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Parsing the craniofacial phenotype: effect of weight change in an obstructive sleep apnoea population

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Abstract

Purpose Craniofacial structure is an important risk factor in the development of obstructive sleep apnoea. Most craniofacial imaging methods are not feasible for large-scale studies or the clinic. Craniofacial photography is a high-throughput technique for facial phenotyping; however, derived measurements are a composite of skeletal and soft tissue craniofacial information. Weight change is a paradigm to help determine which facial measurements most relate to regional soft tissue (i.e. change with weight) versus skeletal structure (i.e. stable with weight changes). We aimed to assess the association between weight change and changes in key facial measurements from facial photography.

Methods Calibrated frontal and profile photographs were taken of participants in weight loss studies ($N = 106$). Univariate linear regression was used to assess whether weight change explained changes in facial dimensions.

Results Patients lost 11.7 ± 10.8 kg body weight and 2.0 ± 2.0 cm of neck circumference. Weight changes influenced face width ($r = 0.3$, $p < 0.001$), mandibular width ($r = 0.4$, $p < 0.001$) and cervicomental angle ($r = 0.3$, $p = 0.001$). Facial angles, facial heights and mandibular length were not influenced by weight change.

Conclusions A weight loss paradigm suggests that face and mandibular width and cervicomental angle most strongly reflect regional adiposity. Facial angles and heights are insensitive to weight change and could be more representative of craniofacial skeletal structure. This study informs the interpretation of facial phenotype assessed by this craniofacial photographic method which can be applied to future studies of craniofacial phenotype in OSA.

Keywords Obstructive sleep apnoea · Craniofacial photography · Facial phenotype · Obesity · Weight loss

Introduction

Obstructive sleep apnoea (OSA) is a common sleep disorder in which the pharyngeal airway partially or completely closes preventing airflow and resulting in sleep fragmentation and intermittent hypoxia. OSA is associated with daytime symptoms, motor vehicle accidents [1, 2], cardiovascular disease [3, 4] and metabolic dysregulation [5, 6]. Therefore, recognition of OSA risk factors is important in order to facilitate diagnosis and treatment.

Craniofacial structure is a risk factor for OSA [7]. Restriction of the craniofacial skeleton or enlarged upper airway soft tissues, or a combination of both, can impact on pharyngeal airway space and predispose to OSA [8, 9]. Much of the work understanding craniofacial risk factors in OSA has been performed using complex or radiographic imaging methods, such as magnetic resonance imaging (MRI), computed tomography (CT) or

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cephalometric x-rays. Although such studies have provided important insights into soft tissue and skeletal craniofacial risk factors, they are not applicable for rapid facial phenotyping, either in the clinic or in large-scale studies.

To address this, we have previously reported a method to quantify craniofacial phenotype from facial photographs [10]. We have shown that quantitative facial measurements derived from frontal and profile photographs (including linear distances, facial angles and areas) can provide information about OSA risk in sleep clinic populations [11, 12]. Additionally, we have shown that facial surface measures from photographs convey phenotypic information about the underlying soft tissue and skeletal structures that contribute to OSA risk [13, 14]. This work has supported use of this photographic technique for facial phenotyping as a high throughput surrogate when other imaging is not feasible or desirable. However, the facial surface is a composite of the craniofacial skeleton and regional adiposity. Therefore, it is not clear whether craniofacial photographic measurements are reflecting aspects of soft tissue or skeletal risk, or which measurements may be more closely related to one or the other. Clarification of this uncertainty has the potential for development of a metric that is reflective of anatomical balance, i.e. the interaction between the skeletal substrate and the surrounding soft tissues.

Weight loss offers a paradigm to assess which facial measures are most related to soft tissue (i.e. *change with weight change*) versus those more related to skeletal structure (i.e. *stable with weight changes*). The aim of this study was to examine changes in facial measurements with deliberate weight loss using an OSA clinical population. The ultimate goal of this analysis is to help understand the craniofacial phenotyping technique in order to apply it to future studies for assessment of OSA risk. We selected a core set of facial measures representing facial heights/widths and facial angles. Based on associations with obesity from our previously published cross-sectional datasets [13, 14], we hypothesised that facial heights and angles would be *stable measurements*, facial widths and cervicomental angle would be *changing measurements*, while mandibular length, nose and eye widths are likely intermediate.

