Craniofacial form differences between obese and nonobese children

Siddharth R. Vora,[a] Samuel Tam,[a] Motoki Katsube,[b] Benjamin Pliska,[a] and Kiran Heda[a]
Vancouver, Canada, and Kyoto, Japan

Introduction: Current evidence suggests that obesity is correlated with differences in craniofacial form in children and adolescents. Here, we sought to test this hypothesis by evaluating the craniofacial form of obese and nonobese preorthodontic patients, using 2D cephalometric data combined with cephalometric and geometric morphometric approaches. **Methods:** Height, weight, age, and lateral cephalometric radiographs were gathered from patients aged 7-16 years before beginning orthodontic treatment at the University of British Columbia. Based on their body mass index, 24 obese patients were age, sex, and Angle classification of malocclusion matched with nonobese controls. Cephalometric radiographs were annotated, and coordinates of landmarks were used to obtain linear and angular cephalometric measurements. Geometric morphometric analyses were performed to determine overall craniofacial form differences between cohorts. Dental maturation index scores and cervical vertebral maturation scores were recorded as an indicator of skeletal maturation. **Results:** Cephalometric analysis revealed that the maxillary length and gonial angle are the only marginally larger metrics in obese subjects than in control subjects. However, principal component and discriminant analyses (geometric morphometrics) confirmed that the overall craniofacial form of obese patients differs statistically from that of control patients. Obese patients tend to be slightly mandibular prognathic and brachycephalic. Dental maturation index scores were statistically higher in the obese group than in the control group, with no statistical difference in cervical vertebral maturation scores. **Conclusions:** Our data reveals a subtle but significant difference in cranial skeletal morphology between obese and nonobese children and adolescents, suggesting a correlation between craniofacial form and physiological/metabolic phenotypes of subjects. It is likely that with continued growth, these differences may increase. Recording body mass index as part of the orthodontic records for patients may help in supporting the assessment of craniofacial form. (Am J Orthod Dentofacial Orthop 2022;162:744-52)

Childhood obesity is an increasing medical and public health care problem worldwide.[1,2] The prevalence of obesity in the United States is ~20% for children and adolescents aged 2-19 years (National Health and Nutrition Examination Survey, 2015-16), whereas, in Canada, the prevalence of obesity is 13% in children and adolescents aged 5-19 years.[3,4] Apart from comorbidities like type 2 diabetes mellitus, elevated blood pressure, sleep-disordered breathing, and other cardiometabolic conditions,[5,6] obese patients also display related psychological problems that are important to orthodontic treatment, including signs of social isolation, poor self-esteem and body image, poor compliance because of a defense mechanism to downplay overall appearance or a hyper-realization of appearance leading to unrealistic treatment expectations.[7] Several studies have confirmed that the majority of children maintain or worsen their weight problems as they move from childhood to adolescence and onto adulthood.[8-10]

Apart from socioeconomic, maternal, and lifestyle risk factors,[3,4,11,12] numerous genes have been linked to obesity, including melanocortin-4 receptor,[11] leptin, adiponectin,[13] and insulin-like growth factor-1.[7] Consequently, obesity in children has been linked to precocious puberty, altered bone metabolism and accelerated dental and skeletal maturity, assessed using methods such as the dental maturation index, tooth eruption charts, cervical vertebral maturation index, hand-wrist film assessment, and dual-energy x-ray absorptiometry.[13-17] It has been

[a]Oral Health Sciences, University of British Columbia, Vancouver, Canada.
[b]Plastic and Reconstructive Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan.
All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and none were reported.
Siddharth R. Vora was supported by an Orthodontic Faculty Development Award through the American Association of Orthodontists Foundation.
Address correspondence to: Siddharth R. Vora, Oral Health Sciences, University of British Columbia, JBM 372-2199 Wesbrook Mall, Vancouver, British Columbia V6T 1Z3, Canada; e-mail, svora@dentistry.ubc.ca.
Submitted, April 2021; revised and accepted, July 2021.
0889-5406/$36.00

https://doi.org/10.1016/j.ajodo.2021.07.018

proposed that obese children are ~12-21 months ahead of their normal weight peers in their dental and/or skeletal maturity.[13,18-20]

Because obesity and skeletal maturity are related, it has been suggested that craniofacial form in obese subjects may be altered compared with normal-weight counterparts. Indeed, several authors have examined cephalometric variables and found unique craniofacial characteristics in obese than nonobese control subjects. However, most of these studies have focused on older, postpubertal adolescents.[21-25] In addition, previous studies have used conventional cephalometric analyses, which rely on discrete linear distances and angular measurements. Although valuable, such conventional analyses fail to capture the overall shape of the craniofacial region.[26,27] Geometric morphometric analyses retain geometric information and apply multivariate statistics, enabling comprehensive quantification and visualization of shape differences between subjects. This study investigated differences in craniofacial form between obese and nonobese children and adolescents aged 6-16 years, using conventional cephalometrics and geometric morphometric (GM) approaches.

MATERIAL AND METHODS

A retrospective review of orthodontic records at the University of British Columbia (Ethics approval no. H17-03043) was performed to identify obese and control cohorts. Included patients were free of any craniofacial abnormalities, had nonsignificant medical histories, were not taking any medications, had never received orthodontic treatment, and had clear cephalometric images (teeth occluded, relaxed lip position, devoid of significant asymmetry as noted by absence of double mandibular borders) and had their weight and height measured at the time of cephalogram capture as part of their intake records. A body mass index (BMI) ≥95th percentile for the age- and sex-specific is considered obese per the Centers for Disease Control and Prevention (CDC) growth charts.[3] Based on a power calculation (power = 0.80; $\alpha = 0.05$; determined using maxillary length measurements[22,24]), 24 obese and 24 control subjects were identified. Control group matching was done by prioritizing age (within 6 months of obese subjects), gender, and then Angle classification of malocclusion (Table I).

