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Original Article

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Does craniofacial morphology relate to sleep apnea severity reduction following weight loss intervention? A patient-level meta-analysis

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Abstract

Study Objectives: Obesity is a common and reversible risk factor for obstructive sleep apnea (OSA). However, there is substantial unexplained variability in the amount of OSA improvement for any given amount of weight loss. Facial photography is a simple, inexpensive, and radiation-free method for craniofacial assessment. Our aims were (1) to determine whether facial measurements can explain OSA changes, beyond weight loss magnitude and (2) whether facial morphology relates to how effective weight loss will be for OSA improvement.

Methods: We combined data from three weight loss intervention trials in which participants had standardized pre-intervention facial photography (N = 91; 70.3% male, mean ± SD weight loss 10.4 ± 9.6% with 20.5 ± 51.2% apnea–hypopnea index [AHI] reduction). Three skeletal-type craniofacial measurements (mandibular length, lower face height, and maxilla-mandible relationship angle) were assessed for relationship to AHI change following weight loss intervention.

Results: Weight and AHI changes were moderately correlated (rho = 0.3, p = 0.002). In linear regression, an increased maxilla-mandible relationship angle related to AHI improvement (β [95% CI] −1.7 [−2.9, −0.5], p = 0.004). Maxilla-mandible relationship angle explained 10% in the variance in AHI over the amount predicted by weight loss amount (20%). The relationship between weight change and AHI was unaffected by the maxilla–mandible relationship angle (interaction term p > 0.05).

Conclusions: Regardless of facial morphology, weight loss is similarly moderately predictive of OSA improvement. Increased maxilla-mandible relationship angle, suggestive of retrognathia, was weakly predictive of OSA response to weight loss. Although this is unlikely to be clinically useful, exploration in other ethnic groups may be warranted.

Statement of Significance

Weight loss therapy can be used to reduce obstructive sleep apnea (OSA) severity, but individual results are highly variable and not necessarily related to the amount of weight loss achieved. The craniofacial skeleton may influence the OSA response to weight loss. Facial photography is a simple, inexpensive, and radiation-free method for craniofacial assessment. We found that facial photographic measurements can explain a small amount of variance in the effectiveness of weight loss therapy for OSA reduction, although weight loss appears beneficial regardless of your face type.

Key words: obesity; obstructive sleep apnea; weight loss; face

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Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder associated with heterogeneous health consequences [1, 2]. Obesity is a well-recognized risk factor for OSA [2–4]. Reversing obesity through weight loss is, therefore, a sensible strategy to treat OSA with numerous additional cardiometabolic and quality-of-life benefits [5–7]. However, weight loss therapy for OSA has variable success. Even with large amounts of weight loss, as achieved with bariatric surgery, only 38% of OSA is completely reversed [8]. Conversely, some people will experience significant OSA improvement from a small amount of weight loss [9].

Given that the magnitude of weight loss only moderately correlates with OSA improvement, there may be other factors that influence the success of weight loss therapy. Craniofacial structure also predisposes to OSA [10]. The combination of reduced craniofacial skeletal dimensions and enlarged upper airway soft tissues encroach on the pharyngeal airway space, making it anatomically vulnerable to collapse [11]. Craniofacial restriction (reduced maxillary-mandibular dimensions) has been associated with a favorable OSA response to weight loss in radiographic imaging studies (computed tomography or cephalometric X-rays) [12, 13]. Therefore, smaller craniofacial structure may indicate an identifiable OSA risk factor, representing greater anatomical imbalance that responds favorably to weight loss therapy. However, imaging methods such as computed tomography and cephalometry involve radiation exposure and may not be practical or cost-effective in clinical practice. We have previously identified a method for facial phenotyping using standard photography [14] which is associated with OSA risk [15, 16]. Photography-based facial morphology is a composite of both skeletal dimensions and regional adiposity, but we have previously identified measurements that are stable with weight loss (facial profile angles, face height, and mandibular length), suggesting they predominantly reflect the underlying skeletal substrate [17].