Methods

Participants

Subjects were participants in one of three weight loss trials in obstructive sleep apnoea. Craniofacial photographs and anthropometric measurements were taken at baseline and after a period of weight loss. Study 1 involved a very low calorie diet (VLCD), with measurements at baseline, 2 and 12 months (a subset of $N = 38$ subjects with craniofacial photographs available) [15]. Study 2 involved a hypocaloric diet and lifestyle program with photos at baseline, 6 and 12 months (a subset of $N = 57$ subjects with craniofacial photographs available) [16]. Study 3 involved bariatric surgery for weight loss with photos taken at baseline and 6 months post-surgery ($N = 10$ subjects) [17]. All three studies were approved by the institutional Human Research Ethics Committees (Sydney Local Health District; study 1 protocol HREC/12/RPAH/533, study 2 protocol X11-0088. Northern Sydney Local Health District; study 3 protocol HREC/15/HAWKE/386). Written informed consent was obtained from all participants.

Craniofacial photography and analysis

Craniofacial photography was performed according to previously described protocols [12, 14]. Frontal and profile digital photographs were obtained by asking the patient to maintain a neutral facial expression with lips softly touching. Patients were asked to assume their natural head position by asking them to imagine looking into their own eyes in a mirror. For each photograph a calibration marker (30-mm diameter nylon washer) was affixed to the face. For the profile photograph, a skin-appropriate marker was used to mark the *gonion* point (corner of the mandible), identified by palpitation, which is not otherwise visible in the facial profile photographs. For analysis, the facial photographs are imported into image analysis software (ImageJ 1.48v, National Institutes of Health, USA). Facial surface landmarks are marked using the point tool to obtain x and y coordinates. These coordinates are imported into a customised spreadsheet for calculation of quantitative facial dimensions. Facial landmark placement was performed by a single operator. To confirm intra-rater reliability of facial measurements, a random sample of $N = 10$ subjects were re-analysed. Craniofacial photographs from baseline and the time point corresponding to maximum weight loss were used in the analysis.

Craniofacial measurements

A select set of 11 facial measurements were used to cover the core linear distances (facial heights and widths) and facial angles. These facial measurements encompass regions of the face, mandible and neck. The facial measurements analysed are described in Table 1 and facial surface landmarks and measurements illustrated in Fig. 1. We assessed the relationship of these core variables with obesity in our previously published cross-sectional datasets of facial photography [13, 14]. In these previous studies, we had assessed the correlation with BMI to inform our hypothesis of which measurements were likely to be most related to obesity and hence potentially sensitive to weight changes. Those not showing a relationship with BMI were facial heights and facial angles. The strongest relationships ($r \geq 0.5$) were with facial widths and cervicomental angle. Minimal associations ($r < 0.3$) were noted with mandibular length, nose and eye widths.

Table 1 Craniofacial measurements from facial photographs. The 11 craniofacial measurements selected include a mixture of facial heights and widths, mandibular length, facial angles, areas and volumes. Most lengths or angles are taken from a single photo or facial orientation (profile or front). However, some of the measurements are a composite of dimensions from both photographs resulting in a three-dimensional measurement (profile, front)

Measurement	Type (unit)	Facial landmarks	Photo
Upper face height	Linear (cm)	*n-sn*	Profile
Lower face height	Linear (cm)	*sn-gn*	Profile
Mandibular length	Linear (cm)	gn-go	profile, front
Face width	Linear (cm)	*t(L)-t(R)*	Front
Mandibular width	Linear (cm)	*go(L)-go(R)*	Front
Intercanthal width	Linear (cm)	*en(L)-en(R)*	Front
Biocular width	Linear (cm)	*ex(L)-ex(R)*	Front
Nose width	Linear (cm)	*al(L)-al(R)*	Front
Maxillary depth angle	Angle (°)	*t-n-sn*	Profile
Mandibular depth angle	Angle (°)	*t-n-sl*	Profile
Cervicomental angle	Angle (°)	*nec-cer-me*	Profile