Cephalometric radiographs were traced and annotated with landmarks (Supplementary Table 1) using Dolphin Imaging Software (Dolphin Imaging and Management Solutions, Chatsworth, Calif). Linear and angular cephalometric measurements (Table II) were obtained directly from Dolphin. We limited our conventional cephalometric analysis to variables that previous studies identified as showing differences between comparable cohorts.[22-24] The x and y-coordinates of subjects' configurations were obtained from Dolphin and were used for error and GM analyses. The intraexaminer error was performed for 10 randomly selected subjects by repeating measurements 2 weeks apart. The Euclidean distance between the repeat and original landmarks was calculated as error. Mean errors across landmarks were found to be low, indicating very good consistency of landmark identification (average range, 0.03-0.24 mm; Supplementary Table I).[28]

All x and y-coordinates were subjected to a generalized Procrustes analysis (GPA), which translates all configurations to share a common centroid (geometric center of entire landmark configuration) and scales them to unit centroid size. This was followed by an iterative rotation step, which uses the least-squared criterion to obtain the optimal fit between all configurations. Once completed, the GPA step yielded new Procrustes coordinates maintaining original geometry, which were subjected to further analysis. Our dataset did not contain any outliers, as assessed by the Procrustes distance of each sample from the median. Because subjects in our dataset have a large age range, we removed the allometric component of shape, using the patient's age (rounded to the closest month) at the time of cephalogram capture. Briefly, the residuals from the multivariate regression (ordinary least squares) on patients' age (as a representation for size) were used as size-adjusted shape data for all downstream analyses.[29] After this, a principal component analysis

Table I. Patient demographics

	Cohort		
Characteristic	*Nonobese*	*Obese*	P *value*
No. of patients	24	24	
Mean age, y (range)	11.3 (8.0-16.1)	11.2 (7.6-16.4)	0.851
Mean BMI	18.0 ± 1.7	25.4 ± 3.4	<0.001*
Mean weight, kg	40.7 ± 11.9	57.8 ± 20.3	0.001*
Mean height, m	1.49 ± 0.16	1.48 ± 0.17	0.965
Sex			
Male	16 (67)	16 (67)	
Female	8 (33)	8 (33)	
Angle classification			
Class I	11 (46)	11 (46)	
Class II Division 1	8 (33)	5 (21)	
Class II Division 2	1 (4)	1 (4)	
Class III	4 (17)	7 (29)	

Note. Presented values are mean ± standard deviation or n (%).
*Difference is statistically significant ($P < 0.05$).

Table II. Conventional cephalometric analysis

Cephalometric measurement	Cohort average		P value
	Obese subjects	Controls	
Linear variables (mm)			
Posterior facial height (S-Go)	74.2 ± 7.5	75.8 ± 7.8	0.483
Lower face height (ANS-Gn)	57.5 ± 6.7	57.3 ± 4.4	0.923
Anterior cranial base (S-N)	64.9 ± 3.9	64.7 ± 3.8	0.833
Maxillary length (PNS-A)	44.3 ± 3.5	42.3 ± 3.1	0.041*
Mandibular unit length (Co-Pog)	98.3 ± 8.5	96.0 ± 6.6	0.282
Length of mandibular base (Go-Pg)	65.0 ± 5.3	63.9 ± 3.8	0.411
Maxillary dental protrusion (U1-NA)	3.6 ± 2.9	3.9 ± 2.8	0.725
Mandibular dental protrusion (L1-NB)	4.3 ± 1.8	4.4 ± 1.7	0.945
Lower lip to E-plane	−0.6 ± 3.1	0.8 ± 2.9	0.099
Upper lip to E-plane	−1.5 ± 2.7	−1.3 ± 2.7	0.865
Angular variables (°)			
Mandible to cranial base (SN-MP)	32.8 ± 7.1	31.2 ± 5.2	0.366
Gonial angle (Ar-Go-Gn)	129.7 ± 6.0	126.0 ± 5.1	0.028*
Maxilla to cranial base SNA	82.1 ± 3.3	81.0 ± 4.8	0.361
Mandible to cranial base SNB	78.6 ± 4.5	77.7 ± 4.9	0.506
Mandible to cranial base FMA (MP-FH)	25.8 ± 5.9	27.4 ± 4.2	0.304
Maxillomandibular ANB	3.8 ± 2.1	3.2 ± 2.9	0.405
Maxillary incisor proclination (U1-SN)	104.5 ± 11.0	102.8 ± 10.7	0.582
Mandibular incisor proclination (L1-MP)	91.0 ± 8.2	91.7 ± 5.4	0.729

Note. Presented values are mean ± standard deviation.
*Difference is statistically significant ($P < 0.05$).

(PCA) was performed as an unbiased method to identify the major axes of shape variation in the dataset (obese + controls combined). PCA transforms multiple variables (in this case, the x and y-coordinates) into a set of orthogonal uncorrelated axes (principal component [PC]), which account for the maximum possible variance in multivariate data sets, thereby compacting it to only a few variables.[27] In addition, a discriminant function analysis was used to project our multivariate dataset to 1 dimension, thereby maximizing the shape separation between the cohorts of interest (obese and control). This also allowed for visualizing the morphologic differences between the cohorts. All GM analyses were performed using the Momocs and Geomorph packages in RStudio (version 1.2.5033; Rstudio Inc, Boston, Mass) and MATLAB (version 9.0.1; Mathworks, Natick, Mass).

Dental maturation index scores were assessed from panoramic radiographs, based on 7 permanent mandibular teeth (excluding third molars), rated according to tooth follicle shape, pulp chamber, dentin deposition, and root formation on a 7-point scale.[30] Skeletal maturation was determined using the cervical vertebral maturation (CVM) method.[14]

Statistical analysis

SPSS (version 25; IBM Corp, Armonk, NY), Microsoft Excel, and RStudio were used for statistical analyses. A $P < 0.05$ was used for all tests comparing obese and control cohorts (unless otherwise indicated). A 2-sample t test was used for selected cephalometric linear and angular measurements and to compare dental maturation indexes. CVM scores were compared using a χ^2 test. For the GM analysis, an unbiased analysis of variance was first performed to assess whether BMI, sex, or Angle's classification of malocclusion correlated significantly with the shape distribution contained within each PC. A multivariate analysis of variance (MANOVA) was performed using the PCs, which together explain ~90% of the variation, to evaluate if any of the variables of interest had a significant impact on the overall shape variation within our dataset (obese + controls combined). Hotelling-Lawley Trace was calculated for the MANOVA tests.

