CRANIOFACIAL DIFFERENCES BETWEEN OBESE AND NON-OBESE ORTHODONTIC PATIENTS

by

Samuel P. Tam

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, the dissertation entitled:

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submitted by Samuel Tam in partial fulfillment of the requirements for

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in Craniofacial Science

Examining Committee:

Dr. Siddharth Vora, Faculty of Dentistry
Supervisor

Dr. Benjamin Pliska, Faculty of Dentistry
Supervisory Committee Member

Dr. Edwin Yen, Faculty of Dentistry
Supervisory Committee Member

Dr. Fernanda Almeida, Faculty of Dentistry
Additional Examiner

Dr. Flavia Lakschevitz, Faculty of Dentistry
Additional Examiner

Abstract

Introduction: Although childhood obesity has recently seen a plateau in the USA and Canada, it still effects 10-20% of children and adolescents. Increasing evidence points to obesity contributing to changes in growth and development, puberty, bone metabolism and tooth movement. For this study, we compared craniofacial differences in obese and non-obese orthodontic patients between the ages of 7-16 years old, focusing on a younger age cohort than studied previously.

Objectives: To evaluate the craniofacial form of obese and non-obese adolescent patients using 2D cephalometric data and geometric morphometric approaches.

Methods: Height, weight, age, and lateral cephalometric radiographs were gathered from patients aged 7-16, before beginning orthodontic treatment at the University of British Columbia (UBC). A group of 24 obese patients were age, sex and Angle-classification of malocclusion matched, with non-obese controls. Cephalometric radiographs were annotated, and coordinates of landmarks used to obtain traditional linear and angular measurements. Additionally, geometric morphometric (GM) analyses was performed to determine overall craniofacial form. Dental maturation index scores were assessed from panoramic films using the Demerijian method and cervical vertebral maturation (CVM) scores were recorded from the cephalograms, as an indicator for skeletal maturation.

Results: Our conventional cephalometric analysis revealed that the maxillary length and gonial angle are larger in obese individuals (p=0.041 and p=0.028 respectively). GM analyses confirmed that the overall craniofacial form of obese patients differs statistically from the form of control patients and also reveal that obese patients present with a more dolichocephalic facial type. Dental maturation index scores were statistically higher in the obese group compared to the control group with no statistical difference in CVM scores.

Conclusions: Our data reveals a subtle but significant difference in cranial skeletal morphology between obese and non-obese adolescent patients, suggesting a correlation between dental maturation, craniofacial form and physiologic/metabolic phenotypes of individuals. Body Mass Index should be included as part of the orthodontic assessment to aid in appropriate diagnosis of the underlying craniofacial form.

Lay Summary

Childhood obesity in the US and Canada effects 10-20% of children and adolescents with evidence pointing to obesity contributing to changes in growth and development, puberty, bone metabolism and tooth movement. This study evaluated differences in facial skeletal morphology, in adolescent obese orthodontic patients compared to normal weight patients. Through various analyses, this study found a larger upper jaw length and more vertical angulated lower jaw in the obese group compared to non-obese individuals. Additionally, this study found accelerated tooth development and tooth eruption in the obese individuals. These findings support the need to include height and weight measurements to monitor for childhood obesity as part of a normal orthodontic assessment and record keeping. This will aid in appropriate diagnosis and ultimately aid in efficient orthodontic treatment planning decisions.

Preface

The research topic of this project was developed by Dr. Sid Vora and Dr. Benjamin Pliska with the intention of this study to compare differences of craniofacial form between obese and non-obese orthodontic patients.

The data was collected by Samuel Tam, with conventional morphometric analysis done by Samuel Tam and geometric morphometric analysis done by Dr. Motoki Katsube at the Kyoto University, Kyoto Japan. Statistical analysis was completed with the guidance of Dr. Sid Vora. Samuel Tam prepared the manuscript with content editing by Dr. Sid Vora, Dr. Benjamin Pliska and Dr. Edwin Yen.

This research was approved by the Research Ethics Board at the University of British Columbia, ethics certificate number H17-03043.