Statistical analysis

Statistical analysis was performed using SPSS software (Version 24, IBM). Intra-rater reliability in analysis of facial measurements was assessed using the intra-class correlation coefficient (ICC, two-way mixed effects model). Changes in total body weight (kg) and neck circumference (cm), as measures of total and regional obesity changes respectively, were used for comparison to changes in facial photographic measurements. Linear regression models were used to understand the effect of weight change (body weight or neck circumference, *independent variable*) on changes in facial structures (*dependent variable*). The associations between weight changes and craniofacial changes is represented by the β-coefficients, which are equal to the expected increase in facial measurement change per 1 unit increase in weight change. To enhance clinical applicability of our findings, we used a predetermined Spearman's rank correlation coefficient of > 0.3 as indicating a relationship of potential clinical significance [18]. Additionally, statistical significance was accepted at a Bonferroni adjusted level of $p < 0.0045$ (adjusted for 11 craniofacial measurements) to limit false-positive relationships (type I errors).

Results

Subject characteristics

Characteristics of the subjects analysed are shown in Table 2. Subjects were predominantly male, Caucasian ethnicity, middle-aged and obese. On average, there was an 11.7 ± 10.8 kg decrease in weight between the pre- and post-weight loss study photographs and a 2.0 ± 2.0-cm decrease in neck circumference. There was a wide variation in the amount of weight change seen between subjects due to the different weight loss methods applied in the primary studies and potentially also inter-individual variation in response to intervention. Study 2 showed the least amount of weight loss (− 5.6 ± 6.2 kg, range − 21.0 to + 12.0 kg, $p < 0.001$). The highest weight loss was in study 3 (bariatric surgery, − 35.0 ± 6.5 kg, range − 50.8 to − 29.0 kg, $p < 0.001$), followed by study 1 (VLCD, − 13.4 ± 6.2 kg, range − 29.8 to + 0.8 kg, $p < 0.001$). This variation was intended to aid in the quantification of the hypothesised associations.

Relationships between changes in craniofacial measurements and weight

Intra-rater reliability analysis showed excellent reliability of repeated measures of the same photos (ICC 0.89-0.99). The strength of the relationships between weight change and facial measurement changes is shown in Table 3. Facial measurements that changed with weight were both facial widths at the level of upper bizygomatic arch and the mandible. The cervicomental angle, under the chin and neck, also related to weight changes. These relationships were evident with both total body (weight) and regional (neck circumference) fat loss. Cervicomental angle was not related to head position angle ($r = -0.031$, $p = 0.753$) and head position angle did not change between photographs ($p = 0.314$).

Facial heights and angles and mandibular length did not have a relationship with weight change. Figure 2 illustrates graphically the relationship between obesity change and photographic measurements for a weight-sensitive measure (cervicomental angle) and a weight-insensitive measure (maxillary depth angle). There was a tendency ($p < 0.05$) towards relationships with measurements relating to the eyes (intercanthal and biocular width) and neck circumference, although these relationships were not statistically significant in this study and did not meet the pre-set level of clinical significance ($r \geq 0.3$).

Discussion

We present an investigation of the method of craniofacial phenotyping using OSA patients losing weight via three methods. Facial phenotyping using high throughput photography offers a potential method to capture information about craniofacial risk in large clinical and population samples [13, 14]. However, some detail is lost using facial surface information as skeletal structure and regional adiposity cannot be separated. Weight loss offers the opportunity to understand which facial measurements are influenced by changes in weight

