SLEEP DISORDERED BREATHING

# Maxillomandibular Volume Influences the Relationship between Weight Loss and Improvement in Obstructive Sleep Apnea

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**Study Objectives:** Obesity is the major risk factor for OSA; however, weight loss reduces OSA to a variable extent. We aimed to assess whether size of the maxillomandibular skeletal enclosure influences the relationship between weight loss and OSA reduction.

**Methods:** Obese males (≥ 30 kg/m$^2$) with moderate-severe OSA (AHI > 15/h) participating in a 6-mo open-label weight loss program had craniofacial computed tomography (CT) scans before and after weight loss. CT scans were analysed using three-dimensional cephalometry. Maxillomandibular volume was calculated from skeletal landmarks on the mandible (condyle, gonion, menton) and maxilla (anterior nasal spine). Multiple regression analysis was used to test for moderating effects of maxillomandibular volume on relationship between changes in weight and apnea-hypopnea index (AHI).

**Results:** Fifty-two men (age 44.3 ± 8.8 y, AHI 42.9 ± 21.3 events/h, body mass index [BMI] 34.0 ± 2.7 kg/m$^2$) had 7.4 ± 4.1% weight loss and 34.1 ± 32.4% AHI reduction at 6 months. BMI reduction modestly predicted AHI change ($r^2$ = 0.17, P = 0.002). The interaction term of maxillomandibular volume and BMI change was a predictor of OSA improvement (P = 0.03), indicating maxillomandibular volume moderates this relationship. Subgroup analyses of patients by small, medium, and large maxillomandibular volume showed a strong correlation between weight loss and OSA improvement only in the small volume group (r = 0.654, P = 0.004). There was no relationship evident in those with large maxillomandibular volume (r = 0.05, P = 0.9).

**Conclusion:** Maxillomandibular volume influences the relationship between weight loss and OSA improvement with an effect on AHI more evident in those with a smaller craniofacial skeleton.

**Keywords:** computed tomography, craniofacial structure, maxillomandibular volume, obesity, obstructive sleep apnea, weight loss

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**Significance**

The effectiveness of weight loss as a treatment for OSA is variable and identification of patient factors which relate to weight loss therapy responsiveness would be clinically useful. Our findings support a role for craniofacial skeletal size in the relationship between weight loss and OSA reduction and suggests those with smaller maxillary-mandibular dimensions have greatest benefit from weight loss. Therefore craniofacial skeletal structure is a potential predictor of effectiveness of weight loss for OSA reduction. Reduced craniofacial dimensions could represent a phenotype of OSA patient most suitable for weight loss therapy.

## INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by repetitive upper airway obstruction resulting in oxygen desaturation and sleep disturbance and is associated with adverse cardiovascular and neurobehavioral consequences. Recent prevalence data from a middle-aged population shows that 17% of men and 9% of women older than 50 y have moderate to severe OSA.[1] Increasing obesity likely explains a rise in OSA prevalence in the past 20 y.[2] Obesity is well recognized as a major risk factor for OSA and 58% of adult OSA can be attributed to being overweight.[3] Weight gain of 10% can increase apnea-hypopnea index (AHI) by approximately 30%, whereas the same weight loss can decrease AHI by 26%.[4]

Weight loss is therefore a treatment strategy with dietary and lifestyle interventions for weight loss in OSA showing an overall positive effect in reducing AHI.[5] However, weight loss does not offer a consistent cure for OSA and there is much heterogeneity in the OSA response to weight loss.[6] This suggests that other underlying pathogenic mechanisms are still contributing to residual OSA.

Collapsing forces on the upper airway include extraluminal pressure from surrounding tissue structures.[7] Reducing adipose tissue deposits through weight loss would therefore be expected to reduce extraluminal tissue pressure and help stabilize the airway.[8] However, extraluminal tissue pressure is also governed by the surrounding rigid enclosure of the craniofacial skeleton. Craniofacial skeletal restriction is also a strong risk factor for OSA,[9] especially in some ethnic groups.[10] The balance between the size of the maxillomandibular bony enclosure as well as the amount of soft tissue contained within ultimately governs these extraluminal collapsing forces.[11–13] In OSA caused by overweight, adipose tissue may be the major contributor to increased extraluminal tissue pressure; however, the size of the maxillomandibular enclosure is still likely to have an influence on how much local tissue reduction affects upper airway function. We hypothesized that maxillomandibular bony volume would affect the effectiveness of weight loss as a treatment for OSA. Our objective was to assess whether the maxillomandibular skeletal volume influences the relationship between weight loss and OSA improvement.

