

RESEARCH ARTICLE

Pediatric sleep apnea and depressive disorders risk: A population-based 15-year retrospective cohort study

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Abstract

Background

Studies have shown a higher risk of depressive disorders in children with sleep apnea than in those without sleep apnea. However, the association between sleep apnea and subsequent depressive disorders in the pediatric population remains undetermined. Thus, this study investigated the risk of depressive disorders among pediatric patients with sleep apnea.

Methods

In this study, the population-based National Health Insurance Research Database of Taiwan was used to identify patients who had first been diagnosed with sleep apnea between 1999 and 2013. Patients with sleep apnea who were younger than 18 years were included in the sleep apnea group. Controls (those without sleep apnea) were matched to patients with sleep apnea at a 1:10 ratio by age, sex, and index year. Patients who had baseline or inherited depressive disorders before the enrollment date were excluded. The two groups were followed up until December 31, 2013. The primary endpoint was the occurrence of one or more depressive disorders.

Results

At the end of this study, 6,237 children had been enrolled, comprising 567 children with sleep apnea and 5,670 children without sleep apnea. During the mean follow-up period of 5.87 years, a total of 77 children (1.23%) developed one or more depressive disorders; 14 (2.46%) from the sleep apnea group and 63 (1.11%) from the control group. Kaplan–Meier analysis showed that children with sleep apnea had a significantly higher risk of depressive disorders (log-rank test, $p = 0.002$). After adjusting for covariates, the risk of subsequent

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depressive disorders among children with sleep apnea was still significantly higher (hazard ratio [HR] = 2.25; 95% confidence interval [CI] = 1.25–4.05; $p = 0.006$). Moreover, boys with sleep apnea had a significantly higher risk than those without sleep apnea (adjusted HR = 3.77; 95% CI, 1.82–7.54; $p < 0.001$). Furthermore, in sleep apnea group, children older than 12 years of age had more risk to depression (hazard ratio (HR) = 7.1833, 95% confidence interval (CI), 2.3734 to 21.7411; $p = 0.0004$).

Conclusions

This study found a significantly higher subsequent risk of depressive disorders in children with sleep apnea, particularly boys and those older than 12 years of age. The study findings strongly suggest that clinicians should provide psychological evaluation and supportive care for children with sleep apnea, in addition to medical treatment.

Introduction

Sleep apnea is characterized by repeated episodes of apnea and hypopnea during sleep, which result from the complete or partial collapse of the upper airway. The prevalence of sleep apnea in children ranges from 1% to 4% according to the varying criteria of diagnostic studies, and it is more common in boys than in girls [1]. Previous studies have demonstrated an association between sleep apnea and cardiovascular diseases, neurocognitive dysfunction, and behavioral disorders [2, 3].

As is found in adults, pediatric patients with sleep apnea may have substantial comorbid mental disorders such as depression or attention deficit hyperactivity disorder (ADHD) [4, 5]. An increase in depressive symptoms among pediatric patients with sleep apnea has been noted. Studies have shown increasing incidence rates of depressive symptoms among pediatric patients with sleep apnea [6–16]. However, depression was based on scale diagnosis rather than clinical diagnosis. Depressive disorders are widespread chronic diseases that are characterized by sadness or irritability and are accompanied by several psychophysiological symptoms [17]. The long-term risk of physician-diagnosed depressive disorders among pediatric patients with sleep apnea remains unknown.

This study investigated the risk of depressive disorders among pediatric patients (aged less than 18 years) with sleep apnea by using the population-based database of the National Health Insurance Research Database (NHIRD) of Taiwan.

Methods

Data source

The National Health Insurance (NHI) program is a mandatory universal health insurance program launched by the Taiwanese government in 1995, and it provides comprehensive medical services to almost all residents of Taiwan. The National Health Research Institute (<http://nhird.nhri.org.tw/en>) is responsible for maintaining the claims data of the NHI program, which is held in the NHIRD. The NHIRD contains the health care insurance data of 98.29% of Taiwan's population of 23 million. The National Health Research Institute validates the released database, which is representative of the entire Taiwanese population. The diagnostic and procedure codes used are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Our study was approved by the Institutional Review Board of China Medical University Hospital (CMUH103-REC3-077).