We hypothesize that facial measurements could predict the magnitude of OSA reduction in response to weight loss. The aims of this study were firstly to determine whether the photographic facial measurements most indicative of skeletal structure (mandibular length, face height, and maxilla-mandible relationship angle) can explain OSA changes following weight loss intervention, beyond that predicted by the amount of weight loss. Secondly, to determine whether facial morphology relates to how effective weight loss will be for OSA reduction.

Methods

Participants and weight loss intervention

These are secondary data analyses of three weight loss intervention trials for OSA conducted in Sydney, in which we included a standardized protocol for facial photography at their inception to facilitate exactly these sorts of analyses. In all three weight loss intervention trials, participants underwent in-laboratory polysomnography and craniofacial photography before commencing the weight loss intervention. Participants were included in the analysis if they had a photograph, and a follow-up polysomnography sleep study to determine the effects of the weight loss intervention. The three weight loss trials used three different interventions which cause differing amounts of weight loss to facilitate these correlational analyses. Briefly, study 1 (Clinical Trial registration number ACTRN 12611000847910) used a hypocaloric diet and lifestyle program for 6 months (n = 58, 63.7% of data sample) [18]. Study 1 recruited participants 18–70 years, with AHI > 15 events/h, BMI 27–40 kg [2] who were sleepy (Epworth Sleepiness Score >10) and had rejected continuous positive airway pressure (CPAP) or oral appliance therapies. The weight loss intervention for study 2 (ACTRN 12613000191796) was a 2-month very low energy diet (VLED), followed by a maintenance diet out to 12 months (n = 17, 18.7% of data) [19]. Participants on CPAP in this study were not included in this analysis because they did not have sleep study data where their OSA was not controlled by CPAP. Study 2 inclusion criteria were age 18–65 years, BMI > 30 kg [2] and AHI > 5 events/h. Study 3 (protocol 2019/ETH08182 Northern Sydney Local Health District) participants (n = 16, 17.6% of data) underwent bariatric surgery with follow-up 6 months after surgery [20]. Inclusion criteria for study 3 were age 18–75 years, BMI > 30 kg [2] (with size restrictions of weight <200 kg and waist circumference <220 cm due to scanner size limits for imaging) with AHI > 5 events/h.

Within each trial, baseline and follow-up polysomnography was performed at the same center and scored according to the same American Academy of Sleep Medicine scoring rules. The effects of weight loss on OSA were assessed by the change in total AHI in the follow-up study compared with the baseline study (expressed as both absolute and percentage change).

Craniofacial photography and analysis

Before undergoing the weight loss intervention, subjects had craniofacial photographs taken according to previously published protocols [16, 21]. Briefly, the front and profile are calibrated by affixing a known diameter marker to the face. Photographs are analyzed by obtaining x- and y-coordinates of specific craniofacial landmarks, which are used to calculate facial dimensions. The analysis was performed by a single operator (AL) who was blind to the participant's clinical information. Intra-rater reliability assessment showed excellent reliability of repeated measures of the same photos on separate occasions (intra-class correlation coefficient, ICC 0.89–0.99). We have previously determined that four measurements from the profile photograph are not affected by weight loss [17], suggesting that these predominantly represent the underlying skeletal substrate. These are lower face height, mandibular length, and maxillary-mandibular relationship angle. These facial measurements and the facial landmarks used to define them are illustrated in Figure 1. These measurements also represent mandibular dimensions and position, with maxilla-mandibular dimensions previously associated with OSA changes following weight loss in photographic studies [12, 13].

Statistical analysis

Statistical analysis was performed using SPSS software (Version 26, IBM). Data are presented as mean ± standard deviation. Statistical significance was accepted as p < 0.05. Patient characteristics at baseline and after weight loss intervention were compared using paired t-tests. Study populations were compared by ANOVA (Supplementary Table S1).