## METHODS

### Subjects

Subjects were participants in a previously described pharmacological-assisted weight loss study in obese men with OSA.[14–16] Specific study entry criteria included an age range between 30 and 70 y, body mass index (BMI) in the obese range (≥ 30 kg/m$^2$) and moderate to severe symptomatic OSA (AHI ≥ 15

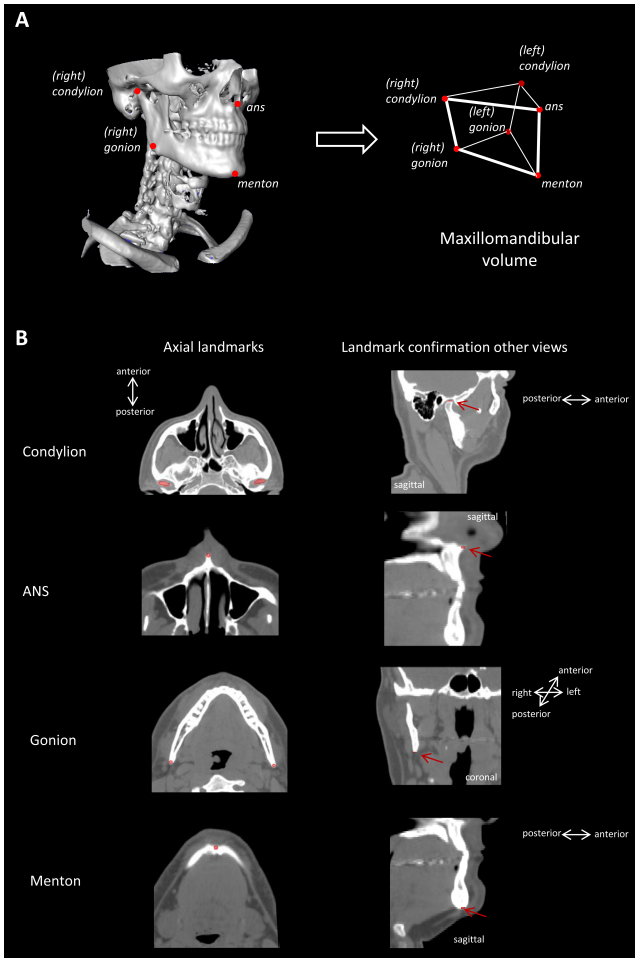


**Figure 1**—Analysis of maxillomandibular volume from computed tomography scans of the head. A maxillomandibular volume was calculated from the polyhedral volume made of vectors connecting points of the left and right condyle, left and right gonion, anterior nasal spine (ans), menton. **(A)** Three-dimensional reconstruction of the craniofacial skeleton showing visible craniofacial landmarks. The three dimensional coordinates were used to construct a polyhedral volume as shown. **(B)** Craniofacial landmarks were marked on axial image slices using the brush tool of the imaging software and centroid coordinates (*x,y,z*) of each landmark exported into a customized spreadsheet for volume calculation. Axial slices are shown for each landmark with corresponding sagittal or coronal views to confirm correct placement of each landmark.

events/h and an Epworth Sleepiness Scale score > 10). This study was performed in an Australian sleep clinic. Ethnicity data was not formally collected but participants were predominantly Caucasian.

