

Association of Childhood Asthma and Pediatric Obstructive Sleep Apnea: A Retrospective Cohort Study from a Nationwide Population-based Database

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Abstract

Background and objective: Asthma is a risk factor for obstructive sleep apnea (OSA) in adult patients. However, the relationship between pediatric OSA and childhood asthma remains unclear. Here, we conducted a large-scale population-based cohort study for evaluating our hypothesis that childhood asthma is a risk factor for pediatric OSA.

Methods: From 2000 to 2007, children with and without asthma who were frequency matched by age, sex, urbanization level, comorbidities, and baseline year were enrolled from the Taiwan National Health Insurance Research Database (NHIRD). We compared pediatric OSA risk between asthma and non-asthma cohorts by using multivariable Cox regression analysis.

Results: We observed a significant relationship between asthma and OSA. In total, we included 305094 children with asthma and 305094 without asthma. The overall incidence rate ratio of OSA was 3.56-fold higher in the asthma cohort than in the non-asthma cohort (566 vs. 249 per 1000 person-year). After adjustment for potential risk factors, the adjusted hazard ratio (HR) of OSA was 1.82 [95% confidence interval (CI)=1.56-2.13]. Regardless of sex, the asthma cohort had a higher OSA risk than the non-asthma cohort did. Patients with asthma, excluding particular comorbidities, had a significantly increased OSA risk. Compared with those without asthma, patients with asthma who had more medical visits for asthma per year (particularly >5 visits per year) had a higher subsequent OSA risk (adjusted HR, 10.1, 95% CI=8.13-12.6).

Conclusion: This nationwide retrospective cohort study demonstrated that childhood asthma may increase subsequent pediatric OSA risk.

Keywords: Asthma; ICD-9-CM code; National Health Insurance Research Database; Population-based study; Obstructive sleep apnea

Abbreviations: CI: Confidence Interval; HR: Hazard Ratio; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; NHIRD: National Health Insurance Research Database; OSA: Obstructive Sleep Apnea

Introduction

Pediatric obstructive sleep apnea (OSA) is a sleep disorder characterized by repeated episodes of apnea and hypopnea. The upper airway obstruction resulting from adenotonsillar hypertrophy, neuromuscular disease, and craniofacial abnormality usually causes pediatric OSA [1]. The major symptom of pediatric OSA is snoring or mouth breathing during sleep, affecting approximately 3% to 12% of the pediatric population [2,3].

Early diagnosis and treatment of OSA is crucial because of associated comorbidities, and untreated OSA can lead to serious complications and consequences, such as failure to thrive, behavioral and neurocognitive dysfunction, metabolic syndrome, and pulmonary hypertension [1,4,5]. Numerous studies have investigated male sex, age, obesity, and nasal disease as risk factors for subsequent OSA [2-5].

Asthma is the most common chronic respiratory inflammatory disease in childhood and has various comorbidities such as overweight, allergic rhinitis, dysfunctional breathing, depressive disorders, and, perhaps, gastro esophageal reflux disease (GERD) [6]. Children with

asthma often have poor sleep quality, which contributes to the nocturnal deterioration of symptoms [7].

Several authors have reported a relationship between asthma and OSA [8-14]. The prevalence of OSA is higher among patients with adult asthma; OSA symptoms, which further deteriorate asthma symptoms, are commonly observed in the asthmatic population; thus, treating OSA can improve asthma symptoms [9-12]. Recent studies have shown that adult patients with asthma have a significantly higher risk of OSA [14,15]. However, a large-scale population-based cohort study evaluating the risk factors for OSA in pediatric patients with asthma has not been performed.

We hypothesized that childhood asthma is a risk factor for pediatric OSA. Therefore, we conducted a population-based retrospective

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cohort study by using data from the Taiwan National Health Insurance Research Database (NHIRD) for investigating the relationship between asthma and subsequent OSA risk.

Methods

The Taiwan National Health Insurance (NHI) program is a compulsory insurance program for Taiwanese citizens, and 99% of Taiwan's 23 million residents were enrolled in 1998 [16]. The NHIRD contains all reimbursement claims data from the Taiwan NHI program, including beneficiary registries, medical records, and registries for drug prescriptions and other medical services [17,18].

The NHIRD includes all claims data for children aged ≤ 18 years from 2000 to 2008; these data were a selected sample of half of all insured children. Detailed information on half of all the insured children has been provided in previous high-quality studies. To protect patient privacy, the Taiwan government eliminated original identification numbers and encrypted all personal identification information before releasing the database for research. The medical records were compiled on the basis of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. This study was approved by the Ethics Review Board of China Medical University and Hospital in Taiwan (CMUH104-REC2-115).