RESULTS

The obese and control cohorts were well-matched for age, sex, and Angle's classification of malocclusion, differing significantly only in BMI values, as expected (Table I). Based on CDC charts, BMI for the control subjects fell within the 42-75 percentile range. The mean BMI of the obese group was 25.4, comparable to the U.S. national average of adult men and women (CDC). In line with previous studies, we found a statistically significant difference ($P < 0.0048$) in dental maturity, with the obese group having higher dental maturation scores (Supplementary Table II). However, the assessment of

Table III. Procrustes analysis of variance for PCs 1-4 (allometry removed)

Variable	*Df*	*Sum of squares*	*Mean of squares*	*F value*	*Pr (>F)*
PC1					
BMI	1	0.00540	0.00540	12.06000	0.00139**
Angle Class	3	0.02248	0.00749	16.74340	<0.001***
Sex	1	0.00022	0.00022	0.49560	0.48612
Residuals	35	0.01566	0.00045		
PC2					
BMI	1	0.00541	0.00541	8.01510	0.00764**
Angle Class	3	0.00238	0.00079	1.17570	0.33297
Sex	1	0.00011	0.00011	0.16920	0.68329
Residuals	35	0.02361	0.00067		
PC3					
BMI	1	0.00102	0.00102	1.69540	0.20140
Angle Class	3	0.00122	0.00041	0.67630	0.57240
Sex	1	0.00001	0.00001	0.01320	0.90920
Residuals	35	0.02098	0.00060		
PC4					
BMI	1	0.00362	0.00362	10.00050	0.00323**
Angle Class	3	0.00136	0.00045	1.25290	0.30551
Sex	1	0.00016	0.00016	0.44620	0.50855
Residuals	35	0.01266	0.00036		

Df, degrees of freedom.
**P <0.01; ***P <0.001.

skeletal maturation using the CVM method revealed no statistically significant difference between groups (Supplementary Table III; χ^2: 34.384; degrees of freedom, 20; P <0.024) in the age range studied here.

The maxillary length (PNS-A-point), and the gonial angle (Ar-Go-Gn), were the only cephalometric variables significantly greater by ~ 2 mm and 3.7°, respectively, in the obese group (Table II, Welch 2-sample t test; P <0.05). However, after applying Bonferroni's correction for multiple testing, which set the new α to 0.0028, neither of these differences remained statistically significant.

To better evaluate craniofacial form, we performed GM analysis using the x and y-coordinates of landmark configurations. First, new Procrustes coordinates were obtained for each patient using a GPA (see Material and Methods). To assess the overall size of the craniofacial regions, we compared the mean centroid sizes of each cohort and found no difference between obese and control patients (Supplementary Fig 1). For shape assessment, a PCA was performed using the Procrustes coordinates. The patients' age correlated strongly (P <0.001) with the shape distribution (an allometric component of shape) along the first few PCs. We adjusted our model for this allometric shape component because it was not the focus of our study, after which the first 19 PCs explained ~90% of the overall shape variation (Supplementary Fig 2). Markedly, the distribution along PCs 1, 2, 4, and 8 significantly correlated with the patient's BMI (P <0.01 for PCs 1, 2, and 4; Table III). In addition, PCs 1 and 7 significantly correlated with the patients' Angle classification of malocclusion (P <0.001 for PC1; Table III). After correction for allometry, we did not find a significant correlation with sex with any of the first 19 PCs.

When viewing PCs 1 vs 2, the obese patients tended to cluster toward the positive ends of both PCs 1 and 2 (Fig 1, *B*, *red*), which are characterized by a mandibular prognathic profile (Fig 1, *A*, top row-right, solid wireframe) and shorter vertical facial height, brachycephalic appearance (Fig 1, *A*, left column-top, solid wireframe), respectively. Notably, the distribution of obese and control patients along the PC 1 and 2 plots (Fig 1, *B*) is almost perpendicular in direction to the gender distribution (Fig 1, *D*) and that of Angle's classification of malocclusion (Fig 1, *C*), once again demonstrating that our obese and control cohorts were well-matched for these variables.

Because BMI correlated with the shape distribution along multiple PCs, we performed a MANOVA using loadings from the first 19 PCs together. Once again, BMI and Angle's classification of malocclusion displayed a significant correlation to the overall shape variation (Table IV; P <0.01 and P <0.001, respectively), indicating a strong influence of both these variables on overall craniofacial shape.

Because we had deliberately chosen matched cohorts in this study, the shape separation between them was

