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Correlations between obstructive sleep apnea and adenotonsillar hypertrophy in children of different weight status

Jing Wang¹, Yu Zhao¹, Wen Yang¹, Tian Shen¹, Pei Xue², Xiaohong Yan¹, Danni Chen¹, Yixin Qiao¹, Min Chen¹, Rong Ren², Jianjun Ren¹, Yang Xu¹, Yongbo Zheng¹, Jian Zou¹ & Xiangdong Tang²

The present study aimed to evaluate the relationship between OSA and adenotonsillar size in children of different weight status. A total of 451 patients aged 2–13 years with suspected OSA were retrospectively enrolled in the study. Correlations between the apnea-hypopnea index (AHI) and adenotonsillar size in different weight status were investigated. The adenoidal/nasopharyngeal (A/N) ratio of underweight children was significantly higher than that of normal-weight children ($P = 0.027$). Both adenoid and tonsil size were positively correlated with logAHI in children of normal weight ($r = 0.210$, $P = 0.001$; and $r = 0.212$, $P = 0.001$) but uncorrelated in the other groups. Gender (OR = 1.49, 95% CI: 1.01–2.20, $P = 0.043$), obese (OR = 1.93, 95% CI: 1.10–3.40, $P = 0.012$), A/N ratio (OR = 1.55, 95% CI: 1.28–1.88, $P < 0.001$) and tonsil size (OR = 1.36, 95% CI: 1.18–1.57, $P < 0.001$) were all associated with the severity of OSA. Adenotonsillar hypertrophy contributed to OSA in normal-weight children. In children of abnormal weight, instead of treatment for adenotonsillar hypertrophy, appropriate treatments for other factors are required.

Sleep-disordered breathing (SDB) is highly prevalent in the general population ranging from primary snoring to obstructive sleep apnea (OSA)¹. The OSA prevalence in children is 1–3%^{2–4}, characterized by partial or complete obstruction of the upper airway during sleep, is associated with pulmonary hypertension, ventricular hypertrophy^{5,6}, behavioral and cognitive problems such as impulsivity, anxiety, aggression and hyperactivity⁷. Polysomnography (PSG) is recommended as the gold standard for diagnosing OSA⁸. Adenotonsillar hypertrophy and craniofacial anomalies have been demonstrated as factors that increase the incidence of OSA^{9,10}. Besides anatomic factors, obesity has been also suggested as contributor to OSA. Sakamoto *et al.*¹¹ observed that SDB is more prevalent in obese than in non-obese children. In addition, Kang *et al.*¹² found that obesity increased OSA risk in children. Furthermore, one study indicated underweight may also contribute to OSA. However, the pathophysiology of remains unclear¹³. Dayyat *et al.*¹⁴ indicated that non-obese children may have larger adenotonsillar than obese children. The magnitude of adenotonsillar hypertrophy may be smaller in obese children. However, these studies didn't analyse the correlation between different degree of adenotonsillar size with the severity of OSA in underweight, normal-weight, overweight, and obese children, respectively. Adenotonsillectomy and medical therapies are both commonly used to treat pediatric OSA patients with adenotonsillar hypertrophy. Obese children may be at greater risk of residual disease after adenotonsillectomy^{15,16}. Medical therapies, such as nasal corticosteroids or montelukast, are minimally effective in obese children¹⁷. We hypothesized that adenotonsillar hypertrophy may not be the major contributor to OSA severity in obese children. Meanwhile, adenotonsillectomy has only a modest effect in OSA children with craniofacial abnormalities or neuromuscular disorders^{18–20}. Therefore, it is important to define risk factors for OSA that may allow treatment individualization.