Study sample and controls

In this study, we identified pediatric patients who were newly diagnosed with sleep apnea (ICD-9-CM codes 780.51, 780.53, and 780.57) from 1999 to 2013 of the database, and enrolled them as the sleep apnea group. In Taiwan, a diagnosis of sleep apnea was made according to polysomnography (PSG) by board-certified pediatricians and physicians. In this study, only those having at least three consecutive corresponding diagnoses were designated as having sleep apnea for better diagnostic validity. We defined the enrollment date as the date when sleep apnea was initially diagnosed. Controls (those without sleep apnea) were selected from the NHIRD using the simple random sampling method. Controls were matched to patients in the sleep apnea group at a 1:10 ratio by age, sex, and index year. Pediatric patients who were diagnosed with a depressive disorder (ICD-9-CM codes 296.2X-296.3X, 300.4, and 311.X) before the enrollment date were excluded.

Matching for the age and year of enrollment was allowed within a tolerance range of ± 1 year. For the control group, the beginning date of a follow-up was defined as the first date of visit to a clinic or hospital within the enrollment year.

Main outcome measures

The primary endpoint of this study was the occurrence of one or more depressive disorders. Both groups were followed up until the first diagnosis of depressive disorder, death, withdrawal from the NHI program, or the study end date of December 31, 2013. In Taiwan, a diagnosis of depressive disorders was made according to ICD-9 CM code and Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV [18] by board-certified psychiatrists and physicians. In this study, only those having at least three consecutive corresponding diagnoses were designated as having depressive disorders for better diagnostic validity.

Variables

In this study, demographic characteristics—such as age, sex, and index year—were retrieved and matched between the two groups. According to previous studies, the risk factors for depressive disorders and the major comorbidities linked to pediatric sleep apnea include hypertension, diabetes mellitus, insomnia, ADHD, and asthma, which were assessed in our analyses. The Charlson comorbidity index score, which is representative of the baseline comorbidity profile, was also calculated.

Statistical analysis

We used descriptive statistics to investigate demographic characteristics. To investigate the risk factors for depressive disorders, patients were divided into two groups—pediatric patients with sleep apnea (sleep apnea group) and pediatric patients without sleep apnea (control group). A Cox proportional hazard regression model was used to investigate the risk factors for sleep apnea. MY Structured Query Language was used for the extraction, linkage, and processing of data in the study database. All statistical analyses were performed using IBM SPSS statistical software (version 20.0 for Windows; IBM Corp., New York, NY). A two-tailed *p* value of <0.05 was considered statistically significant.

Results

Demographic characteristics

A total of 567 pediatric patients with sleep apnea and 5,670 pediatric patients without sleep apnea were included in the sleep apnea and control groups, respectively. The flowchart for

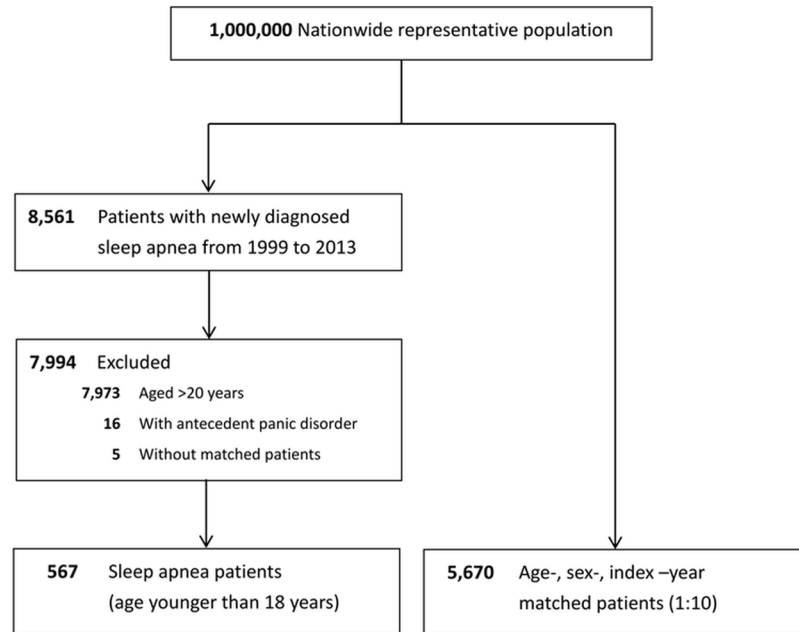


Fig 1. Flowchart summarizing the process of enrollment and follow-up.

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enrollment is shown in Fig 1. The demographic characteristics of the sleep apnea and control groups are shown in Table 1. Compared with the control group, the sleep apnea group had more comorbidities and higher Charlson comorbidity index scores.

Cumulative incidence of depressive disorders

The mean follow-up period was 5.87 years. The sleep apnea group had a higher rate of depressive disorders than the control group (14 [2.46%] vs 63 [1.11%]; $p < 0.001$). The sleep apnea

Table 1. Demographic profile of study patients (n = 6,237).