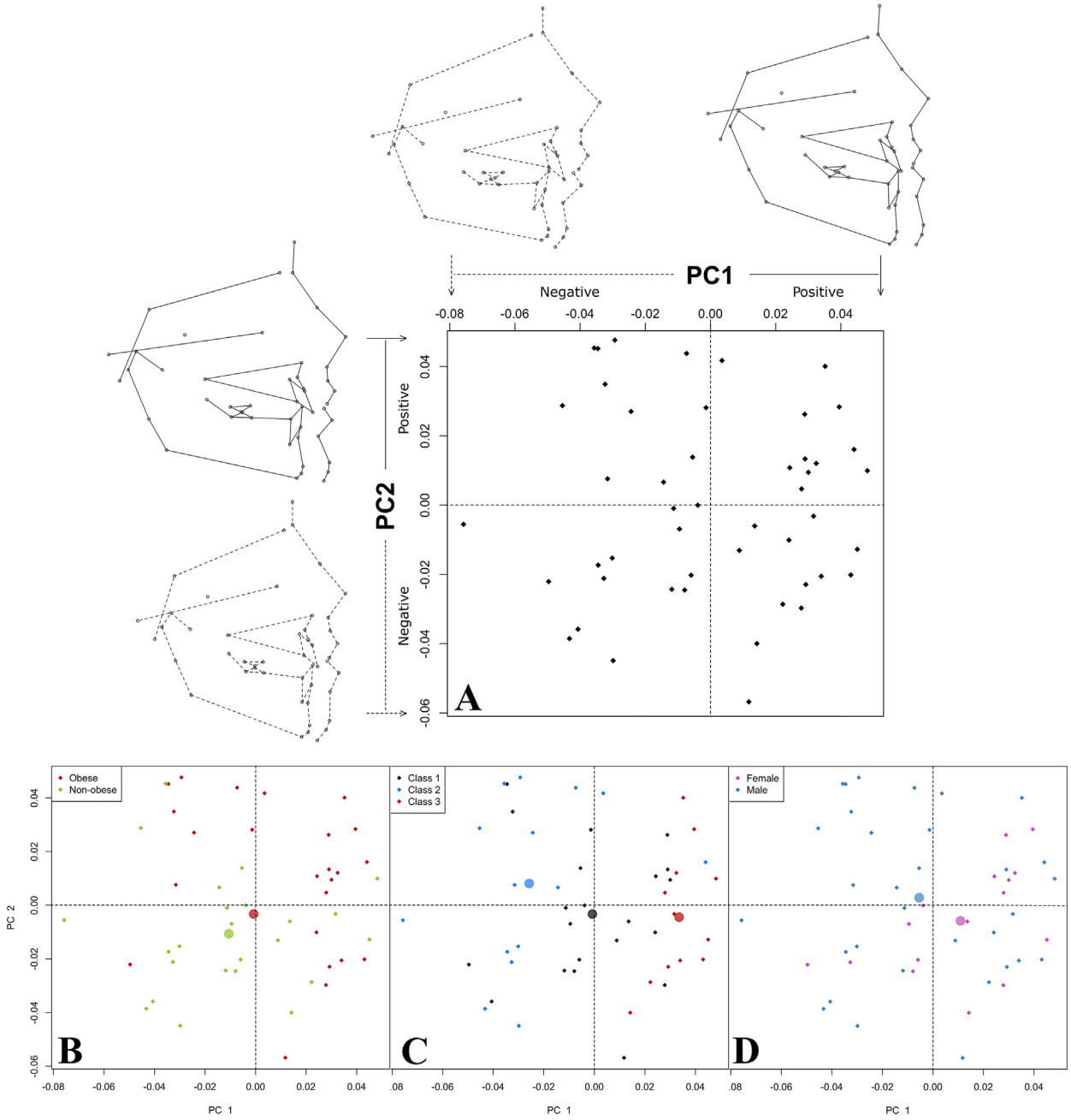


Fig 1. Principal component analysis: **A,** PC1 v/s PC2 plot with wireframes depicting the craniofacial shape corresponding to the positive (*solid*) and negative (*dashed*) ends of PC1 (*top*) and PC2 (*left*); **B,** Obese and control subjects are labeled *red* and *green*, respectively; **C,** Subjects with Angle's Class 1, 2, and 3 malocclusions are labeled with *black*, *blue*, and *red*, respectively; **D,** Female and male subjects are labeled *pink* and *blue*, respectively.

visualized using a discriminant function analysis (Fig 2). When assessing landmark displacements in obese patients compared with controls, large deviations were found in cranial base landmarks (basion, porion, nasion; Figs 2, *A-C*; top wireframes), with the obese cohort appearing to have a clockwise rotation in these landmarks around sella. In addition, the landmarks associated with the soft tissue chin were displaced forwards in the obese

Table IV. MANOVA using the first 19 PCs

Variables	*Df*	*Hotelling-Lawley trace*	*Approximate* F *value*	*Probability (>*F *value)*
BMI	1	0.85161	5.13480	0.00068***
Angle class	3	1.92653	1.79470	0.01453*
Sex	1	0.38189	0.55280	0.89341
Residuals	35			

Df, degrees of freedom.
*P <0.05; ***P <0.001.

cohort compared with controls (Figs 2, *A* and *C*; top wireframes). To visualize the facial skeletal form differences compared with the cranial base, we registered the discriminate analyses outputs on the sella-nasion-basion landmarks using a manual best-fit superimposition. When registering on these cranial base landmarks, the obese cohort appears to have more forward-positioned maxillary and mandibular skeletal bases and dentition, with a slightly brachycephalic appearance (Fig 2, *C*; bottom, *red*) compared with controls (Fig 2, *C*; bottom, *green*). Finally, the reliability of the discrimination was assessed by a leave-one-out cross-validation analysis, which resulted in 20 out of 24 patients in the control group and 22 out of 24 patients in the obese group being correctly classified on the basis of their shapes, providing an overall classification accuracy of 87.5% with a kappa statistic of 0.75.

To evaluate shape differences in younger and older patients within our cohorts, we split the group by the median age (10.6 y) and reperformed the discriminate analyses. When superimposed on the sella-nasion-basion points, the obese patients in both the younger and older groups displayed more forward positions of the maxillary and mandibular skeletal bases, whereas the older obese group additionally displayed the brachycephalic appearance compared with controls (Supplementary Fig 3). The shape distributions along PC1 for the younger and the older groups displayed a significant correlation with BMI ($P = 0.033$ and 0.024, respectively). However, our MANOVA analyses did not reveal a significant shape difference associated with BMI in either group, likely owing to the small sample size when splitting the cohorts into the 2 age groups.

DISCUSSION

For decades, 2-dimensional cephalograms have been used in orthodontic and anthropomorphic studies. Most of these studies use conventional cephalometric analyses to assess craniofacial shape differences between cohorts of interest, which primarily rely on linear and angular measurements. Such analyses pose several limitations, including statistical problems resulting from multiple testing and the inability to study overall craniofacial shape as a single entity.[26,31,32] Hence, we chose to employ multivariate statistical GM approaches, in which subjects are represented by their landmark configurations, allowing for a more robust statistical assessment of craniofacial shape.[26,27,31,33-35]