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List of Abbreviations

BMI: Body mass index

CDC: Center of Disease Control

CVM: Cervical vertebral maturation

CVMS: Cervical vertebral maturation stage

DMI: Dental maturation index

DFA: Discriminant function analysis

GMA: Geometric morphometric analysis

GPA: Generalized procrustes analysis

Pm: Pterygomaxillary fissure

NHANES: National Health and Nutrition Examination Survey

LDA: Linear discriminant analysis

PCA: Principle component analysis

PNS: Posterior nasal spine

Std Dev: Standard deviation

UBC: University of British Columbia

USA: United States of America

Acknowledgements

I would like to express my sincerest gratitude to Dr. Sid Vora who has served as my research supervisor and has guided and advised me during my orthodontic program from both a clinical and research perspective.

I would also like to acknowledge all the advice and encouragement from my research committee members Dr. Benjamin Pliska and Dr. Edwin Yen in helping me complete and providing me with direction throughout this research project. I could not have completed this research project without the help of Mary Wong who helped provide with the orthodontic records as well as the past UBC orthodontic residents and staff who had recorded heights and weights of patients when they had obtained the records. I would also like to acknowledge Dr. Kiran Heda who helped in obtaining the dental maturation scores from panoramic radiographs.

Dedication

This thesis is dedicated to the multiple people who have supported and helped me throughout my life not only in my professional but personal development; namely Dr. Sid Vora for serving as my supervisor throughout this research project as well as my wife Allison and my parents Timothy and Remedios and siblings Esther and Isaac for their advice and tireless support and sacrifice throughout the years.

Chapter 1: Introduction

Obesity has proven to be a major medical and public healthcare problem in the USA and Canada, leading to the development of such co-morbidities like coronary heart disease, congestive heart failure, type II diabetes mellitus, high blood pressure, obstructive sleep apnea, osteoarthritis, and cancer (ex. stomach, breast, prostate, ovarian) just to name a few (Friedman & Fanning, 2004). According to the National Health and Nutrition Examination Survey (NHANES), the prevalence of obesity in the United States for children and adolescents (aged 2-19 years) in 2016 was 18.5% of the total population (Hales, Carroll, Fryar, & Ogden, 2017). The number and prevalence of obese children and adolescent individuals steadily increased from the 14% in the year 2000 to 18.5% in 2016 (Hales et al., 2017). In Canada, the prevalence of obesity amongst children and adolescents aged 5-19 years old is 13% with 1 in 7 children being obese (Rao, Kropac, Do, Roberts, & Jayaraman, 2016).

In the medical community, obesity is defined as the accumulation of fatty tissue to such a level that the overall health is adversely affected (Kopelman, 2000; Rao et al., 2016). There is a difference between how obesity in adults (over 20 years old) and children and adolescents (2-19 years old) is calculated. In adults, body mass index (BMI) is calculated as weight in kilograms (kg) divided by height in meters squares (m^2) with obesity being a BMI of greater or equal to 30. In children and adolescents, obesity is defined as a BMI greater or equal to the 95th percentile for age and sex specific Center of Disease Control (CDC) growth charts (Hales et al., 2017).

