ORIGINAL RESEARCH

The 3% Oxygen Desaturation Index is an Independent Risk Factor for Hypertension Among Children with Obstructive Sleep Apnea

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Background: Obstructive sleep apnea (OSA) and obesity are both directional risk factors of hypertension. Chronic intermittent hypoxemia (IH) is a commonly observed pathophysiological mechanism involved in multiple comorbidities of OSA. However, their interactions are not well understood in children. This study aimed to investigate the associations of IH indexes (oxygen desaturation index 3% [ODI3], mean peripheral oxygen saturation [SpO₂], least SpO₂, and time with SpO₂ < 85%), apnea-hypopnea index, and weight status with hypertension in a sample of pediatric OSA patients.

Methods: The medical records of 365 pediatric OSA patients were retrospectively reviewed in this cross-sectional study. Demographics, anthropometrics, standard in-laboratory polysomnography, and nocturnal blood pressure were collected. Multivariate logistic regression with forward selection was used to identify independent predictors of hypertension.

Results: Multivariate logistic regression analysis showed that ODI3 (odds ratio [OR] = 1.02, 95% confidence interval [CI] = 1.01-1.03) and body mass index z-score (OR = 1.34, 95% CI = 1.12-1.60) were independent continuous predictors of pediatric hypertension, whilst severe OSA (OR = 2.62, 95% CI = 1.60-4.29) and overweight/obesity (OR = 2.63, 95% CI = 1.59-4.34) were independent categorical predictors. Traditional risk factors including male sex (OR = 2.33, 95% CI = 1.02-5.33), late childhood/ adolescence (OR = 1.98, 95% CI = 1.01-3.88), and overweight/obesity (OR = 2.97, 95% CI = 1.56-5.67) combined with sleep hypoxemia (least SpO₂ \leq 95%) (OR = 2.24, 95% CI = 1.16–4.04) predicted hypertension ($R^2 = 0.21$) in the severe IH subgroup (n = 205), while the no/mild IH subgroup (n = 160) had an entirely different predictor, severe OSA (OR = 3.81, 95% CI = 1.49–9.74) (R^2 = 0.07).

Conclusion: The close relationships among IH, overweight/obesity, and hypertension highlight the importance of reducing IH and body weight in children with OSA.

Keywords: children, oxygen desaturation index, intermittent hypoxemia, obesity, obstructive sleep apnea, predictive model

Introduction

Obstructive sleep apnea (OSA) is a chronic sleep condition characterized by repetitive partial collapses and/or complete obstructions of the upper airway due to respiratory control instability and upper airway dysfunction.¹ The prevalence of OSA ranges between 1% and 6% among children.² The diagnosis of OSA requires comprehensive history taking and physical examination prior to a standard polysomnography (PSG), and congenital structural abnormalities should be carefully inspected and exclusion. OSA can induce intermittent hypoxemia (IH), oxidative stress, elevated sympathetic

cc 0 S © 2022 Chuang et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms by not and incorporate the Creative Commons Attribution — Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php). nerve activity, vascular endothelial dysfunction, inflammation, and metabolic dysregulation, leading to a wide range of adverse outcomes on multiple organ systems.³

IH, a pathophysiological manifestation commonly observed in OSA, is considered involved in the elevation of blood pressure (BP) in patients with disordered sleep.⁴ IH dysregulates hypoxia-inducible factors, increases reactive oxygen species, activates chemoreflex, suppresses baroreflex, stimulates the sympathetic nervous system, and leads to hypertension.⁵ In adults with OSA, nocturnal IH (in terms of oxygen desaturation index 4% [ODI4]⁶ and oxygen desaturation rate⁷) played a more important role in hypertension than AHI. Adenotonsillectomy has been shown to significantly reduce IH and improve office⁸ as well as nocturnal BP⁹ among pediatric OSA patients with hypertension. Moreover, chronic IH has been associated with growth delay, behavioral impairment, and academic underperformance in children with SDB.¹⁰

Obesity is another well-known risk factor for pediatric hypertension.¹¹ In healthy school-aged children, a body mass index (BMI) $\geq 18.75 \text{ kg/m}^2$ has been independently associated with hypertension.¹² Among children with SDB, obesity (defined as BMI z-score $\geq 1.645^{13}$) has been shown to be an independent predictor of hypertension, along with older age and severe SDB (apnea-hypopnea index [AHI] ≥ 10 events/h^{14,15}). Previous studies have suggested that pediatric hypertension increases along with childhood obesity,¹⁶ and that hypertension further contributes to the clustering of obesity-related cardio-metabolic risk factors.¹⁷ Moreover, obesity increases fat accumulation in the parapharyngeal space¹⁸ and reduces lung volume,¹⁹ which can also cause or aggravate OSA. Notably, pediatric OSA, obesity, and hypertension are likely to persist into adulthood and then further increase the risks of cardiovascular diseases and mortality.²⁰ As the detrimental physiological effects of these chronic conditions develop and progress over time, early recognition with timely management is essential.

Hypertension is one of the earliest recognized comorbidities of OSA, and it plays a cardinal role in the development of other unfavorable health outcomes including premature mortality.^{4,21,22} A Taiwan National Health Insurance Research Database study reported that the prevalence of hypertension in patients with OSA was as high as 37%, and that cardiovascular events were the most common cause of death.²³ In addition, the Wisconsin Sleep Cohort Study reported that patients with severe sleep-disordered breathing (SDB) had a 3.8-fold higher risk of all-cause mortality after 18 years of follow-up, and an even higher 5.2-fold higher risk of cardiovascular mortality.²⁴ Similar to that in adults, hypertension is a common comorbidity among pediatric OSA patients. A hospital-based study in Taiwan reported a prevalence of hypertension of 27% among children with SDB.¹⁴

Both obesity and OSA are well-known to have bidirectional associations with hypertension in adults.^{25,26} However, little is known about the relationships among IH, weight status, and hypertension in children with OSA. We hypothesized that IH may be an independent risk factor for hypertension in this disease population. Therefore, this study aimed to investigate the associations of oxygen desaturation index 3% (ODI3), mean peripheral oxygen saturation (SpO₂), least SpO₂, time with SpO₂ < 85%, AHI, and weight status with hypertension in a cohort of pediatric OSA patients.

Materials and Methods

Data Availability Statement

The data underlying this article cannot be shared publicly due to the privacy of the individuals who participated in the study. The data can be shared at reasonable request to the corresponding author.

Study Design and Subjects

The investigators retrospectively reviewed the medical charts of pediatric patients with OSA at the ear, nose, and throat outpatient clinic of a tertiary medical center (Chang Gung Memorial Hospital, Linkou Main Branch) in northern Taiwan between 01 January 2010 and 31 December 2019. This study was approved by the Institutional Review Board of Chang Gung Medical Foundation, Taiwan (No. 202000873B0; date of approval: 22 May 2020). The requirement for written informed consent was waived. This study followed the guidelines of the World Medical Association Declaration of Helsinki²⁷ and the Strengthening the Reporting of Observational Studies in Epidemiology.²⁸

The inclusion criteria were: (a) age 2–18 years, and (b) PSG-diagnosed OSA (an obstructive AHI \ge 2.0 events/h or an obstructive apnea index \ge 1.0 events/h²⁹). The exclusion criteria were: (a) lack of complete PSG data, (b) absence of BP data, (c) chronic inflammatory disorders such as asthma, allergies, eczema, or other atopic/autoimmune diseases,³⁰ and (d) craniofacial or neuromuscular disorders.³¹

Demographics

Age at the diagnosis of OSA and sex were recorded. The overall cohort was further divided into three development stage subgroups: toddler/preschool (≥ 2 years old and < 5 years old), early childhood (≥ 5 years old and < 8 years old), and late childhood/adolescence (≥ 8 years old and < 18 years old).¹⁴

Anthropometrics

BMI z-score was calculated based on the United States Centers for Disease Control and Prevention 2000 growth charts.³² Weight status was categorized into three subgroups based on BMI z-score: underweight (≤ -1.645), normal weight (≥ -1.645 and < 1.036), and overweight/obesity (≥ 1.036).³³

Neck circumference (NC) has been associated with systolic BP,³⁴ and it was measured at the thyroid cartilage level.³⁵ Neck size was further categorized into three subgroups according to NC: small (< 26.0 cm), middle (\geq 26.0 cm and < 31.0 cm), and large (\geq 31.0 cm).

