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RESEARCH ARTICLE

The interaction of obesity and craniofacial deformity in obstructive sleep apnea

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Objective: Both obesity and craniofacial deformity are important etiologies of obstructive sleep apnea (OSA). The present research aimed to explore their interaction and different impacts on OSA severity.
Methods: A total of 207 consecutive OSA patients (169 males, 38 females) were included in the research. Based on the body mass index (BMI) value, patients were divided into 77 normal-weight patients (BMI <24 kg m^{-2}), 105 overweight patients (24 ≤ BMI<28 kg m^{-2}) and 26 obese patients (BMI ≥28 kg m^{-2}). All accepted overnight polysomnography and standard lateral cephalogram. Cephalometric measurements involved 25 cephalometric variables. The correlations between these cephalometric variables, BMI and the apnea-hypopnea index (AHI) were evaluated.
Results: For the whole sample after controlling for gender and age, stepwise regression analysis showed that the factors affecting AHI were increased BMI, narrowing posterior airway space, inferior displacement of hyoid and elongation of the tongue. When grouped by BMI, normal-weight group exhibited with more reduced maxillary length and mandible length, and steeper mandible plane than overweight and obese patients ($p < 0.0167$). Obese group showed least skeletal restriction and most prominent soft tissues enlargement ($p < 0.0167$). However, these skeletal indexes were not statistically correlated with AHI.
Conclusions: Obesity and skeletal malformations were both etiological factors of OSA, but obesity seemed to have a greater influence on AHI severity in all kinds of obese and thin OSA patients. Only in normal-weight group, it was affected by both cephalometric variables and BMI.
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Introduction

Obstructive sleep apnea (OSA) is an increasingly common disorder, which is characterized by a recurrent partial or complete collapse of the upper airway during sleep.[1,2] The mechanisms of the pharyngeal collapse are complex and multifactorial, and the upper airway reduction due to obesity and/or craniofacial deformity is an important reason for the upper airway obstruction.[3,4]

Although many studies have assessed the craniofacial morphology features with more sophisticated and expensive techniques (including awake endoscopy, endoscopy, fluoroscopy, CT scanning, MR scanning, manometry and acoustic reflection),[5] lateral cephalogram is still suitable as a screening procedure to evaluate skeletal and soft tissue characteristics since it is easy, well-standardized, low-cost, low-radiation and is widely available in the majority of hospitals.[6,7]

Obesity is the most important and well-recognized risk factor for OSA.[8] The Wisconsin sleep cohort study found that a gain of 10% in body weight among mild OSA patients predicted a corresponding 32% in the Apnea-Hypopnea Index (AHI) and increased their risk of progression of OSA severity sixfold.[9] OSA has been reported to be present in more than 40% of persons with

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a BMI of more than 30.[10] Craniofacial abnormality is an important predisposing factor in development of OSA.[11,12] Several studies revealed the cephalometric differences between OSA patients and control samples. Most commonly associated craniofacial characteristics in OSA patients include decreased cranial base length, a greater flexion of the cranial base, longer anterior facial height, maxillary hypoplasia, mandibular deficiency, clockwise rotation of mandible, inferior displacement of the hyoid bone, a narrowed posterior airway space and elongation of the soft palate.[13–15]

Generally, it is clear that both obesity and craniofacial morphology are key anatomical risk factors that predispose to the development of OSA.[16] However, most studies separately identified the relationship between OSA and craniofacial morphology or obesity. Actually, obesity and craniofacial abnormalities contribute synergistically to increase narrowing of the pharyngeal airway in patients with sleep-disordered breathing (SDB).[17] Some studies suggested that body mass index (BMI) might be related to cephalometric measurements.[18–27] A review summarized that non-obese patients tend to display more craniofacial skeletal abnormalities, whereas obese patients show less skeletal restriction and instead have a larger soft palate and tongue, and associated anteroinferior positioning of the hyoid bone.[16] Several studies have explored the contribution of variance in BMI in combination with cephalometric parameters to OSA severity.[19,22–24,26,27] Hou et al[24] indicated body weight, lower posterior facial height, mandibular body length, craniocervical extension and sella-hyoid distance were significant predictor of AHI. Pae et al[26] revealed OSA severity in non-obese severe patients may be associated with a vertical skeletal disharmony. Liao et al[27] identified soft palate thickness as predictor in non-obese patients and soft palate length, hyoid position and BMI as predictors in obese patients. Dempsey et al[28] concluded that four cephalometric dimensions of the upper airway in combination with BMI accounted independently for up to two-thirds of the variation in AHI. Sample size in these studies ranged from 62 to 161. And few studies were based on Asian population.[22–24,27] Asian OSA patients seemed to have a lower body mass index (BMI) than their Caucasian counterparts who possess a similar degree of OSA severity.[29,30] The interaction between BMI, craniofacial features and OSA severity may be different from Caucasians.