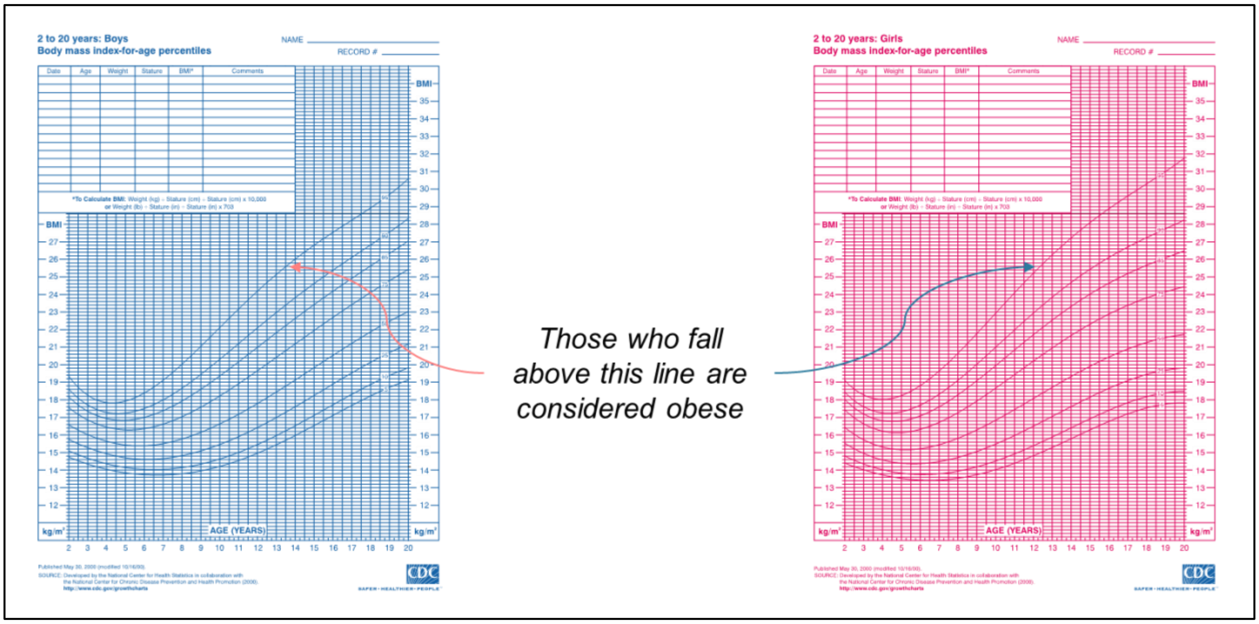


Figure 1.1 Male and female CDC growth charts indicating percentile cutoff lines for overweight and obese categories.

When examining the risks and etiology of childhood obesity, previous literature points out the obvious risk factors such as increased hours of television and video games, increased consumption of low nutrition and high caloric fatty foods and increased consumption of sugary drinks with high fructose corn syrup. Also highlighted are numerous genes which play a role in obesity including Melanocortin-4 receptor (Behrman & Vaughan, 1983), Leptin, Adiponectin (Costacurta et al., 2012) and Insulin-like growth factor 1 (IGF-1) (Neeley & Gonzales, 2007). Other risk factors include maternal gestational diabetes, parental obesity, low socioeconomic status, low education levels and ethnicity (African American, Hispanic children in the USA and First Nation aboriginals in Canada) (Behrman & Vaughan, 1983; Hales et al., 2017; James, 2004; Rao et al., 2016).

1.1 Relevance of obesity to orthodontics

When looking into the past literature of obesity and its effects on orthodontic treatment, Neely and Gonzales found relevant issues such as hormonal changes causing precocious pubertal development (i.e. high BMI corelates with an early onset in menarche). Additionally, they found changes in bone metabolism and tooth movement, where children with increased BMI have increased bone density and size. They also described differences in growth and development with obese children having accelerated skeletal growth. In addition, they identified psychological issues in patients with increased BMI, showing signs of social isolation, poor self-esteem and body image leading to a higher propensity to develop eating disorders, poor compliance due to a defense mechanism to downplay overall appearance, or the opposite where the obese individual develops a hyper-realization of their appearance leading to unrealistic expectations (Neeley & Gonzales, 2007).

1.2 Obesity and its effects on growth, skeletal and dental maturation

When we examine obesity and its effect on growth, skeletal and dental maturation, the previous literature provides convincing evidence on a meaningful link. Hilgers et. al looked at dental age in comparison to chronologic age for normal, overweight and obese youth (8-15 yrs) based on BMI. They included 23 overweight (65% female, 35% male) and 18 (44% female, 56% male) obese children. Sex specific tooth eruption tables and scoring panoramic radiographs using the Demirjian method (Demirjian, Goldstein, & Tanner, 1973), they found an accelerated dental development in children with higher BMI's after controlling for age and gender. The author thus suggested overweight and obese children should have earlier orthodontic consultations, along with potential alterations of serial extraction timing, space maintenance and growth modification (Hilgers, Akridge, Scheetz, & Kinane, 2006).