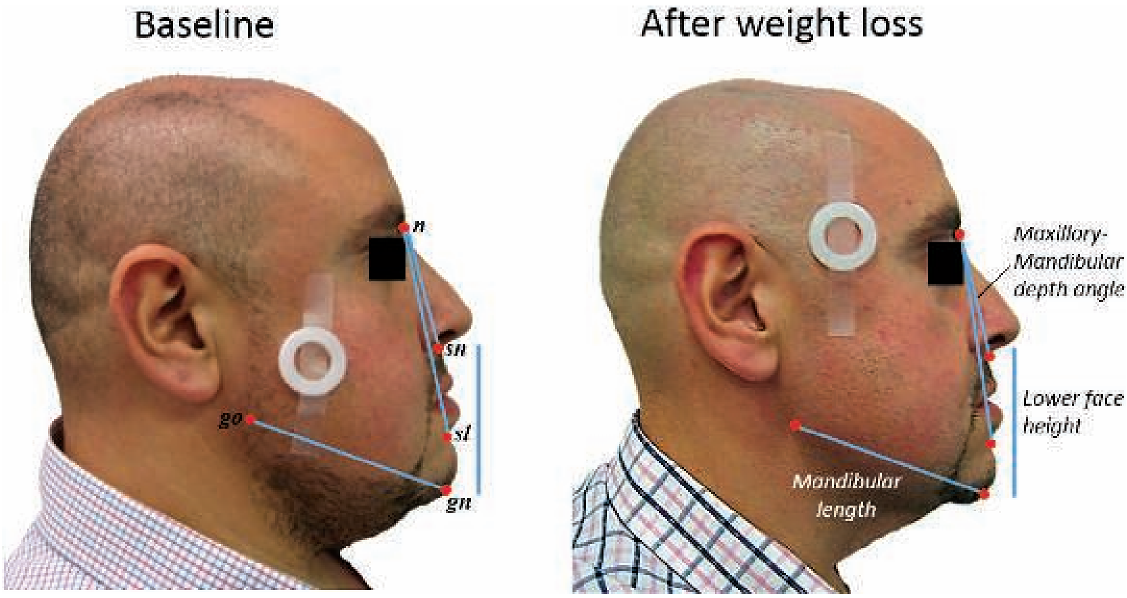

Figure 1. Craniofacial photographic measurements. Craniofacial structure was assessed using three measurements from a profile photograph (maxillary-mandibular relationship angle, lower face height, and mandibular length), which are weight-stable and hence convey craniofacial skeletal structure. Measurements are obtained using facial landmarks. Craniofacial measurements are depicted on a participant with a significant weight loss (39.3 kg) following weight loss intervention (bariatric surgery, study 3). Craniofacial measurements from the baseline photo were used to explore whether they related to OSA response to weight loss intervention. Maxillary–mandibular depth angle is the angle formed between landmarks *sl-n-sn*. Mandibular length is the length calculated between *go* and *gn* landmarks. Lower face height is the distance between landmarks *sn* and *gn*. Facial landmarks: *gn*, *gnathion*; *go*, *gonion*; *n*, *nasion*; *sl*, *sublabiale*; *sn*, *subnasion*, point; *t*, *tragion*.

Univariate linear regression was used to assess the influence of different baseline characteristics (age, gender, study, BMI, and neck/waist circumference) on AHI change to identify potential confounders (Supplementary Table S2). A hierarchical linear regression process was used to assess the relationship of weight changes to change in AHI (with separate models for corresponding absolute and percentage change). Firstly, weight change was assessed as an independent variable in unadjusted models, and adjusted models to account for potential baseline confounders identified in univariate linear regression. Secondly, the three craniofacial variables were assessed (stepwise regression) to determine if they had any additional explanatory power for changes in AHI, beyond the anthropometry models alone. Linear regression models were inspected for adherence to assumptions of normality of residuals and homoscedasticity. Craniofacial variables showing evidence of influence on OSA improvement were further considered for an interaction effect on the relationship between weight and AHI changes. Firstly, the craniofacial variables with predictive utility were classified into three facial measurements (small, medium, and large) by dividing into tertiles, within gender, as craniofacial size differs by gender [22]. Linear regression models were used to assess for interaction effects between craniofacial morphology and weight change on AHI following weight loss intervention. A significant interaction term (craniofacial variable * weight change) would indicate that the relationship between changes in weight and AHI differs by craniofacial morphology. Spearman's rank correlation was used to assess the relationship between weight and AHI changes. Weight loss is presented as a change in total body weight. Neck and waist circumference changes were highly correlated to weight change. Total body weight changes were most strongly related to AHI changes of the three (data not shown) and was used as the measure of weight loss in this analysis. However, results were very similar using either neck or waist circumference as the weight loss measure. These analyses are presented in Supplementary Tables S3–S4 and Supplementary Figure S1).

