

The Association Between Asthma and Narcolepsy: A Nationwide Case-Control Study in Taiwan

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Purpose: Asthma, which is caused by inflammation of the airways, affects the sensitivity of nerve endings. Narcolepsy is a chronic sleep disorder that may be caused by autoimmunity. Recent studies have reported a positive association between narcolepsy and asthma. We aimed to examine the association between asthma and narcolepsy and determine the effects of therapeutic corticosteroid or bronchodilator use.

Materials and Methods: We conducted a nationwide population-based, nested case-control study using Taiwan's National Health Insurance Research Database (NHIRD) between 2000 and 2013. Subjects with narcolepsy (ICD-9-CM code 347) were enrolled, with 1:3 estimated propensity score-matched controls based on sex, age, and index year. The association between narcolepsy and asthma was assessed using multiple logistic regression analyses. The covariates included sex, age, monthly insurance premiums, geographical area of residence, urbanization level of residence, level of care, and presence of diseases related to immune response and central nervous system. The effects of corticosteroid and bronchodilator use were also analyzed.

Results: Overall, 2008 subjects were identified from the NHIRD (502 patients with narcolepsy and 1506 controls). The participants with narcolepsy had almost three times the level of previous asthma diagnosis than controls. Compared to those without asthma, patients with asthma had an adjusted odds ratio (OR) of 3.181 for narcolepsy comorbidity (95% confidence interval [CI]: 2.048–4.941, $p < 0.001$). The use of inhaled corticosteroids was associated with a lower risk of narcolepsy comorbidity, with an adjusted OR of 0.465 (95% CI, 0.250–0.634; $p < 0.001$), in patients with asthma when compared to those without treatment.

Conclusion: This study demonstrated a significantly higher level of previous asthma diagnosis in patients with narcolepsy. The use of inhaled corticosteroids was associated with a lower risk of narcolepsy comorbidity in asthma patients, compared to those without treatment.

Keywords: asthma, narcolepsy, corticosteroid, bronchodilators

Introduction

Narcolepsy is a neurological disorder that affects the brain's ability to control sleep and wakefulness. There are two main types of narcolepsy: type 1 and type 2.¹⁻³ All types of narcolepsy may cause excessive daytime sleepiness, sleep paralysis, hypnagogic/hypnopompic hallucination, early rapid eye movement (REM) sleep, and fragmented sleep. The difference between type 1 and type 2 narcolepsy is that the former may cause sudden loss of muscle tone (cataplexy).¹⁻³ Multiple factors may be related to the pathophysiology of narcolepsy. Besides impaired function due to excessive daytime sleepiness, the high incidence of comorbidities, including mood disorders and other sleep disorders, affects daily function⁴⁻⁷ and may

contribute to incidents such as motor vehicle accidents.^{6,8,9} A previous review reported a delayed diagnosis of narcolepsy by up to 15 years.¹⁰ Although variables associated with delayed narcolepsy diagnosis have been identified, a lack of symptom recognition and the abovementioned comorbidities can result in misdiagnosis prior to the final narcolepsy diagnosis.^{10–13}

Asthma is a chronic inflammatory lung disease with exacerbation, which may contribute to morbidity and mortality.^{14–16} Several recent studies have reported a positive association between narcolepsy and asthma. Early REM sleep and fragmented sleep in narcolepsy can cause irregular respiratory responses and result in breathing disorders, such as asthma.¹⁷ Asthma and narcolepsy are considered to share common immunopathological mechanisms.^{18,19} One study reported that the prevalence of comorbid immunopathological diseases is high in patients with narcolepsy and that cataplexy is significantly more severe in patients with comorbid immunopathological disease and narcolepsy.²⁰ Another study conducted by Aydinoz et al reported contrasting results in childhood narcolepsy; they found that the frequency of allergic conditions, particularly asthma and allergic rhinitis, was markedly lower in type 1 narcolepsy than in type 2 narcolepsy.²¹ Alomar et al, in a study from Saudi Arabia, enrolled 80 consecutive patients with narcolepsy and found that allergic disorders were associated with both type 1 and type 2 narcolepsy.²² Since most of the results reported to date are controversial and no nationwide population-based study has clarified the association between asthma and narcolepsy, the present study aimed to investigate the association between asthma and narcolepsy in Taiwan using the National Health Insurance Research Database (NHIRD), a nationwide population-based claims database.