The age range in our study is wide (7.6-10.6 y) and included younger ages than previously studied.[22-24] To ensure that the age-related size changes do not influence our craniofacial shape assessment, we accounted for allometry by using the residuals from a multivariate regression on patients' age (see Material and Methods) before performing our GM analyses. In addition, we also split the patients into 2 groups using the median age (10.6 y). Indeed, the older obese patients display more dramatic shape differences compared with younger (Supplementary Fig 2). However, the more forward position of the maxillary and mandibular skeletal bases in the obese cohorts are also visible in the younger patients (Supplementary Fig 2). Although the BMI correlates significantly with the shape differences along PC1 in both age groups, our MANOVA analyses did not demonstrate significance with BMI, likely because of smaller sample sizes when splitting the patients into 2 groups. However, when all ages were analyzed together, our GM analyses suggested significant craniofacial form differences between the obese and control cohorts could be recognized. Obese patients (Fig 1, *B*, *red*) tend to segregate with positive ends of PC1 and PC2, characterized respectively by more mandibular prognathic (PC1; Fig 1, *A*; top-right wireframe) and brachycephalic craniofacial forms (PC2; Fig 1, *A*; left column-top wireframe). These differences are in line with earlier studies.[22-24] In addition, our MANOVA suggests a strong and statistically significant correlation (and covariation) between BMI and overall craniofacial shape. Interestingly, when visualizing landmark displacements which characterize the difference between obese and control patients superimposed on the cranial base landmarks (Fig 2, *C*; bottom), the obese cohorts' wireframe tends to show facial skeletal differences analogous to those found cephalometrically in older subjects'[23]; such as a more anteriorly positioned maxilla and mandible, increased inferior mandibular border length and maxillary vertical height (Fig 2, *C*; bottom).

Previous studies comparing craniofacial differences between obese and nonobese subjects using conventional cephalometric analyses have found varying results.[22-24] When compared with these studies, only the maxillary length and the gonial angle appeared to match previous findings, being larger in the obese than

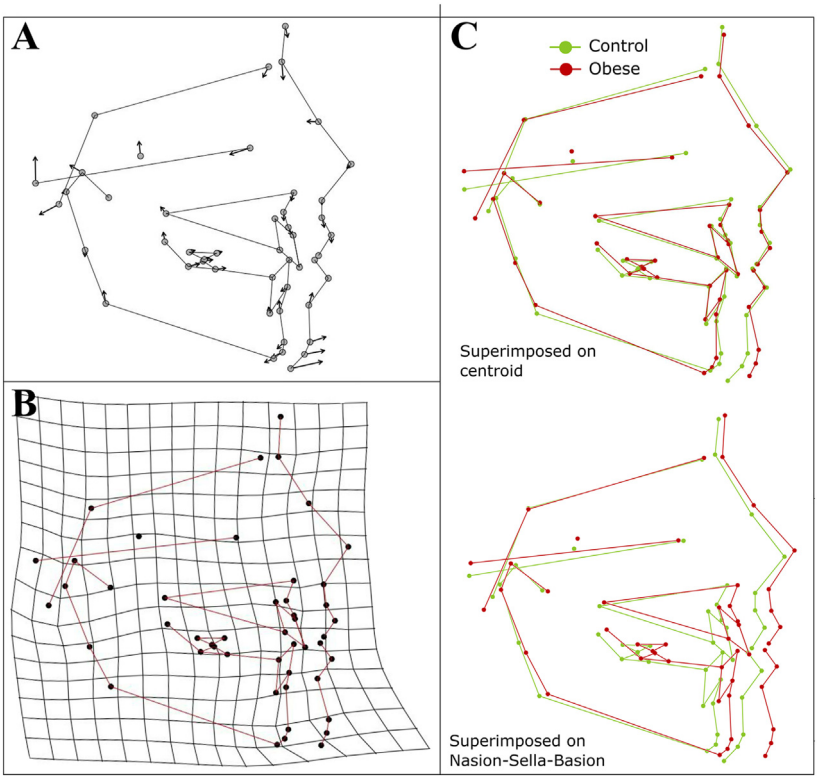


Fig 2. Shape differences between obese and control patients were visualized using the discriminate analysis: **A,** Arrowheads depict the vector displacement of landmarks in the obese cohort compared with controls (*black*) along the linear discriminate axis; **B,** Landmark displacements of obese cohort compared with control, warped onto a thin-plate spline grid depicting the deformation resulting from landmark displacements (*black*) in the obese cohort; **C,** Wireframes depicting the shape variation along the linear discriminate axis superimposed on the centroid (*top*) and nasion-sella-basion points (*bottom*).

control subjects. As discussed, one explanation for these differences is that our study included younger subjects; hence, it is possible that the craniofacial form differences related to BMI found in older patients,[22-24] have not yet manifested and may develop as the patients age through puberty. Indeed, there is strong support for an increased risk of overweight children becoming obese; and for obese children to remain obese as they enter adolescence.[8-10] This may explain the subjective differences in our age groups, in which the overall craniofacial phenotypic changes appear more pronounced in the older vs younger cohorts. A counterclockwise rotation of the mandible, lending to a more brachycephalic form, may occur in obese patients more than in controls as they age. Future, larger-scaled, longitudinal cephalometric and BMI studies will be beneficial for exploring questions about age-related craniofacial form differences related to obesity.

Our finding that the obese cohort has an increased gonial angle (Table II) somewhat conflicts with the GM analysis findings that the obese cohort has a slightly brachycephalic appearance. Indeed, the former is a single angular measurement, which does not hold up when more stringent statistical constraints are applied. In contrast, the descriptive, qualitative output of the GM analysis used all the landmarks in our dataset and was strongly supported by multivariate statistical testing. This discrepancy underscores the complex nature of morphometric analysis and highlights the advantages GM can afford to this line of scientific investigation.[26,31] It should be noted that we did find higher dental maturation scores in patients with higher BMI, suggesting they are further along in dental age than the control group. This is in line with previous findings and validates the cohort selection in our study.[18,20,22]

It remains to be established whether a true causal relationship exists between increased BMI and craniosskeletal form, as opposed to correlations noted in this and previous studies.[22-24] A strong association

between genetics and BMI has been noted in large twin studies, including subjects from infancy to adulthood.[36,37] Genome-wide association studies have identified potential links between several single nucleotide polymorphisms and genetic loci with BMI.[37] At the same time, negative changes in the environment, lifestyle, and socioeconomic conditions have also been identified as determinants of the obesity epidemic,[38,39] whereas animal studies have shown strong epigenetic and environmental influences on BMI.[40,41] Similarly, the development of the craniofacial skeleton has strong genetic, epigenetic, and environmental controls. Hence, the cranioskeletal form differences in obese subjects may be inherited along with the genetic and epigenetic determinants for elevated BMI. This would explain why shape differences can be seen in younger and older subjects.