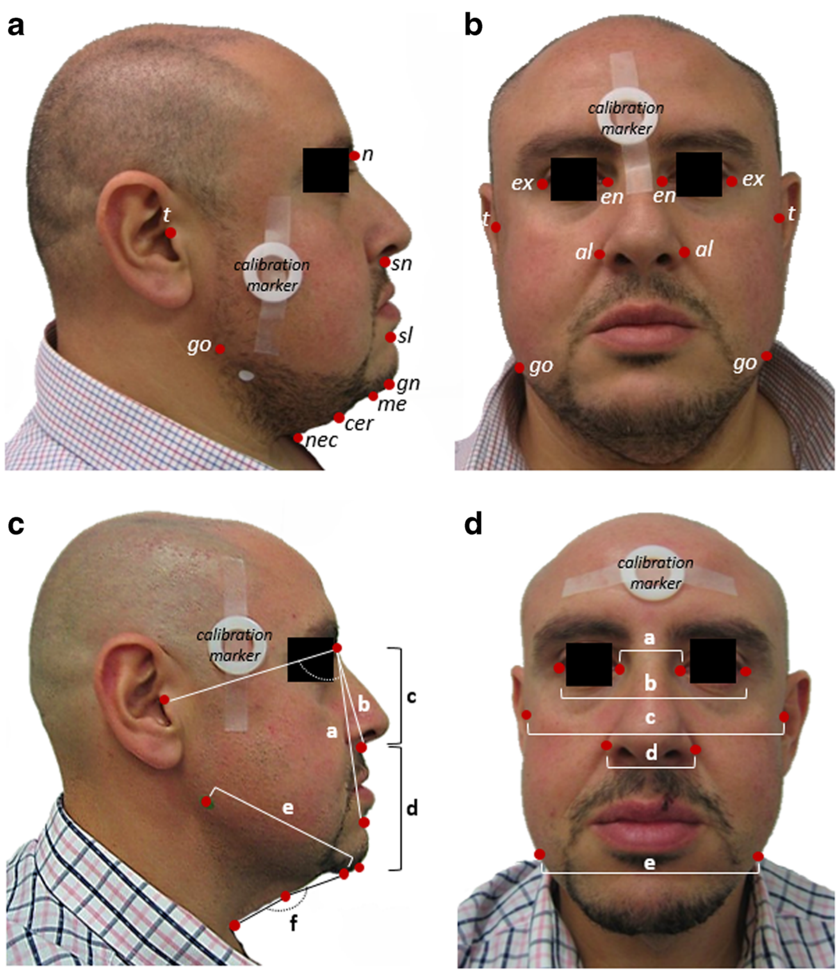

Fig. 1 Craniofacial photography analysis method illustrated in study patient before weight loss (upper panel **A**, **B**) and after weight loss (lower panel **C**, **D**). This male patient was part of study 3 (bariatric weight loss) and lost a total of 39.3 kg between the upper panel photographs (**A**, **B**) taken pre-surgery and the lower panel photographs (**C**, **D**) taken 6 months post-surgery. A profile (**A**, **C**) and front (**B**, **D**) are used to derive facial measurements. The upper panel (**A**, **B**) shows facial landmarks on the profile and front photograph. The bottom panel (**C**, **D**) illustrates the measurements calculated from these facial landmarks. Facial landmarks (A, B): al *alare*, lateral point on the nasal ala; cer soft tissue point midway between menton and cricoids; en *endocanathion*, inner commissure of eye fissue; ex *exocanathion*, outer commissure of the eye fissure; gn gnathion, anter-inferior border of the chin; go – *gonion*, most lateral point at the angle of the mandible; me *menton*, lowest point on the chin; n *nasion*, midline point of the nasofrontal suture; nec inferior point of the anterior neck plane; sl *sublabiale*, deepest point of curvature of the labiomental space; sn *subnasion*, point between septum and upper lip; t *tragion*, notch above the tragus of the ear; Facial measurements-C: (a) mandibular depth angle, (b) maxillary depth angle, (c) upper face height, (d) lower face height, (e) mandibular length (three-dimensional measurement constructed from front and profile photographs), (f) cervicomental angle. D: (a) intercanthal width, (b) biocular width, (c) mid-face width, (d) nose width, (e) mandibular width

Table 2 Subject characteristics. Descriptive data of the $N = 106$ participants in weight loss trials

	Mean ± standard deviation	Range
Gender (% male)	67.2	
Age (years)	50.0 ± 11.0	24–71
BMI at study entry (kg/m^2)	34.1 (8.0)^	26.11–58.06
Weight change (kg)	− 8.9 (10.7)^	− 50.8–+ 4.6
Δ Neck circumference (cm)	− 1.6 (2.8)^	− 8.0–2.5

^Data are presented as mean ± standard deviation if data normally distributed, otherwise as median (interquartile range)

and therefore suggest a stronger component of regional adiposity in those measures. This is preliminary work in order to better understand this phenotyping methodology for application for future studies related to OSA characteristics. We have found that weight-sensitive measures are facial widths, at the level of the bizygomatic arch and mandible, and the cervicomental angle between the chin and neck. Facial measurements not reflecting weight changes (weight-insensitive measures) were primarily facial angles (maxillary and mandibular depth), upper and lower facial height and mandibular length. These associations from longitudinal analysis with deliberately induced weight change largely support our