Study participants

The asthma cohort included patients <18 years with asthma (ICD-9-CM codes 493 and 494) diagnosed from 2000 to 2007, with the date of asthma diagnosis as their index date. For each child with asthma, we selected simultaneously one child without asthma matched by age (within a 1-year interval), sex, urbanization level, and year of asthma diagnosis. Children with pre-existing OSA (ICD-9-CM codes 327.23, 780.51, 780.53, and 780.57) were excluded. Tonsillectomy and adenoidectomy before a diagnosis of OSA were all excluded. All children were followed up from the index date until the date of OSA diagnosis, withdrawal of insurance, death, or 31 December 2008.

The type of medical visit is defined as medical visit for asthma. The baseline comorbidities considered were GERD (ICD-9-CM codes 530.11 and 530.81), craniofacial abnormalities (ICD-9-CM code 756.0), neuromuscular abnormalities (ICD-9-CM codes 330-337), prematurity (ICD-9-CM codes 764 and 765), genetic syndrome (ICD-9-CM code 758), laryngomalacia or tracheomalacia (ICD-9-CM codes 748.3 and 519.19, respectively), diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401-405), hyperlipidemia (ICD-9-CM code 272), obesity (ICD-9-CM code 278), rhinitis (ICD-9-CM codes 472-477), chronic sinusitis (ICD-9-CM code 473), and adenotonsillar hypertrophy (ICD-9-CM codes 474.10, 474.11, and 474.12).

Statistical analysis

The chi-square test was used for examining the distribution of demographic data between asthma and non-asthma cohorts. Continuous data were presented as mean \pm standard deviation (SD) and examined using the Student t test. We calculated the overall, age-specific, sex-specific, urbanization level-specific, and comorbidity-specific incidence density rates of OSA (per 100000 person/year) in each cohort.

The multivariate Cox proportional hazards model was used for calculating the hazard ratios (HRs) and 95% confidence intervals (CIs) of developing OSA in association with asthma. The multivariable models were simultaneously adjusted for age, sex, urbanization level, and comorbidity. Further analysis was performed for assessing the dose

response on OSA risk according to the average frequency of medical visits for asthma. All data analyses were conducted using the Statistical Analysis System software (Version 9.3 for Windows; SAS Institute, Inc., Cary, NC, USA). $P < 0.05$ was considered significant for a 2-tailed test.

Results

We included 305,094 children in the asthma cohort and 305,094 children in the nonasthma cohort. In the asthma cohort, 37.5% children were aged <3 years and 58.9% were boys. The mean age of children in both cohorts was 4.71 years. More than half of the children lived in urbanized areas. The prevalence of GERD, neuromuscular abnormalities, prematurity, genetic syndrome, laryngomalacia or tracheomalacia, diabetes, hypertension, hyperlipidemia, obesity, rhinitis, chronic sinusitis, and adenotonsillar hypertrophy was higher in the asthma cohort than in the nonasthma cohort ($P < 0.05$). The mean follow-up period in the asthma and nonasthma cohorts was 5.22 years (SD=2.30) and 5.19 years (SD=2.31), respectively. The Kaplan-Meier plots in Figure 1 show that the 9-year cumulative incidence of OSA was greater in the asthma cohort than in the nonasthma cohort (log-rank test, $P < 0.001$) (Figure 1).

The overall incidence of OSA in the asthma and nonasthma cohorts was 3.56 and 1.57 per 10000 person-years, respectively (Table 2). In total, 194 (34.3%) and 79 (31.78%) patients underwent tonsillectomy and adenoidectomy in the asthma and nonasthma cohorts, respectively. After adjustment for age, sex, urbanization level, and comorbidities, children with asthma were associated with an increased OSA risk compared with those without asthma [adjusted HR (aHR)=1.82, 95% CI=1.56-2.13]. The age-specific aHRs of OSA were higher for all age subgroups in both cohorts. After stratification by sex, the relative OSA risk was higher in both the girls (aHR=2.03, 95% CI=1.47-2.80) and boys (aHR=1.78, 95% CI=1.49-2.13) of both cohorts. The OSA risk was higher among those of all urbanization levels in both cohorts (Table 1). After stratification by comorbidity, the relative OSA risk was higher in the asthma cohort than in the nonasthma cohort for both patients without (aHR=1.84, 95% CI=1.50-2.26) and with comorbidity

