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Article type : Original

Association of between Obstructive Sleep Apnea and Atopic Dermatitis in Children: A Nationwide, Population-Based Cohort Study

Running Title: Atopic Dermatitis associated with Obstructive Sleep Apnea risk

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12853

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Author contributions: All authors have substantially contributed to the study and agree the

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Acknowledgments:

This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW106-TDU-B-212-113004), China Medical University Hospital, Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10601010036), Taiwan Clinical Trial Consortium for Stroke (MOST 106-2321-B-039-005), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding was received for this study.

Conflict of interest:

All authors report no conflicts of interest.

Abstract

Background: Atopic dermatitis (AD) is associated with systemic inflammation and may have a similar pathogenesis as obstructive sleep apnea (OSA). However, to date, studies on the association between AD and OSA is limited.

Objectives: This study evaluated the association between OSA and AD in children in a large-scale, population-based cohort.

Methods: A total of approximately 120,736 children (<18 years) with newly diagnosed AD and 120,736 age- and sex-matched patients without AD from 2000 to 2007 were identified from Taiwan's National Health Insurance Research Database from 2000 to 2007. The Kaplan–Meier test was used for measuring the cumulative incidence of OSA in each cohort. Cox proportional hazard regression models were used for evaluating the risk of OSA in patients with or without AD between the two cohorts.

Results: The Kaplan–Meier analysis revealed that the cumulative incidence curves of OSA were significantly higher in patients with AD than in those without AD (log-rank test, $P < 0.001$). After adjusting for age, sex, urbanization level, and comorbidities, patients with AD had a higher risk of OSA than those without AD (adjusted hazard ratio = 1.86, 95% confidence interval = 1.43–2.42). Compared with patients without AD, patients with AD exhibited a higher risk of developing OSA, irrespective of underlying comorbidities.

Conclusion: This nationwide, population-based cohort study revealed an increased risk of

OSA in children with AD. Therefore, comprehensive evaluation and aggressive risk reduction for OSA are recommended in these patients.

Keywords: Atopic dermatitis (AD), Obstructive sleep apnea (OSA), Taiwan's National Health Insurance Research Database (NHIRD), population-based cohort study

Introduction

Atopic dermatitis (AD) is the most prevalent sustained chronic inflammation and pruritic skin disease, affecting many infants and children in industrialized countries.(1, 2) It is also known as eczema or neurodermatitis and is associated with a high risk of allergic rhinitis or asthma.(3) In addition to suffering from the skin disorder, individuals with AD often experience medical burden and psychological problems (such as depression, poor sleep quality, and intense pruritus), leading to considerable absence from school, family stress, and healthcare expenditure. The prevalence of AD in Taiwan is 6.7% in the whole population and 9.6% in those aged < 20 years.(4, 5) Because AD can be a lifelong disorder, it is important to learn how to take care of its symptoms and comorbidities.

Obstructive sleep apnea (OSA), a common and important disorder in children, is defined as a disorder of recurrent pharyngeal collapses of the upper airway during sleep, which is the main pathophysiological mechanism of chronic sleep fragmentation and

intermittent hypoxemia (IH). OSA is associated with an increased risk of cardiovascular disease, insulin resistance, metabolic complications, behavioral impairment, mental illness, and neurocognitive dysfunction.(6, 7) Symptoms of OSA include habitual snoring and disturbed sleep. The main risk factor for OSA in children is adenotonsillar hypertrophy, which is related to the repetitive upper airway collapse observed in OSA.(8) Although the underlying mechanism of OSA remains unclear, accumulative evidence has suggested that IH contributes to hemodynamic, hormone-metabolic, and oxidative stress and immuno-inflammatory changes, which may be involved in the pathophysiology of OSA.(9, 10) Among these, inflammation mechanically alters conventional OSA risk factors, such as obesity, adenotonsillar hypertrophy, diabetes mellitus (DM), hyperlipidemia, hypertension, and biological modifications of the arterial walls that play a major role in OSA.