Materials and Methods

Data Source

The National Health Insurance (NHI) Program was launched in Taiwan in 1995. As of June 2009, the program had established contracts with 97% of medical providers with approximately 23 million beneficiaries, accounting for more than 99% of the entire population. Details of the program have been provided in previous reports.^{6,7,23–28} The NHIRD contains all the claims data of the beneficiaries, and it uses the International Classification of Diseases, 9th Revision, Clinical

Modification (ICD-9-CM) codes to record the diagnoses. The accuracy of diagnoses recorded in the NHIRD, such as pneumonia,²⁵ asthma,²⁹ sleep apnea,³⁰ and tuberculosis,³¹ has been validated.

A subset of the NHIRD, the Longitudinal Health Insurance Database (LHID), which consists of the data of 1 million randomized population samples accrued between 2000 and 2013, was used to study the association between asthma and the risk of narcolepsy. The Institutional Review Board of the Tri-Service General Hospital approved this study and waived the requirement for written informed consent (IRB No. 2-107-05-026).

Study Design and Sampled Participants

To undertake this population-based, retrospective case-control study, we included subjects aged ≥ 6 years diagnosed with narcolepsy, based on the ICD-9-CM code (347), by board-certified sleep medicine specialists, including neurologists, psychiatrists, pulmonologists, and otorhinolaryngologists, between January 1, 2000, and December 31, 2013. The exclusion criteria were as follows: (1) age of <6 years on the study entry date and (2) unknown sex. The patients with narcolepsy and the control subjects were selected using a 1:3 estimated propensity score-matching based on sex, age, and index year.

Major Outcome Measure

The study aimed to evaluate the association between asthma and narcolepsy. Previous asthma diagnosis was investigated in both the narcolepsy and control groups. Each enrolled subject with asthma was required to have had at least six outpatient clinic visits or one hospitalization during the study period with a diagnosis code of 493. This method used in this study to choose the subjects with asthma was validated in a previous study with 92% sensitivity.²⁹ Figure 1 shows a detailed flowchart of the subject selection process.

Potential Confounders

The covariates included sex, age group (6–11, 12–19, 20–44, 45–64, and ≥ 65 years), monthly insurance premium (in New Taiwan Dollars [NT\$]; $<18,000$, 18,000–34,999, and $\geq 35,000$), geographical area of residence (northern, central, southern, eastern Taiwan, and the outer islands), urbanization level of residence (levels 1–4), and level of care (medical center, regional, and local hospital). The urbanization level of residence was defined based on the population and various indicators of the level of