Table 3 Influence of weight loss on change in craniofacial measurements. Linear regression models were applied to investigate the strength of relationship between changes in weight and changes in craniofacial measurements (cm or degrees for craniofacial angles). Total body weight (kg) was used as a measure of total obesity and neck circumference (cm) as regional obesity. Beta coefficients (β) indicate the expected increase in facial measurement change per one unit change in weight loss or neck circumference reduction. The standardised beta coefficient (Std.β) indicates the expected increase in facial measurement change per one standard deviation of weight loss or neck circumference reduction

Facial variables	Total body weight				Neck circumference			
	R^2	β (95% CI)	Std. β	p	R^2	β (95% CI)	Std. β	p
Upper face height	0.007	− 0.002 (− 0.008, 0.003)	− 0.083	0.404	0.001	− 0.005 (− 0.036, 0.026)	− 0.032	0.746
Lower face height	0.004	− 0.002 (− 0.010, 0.005)	− 0.060	0.548	0.016	− 0.025 (− 0.064, 0.013)	− 0.127	0.198
Mandibular length	0.004	− 0.006 (− 0.023, 0.012)	− 0.064	0.517	0.003	0.025 (− 0.068, 0.118)	0.053	0.594
Face width	0.093	0.024 (0.009, 0.038)	0.305	0.002*	0.093	0.127 (0.049, 0.204)	0.305	0.002*
Mandibular width	0.126	0.031 (0.015, 0.046)	0.355	< 0.001*	0.148	0.177 (0.094, 0.260)	0.385	< 0.001*
Intercanthal width	0.014	0.002 (− 0.002, 0.006)	0.119	0.229	0.056	0.025 (0.005, 0.045)	0.237	0.015
Biocular width	0.041	− 0.006 (− 0.085, 0.073)	0.203	0.039	0.059	0.034 (0.007, 0.061)	0.242	0.013
Nose width	0.012	0.002 (− 0.002, 0.006)	0.110	0.268	0.028	0.017 (− 0.003, 0.037)	0.168	0.088
Maxillary depth angle	< 0.001	− 0.005 (− 0.080, 0.069)	− 0.014	0.887	0.001	0.056 (− 0.370, 0.482)	0.026	0.794
Mandibular depth angle	0.002	0.016 (− 0.059, 0.091)	0.042	0.673	0.011	0.222 (− 0.200, 0.645)	0.103	0.300
Cervicomental angle	0.108	0.289 (0.125, 0.454)	0.329	0.001*	0.122	1.589 (0.747, 2.431)	0.424	< 0.001*

*A Bonferroni adjustment for multiple comparisons (11 facial variables) was made and statistical significance is accepted as $p < 0.0045$

hypotheses of which measurements would change based on cross-sectional analysis of relationships to obesity [10, 12]. These findings give important information for the interpretation of quantitative facial measurements in future OSA phenotyping studies. In studies of craniofacial phenotype, it will inform interpretation of whether photographic measurements are reflecting soft tissue or skeletal aspects of OSA risk. Particularly in the context of weight loss therapy, this provides a framework for the exploration of whether facial measurements could inform which OSA patients may benefit most, or least, from weight loss to enable other OSA treatment strategies to be applied without delay.

Changes in facial measurements were compared with changes in two anthropometric measurements, total body weight and neck circumference, as a potentially closer marker of regional weight loss in the face. There tended to be a slightly stronger relationship with most weight-sensitive craniofacial measurements with neck circumference than total body weight, particularly for cervicomental angle. Therefore, neck circumference appears somewhat more specific to regional changes in the face, although body weight followed this pattern closely. The cervicomental angle had the strongest relationship with change in neck circumference. This angle is a measurement of the space between the chin and anterior neck and can therefore indicate neck and submental adiposity. Although, it may also relate to aspects of craniofacial risk including position of the hyoid bone, which could shift superiorly with reductions in tongue volume secondary to weight loss. This angle has been shown to be increased in clinical OSA patients compared to controls [10, 19]. This current analysis confirms that there is a component related to adiposity captured in this measure, likely regional neck fat but potentially also reflecting enlarged upper airway soft tissues and downward pressure on the hyoid bone. This angle could be influenced by head position; subjects were required to assume their own natural head position for the photographs. We confirmed there was no difference between head position angle measured on the photographs between repeat photographs and no relationship between the head position angle and cervicomental angle (data not shown).