AD and OSA are common childhood diseases that can impair normal sleep and child development.(11) Although inflammatory mechanisms potentially link AD and OSA, evidence regarding this association is limited. In the current study, we used Taiwan's National Health Insurance Research Database (NHIRD) to explore the risk of OSA in patients with AD and to examine the association between the two disorders.

Materials and Methods

Data source

We conducted a retrospective population-based cohort study using a nationwide database of children (aged <18 years) which contained half of all insured children (approximately 3,500,000 individuals) from NHIRD in Taiwan. NHIRD was derived from a single-payer National Health Insurance (NHI) program by the Bureau of NHI and maintained by the National Health Research Institutes (NHRI). The NHI program, which began in March 1995, offers comprehensive medical coverage to 99% of the total 23 million residents of Taiwan.⁽¹²⁾ The details of this database have been well described in previous reports.^(13, 14) Diseases were defined based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved by the ethics review board of the China Medical University and Hospital in Taiwan (CMUH104-REC2-115-CR2).

Study design and subjects

We identified children aged <18 years with newly diagnosed AD (ICD-9-CM code 691.8) between 2000 and 2007. The date of AD diagnosis was defined as the index date. Children with a history of OSA (ICD-9-CM codes 327.23, 780.51, 780.53, and 780.57) were excluded. The comparison cohort included children without a history of AD and who were randomly selected from the database. For each case with AD, we randomly selected one control without AD and conducted frequency matching based on age (every 1 year), sex,

urbanization level, and year of the index date. The same exclusion criteria were applied to the comparison cohort. All subjects were followed up until they were diagnosed with OSA or censored because of withdrawal from insurance, death, or the end of 2008 (Figure 1).

Variables of interest

Sociodemographic variables used in this study comprised age, sex, and urbanization level. The urbanization levels was divided into four levels (level 1 = most urbanized area and level 4 = least urbanized area) based on the NHRI report. We defined baseline comorbidities including craniofacial abnormalities (ICD-9-CM code 756.0), gastroesophageal reflux disease (GERD) (ICD-9-CM codes 530.11, 530.81), prematurity (ICD-9-CM codes 764, 765), neuromuscular abnormalities (ICD-9-CM codes 330–337), laryngomalacia/tracheomalacia (ICD-9-CM codes 748.3/519.19), genetic syndromes (ICD-9-CM code 758), hypertension (ICD-9-CM codes 401–405), DM (ICD-9-CM code 250), obesity (ICD-9-CM code 278), and hyperlipidemia (ICD-9-CM code 272).

Statistical analysis

Distributions of sociodemographic data and comorbidities were compared between the AD cohort and comparison cohort using chi-squared test for categorical variables and *t*-test for continuous variables. The Kaplan–Meier test depicted the curves of cumulative incidence

of OSA for the two cohorts, and using the log-rank test, we examined the difference between the curves. We computed the incidence density rate of OSA (per 10,000 person-years) at follow-up for each cohort. Univariate and multivariable Cox proportional hazards regression models were used for examining the effect of AD on the risk of OSA, presented as a hazard ratio (HR) with a 95% confidence interval (CI). The multivariable models were adjusted for age, sex, urbanization level, and all abovementioned comorbidities. Further analysis was performed for assessing the dose-response effect of AD on the risk of OSA according to the average number of medical visits for AD. SAS 9.4 software (SAS Institute, Cary, NC, USA) was used for data analysis. A significance level of $P < 0.05$ was used for two-sided testing.