To date, the relationship between adenotonsillar size and OSA severity in children of different weight status has not been defined. Here, we divided children into four groups by weight status. Polysomnography was used to evaluate OSA severity. The effects of age, gender, and adenoid and tonsil sizes on OSA severity were explored. The

¹Department of Oto-Rhino-Laryngology, West China Hospital, West China Medical School, Sichuan University, Chengdu, Sichuan, China. ²Sleep Medicine Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China. Correspondence and requests for materials should be addressed to Y. Zhao (email: yutzhao@163.com)

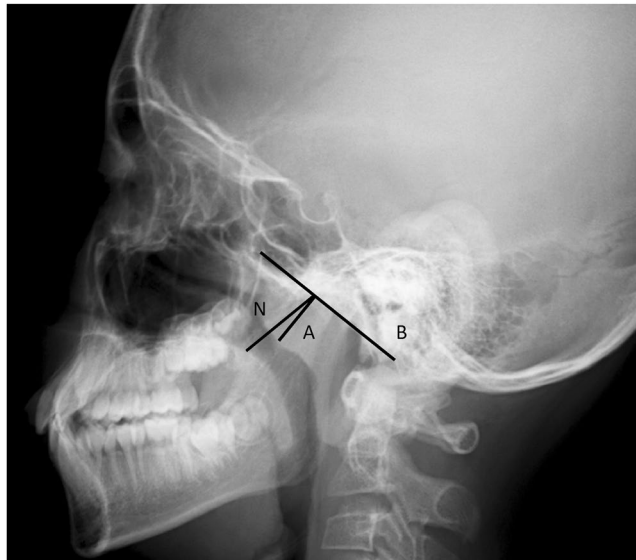


Figure 1. Measurement of the adenoidal/nasopharyngeal (A/N) ratio on lateral cephalometric radiographs. The distance A is measured along the line running perpendicular from the point of maximal convexity along the inferior margin of the adenoidal shadow to the point of intersection with line B. The nasopharyngeal space N is the distance between the posterior/superior edge of the hard palate and the anterior/inferior edge of the sphenobasioccipital synchondrosis. The A/N ratio is obtained by dividing A by N.

results yielded indications for prescription of operative and medical therapies for children with OSA exhibiting adenotonsillar hypertrophy.

Methods

Study design and participants. This cross-sectional study was approved by the Ethics Committee of West China Hospital (approval #146, 2018) and was registered at chictr.org (ChiCTR1800017895). The study was performed in accordance with relevant guidelines and regulations. Written informed consent was obtained from all of the parents. We included children who were diagnosed at the Department of Otolaryngology of West China Hospital in Chengdu, China from January 2013 to June 2018. Patients aged 2–13 years were eligible for inclusion if they were suspected to have OSA, underwent full-night polysomnography (PSG), and complete clinical data were available. Patients with any craniofacial abnormality, any genetic or neuromuscular disease, or who had undergone adenotonsillectomy were excluded. OSA was defined as an apnea-hypopnea index (AHI) ≥ 1 event/h. The primary snoring (control) group included children with AHI < 1 event/h.

Clinical data. We collected polysomnographic data and electronic medical records; we recorded age, gender, height, weight, and tonsil and adenoid sizes.

Tonsil size. Tonsils were graded using the Brodsky scheme²¹. The tonsil size was the sum of the sizes of the two sides of either tonsil; this reduces any effect of tonsil asymmetry. The grades were defined as follows: grade I, small tonsils confined to the tonsillar pillars; grade II, tonsils extending just outside the pillars; grade III, tonsils extending outside the pillars, but not meeting in the midline; and grade IV, large tonsils meeting at the midline.

Adenoid size. Adenoids were measured using the method of Fujioka²². We measured the adenoidal/nasopharyngeal (A/N) ratio on lateral cephalometric radiographs and then calculated adenoid sizes. The A parameter is the distance from the point of maximal convexity along the inferior margin of the adenoidal shadow to the line B drawn along the straight region of the anterior basiocciput margin. A is measured along the line drawn perpendicular from the point of maximal convexity along the inferior margin of the adenoidal shadow to its point of intersection with line B. The nasopharyngeal parameter N is the distance between the posterior/superior edge of the hard palate and the anterior/inferior edge of the sphenobasioccipital synchondrosis. The A/N ratio is obtained by dividing A by N (Fig. 1). An A/N ratio > 0.67 was considered to indicate adenoidal hypertrophy.

Weight status. We divided children into four groups by age- and gender-corrected body mass index (BMI) using the recognized Chinese guidelines²³. The underweight group included those of BMI \leq percentile 5; the normal-weight group, children of BMI $>$ percentile 5 but $<$ percentile 85; the overweight group, children of BMI $>$ percentile 85 but $<$ percentile 95; and the obese group, children of BMI $>$ percentile 95.