### Weight Loss and Study Measurements

Subjects underwent a 6-mo weight loss program consisting of a 2,500 kJ daily deficit diet with exercise advice supplemented with a daily 10- or 15-mg dose of weight-reducing medication Sibutramine (Abbott Laboratories, Abbott Park, IL, USA). Weight loss was monitored by anthropometry (weight/BMI, neck and waist circumference). Computed tomography (CT) scans of the head/neck region were performed at study entry and upon completion of the weight loss intervention at 6 mo. Standard in-laboratory polysomnography (Compumedics, Melbourne, Australia) was also repeated at 6 mo to reassess OSA severity in terms of the AHI. Details of study procedures have been previously described.[14,16]

### Craniofacial Analysis of CT Scans

CT images of the head were used to assess the size of the maxillomandibular skeletal enclosure around the upper airway region using image analysis software (Amira 4.1; Visage Imaging Inc, Carlsbad, CA, USA). Image data underwent preprocessing to transform scan data to align axial slices parallel to the Frankfort horizontal plane (identified by three landmarks on a surface reconstruction of the skeleton: left porion, right porion, and left inferior orbital point) before analysis.

The upper airway and its surrounding soft tissues have previously been described as enclosed within a "box" composed of the skeletal boundaries of the maxilla, mandible, and spinal column. However, in reality, this box does not form a complete enclosure with no real "floor" and no meeting of the mandibular lateral and spinal posterior sides. Therefore, in order to construct a maxillomandibular skeletal "box," coordinates of three-dimensional (3D) cephalometric landmarks on the maxilla and mandible need to be used to calculate maxillomandibular volume based on the polyhedral volume bounded by the outer vectors connecting these points (Figure 1A). Mandibular cephalometric landmarks identified were left and right condylion (co, superior point of the condylar head of the mandible), left and right gonion (go, point on the lateral edge of the mandible at which tangents along the lower and posterior mandibular borders bisect) and menton (me, the most inferior anterior point on the lower border of the mandibular bony symphysis). The maxillary boundary was defined by the anterior nasal spine (ans, tip of the bony process of the palatine bone). Cephalometric points were identified with the aid of 3D reconstructions of the craniofacial skeleton. Cephalometric points were marked using the brush tool of the imaging software on axial slices and confirmed in sagittal views (Figure 1B). Coordinates (*x, y, z*) of cephalometric landmarks were exported as the centroid of each mark into a customized spreadsheet for calculation of polyhedral volumes. The maxillomandibular volume was calculated as the volume of the polyhedron constructed from the intercondyle width (co-co), inter-gonion width (go-go), lower face height (ans-me), mandibular length (go-me), and maxilla-mandibular condyle width (ans-co) vertices, illustrated in Figure 1A. Calculation of maxillomandibular volume was restricted to scans with no observable mouth opening that would increase dimensions of the box (n = 52, 70% of total scans). All craniofacial measurements were made by a single assessor. Analysis was performed blind to knowledge of weight loss and AHI data. A subset of 15 scans were reanalyzed on a separate occasion several months after completion of image analysis to assess reproducibility of landmark placement and volume measurements. These 15 patients also had a repeat head scan at 6 mo after completion of the weight loss program. Analysis of maxillomandibular volume was repeated on these second scans to check reliability of the measurement.

### Statistical Analysis

Statistical analysis was performed using statistical software package SPSS (Version 21, IBM Corporation, Armonk, NY, USA). Changes in anthropometric variables from baseline to end of the 6-mo weight loss program were compared using paired *t*-tests. The relationship between anthropometric measures of weight loss and change in OSA severity (% change AHI) was assessed using linear regression. The potential influence of craniofacial size on the relationship between weight loss and OSA severity was assessed by testing maxillomandibular volume for moderation effects.[17] A moderator is a variable that affects the direction and/or strength of the relationship between a predictor and outcome variable.[17,18] Moderation can be tested for using a series of regression analyses of the effects of three factors of predictor variable, moderator, and their interaction on the outcome variable as described by Baron and Kenny.[17] The effect of the independent variable, the moderator, and the interaction term or cross-variable product of the moderator and the predictor (moderator*predictor) are assessed. The moderator hypothesis is supported if the interaction term is significant. Main effects of the predictor and moderator may also be significant but are not directly relevant to testing of the moderator hypothesis. Linear regression with outcome variable (% change AHI) and predictors of change in anthropometric measures (BMI, Neck Circumference, and Waist Circumference) were performed and with testing of moderation effects of maxillomandibular volume. Correlations between changes in BMI and AHI are presented as Spearman rho for nonparametric variables. In subgroup analyses, patients were categorized into small, medium, and large maxillomandibular size by division on maxillomandibular volume into tertiles. Small, medium, and large maxillomandibular volumes were arbitrarily defined by rank position over the spread of the data because there are no known standard values for maxillomandibular volume derived from this method. Maxillomandibular volume was corrected for height in all analyses to account for influence of anthropometric dimensions in craniofacial size. Reproducibility of landmark placement and maxillomandibular volume measurements was assessed by the intraclass correlation coefficient (ICC) computed as a two-way mixed-effects model (consistency definition). Statistical significance was accepted as $P < 0.05$.