	Sleep Apnea (n = 567) M±SD/n(%)	Non-Sleep Apnea (n = 5,670) M±SD/n(%)	t/χ^2	p-value
Age (yrs)	9.70±4.21	9.70±4.20	0.966	1.000
Sex				
Men	381(67.19)	3810(67.2)		1.000
Women	186(32.80)	1860(32.8)		1.000
Follow up, y	5.52±3.74	5.91±3.74	0.949	0.017
Major coexisting diseases				
Hypertension	2 (0.35)	0 (0.00)	19.326	<0.001
Diabetes	3 (0.52)	20 (0.35)	0.088	0.766
Insomnia	4 (0.70)	6 (0.10)	8.136	0.004
ADHD	51 (8.99)	177 (3.12)	48.827	<0.001
Obesity	17 (2.99)	16 (0.28)	67.180	<0.001
Asthma	151 (26.63)	1069 (18.85)	19.326	<0.001
Charlson comorbidity score	0.021±0.166	0.015±0.137		0.421

Abbreviations: ADHD = Attention deficit hyperactivity disorder.

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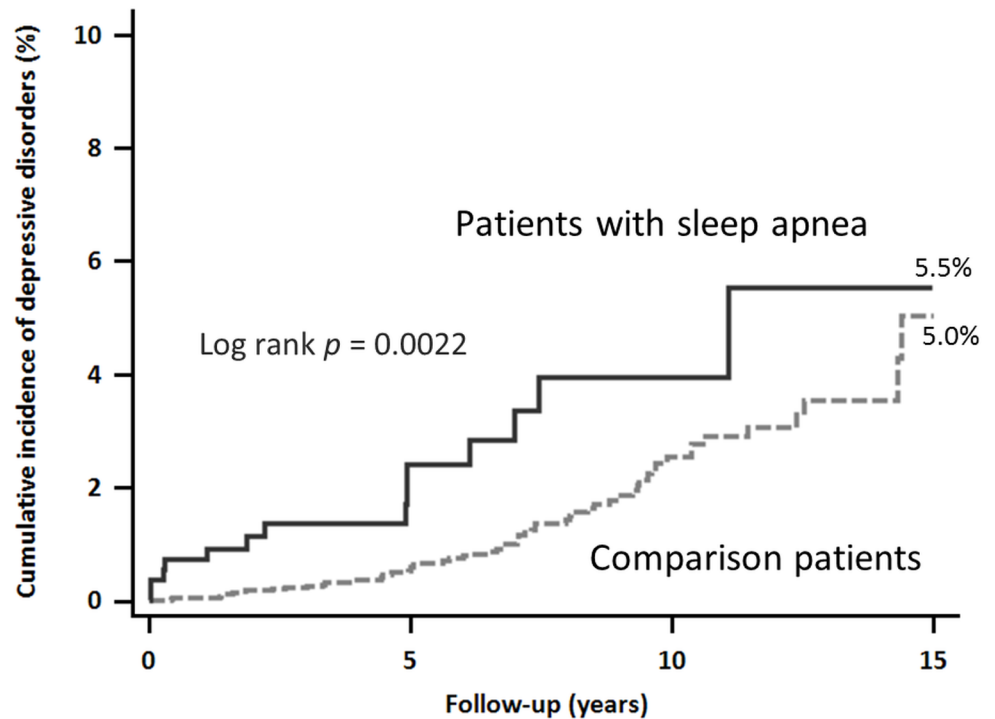


Fig 2. Cumulative incidence of depressive disorders in pediatric patients with sleep apnea.

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group had a significantly higher risk of depressive disorders than the control group (log-rank test, $p < 0.001$, Fig 2). The incidence of depressive disorders in the sleep apnea and control groups was 181.0 and 169.0 per 1,000 person-years, respectively ($p < 0.001$). Comparing patients with and without depressive disorders, patients with incident depressive disorders were mostly male (57.14%) and had higher incidence of hypertension, diabetes mellitus, insomnia, ADHD, obesity, and asthma. The results of multivariate analysis indicated that sleep apnea was independently associated with incident depressive disorders (Table 2; adjusted hazard ratio [aHR] = 2.25; 95% confidence interval [CI] = 1.25–4.05; $p = 0.006$). In addition, boys with sleep apnea had a significantly higher risk than those without sleep apnea (aHR = 3.77; 95% CI = 1.82–7.54; $p < 0.001$) (Table 3). Moreover, in sleep apnea group, children older than 12 years of age had more risk to depression (hazard ratio (HR) = 7.1833, 95% confidence interval (CI), 2.3734 to 21.7411; $p = 0.0004$). (Fig 3)

Table 2. Hazard ratios of depressive disorders among study patients during 15-year follow-up period (n = 6,237).