Tonsil size was graded according to occupation of the oropharynx (grade 1: 0%-25%; grade 2: 26%-50%; grade 3: 51%-75%; and grade 4: 76-100%),³⁶ and adenoid size was graded according to the degree of obstruction of the posterior choana (grade 1: 0%-25%; grade 2: 26%-50%; grade 3: 51%-75%; and grade 4: 76-100%)³⁷ by two senior investigators (Li, H.-Y. and Lee, L.-A.) following a previously reported procedure.³⁸ Tonsil size and adenoid size were further categorized into three subgroups: grades 1 and 2, grade 3, and grade 4.

Polysomnography

All participants underwent whole night, board-certified sleep technician-attended, in-laboratory PSG (Nicolet Biomedical Inc., Madison, WI, USA) accompanied by a family member.³⁹ The PSGs were performed by the same registered sleep technologists and manually verified by the study investigators (Chuang, L.-P. and Huang, Y.-S.). Using the 2012 American Academy of Sleep Medicine Scoring Manual,⁴⁰ apnea was defined as \geq 90% reduction of airflow for \geq 2 breaths, and hypopnea was defined as \geq 30% reduction of airflow with either oxygen desaturation \geq 3% or electro-encephalographic arousal for \geq 2 breaths. Obstructive AHI and apnea index were then calculated accordingly. The following disease parameters for OSA were also obtained: AHI, ODI3, mean SpO₂, least SpO₂, and time with SpO₂ < 85%.

The subjects were further divided into three OSA severity subgroups according to AHI: mild OSA (< 5.0 events/h), moderate OSA (\geq 5.0 events/h and < 10.0 events/h), and severe OSA (\geq 10.0 events/h).⁴⁰

ODI3 was defined as the number of times SpO₂ dropped to \geq 3% per hour of recording. The subjects were further categorized into three desaturation subgroups based on ODI3: mild desaturation (< 5.0 events/h), moderate desaturation (\geq 5.0 events/h) and severe desaturation (\geq 10.0 events/h).⁴¹

The subjects were further categorized into three subgroups of sleep hypoxemia according to the mean SpO₂: no sleep hypoxemia (> 95.0%), mild sleep hypoxemia (> 90.0% and \leq 95.0%), and severe sleep hypoxemia (\leq 90.0%).⁴²

The overall cohort was also divided into three subgroups of IH according to least SpO₂: no IH (> 94.0%), mild IH (> 88% and \leq 94%), and severe IH (\leq 88%).^{43,44}

The subjects were further categorized into three hypoxemia time subgroups according to time with $\text{SpO}_2 < 85\%$: zero hypoxemia time (time with $\text{SpO}_2 < 85\% = 0$), short hypoxemia time (> 0 min and ≤ 3.0 min), and long hypoxemia time (> 3.0 min).⁴³

Blood Pressure

Nocturnal BP was measured using an optimal cuff for children.⁴⁵ Routine BP measurements were performed three times using a standard automatic sphygmomanometer on the night of PSG between 10:00 and 11:00 PM.⁴⁶ Sleep technicians

used the auscultatory method to confirm pediatric hypertension in those with a high systolic or diastolic BP. Systolic and diastolic BP z-scores were calculated after adjusting for age, sex, and height z-score. Pediatric hypertension was defined as an SBP z-score ≥ 1.645 or DBP z-score ≥ 1.645 .⁴⁷ The patients were then categorized into two BP subgroups: normotensive subgroup (neither SBP z-score ≥ 1.645 nor DBP z-score ≥ 1.645), and hypertensive subgroup (either SBP z-score ≥ 1.645).

Statistical Analysis

The normality of continuous variables was analyzed using the Kolmogorov–Smirnov test and none of them was normally distributed. Data were reported as medians (interquartile ranges) for non-normally distributed continuous and ordinal variables, and absolute numbers (percentages) for nominal variables. Skewed continuous and ordinal data were compared using the Mann–Whitney *U*-test. Categorical data were compared using the X^2 test or Mantel-Haenszel test for trend, as appropriate. Associations between the selected variables were analyzed using the Spearman correlation test and point biserial correlation test, as appropriate.

For the best trade-off between sensitivity and specificity of the selected variables to detect pediatric hypertension, the Youden's J static was used to determine the optimal cut-off value of receiver operating characteristic curves.⁴⁸ Furthermore, univariate and multivariate logistic regression models were used to assess the categorical and dichotomized variables. To improve the regression performance, variables with a *P*-value ≤ 0.10 were included in the full model, and forward selected to obtain the parsimonious model. Statistical significance was accepted at a two-sided *P*-value < 0.05. The collected data were statistically analyzed using SPSS software version 25.0 (International Business Machines Corp., Armonk, NY, USA).

Results

Case Inclusion Flow Chart

Figure 1 demonstrates the case inclusion flow chart. A total of 458 surgery-naïve children with OSA were identified, of whom 35 were not included due to being < 2 years of age (n = 5) and not undergoing standard PSG (n = 30). Among the remaining 423 eligible patients, 58 were excluded due to a lack of complete PSG data (n = 29), lack of BP data (n = 18), chronic inflammation disorders (n = 9), and craniofacial/neuromuscular disorders (n = 2). Consequently, 365 children



Figure I Inclusion flow chart of the study participants. Abbreviation: OSA, obstructive sleep apnea.

with OSA (265 [72.6%] boys and 100 [27.4%] girls) were analyzed (Table 1). Ninety-nine (27.1%) of the children had hypertension, and 266 (72.9%) had normal BP.

The median age was 7 (interquartile range = 5-9) years. There were 133 (36.4%) toddlers/preschoolers, 129 (35.1%) early childhood patients, and 104 (28.5%) late childhood patients/adolescents.

The median BMI z-score was 0.800 (interquartile range = -0.285-1.810). Of the enrolled children, 22 (6.0%) were underweight, 237 (64.9%) had normal weight, and 106 (29.0%) had overweight/obesity. Furthermore, the median NC was 28 (26–31) cm, including 83 (22.7%) children with a small neck size, 188 (51.5%) with a middle neck size, and 94 (25.8%) with a large neck size.

The median tonsil size was grade 3 (interquartile range: 3-4), including 60 (16.4%) patients who had grade 1 or grade 2 tonsils, 173 (47.4%) who had grade 3 tonsils, and 132 (36.2%) who had grade 4 tonsils. The median adenoid size was grade 3 (2–4). The three tonsil size subgroups included 102 (28.0%) with grade 1 and 2 adenoids, 126 (34.5%) with grade 3 adenoids, and 137 (37.5%) with grade 4 adenoids.

The median AHI was 9.1 (4.1–20.8) events/h, including 108 (29.6%) children with mild OSA, 87 (23.8%) with moderate OSA, and 170 (46.6%) with severe OSA. The median ODI3 was 6.4 (2.4–17.9) events/h, including 149 (40.8%) children with mild desaturation, 69 (18.9%) with moderate desaturation, and 147 (40.3%) with severe desaturation. In addition, the median ODI3 was 6.4 (2.4–17.9) events/h, including 149 children (40.8%) with moderate desaturation, 69 (18.9%) with moderate desaturation. The median mean SpO₂ was 96% (95–97%), including 258 (70.7%) children with no sleep hypoxemia, 87 (23.8%) with mild sleep hypoxemia, and 20 (5.5%) with severe sleep hypoxemia. The median least SpO₂ was 87% (82–91%), including 26 (7.1%) children with severe IH. Finally, the median time with SpO₂ < 85% was 0 (0–0.45) min, including 218 (59.7%) children with zero hypoxemia time, 102 (28.0%) with a short hypoxemia time, and 45 (12.3%) with a long hypoxemia time.