In contrast, if environmental factors contributing to obesity are responsible for the unique craniofacial phenotype in this group of patients, likely, they are more significantly expressed with continued growth and development, explaining why larger differences are seen in older subjects. For example, Ohrn et al[23] speculated that higher free circulating serum insulin-like growth factor-1 might be responsible for the accelerated craniofacial growth in obese subjects. Hence, consistently high levels of such factors over a prolonged period during growth may be required to fully manifest the craniofacial phenotypes identified in older patients. Many of the single nucleotide polymorphisms identified in Genome Wide Association Studies for BMI occur in regulatory genes.[37] Hence, it is conceivable that obese subjects may have global epigenetic changes which influence multiple system developmental cascades, including those responsible for craniofacial growth. For example, in a DNA-methylation and transcriptome analysis, *HAND2*, a transcription factor important for maxilla/mandible identity,[42] were identified as an obesity-associated gene.[43] Given the strong correlation between metabolism and growth, it is not unexpected that a relationship between BMI and craniofacial form exists. Other environmental factors, such as high-fat diets, may also contribute to increased BMI levels,[40,41] and craniofacial shape differences, indirectly affecting cartilaginous growth centers and/or bone remodeling. In addition, patients in the obese cohort may experience sleep-disordered breathing, which has also been shown to correlate with specific craniofacial phenotypes.[44,45] Carefully planned animal studies can help address some questions about links between epigenetics, environment BMI, and craniofacial form.

The precocious dental and skeletal maturation finding in obese patients has suggested potentially advancing treatment timing when serial extraction, space maintenance, and growth modification are considered part of orthodontic treatments. Future longitudinal studies focusing on orthodontic treatment outcomes in obese patients about the craniofacial form would also be beneficial in supporting such practices. Nevertheless, our findings, combined with previous studies, reinforce the notion that orthodontists should closely record BMI as part of their diagnosis, as it potentially relates to facial growth changes in children.

CONCLUSIONS

1. Young obese patients display craniofacial shape differences compared with matched nonobese controls.
2. Shape differences include a clockwise rotation of the cranial base, a relatively prognathic mandible, and a slight brachycephalic appearance in obese patients compared with controls.
3. Recording BMI as part of the orthodontic records for patients may help in supporting the assessment of craniofacial form.

AUTHOR CREDIT STATEMENT

Siddharth Vora contributed to conceptualization, methodology, data analysis, and original draft preparation; Samuel Tam contributed to data collection, data analysis, and original draft preparation; Motoki Katsube contributed to data analysis and manuscript review and editing; Benjamin Pliska contributed to conceptualization and manuscript review; and Kiran Heda contributed to data analysis.

ACKNOWLEDGMENTS

The authors would like to thank Dr E. Yen for their critical insights and suggestions on the research project.

SUPPLEMENTARY DATA

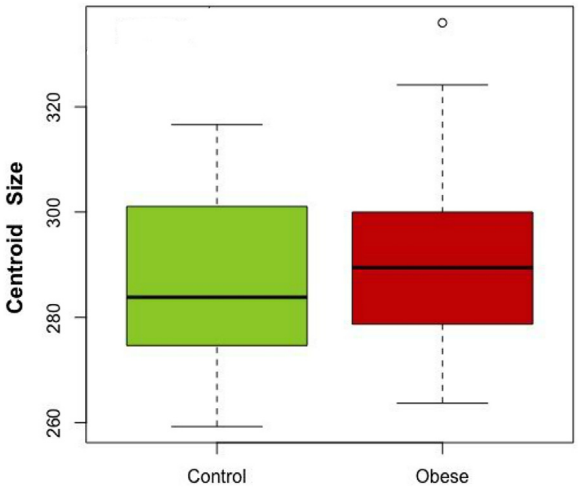
Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ajodo.2021.07.018.

REFERENCES

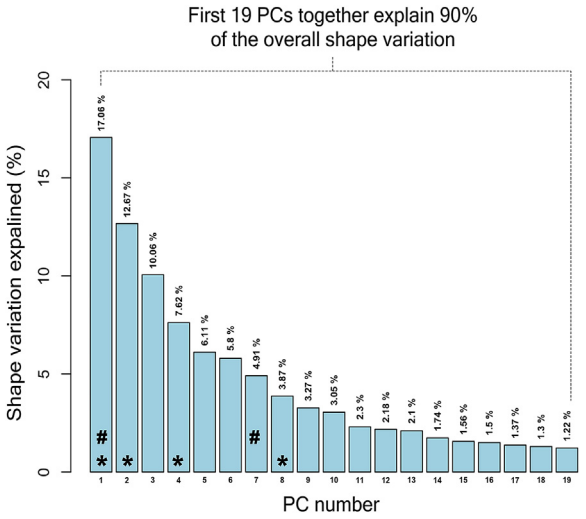
1. Lobstein T, Jackson-Leach R, Moodie ML, Hall KD, Gortmaker SL, Swinburn BA, et al. Child and adolescent obesity: part of a bigger picture. Lancet 2015;385:2510-20.
2. Cunningham SA, Kramer MR, Narayan KM. Incidence of childhood obesity in the United States. N Engl J Med 2014;370:403-11.
3. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity Among adults and youth: United States, 2015-2016. NCHS Data Brief; 2017:1-8.