## RESULTS

### Reproducibility of Craniofacial Measurements

Craniofacial analysis was repeated in 15 randomly selected scans. Reproducibility of landmark placement was assessed by ICC analysis of *x*, *y*, and *z* coordinates for all landmarks. The average ICC for all landmarks (condylion, ans, gonion, menton) was 1.0 ± 0.0 (mean ± standard deviation) for *x* coordinates, 0.97 ± 0.02 for *y* coordinates, and 0.97 ± 0.05 for *z* coordinates. Maxillomandibular volume measurements were also highly reproducible, ICC 0.992 (0.976–0.997 95% confidence interval [CI]). Maxillomandibular volumes also showed good concordance between measurements performed on repeated scans, ICC 0.97 (0.91–0.99 95% CI).

**Table 1**—Patient characteristics.

| | Baseline | 6 mo | % Change |
|---|---|---|---|
| Age (y) | 44.3 ± 8.8 | | |
| Weight (kg) | 107.0 ± 12.4 | 99.2 ± 12.8* | −7.4 ± 4.1 |
| BMI (kg/m$^2$) | 34.0 ± 2.7 | 31.5 ± 2.9* | −7.4 ± 4.1 |
| Neck circumference (cm) | 44.7 ± 2.2 | 43.1 ± 2.4* | −3.4 ± 3.3 |
| Waist circumference (cm) | 115.3 ± 7.8 | 107.7 ± 8.7* | −6.6 ± 3.4 |
| AHI (events/h) | 42.9 ± 21.3 | 26.8 ± 15.9* | −34.1 ± 32.4 |

Data shown for 52 obese males with obstructive sleep apnea at baseline and after the 6-mo weight loss intervention. All anthropometric obesity measures and AHI were reduced at end intervention. Data are presented as mean ± standard deviation. Negative % change indicates a reduction. *P < 0.001, paired *t*-test baseline versus 6 mo. AHI, apnea-hypopnea index; BMI, body mass index.

### Weight Loss Effectiveness

Characteristics before and after the 6-mo weight loss intervention are shown in Table 1 for 52 males with baseline head CT scans. Participants were on average middle-aged (range 30 to 65 years), with the majority (65%) having severe OSA. Weight and BMI were reduced at the end of the program by approximately 7%, with associated reductions in neck and waist circumference as previously reported.[15,16] AHI was reduced after the weight loss program by an average of 34%.

### Relationship between Weight Loss and OSA and Influence of Maxillomandibular Volume

As previously reported,[15,16] there was a relationship between improvement in OSA and weight loss as measured by anthropometry in these patients. In the current subgroup of patients with maxillomandibular volume analysis, change in AHI after the weight loss program showed a modest correlation with change in BMI (rho = 0.37, P = 0.007, n = 52, Figure 2). Change in waist circumference also correlated with change in AHI (rho = 0.32, P = 0.02), although neck circumference did not (rho = 0.16, P = 0.3).

Univariate regression analysis showed that change in BMI explained 17% of the variance in the change in OSA severity after the intervention period (Table 2). Maxillomandibular volume itself did not relate to change in AHI with weight loss. However, the interaction term of the BMI predictor and maxillomandibular volume was significant (P = 0.03, Table 2, model 3). There was no correlation between the moderator (maxillomandibular volume) and either the predictor (change in BMI, P = 0.4) or outcome (change in AHI, P = 0.9) variable, as is preferable when testing for moderation.[17] Therefore, this analysis supports a role of maxillomandibular volume as a potential moderator of the relationship between weight loss and OSA improvement.[17]

We additionally assessed the other anthropometric measures of weight loss, neck and waist circumference, for prediction of OSA improvement for moderation effects of maxillomandibular volume. There was a trend toward reduced waist circumference and OSA improvement to be moderated by maxillomandibular volume (P = 0.072). However, reduced neck circumference did not predict OSA improvement

(P = 0.169) and maxillomandibular volume did not influence this relationship.