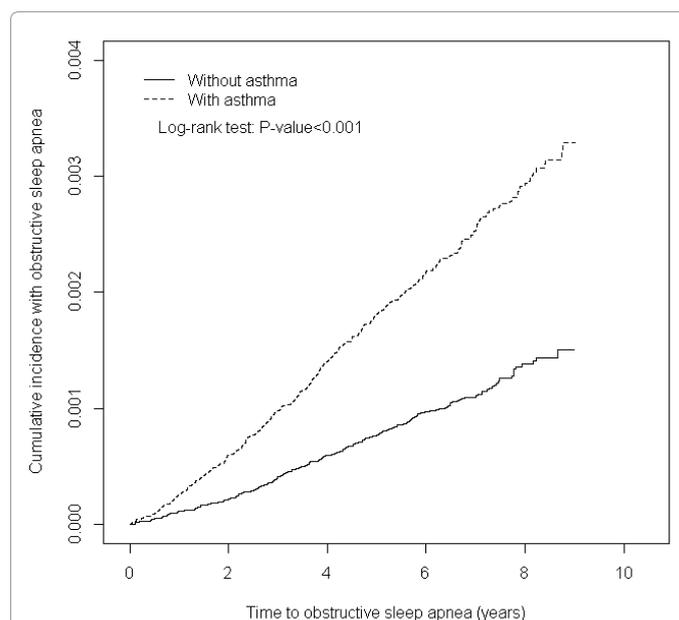


Figure 1: Kaplan-Meier analysis of the cumulative incidence of obstructive sleep apnea for the asthma cohort compared with the non-asthma cohort.

Variables	Non-Asthma		Asthma		p-value
	(N=305094)		(N=305094)		
	n	(%)	n	(%)	
Age, years, mean (SD) [†]	4.71	-3.61	4.71	-3.59	0.68
Stratified age, years					
<3	114542	-37.5	114542	-37.5	0.99
03-Jun	112712	-36.9	112712	-36.9	
06-Dec	60613	-19.9	60613	-19.9	
≥ 12	17227	-5.65	17227	-5.65	
Sex					
Girl	125556	-41.2	125556	-41.2	0.99
Boy	179538	-58.9	179538	-58.9	
Urbanization level[†]					
1 (highest)	89154	-29.2	89154	-29.2	0.99
2	92889	-30.5	92889	-30.5	
3	55357	-18.1	55357	-18.1	
4 (lowest)	67694	-22.2	67694	-22.2	
Comorbidity					
GERD	167	-0.05	371	-0.12	<0.001
Craniofacial abnormalities	75	-0.02	80	-0.03	0.69
Neuromuscular abnormalities	683	-0.22	961	-0.31	<0.001
Prematurity	2446	-0.8	4598	-1.51	<0.001
Genetic syndrome	196	-0.06	271	-0.09	0.001
Laryngomalacia/tracheomalacia	216	-0.07	472	-0.15	<0.001
Diabetes	170	-0.06	266	-0.09	<0.001
Hypertension	110	-0.04	146	-0.05	0.02
Hyperlipidemia	69	-0.02	155	-0.05	<0.001
Obesity	207	-0.07	391	-0.13	<0.001
Rhinitis	61858	-20.3	138067	-45.3	<0.001
Chronic sinusitis	4286	-1.4	12799	-4.2	<0.001
Hypertrophy of tonsil with adenoid	526	-0.17	742	-0.24	<0.001

Chi-square test and [†]Student t-test comparing children with and without asthma; [†]The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

Table 1: Demographics of children with and without asthma.

(aHR=1.77, 95% CI=1.40-2.25). Table 3 shows that the aHR of OSA increased to 10.1 (95% CI=8.13-12.6) for patients with asthma with >5 medical visits for asthma per year compared with that for patients without asthma (P for trend<0.0001). In addition, similar trends were observed for both girls and boys.

Discussion

On the basis of the literature review, this is the first population-based case-control study to demonstrate an increased pediatric OSA risk in children with asthma compared with that in those without asthma. We observed that this association was independent of other risk factors, such as age, sex, urbanization level, and comorbidity (adjusted for HR). In addition, these patients with asthma seeking medical visits more often 5 times per year for asthma have increased OSA risk.