Therefore, the purpose of this study was to clarify the relationship between cephalometric variables, BMI, and OSA severity (evaluated by AHI) in Asian patients. The hypothesis is that thinner patients are affected mostly by skeletal reasons and obese patients are mainly affected by obesity.

Methods and materials

Study design and sample

This study was a retrospective cross-sectional study, which had been approved by the ethics committee of Stomatology School and Hospital of Peking University (PKUSSIRB-202054026). This study was in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consecutive OSA patients from January 2014 to December 2017 entered the study, who referred to the Department of Orthodontics in Stomatology School and Hospital of Peking University for mandibular advancement device (MAD) treatment. The inclusion criteria were as follows: (1) adults older than 18 years; (2) baseline polysomngraphy (PSG) showed AHI equal to or over five events/h, and (3) with standardized lateral cephalogram. The exclusion criteria were as follows: (1) PSG support other sleep disorders; (2) incomplete or poor imaging data; (3) with cleft lip and palate, or other congenital syndrome; (4) history of craniofacial trauma or surgery. Finally, 207 OSA patients (169 males,38 females) were included in the study. On the basis of BMI value, they were categorized into three subgroups: 77 normal patients (37.3%): BMI <24 kg m^{-2}; 105 overweight patients (50.2%): 24 ≤ BMI<28 kg m^{-2}; 26 obese patients (12.4%): BMI ≥28 kg m^{-2}.[31]

Polysomngraphy

Each patient in our study was diagnosed in eligible sleep center of general hospital and all underwent overnight PSG which included full EEG, EOG, chin EMG, leg EMG, ECG, nasal/oral airflow thermistor, pulse oximetry, and body position sensors. PSG was scored following the guidelines of the American Academy of Sleep Medicine 2012.[32] AHI (event/hour), apnea index (AI, event/hour), hypopnea index (HI, event/hour) and the minimum O_2 saturation (SaO_2Min, per cent) were extracted from the PSG reports.

Cephalometric analysis

Lateral cephalogram were routinely performed in all patients before MAD treatment. The cephalograms were taken with an Orthoceph OC200 digital X-ray machine (Instrumentarium Dental Inc, Tuusula, Finland). The magnification of the particular machine used in this study was 1.144 for all subjects. The cephalograms were taken in the upright position and during the end-expiration phase. The patients were told to keep teeth in centric occlusion with tongue tip touching the incisors and without swallowing as well as speaking. A cephalostat was used to keep the subject's head in a position so that the Frankfort horizontal line was parallel to the floor during exposure.

The cephalometric landmarks and measurements used in this study were outlined in Figure 1, which based on the methods described previously by Lowe, Tangugsorn and Liu et al.[33–35] The cephalometric variables used in this study were divided into six parts: cranial base (anterior cranial base length: S-N), maxilla and mandible (for position: SNA to indicate the maxillary position, SNB to indicate the mandibular position, ANB to indicate the relationship between two jaws,

