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The association between obstructive sleep apnea and the risk of poor delivery events in women: A population-based nested case–control study

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Abstract

Purpose: To investigate the risk of poor delivery events (PDEs; premature delivery, abortion, and stillbirth) in female subjects with obstructive sleep apnea (OSA).

Methods: The study identified 8346 female subjects with PDEs as cases between January 1, 2000 and December 31, 2015 from the Longitudinal Health Insurance Database 2005 in Taiwan. A total of 33,384 controls were also identified based on frequency matching for age and year of index date. Diagnoses of OSA and PDEs were determined according to the International Classification of Diseases, 9th Revision. The risk of PDEs in female subjects with OSA was estimated with conditional logistic regression analyses.

Findings: The mean age of the 41,730 female subjects was 35.53 years. The overall incidence rate of PDEs was 506.22 per 100,000 person-years for subjects with OSA, which was significantly higher than that for the controls (501.95 per 100,000 person-years). The risk of PDEs was higher in subjects with OSA than in controls (adjusted odds ratio [AOR] = 1.19; 95% confidence interval [CI] [95% CI]: 1.08–1.43), including for premature delivery (AOR = 1.20; 95% CI: 1.16–1.50), and abortion (AOR = 1.19; 95% CI: 1.09–1.47). OSA showed no relation to stillbirth (AOR = 1.04; 95% CI: 0.99–1.31). The findings indicate that the longer a subject has been experiencing OSA, the higher the probability of PDEs.

Conclusions: The risk of PDEs associated with OSA was found in this study. In particular, the longer a subject has OSA, the higher the likelihood of PDEs, exhibiting a dose–response effect.

Clinical relevance: To effectively promote maternal health in clinical practice, health providers need to recognize OSA as a risk factor associated with negative pregnancy outcomes. Furthermore, OSA symptoms should be assessed and managed in all pregnant women to enable more comprehensive maternal care.

KEYWORDS
abortion, nested case–control study, obstructive sleep apnea, poor delivery events, premature delivery, stillbirth

INTRODUCTION

Obstructive sleep apnea (OSA) is a pervasive sleep disorder with an estimated global prevalence of 9%–38% (Senaratna et al., 2017). OSA is a confirmed risk factor associated with hypertension (Hou et al., 2018), type 2 diabetes (Lee et al., 2019), and motor vehicle crashes (Purtle et al., 2020). A previous study indicated that the male sex, older age, greater neck circumference, and obesity are factors associated with OSA (Hsu et al., 2019).

Recently, the relationship between sleep and pregnancy outcomes has become a matter of concern in the research field, and studies have reported that the prevalence of OSA in late pregnancy is as high as 15% (Pien et al., 2014). Maternal sleep-disordered breathing is also associated with an increased risk of gestational hypertension and gestational diabetes (Pamidi et al., 2014); chronic sleep loss during pregnancy may lead to stress overload, contributing to adverse pregnancy events (Palagini et al., 2014); and OSA during pregnancy can negatively impact perinatal outcomes, including preeclampsia, preterm delivery, low birth weight, and neonatal intensive care unit (NICU) admissions (Ding et al., 2014). Another study showed that pregnant women with a high risk of OSA were at an increased risk of preterm delivery compared with controls (Narungsri et al., 2016).

However, some conflicting studies have provided different viewpoints, where one study found no association between snoring or daytime sleepiness and the risk of late stillbirth (Stacey et al., 2011). Another study indicated no relationship between self-reported symptoms of sleep apnea for women who had stillborn fetuses (Gordon et al., 2015) or preterm births (Facco et al., 2014).

A previous study suggested that there is limited information on maternal sleep disorders and fetal outcomes, and existing evidence suggests that this is an important domain for future research (Warland et al., 2018). Therefore, this study is aimed at assessing the risk of poor delivery events (PDEs, including premature delivery, abortion, and stillbirth) among subjects with OSA using the Taiwan National Health Insurance Research Database (NHIRD).