Results

Participant characteristics and effectiveness of weight loss intervention

Characteristics of the 91 participants with OSA undergoing weight loss intervention are shown in Table 1. On average, participants were middle-aged, predominantly male with severe OSA and obese as per inclusion criteria of the original weight loss trials. There was an average of ~10% weight loss (range –34.6% to 3.75%) between baseline polysomnography and follow-up post-intervention. The average AHI decreased by ~20% (range –97.6% to 170.1%), bringing the group OSA severity down into the moderate OSA category (27.0 ± 20.4 events/h). There was a difference in the amount of weight loss achieved using the different methods in the three trials ($p < 0.001$). Bariatric surgery (study 3) achieved the greatest weight reduction (–27.4 ± 4.9%), followed by the VLED (study 2, –11.3 ± 4.1%). The hypocaloric diet/lifestyle intervention produced the least weight loss (–5.4 ± 5.3%). There was additionally a difference in the amount of weight loss achieved between genders (study 3 with bariatric surgery contained a greater proportion of females, Supplementary Table S1).

Relationship between changes in weight and AHI

The relationship between weight change and AHI following weight loss intervention is shown in Figure 2. In univariate analysis of baseline variables, there was evidence that sex, baseline

Table 1. Participant characteristics and results of weight loss intervention

	Baseline	Post-weight loss	Change	% Change
Total sample (*N* = 91, 100%)				
Age (years)	49.2 ± 11.3			
Gender (% male)	70.3			
Lower face height (cm)	6.3 ± 0.7			
Mandibular length (cm)	11.1 ± 1.5			
Maxillary-mandibular relationship angle (°)	6.8 ± 2.7			
BMI (kg/m^2)	35.5 ± 6.6	31.6 ± 5.1*	−4.0 ± 4.3	−10.4 ± 9.6
Weight (kg)	106.4 ± 17.7	94.8 ± 15.4*	−11.6 ± 11.8	−10.4 ± 9.6
Neck circumference (cm)	41.8 ± 3.6	39.9 ± 3.4*	−1.9 ± 2.7	−4.2 ± 7.0
Waist circumference (cm)	112.7 ± 13.3	104.1 ± 11.7*	−8.6 ± 10.0	−7.2 ± 8.2
AHI (events/h)	36.2 ± 21.3	27.0 ± 20.4*	−9.2 ± 16.7	−20.5 ± 51.2
AHI non-supine	33.6 ± 27.7	21.5 ± 34.5*	−12.4 ± 23.9	−23.6 ± 69.8
AHI supine	57.3 ± 33.1	45.8 ± 32.5*	−11.8 ± 28.3	−16.0 ± 62.0

AHI, apnea–hypopnea index; BMI, body mass index. A total sample of *N* = 91 participants from three weight loss trials in OSA were included in the analysis. Facial measurements were obtained by quantitative craniofacial photography (Figure 1). Data are presented as mean ± standard deviation. Paired *t*-test, baseline vs. post-weight loss intervention.
*$p < 0.001$.