Results

We selected a cohort of 120,736 children with AD and a comparison cohort of 120,736 children with similar distributions of age, sex, and urbanization level (Table 1). The mean age of the AD cohort was 4.95 years and that of the comparison cohort was 4.99 years; nearly 48.5% of the children were aged <3 years. Approximately 55% of the children were boys and 64.6% lived in urbanized areas. Children in the AD cohort were more likely to have comorbidities, such as GERD, neuromuscular abnormalities, genetic syndrome, hypertension, hyperlipidemia, obesity, rhinitis, and chronic sinusitis, than those in the comparison cohort (P

< 0.05). During the mean follow-up of 4.88 years for the AD cohort and that of 4.86 years for the comparison cohort, the cumulative incidence of OSA in the AD cohort was significantly higher than that in the comparison cohort ($P < 0.001$; Figure 2). Results of the follow-up revealed that the AD cohort was 2.19-fold more likely to develop OSA than the comparison cohort (3.09 vs. 1.41 per 10,000 person-years), with an adjusted HR (aHR) of 1.86 (95% CI = 1.43–2.42) after controlling for age, sex, urbanization level, and comorbidities (Table 2). Polysomnography is challenging in children because they have a limited ability to cooperate with the setup, and have trouble of sleeping in an unfamiliar environment. Therefore, relying on polysomnography for the diagnosis of children with OSA may not be clinically feasible. While 43% of children were diagnosed by polysomnography in our study, the risk of OSA in this subgroup who received polysomnography remained significantly in the AD cohort compared with control (aHR 1.62; 95% CI, 1.09–2.4), indicating the strong association between AD and OSA in children. The age-specific hazard of OSA in the <3- and 3–6-year-old groups of the AD cohort was significant compared with that in the <3- and 3–6-year-old groups of the comparison cohort (<3 years, aHR = 2.21, 95% CI = 1.49–3.27 and 3–6 years, aHR = 2.00, 95% CI = 1.18–3.37). The incidence density rate of OSA was greater in boys than in girls in both cohorts. The gender-specific hazard of OSA for both girls (aHR = 1.83, 95% CI = 1.10–3.04) and boys (aHR = 1.87, 95% CI = 1.37–2.54) in the AD cohort was significant compared with that for girls and boys in the comparison

cohort. The urbanization level-specific AD to comparison aHR of OSA was significant for children living in the most highly urbanized (aHR = 1.76, 95% CI = 1.21–2.57) and second-most highly urbanized areas (aHR = 2.39, 95% CI = 1.36–4.20). The comorbidity-specific aHR of OSA showed that the AD cohort had a higher risk of OSA than the comparison cohort, both in those with (aHR = 1.81, 95% CI = 1.23–2.66) and without comorbidities (aHR = 1.92, 95% CI = 1.34–2.75).

Table 3 shows that the aHR of OSA was higher than that of the comparison cohort among children with AD who had 5 (aHR = 21.1, 95% CI = 13.6–32.6), 4–5 (aHR = 8.04, 95% CI = 4.14–15.6), and ≤ 3 (aHR = 1.51, 95% CI = 1.15–1.98) medical visits per year because of AD (P for trend < 0.0001). Similar trends were observed in both girls and boys.

Discussion

This large-scale, population-based cohort study indicated that children with AD have a significantly higher risk of OSA than those without AD (Figure 1). After adjusting for age, sex, urbanization level, and underlying comorbidities (craniofacial abnormalities, prematurity, laryngomalacia/tracheomalacia, DM, and adenotonsillar hypertrophy), patients with AD had a 1.86-fold increased risk of OSA (Table 2). AD is an independent risk factor for OSA; patients with severe AD have additive effects contributing to the risk of OSA

(Table 3), suggesting an association between AD and OSA.

Data from the NHI program, a universal single-payer health insurance system, have been widely used for academic research.⁽¹⁴⁾ Data for our cohort study were obtained from NHIRD, which comprises comprehensive information on clinical visits by each insurant, including demographic data, dates of visits, and medical services. Because all patients in the NHI program receive optimal medical care at a low cost, loss to follow-up is low, and the database can, therefore, provide approximately 20 years of follow-up data for the study sample. Advantages of NHIRD include its large sample size and lack of selection and participation bias.⁽¹⁴⁾ The criteria of AD and OSA were defined according to ICD-9-CM. Because these data are monitored and strictly evaluated by the Bureau of NHI for reimbursement, recorded diagnoses of OSA and AD are highly reliable.