METHODS

Data source

Our study data come from the Longitudinal Health Insurance Database 2005 (National Health Insurance Research Database, 2005). LHID is managed by the Taiwan Health and Welfare Data Science Centre and approximately 23 million Taiwanese residents are under the National Health Insurance (NHI) program. Disease diagnoses were collected from inpatient and outpatient files, which are categorized based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The NHIRD provides comprehensive information on the medical utilization of nearly all pregnant women and birth register records in Taiwan, thus offering a highly reliable opportunity to examine the relationship between OSA and pregnancy outcomes (Chen et al., 2012). To protect subjects' privacy, all identifiable information was encrypted and removed before the data was released. This study was approved by the Ethics Review Board of Tri-Service General Hospital, National Defence Medical Centre (TSGHIRB No. 1-106-05-169).

Study design and sampled subjects

This study applies a population-based nested case–control design. The case group was defined with subjects having an incident of PDEs by ICD-9-CM codes, including premature delivery (ICD-9-CM code 644.21), abortion (ICD-9-CM code 634.9), or stillbirth (ICD-9-CM code 656.43) that occurred between 2000 and 2015. The control group was selected from subjects without PDEs and was frequency-matched by age group and index year, with a control-to-case ratio of 4:1 using propensity scores (Figure 1). The exclusion criteria were women aged between <15 and >50.

Identification of OSA subjects

Using NHIRD, we selected subjects who had been diagnosed with OSA and had at least three outpatient sessions or one inpatient record based on ICD-9-CM codes (780.51, 780.53, and 780.57) between 2000 and 2015.

The definition of comorbidity and urbanization level

The comorbidities evaluated by ICD-9-CM in this study included type 2 diabetes, gestational diabetes mellitus, pre-eclampsia, eclampsia, cardiovascular disease, obesity, anxiety, thalassemia, depression, syphilis, and alcoholism. Additionally, the urbanization levels 1 (highest) to 4 (lowest) was defined based on previous studies (Liu et al., 2006; Tsai et al., 2018).

Statistical analysis

The descriptive statistics of the subjects' characteristic information includes the percentage, mean, and standard deviation. Chi-squared tests and Student's *t*-tests were used to compare the differences in terms of age, comorbidities, urbanization levels, parity, and delivery types. Additionally, conditional logistic regression was performed to evaluate the correlation between previous OSA history and the occurrence of PDEs among female subjects. Data are presented as odds ratios (ORs) with 95% confidence intervals (CIs). The threshold for statistical significance is $p < 0.05$. This study used SPSS (version 22, IBM Corp.) to perform all data analyses.