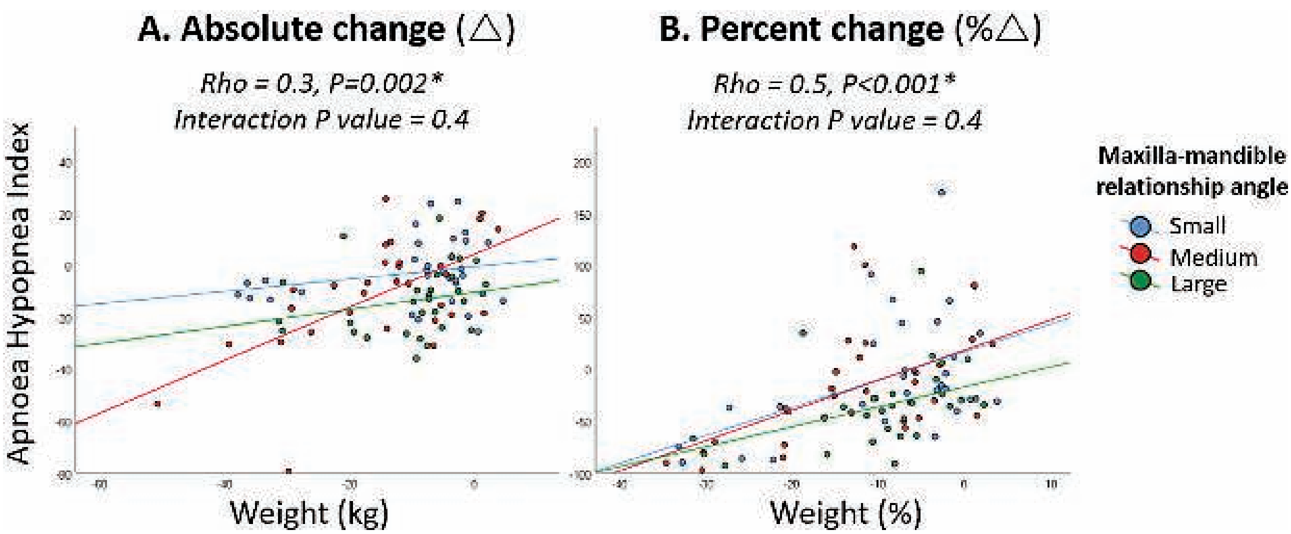

Figure 2. Relationship between weight and AHI changes following weight loss intervention, by craniofacial category. Changes in weight and AHI are expressed as both absolute values (A) and percentage (B). Data are displayed for craniofacial categories based on size of the maxillary-mandibular angle: small (blue), medium (red), and large (green). The interaction *p* value is not significant, indicating that the relationship between anthropometry and AHI change does not differ by craniofacial category.
*$p < 0.05$.

obesity levels (BMI, weight, and waist circumference) and which study they participated in were related to AHI changes following weight loss intervention (Supplementary Table S2). We additionally present equivalent tables in the online supplement for AHI in supine and non-supine body position (Supplementary Tables S3–S4). Linear regression models for the effect of weight change on AHI following weight loss intervention are shown in Table 2. Weight change explained 20% of the variance in AHI change and remained significant when adjusted for baseline confounders.

Craniofacial measurements as additional explanatory variables of AHI change

The three craniofacial measurements were assessed for additional predictive value for AHI change following weight loss intervention, beyond weight change alone, using the stepwise method of entering and retaining any significant predictors on top of the weight change only model. The results are shown in Table 3. Maxilla-mandible relationship angle was an additional predictor of AHI change in the adjusted model for absolute weight change, but not weight change as percentage (in which it was not sufficiently predictive to be entered into the model, $p = 0.067$). A larger maxilla-mandible relationship angle (more distance between the maxilla and the mandible, suggestive of retrognathia) was associated with greater improvement in AHI following weight loss intervention. The addition of maxilla–mandibular relationship angle explained a further 10% of variance on top of weight change alone in absolute change models. Specifically, while accounting for weight change and confounders, a 1° increase in maxilla-mandible relationship angle predicts a decrease in AHI of 4.1% or 1.7 events/h. Looking at changes in supine AHI and non-supine AHI, instead of total AHI, similar results were evident for non-supine AHI changes but not supine AHI changes (Supplementary Tables S6 and S7).

Table 2. Influence of weight change on AHI following weight loss intervention

	Dependent variable	ΔAHI				%ΔAHI			
Independent variable	Model	R^2	*B* (95% CI)	β	*P* value	R^2	*B* (95% CI)	β	*P* value
Weight change	Unadjusted	0.2	0.6 (0.3, 0.8)	0.4	<0.001*	0.2	2.5 (1.5, 3.5)	0.5	<0.001*
	Adjusted	0.2	1.1 (0.5, 1.7)	0.8	<0.001*	0.3	2.4 (0.5, 4.3)	0.5	0.013*

B, unstandardized coefficients; β, standardized coefficients; CI, confidence interval. The relationship between weight changes (independent variable) and AHI change (dependent variable) was assessed in (1) unadjusted (univariate) regression models and (2) adjusted (multivariable) regression models for the effects of confounders (identified in Supplementary Table S2). AHI and weight changes are both expressed as either absolute change (Δ) and percent change (%Δ) in the respective models. The adjusted model for absolute AHI change (Δ) included baseline BMI and waist circumference, as well as the original study participant, was recruited for (study). The adjusted model for percent AHI change (%Δ) included sex, baseline BMI, and waist circumference, as well as study.
*$p < 0.05$.