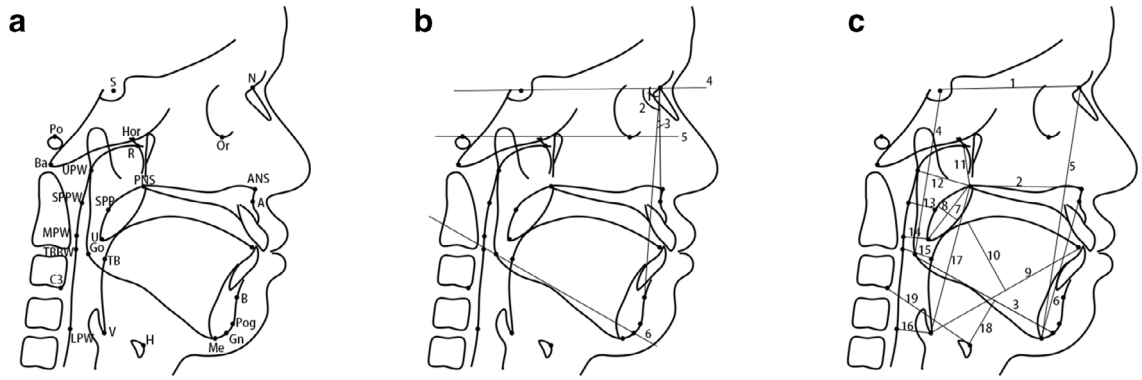

Figure 1 Cephalometric measurements: (a) Landmarks: S-Center of the sella turcica. N-Nasion, the deepest point in the concavity of the nasofrontal suture. Po-Porion, the most superior point of the bony external auditory meatus. Or-Orbitale, the most inferior point on the infraorbital margin. Ba-Basion, the most inferior point on the anterior margin of the foramen magnum. ANS-Anterior nasal spine. PNS-Posterior nasal spine. A-A point, the deepest point in the concavity of the anterior maxilla between the anterior nasal spine and the alveolar crest. B-B point, the deepest point in the concavity of the anterior mandible between the alveolar crest and pogonion. Pog-Pogonion, the most anterior point on the bony chin. Me-Menton, the most inferior point on the body chin. Gn-Gnathion, the most anteroinferior point on the bony chin. Go-Gonion, the most posterior-inferior point on the angle of the mandible. Hor-Hormion, the anterior border of the lateral pterygoid lamina intersects the lower border of the posterior skull base. R-The line between Hor and PNS intersects with the posterior pharyngeal wall. UPW-Upper pharyngeal wall point, the line between Ba and PNS intersects with the posterior pharyngeal wall. SPP-The intersection of a vertical line from the center of the soft palate to the posterior pharyngeal wall and the posterior margin of the soft palate. SPPW-The point perpendicular to the posterior pharyngeal wall through the center of the soft palate. U-The tip of the uvula. TT-Most anterior point of the tip of the tongue. TB-Through the line between Go and B and the intersection of the tongue base. TPPW-Through the line between Go and B and the intersection of the posterior pharyngeal wall. V-Vallecula, the most posteroinferior base of the tongue. LPW-The point perpendicular to the posterior wall of the pharynx by V. H-The most superior and anterior point on the body of the hyoid bone.C3-anterorinferior limit of third cervical vertebra. (b) Angular measurements and reference plane: (1) SNA; (2) SNB; (3) ANB. (4) SN plane-Anterior cranial base plane, the line joining S and N. (5) FH plane-Frankfort horizontal plane, the line joining Po and Or. (6) MP plane-Mandibular plane, the line joining Go and Gn. (c) Linear measurements: (1) SN. (2) ANS-PNS: Maxillary length. (3) Go-Gn: Mandibular length. (4) PFH: Posterior face height (S-Go); (5) AFH: Anterior face height (N-Me). (6) LAFH: Lower anterior face height (ANS-Me). (7) PNS-U: Soft palate length. (8) MPT: Soft palate thickness (maximum thickness of soft palate measured on line perpendicular to PNS-U line). (9) TGL: Tongue length (V-TT). (10) TGH: Tongue height (maximum height of tongue along perpendicular line of V-TT line to tongue dorsum). (11) PNS-R. (12) PNS-UPW. (13) SPP-SPPW. (14) U-MPW. (15) PAS: Posterior airway space (TB-TPPW). (16) V-LPW. (17) VAL: Vertical airway length (PNS-V). (18) H-MP: Perpendicular distance from the MP to H. (19) C3-H.

MP-SN to indicate mandibular inclination; for length: ANS-PNS to indicate the maxillary length, Go-Gn to indicate the mandibular length), facial height (PFH to indicate posterior facial height, AFH to indicate anterior facial height, LAFH to indicate lower anterior facial height, PFH/AFH indicate the relationship between posterior and anterior facial height, LAFH/AFH indicate the relationship between lower and total anterior facial height), soft palate (PNS-U to indicate soft palate length, MPT to indicate soft palate thickness), tongue (TGL to indicate tongue length, TGH to indicate tongue height), pharyngeal airway (for width: PNS-R/PNS-UPW to indicate nasopharyngeal airway width, SPP-SPPW/U-MPW/PAS to indicate oropharyngeal airway width, V-LPW to indicate hypopharyngeal airway width; for length: VAL to indicate pharyngeal airway length) and hyoid bone (H-MP, C3-H to indicate the hyoid bone position). Cephalometric measurements were accomplished by a single orthodontist (HLP) using the Photoshop CC 2018 software. Four weeks later, method error was estimated by repeating the digitization process for 25 randomly selected radiographs. Differences calculated using Dahlberg's formula ranged from 0.21 to 0.69 mm for the linear measurements and from 0.71 to 0.83 degrees for the angular measurements. No systematic errors were detected.