Demographic, Anthropometric, and Polysomnographic Characteristics of the Two Subgroups Stratified by Pediatric Hypertension

Notably, significantly more of the children with hypertension were male (P = 0.02), had a higher BMI z-score (P < 0.001; Figure 2A), and had a higher NC (P < 0.001) compared to the children without hypertension (Table 1). Furthermore, the hypertensive subgroup had a higher median AHI ($P \le 0.001$), ODI3 ($P \le 0.001$; Figure 2B), and time with SpO₂ $\le 85\%$ (P = 0.004), and a lower median mean SpO₂ (P = 0.002) and least SpO₂ (P = 0.01) than the normotensive subgroup. Trends of the increasing prevalence of pediatric hypertension were observed in the overweight/obesity subgroup ($P \le 0.001$; Figure 3A), in the large neck size subgroup (P = 0.002), in the severe OSA subgroup ($P \le 0.001$; Figure 3B), severe desaturation subgroup (P = 0.001; Figure 3C), mild/severe sleep hypoxemia subgroup ($P \le 0.001$; Figure 3F).

Associations Between Pediatric Hypertension and Selected Variables in the Overall Cohort

In the overall cohort, hypertension was significantly associated with male sex (r = 0.13, P = 0.02), BMI z-score (r = 0.21, P < 0.001), weight status (r = 0.22, P < 0.001), NC (r = 0.19, P < 0.001), neck size (r = 0.16, P = 0.002), AHI (r = 0.21, P < 0.001), OSA severity (r = 0.20, P < 0.001), ODI3 (r = 0.19, P < 0.001), desaturation severity (r = 0.18, P = 0.001), mean SpO₂ (r = -0.16, P = 0.002), sleep hypoxemia (r = 0.19, P = 0.001), least SpO₂ (r = -0.14, P = 0.01), IH (r = 0.12, P = 0.03), time with SpO₂ < 85% (r = 0.15, P = 0.004), and hypoxemia time (r = 0.16, P = 0.002). In contrast, pediatric hypertension was not statistically significantly associated with age (r = 0.06, P = 0.28), development stage (r = 0.09, P = 0.10), tonsil size (r = 0.05, P = 0.34), tonsil size subgroup (r = 0.05, P = 0.34).

Male sex was associated with age (r = 0.13, P = 0.01), BMI z-score (r = 0.13, P = 0.01), NC (r = 0.16, P = 0.003), and adenoid size (r = -0.11, P = 0.04). Age was also associated with NC (r = 0.63, P < 0.001), BMI z-score (r = 0.27, P < 0.001), adenoid size (r = -0.34, P < 0.001), ODI3 (r = 0.11, P = 0.046), and mean SpO₂ (r = -0.13, P = 0.02). In addition, BMI

Table I	Demographic,	Anthropometric,	and	Polysomnographic	Measures	of	the	Overall	Cohort a	: Well	as	Normotensive	and
Hyperter	sive Subgroups												

Characteristics	All Participants	Normotensive Subgroup	Hypertensive Subgroup	P -value	
	(n = 365)	(n = 266)	(n = 99)		
Demographic measures					
Sex subgroup					
Female sex	n = 100	82 (82.0)	18 (18.0)	0.02 ^a	
Male sex	n = 265	192 (69.1)	86 (30.9)		
Age, y	7 (5–9)	7 (5–9)	8 (5-10)	0.28 ^b	
Development stage					
Toddler/preschooler	n = 133	99 (74.4)	34 (25.6)	0.08 ^c	
Early childhood	n = 129	101 (78.9)	27 (21.1)		
Late childhood/adolescence	n = 104	66 (63.5)	38 (36.5)		
Anthropometric measures		I			
BMI z-score	0.800 (-0.285-1.810)	0.565 (-0.353-1.428)	1.540 (-0.080-2.170)	< 0.001 ^b	
Weight status					
Underweight	n = 22	18 (81 8)	4 (182)	< 0.001°	
Normal weight	n = 237	188 (79.3)	49 (20.7)	0.001	
	n = 106	60 (56 6)	46 (43.4)		
NC cm	28 (26-31)	27 (26-30)	29 (27-33)	< 0.001 ^b	
Neck size	10 (10 51)	27 (20 50)	27 (27 55)	0.001	
Small neck size	n = 83	66 (79 5)	17 (20 5)	0.002°	
Middle neck size	n = 188	144 (76.6)	44 (23.4)	0.002	
	n = 94	56 (59 6)	38 (40.4)		
Tonsil size grade	3 (3-4)	3 (3-4)	3 (3-4)	0 34 ^b	
Tonsil subgroup	5 (5 1)	5 (5 1)	5 (5 1)	0.01	
Grades L and 2	n = 60	45 (75 0)	15 (25 0)	0.36°	
Grade 3	n = 173	129 (74 6)	44 (25.4)	0.50	
Grade 4	n = 132	92 (69 7)	40 (30 3)		
Adenoid size	3 (2-4)	3 (2-4)	3 (2-4)	0.34 ^b	
Adenoid subgroup	• (= -)	- (- ·)	• ()		
Grades L and 2	n = 102	77 (75 5)	25 (24 5)	0 34 ^c	
Grade 3	n = 126	93 (73.8)	33 (26.2)		
Grade 4	n = 137	96 (70.1)	41 (29.9)		
			(=)		
Polysomnographic measures					
AHI, events/h	9.1 (4.1–20.8)	8.0 (3.7–17.5)	16.5 (7.0–27.6)	< 0.001 ^b	
OSA severity				_	
Mild OSA	n = 108	87 (80.6)	21 (19.4)	< 0.001°	
Moderate OSA	n = 87	74 (85.1)	13 (14.9)		
Severe OSA	n = 170	105 (61.8)	65 (38.2)	_	
ODI3, events/h	6.4 (2.4–17.9)	5.4 (2.2–14.7)	12.5 (3.6–27.8)	< 0.001°	
Desaturation degree				_	
Mild desaturation	n = 149	119 (79.9)	30 (20.1)	0.001°	
Moderate desaturation	n = 69	55 (79.7)	14 (20.3)		
Severe desaturation	n = 147	92 (62.6)	55 (37.4)	r b	
Mean SpO ₂ , %	96 (95–97)	97 (95–97)	96 (94–97)	0.002 ^b	
Sleep hypoxemia			_		
No sleep hypoxemia	n = 258	201 (77.9)	51 (22.1)	0.004 ^c	
Mild sleep hypoxemia	n = 87	53 (60.9)	34 (39.1)		
Severe sleep hypoxemia	n = 20	12 (60.0)	8 (40.0)		

(Continued)

Table I (Continued).

Characteristics	All Participants (n = 365)	Normotensive Subgroup (n = 266)	Hypertensive Subgroup (n = 99)	P-value
Least SpO ₂ , %	87 (82–91)	88 (83–91)	85 (79–90)	0.01 ^b
IH				
No IH	n = 44	34 (77.3)	10 (22.7)	0.04 ^c
Mild IH	n = 116	93 (80.2)	23 (19.8)	
Severe IH	n = 205	139 (67.8)	66 (32.2)	
Time with SpO ₂ <85%, min	0 (0–0.45)	0 (0–0.26)	0.03 (0-1.22)	0.004 ^b
Hypoxemia time				
Zero hypoxemia time	n = 218	169 (77.5)	49 (22.5)	< 0.001°
Short hypoxemia time	n = 102	75 (73.5)	27 (26.5)	
Long hypoxemia time	n = 45	22 (48.9)	23 (51.1)	

Notes: Continuous data are displayed as medians (interquartile ranges); categorical data are expressed as numbers (percent). ^aDifferences between groups were compared using the X^2 test. ^bThe Mann–Whitney *U*-test was performed between normotensive and hypertensive subgroups. ^cData were compared using the Mantel-Haenszel test for trend.