Table 3. Craniofacial variables as predictors of AHI change following weight loss interventions beyond weight change alone

		Dependent variable	ΔAHI				%ΔAHI			
Independent variable	Model	Craniofacial predictor	Change R^2	*B* (95% CI)	β	*P* value	Change R^2	*B* (95% CI)	β	*P* value
Weight	Unadjusted	Maxilla-Mandible relationship angle	0.1	−1.7 (−2.9, −0.5)	−0.3	0.004*	–	–	–	–
	Adjusted	Maxilla-Mandible relationship angle	0.1	−1.5 (−2.7, −0.3)	−0.2	0.02*	–	–	–	–

B, unstandardized coefficients; β, standardized coefficients; CI, confidence interval. The three craniofacial variables (lower face height, mandibular length, and maxilla-mandible relationship angle) were assessed for additional explanatory power for AHI changes, beyond weight change. The three craniofacial variables were considered as potential additional predictors (stepwise regression) to the unadjusted and adjusted models in Table 2. AHI and weight change are both expressed as either absolute change (Δ) and percent change (%Δ) in the respective models. The adjusted model for absolute AHI change (Δ) included baseline BMI and waist circumference, as well as the original study participant, was recruited for (study). The adjusted model for percent AHI change (%Δ) included sex, baseline BMI, and waist circumference, as well as study.
*$p < 0.05$.
– No craniofacial variables entered into the model (maxilla-mandible relationship angle was insufficiently predictive, $p = 0.067$).

Influence of craniofacial morphology on the AHI response to weight loss intervention

Since maxilla–mandible relationship angle was predictive of the AHI response to weight loss intervention, three craniofacial groups based on the size of this angle (small, medium, and large from tertiles, within genders) were defined. Interaction terms for a craniofacial group and weight change were assessed in linear regression models to determine if the relationship between obesity reduction and AHI change was modified by craniofacial morphology. The relationship between weight and AHI changes by craniofacial morphology is illustrated in Figure 2. The *p* values for each interaction term in the regression models are also given in Figure 2. There were no significant interaction terms, indicating that craniofacial morphology does not alter the effect of weight loss changes on AHI. The slopes of all craniofacial groups lie in the direction of greater weight loss relating to a greater reduction in AHI.

Discussion

The findings from our study suggest that weight loss appears to be modestly effective for reducing OSA severity regardless of facial morphology (maxilla-mandible relationship angle). Essentially, the greater the amount of weight an OSA patient can lose the greater their sleep apnea improvement. However, the moderate correlations around this relationship plus significant heteroscedasticity mean that there is a great deal of uncertainty in any individual patient about how much AHI reduction they might expect per kilogram lost. Our models suggest that on average a 10% decrease in body weight will on average produce an AHI decrease in the order of 14%–34%, similar to previously reported observational data [23]. A greater maxilla-mandible relationship angle, suggestive of retrognathia, initially provided some additional predictability. However, although this relationship is statistically significant, it is too weak to recommend for clinical use, explaining only an additional 10% of variance above weight loss. Therefore, the key message from these analyses, utilizing a photography-based method, is that there is no group of patients based on facial morphology in which weight loss was a futile exercise for sleep apnea severity reduction. Practicing clinicians should also note that the significant heteroscedasticity evident in the panels in Figure 2 are evidence that uncertainty around AHI reduction varies across the amount of weight loss a patient achieves.