In children, OSA often results from adenotonsillar hypertrophy, neuromuscular diseases, and craniofacial abnormalities [1], whereas in adults, it results from velopharyngeal narrowing and obesity [19]. Teodorescu et al. reported that patients aged 30 years to 60 years with self-reported asthma had the risk of developing OSA [15]. Shen et al. reported that patients aged >20 years have a significantly higher risk of OSA than the general population does [14]. The adjusted relative risk of OSA was 1.39 (95% CI=1.06-1.82) and 2.51 (95% CI=2.19-2.89) in the studies by Teodorescu et al. and Shen et al. respectively. We used the

same NHI database as that used in the study by Shen et al. moreover, our study included patients aged <18 years [15]. The adjusted relative risk was 1.82 (95% CI=1.56-2.13) in our study, and we did not observe the combined effects of comorbidities on pediatric OSA risk. However, comorbid conditions such as GERD, rhinitis, and obesity are more crucial risk factors for OSA in adult patients with asthma compared with the general population [14].

In our study, we observe that asthma is the primary risk factor for sequent OSA and three mechanisms may explain why childhood asthma increases OSA risk. First, the systemic inflammation may affect the strength or force generation of respiratory muscles, including the upper airway dilator muscles, and then destabilize the central breathing controller [20]. Second, the deformable pharyngeal airway duration inspiration and the active contraction of respiratory muscles during forced exhalation in an asthma attack could promote the collapse of the upper airway at night [21]. Third, corticosteroid therapy may affect the pharyngeal airway and render pharyngeal dilators more floppy, thus reducing their ability to protect the upper airway patency during sleep [22,23]. More clinical trials or animal studies should be performed to confirmed these mechanisms or pathophysiology.

In our study, children with asthma had a higher incidence of subsequent OSA when the frequency of medical visits per year was more than two, and the hazard ratios increase when the medical visits

Variables	Non- Asthma			Asthma			Adjusted HR† (95% CI)
	Event	Person-years	IR	Event	Person-years	IR	
All	249	1583683	1.57	566	1591841	3.56	1.82(1.56, 2.13)***
Stratified age							
<3	93	618282	1.5	219	623819	3.51	2.07(1.61, 2.65)***
03-Jun	113	577969	1.96	232	578804	4.01	1.57(1.24, 1.98)***
06-Dec	39	333522	1.17	99	334865	2.96	1.96(1.33, 2.90)***
≥ 12	4	53910	0.74	16	54353	2.94	3.48(1.12, 10.8)***
Sex							
Girl	56	647225	0.87	135	650604	2.07	2.03(1.47, 2.80)***
Boy	193	936458	2.06	431	941238	4.58	1.78(1.49, 2.13)***
Urbanization level†							
1 (highest)	101	460372	2.19	202	462735	4.37	1.68(1.31, 2.16)***
2	59	480489	1.23	172	483187	3.56	2.22(1.63, 3.02)***
3	39	287940	1.35	101	289272	3.49	2.07(1.41, 3.03)***
4 (lowest)	50	354883	1.41	91	356647	2.55	1.48(1.03, 2.12)†
Comorbidity‡							
No	164	1286744	1.27	214	896016	2.39	1.84(1.50, 2.26)***
Yes	85	296940	2.86	352	695825	5.06	1.77(1.40, 2.25)***

IR: incidence rate, per 10,000 person-y; Adjusted HR†: adjusted for age, sex, urbanization level; comorbidities such as GERD, craniofacial abnormalities, neuromuscular abnormalities, prematurity, genetic syndrome, laryngomalacia or tracheomalacia, diabetes, hypertension, hyperlipidemia, obesity, rhinitis, chronic sinusitis, and adenotonsillar hypertrophy; †The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized; Comorbidity‡: Patients with any of the comorbidities, including GERD, craniofacial abnormalities, neuromuscular abnormalities, prematurity, genetic syndrome, laryngomalacia or tracheomalacia, diabetes, hypertension, hyperlipidemia, obesity, rhinitis, chronic sinusitis, and adenotonsillar hypertrophy were classified as the comorbidity group; *P <0.05, **P <0.01, ***P <0.001.

Table 2: Risk of obstructive sleep apnea compared with children without asthma and stratified by demographics in Cox proportional hazards regression.