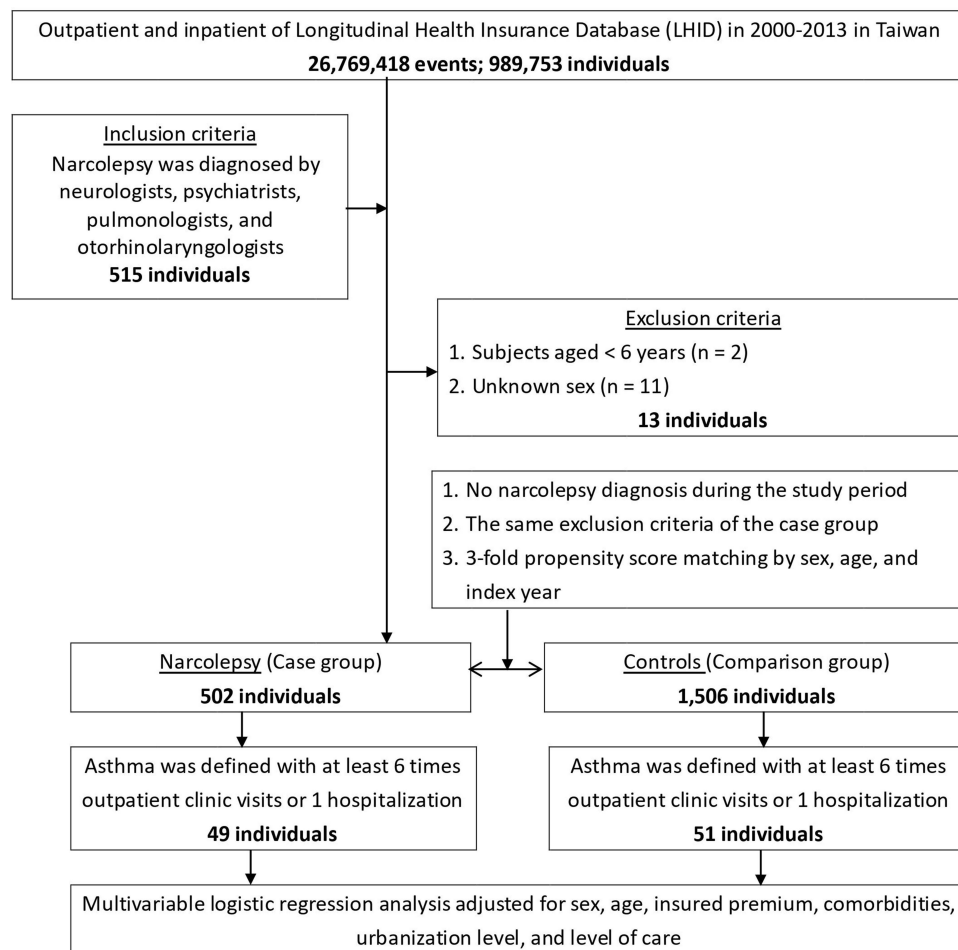


Figure 1 Flowchart outlining the sample selection procedure from Taiwan's National Health Insurance Research Database.

development. Level 1 was characterized by a population of >1,250,000 individuals in a region with political, economic, cultural, and metropolitan development. Level 2 was characterized by a population of 500,000–1,249,999 individuals, with the area playing an important role in politics, economy, and culture. Urbanization levels 3 and 4 were characterized by populations of 149,999–499,999 and <149,999 individuals, respectively.³²

Several confounders may be associated with asthma and narcolepsy. We selected several diseases related to immune response, such as atopic dermatitis, allergic rhinitis, influenza, and autoimmune diseases, as confounding factors because of the possible immune impacts on both asthma and narcolepsy. Diseases related to the central nervous system (CNS), such as psychiatric disorders, CNS infection, cerebral palsy, obstructive sleep apnea (OSA), and insomnia, were also selected as confounders due to their possible impacts on sleep and breathing. These factors were assessed in the year preceding the study

entry year. The concomitant use of medications for obstructive lung diseases, such as inhaled/oral/injected corticosteroids and bronchodilators, was also evaluated.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows (version 22.0; IBM Corp., Armonk, NY, USA). The distributions of age, sex, and comorbidities in the patients with narcolepsy and the controls were evaluated using the Chi-square test. Multivariate logistic regression analyses were used to calculate the odds ratios (ORs) with 95% confidence intervals (CIs; 95% CI) to assess the association between asthma and narcolepsy, after adjusting for the potential confounding effects of comorbidities. Our logistic regression analyses used narcolepsy diagnosis as the dependent variable and other clinical predictors or potential confounders as the independent variables. Subgroup analyses for evaluating the association between asthma diagnosis and the risk of narcolepsy were

conducted after stratification based on sex, age, and comorbidities. Logistic regression analysis was used to assess the association between medications used for obstructive lung diseases in asthma patients and narcolepsy comorbidity. Statistical significance was set at $p < 0.05$.