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; IH, intermittent hypoxemia; NC, neck circumference; ODI3, 3% oxygen desaturation index; OSA, obstructive sleep apnea; SpO₂, peripheral oxygen saturation.

z-score was further correlated with NC (r = 0.72, P < 0.001), AHI (r = 0.22, P < 0.001), ODI3 (r = 0.29, P < 0.001), mean SpO₂ (r = -0.27, P < 0.001), least SpO₂ (r = -0.26, P < 0.001), and time with SpO₂ < 85% (r = 0.28, P < 0.001).

Important Variables Predicting Hypertension Using Univariate Logistic Regression Analysis

Table 2 shows the regression performance of the important variables predicting pediatric hypertension in the overall cohort according to the Youden's J static.⁴⁹ Using univariate logistic regression analysis, male sex (odds ratio [OR]= 2.01, 95% confidence interval [CI] = 1.13-3.56), late childhood/adolescence (OR = 1.89, 95% CI = 1.16–3.09), overweight/obesity (OR = 2.98, 95% CI = 1.83–4.86), large neck size (OR = 2.34, 95% CI = 1.42–3.86), severe OSA (OR = 2.93, 95% CI = 1.81–4.75), severe desaturation (OR = 2.36, 95% CI = 1.48–3.78), mild/severe sleep hypoxemia (OR = 2.28, 95% CI = 1.40–3.71), severe intermittent hypoxemia (OR = 1.83, 95% CI = 1.15–3.20), and long hypoxemia time (OR = 3.36, 95% CI = 1.13–2.96) best predicted pediatric hypertension in the children.



Figure 2 Violin charts showing the distributions of the (A) body mass index z-score and (B) oxygen desaturation index \geq 3% between the normotensive and hypertensive subgroups. Non-normally distributed continuous data were compared using the Mann–Whitney U-test. Abbreviations: BMI, body mass index; ODI3, oxygen desaturation index 3%.



Figure 3 Bart charts showing the relationships between hypertension and various subgroups. (A) Weight status subgroups; (B) Obstructive sleep apnea severity subgroups; (C) Desaturation degree subgroups; (D) Sleep hypoxemia subgroups; (E) Intermittent hypoxemia subgroups; (F) Hypoxemia time subgroups. Categorical data were compared using the Mantel-Haenszel test for trend. Abbreviation: OSA, obstructive sleep apnea.

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Predictors	Odds Ratio	95% CI	P-value ^a	R ²	
Demographic measures					
Sex subgroup					
Female sex	Reference				
Male sex	2.01	1.13-3.56	0.02	0.02	
Age, y	1.06	0.97-1.15	0.22	0.01	
Development stage					
Toddler/preschooler/early	Reference				
childhood					
Late childhood/adolescence	1.89	1.16–3.09	0.01	0.03	
Anthropometric measures					
BMI z-score	1.41	1.18–1.68	< 0.001	0.06	
Weight status					
Underweight/normal weight	Reference				
Overweight/obesity	2.98	1.83-4.86	< 0.001	0.07	
NC, cm	1.14	1.07-1.21	< 0.001	0.07	
Neck size					
Small/middle neck size	Reference				
Large neck size	2.34	1.42-3.86	< 0.001	0.04	
Tonsil size, grade	1.16	0.83-1.60	0.39	0.003	
Adenoid size	1.13	0.89–1.42	0.31	0.004	
Polysomnographic measures		•			
AHI, events/h	1.02	1.01-1.03	0.002	0.04	
OSA severity					
Mild/moderate OSA	Reference				
Severe OSA	2.93	1.81-4.75	< 0.001	0.08	
ODI3, events/h	1.02	1.01-1.03	< 0.001	0.05	
Desaturation degree					
Mild/moderate desaturation	Reference				
Severe desaturation	2.36	1.48–3.78	< 0.001	0.05	
Mean SpO ₂ , %	0.92	0.85-0.98	0.02	0.02	
Sleep hypoxemia					
No sleep hypoxemia	Reference				
Mild/severe sleep hypoxemia	2.28	1.40-3.71	0.001	0.04	
Least SpO ₂ , %	0.96	0.94–0.99	0.002	0.04	
IH					
No/mild IH	Reference				
Severe IH	1.83	1.13-2.96	0.01	0.02	
Time with SpO_2 <85%, min	1.02	1.00-1.03	0.07	0.02	
Hypoxemia time					
Zero/short hypoxemia time	Reference				
Long hypoxemia time	3.36	1.77–6.36	< 0.001	0.05	

Table	2	Single	Epidemiologic,	Anthropometric,	and	Polysomnographic	Measure	as	a	Predictor	of	Pediatric
Hypert	ens	ion in	Children with C	SA								

 $\ensuremath{\textbf{Notes}}\xspace^a\ensuremath{\textbf{Data}}\xspace$ were compared using univariate logistic regression models.

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CI, confidence interval; IH, intermittent hypoxemia; NC, neck circumference; ODI3, 3% oxygen desaturation index; OSA, obstructive sleep apnea; SpO₂, blood oxygen saturation measured by pulse oximetry.

Variables Independently Predicting Pediatric Hypertension Using Multivariate Logistic Regression Models

To improve regression performance, traditional hypertensive risk factors such as male sex, age (or development stage or late childhood/adolescence), and BMI z-score (or weight status or overweight/obesity) were included in multivariate logistic regression models. Furthermore, known or potential risk factors for hypertension with an alpha level of 0.50 were also included in the multivariate regression models,⁴⁹ including NC (or large neck size), tonsil size, adenoid size, AHI (or severe OSA), ODI3 (or severe desaturation), mean SpO₂ (or mild/severe sleep hypoxemia), least SpO₂ (severe IH), and time with SpO₂ < 85% (or long hypoxemia time). Notably, overlapping information were not simultaneously included for the multivariate logistic regression analyses and variables with an incorrect sign of regression coefficient were further removed from the regression models. Table 3 shows the multivariate regression models used to predict pediatric hypertension in the children.

Using continuous variables and traditional hypertension risk factors in the multivariate regression models, ODI3 (OR = 1.02, 95% CI = 1.01-1.03) and BMI z-score (OR = 1.34, 95% CI = 1.12-1.60) were independent predictors of

Predictors	OR (95% CI)	P -value	OR (95% CI) P-value							
Models including continuous and categorical predictors of hypertension in the overall cohort (n = 365)										
	Parsimonio R ² = 0	us model ^a 0.09	Parsimonious model ^b $R^2 = 0.11$							
ODI3, events/h	1.02 (1.01–1.03)	0.01	1.02 (1.01–1.03)	0.007						
BMI z-score	1.34 (1.12–1.60)	0.002	1.31 (1.09–1.57)	0.004						
Male sex		NS	1.77 (0.98–3.20)	0.057						
Age, years		NS	1.00 (0.91–1.10)	0.964						
Models including categorical pr	edictors of hypertension in	the overall cohort (n = 365)							
	Parsimonious model ^c Parsimonious model ^d									
	$R^2 = 0$	$R^2 = 0$	0.15							
Severe OSA	2.62 (1.60-4.29)	< 0.001	2.62 (1.60–4.29)	< 0.001						
Overweight/obesity	2.63 (1.59-4.34)	0.001	2.41 (1.45–4.01)	0.001						
Male sex		NS	1.76 (0.97–3.21)	0.06						
Late childhood/adolescence		NS	1.60 (0.95–2.69)	0.08						
Models including categorical pre	edictors of hypertension in t	he no/mild IH subgroup (n =	160) and the severe IH	I subgroup (n = 205).						
	No/mild IH Subgroup Severe IH subgroup									
	Parsimoni	ous model ^c								
	R ² =	= 0.07	$R^2 = 0.21$							
Severe OSA	vere OSA 3.81 (1.49–9.74)			NS						
Mild/severe sleep hypoxemia	re sleep hypoxemia		2.24 (1.16-4.04)	0.02						
Overweight/obesity		NS	2.97 (1.56-5.67)	0.001						
Male sex		NS	2.33 (1.02-5.33)	0.04						
Late childhood/adolescent NS 1.98 (0.046						