Statistical analysis

According to the results of normality by the Kolmogorov–Smirnov test, continuous variables were identified as normally distributed data or non-normally distributed data. Normally distributed data are expressed as a mean and standard deviation (mean ± SD) and compared among groups using analysis of variance. And non-normally distributed data are expressed as a median and interquartile range [median (interquartile range, IQR)] and compared using non-parametric Kruskal-Wallis tests. Categorical variables were summarized using percentages and compared among groups using chi-square tests. The correlation between variables was examined by calculating the Spearman correlation coefficient. Multiple linear regression analysis was then used to identify BMI and the cephalometric measurement variables that had significant effects on AHI values in overall OSA patients after controlling the age and gender. The predicted value of each indicator was determined by the additional R^2 value corresponding to the proportion of OSA total variance interpreted by it. And multiple linear regression analysis was also performed in subgroups. Subsequent pairwise comparisons were performed to define between group differences by Bonferroni posthoc analysis.

Table 1 Patients' demographic and PSG characteristics (n = 207)

Variable	*Total* (n = *207*)	*Normal-weight (N)* (n = *76*)	*Overweight (OW)* (n = *105*)	*Obese (OB)* (n = *26*)	p *value*
Gender (% male)	81.6	72.4	86.7	88.5	0.031[a]
Age (yr)	43 (35, 52)	39 (34, 50)	45 (36, 52)	44.5 (39.5, 52)	0.392
BMI (kg m^{-2})	24.8 (23.4, 26.6)	22.8 (21.6, 23.5)	25.4 (24.8, 26.6)	29.95 (28.4, 31.08)	<0.001[b]
AHI (events/h)	18.5 (12.2, 32.8)	15.5 (11, 25.9)	21.8 (12.4, 33.7)	33.35 (15.92, 45)	<0.001[b]
AI (events/h)	9.9 (4.1, 20.35)	8.08 (5.2, 14.7)	10.61 (3.5, 19.7)	18.92 (3.17, 26.85)	0.201
HI (events/h)	8.09 (4.3, 14.97)	6 (3, 9.8)	9.1 (4.68, 16.7)	11.95 (6.17, 18.32)	<0.001[b]
SaO2Min (%)	83 (78, 87)	85.5 (81, 89)	82 (76, 86)	80 (75.25, 86)	<0.001[b]

AHI, Apnea-hypopnea index; AI, Apnea index; BMI, Body mass index; HI, Hypopnea index; SaO_2Min, Minimum oxygen saturation.
Data presented as median (interquartile range) or percentage.
[a]$p < 0.05$.
[b]$p < 0.001$.

All data were analysed using SPSS, v. 22.0 (22.0, SPSS Inc., Chicago, IL, USA) and the software program R, v. 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria). All p values given are two-sided, and the significance level was set at $p < 0.05$. The significance difference level of Bonferroni corrected for three pairwise comparisons was $p < 0.0167$.

Results

The characteristics of the subjects are presented in Table 1. The obese group had the highest AHI and hypopnea index (HI) value. The SaO_2Min of normal-weight group was the highest among three groups.

Table 2 showed the statistically significant indicators associated with AHI in overall patients and for each subgroup. In all patients with OSA, the AHI showed a correlation with BMI, airway length (VAL), tongue length (TGL), hyoid position (H-MP), anteroposterior width of the bony nasopharynx and oropharynx (PNS-UPW, U-MPW and PAS) and gender. In the normal-weight subgroup, the AHI showed a correlation with BMI, VAL, H-MP, and PAS. And in overweight patients, the AHI showed a significant negative correlation with bony nasopharynx and oropharynx (PNS-UPW, U-MPW, PAS and VLPW). In obese patients, the AHI showed a correlation with VAL and gender.

Stepwise regression analysis of AHI was performed for all patients with OSA and each subgroup. The regression model for AHI was significant with the following determinants: BMI, PAS, H-MP and TGL ($R^2 = 0.230$, $p < 0.001$). The regression model could account for 23.9% of the variance of AHI with the following determinants: PAS, H-MP and BMI in normal-weight patients. And the multiple stepwise linear regression identified PAS as the significant predictive variable in overweight group ($R^2 = 0.117$, $p < 0.001$). For obese patients, we could not obtain a significant regression model for AHI (Table 3). BMI seemed to be most significant determinants in all patients, while PAS was identified as most significant predictor in normal-weight subgroup and only predictor in overweight subgroup.