Depressive disorders	Total (n = 6,237)	Patients with sleep apnea (n = 567)	Comparison patients (n = 5,670)	p Value
n (%)	77 (1.23)	14 (2.46)	63 (1.11)	-
Crude HR (95% CI)	-	2.40** (1.34–4.29)	1.00	0.003
Adjusted HR (95% CI) ^a	-	2.25** (1.25–4.05)	1.00	0.006

HR, hazard ratio. HR was calculated by stratified Cox proportional hazard regressions (stratified by sex)

* $p < 0.05$.

** $p < 0.01$.

^a Adjustments are made for age, sex, hypertension, diabetes, insomnia, ADHD, obesity, asthma, and Charlson comorbidity score.

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Table 3. Hazard ratios of depressive disorder by gender among the sample patients during the 15-year follow-up periods.

Depressive disorders	Male		Female	
	Patients with sleep apnea (n = 381)	Comparison patients (n = 3,810)	Patients with sleep apnea (n = 186)	Comparison patients (n = 1,860)
n (%)	11 (2.89)	33 (0.87)	3 (1.61)	30 (1.61)
Crude HR (95% CI)	3.66*** (1.85 to 7.26)	1.00	1.05 (0.32 to 3.45)	1.00
Adjusted HR (95% CI) ^a	3.77*** (1.82 to 7.54)	1.00	1.05 (0.32 to 3.44)	1.00

HR, hazard ratio. HR was calculated by stratified Cox proportional hazard regressions (stratified by sex)

*p < 0.05

**p < 0.01

***p < 0.001

^a Adjustments are made for age, sex, hypertension, diabetes, insomnia, ADHD, obesity, asthma, and Charlson comorbidity score.

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Discussion

To the best of our knowledge, the present study is the first and largest cohort study to analyze the subsequent risk of depressive disorders in adolescent patients (<18 years of age) with sleep apnea. The results of this nationwide, population-representative cohort study showed that (1) the risk of depressive disorders was higher in children with sleep apnea, (2) the risk of depressive disorders was higher in boys, and (3) compared to children younger than 12 years of age, children older than 12 years of age had more risk to depression.

Our findings showed that the sleep apnea group had a higher risk of depressive disorders than the control group (14 [2.46%] vs 63 [1.11%]; p < 0.001). This result is consistent with

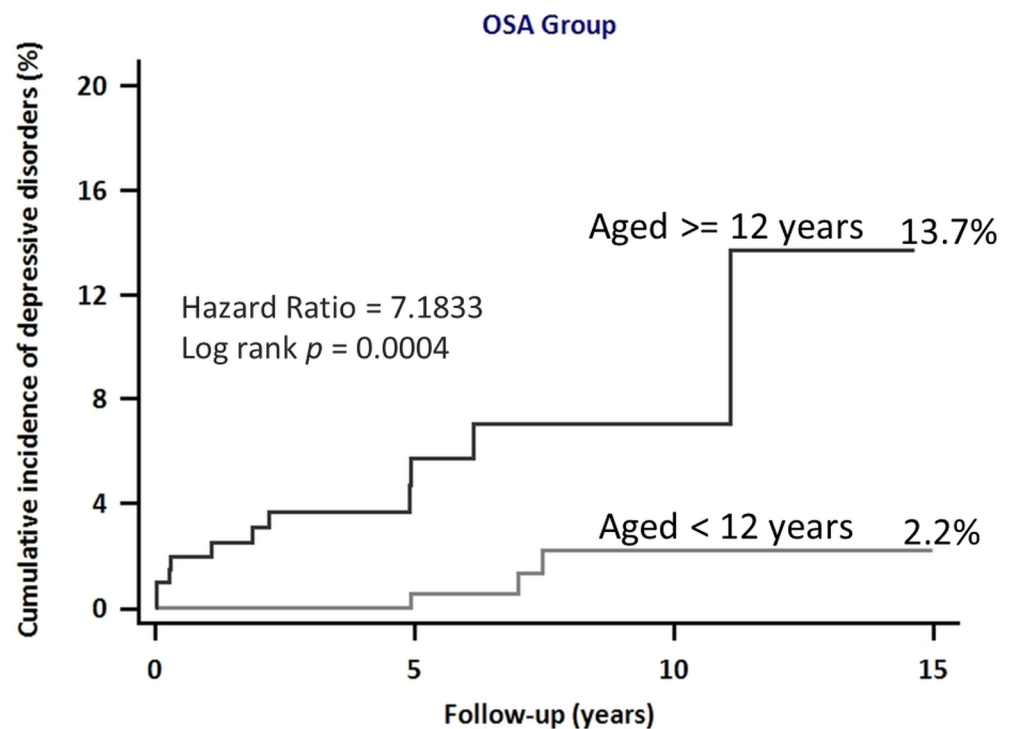


Fig 3. Cumulative incidence of depressive disorders after sleep apnea in two age groups.