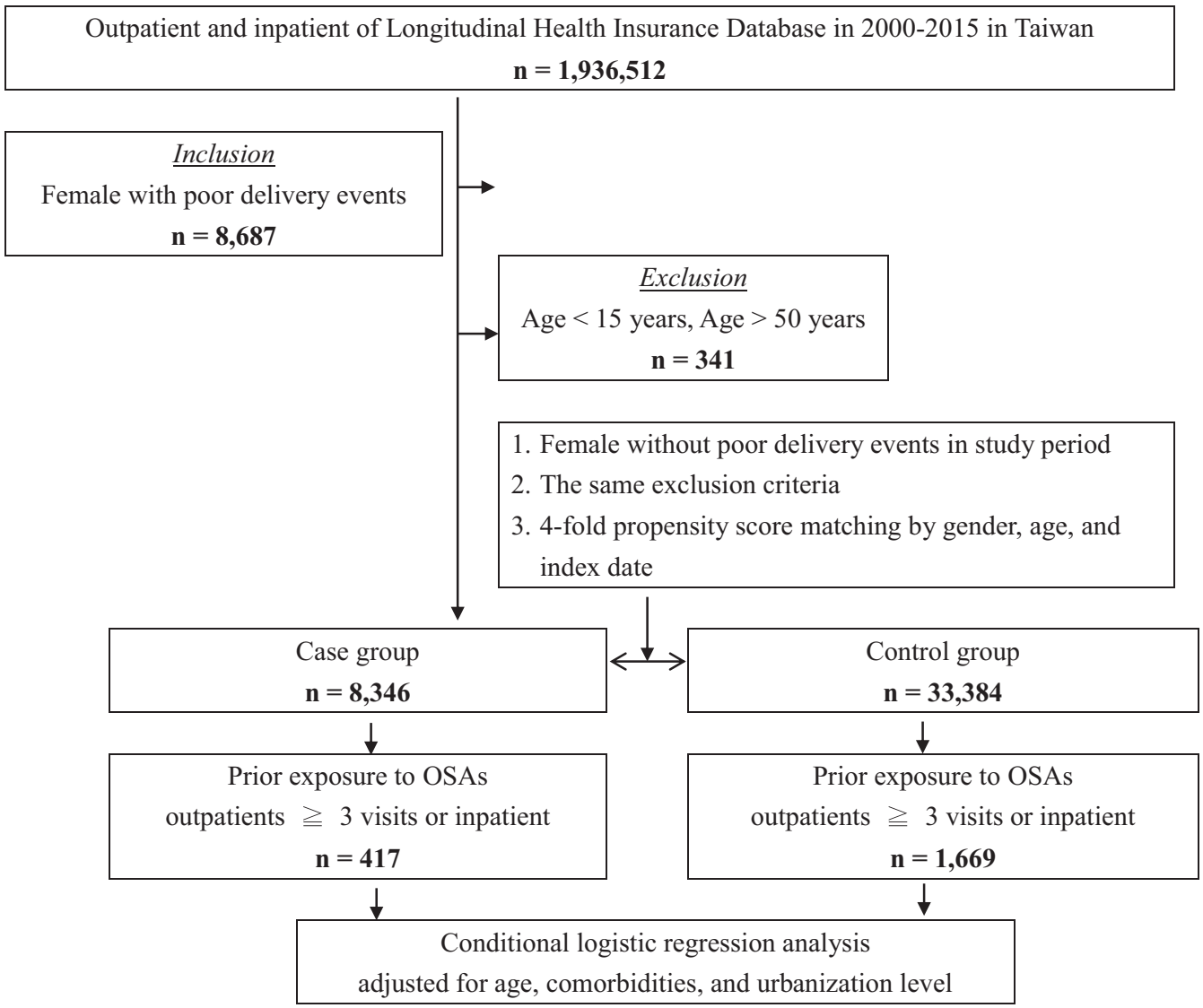

FIGURE 1 The flowchart of study design (nested case-control study) from national health insurance research database in Taiwan

RESULTS

As seen in Table 1, there are 8346 cases and 33,384 controls, with a mean age of 35.72 ± 19.20 and 35.48 ± 19.16 of the subjects, respectively. Compared with the controls, the subjects in the PDEs group had a higher prevalence of T2DM, anxiety, and depression. In the case group, those who were para 1 and had a cesarean section accounted for the majority.

Table 2 shows a significantly higher risk of PDEs in the subjects with OSA than in the controls (AOR = 1.19; 95% CI: 1.08–1.43). When the age group was considered, a significantly higher risk of PDEs in subjects aged 15–19 years and 45–49 years produced a smile curve (AOR = 1.22, 95% CI: 1.11–1.43; AOR = 1.24; 95% CI: 1.13–1.50, respectively). Subjects with a total number of comorbidities ≥3 had the highest risk of PDEs (AOR = 1.27; 95% CI: 1.15–1.52). Table 3 indicates that the risk of PDEs subtypes–premature delivery and abortion was higher in subjects with OSA than in controls according to conditional logistic regression analyses, yet no correlation between OSA and stillbirth was found. In addition, subjects with a longer history of OSA had a higher risk of PDEs (Table 4).

DISCUSSION

The present study shows that after adjustment for potential confounders (age, sex, comorbidities, urbanization levels, parity, and delivery types), subjects with OSA had a 19% higher risk of PDEs than controls. Furthermore, the PDEs that occurred were primarily premature delivery and abortion. In addition, this study found that the dose–response tended to increase with the duration of follow-up. When subjects had a history of OSA for <1 year, 1–2 years, and >2 years, the risk of PDEs increased by 14%, 20%, and 26%, respectively, compared with controls. These results display the risk of PDEs (premature delivery and abortion) associated with an OSA diagnosis in a nested case–control study, and these results are partially consistent with previous studies (Chen et al., 2012; Liu et al., 2019; Warland et al., 2018).