Table 3 Multivariate Logistic Regression Models for Predicting Pediatric Hypertension of the Overall Cohort as Well asNo/Mild IH and Severe IH Subgroups

Notes: ^aData were calculated using multivariate logistic regression models of all continuous and ordinal variables and the male sex with a forward selection method with a significance level alpha of 0.10. ^bThe parsimonious model were adjustment for the male sex and age using the multivariate logistic regression analysis. ^cData were calculated using multivariate logistic regression models of all categorical variables with a forward selection method with a significance level alpha of 0.10. ^bThe parsimonious model were adjustment for the male sex and late childhood/adolescent using multivariate logistic regression analysis. **Abbreviations:** BMI, body mass index; CI, confidence interval; IH, intermittent hypoxemia; ODI3, 3% oxygen desaturation index; OR, odds ratio; OSA, obstructive sleep apnea.

pediatric hypertension ($R^2 = 0.09$). After adjusting for male sex and age, ODI3 (OR = 1.02, 95% CI = 1.01–1.03) and BMI z-score (OR = 1.31, 95% CI = 1.09–1.57) remained significant predictors of pediatric hypertension ($R^2 = 0.11$).

Furthermore, severe OSA (OR = 2.62, 95% CI = 1.60–4.29) and overweight/obesity (OR = 2.63, 95% CI = 1.59– 4.34) were independent predictors of pediatric hypertension ($R^2 = 0.13$) in the multivariate regression models of all categorical variables. Notably, severe OSA (OR = 2.62, 95% CI = 1.60–4.29) and overweight/obesity (OR = 2.41, 95% CI = 1.45–4.01) remained significant predictors of pediatric hypertension after controlling for male sex and late childhood/adolescence ($R^2 = 0.16$).

Variables Independently Associated with Hypertension in the Children with or Without Severe Intermittent Hypoxemia Using Logistic Regression Analysis

We wondered whether some classifications based on categorical hypoxemia indexes may be associated with the prediction of hypertension. Therefore, we compared differences in the associations of categorical variables between various subgroups (mild/moderate desaturation and severe desaturation; no sleep hypoxemia and mild/severe sleep hypoxemia; no/mild IH and severe IH; zero/short hypoxemia time and long hypoxemia time).

In the no/mild IH subgroup (n = 160), the prevalence rate of hypertension was 20.6%, and severe OSA (OR = 3.81, 95% CI = 1.49–9.74, P = 0.01) was shown to be an independent risk factor using multivariate logistic regression ($R^2 = 0.07$).

In the severe IH subgroup (n = 205), the prevalence rate of hypertension was 32.2%. Severe sleep hypoxemia (OR = 2.24, 95% CI = 1.16–4.04, P = 0.02), male sex (OR = 2.33, 95% CI = 1.02–5.33, P = 0.04), late childhood/adolescence (OR = 1.98, 95% CI = 1.01–3.88, P = 0.046), and overweight/obesity (OR = 2.97, 95% CI = 1.56–5.67, P = 0.001) were shown to be independent predictors of hypertension in multivariate analysis ($R^2 = 0.21$).

Discussion

In the present study, we investigated the relationships of IH and weight status with hypertension among pediatric OSA patients. Significant associations were observed between pediatric hypertension and its known demographic and anthropometric risk factors, namely male sex, older age, BMI z-score, and overweight/obesity. Moreover, polysomnographic measures including severe OSA (defined with AHI), severe desaturation (defined with ODI3), sleep hypoxemia (defined with mean SpO₂), severe IH (defined with least SpO₂), and long hypoxemia time (defined with time with SpO₂ < 85%) were significantly associated with pediatric hypertension in the overall cohort. ODI3 and BMI z-score were independent predictors in the parsimonious model of continuous variables (unadjusted $R^2 = 0.09$, adjusted $R^2 = 0.11$), whilst severe OSA and overweight/obesity were independent predictors in the parsimonious model of categorical variables (unadjusted $R^2 = 0.13$, adjusted $R^2 = 0.15$). After the patients were stratified by IH level, traditional risk factors combined with hypoxemia-related variables predicted hypertension in the severe IH subgroup ($R^2 = 0.21$), while the no/mild IH subgroup had an entirely different predictor, severe OSA ($R^2 = 0.07$).

In our cohort, hypertension was more prevalent in the boys than in the girls. This finding is consistent with national data showing that the prevalence of hypertension has been consistently higher in male children and adolescents for over a decade in Taiwan.⁵⁰ Also, it has been long evident that the risk for OSA differs by sex. Male sex is a key risk factor for severe adolescent OSA⁵¹ and OSA evolving from childhood to young adulthood.⁵² In this study, male sex was an independent risk factor for pediatric hypertension in the severe IH subgroup. Although the exact mechanisms are unknown, sex difference may be a confounding factor for both OSA⁵³ and BP.⁵⁴ Sex differences warrant special considerations among pediatric OSA patients in the management of co-morbid secondary hypertension.

Another finding was the higher prevalence of hypertension in the late childhood/adolescence subgroup compared to the toddler/preschool/early childhood subgroup. A recent meta-analysis found that the global prevalence of hypertension increased significantly from 6 to 12 years old and reached a peak in late puberty.⁵⁵ Hormonal changes and growth spurts are widely accepted mechanisms to explain the elevation in BP during puberty.⁵⁵ However, considering the discrepancy in the prevalence of hypertension between children with OSA and the general pediatric population, we postulate that the increase in BP along with age may also be partly due to the accumulative effect of OSA over time.

Obesity is a well-established risk factor for hypertension and cardiovascular diseases.⁵⁶ Possible mechanisms of hypertension development in overweight/obese children and adolescents include increased intravascular volume, disturbed sodium excretion, abnormal adipocyte secretory function, insulin resistance, and dysregulated renin-angiotensinaldosterone axis.⁵⁷ The positive association between obesity and hypertension observed in our study is compatible with the literature.^{55,58} In addition, we found that BMI z-score was closely related to IH indexes. Both obesity and IH worsen metabolic dysregulation⁵⁹ and consequently worsen hypertension⁶⁰ in children, and the effects of weight status and OSA severity on BP may be age-dependent.⁶¹ In obese children, AHI and ODI have been associated with elevated systolic BP.⁶² Moreover, in adolescents, the relationship between obesity and hypertension has been shown to be stronger than that between OSA and hypertension.⁶³ Obesity, OSA, and hypertension can all be improved by diet control and physical activity.^{64,65} Our findings support the importance of weight control to manage hypertension in children with OSA.

In this study, hypertension was notably more prevalent among the children with OSA (27.1%) compared to the global prevalence of childhood hypertension (4%).⁵⁵ As mentioned above, OSA is a well-known risk factor for secondary hypertension in adults²¹ and in children.⁴⁷ Obstructive events and oxygen desaturations have been shown to induce acute cardiovascular changes, such as increased pulse transit time, in children with OSA, consequently causing an elevation in BP.⁶⁶ Hypertension, in turn, has been shown to exacerbate OSA.^{9,67,68} Higher BP itself has been associated with a reduction in genioglossus activity and disruption of upper airway stability.⁶⁹ Moreover, primary aldosteronism, which is not uncommon in hypertensive patients, can cause rostral fluid accumulation and increase upper airway collapsibility.⁷⁰ The use of diuretics to control BP has been shown to confer a small but significant reduction in OSA severity.⁷¹ In addition, Lee et al reported that adenotonsillectomy resulted in a dramatic decrease in the prevalence of hypertension from 34% to 14%.⁹

However, despite the known bidirectional effects of OSA on BP,^{25,26} inconsistencies and knowledge gaps still exist within the current understanding of the interactions between OSA and hypertension in children. A meta-analysis conducted by Zintzaras and Kaditis (2007) found that moderate-to-severe SDB in children did not significantly increase the risk of elevated BP.⁷² In addition, contradicting the known epidemiology of hypertension, Chuang et al reported that neither family history of hypertension nor family history of SDB predicted pediatric hypertension for children with SDB.¹⁴ Furthermore, Kang et al reported that adenotonsillectomy had no significant effect on BP, except in children with both OSA and hypertension.⁸ In our previous work, we found that considerable heterogeneity existed among pediatric patients diagnosed with SDB or OSA regarding their comorbidities, inflammatory status, microbiome, and treatment responses, even after adjusting for disease severity, and that the phenotype subgroups were mainly stratified by weight status and hypoxemic level.^{9,14,30,31,39,73} We postulated that the pathogenesis and progression of BP elevation were diverse across different phenotype patient groups.