4. Rao DP, Kropac E, Do MT, Roberts KC, Jayaraman GC. Childhood overweight and obesity trends in Canada. Health Promot Chronic Dis Prev Can 2016;36:194-8.
5. Daniels SR. The consequences of childhood overweight and obesity. Future Child 2006;16:47-67.
6. Caprio S, Santoro N, Weiss R. Childhood obesity and the associated rise in cardiometabolic complications. Nat Metab 2020;2:223-32.
7. Neeley WW 2nd, Gonzales DA. Obesity in adolescence: implications in orthodontic treatment. Am J Orthod Dentofacial Orthop 2007;131:581-8.
8. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. Obes Rev 2016;17:95-107.
9. Geserick M, Vogel M, Gausche R, Lipek T, Spielau U, Keller E, et al. Acceleration of BMI in early childhood and risk of sustained obesity. N Engl J Med 2018;379:1303-12.
10. Reilly JJ, Bonataki M, Leary SD, Wells JC, Davey-Smith G, Emmett P, et al. Progression from childhood overweight to adolescent obesity in a large contemporary cohort. Int J Pediatr Obes 2011;6:e138-43.
11. Behrman RE, Vaughan VC III. Nelson textbook of pediatrics. Philadelphia: WB Saunders Company; 1983.
12. James PT. Obesity: the worldwide epidemic. Clin Dermatol 2004; 22:276-80.
13. Costacurta M, Sicuro L, Di Renzo L, Condò R, De Lorenzo A, Docimo R. Childhood obesity and skeletal-dental maturity. Eur J Paediatr Dent 2012;13:128-32.
14. Baccetti T, Franchi L, McNamara JA. The cervical vertebral maturation (CVM) method for the assessment of optimal treatment timing in dentofacial orthopedics. Semin Orthod 2005;11:119-29.
15. Hilgers KK, Akridge M, Scheetz JP, Kinane DE. Childhood obesity and dental development. Pediatr Dent 2006;28:18-22.
16. Mack KB, Phillips C, Jain N, Koroluk LD. Relationship between body mass index percentile and skeletal maturation and dental development in orthodontic patients. Am J Orthod Dentofacial Orthop 2013;143:228-34.
17. Šindelářová R, Soukup P, Broukal Z. The relationship of obesity to the timing of permanent tooth emergence in Czech children. Acta Odontol Scand 2018;76:220-5.
18. Giuca MR, Pasini M, Tecco S, Marchetti E, Giannotti L, Marzo G. Skeletal maturation in obese patients. Am J Orthod Dentofacial Orthop 2012;142:774-9.
19. Hedayati Z, Khalafinejad F. Relationship between body mass index, skeletal maturation and dental development in 6- to 15- year old orthodontic patients in a sample of Iranian Population. J Dent (Shiraz) 2014;15:180-6.
20. DuPlessis EA, Araujo EA, Behrents RG, Kim KB. Relationship between body mass and dental and skeletal development in children and adolescents. Am J Orthod Dentofacial Orthop 2016;150: 268-73.
21. Ferrario VF, Dellavia C, Tartaglia GM, Turci M, Sforza C. Soft tissue facial morphology in obese adolescents: a three-dimensional noninvasive assessment. Angle Orthod 2004;74:37-42.
22. Sadeghianrizi A, Forsberg CM, Marcus C, Dahllöf G. Craniofacial development in obese adolescents. Eur J Orthod 2005;27:550-5.
23. Ohrn K, Al-Kahlili B, Huggare J, Forsberg CM, Marcus C, Dahllöf G. Craniofacial morphology in obese adolescents. Acta Odontol Scand 2002;60:193-7.
24. Giuca MR, Giannotti L, Saggese R, Vanni A, Pasini M. Evaluation of cephalometric, hormonal and enzymatic parameters in young obese subjects. Eur J Paediatr Dent 2013;14:175-80.
25. Windhager S, Patocka K, Schaefer K. Body fat and facial shape are correlated in female adolescents. Am J Hum Biol 2013;25:847-50.
26. Bookstein FL. Reconsidering "The inappropriateness of conventional cephalometrics." Am J Orthod Dentofacial Orthop 2016; 149:784-97.
27. Cleall JF, BeGole EA, Chebib FS. Craniofacial morphology: a principal component analysis. Am J Orthod 1979;75:650-66.
28. Richtsmeier JT, Paik CH, Elfert PC, Cole TM 3rd, Dahlman HR. Precision, repeatability, and validation of the localization of cranial landmarks using computed tomography scans. Cleft Palate Craniofac J 1995;32:217-27.
29. Klingenberg CP. Size, shape, and form: concepts of allometry in geometric morphometrics. Dev Genes Evol 2016;226:113-37.
30. Demirjian A, Goldstein H, Tanner JM. A new system of dental age assessment. Hum Biol 1973;45:211-27.
31. Moyers RE, Bookstein FL. The inappropriateness of conventional cephalometrics. Am J Orthod 1979;75:599-617.
32. Halazonetis DJ. Morphometrics for cephalometric diagnosis. Am J Orthod Dentofacial Orthop 2004;125:571-81.
33. Corti M. Geometric morphometrics: an extension of the revolution. Trends Ecol Evol 1993;8:302-3.
34. Bilfeld MF, Dedouit F, Sans N, Rousseau H, Rougé D, Telmon N. Ontogeny of size and shape sexual dimorphism in the ilium: a multislice computed tomography study by geometric morphometry. J Forensic Sci 2013;58:303-10.
35. Roussos P, Mitsea A, Halazonetis D, Sifakakis I. Craniofacial shape in patients with beta thalassaemia: a geometric morphometric analysis. Sci Rep 2021;11:1686.
36. Silventoinen K, Jelenkovic A, Sund R, Hur YM, Yokoyama Y, Honda C, et al. Genetic and environmental effects on body mass index from infancy to the onset of adulthood: an individual-based pooled analysis of 45 twin cohorts participating in the COllaborative project of Development of Anthropometrical measures in Twins (CODATwins) study. Am J Clin Nutr 2016;104:371-9.
37. Silventoinen K, Jelenkovic A, Sund R, Yokoyama Y, Hur YM, Cozen W, et al. Differences in genetic and environmental variation in adult BMI by sex, age, time period, and region: an individual-based pooled analysis of 40 twin cohorts. Am J Clin Nutr 2017;106:457-66.
38. Silventoinen K, Jelenkovic A, Latvala A, Yokoyama Y, Sund R, Sugawara M, et al. Parental education and genetics of BMI from infancy to old age: A pooled analysis of 29 twin cohorts. Obesity (Silver Spring) 2019;27:855-65.
39. Rohde K, Keller M, la Cour Poulsen L, Blüher M, Kovacs P, Böttcher Y. Genetics and epigenetics in obesity. Metabolism 2019;92:37-50.
40. Widiker S, Karst S, Wagener A, Brockmann GA. High-fat diet leads to a decreased methylation of the Mc4r gene in the obese BFMI and the lean B6 mouse lines. J Appl Genet 2010;51:193-7.
41. Milagro FI, Campión J, García-Díaz DF, Goyenechea E, Paternain L, Martínez JA. High fat diet-induced obesity modifies the methylation pattern of leptin promoter in rats. J Physiol Biochem 2009;65:1-9.
42. Funato N, Kokubo H, Nakamura M, Yanagisawa H, Saga Y. Specification of jaw identity by the *Hand2* transcription factor. Sci Rep 2016;6:28405.
43. Keller M, Hopp L, Liu X, Wohland T, Rohde K, Cancello R, et al. Genome-wide DNA promoter methylation and transcriptome analysis in human adipose tissue unravels novel candidate genes for obesity. Mol Metab 2017;6:86-100.
44. An HJ, Baek SH, Kim SW, Kim SJ, Park YG. Clustering-based characterization of clinical phenotypes in obstructive sleep apnoea using severity, obesity, and craniofacial pattern. Eur J Orthod 2020;42:93-100.
45. Ito D, Akashiba T, Yamamoto H, Kosaka N, Horie T. Craniofacial abnormalities in Japanese patients with severe obstructive sleep apnoea syndrome. Respirology 2001;6:157-61.