Interest in the association between AD and OSA is rapidly increasing. AD is typically considered to be an inflammatory skin disease and shares many risk factors with OSA, such as comorbidity (obesity), genetics, allergic diseases (asthma, allergic rhinitis, and AD), and environmental exposure (maternal smoking and breastfeeding).⁽¹⁵⁻¹⁷⁾ Despite this, few studies have investigated the possible relationship between AD and OSA. Children with AD frequently have more severe asthma than asthmatic children without AD.⁽¹⁸⁾ Nearly 80% children with AD eventually experience allergic rhinitis or asthma, suggesting that respiratory allergies and AD have a common systemic link. Previous research has reported that asthma

and allergic rhinitis increased the risk of snoring and OSA.(16) In the review conducted by Bieber et al., it was reported that patients with AD, characterized by skin inflammation associated with airway inflammation and narrowing, have an elevated number of circulating eosinophils and increased serum IgE levels, which triggers an inflammatory cascade and results in a generalized T-helper 2 (Th2) deviated immune response.(19) Some studies have reported that OSA, now considered to be a chronic, low-grade airway inflammatory disease with disturbed neuromuscular control of breathing,(20, 21) increases the release of catecholamine, which might induce Th2 cells deviated immune response. However, thus far, information on the association between AD and OSA is lacking. Herein, we have postulated that both AD and OSA are considered systemic diseases and that they share similar immunopathological pathways.

According to a study by Hersoug and Linneberg, there is increasing epidemiologic evidence that obesity also increases the risk of AD. Since then, several studies have demonstrated that obese individuals are at an increased risk of OSA and that OSA is a major complication of obesity.(22, 23) It is possible that obesity might reduce immune tolerance and result in atopy.(24) Upper airway anatomy represents one potential obesity-independent genetic pathway. We have postulated that the association between OSA and AD may be, in part, due to obesity. The main risk factor for OSA in children is adenotonsillar hypertrophy, which is related to the propensity for repetitive upper airway collapse.(8) Previous reports

have established the association between clinical allergic or AD and adenoids/adenotonsillar hypertrophy as a well-known co-morbid factor in children.(25) Alexopoulos E. et. al. indicated that AD was not related to adenotonsillar hypertrophy or OSA in children who snore.(26) Possible explanations of the discrepancy might be different study design (cohort v.s. cross-sectional design) and different patient population. Such evidence partly explains the linking mechanism between AD and OSA.

This study also showed that the incidence of OSA was 1.86-fold higher in the AD cohort than in the comparison cohort after controlling for age, sex, urbanization level, and comorbidities. Subgroup analysis revealed that the risk of developing OSA was greater in younger children with AD aged 0–3 and 3–6 years and those living in highly urbanized areas. After stratification for age, aHRs of OSA was the highest in younger children. The underlying reason for the relationship between age and incidence of OSA in patients with AD is unclear. A possible explanation is that younger children tend to have a higher sensitivity to modern pollutants and chemicals and there has been a remarkable increase in allergies and inflammatory diseases. Moreover, children living in highly urbanized areas have a greater risk of OSA, which may be due to greater exposure to high-dose pesticides, modern pollutants, and chemicals. This increase has been attributed to environmental factors, including perfluorinated (endocrine-disrupting) chemicals and modern air pollutants, such as hydrogen sulfide, nitrogen dioxide, carbon monoxide, and formaldehyde, which have resulted

in high rates of allergic sensitization.(27)

Although AD is not considered to be a life-threatening disease, it can interfere with many important aspects of life quality. The risk of OSA in AD may be cumulative. Because of the combination of the severity of AD and its complex comorbidities (allergic rhinitis and asthma), patients may have had an increased average frequency of medical visits per year. The results of our study suggest that severe AD symptoms in children results in a high risk of developing OSA, indicating a strong association between the two diseases.