TABLE 1 Characteristics of case group and matched control group

Poor delivery events	Overall ($n = 41,730$)		With, case group ($n = 8346$)		Without, control group ($n = 33,384$)		
Variables	*n*	%	*n*	%	*n*	%	*p*
Age (year)	35.53 ± 19.17		35.72 ± 19.20		35.48 ± 19.16		0.306
Age group (year)							0.999
15–19	1670	4.00	334	4.00	1336	4.00	
20–24	4860	11.65	972	11.65	3888	11.65	
25–29	4440	10.64	888	10.64	3552	10.64	
30–34	7135	17.10	1427	17.10	5708	17.10	
35–39	7865	18.85	1573	18.85	6292	18.85	
40–44	7800	18.69	1560	18.69	6240	18.69	
45–49	7960	19.08	1592	19.08	6368	19.08	
Comorbidities							
DM	7329	17.56	1577	18.90	5752	17.23	<0.001***
GDM	670	1.61	281	3.37	389	1.17	<0.001***
Preeclampsia	568	1.36	491	5.88	77	0.23	<0.001***
Eclampsia	395	0.95	351	4.21	44	0.13	<0.001***
CVD	3922	9.40	1026	12.29	2896	8.67	<0.001***
Thalassemia	211	0.51	44	0.53	167	0.50	0.731
Obesity	321	0.77	77	0.92	244	0.73	0.080
Anxiety	2570	6.16	1556	18.64	1014	3.04	<0.001***
Depression	2108	5.05	1322	15.84	786	2.35	<0.001***
Syphilis	102	0.24	39	0.47	63	0.19	<0.001***
Alcoholism	99	0.24	29	0.35	70	0.21	0.031*
Urbanization level							0.293
1 (The highest)	10,460	25.07	2125	25.46	8335	24.97	
2	11,144	26.71	2264	27.13	8880	26.60	
3	9962	23.87	1986	23.80	7976	23.89	
4 (The lowest)	10,164	24.36	1971	23.62	8193	24.54	
Parity							<0.001***
1	25,294	60.61	5562	66.64	19,732	59.11	
≧2	16,436	39.39	2784	33.36	13,652	40.89	
Delivery type							<0.001***
Normal spontaneous delivery	21,523	51.58	4003	47.96	17,520	52.48	
Cesarean section	20,207	48.42	4343	52.04	15,864	47.52	

Abbreviations: CVD, cardiovascular disease; DM, type 2 diabetes; GDM, Gestational diabetes mellitus.
*$p < 0.05$; ***$p < 0.001$.

Although the mechanism by which OSA increases the risk of PDEs remains unclear, previous studies suggested some plausible pathophysiological mechanisms that may explain these findings. OSA was confirmed to increase metabolic impairment, which was well understood to contribute to the development of insulin resistance, lipolysis, and gestational diabetes (Izci-Balserak & Pien, 2014; Peled et al., 2007). OSA also leads to greater resistance to airflow as a stimulus to elevate sympathetic nervous system activity, leading to a significantly greater impact on overall oxygen homeostasis in pregnant women (Peled et al., 2007; Unnikrishnan et al., 2015). Over time, repeated hypoxemia, hemodynamic loading, and adrenergic activation lead to chronic systemic inflammation and oxidative vascular injury (Louis et al., 2014). Vascular inflammatory processes leading to endothelial dysfunction increase peripheral vascular resistance and decrease cardiac output, which may then worsen uterine and placental blood flow and increase the risk of fetal compromise (Pien et al., 2014). Another study showed that chronic hypoxemia may activate the stress-related hypothalamic-pituitary-adrenal axis, triggering an abnormal immune response and leading to adverse pregnancy outcomes

TABLE 2 Factors of poor delivery events stratified by variables listed in the table by using conditional logistic regression