Results

In this study, 2008 subjects were enrolled (502 subjects with narcolepsy and 1506 subjects without narcolepsy). Table 1 shows the sex, age, monthly insurance premiums, comorbidities, area of residence, urbanization level, level of care, and medication use for obstructive lung diseases in narcolepsy patients and controls. Compared with the controls, a higher proportion of narcoleptic patients tended to have asthma, psychiatric disorders, CNS infection, OSA, and insomnia, but a lower proportion of the patients had influenza; they also had a higher likelihood of living in urbanization levels 1 or 2 and in the northern region and outer islands of Taiwan. In addition, narcoleptic patients tended to have a higher likelihood of inhaled/oral/injected corticosteroid use.

Table 2 shows the outcomes of multivariate logistic regression analysis of the factors associated with the risk of narcolepsy comorbidity. Compared with patients without asthma, those with asthma had a crude OR of 3.086 (95% CI, 2.056–4.631; $p < 0.001$) for narcolepsy comorbidity. After adjusting for sex, age, monthly income, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, psychiatric disorders, CNS infection, cerebral palsy, OSA, insomnia, influenza, autoimmune diseases, geographical area of residence, urbanization level of the residence, and level of care, the adjusted OR was 3.181 (95% CI, 2.048–4.941; $p < 0.001$).

Table 3 shows the effects of medication use on the association between asthma and narcolepsy comorbidity. Compared with the patients in the asthma group who did not use medication, those who used only inhaled corticosteroids had an adjusted OR of 0.465 (95% CI, 0.250–0.634; $p < 0.001$) for narcolepsy comorbidity; no significant difference was observed for the bronchodilator-only group among the patients with asthma.

Discussion

Asthma, Narcolepsy, and Corticosteroid Use

This study reports several noteworthy findings. First, previous asthma diagnosis in patients with narcolepsy was

almost three times higher than that in the controls. In contrast to previous studies on the relationship between asthma and narcolepsy,^{17,20–22} we used a nationwide claims database and a larger sample. Second, compared to those without asthma, patients with asthma had an adjusted OR of approximately 3.181 for narcolepsy comorbidity. Third, we investigated the effects of corticosteroid and bronchodilator use and found that the use of inhaled corticosteroids, as opposed to bronchodilators, was associated with a lower risk of narcolepsy comorbidity in patients with asthma. To the best of our knowledge, this is the first study to examine the association between asthma and narcolepsy and the effects of medication use for obstructive lung diseases in asthma using a nationwide population-based database.

Compared with previous studies on the association between asthma and narcolepsy, this study has several key points. First, it was a retrospective case-control study that used a large nationwide database, when compared with other retrospective chart reviews that used small sample sizes.^{20,21} Second, we exclusively examined the association between asthma and narcolepsy instead of analyzing the relationship between several sleep disorders and allergic diseases.^{17,20,21} Third, we examined the effects of inhaled corticosteroids on the risk of narcolepsy comorbidity in patients with asthma; the results showed an almost 50% decrease of narcolepsy comorbidity compared with those without medication use.

Previous studies have reported that corticosteroid treatment for patients with asthma may decrease the risk of asthma-related death,³³ lung cancer,³⁴ and chronic kidney disease (CKD).²³ However, some studies have found that the effects of corticosteroids vary with other diseases such as cancer, schizophrenia, and dry eye syndrome.^{35–37} A larger clinical trial for asthma patients using corticosteroids or other medications is therefore needed to confirm this association.

Potential Mechanisms of the Association Between Asthma and Narcolepsy

The “orchestration” of pro-inflammatory cytokines plays an important role in the pathogenesis of allergy-related diseases such as asthma.³⁸ T-helper lymphocytes, key factors in the pathogenesis of asthma, can induce B cells to synthesize and secrete immunoglobulin E through the production of interleukin-4. Histamine, prostaglandins, leukotrienes, and kinins also contribute to the pathogenesis of