In subgroup analyses we assessed the relationship between weight loss and OSA improvement in patients divided into small, medium, and large maxillomandibular volume categories (height adjusted). In the small maxillomandibular group there was a strong correlation between weight loss and OSA improvement (rho = 0.65, P = 0.004, Figure 3). However, this relationship was not evident in the medium (rho = 0.25, P = 0.3) or large (rho = 0.05, P = 0.9) maxillomandibular volume groups. Equality of regression slopes for the weight loss/OSA relationship between maxillomandibular size subgroups was assessed.

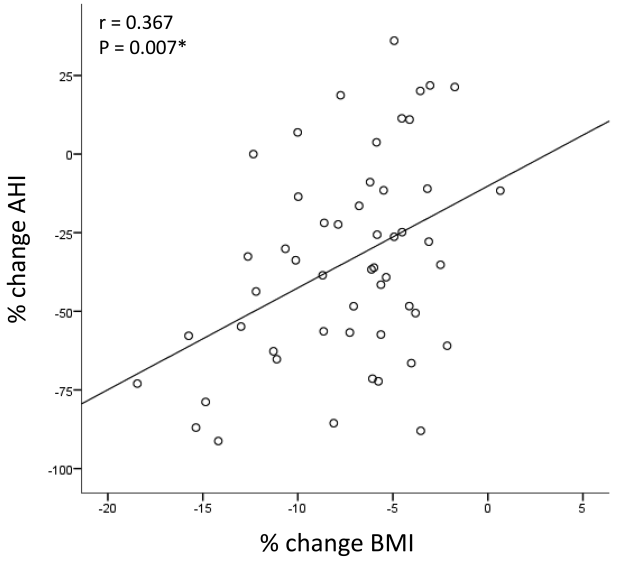


**Figure 2**—Relationship between weight loss and change in apnea-hypopnea index (AHI). Weight loss (percent change in body mass index [BMI]) and obstructive sleep apnea improvement (% change AHI) were correlated (rho = 0.37, P = 0.007) in the entire study sample (n = 52).

**Table 2**—Regression analysis to assess maxillomandibular volume as a moderator of the relationship between weight loss and obstructive sleep apnea improvement (% change in apnea-hypopnea index).

| Model | $R^2$ | P (model) | Variables | B (95% CI) | P |
|---|---|---|---|---|---|
| 1 | 0.17 | 0.002 | %Δ BMI | 3.2 (1.2 to 5.3) | 0.002 |
| 2 | 0.17 | 0.010 | %Δ BMI | 3.2 (1.2 to 5.3) | 0.003 |
| | | | MM volume | 0.05 (−0.3 to 0.4) | 0.790 |
| 3 | 0.24 | 0.004 | %Δ BMI | 2.9 (0.8 to 4.9) | 0.006 |
| | | | MM volume | −0.7 (−1.6 to 0.1) | 0.086 |
| | | | Interaction (%Δ BMI*MM) | −2.2 (−4.3 to −0.06) | 0.030 |

A series of hierarchical regression analysis was used to test for potential moderation effects of maxillomandibular volume. Model 1: Percent change in BMI (%Δ BMI) as a single predictor of % change in AHI. Model 2: Maxillomandibular volume does not predict change in AHI and does not improve the prediction model. Model 3: the interaction variable, product of change in BMI and MM volume (%Δ BMI*MM) is significant suggesting moderation of the relationship between BMI and AHI by MM volume. AHI, apnea-hypopnea index; BMI, body mass index; CI, confidence interval; MM, maxillomandibular volume.

The fixed factor-by-covariate interaction term (maxillomandibular size group*BMI change) was significant (P = 0.04), indicating variation between maxillomandibular size subgroups. There appears to be a progressive weakening of the relationship between weight loss and OSA severity with increasing maxillomandibular enclosure size. There was no relationship at all evident in those with the largest maxillomandibular volumes. These data show that the link between weight loss and OSA improvement is much stronger in those with a smaller craniofacial skeletal enclosure and suggest these patients will respond to weight loss with a greater reduction in AHI. There was no difference in baseline measures of BMI, AHI, or height or changes in BMI or AHI at the end of the study between the small, medium, and large subgroups (Table 3).