The results of the current study support our hypotheses of IH relating to elevated BP. The severe IH subgroup had a notably higher prevalence of hypertension, suggesting the role of IH in BP elevation. OSA-induced IH has been shown to activate the sympathetic nervous system,⁷⁴ dysregulate the renin-angiotensin-aldosterone system,⁷⁵ and then contribute to hypertension.⁷⁶ A considerable volume of evidence suggests that IH is more severe during rapid eye movement sleep.^{77,78} In 2020, Brooks et al further indicated that OSA patients have higher BP during rapid eye movement sleep.⁷⁹ Chronic IH changes the neurotransmission direction of the brain stem to decrease cardioprotective parasympathetic activity and increase cardiovascular events.⁷⁷ Taken together with the present study, these findings suggest that for pediatric OSA patients who have profound desaturation as the disease presentation, IH may be the cardinal pathogenic driver of BP elevation. On the other hand, for those with none or only mild desaturation, disease severity itself, defined by respiratory events, may play a more important role in the development of hypertension.

According to the American Academy of Pediatrics clinical practice guideline for screening and management of high BP in children and adolescents, adenotonsillar hypertrophy should be assessed because the large size of the tonsils and adenoids is a sign of pediatric SDB, and the latter is a secondary cause of pediatric hypertension (Flynn et al). In the current study, we further discovered that in this cohort of pediatric OSA patients, neither tonsil size (odds ratio = 1.16; 95% CI: 0.83-1.60; P = 0.39) nor adenoid size (odds ratio = 1.13; 95% CI: 0.89-1.42; P = 0.31) was a significant risk factor for hypertension (Table 2). Adenotonsillar hypertrophy is an essential risk factor for secondary hypertension in the general pediatric population; however, as for children with OSA, neither seems to be an

independent factor for hypertension. The literature and our data in combination suggest that the greater risk of secondary hypertension possessed by children with adenotonsillar hypertrophy is probably not caused by the gland sizes themselves, but more likely mediated by OSA, and severe desaturation may be implicated as a cardinal pathogenic pathway. This finding is novel and yields important clinical implications, suggesting that severe desaturation should be identified and managed promptly in children with OSA to better prevent or minimize secondary hypertension.

A very interesting and similar result was observed with NC as with adeno/tonsillar sizes. NC is closely related to body weight status and elevated BP in children.⁸⁰ In a very recent meta-analysis, NC was an anthropometric predictor of elevated BP in children and adolescents regardless of the presence of OSA.⁸¹ We also demonstrated that NC was significantly associated with OSA in younger children.³⁰ Wide NC (ie, large neck size) cluster many risk factors for pediatric hypertension. However, from our data, neither NC nor neck size was an independent predictor for hypertension among children and adolescents with OSA. The greater risk of secondary hypertension possessed by children with wider NC may not be brought by the neck size itself but more likely mediated by pathophysiological effects caused by obesity or OSA. Nevertheless, NC is a readily available measurement in general clinical settings and can be used to screen pediatric hypertension before polysomnography in children with SDB.

In the current study, we identified relationships among IH, weight status, demographic variables, and hypertension in a sample of children with OSA. ODI3, severe OSA, BMI z-score, and overweight/obesity were important risk factors for hypertension. However, independent predictors of hypertension differed across the patients with different IH levels. There were several limitations to the study. First, the investigation was conducted at a tertiary medical center in Taiwan, and the sample was predominantly male, mostly of Han ethnicity, and had severe OSA, which may limit the generalizability of our findings. Second, this study was cross-sectional, thus we could not assess causality. Longitudinal case-control or interventional studies are warranted to confirm the roles of IH and weight status in hypertension among children with OSA.

Conclusion

We found that ODI3 was a major risk factor for hypertension in the children with OSA. In the children with less significant IH, AHI was a better predictor of hypertension, whereas in the children with more significant IH, mean SpO_2 was a suitable predictor of hypertension together with overweight/obesity, older age, and male sex.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Li HY, Lee LA, Hsin LJ, et al. Intrapharyngeal surgery with integrated treatment for obstructive sleep apnea. *Biomed J.* 2019;42(2):84–92. doi:10.1016/j.bj.2019.02.002

