenesis of allergy-related diseases, such as asthma (73). Reports have shown that cytokines such as interleukin (IL)-6, tumor necrosis factor-alpha (TNF- $\alpha$ ), IL-10, and monocyte

chemoattractant protein-1/CCL2 might be well associated with depressive, bipolar, or anxiety disorders (74, 75). Reports also show that dementia is related to peripheral pro-inflammatory factors released by periodontal inflammatory mediators such as C-reactive protein, IL-6, haptoglobin, TNF- $\alpha$ , and fibrinogen (76–78). Furthermore, some studies have also found that inflammation play an important role in eating disorders (79, 80) and sleep disorders (81–83).

Additionally, we have included several psychosocial factors in the analysis, such as marital status, educational level, monthly insured premiums, urbanization level, and residence. In comparison to the allergy-disease subjects who sought medical help in the local hospitals, study subjects who received medical help from medical centers or regional hospitals were associated with a lower risk of psychiatric disorders. These findings suggest that disadvantageous socioeconomic factors might well contribute to the risk of psychiatric disorders.

We found that the study subjects of those aged < 20 years had a lower risk in developing psychiatric disorders. We therefore hypothesize that the reason for a lower risk is that the maximal follow-up time is 15 years, which might not have, as yet, reached the age of onset of the most major psychiatric disorders for the patients of allergic diseases (84). Further study is needed to clarify the association between age and the risk of psychiatric disorders in the patients with allergic diseases.

Furthermore, we found that oral prednisolone usage was associated with a lower risk of developing psychiatric disorders in bronchial asthma patients. Moreover, the usage of beta-agonist, aminophylline, and leukotriene receptor antagonists was also associated with a lower risk of developing psychiatric disorders, with or without prednisolone usage. The mechanisms and effects

of these medications on the risk of psychiatric disorders in bronchial asthma patients merit further study.

## Limitations

The present study has several limitations that warrant consideration. First, similar to previous studies using the NHIRD on allergic diseases as aforementioned, not all the data were recorded in the NHIRD, and we were unable to evaluate the severity, weakness severity, laboratory parameters, or lung function examinations in asthma patients. Second, other factors, such as genetic, psychosocial, and environmental factors, were not included in the dataset. Third, for patients who have to pay for their own for over-the-counter drugs for the allergic diseases, their self-medications would not have been included in the NHIRD. There is no study about the rates of self-medications for these allergic diseases. However, due to the high coverage of medical providers (97%) and beneficiaries (more than 99%) of the NHI system in Taiwan, most of the people would ask for help from the NHI-contracted hospital or clinics for their allergic diseases.

## Strength of This Study

One of the primary strengths of this study is the use of ICD-9 codes, and a number of studies have demonstrated the accuracy and validity of several diagnoses in the NHIRD, including DM (85, 86), cancer (87–89), myocardial infarction (85, 90, 91), and central nervous system diseases, such as Tourette syndrome (92), and stroke (85, 93–95), outcomes (89), mortality (85, 96), or comorbidity (89, 96). In a wide spectrum of conditions, some studies have also demonstrated the concordance between Taiwan's National Health Survey and the NHIRD on various diagnoses (97), medication usage (97), and health system utilizations (97, 98). Correspondingly, the long-term observation period from 2000 to 2015 allowed for more credibility, when compared with other similar studies, to propose physical mechanisms and plausible hypotheses. Finally, and most importantly, we have tried to explain the mutual biological and psychological mechanism between the allergic diseases and the psychiatric disorders.

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## CONCLUSION

We have evaluated the risk of psychiatric disorders in association with the allergic diseases such as asthma, allergic rhinitis, and atopic dermatitis in Taiwan's population, using the representative population-based data. We have demonstrated that the patients with allergic diseases were at a significantly higher risk of psychiatric disorders than the control group. Further studies are therefore needed for patients with allergic diseases not only to prevent its clinical exacerbation but also to decrease the possibility of developing psychiatric disorders. We sincerely hope that this study will provide the necessary information for an earlier intervention for patients with allergic diseases.

## ETHICS STATEMENT

The Institutional Review Board of the Tri-Service General Hospital approved this study and waived the need for individual written informed consent (IRB No. 2-105-05-040 and IRB No. 2-105-05-082).

## AUTHOR CONTRIBUTIONS

N-ST, H-AC, and W-CC conceived, planned, and conducted this study. C-HC and W-SC contributed to the data analysis and interpretation. Y-CK, C-CC, H-WY, Y-CC, and S-Y contributed to this data interpretation. N-ST wrote the draft. All the authors approved this manuscript.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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