After matching age and gender, the cephalometric differences among the three obesity groups are shown in Table 4. There were statistically significant differences in anterior cranial base length (S-N), maxilla position

Table 2 The general condition and cephalometric measurements related to AHI in overall patients and within subgroups

	Overall patients (207)		*Normal-weight patients (76)*		*Overweight patients (105)*		*Obese patients (26)*	
Variables	*r*	p	*r*	p	*r*	p	*r*	p
BMI	0.303	<0.001[c]	0.279	0.014[a]				
Gender (M = 1; F = 2)	−0.187	0.007[b]					−0.506	0.008[b]
PNS-UPW	−0.185	0.008[b]			−0.345	<0.001[b]		
U-MPW	−0.187	0.007[b]			−0.316	0.001[b]		
PAS	−0.219	0.002[b]	−0.249	0.029[a]	−0.374	<0.001[c]		
V-LPW					−0.234	0.016[a]		
VAL	0.213	0.002[b]	0.258	0.023[a]			0.394	0.047[a]
TGL	0.188	0.007[b]						
H-MP	0.224	0.001[b]	0.297	0.009[b]				

BMI, Body mass index; PAS, Posterior airway space; TGL, Tongue length; VAL, Vertical airway length.
[a]$p < 0.05$.
[b]$p < 0.01$.
[c]$p < 0.001$.

Table 3 Multiple stepwise linear regression analysis evaluating predictors of AHI for all OSA patients and within subgroups

	Overall patients (207)					*Normal-weight patients (76)*					*Overweight patients (105)*				
Independent variable	*B*	*SE*	*β*	*t*	p	*B*	*SE*	*β*	*t*	p	*B*	*SE*	*β*	*t*	*p*
Constant	−37.4	11.967		−3.125	0.002	−28.663	21.631		−1.325	0.189	37.611	3.792		9.918	<0.001
BMI	1.407	0.364	0.265	3.861	<0.001	2.037	0.942	0.223	2.163	0.034					
PAS	−1.155	0.243	−0.311	−4.758	<0.001	−1.148	0.336	−0.357	−3.422	0.001	−1.213	0.328	−0.343	−3.702	<0.001
H-MP	0.424	0.175	0.166	2.42	0.016	0.699	0.228	0.319	3.059	0.003					
TGL	0.367	0.176	0.162	2.074	0.039										

BMI, Body mass index; PAS, Posterior airway space; TGL, Tongue length.

(SNA), mandible position (SNB), mandible rotation (MP/SN), maxillary length (ANS-PNS), mandibular length (Go-Gn), posterior facial height (PFH), soft palate thickness (MPT), tongue length (TGL), oropharyngeal airway space (U-MPW, PAS) and hyoid position(H-MP,C3-H) among the three obesity groups ($p < 0.05$). After Bonferroni's posthoc analysis for pairwise comparisons, normal-weight group exhibited more posteriorly positioned mandible and shorter maxilla than overweight and obese patients ($p < 0.0167$). Normal-weight patients manifested shorter anterior cranial base, more retruded maxilla, and less inferiorly positioned hyoid than obese patients. While obese group showed thicker soft palate, longer tongue, wider oropharyngeal (U-MPW, PAS) and more anterior-inferiorly positioned hyoid bone than normal-weight and overweight patients ($p < 0.0167$).

Discussion

Craniofacial features and pharyngeal soft tissues are considered to affect upper airway patency and lead to apnea. Although the anatomic factors are not the only key to explain the severity of OSA but they may be helpful in distinguishing subgroups of small differences. Neelapu et al[15] summarized that some cephalometric variables were associated craniofacial characteristics in OSA patients. As we know, lateral cephalogram is easy, well-standardized, low-cost, low-radiation and is widely available in the majority of hospitals.[6,7] And it is suitable as a screening procedure to evaluate skeletal and soft tissue characteristics and to find the asymptomatic OSA patients.