Polysomnography. All patients underwent full-night polysomnography (Philips Respironics, Bend, OR, USA). In line with the criteria of the American Academy of Sleep Medicine. Apnea was defined as a $> 90\%$ reduction in airflow for at least the duration of 2 breaths, hypopnea as a $\geq 30\%$ reduction of airflow for at least 2 breaths associated with a $\geq 3\%$ desaturation from pre-event baseline or the event is associated with an arousal. The AHI was

Variable	Underweight (n = 62)	Normal-weight (n = 273)	Overweight (n = 52)	Obese (n = 64)	P-value
Age, years	5.16 ± 1.77	5.56 ± 2.40	5.81 ± 2.74	5.69 ± 2.45	0.476
Gender, male (No. %)	42 (67.74)	186 (68.13)	33 (63.46)	54 (84.38)	0.063
BMI, kg/m ²	12.94 ± 0.91 ^d	15.58 ± 1.21 ^c	18.41 ± 1.85 ^b	20.94 ± 2.56 ^a	<0.001
A/N ratio	0.69 ± 0.11 ^a	0.65 ± 0.10 ^b	0.67 ± 0.08 ^{ab}	0.66 ± 0.09 ^{ab}	0.034
Tonsil size	6.52 ± 1.41	6.66 ± 1.26	6.79 ± 1.11	6.83 ± 1.28	0.498
TST, min	492.27 ± 53.67	477.86 ± 52.25	464.71 ± 59.99	473.69 ± 71.65	0.067
Sleep efficiency, %	90.97 ± 6.87	89.54 ± 7.96	88.01 ± 8.26	87.41 ± 9.97	0.059
N1, %	12.91 ± 6.45	14.94 ± 9.70	14.10 ± 7.67	14.98 ± 8.65	0.411
N2, %	40.00 ± 10.22	40.25 ± 10.50	40.41 ± 9.26	40.99 ± 9.49	0.949
N3, %	29.47 ± 8.54	26.79 ± 8.02	29.26 ± 7.33	27.33 ± 8.35	0.040
REM, %	17.63 ± 5.28	17.90 ± 5.60	16.23 ± 4.67	16.71 ± 4.32	0.111
Awakenings	12.60 ± 8.68	13.92 ± 9.86	14.35 ± 9.79	14.28 ± 8.68	0.716
Total arousal index, h TST	11.99 ± 8.92	11.63 ± 5.81	12.34 ± 6.80	13.30 ± 9.81	0.392
Respiratory arousal index, h TST	3.51 ± 5.29	2.85 ± 3.90	3.86 ± 5.21	4.44 ± 6.24	0.047
AHI	17.03 ± 18.51 ^b	13.53 ± 14.90 ^b	15.94 ± 18.65 ^b	25.75 ± 25.18 ^a	<0.001
Apnea index, h TST	7.09 ± 12.60 ^{ab}	5.38 ± 9.11 ^b	7.00 ± 12.06 ^{ab}	9.42 ± 12.61 ^a	0.043
Hypopnea index, h TST	9.94 ± 10.92 ^b	8.15 ± 8.82 ^b	8.94 ± 10.02 ^b	16.34 ± 17.82 ^a	<0.001
Obstructive AHI, h TST	5.69 ± 10.56 ^{ab}	4.21 ± 8.45 ^b	5.89 ± 11.61 ^{ab}	8.13 ± 11.82 ^a	0.029
Minimal SaO ₂ , %	73.23 ± 14.25	74.84 ± 12.96	76.15 ± 13.26	71.19 ± 14.68	0.155
Mean oxygen saturation, %	94.82 ± 4.08	95.73 ± 1.71	95.38 ± 2.90	95.08 ± 2.88	0.031
Desaturation index, h TST	17.90 ± 19.38 ^b	14.92 ± 15.32 ^b	18.01 ± 18.65 ^b	30.41 ± 28.06 ^a	<0.001

Table 1. Demographic and clinical characteristics by weight status. The values are means ± standard deviations. Gender is expressed as frequencies with percentages. A/N ratio, adenoidal/nasopharyngeal ratio; TST, total sleep time; N, no rapid eye movement; REM, rapid eye movement; AHI, apnea-hypopnea index. Means with different lower case letters represent a statistically significant difference within each different groups ($P < 0.05$).

defined as the average number of apneas and hypopneas per hour of sleep. Mild disease was defined as an AHI ≥ 1 but < 5 events/h; moderate disease by an AHI ≥ 5 but < 10 events/h; and severe disease by an AHI ≥ 10 events/h²⁴.