The other weight-sensitive facial measures were facial widths. We have previously shown in MRI studies that facial width at the

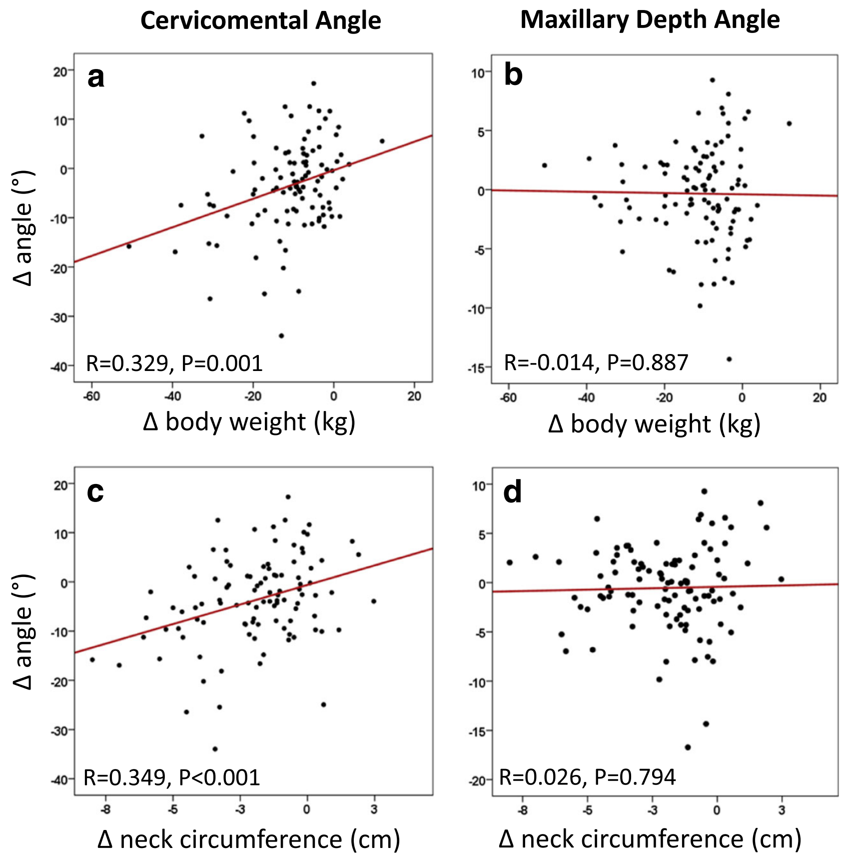

Fig. 2 Weight-sensitive and weight-insensitive craniofacial angles. Changes in cervicomental angle across the weight loss period were related to changes in **a** body weight and **c** neck circumference, suggesting this measure is sensitive to weight change and thus reflects information about regional adiposity. Maxillary depth angle did not relate to changes in either **b** body weight or **d** neck circumference, suggesting this craniofacial angle may be more related to craniofacial skeletal structure than regional adiposity

bizygomatic arch and mandible correlate with tongue size [13]. When controlled for obesity (BMI, neck circumference), tongue volume is no longer associated with facial dimensions [14], suggesting that the tongue relates to the face through a shared relationship with obesity. This would suggest that facial widths also reflect regional obesity, and in the current study, we have found these measures to be weight-sensitive. Although not statistically significant due to the Bonferroni adjustment for multiple comparisons, eye width measurements (biocular and intercanthal widths) showed a trend towards an association with neck circumference changes, that these widths decrease with a decrease in neck adiposity. This could reflect changes in size of the ocular fat pads [20, 21], which could affect the appearance of the eyes following weight change. Facial heights and facial angles were not influenced by weight changes. The facial angles (maxillary and mandibular depth angles) are the facial surface equivalents of SNA and SNB angles in cephalometry, which describe the position of the maxilla and mandible, respectively, in relation to the skull base. These measurements have been associated with the presence of OSA [22]. Facial height, particularly a longer lower face, has also been associated with OSA [22]. It appears that these measurements are not sensitive to weight and therefore, these photographic measurements are likely informative of the underlying skeletal substrate. Shorter mandibular length is also associated with the presence of OSA [23]. Our cross-sectional photographic data showed a borderline ($r < 0.3$) association with obesity (BMI) and mandibular length from craniofacial photography. In the weight loss paradigm, there was no influence of weight changes on mandibular length, suggesting this measurement is also related to skeletal structure.