Obesity is a major and well-recognized risk factor for OSA, and craniofacial morphology is increasingly acknowledged as an important interacting factor in the pathogenesis of OSA.[16] Several studies have explored the contribution of variance in BMI in combination with cephalometric parameters to OSA severity.[7,19,22–27] Nevertheless, these studies were based on relatively small study sample. And few studies have derived the relationship between BMI, cephalometric parameters and AHI on OSA patients.[22–24,27] Our study had been interested in exploring the co-existence of obesity and craniofacial factors, and used statistical methods to screen out the influence of age and gender.

Our study agrees that BMI plays an important role in AHI. Multiple linear regression model in this study showed increased BMI aggravated OSA severity in overall sample. Compared to cephalometric variables, BMI contributed more to the variation of AHI in all OSA patients. It is a consensus that increased BMI are linked to the occurrence of OSA.[9] For the first, obesity causes increased fat deposition around the soft tissues of the neck and the tongue, and promotes enlargement of soft tissue structures within and surrounding the airway, thereby contributing significantly to pharyngeal airway narrowing elevating the pharyngeal critical pressure.[36,37] The second, obesity also affects airway neuromuscular control through specific molecular signalling pathways in the central nervous system.[38] However, the association between OSA and obesity is complex. Liao et al[27] and Kim et al[39] showed that BMI was identified as independent factor contributing to AHI only in obese patients. Yu et al[22] and indicated BMI correlated to AHI both in non-obese and obese patients. While Hou et al[24] did not confirm BMI was a predictor for AHI. Furthermore, Serafini et al[40] found no correlation between BMI, and the severity of OSA in severely obese patients who underwent bariatric surgery.

Hence, it is guessed that BMI may display different relevance in different obesity subgroups. Previous studies showed that non-obese patients tend to display more craniofacial skeletal abnormalities, while obese patients show less skeletal restriction and instead have a larger soft palate and tongue, and associated antero inferior positioning of the hyoid bone.[16,22–26] In our study, BMI in obese group shown no correlation with AHI, but in normal weight group and patients in whole revealed the increased BMI exacerbated OSA severity. The underlying reason may be that a very large BMI can cover all other anatomical factors even itself. If the BMI reached a certain level, no matter how good the skeletal framework was, it could not provide smooth ventilation, and there was no difference between them. Contrary to that, small BMI group was affected by both bony and BMI reasons. The results suggested that weight loss or weight control may also be necessary in normal-weight patients.