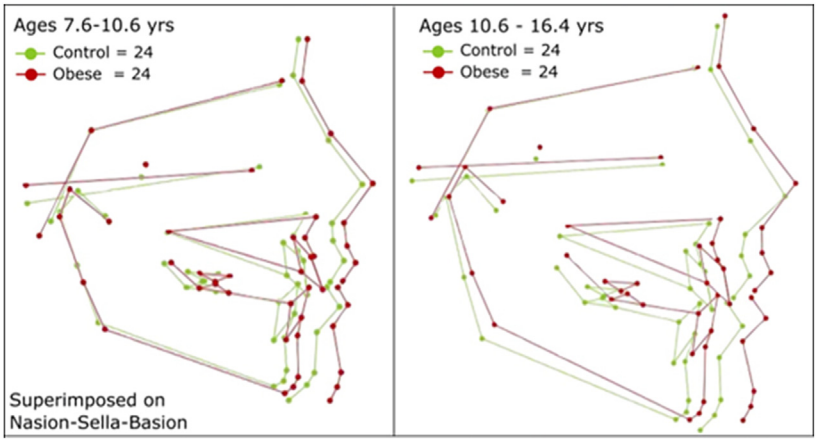
SUPPLEMENTARY DATA



Supplementary Fig 1. Box plots depicting centroid sizes of the control (*green*) and obese (*red*) cohorts.



Supplementary Fig 2. The plot depicts the percentage of shape variation (y-axis, number above each bar) explained by PCs 1-19 (x-axis). Cumulatively, the first 4 PCs explain ∼50% of the overall shape variation, whereas the first 19 PCs explain 90% of the overall shape variation. The remaining PCs explain <1% of the shape variation each and are not shown here. *PCs in which shape distribution correlated significantly with the patient's BMI; #PCs in which shape distribution correlated significantly with Angle's classification.



Supplementary Fig 3. Shape differences between obese and control patients were split into 2 age groups and visualized using the discriminate analysis. Wireframes depicting the shape variation along the linear discriminate axis superimposed on the sella-basion points for the younger patients (*left*) and older patients (*right*) in our cohorts.

Supplementary Table I. Landmarks and measurement errors

	Measurement error, mm	
Landmark	*Average*	*Standard deviation*
Nasion	0.061	0.105
Orbitale	0.069	0.114
Posterior nasal spine	0.043	0.034
Prosthion	0.096	0.105
Pterygomaxillary point	0.106	0.125
Anterior nasal spine	0.041	0.041
A-Point	0.091	0.078
Porion	0.170	0.317
Basion	0.104	0.067
Sella	0.032	0.023
Articulare	0.301	0.428
B-Point	0.240	0.255
Pogonion	0.093	0.100
Gnathion	0.061	0.051
Menton	0.057	0.030
Gonion	0.161	0.178
Condylion	0.168	0.139
Sigmoid notch	0.114	0.089
Ramus point	0.361	0.348
Midramus point	0.236	0.244
Mandibular incisor gingival border (labial)	0.076	0.066
Mandibular incisor gingival border (lingual)	0.032	0.027
Mandibular incisor root apex	0.054	0.065
Mandibular incisor incisal tip	0.031	0.017
Maxillary incisor gingival border (labial)	0.131	0.143
Maxillary incisor gingival border (lingual)	0.045	0.049
Maxillary incisor root apex	0.070	0.117
Maxillary incisor incisal tip	0.038	0.023
Mesial surface of mandibular first molar	0.104	0.121
Mesial surface of the maxillary first molar	0.102	0.049
The maxillary first molar occlusal surface	0.082	0.095
The distal surface of the mandibular first molar	0.124	0.125
The distal surface of the maxillary first molar	0.107	0.119
Mandibular first molar occlusal surface	0.099	0.131

Supplementary Table II. Comparison of obese and control cohorts in age and dental maturity

Variables	*Obese*	*Control mean*	*Difference*	*P value (t test)*
Chronological age, y	11.19 ± 2.50	11.28 ± 2.36	0.09	0.8957
Dental maturity score	90.71 ± 6.07	85.06 ± 6.52	5.65	0.0048

Note. Presented values are mean ± standard deviation.

Supplementary Table III. CVM stage assessments

CVM stage	*1*	*2*	*3*	*4*	*5*	*6*	*Median*
Obese (n = 24)	7 (29)	5 (21)	7 (29)	2 (8)	3 (13)	0 (0)	2.5 (2-3)
		19 (79)			5 (21)		
Control (n = 24)	6 (25)	4 (17)	7 (29)	4 (17)	1 (4)	2 (8)	3
		17 (71)			7 (29)		

Note. Presented values are n (%).