Average frequency for medical visit, per years	Event	Person-years	IR	Adjusted HR† (95% CI)
All				
None	249	1583683	1.57	1.00(Reference)
≤ 3	384	1469305	2.61	1.36(1.15, 1.60)***
04-May	46	54496	8.44	4.31(3.13, 5.93)***
>5	136	68040	20	10.1(8.13, 12.6)***
p for trend				<0.001
Girl				
None	56	647225	0.87	1.00(Reference)
≤ 3	86	606104	1.42	1.42(1.00, 2.01)†
04-May	11	20269	5.43	5.40(2.79, 10.4)***
>5	38	24230	15.7	15.6(10.1, 24.1)***
p for trend				<0.001
Boy				
None	193	936459	2.06	1.00(Reference)
≤ 3	298	863201	3.45	1.34(1.11, 1.62)**
04-May	35	34226	10.2	3.88(2.70, 5.60)***
>5	98	43810	22.4	8.46(6.57, 10.9)***
p for trend				<0.001

IR: Incidence rate, per 10000 person-y; Adjusted HR†: adjusted for age, sex, urbanization level, and comorbidities such as GERD, craniofacial abnormalities, neuromuscular abnormalities, prematurity, genetic syndrome, laryngomalacia or tracheomalacia, diabetes, hypertension, hyperlipidemia, obesity, rhinitis, chronic sinusitis, and adenotonsillar hypertrophy; *P <0.05, **P <0.01, ***P <0.001.

Table 3: Risk of obstructive sleep apnea according to average frequency of medical visits for asthma per year in Cox proportional hazards regression.

increase. The same phenomenon was noted in the study of Shen et al. showed that the more medical visits per year for asthma, the more risk of subsequent OSA in adults [14]. Teodorescu et al. reported that the association between asthma and OSA was significantly dose dependent on the duration of asthma [15]. Julien et al. also reported that obstructive sleep apnea-hypopnea was significantly more prevalent among patients with severe compared with moderate asthma [24]. In our study, we did not know if the severity of asthma is the risk of subsequent OSA, but only know that the frequency of medical visits per year, which meaning the poor control of childhood asthma, increases the risk of subsequent OSA.

The strength of the current study is the precise analysis of the future OSA risk in children with asthma on the basis of a large population database with a minimal selection bias. Although differences in comorbidities between asthma and non-asthma cohorts were significant, we adjusted the data for various comorbidities, such as GERD, craniofacial abnormalities, neuromuscular abnormalities, prematurity, genetic syndrome, laryngomalacia or tracheomalacia, diabetes, hypertension, hyperlipidemia, obesity, rhinitis, chronic sinusitis, and adenotonsillar hypertrophy; we observed that the asthma cohort still had a higher OSA risk than the non-asthma cohort did, even after propensity score matching. Our results demonstrate that

childhood asthma increases subsequent OSA risk with or without comorbidities.

However, our study has some limitations that should be addressed. First, the diagnoses of asthma and OSA were made on the basis of ICD-9-CM codes, and serum laboratory data on IGE or specific I_E as well as the results of the pulmonary function test and polysomnography were not available. However, the diagnoses of asthma and OSA in children mainly depend on the detailed medical history and not on the results of the pulmonary function test and polysomnography, respectively. In addition, we enrolled only patients that were diagnosed at least twice within a year for increasing the validity and accuracy of diagnosis. The NHIRD covers a highly representative sample of Taiwan's general population because the reimbursement policy is universal and operated by a single buyer, the Taiwan government. All insurance claims are scrutinized by medical reimbursement specialists and subjected to peer review according to standard diagnosis criteria. When specialists or physicians misdiagnose diseases or miscode diagnoses, they are criticized and the revision of diagnosis code will be made by reviewers. Therefore, the diagnoses of asthma and OSA in this study were highly reliable.

Additionally, information on the severity of asthma and OSA is unavailable in the NHIRD; therefore, we could not evaluate the correlation between the severities of these two diseases. Furthermore, information on other confounding factors, such as oral or inhaled steroid use and body mass index, which may be related to subsequent pediatric OSA risk, was unavailable in our study. Therefore, further prospective and case-control studies with larger cohorts and expanded diagnostic testing are warranted.

Conclusion

In conclusion, the risk of OSA was significantly higher in sexes, all age groups, and all urbanization levels in patients with asthma compared to patients without asthma, even with and without comorbidities. In addition, children with >5 medical visits per year for asthma have increased subsequent OSA risk. Further studies evaluating the mechanism of childhood asthma that increases pediatric OSA risk are warranted.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Chien-Heng Lin, Wei-Ching Lin and Liang-Wen Hang conceptualized and designed the study, drafted the initial manuscript, and approved the manuscript. Cheng-Li Lin conducted the initial analysis, reviewed and revised the manuscript, and approved the final manuscript. Liang-Wen Hang coordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript.

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