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those of previous studies. A meta-analysis of 11 studies assessed depressive symptoms in both children diagnosed with obstructive sleep apnea (OSA) ($n = 894$) and a comparison group ($n = 1,096$) and revealed a significant relationship between depressive symptoms and OSA (Hedges' $g = 0.43$; 95% CI = 0.22–0.64; $p = 0.00005$) [6]. However, the studies in that meta-analysis addressed depressive symptoms, whereas the present study investigated physician-diagnosed depressive disorders.

The cumulative incidence between OSA group and non-OSA group was 5.5% and 5% respectively. There are some possible reasons. First, children with OSA may have more clinic visits and then result in more opportunity to be diagnosed depression by physician. This may result in the faster onset of depression in OSA group than the non-OSA group. Second, OSA treatment may reduce the depression risk. A meta-analytic study assessed 379 children across nine studies for depressive symptoms both pre- and post-surgery. Their finding shows the overall effect size (ES) change between pre- versus post-surgery was 0.41 (95% CI = 0.20–0.62; $p \leq 0.001$), indicating a medium improvement occurred in depressive symptoms after adenotonsillectomy(AT). Further study may need to investigate the OSA severity and treatment effect.[6]

Several explanations have been provided for the association between sleep apnea and depressive disorders. First, sleep apnea is associated with blood oxygen desaturation during night time, which may cause daytime fatigue and depressive symptoms [19, 20]. Second, hypoxia resulting from desaturation might also lead to structural changes in the brain, which in turn lead to depressive symptoms [21]. Third, changes in hormones such as leptin may lead to depressive symptoms [22]. Leptin is involved in the regulation of food intake; therefore, leptin insensitivity may lead to obesity [23]. Obesity is a risk factor for both sleep apnea and depression[24]. Fourth, sleep apnea has been linked to low serotonin levels, which are associated with depression [21, 25].

In the present study, we found that boys with sleep apnea had a higher risk of depressive disorders than boys without sleep apnea (aHR = 3.77; 95% CI = 1.82–7.54; $p < 0.001$). Yilmaz et al. reported that a higher percentage of male patients had a higher effect size (beta = 0.66, $p = 0.03$), and their finding suggested that the relationship between depressive symptoms and sleep apnea is stronger for boys than for girls [6]. This stronger relationship may result from obesity, which is more strongly associated with depression in male patients than in female patients during adolescence[26].

The strength of our study is its nationwide, population-based cohort design. All respiratory and psychiatric disorders are recorded in the database. Thus, we could trace all cases of newly diagnosed sleep apnea and depressive disorders. Moreover, we used a large sample size to detect differences between the two groups with statistical power.

Our study had several limitations. First, the NHIRD does not provide some relevant data including body mass index, smoking history, genetic or environmental factors, which are potential confounders associated with the risk of depressive disorders. Therefore, we used a nationwide database to lower the sample bias as much as possible. Second, the patients in this study were mainly of Chinese descent. The results of this study might not be generalizable to other ethnic populations. Third, sleep apnea types, polysomnography reports, obstructive apnea hypopnea index, or adenotonsillectomy records are not kept in the database. Besides, the number of children having HTN, DM and insomnia is so small that the bias could not be excluded. Further study may need more large sample to evaluate these variables when analyzing the relationship between sleep apnea and depressive disorders.

Our study showed that pediatric patients with sleep apnea have a significantly higher risk of depressive disorders, and the risk is higher in boys and those older than 12 years of age. Clinicians should be aware that depressive disorders are possible serious comorbidities in pediatric patients with sleep apnea.

Author Contributions

Conceptualization: Chun-Hung Chang, Shaw-Ji Chen, Chieh-Yu Liu.

Data curation: Chun-Hung Chang.

Formal analysis: Chun-Hung Chang.

Investigation: Chun-Hung Chang.

Methodology: Chun-Hung Chang.

Project administration: Chieh-Yu Liu.

Resources: Shaw-Ji Chen, Chieh-Yu Liu.

Software: Chieh-Yu Liu.

Supervision: Chieh-Yu Liu.

Writing – original draft: Chun-Hung Chang.

Writing – review & editing: Chieh-Yu Liu.

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