## DISCUSSION

We have identified an influence of craniofacial skeletal volume on the relationship between weight reduction and AHI in obese males with OSA following a 6-mo weight loss program. As previously reported,[15,16] this particular weight loss intervention resulted in an overall 7% reduction in BMI and improvement in AHI by more than 30%. This amount of OSA reduction corresponds to previously observed effects of weight change.[4] Although OSA improvement linearly relates to amount of weight loss, there is much variability and clearly other factors are playing a role in the OSA response to weight reduction. To our knowledge, this is the first investigation to provide evidence that maxillomandibular volume may be one of these moderating factors, using a 3D assessment of maxillomandibular enclosure volume. Craniofacial assessment may help in the understanding of weight loss effects and better stratify patients into weight loss treatment for OSA. Our findings suggest that those with a small maxillomandibular skeleton may receive most benefit from weight loss intervention as a treatment for OSA.

The factors underlying the OSA response to weight loss are still not well understood, although fat deposition producing mechanical loads that compromise upper airway structure and function likely underpin the effect of obesity on OSA. We have previously shown that a change in airway length with weight loss somewhat explains AHI reduction.[15] Abdominal fat reduction is also a predictor of OSA responsiveness and may reflect a secondary increase in lung volume, which may increase airway pharyngeal cross-sectional area and decrease length, reducing propensity to collapse.[15,19] Local fat deposition around the pharynx is also likely to be a factor. In obesity, excess adipose tissue deposition around the pharynx and in pharyngeal tissues such as the tongue[20] may result in extraluminal tissue pressure, leading to increased upper airway collapsibility and OSA. However, because both pharyngeal soft tissue and the size of the surrounding skeletal enclosure play a role in setting this extraluminal tissue,[11–13] maxillomandibular size may be an important determinant of weight

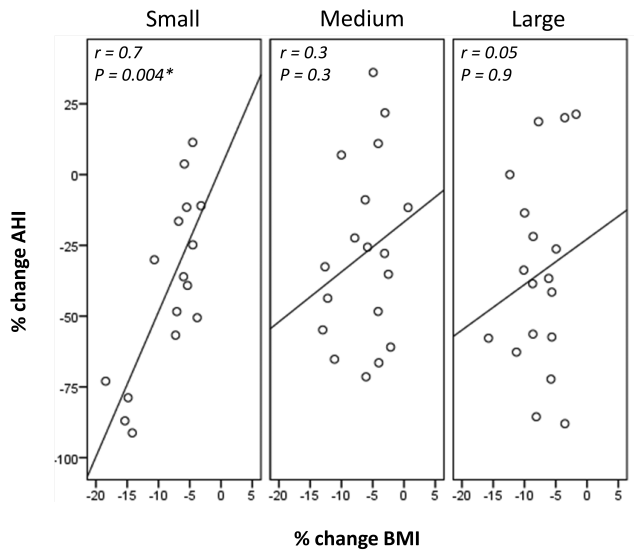


**Figure 3**—Relationship between weight loss and change in apnea-hypopnea index (AHI) by maxillomandibular size. Subjects were divided into small, medium, or larger maxillomandibular size by division of the volume measurement into tertiles (range of absolute values; small 159.7–212.7 $cm^3$, medium 212.8–237.8 $cm^3$, 238–281.6 $cm^3$). Change in body mass index (BMI) and change in AHI were only correlated in the small maxillomandibular volume group (rho = 0.65, P = 0.004, n = 17). There was a progressive weakening of this relationship in the medium (n = 18) and large (n = 17) maxillomandibular size group.