The present study had several limitations. First, the diagnoses of AD and OSA were based on diagnostic codes recorded by physicians in the NHI claim database; therefore, some registration bias may have been involved in the calculation of OSA risk and could act as a potential confounding factor, which were not excluded from the study. Second, the household income and economic status, which were not measured herein, are other indices besides urbanization or the geographic region that could be important for the evaluation of medical access or utilization. Third, the severity of AD and OSA, functional status in patients after AD, and outcomes in patients with AD and OSA were not evaluated in the Taiwanese pediatric population. Moreover, the risk of OSA was evaluated using ICD-9-CM codes rather than a screening program. Fourth, the evidence derived from this retrospective cohort study is generally of lower methodological evidence than that from randomized controlled trials. Patients with asymptomatic OSA may not seek healthcare until they experience considerable

discomfort, leading to an underestimation of the risk of OSA among patients with AD.

Despite these limitations, the use of a nationwide dataset (which provided a large sample size) and adjustment for certain covariates related to OSA enabled the detection of a significant relationship between AD and the risk of developing OSA in childhood.

To the best of our knowledge, this is the first study to indicate an increased risk of OSA in children with AD. OSA risk was more pronounced in younger children (<6 years) and those living in highly urbanized areas. Because the onset of AD occurs relatively early in life, early identification of risk factors and symptoms are critical for preventing the development of OSA. Although additional prospective randomized studies are necessary to verify the effects of AD on OSA, in the meantime, meticulous evaluation and aggressive risk reduction for OSA are recommended in children with AD.

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Figure Legend:

Figure 1. Subject selection for the analysis on the association between AD and risk of OSA.

Figure 2. The Kaplan-Meier analysis of cumulative incidence of obstructive sleep apnea for atopic dermatitis (AD) cohort compared to non- AD cohort.

Table 1. Demographics between children with and without atopic dermatitis (AD)

	Non- AD (N=120736)		AD (N=120736)		p-value
	n	(%)	n	(%)	
Age, years, mean (SD)*	4.99	(4.83)	4.95	(4.85)	0.04
Stratified age, years					0.99
<3	58572	(48.5)	58572	(48.5)	
3-6	20433	(16.9)	20433	(16.9)	
6-12	27346	(22.7)	27346	(22.7)	
≥ 12	14385	(11.9)	14385	(11.9)	
Sex					0.99
Girl	54913	(45.5)	54913	(45.5)	
Boy	65823	(54.5)	65823	(54.5)	
Urbanization level †					0.99
1 (highest)	42431	(35.1)	42431	(35.1)	
2	35603	(29.5)	35603	(29.5)	
3	20166	(16.7)	20166	(16.7)	
4 (lowest)	22536	(18.7)	22536	(18.7)	
Comorbidity					
GERD	110	(0.09)	192	(0.16)	<0.001
Craniofacial abnormalities	22	(0.02)	26	(0.02)	0.56
Neuromuscular abnormalities	254	(0.21)	333	(0.28)	0.001

Prematurity	1110	(0.92)	1061	(0.88)	0.29
Genetic syndrome	80	(0.07)	116	(0.10)	0.01
Laryngomalacia/tracheomalacia	103	(0.09)	126	(0.10)	0.13
Diabetes	81	(0.07)	103	(0.09)	0.10
Hypertension	33	(0.03)	73	(0.06)	<0.001
Hyperlipidemia	48	(0.04)	96	(0.08)	<0.001
Obesity	134	(0.11)	202	(0.17)	<0.001
Rhinitis	25427	(21.1)	41394	(34.3)	<0.001
Chronic sinusitis	2434	(2.02)	4937	(4.090)	<0.001
Hypertrophy of tonsil with adenoid	215	(0.18)	249	(0.21)	0.11

Chi-square test, and * t-test comparing subjects with and without AD

[†]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.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12853

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Table 2. The risk of obstructive sleep apnea compared to children without atopic dermatitis (AD) stratified by demographics in Cox proportional hazard regression