- 2. Gallucci M, Gessaroli M, Bronzetti G, et al. Cardiovascular issues in obstructive sleep apnoea in children: a brief review. *Paediatr Respir Rev.* 2021;38:45–50. doi:10.1016/j.prrv.2020.05.007
- 3. Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol.* 2017;69(7):841–858. doi:10.1016/j.jacc.2016.11.069
- 4. Gonzaga C, Bertolami A, Bertolami M, Amodeo C, Calhoun D. Obstructive sleep apnea, hypertension and cardiovascular diseases. J Hum Hypertens. 2015;29(12):705–712. doi:10.1038/jhh.2015.15
- 5. Prabhakar NR, Peng YJ, Nanduri J. Hypoxia-inducible factors and obstructive sleep apnea. J Clin Invest. 2020;130(10):5042–5051. doi:10.1172/ JCI137560
- 6. Tkacova R, McNicholas WT, Javorsky M, et al. Nocturnal intermittent hypoxia predicts prevalent hypertension in the European Sleep Apnoea Database cohort study. *Eur Respir J.* 2014;44(4):931–941. doi:10.1183/09031936.00225113
- 7. Wang N, Meng Z, Ding N, et al. Oxygen desaturation rate as a novel intermittent hypoxemia parameter in severe obstructive sleep apnea is strongly associated with hypertension. *J Clin Sleep Med.* 2020;16(7):1055–1062. doi:10.5664/jcsm.8396
- Kang KT, Chiu SN, Lee CH, Lin MT, Hsu WC. Effect of adenotonsillectomy on blood pressure in children with obstructive sleep apnea: a meta-analysis. Sleep Med. 2021;84:334–342. doi:10.1016/j.sleep.2021.06.017
- 9. Lee LA, Li HY, Lin YS, et al. Severity of childhood obstructive sleep apnea and hypertension improved after adenotonsillectomy. *Otolaryngol Head Neck Surg.* 2015;152(3):553-560. doi:10.1177/0194599814561203
- 10. Bass JL, Corwin M, Gozal D, et al. The effect of chronic or intermittent hypoxia on cognition in childhood: a review of the evidence. *Pediatrics*. 2004;114(3):805–816. doi:10.1542/peds.2004-0227
- 11. Seravalle G, Grassi G. Obesity and hypertension. Pharmacol Res. 2017;122:1-7. doi:10.1016/j.phrs.2017.05.013
- 12. Hsu CY, Lin RH, Lin YC, et al. Are body composition parameters better than conventional anthropometric measures in predicting pediatric hypertension? Int J Environ Res Public Health. 2020;17(16):16. doi:10.3390/ijerph17165771
- 13. Kuczmarski RJ, Ogden CL, Guo SS, et al. CDC growth charts for the United States: methods and development. Vital Health Stat. 2000;2002 (246):1–190.
- 14. Chuang HH, Hsu JF, Wang CY, et al. Hypertension in children with obstructive sleep apnea syndrome-age, weight status, and disease severity. Int J Environ Res Public Health. 2021;18(18):9602. doi:10.3390/ijerph18189602
- 15. Chang IS, Kang KT, Tseng CC, et al. Revisits after adenotonsillectomy in children with sleep-disordered breathing: a retrospective single-institution study. *Clin Otolaryngol.* 2018;43(1):39–46. doi:10.1111/coa.12899
- 16. Fox C. Pediatric Hypertension. Prim Care. 2021;48(3):367-378. doi:10.1016/j.pop.2021.04.001
- 17. Wuhl E. Hypertension in childhood obesity. Acta Paediatr. 2019;108(1):37-43. doi:10.1111/apa.14551
- 18. Chen HC, Wang CJ, Lo YL, et al. Parapharyngeal fat pad area at the subglosso-supraglottic level is associated with corresponding lateral wall collapse and apnea-hypopnea index in patients with obstructive sleep apnea: a pilot study. *Sci Rep.* 2019;9(1):17722. doi:10.1038/s41598-019-53515-5
- 19. Avraam J, Dawson A, Rochford PD, et al. The effect of sex and body weight on lung volumes during sleep. 2019;42(10). doi:10.1093/sleep/ zsz141
- 20. Brady TM. Obesity-related hypertension in children. Front Pediatr. 2017;5:197. doi:10.3389/fped.2017.00197
- 21. Hou H, Zhao Y, Yu W, et al. Association of obstructive sleep apnea with hypertension: a systematic review and meta-analysis. *J Glob Health*. 2018;8(1):010405. doi:10.7189/jogh.08.010405
- 22. Salman LA, Shulman R, Cohen JB. Obstructive sleep apnea, hypertension, and cardiovascular risk: epidemiology, pathophysiology, and management. Curr Cardiol Rep. 2020;22(2):6. doi:10.1007/s11886-020-1257-y
- 23. Chiang CL, Chen YT, Wang KL, et al. Comorbidities and risk of mortality in patients with sleep apnea. Ann Med. 2017;49(5):377-383. doi:10.1080/07853890.2017.1282167
- 24. Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep*. 2008;31(8):1071–1078.
- 25. Torres G, Sanchez-de-la-Torre M, Barbe F. Relationship between OSA and hypertension. Chest. 2015;148(3):824-832. doi:10.1378/chest.15-0136
- 26. Wang Y, Li CX, Lin YN, et al. The role of aldosterone in OSA and OSA-related hypertension. Front Endocrinol. 2021;12:801689. doi:10.3389/ fendo.2021.801689
- 27. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191–2194. doi:10.1001/jama.2013.281053
- 28. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med.* 2007;4(10):e296. doi:10.1371/journal.pmed.0040296
- 29. Marcus CL, Moore RH, Rosen CL, et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. N Engl J Med. 2013;368 (25):2366-2376. doi:10.1056/NEJMoa1215881
- 30. Chuang HH, Hsu JF, Chuang LP, et al. Differences in anthropometric and clinical features among preschoolers, school-age children, and adolescents with obstructive sleep Apnea-A Hospital-Based Study in Taiwan. Int J Environ Res Public Health. 2020;17:13. doi:10.3390/ijerph17134663
- 31. Huang YS, Guilleminault C, Hwang FM, et al. Inflammatory cytokines in pediatric obstructive sleep apnea. *Medicine*. 2016;95(41):e4944. doi:10.1097/MD.00000000004944
- 32. Flegal KM, Cole TJ. Construction of LMS parameters for the Centers for Disease Control and Prevention 2000 growth charts. *Natl Health Stat Report*. 2013;2013(63):1–3.
- 33. Kaditis AG, Alexopoulos EI, Hatzi F, et al. Adiposity in relation to age as predictor of severity of sleep apnea in children with snoring. *Sleep Breath*. 2008;12(1):25-31. doi:10.1007/s11325-007-0132-z
- 34. Androutsos O, Grammatikaki E, Moschonis G, et al. Neck circumference: a useful screening tool of cardiovascular risk in children. *Pediatr Obes*. 2012;7(3):187–195. doi:10.1111/j.2047-6310.2012.00052.x
- Nafiu OO, Burke C, Lee J, Voepel-Lewis T, Malviya S, Tremper KK. Neck circumference as a screening measure for identifying children with high body mass index. *Pediatrics*. 2010;126(2):e306–e310. doi:10.1542/peds.2010-0242
- 36. Brodsky L. Modern Assessment of Tonsils and Adenoids. Pediatr Clin North Am. 1989;36(6):1551–1569. doi:10.1016/S0031-3955(16)36806-7