Table I Characteristics of Study at the Baseline

Variables	Total		Narcolepsy		Controls		P
	n	%	n	%	n	%	
Total	2008		502	25.00	1506	75.00	
Previous Asthma Diagnosis	100	4.98	49	9.76	51	3.39	<0.001
Sex							0.999
Male	1200	59.76	300	59.76	900	59.76	
Female	808	40.24	202	40.24	606	40.24	
Age (years)	43.53±24.29		42.46±24.57		43.88±24.20		0.255
Age group (years)							0.999
6–11	112	5.58	28	5.58	84	5.58	
12–19	420	20.92	105	20.92	315	20.92	
20–44	608	5.58	152	5.58	456	5.58	
45–64	352	5.58	88	5.58	264	5.58	
≥65	516	25.70	129	25.70	387	25.70	
Insurance premium (NT\$)							0.993
<18,000	1598	79.58	400	79.68	1198	79.55	
18,000–34,999	247	12.30	61	12.15	186	12.35	
≥35,000	163	8.12	41	8.17	122	8.10	
Atopic dermatitis	2	0.10	0	0.00	2	0.13	0.414
Allergic rhinitis	6	0.30	0	0.00	6	0.40	0.347
Psychiatric disorders	186	9.26	87	17.33	99	6.57	<0.001
CNS infection	11	0.55	6	1.20	5	0.33	0.034
Cerebral palsy	15	0.7	7	1.39	8	0.53	0.069
OSA	25	1.25	21	4.18	4	0.27	<0.001
Insomnia	37	1.84	28	5.58	9	0.60	<0.001
Influenza	23	1.15	1	0.20	22	1.46	0.026
Autoimmune diseases	14	0.70	4	0.80	10	0.66	0.759
Location							<0.001
Northern Taiwan	863	42.98	296	58.96	567	37.65	
Middle Taiwan	559	27.84	88	17.53	471	31.27	
Southern Taiwan	458	22.81	79	15.74	379	25.17	
Eastern Taiwan	108	5.38	28	5.58	80	5.31	
Out islands	20	1.00	11	2.19	9	0.60	
Urbanization level							<0.001
1 (The highest)	640	31.87	188	37.45	452	30.01	
2	925	46.07	254	50.60	671	44.56	
3	159	7.92	20	3.98	139	9.23	
4 (The lowest)	284	14.14	40	7.97	244	16.20	
Level of care							<0.001
Hospital center	755	37.60	249	49.60	506	33.60	
Regional hospital	898	44.72	197	39.24	701	46.55	
Local hospital	355	17.68	56	11.16	299	19.85	

(Continued)

Table 1 (Continued).

Variables	Total		Narcolepsy		Controls		P
	n	%	n	%	n	%	
Medication for obstructive lung diseases							<0.001
No use	1066	53.0	240	47.81	826	54.85	
Inhaled CS only	250	12.45	71	14.14	179	11.89	
Bronchodilator only	201	10.01	50	9.96	151	10.03	
Inhaled CS & bronchodilator	170	8.47	42	8.37	128	8.50	
Oral or injected CS	321	15.99	99	19.72	222	14.4	

Note: P: Chi-square/Fisher exact test on category variables and t-test on continuous variables.

Abbreviations: CNS, central nervous system; OSA, obstructive sleep apnea; CS, corticosteroid.

asthma.³⁹ Several previous reports demonstrated the global activation of T-cells, including CD4+ T cells and regulatory T cells, in type 1 narcolepsy patients.⁴⁰ Recent data regarding Pandemrix-vaccination-associated type 1 narcolepsy have shown that the vaccinated patients had enhanced T-cell immunity to orexins possibly triggered by viral antigens.^{41,42} These findings provide evidence for the T-cell-mediated autoimmune origin of type 1 narcolepsy. In type 2 narcolepsy, the role of the immune system is unclear. However, some studies have reported that autoimmune diseases are associated with type 2 narcolepsy.^{22,43} Further research is warranted to investigate the association between narcolepsy and autoimmune response.

Another study has shown that narcolepsy with hypocretin deficiency is associated with human leukocyte antigen (HLA) and T-cell receptor (TCR) polymorphisms, suggesting that an autoimmune process targets a peptide unique to hypocretin-producing neurons via specific HLA-peptide-TCR interactions.⁴⁴ In the present study, corticosteroid use was associated with a lower risk of narcolepsy comorbidity in patients with asthma. Since corticosteroids can suppress the autoimmune process, we hypothesize that corticosteroids may decrease the risk of narcolepsy comorbidity by the mechanism of inhibition of autoimmune processes as a collateral effect.