Statistical analysis. SPSS software (ver. 22; IBM SPSS, Armonk, NY, USA) was used to perform all statistical analyses. Continuous data are expressed as means with standard deviations, and categorical variables as frequencies with percentages. Data that were normally distributed and that exhibited variance homogeneity were subjected to one-way analysis of variance with the Bonferroni post-hoc test, and other data were analyzed using the Kruskal–Wallis test. Categorical variables were compared using the chi-squared test. Correlations between the AHI and adenotonsillar size were investigated with the aid of the Pearson test and Spearman test. We used multivariate logistic regression to seek independent predictors of OSA. A P -value < 0.05 was considered to reflect statistical significance.

Results

Patient characteristics. We included 451 children of mean age 5.5 ± 2.4 years (69.6% boys), who were divided into underweight, normal-weight, overweight, and obese groups. We enrolled more males than females, but there was no significant difference of sex ratio among the four groups. The baseline demographics and PSG parameters of the four groups were summarized in Table 1. Compared to the underweight ($P = 0.034$), normal-weight ($P < 0.001$) and overweight group ($P = 0.018$), obese children had a significantly higher AHI. Both apnea index ($P = 0.037$) and obstructive AHI ($P = 0.022$) were significantly higher in obese children than those in normal weight children. In addition, obese children had a significantly higher hypopnea index and desaturation index than those in underweight ($P = 0.007$ and $P = 0.001$), normal-weight ($P < 0.001$ and $P < 0.001$), and overweight children ($P = 0.002$ and $P = 0.002$). The A/N ratio of underweight children was significantly higher than that of normal-weight children ($P = 0.027$). However, tonsil size did not differ among the four groups.

Correlation between adenotonsillar size and the logAHI. Figures 2 and 3 presents how different adenotonsillar size and the severity of OSA are related in. As shown in Fig. 2, adenoid size was positively associated with the logAHI in the normal-weight group ($r = 0.210$; $P = 0.001$) but not in the underweight, overweight or obese groups. Figure 3 shows that tonsil size was positively correlated with the logAHI in the normal-weight group ($r = 0.212$; $P = 0.001$) but uncorrelated in the other groups.

Multivariable logistic regression. We used multivariable ordinal logistic regression to define risk factors for OSA in children. We found gender (odds ratio: 1.49, 95% CI: 1.01–2.20, $P = 0.043$), the A/N ratio (odds ratio: 1.55, 95% CI: 1.28–1.88, $P < 0.001$) and tonsil size (odds ratio: 1.36, 95% CI: 1.18–1.57, $P < 0.001$) independently predicted OSA severity after adjustment for age. Obese (compared to normal-weight) children were at higher risk of more severe OSA (odds ratio: 1.93, 95% CI: 1.10–3.40, $P = 0.012$) (Fig. 4).