**Table 3**—Baseline characteristics of patient subgroups based on maxillomandibular volume size.

| | Maxillomandibular Volume | | | |
|---|---|---|---|---|
| | **Small** | **Medium** | **Large** | **P** |
| Height (m) | 1.8 ± 0.07 | 1.8 ± 0.8 | 1.8 ± 0.9 | 0.193 |
| BMI ($kg/m^2$) | 33.0 ± 2.6 | 34.3 ± 2.9 | 34.8 ± 2.5 | 0.152 |
| ΔBMI | −2.8 ± 1.6 | −2.2 ± 1.4 | −2.7 ± 1.2 | 0.408 |
| AHI (events/h) | 43.1 ± 22.9 | 43.0 ± 20.3 | 42.7 ± 21.3 | 0.998 |
| ΔAHI | −17.2 ± 15.1 | −15.3 ± 19.4 | −15.9 ± 17.5 | 0.953 |

There were no differences in height, BMI or AHI at baseline between patients with small, medium of large maxillomandibular volume. The change in weight or AHI at the end of study also did not differ between groups. Data are presented as mean ± standard deviation. AHI, apnea-hypopnea index; BMI, body mass index.

loss effectiveness in reducing pharyngeal tissue pressure. Our findings support that maxillomandibular volume influences the effectiveness of weight loss in OSA reduction. Greater effectiveness in AHI reduction was found in obese males with OSA with the smallest maxillomandibular enclosure size. In fact, a relationship between change in weight and OSA reduction was only evident in subgroup analysis in those with small maxillomandibular volume. The relationship between weight loss and OSA was more robust in the small maxillomandibular patient subgroup then in the group as a whole, and there was a progressive weakening of the relationship with increasing skeletal enclosure size categories. Alteration of anatomical balance has been demonstrated by increasing the maxillomandibular enclosure size, using mandibular advancement, which results in a reduction in extraluminal tissue pressure and reduces pharyngeal closing pressure.[21–23] However, this effect on pharyngeal function is not evident in obese subjects.[24] This suggests that a small increase in the mandibular enclosure size may be inefficient to overcome the imbalance from excess pharyngeal tissues, and extraluminal tissue pressure remains a collapsing force. In the current study we present the converse, where a small amount of weight loss or soft tissue reduction in those with a larger maxillomandibular enclosure did not relate to OSA improvement either. A larger maxillomandibular size may be somewhat protected from the OSA mechanism of increased extraluminal pharyngeal tissue pressure due to obesity. Our findings suggest that small adjustments in pharyngeal tissue volume, as a result of weight loss, will have the greatest effect in those with an already anatomically compromised maxillomandibular skeleton. Our findings using 3D analysis are in support of recent findings using two-dimensional cephalometric analysis to measure mandibular body length in a study of weight loss treatments in OSA.[25] This study showed that greater improvement in OSA (% change AHI) with weight loss was associated with a shorter mandibular length.

In addition to changes in total body weight, we also looked at neck and waist circumference measures in relation to OSA improvement. The waist circumference measure of obesity also related to AHI reduction, although not quite as strongly, and maxillomandibular volume showed a trend toward moderating this relationship also. Neck circumference, however, did not relate to AHI reduction, and taking maxillomandibular volume into account also did not influence this relationship. It may seem that neck circumference would be a closer approximation of adipose tissue loss around the pharyngeal airway than total body weight. However, we have previously investigated the relationship between these anthropometric body measures and the volume of the parapharyngeal fat pads measured on CT in these patients.[15] This analysis showed that pharyngeal fat volume correlated with total body weight but had absolutely no relationship to the measure of neck circumference. Therefore, we conclude that total body weight is actually a closer approximation of pharyngeal fat deposition than neck circumference and this may somewhat explain a lack of relationship between changes in neck circumference and AHI improvement.

Although weight reduction was a significant predictor of OSA improvement, only 24% of the variance in AHI after weight loss was explained in our moderation model. Therefore, the majority of the difference in OSA after weight loss was not accounted for by the factors investigated in this analysis. Obesity may induce upper airway dysfunction by multiple mechanisms in addition to an increase in extraluminal tissue pressure around the pharynx. The increased fat deposition in the tongue seen in patients with OSA could additionally potentially interfere with compensatory muscle function as well as increase pharyngeal tissue volume.[20] There are also the effects