	With OSAs			Without OSAs			With OSAs versus Without OSAs (Reference)		
Stratified	**Espouse**	**PYs**	**Rate**	**Espouse**	**PYs**	**Rate**	**AOR**	**95% CI**	***p***
Overall	417	82,375.02	506.22	1669	332,504.64	501.95	1.19	1.08–1.43	0.010*
Age group (year)									
15–19	39	7502.44	519.83	150	29,884.25	501.94	1.22	1.11–1.43	0.001**
20–24	44	8678.26	507.01	184	36,701.08	501.35	1.19	1.08–1.43	0.016*
25–29	59	11,689.13	504.74	244	48,605.47	502.00	1.18	1.07–1.42	0.021*
30–34	69	13,802.44	499.91	279	55,597.22	501.82	1.17	1.06–1.41	0.039*
35–39	60	10,375.24	578.30	297	51,383.16	578.01	1.18	1.07–1.42	0.024*
40–44	65	12,645.39	514.02	266	52,997.11	501.91	1.20	1.00–1.44	0.007**
45–49	81	17,682.12	458.09	249	57,336.35	434.28	1.24	1.13–1.50	<0.001***
Comorbidities									
Without	89	19,860.55	448.12	307	62,279.22	492.94	1.07	0.97–1.28	0.203
1–2 type	125	25,011.40	499.77	571	112,701.54	506.65	1.16	1.05–1.39	0.042*
≥3 type	203	37,503.07	541.29	791	157,523.88	502.15	1.27	1.15–1.52	0.001**
Urbanization level									
1	106	20,876.55	507.75	420	84,869.72	494.88	1.21	1.10–1.43	0.007**
2	128	25,701.20	498.03	486	99,702.56	487.45	1.20	1.09–1.43	0.011*
3	84	16,979.31	494.72	334	66,678.03	500.91	1.16	1.03–1.40	0.042*
4	99	18,817.96	526.09	429	81,254.33	527.97	1.17	1.07–1.42	0.031*
Parity									
1	214	42,256.21	506.43	844	169,051.72	499.26	1.18	1.08–1.43	0.017*
≧2	203	40,118.81	506.00	825	163,452.92	504.73	1.19	1.09–1.45	0.003**
Delivery type									
Normal spontaneous delivery	159	30,978.75	513.26	780	152,780.67	510.54	1.18	1.07–1.42	0.013*
Cesarean section	258	51,396.27	501.98	889	179,723.97	494.65	1.20	1.11–1.52	<0.001***

Notes: Rate: per 100,000 PYs. Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.
Interaction term (Age group × Comorbidities): $p = 0.238$.
Interaction term (Age group × Parity): $p = 0.176$.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

TABLE 3 Factors of poor delivery events subtypes by using conditional logistic regression

	With OSAs			Without OSAs			With OSAs versus Without OSAs (Reference)		
Poor delivery events subtypes	**Espouse**	**PYs**	**Rate**	**Espouse**	**PYs**	**Rate**	**AOR**	**95% CI**	***p***
Overall	417	82,375.02	506.22	1669	332,504.64	501.95	1.19	1.08–1.43	0.010*
Premature delivery	180	82,375.02	218.51	683	332,504.64	205.41	1.20	1.16–1.50	0.003**
Abortion	133	82,375.02	161.46	531	332,504.64	159.70	1.19	1.09–1.47	0.011*
Stillbirth	104	82,375.02	126.25	455	332,504.64	136.84	1.04	0.99–1.31	0.059

Note: Rate: per 100,000 PYs. Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; OSA, obstructive sleep apnea; PYs, person years.
*$p < 0.05$; **$p < 0.01$.

(Palagini et al., 2014). This evidence may explain the results, as subjects with a longer history of OSA show a higher risk of PDEs (premature delivery and abortion).