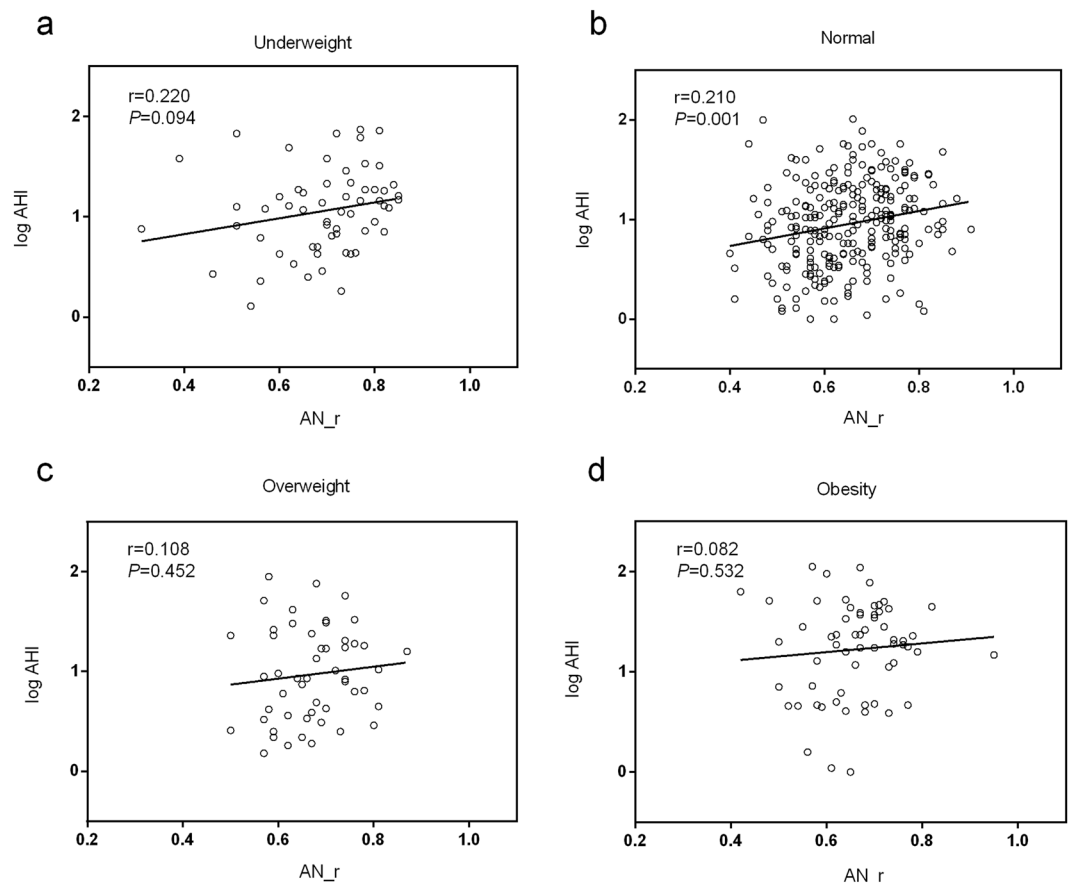


Figure 2. Relationships between adenoidal size and logAHI in children of different weight status (**a,c,d**). No correlation between adenoidal size and logAHI was evident in the underweight, overweight, or obese groups. (**b**) Adenoidal size was positively correlated with logAHI in the normal-weight group ($r = 0.210$; $P = 0.001$).

Discussion

Mental spine - clivus length and intermandibular length of children increase linearly with the age. Meanwhile, tonsils and adenoid grow proportionally to the skeletal structures at the same time²⁵ A longitudinal observational study showed that the tonsil and adenoid grow to maximum size at about ages of 7–9 and of 12–13, respectively^{15,26} In this study, we included the children aged from 2 to 13 years old, who were the most common candidates for adenotonsillectomy. The results of the present study may be used to evaluate the surgical indications in children with OSA.

According to previous studies, obesity is a risk factor for OSA^{27,28}, which is consistent with our results. Some studies have suggested that OSA is a disease of inflammation²⁹. Intermittent airway obstruction places mechanical stress on mucosa that promotes local airway inflammation³⁰. As obesity is also a systemic inflammatory disease, it may exacerbate this process and contribute to OSA. Furthermore, fat deposition at specific sites may also contribute to the development of OSA, which can lead to increased collapsibility of the upper airways, as well as decreased chest compliance and functional residual capacity³¹. In this study, we found that although obese children exhibited a significantly higher AHI than underweight, normal-weight and overweight children, the adenotonsillar size did not differ when obese children were compared with underweight, normal-weight, and overweight children. Adenoid and tonsil sizes were not associated with AHI in obese children. Our findings were similar to another study, which found less adenotonsillar hypertrophy in obese children at any given level of AHI compared to nonobese children¹⁴. Arens *et al.*³². Used magnetic resonance imaging to compare the airway structure and body fat composition between obese children with or without OSA. They found that BMI was not correlated to the size of lymphoid tissues. Lymphoid proliferation in OSA may be independent of obesity. Meanwhile, Several studies found obese children responded poorly to adenotonsillectomy¹⁷ and were more likely to exhibit residual disease^{15,16}. The cause may be adenotonsillectomy can not eliminate the inflammation induced by obesity. Another cause may be fat deposition at specific sites can not be eliminated by adenotonsillectomy. Therefore, we speculated that there were more risk factors for obese children than normal weight children with OSA. Adenotonsillar hypertrophy may not be the prime cause of OSA in obese children. Weight loss has a high success rate in treating obese adolescents with SDB^{33,34}. However, there was no evidence regarding the efficacy of weight loss for obese children with SDB. This might be due to the difficult to control on weight loss on children. In our study, the A/N ratio of underweight children was significantly higher than that of normal-weight children. However, underweight was not a risk factor for OSA. These results revealed that adenoid hypertrophy may be the