Although obesity and OSA are strongly linked, we still understand little about the underlying mechanisms by which obesity leads to OSA, but it is likely to be multifaceted and complex. Fat deposition around the airway and in soft tissues like the tongue [24] can increase extraluminal tissue pressure [25] and thus increase pharyngeal collapsibility. Central adiposity may have effects through reduced lung volume on gas exchange and decreasing tracheal traction [26]. Adipose tissue is also an active endocrine organ, producing hormones like leptin, which could elicit neurohumoral effects on breathing and pharyngeal stability [27]. In terms of anatomical effects on the pharyngeal airway, the relative size of the maxilla-mandibular skeletal borders appear to be important in determining whether upper airway soft tissue volume is detrimental, termed “anatomical balance” [11]. Therefore, the size of the craniofacial skeleton may have a determining role in the effects of regional soft tissue reduction on pharyngeal collapse. Regional soft-tissue reduction appears to be most effective in those with smaller maxilla-mandibular borders [13], who perhaps are susceptible to a greater anatomical imbalance with small increases in soft tissue and hence see greater effects of a reduction in that tissue through weight loss.

There was no statistically significant evidence that craniofacial morphology modified the effect of weight changes on OSA severity. There are many other potential contributors to the weight/AHI change relationship, including the mechanisms described above. Additionally on the other side of the equation factors such as night-to-night and body position variability in AHI, authors [28–30] could mask an association with craniofacial morphology in OSA response to weight loss. Night-to-night variability in AHI can be significant and change OSA severity category, and tends to increase the higher the measured AHI [29, 30]. Additionally, differences in body position between sleep studies could influence the AHI measure. There is some evidence that weight loss results in a greater reduction in AHI in the non-supine body position compared to the supine position [28]. In our sample, both supine and non-supine AHI reduced with no difference in percent reduction between them. However, we did find that when assessing the influence of maxilla-mandible relationship angle on supine and non-supine AHI individually, the association was only present for changes in non-supine AHI (Supplementary Material). However, there was not an increase in the strength of the relationship with maxilla–mandible relationship angle compared to the total AHI measure. We used total AHI as our primary measure of OSA improvement as this is currently most clinically relevant. The weight loss relationship to OSA reduction is also not necessarily linear [9]. It is important to note these simple linear models do not meet assumptions around heteroscedasticity, and these relationships are not necessarily well modeled by linear regression, as seen in the "trumpet" shape of the data in that the effect on AHI differs across the amount of weight loss. We do not advocate that our linear models are clinically useful, nor should they be applied to predict responses in individual OSA patients; however, they do highlight the variability and complexity of the clinical response to deliberate weight loss [31–33].

This is the first study to explore craniofacial photographic predictors of AHI response to weight loss intervention. This study has several strengths including a large variety of weight changes (from 4.6 kg to −50.8 kg) resulting from the weight loss intervention studies in which to explore these associations. However, there are limitations. The study is a secondary analysis of combined data from three studies with different weight loss methods and different clinical referral biases affecting patient selection (although we have attempted to control for identified differences in analysis). Additionally, there were variable follow-up times between studies. In addition, we may be underpowered to assess interaction effects. Facial photography for craniofacial assessment has the potential to be clinically applicable, however resulting facial measurements are a composite of both soft tissue and the underlying skeletal structure. It may be that this technique is not sensitive enough compared to more sophisticated imaging techniques to identify craniofacial skeletal restriction which may influence the weight loss response. The relationship of craniofacial variables to the effects of weight loss intervention for OSA is also likely influenced by ethnicity. The population assessed was predominantly Caucasian and therefore craniofacial variables may have different relationships in other populations. Previous research suggests that OSA severity is more strongly influenced by craniofacial structure in Chinese with OSA and obesity in Caucasians with OSA; however, this craniofacial restriction makes Chinese OSA patients more vulnerable to increasing OSA severity through weight gain [34]. Potentially craniofacial photographs could be a stronger predictor of weight loss effects in Asian populations.

Conclusion

While we found that one of our candidate craniofacial variables, maxilla-mandible relationship angle, was weakly associated with sleep apnea reduction with weight loss, we deem this association to be too weak to recommend for clinical prediction. Furthermore, we are not able to confirm whether this is a causal effect and instead may be driven by clinical referral bias. The key clinically applicable advice we can give from these analyses is that weight loss was not futile in any craniofacial type, but that predicting the magnitude of response in any individual patient is still not possible with the addition of craniofacial photography. However, we encourage the investigation of facial photography in other ethnic groups, particularly East Asian populations [34], where craniofacial phenotyping could be a more effective prediction tool.

Supplementary material

Supplementary material is available at *SLEEP* online.

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