This method of craniofacial photography and analysis was designed to be simple, high throughput and not dependent on specialised equipment. True three-dimensional facial photography has traditionally required dedicated expensive camera equipment [24], although technology is evolving towards cheaper three-dimensional methods using mobile devices [25]. Three-dimensional analysis of the facial surface provides information akin to computed tomography and gives more information about regional adiposity [24].

This study uses the novel and relatively simple paradigm of weight loss to better understand which aspects of facial phenotype are related to regional obesity. However, there are limitations to the study. A study using either CT or MRI and facial photography in weight loss could more comprehensively assess these associations and confirm the findings, however, were not available in the majority of patients in these trials. Our study was a comparison with anthropometric measures but future studies for relationship to body composition changes would be interesting. It is known that ethnicity has an impact on the relationship of craniofacial structure and obesity to OSA severity [26], and our study sample was a predominantly Caucasian and male group. The associations with facial measurements to craniofacial skeletal structure versus adiposity may also differ and therefore we cannot assume our findings can be generalised to other ethnic groups [7]. Similarly, there may be gender differences and future studies would need to assess this in female samples. Additionally, we used a convenience sample from weight loss studies which used three different weight loss methods. It is possible that the different methods could result in differential relationships between fat loss and total body weight reduction [27], which could in turn affect the relationship with facial surface measures. However, this is an initial investigation and our findings are generalisable to different forms of weight loss. Changes in total body weight and neck circumference were highly correlated in this data, although weight loss may have had differential effects on each in individuals. However, these two measures have been assessed individually and our study was a comparison of anthropometry.

This study has important implications for future work. We now have an indication of whether facial surface measures likely contain information about the underlying craniofacial skeleton, rather than just facial adiposity. Separating these components has important implications for craniofacial phenotyping studies. For example, radiology has shown an influence of craniofacial skeletal restriction on success of weight loss therapy for OSA [28, 29]. To look at facial phenotype as a potential predictor of weight loss response, knowledge of relationship to skeletal structure is needed.

Conclusions

High-throughput facial phenotyping provides an opportunity to collect information on craniofacial risk factors both clinically and in large studies. However, the phenotypic information on regional obesity and craniofacial skeletal structure is intertwined. This study used a weight loss paradigm to understand which measurements are influenced by weight changes. Weight-sensitive measures (facial widths, cervicomental angle) are likely to reflect a component of regional adiposity. Facial angles and height measures are weight-insensitive, and therefore may reflect craniofacial skeletal structure. These findings enhance our interpretation of craniofacial phenotyping studies in OSA with the ability to infer whether measurements which relate to outcomes of interest are likely due to skeletal structure or regional adiposity. This will greatly inform future studies relating facial characteristics to OSA outcomes.

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Study 1: Financial and material support was supplied by the Australian National Health and Medical Research Council (NHMRC) Centres of Research Excellence: Centre for Integrated Research and Understanding of Sleep (571421) and Centre for Translational Sleep and Circadian Neurobiology (1060992); NHMRC project grant 1004528 and the kind contribution of a single VLED sample meal replacement and a meal planning aid (fridge magnet) per patient from Optifast (Market value less than AUD300).

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Compliance with ethical standards All studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave their informed consent prior to their inclusion in the study.

Conflict of interest Dr. Cistulli has an appointment to an endowed academic Chair at the University of Sydney that was established from ResMed funding. He has received research support from ResMed, SomnoMed, and Zephyr Sleep Technologies. He has been a consultant/adviser to Zephyr Sleep Technologies, NovoNordisk, and Bayer. Dr. Marshall has accepted funding in the form of investigational product and matched placebo from Teva Cephalon for a trial which we use data from in this analysis.

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