No statistical significance was found for the association between OSA and stillbirth in this study after adjusting for confounders, consistent with the results of a previous study (Bin et al., 2016; Louis et al.,

TABLE 4 Factors of poor delivery events among different OSAs exposure period by using conditional logistic regression

The first OSAs exposure to the last one before poor delivery events diagnosis	With OSAs versus Without OSAs (Reference)		
	AOR	95% CI	*p*
Overall	1.19	1.08–1.43	0.010*
< 1 year	1.14	1.03–1.38	0.027*
≧1 year, <2 years	1.20	1.16–1.52	0.001**
≧2 years	1.26	1.19–1.58	<0.001***

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

2014). However, the relationship between OSA and stillbirth remains controversial. Some studies support an association between OSA and stillbirth, suggesting that OSA may be related to persistent hypoxia, inflammation, stress oxidation, and compromised sleep positions, thus inducing a negative effect on the fetus (Warland et al., 2018). However, the true mechanisms underlying the relationship between OSA and stillbirth remain unknown. We suggest that those who are interested conduct studies with larger sample sizes or longer observation periods.

Interestingly, our study found a significantly higher risk of PDEs in subjects aged 15–19 years and aged 45–49 years, with the results forming a smile curve. A previous study indicated that the prevalence and severity of OSA increase with age (Senaratna et al., 2017), and the results in this study show that OSA in the 45–49-year age group increased the probability of PDEs by 24%. A previous study demonstrated that pregnant women aged 45 years and older experience significantly more medical and obstetric complications, such as fetal death and gestational diabetes, than women under 35 years of age (Grotegut et al., 2014). The high PDEs risk among women aged 45 years and older is likely multifactorial; these results indicate that age and OSA play an important role in the probability of PDEs. In addition, 15–19-year-old pregnant women with OSA constitute another high-risk group for PDEs. A Swedish study found that teenage girls aged 17 years or younger were at higher risk of preterm birth than women aged 20–24 years, possibly because of the association between pregnancy at younger ages and poor socioeconomic situations (Olausson et al., 1997) or because younger women were more likely to smoke or use drugs, receive inadequate prenatal care, and have inadequate weight gain during pregnancy (Chen et al., 2007; Grotegut et al., 2014).

This study is one of few to utilize diagnostic criteria for OSA and PDEs to perform a population-based case–control study. However, several potential limitations of this study should be considered. First, the NHIRD does not provide detailed information on socioeconomic factors or risky behaviors during pregnancy, such as the use of alcohol, tobacco, and drugs. Second, the NHIRD data do not contain detailed information on the severity of OSA, such as apnea-hypopnea index (AHI) scores, respiratory disturbance index (RDI), or different levels of AHI or RDI to reflect the severity of a subject's OSA condition. Therefore, we could not evaluate the relationship between the severity of OSA and adverse pregnancy outcomes in this study. Third, study subjects were selected using medical records from the NIHRD. Data for subjects who had OSA but did not undergo treatment or assessment in the medical system were not recorded in the NIHRD; therefore, the researchers cannot exclude the probability of underestimating the prevalence of OSA during pregnancy. A previous study also indicated that most pregnant subjects were not routinely screened for OSA symptoms (Spence et al., 2017). Fourth, OSA has a high correlation with body mass index (Dong et al., 2020), however, NHIRD data do not provide the data of body mass index. Although we adjusted confounding factors of obesity by ICD-9-CM, we could not exclude the potential residual bias that might affect the results.

CONCLUSION

The study shows that OSA is associated with an increased prevalence of PDEs (premature delivery and abortion), particularly among younger and older pregnant women. These results can increase healthcare professionals' awareness of OSA's correlation with an increased probability of an abnormal delivery.

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Jui-Chiung Sun, Chia-Ling Lin, and Wu-Chien Chien had the original idea for the study and, with all coauthors, executed the design. Chi-Hsiang Chung was responsible for data cleaning and analyses. Jui-Chiung Sun drafted the manuscript, which was revised by all authors. All authors read and approved the final manuscript.

CLINICAL RESOURCES

- World Health Organization (WHO): Chronic respiratory diseases https://www.who.int/respiratory/other/Obstructive_sleep_apnoea_syndrome/en/
- Breathe: The lung association https://www.lung.ca/lung-health/lung-disease/sleep-apnea
- SleepFoundation.org: Sleep apnea https://www.sleepfoundation.org/sleep-apnea

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