In the present study, higher urbanization level of residence and level of care were associated with the risk of narcolepsy comorbidity. One possible reason is that air pollutants, such as ozone, sulfur dioxide, nitrogen dioxide, and particulates, which are prevalent in the higher urbanization areas, can contribute to the onset or exacerbation of symptoms and decreased pulmonary function in patients by inducing T cell-mediated inflammation;^{45,46} This T-cell induction, consequently,

may be involved in the pathogenesis of narcolepsy. This finding also suggests that socioeconomic status may play a role in the association between asthma and narcolepsy.

Strengths of This Study

This study has several strengths. First, since narcolepsy is a rare disorder, a nationwide population-based study is important for obtaining information. Second, although the diagnosis of narcolepsy in the NHIRD has not been previously validated, the diagnoses of several respiratory diseases, such as asthma,²⁹ sleep apnea,³⁰ pneumonia,³⁰ and tuberculosis,³¹ have been validated. Third, since the NHIRD contains the records of medications for asthma, we analyzed the effects of corticosteroids and bronchodilators and inferred that the appropriate use of inhaled corticosteroids for asthma patients may lower the subsequent risk of narcolepsy comorbidity.

Limitations of This Study

This study had some limitations. First, the diagnoses of asthma and narcolepsy were determined based on the ICD-9-CM codes instead of validated structural diagnostic instruments. Moreover, we could not identify the types of narcolepsy in our study. However, the diagnosis of asthma was previously validated,²⁹ and we used strict criteria to identify cases of narcolepsy in our database. The distinction between type 1 (with cataplexy) and type 2 narcolepsy (without cataplexy) could not be identified using the ICD-9-CM codes. In addition, idiopathic hypersomnia, severe sleep apnea, sleep deprivation, and circadian rhythm disorders may be recorded as narcolepsy, whereas disturbed night sleep in patients with narcolepsy may have been recorded as insomnia. Nonetheless, the National Health Insurance Administration in Taiwan has strived to

Table 2 Multiple Logistic Regression Analysis of Factors Contributing to Narcolepsy Comorbidity

Variables	Crude OR	95% CI	95% CI	P	Adjusted OR	95% CI	95% CI	P
Asthma	3.086	2.056	4.631	<0.001	3.181	2.048	4.941	<0.001
Sex								
Male	1.000	0.814	1.229	0.905	0.998	0.800	1.244	0.983
Female	Reference				Reference			
Age group (years)								
6–11	Reference				Reference			
12–19	1.216	0.415	3.057	0.815	0.925	0.547	1.565	0.772
20–44	0.578	0.208	1.612	0.295	0.848	0.510	1.412	0.527
45–64	1.019	0.365	2.847	0.971	0.911	0.534	1.552	0.730
≥65	1.896	0.773	4.906	0.187	0.968	0.579	1.619	0.901
Insurance premium (NT\$)								
<18,000	Reference				Reference			
18,000–34,999	0.000	–	–	0.991	0.000	–	–	0.997
≥35,000	0.000	–	–	0.991	0.000	–	–	0.997
Atopic dermatitis	0.000	–	–	0.997	0.000	–	–	0.999
Allergic rhinitis	0.000	–	–	0.997	0.000	–	–	0.999
Psychiatric disorders	2.979	2.189	4.055	<0.001	3.272	2.338	4.581	<0.001
CNS infection	3.361	1.103	11.951	0.034	2.296	0.603	8.742	0.223
Cerebral palsy	2.648	0.955	7.339	0.061	3.001	0.988	9.120	0.053
OSA	16.394	5.600	47.994	<0.001	14.245	4.110	49.368	<0.001
Insomnia	9.826	4.604	20.970	<0.001	9.635	4.272	21.728	<0.001
Influenza	0.135	0.018	1.001	0.051	0.228	0.030	1.746	0.155
Autoimmune diseases	1.202	0.375	3.848	0.757	1.097	0.326	3.698	0.881
Urbanization level								
1 (The highest)	2.537	1.744	3.692	<0.001	2.125	1.374	3.285	0.001
2	2.309	1.604	3.324	<0.001	2.214	1.474	3.320	<0.001
3	0.878	0.494	1.561	0.657	0.904	0.495	1.651	0.743
4 (The lowest)	Reference				Reference			
Level of care								
Hospital center	2.627	1.902	2.630	<0.001	1.749	1.206	2.537	0.003
Regional hospital	1.500	1.083	2.079	0.015	1.252	0.884	1.773	0.207
Local hospital	Reference				Reference			
Medication for obstructive lung diseases								
No use	Reference				Reference			
Inhaled CS only	0.498	0.241	0.865	<0.001	0.337	0.198	0.785	<0.001
Bronchodilator only	0.972	0.753	1.184	0.186	0.803	0.660	1.026	0.083
Inhaled CS & bronchodilator	–	–	–	–	–	–	–	–
Oral or injected CS	–	–	–	–	–	–	–	–