- Al-Ammar AY, Shebib D, Bokhari M, Jomah M. Grading adenoid utilizing flexible nasopharyngoscopy. Ann Saudi Med. 2013;33(3):265–267. doi:10.5144/0256-4947.2013.265
- 38. Li HY, Lee LA. Sleep-disordered breathing in children. Chang Gung Med J. 2009;32(3):247-257.
- 39. Huang YS, Guilleminault C, Lee LA, Lin CH, Hwang FM. Treatment outcomes of adenotonsillectomy for children with obstructive sleep apnea: a prospective longitudinal study. *Sleep*. 2014;37(1):71–76. doi:10.5665/sleep.3310
- 40. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. deliberations of the sleep apnea definitions task force of the American Academy of sleep medicine. J Clin Sleep Med. 2012;8 (5):597–619. doi:10.5664/jcsm.2172
- 41. Wu WT, Tsai SS, Lin YJ, et al. Utility of overnight pulse oximeter as a screening tool for sleep apnea to assess the 8-year risk of cardiovascular disease: data from a large-scale bus driver cohort study. *Int J Cardiol*. 2016;225:206–212. doi:10.1016/j.ijcard.2016.09.110
- 42. World Health Organization. Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Illnesses with Limited Resources. 2nd ed. Geneva, Switzerland: World Health Organization; 2013.
- 43. Urschitz MS, Wolff J, Sokollik C, et al. Nocturnal arterial oxygen saturation and academic performance in a community sample of children. *Pediatrics*. 2005;115(2):e204–e209. doi:10.1542/peds.2004-1256
- Shafiek H, Evangelisti M, Abd-Elwahab NH, Barreto M, Villa MP, Mahmoud MI. Obstructive sleep apnea in school-aged children presented with Nocturnal Enuresis. Lung. 2020;198(1):187–194. doi:10.1007/s00408-019-00304-6
- 45. Ostchega Y, Hughes JP, Prineas RJ, Zhang G, Nwankwo T, Chiappa MM. Mid-arm circumference and recommended blood pressure cuffs for children and adolescents aged between 3 and 19 years: data from the National Health and Nutrition Examination Survey, 1999–2010. *Blood Press Monit.* 2014;19(1):26–31. doi:10.1097/MBP.000000000000008
- 46. National High Blood Pressure Education Program Working Group on High Blood Pressure in C, Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2 Suppl):555–576. doi:10.1542/peds.114.S2.555
- 47. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3). doi:10.1542/peds.2017-1904
- 48. Reibnegger G, Schrabmair W. Optimum binary cut-off threshold of a diagnostic test: comparison of different methods using Monte Carlo technique. BMC Med Inform Decis Mak. 2014;14:99.
- Steyerberg EW, Eijkemans MJC, Harrell FE, Habbema JDF. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. *Stat Med.* 2000;19(8):1059–1079. doi:10.1002/(SICI)1097-0258(20000430)19:8<1059::AID-SIM412>3.0. CO;2-0
- 50. Hsu WF, Kao YW, Chen M, et al. A reappraisal of the prevalence of pediatric hypertension through a nationwide database in Taiwan. *Sci Rep.* 2021;11(1):4475. doi:10.1038/s41598-021-84001-6
- 51. Baker M, Scott B, Johnson RF, Mitchell RB. Predictors of obstructive sleep apnea severity in adolescents. JAMA Otolaryngol Head Neck Surg. 2017;143(5):494–499. doi:10.1001/jamaoto.2016.4130
- Chan KC, Au CT, Hui LL, Ng SK, Wing YK, Li AM. How OSA evolves from childhood to young adulthood: natural history from a 10-year follow-up study. *Chest.* 2019;156(1):120–130. doi:10.1016/j.chest.2019.03.007
- 53. Lin CM, Davidson TM, Ancoli-Israel S. Gender differences in obstructive sleep apnea and treatment implications. *Sleep Med Rev.* 2008;12 (6):481–496. doi:10.1016/j.smrv.2007.11.003
- Dasgupta K, O'Loughlin J, Chen S, et al. Emergence of sex differences in prevalence of high systolic blood pressure: analysis of a longitudinal adolescent cohort. *Circulation*. 2006;114(24):2663–2670. doi:10.1161/CIRCULATIONAHA.106.624536
- 55. Song P, Zhang Y, Yu J, et al. Global prevalence of hypertension in children: a systematic review and meta-analysis. *JAMA Pediatr.* 2019;173 (12):1154–1163. doi:10.1001/jamapediatrics.2019.3310
- Fortuno A, Rodriguez A, Gomez-Ambrosi J, Fruhbeck G, Diez J. Adipose tissue as an endocrine organ: role of leptin and adiponectin in the pathogenesis of cardiovascular diseases. J Physiol Biochem. 2003;59(1):51–60. doi:10.1007/BF03179868
- 57. Wojcik M, Koziol-Kozakowska A. Obesity, sodium homeostasis, and arterial hypertension in children and adolescents. *Nutrients*. 2021;13 (11):4032. doi:10.3390/nu13114032
- 58. Sorof J, Daniels S. Obesity hypertension in children: a problem of epidemic proportions. *Hypertension*. 2002;40(4):441-447. doi:10.1161/01. HYP.0000032940.33466.12
- 59. Lesser DJ, Bhatia R, Tran WH, et al. Sleep fragmentation and intermittent hypoxemia are associated with decreased insulin sensitivity in obese adolescent Latino males. *Pediatr Res.* 2012;72(3):293–298. doi:10.1038/pr.2012.73
- 60. Magge SN, Goodman E, Armstrong SC. The metabolic syndrome in children and adolescents: shifting the focus to cardiometabolic risk factor clustering. *Pediatrics*. 2017;140(2). doi:10.1542/peds.2017-1603
- 61. Baker-Smith CM, Isaiah A, Melendres MC, et al. Sleep-disordered breathing and cardiovascular disease in children and adolescents: a scientific statement from the American Heart Association. J Am Heart Assoc. 2021;10(18):e022427. doi:10.1161/JAHA.121.022427
- 62. Tagetti A, Bonafini S, Zaffanello M, et al. Sleep-disordered breathing is associated with blood pressure and carotid arterial stiffness in obese children. *J Hypertens*. 2017;35(1):125–131. doi:10.1097/HJH.00000000001123
- 63. Khan MA, Mathur K, Barraza G, et al. The relationship of hypertension with obesity and obstructive sleep apnea in adolescents. *Pediatr Pulmonol.* 2020;55(4):1020–1027. doi:10.1002/ppul.24693
- 64. Aguilar-Cordero MJ, Rodriguez-Blanque R, Leon-Rios X, Exposito Ruiz M, Garcia Garcia I, Sanchez-Lopez AM. Influence of physical activity on blood pressure in children with overweight/obesity: a randomized clinical trial. Am J Hypertens. 2020;33(2):131–136. doi:10.1093/ajh/ hpz174
- 65. Roche J, Isacco L, Masurier J, et al. Are obstructive sleep apnea and sleep improved in response to multidisciplinary weight loss interventions in youth with obesity? A systematic review and meta-analysis. *Int J Obes*. 2020;44(4):753–770. doi:10.1038/s41366-019-0497-7
- 66. Nisbet LC, Yiallourou SR, Nixon GM, et al. Characterization of the acute pulse transit time response to obstructive apneas and hypopneas in preschool children with sleep-disordered breathing. *Sleep Med.* 2013;14(11):1123–1131. doi:10.1016/j.sleep.2013.06.010
- 67. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. *BMJ*. 2000;320 (7233):479–482. doi:10.1136/bmj.320.7233.479

- Kang KT, Chiu SN, Weng WC, Lee PL, Hsu WC. 24 hour ambulatory blood pressure variability in children with obstructive sleep apnea. Laryngoscope. 2021;131(9):2126–2132. doi:10.1002/lary.29455
- 69. Garpestad E, Basner RC, Ringler J, et al. Phenylephrine-induced hypertension acutely decreases genioglossus EMG activity in awake humans. *J Appl Physiol*. 1992;72(1):110–115. doi:10.1152/jappl.1992.72.1.110
- White LH, Motwani S, Kasai T, Yumino D, Amirthalingam V, Bradley TD. Effect of rostral fluid shift on pharyngeal resistance in men with and without obstructive sleep apnea. *Respir Physiol Neurobiol.* 2014;192:17–22. doi:10.1016/j.resp.2013.11.002
- Khurshid K, Yabes J, Weiss PM, et al. Effect of antihypertensive medications on the severity of obstructive sleep apnea: a systematic review and meta-analysis. J Clin Sleep Med. 2016;12(8):1143–1151. doi:10.5664/jcsm.6054
- 72. Zintzaras E, Kaditis AG. Sleep-disordered breathing and blood pressure in children: a meta-analysis. Arch Pediatr Adolesc Med. 2007;161 (2):172-178. doi:10.1001/archpedi.161.2.172
- 73. Chuang HH, Hsu JF, Chuang LP, et al. Different associations between tonsil microbiome, chronic tonsillitis, and intermittent hypoxemia among obstructive sleep apnea children of different weight status: a pilot case-control study. J Pers Med. 2021;11(6):486. doi:10.3390/jpm11060486
- 74. O'Driscoll DM, Horne RS, Davey MJ, et al. Increased sympathetic activity in children with obstructive sleep apnea: cardiovascular implications. *Sleep Med.* 2011;12(5):483–488. doi:10.1016/j.sleep.2010.09.015
- 75. Shamsuzzaman A, Szczesniak RD, Fenchel MC, Amin RS. Plasma renin levels and renin-blood pressure relationship in normal-weight and overweight children with obstructive sleep apnea and matched controls. *Sleep Med.* 2015;16(1):101–106. doi:10.1016/j.sleep.2014.05.022
- 76. Jehan S, Zizi F, Pandi-Perumal SR, McFarlane SI, Jean-Louis G, Myers AK. Obstructive sleep apnea, hypertension, resistant hypertension and cardiovascular disease. *Sleep Med Disord*. 2020;4(3):67–76.
- 77. Dergacheva O. Chronic intermittent hypoxia alters neurotransmission from lateral paragigantocellular nucleus to parasympathetic cardiac neurons in the brain stem. J Neurophysiol. 2015;113(1):380–389. doi:10.1152/jn.00302.2014
- 78. Choi E, Park DH, Yu JH, Ryu SH, Ha JH. The severity of sleep disordered breathing induces different decrease in the oxygen saturation during rapid eye movement and non-rapid eye movement sleep. *Psychiatry Investig.* 2016;13(6):652–658. doi:10.4306/pi.2016.13.6.652
- 79. Brooks DM, Kelly A, Sorkin JD, et al. The relationship between sleep-disordered breathing, blood pressure, and urinary cortisol and catecholamines in children. J Clin Sleep Med. 2020;16(6):907–916. doi:10.5664/jcsm.8360
- Nafiu OO, Zepeda A, Curcio C, Prasad Y. Association of neck circumference and obesity status with elevated blood pressure in children. J Hum Hypertens. 2014;28(4):263–268. doi:10.1038/jhh.2013.93
- Moradi S, Mohammadi H, Ghavami A, Rouhani MH. Neck circumference and blood pressure among children: a systematic review and meta-analysis. J Am Soc Hypertens. 2018;12(12):822–832. doi:10.1016/j.jash.2018.10.007

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