on upper airway function secondary to reduced lung volume due to abdominal fat deposition.[26] Furthermore, humoral factors and systemic and pharyngeal inflammatory responses to the obesity state may also contribute to disturbances in upper airway neuromuscular control.[27] Therefore, there are a range of mechanisms by which obesity contributes to OSA and the relative contribution of each mechanism is unclear. Furthermore, the relative importance of different mechanisms may vary among individuals, suggesting an importance of phenotyping for tailored treatment approaches (personalized medicine). In this analysis we explain only a small proportion of the improvement in upper airway function by overall weight loss and maxillomandibular size. Weight loss results in greatest reduction of intra-abdominal fat[28] and therefore OSA mechanisms mediated through abdominal fat loss may have a relatively greater influence on the AHI after weight loss.[15] The obese males in our sample only lost a small proportion of weight and remained overweight at the end of the study; greater weight reductions may show a greater influence of craniofacial size. However, our work does implicate a role of maxillomandibular volume in influencing the effect of weight loss on OSA severity. Our study sample was also all male and abdominal fat is the significant contributor to OSA in males, whereas neck fat is associated with OSA in women.[29] Therefore, craniofacial structure may be more important for effectiveness of weight loss treatment for OSA in women and there may be important sex differences in the relationship between obesity and OSA mechanisms.

Ethnicity also influences the importance of craniofacial structure as a risk factor for OSA. We have previously found that for the same degree of OSA severity Hong Kong Chinese patients have greater craniofacial restriction, whereas Caucasian patients show more obesity.[10] Our current sample of patients were predominantly Caucasian and therefore we are unable to determine any differences in the relationship between craniofacial size and OSA reduction through weight loss between different ethnicities. It is possible that in populations with craniofacial restriction related to OSA, such as Asian populations, weight gain and weight loss may have an even greater influence on outcomes.[30]

Craniofacial structure is a recognizable risk factor for OSA and may also be a way to assess likelihood of success with various OSA treatments. Although craniofacial assessment by CT may be unrealistic to assess potential for effective weight loss therapy in OSA in clinical practice, other surrogates may be possible; for example, facial phenotyping using simple digital photography in predicting OSA risk.[31] Assessing facial size by photography may have some utility for capturing craniofacial size, although this method does capture both soft and skeletal tissues in the same measure.

There are several limitations to this study in addition to assessment of patients with OSA in a single weight loss program of the same sex and ethnicity. This is a retrospective analysis of an image dataset from patients with OSA in a weight loss trial. However, these data provide a means for initial investigation of the question of whether maxillomandibular size has any influence on the OSA response to weight loss and description of a method to assess maxillomandibular volume. The measurement itself may have some limitation in that the derived maxillomandibular enclosure volume was based on external points of the maxilla, which may overestimate the intraoral space and also may be influenced by individual differences in bone thickness. An actual intraoral space volume may provide a more accurate measurement of the intracranial tissue space, leading to a potentially stronger relationship. However, such methodology would be technically difficult, and 3D cephalometry provides a relatively quick and reproducible method of constructing a box from a structure that is not a true box. Unfortunately, dental artifact in the majority of scans did not allow detailed analysis of upper airway soft tissues; therefore, we were unable to directly measure upper airway soft tissue to craniofacial enclosure ratio and so body weight had to be used as an approximation. In this sense our measurements are somewhat of an approximation of an anatomical balance measure but our analysis shows a small but significant effect using a statistical method used often that has low power to detect true interaction effects.[18] These data relate craniofacial structure to weight loss effects on OSA in terms of AHI reduction and not other clinical endpoints; however, by the nature of weight loss having 100% compliance as an OSA treatment, AHI is also likely to be a good measure of effectiveness. However, despite these limitations we were able to demonstrate an influence of maxillomandibular structure on the results of weight loss treatment for OSA and this warrants further investigation.

We have shown for the first time that skeletal maxillomandibular volume may influence the results of weight loss treatment for OSA. A smaller maxillomandibular enclosure appears to be a better substrate for reduction in AHI through weight loss. Craniofacial phenotype may prove to be a marker to help select patients for weight loss therapy for OSA. However, further work is needed to better understand the relationship between maxillomandibular size and upper airway effects of weight gain/loss and also differences between sex and ethnicities. Further work is also needed to investigate the mechanisms by which obesity leads to OSA so that appropriate patients can be targeted for weight loss therapy.

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## DISCLOSURE STATEMENT

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