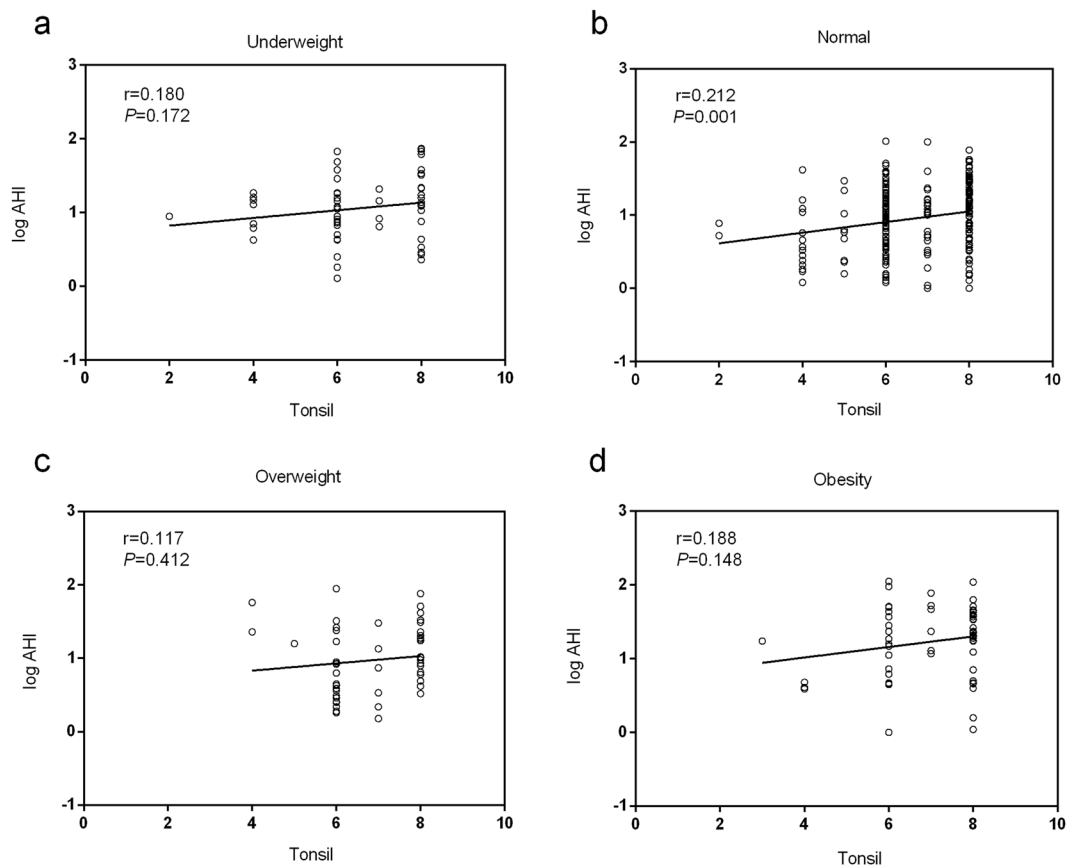


Figure 3. Relationships between tonsil size and logAHI in children of different weight status (a,c,d). No correlation between tonsil size and logAHI was evident in the underweight, overweight, or obese groups. (b) Tonsil size was positively correlated with logAHI in the normal-weight group ($r = 0.212$; $P = 0.001$).