Table 4 Comparison of Normal-Weight, Overweight, and Obese OSA Patients

Variables		*Total* (n = *197*)	*Normal-weight (N)* (n = *66*)	*Overweight (OW)* (n = *105*)	*Obese (OB)* (n = *26*)	*χ2/F/H*	p *value*[a]	*Pairwise Comparisons*[b]		
								N vs *OW*	*N* vs *OB*	*OW* vs *OB*
Gender (%male)		85.8	83.3	86.7	88.5	0.545	0.761			
Age (yr), Median (IQR)		43 (35, 52)	39 (33.25, 50)	45 (36, 52)	44.5 (39.5, 52)	2.616	0.27			
BMI (kg/m^2), Median (IQR)		24.9 (23.5, 26.8)	22.95 (21.72, 23.5)	25.4 (24.8, 26.6)	29.95 (28.4, 31.08)	158.57	<0.001[f]	[c]	[c]	[c]
AHI (events/h), Median (IQR)		19 (12.2, 33.7)	15.5 (11, 27.52)	21.8 (12.4, 33.7)	33.35 (15.92, 45)	12.764	0.002[e]		[c]	
Cranial base	S-N (mm), Mean ± SD	65.12 ± 3.53	64.73 ± 3.02	64.95 ± 3.28	66.81 ± 5.09	3.597	0.029[d]		[c]	
Maxilla & mandible	SNA°, Mean ± SD	82.61 ± 3.82	81.75 ± 3.8	82.8 ± 3.79	83.99 ± 3.6	3.583	0.03[d]		[c]	
	SNB°, Mean ± SD	76.31 ± 3.8	75.19 ± 3.68	76.6 ± 3.62	77.95 ± 4.13	5.871	0.003[e]	[c]	[c]	
	ANB°, Mean ± SD	6.29 ± 2.51	6.53 ± 2.74	6.19 ± 2.24	6.04 ± 2.93	0.524	0.593			
	MP/SN°, Mean ± SD	32.56 ± 6.25	34.37 ± 6.9	31.64 ± 5.74	31.69 ± 5.7	4.303	0.015[d]	[c]		
	ANS-PNS (mm), Mean ± SD	47.47 ± 2.9	46.31 ± 2.73	47.88 ± 2.75	48.77 ± 2.98	9.815	<0.001[f]	[c]	[c]	
	Go-Gn (mm), Median (IQR)	71.8 (68.3, 75.3)	70.5 (67.98, 74.38)	72 (68, 75.4)	73.4 (71.05, 75.7)	5.23	0.073			
Facial height	PFH (mm), Mean ± SD	83.48 ± 7.05	81.83 ± 6.95	84.07 ± 7.09	85.29 ± 6.54	3.093	0.048[d]			
	AFH (mm), Mean ± SD	124.35 ± 6.52	124.24 ± 6.07	123.93 ± 6.84	126.32 ± 6.22	1.418	0.245			
	PFH/AFH, Mean ± SD	0.67 ± 0.05	0.66 ± 0.05	0.68 ± 0.04	0.68 ± 0.05	3.407	0.035[d]	[c]		
	LAFH (mm), Mean ± SD	68.88 ± 5.25	68.77 ± 5.3	68.5 ± 5.18	70.65 ± 5.26	1.778	0.172			
	LAFH/AFH, Mean ± SD	0.55 ± 0.02	0.55 ± 0.02	0.55 ± 0.02	0.56 ± 0.03	0.877	0.418			
Soft palate	PNS-U (mm), Median (IQR)	39.3 (36.7, 42)	38.7 (36.25, 41.18)	39.7 (36.9, 42.4)	40.05 (37.28, 42.55)	2.308	0.315			
	MPT (mm), Median (IQR)	10.9 (10, 12)	10.9 (9.62, 11.88)	10.6 (10, 11.8)	11.75 (11.25, 12.6)	7.41	0.025[d]		[c]	[c]
Tongue	TGL (mm), Mean ± SD	80.55 ± 6.35	77.27 ± 5.34	81.49 ± 6.23	85.06 ± 5.26	19.611	<0.001[f]	[c]	[c]	[c]
	TGH (mm), Mean ± SD	35.28 ± 3.9	35.19 ± 4.38	35.38 ± 3.69	35.12 ± 3.52	0.074	0.928			
Pharynx	PNS-R (mm), Median (IQR)	21.8 (19.6, 23.3)	21.95 (19.9, 23.3)	21.3 (19.5, 23.2)	22.7 (19.75, 23.58)	3.375	0.185			
	PNS-UPW (mm), Mean ± SD	26.38 ± 2.95	26.23 ± 2.66	26.18 ± 3	27.55 ± 3.29	2.392	0.094			
	SPP-SPPW (mm), Median (IQR)	9.3 (7.1, 10.9)	9.35 (6.82, 10.7)	8.9 (7, 10.6)	10.65 (8.62, 11.65)	5.567	0.062			
	U-MPW (mm), Median (IQR)	8.4 (6.9, 10.4)	8.35 (6.05, 10.17)	8.3 (6.7, 10.3)	9.8 (8.17, 11.83)	8.348	0.015[d]		[c]	[c]
	PAS (mm), Median (IQR)	10.8 (7.9, 13.6)	9.8 (7.62, 12.95)	10.7 (7.8, 13.3)	13.3 (9.7, 15.07)	9.417	0.009[e]		[c]	[c]
	V-LPW (mm), Mean ± SD	18.81 ± 4.31	18.35 ± 4.34	18.88 ± 4.34	19.73 ± 4.07	0.988	0.374			
	VAL (mm), Mean ± SD	73.63 ± 6.61	72.29 ± 6.14	74.09 ± 6.83	75.13 ± 6.52	2.308	0.102			
Hyoid	H-MP (mm), Mean ± SD	21.85 ± 5.77	20.65 ± 5.55	22.08 ± 5.49	23.93 ± 6.82	3.3	0.039[d]		[c]	
	C3-H (mm), Mean ± SD	38.37 ± 4.26	37.21 ± 3.96	38.43 ± 4.2	41.1 ± 4.04	8.41	<0.001[f]		[c]	[c]

(Continued)

Table 4 (Continued)

Variables	*Total* (n = *197*)	*Normal-weight (N)* (n = *66*)	*Overweight (OW)* (n = *105*)	*Obese (OB)* (n = *26*)	*χ2/F/H*	p *value*[a]	*Pairwise Comparison*[b]	
							N vs *OW*	*N* vs *OB* *OW* vs *OB*