Note: Location not included given collinearity with urbanization level.

Abbreviations: OR, odds ratio; CI, confidence interval; Adjusted OR, Adjusted OR: Adjusted variables as sex, age, insured premium, atopic dermatitis, allergic rhinitis, psychiatric disorders, CNS infection, cerebral palsy, OSA, insomnia, influenza, autoimmune diseases, urbanization level, level of care.

Table 3 Association Between Medication for Obstructive Lung Diseases in Asthma Patients and Narcolepsy Comorbidity

Medication for Obstructive Lung Diseases	Crude OR	95% CI	95% CI	P	Adjusted OR	95% CI	95% CI	P
No use	Reference				Reference			
Inhaled corticosteroid only	0.442	0.231	0.598	<0.001	0.465	0.250	0.634	<0.001
Bronchodilator only	0.857	0.669	0.997	0.048	0.870	0.683	1.076	0.075
Inhaled corticosteroid and bronchodilator	–	–	–	–	–	–	–	–
Oral or injected corticosteroid	–	–	–	–	–	–	–	–

Note: Location not included given collinearity with urbanization level.

Abbreviations: OR, odds ratio; CI, confidence interval; Adjusted OR, Adjusted variables as sex, age, asthma, insured premium, atopic dermatitis, allergic rhinitis, psychiatric disorders, CNS infection, cerebral palsy, OSA, insomnia, influenza, autoimmune diseases, urbanization level, level of care, medication for obstructive lung diseases; CNS, central nervous system; OSA, obstructive sleep apnea; CS, corticosteroid.

determine the accuracy of diagnoses in the database. Furthermore, we enrolled only narcoleptic patients diagnosed by board-certified sleep medicine specialists. Second, the authors could not measure some factors that may have influenced the results. For instance, coffee consumption and cigarette smoking, which were not assessed in the database, are associated with daytime sleepiness and airway stimulation. Third, the average age at narcolepsy diagnosis was higher in this study than in studies from other countries, and the delayed diagnosis of narcolepsy in Taiwan should be considered. Poor patient insights and low clinician awareness of this disorder may explain this finding. Further verification is required to generalize our findings.

Conclusion

This study demonstrated a significantly higher proportion of previous asthma diagnosis in patients with narcolepsy. Compared with not using medication, the use of inhaled corticosteroids was associated with a lower risk of narcolepsy comorbidity in patients with asthma, and no significant difference was observed for the use of bronchodilators. Clinicians should be aware of the possibility of narcolepsy following the diagnosis of asthma. Further studies are needed to explore the underlying mechanisms of these two diseases.

Abbreviations

CI, confidence interval; CKD, chronic kidney disease; CNS, central nervous system; CS, corticosteroid; HLA, human leukocyte antigen; ICD, International Classification of Diseases; LHID, Longitudinal Health Insurance Database; NHIRD, National Health Insurance Research Database; OR, Odds ratio; OSA, obstructive sleep apnea; TCR, T-cell receptor.

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Disclosure

The authors declare no conflicts of interest for this work.

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