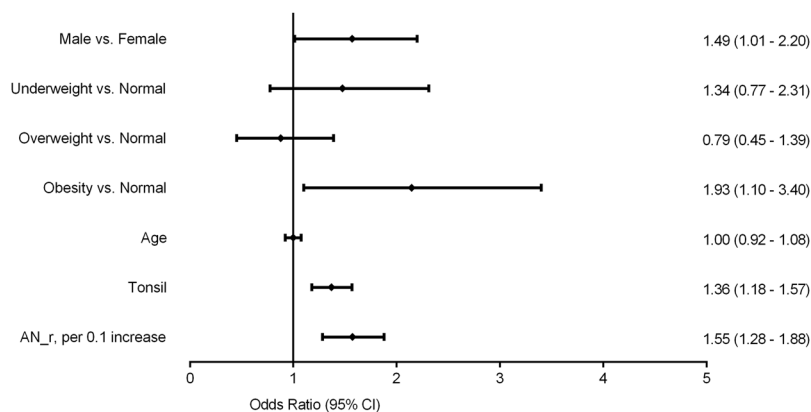


Figure 4. Forest plot of data from multivariate logistic regression revealing factors independently associated with the severity of pediatric OSA. CI = confidence interval.

major contributors to OSA in underweight children. Moreover, both adenoid and tonsil sizes were not associated with AHI in underweight and overweight children. Very few studies have evaluated underweight or overweight children with OSA. One study indicated that underweight may contribute to OSA when used the criterion of AHI of ≥ 5 events/h. On the contrary, underweight may not be a risk factor of OSA when used the criterion of AHI of ≥ 2 events/h in the same study¹³. The most widely used criterion (which we employed) is AHI ≥ 1 event/h in the presence of SDB symptoms¹⁷. The difference of the ages of included patients and the classification criteria in the two studies might explain the discrepancy. Pediatric OSA diagnostic criteria remains controversial.

So far as a large numbers of study showing, adenotonsillar hypertrophy may plays a major role in pediatric OSA¹², similar to our findings that adenotonsillar size independently predicted OSA severity. However, a systematic

review of association between tonsil size and OSAS severity found the correlation between tonsil size and OSAS severity controversial³⁵. The reasons for the differences may due to the tonsil size is measured subjectively. It is possible to be more accurate by objective measurements, such as CT scan or magnetic resonance imaging. In our study, we found the effects of adenotonsillar hypertrophy varied among different populations. Adenoid and tonsil sizes were positively associated with the logAHI in normal-weight children, but not in those who were underweight, overweight, or obese. Therefore, adenoid hypertrophy may be the major contributors to OSA in normal-weight children. Current treatments for adenotonsillar hypertrophy may be useful in normal-weight children.

Earlier studies indicated that boys were more prone to OSA than girls^{3,28}. Similarly, We enrolled more males than females, but there was no significant difference of sex ratio among the four groups. Boys had highest percentages in obese children. The results were consistent with the increasing trend of the prevalence in males with obesity over the past years^{36,37}. According to our study, male gender was an independent predictor of OSA severity after adjustment for age. The pathophysiological mechanism may involve a predisposition to pharyngeal collapse, reflecting the longer length of vulnerable airway and larger soft palate of males^{38,39}. However, several studies found that gender was not a risk factor for pediatric OSA. Future epidemiological studies should explore the association between gender and OSA.

Our study had certain limitations. First, the numbers in the underweight, overweight and obese groups were relatively small. But we did the adjustment of data. Second, owing to ethical considerations, almost all of the children subjected to polysomnography and lateral cephalometric radiography had SDB, and we thus lacked a normal control group. Third, considering about the other factors for OSA, further evaluation of upper airway structure and neuromuscular function in the context of the OSA pathophysiological mechanisms at play in children of various weights status are needed.

Conclusions

Gender, obesity, adenoid and tonsillar size were all associated with pediatric OSA severity. Adenotonsillar hypertrophy was a major risk factor for OSA in normal-weight children. In children of abnormal weight, other risk factors may be in play, and need be defined to allow for appropriate treatment.

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Author Contributions

J.W. and Y.Z. designed experiments; W.Y., T.S., P.X., X.H.Y. recorded polysomnography data, D.N.C., Y.X.Q., M.C. recorded clinic data; J.J.R., Y.X., J.Z., Y.B.Z. analyzed experimental results. J.W. wrote the manuscript. R.R. and X.D.T. revise the manuscript.

Additional Information

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