AFH, Anterior face height; AHI, Apnea-hypopnea index; BMI, Body mass index; LAFH, Lower anterior face height; MPT, Soft palate thickness; PAS, Posterior airway space; PFH, Posterior face height; TGH, Tongue height; TGL, Tongue length; VAL, Vertical airway length.
Data presented as percentage for categorical data, mean ± standard deviation (SD) for normally distributed data and median (interquartile range, IQR) for non-normally distributed data.
[a]*p* value value from chi-square tests (categorical data), analysis of variance (normally distributed data), Kruskal-Wallis (non-normally distributed data) among the three obesity groups
[b]Pairwise comparisons between groups performed when overall $p < 0.05$.
[c]$p < 0.0167$ (Bonferroni corrected for three pairwise comparisons).
[d]$p < 0.05$.
[e]$p < 0.01$.
[f]$p < 0.001$.

There might be a cut-off point or range for BMI threshold. Among previous studies which included small BMI sample would show a correlation between BMI and AHI.[22,27,39] While the sample in Serafini's study was with much more BMI (52 ± 10 kg m^{-2}), they reported no correlation between the two.[40] According to present study, the influence of BMI on AHI was not different if BMI was more than 28 kg m^{-2}. Certainly, the cut-off point needs further study in a more comprehensive and abundant sample.

As a supplement, although BMI was not directly related to AHI in our subgroup studies and other researches, TGL could be used as an indicator of local fat deposition, which could indirectly reflect the impact of BMI. A longer tongue is more likely to cause obstruction of the upper airway.[22] Recent meta-analysis showed increase in length of tongue in OSA patients, but significant heterogeneity among the primary studies.[15]

As for cephalometric variables, it is more like a synergistic factor, showing influence especially in the thin group. When matched the age and gender proportion in this study, normal-weight patients showed most severe skeletal restriction with shortest anterior cranial base and maxilla, most posteriorly positioned maxilla and narrowest posterior airway space.

All relevant anatomic factors accounted could only explain 23% of causes of AHI in our study, which is the result from the complex aetiology of OSA. Almost all the anatomic analysis showed low correlation with AHI. Cillo et al. even concluded that there was no important skeletal or soft tissue parameter directly linked to OSA.[41] However, compared with the central regulation and neuromuscular functions, anatomical factors are the only factors that can be measured and utilized in treatment. H-MP and PAS were also identified as significant determinant factors in our study. Review and meta-analysis showed that there is a strong evidence for inferiorly placed hyoid bone in adult OSA patients compared to control subjects.[15,22,42] Banhiran et al[43] also found that H-MP greater than or equal to 18 mm increased the risk of having AHI greater than or equal to 15. Stipa et al[44] revealed H-MP was significant predictors of AHI in adult Caucasian OSA patients after controlling for the effect of gender, age, and BMI.[44] Recent meta-analysis showed reduced posterior airway space was consistent in OSA when compared to control.[15] Banhiran et al[43] claimed that PAS ≤10 mm increased the risk of having AHI greater than or equal to 15.[43] Now our study is trying to figure out an important cut-off for BMI.

There are several limitations in this study. First, the study population may have referral bias because of the retrospective study design, which means the findings may only applicable to the population referred for MAD. Second, the study population in this study was Asian adult OSA patients with predominantly normal-weight and overweight patients. Therefore, present study did not consider ethnic differences among patients and could not represent the sample with high obesity rate.

Further study should include OSA patients ranging widely in BMI to derive more accurate relationship. Third, our study was based on lateral cephalogram, which is a two-dimensional imaging method and cannot provide three-dimensional information. In addition, upright lateral cephalogram do not reflect dynamic characteristics of upper airway during sleep. Fourth, this study only used BMI to evaluate the obesity, but BMI is not representative of all types of fat deposition, and therefore all types of obesity. Finally, present study only explored the relationship between BMI, craniofacial features and OSA patients. However, there are anatomical and non-anatomical factors contributing to the development of OSA.[45,46] Therefore, non-anatomical factors including increased propensity for awakening during airway narrowing (a low respiratory arousal threshold), ineffective or reduced pharyngeal dilator muscle activity during sleep, and respiratory control instability (high loop gain) should be considered.[46,47]

Conclusion

Obesity and skeletal malformations were both etiological factors of OSA, but obesity seemed to have a greater influence on AHI severity in all kinds of obese and thin OSA patients. Only in normal-weight group, it was affected by both cephalometric variables and BMI.

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