	Non- AD			AD			Adjusted HR [†] (95% CI)
	Event	Person-years	IR	Event	Person-years	IR	
All	83	586739	1.41	182	589191	3.09	1.86(1.43, 2.42)***
With polysomnography	39	586739	0.66	75	589191	1.27	1.62(1.09, 2.40)*
Stratified age							
<3	36	286145	1.26	87	287459	3.03	2.21(1.49, 3.27)***
3-6	21	111682	1.88	49	112108	4.37	2.00(1.18, 3.37)*
6-12	23	147346	1.56	38	147762	2.57	1.25(0.73, 2.12)
≥ 12	3	41566	0.72	8	41863	1.91	2.03(0.52, 7.96)
Sex							
Girl	22	266034	0.83	51	267346	1.91	1.83(1.10, 3.04)*
Boy	61	320705	1.90	131	321844	4.07	1.87(1.37, 2.54)***
Urbanization level [†]							
1 (highest)	41	205815	1.99	87	207032	4.20	1.76(1.21, 2.57)**
2	17	172864	0.98	46	173408	2.65	2.39(1.36, 4.20)**
3	16	98373	1.63	26	98743	2.63	1.39(0.74, 2.63)
4 (lowest)	9	109687	0.82	23	110007	2.09	2.15(0.99, 4.69)
Comorbidity [§]							
No	48	464354	1.03	78	386898	2.02	1.92(1.34, 2.75)***
Yes	35	122385	2.86	104	202293	5.14	1.81(1.23, 2.66)**

IR, incidence rate, per 10,000 person-years

Adjusted HR[†], adjusted for age, sex, urbanization level and comorbidity of GERD, craniofacial abnormalities, neuromuscular abnormalities, prematurity, genetic syndrome, laryngomalacia/tracheomalacia, diabetes, hypertension, hyperlipidemia, obesity, rhinitis, chronic sinusitis, and hypertrophy of tonsil with adenoid

[†]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 one of the comorbidities GERD, craniofacial abnormalities, neuromuscular abnormalities, prematurity, genetic syndrome, laryngomalacia/tracheomalacia, diabetes, hypertension, hyperlipidemia, obesity, rhinitis, chronic sinusitis, and hypertrophy of tonsil with adenoid were classified as the comorbidity group

*p<0.05, **p<0.01,*** p<0.001

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12853

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Table 3. The risk of obstructive sleep apnea among average frequency for medical visits of atopic dermatitis (AD) in Cox proportional hazard regression

Average frequency for medical visit, per years	Event	Person-years	IR	Adjusted HR [†] (95% CI)
All				
None	83	586739	1.41	1.00(Reference)
≤3	144	572957	2.51	1.51(1.15, 1.98)**
4-5	10	7699	13.0	8.04(4.14, 15.6)***
> 5	28	8534	32.8	21.1(13.6, 32.6)***
p for trend				<0.001
Girl				
None	22	266034	0.83	1.00(Reference)
≤3	40	260596	1.53	1.47(0.86, 2.50)
4-5	3	3143	9.55	9.65(2.86, 32.6)***
> 5	8	3608	22.2	22.2(9.71, 50.8)***
p for trend				<0.001
Boy				
None	61	320705	1.90	1.00(Reference)
≤3	104	312362	3.33	1.53(1.11, 2.11)**
4-5	7	4556	15.4	7.78(3.54, 17.1)***
> 5	20	4927	40.6	20.8(12.4, 34.9)***
p for trend				<0.001

IR, incidence rate, per 10,000 person-years

Adjusted HR[†], adjusted for age, sex, urbanization level and comorbidity of GERD, craniofacial abnormalities, neuromuscular abnormalities, prematurity, genetic syndrome, laryngomalacia/tracheomalacia, diabetes, hypertension, hyperlipidemia, obesity, rhinitis, chronic sinusitis, and hypertrophy of tonsil with adenoid

* p<0.001