Costacurta et. al evaluated the cervical vertebral maturation index (CVM) (Baccetti, Franchi, & McNamara, 2005; Rainey, Burnside, & Harrison, 2016) and dental maturation index (Demirjian et al., 1973) as well as Dual Energy X-ray Absorptiometry (DXA) for assessing bone mineralization in overweight and obese children (Mean age = 9yrs , range 6-12 yrs, n = 107 patients, F = 53%, M = 47%). The authors found that with an increase in weight from normal to obese, there was an increase in dental and skeletal maturation. Obese children were found to be 17 months ahead of their normal weight peers using these indices, with respect to chronological age. The author also found higher bone mineralization with increased BMI (Costacurta et al., 2012). In a study by Giuca et. al comparing 25 obese and non-obese patients (F = 44%, M = 56%, mean age = 10 yrs, range = 7-12 yrs), carpal assessment of hand-wrist radiographs (Fishman, 1982) and CVM staging (Baccetti et al., 2005) revealed that the obese group had precocious skeletal maturation. Once again, skeletal age is ahead (by ~12 months) compared to chronological age, encouraging earlier orthodontic examinations in obese individuals (Giuca et al., 2012). Similarly, Mack et. al analyzed the relationship between BMI and skeletal and dental maturity in 540 adolescents (F = 56%, M = 44%, average age = 13 yrs, range 8-17 yrs). Overweight and obese patients had more advanced dental and skeletal maturation with increasing BMI percentiles compared to the normal weight group, encouraging the inclusion of weight status in the orthodontic evaluation for growing children. (Mack, Phillips, Jain, & Koroluk, 2013)

Hedayati and Khalafinejad also investigated whether increased BMI is associated with accelerated skeletal maturation (Baccetti et al., 2005) and dental maturation (Demirjian et al.,

1973) in children with age range from 6-15 years old, (n = 95, F = 68%, M = 32%, ~18 overweight or obese individuals). The authors found that overweight and obese children were 1.8 years ahead in dental age compared to the normal weight subjects with no statistically significant difference in skeletal maturation. Furthermore a dental age formula was proposed by the authors for prediction based on BMI and chronologic age with Dental age = (1.06)(chronologic age) + (.017)(BMI %) (Hedayati & Khalafinejad, 2014). Duplessis et. al also examined if correlations exist between BMI, skeletal age, and dental age (n = 197, F = 58%, M = 42%, mean age = 11 yrs, range = 7-14 yrs). They found that as BMI increased by 1%, the dental age increased by approximately 3 days, a difference that can be clinically significant for children at the extremes. In addition to this, the author found the higher the BMI the higher the CVM stage. This study also found that when race stratification was analyzed, both Hispanic and African American populations had a higher BMI than Caucasians, showing accelerated dental development in the African American and Hispanic groups when compared to Caucasians (DuPlessis, Araujo, Behrents, & Kim, 2016).

Sindelarova et. al examined tooth emergence patterns (defined as tooth penetrated through the gingiva) in overweight and obese youth aged 4- 15 years, compared to a normal weight control group in a Czech Republic population. Using population specific BMI tables to determine weight status (n = 271 overweight and obese subjects, F = 48%, M = 52%), a statistically significant difference was found with respect to the accelerated eruption of permanent teeth compared to the normal weight control group. The study supported the finding that obese children had 1.4 more teeth erupted compared to their normal weight group. The authors also stressed that clinically, the importance of this early dental eruption finding due to obesity leads to increased risk of decay of permanent teeth due to their longer period of time in the mouth combined with an increased difficulty of treatment from childhood dental anxiety, as well as earlier timing and diagnosis for treatment of malocclusions (Sindelarova, Soukup, & Broukal, 2018).

1.3 Obesity and craniofacial shape via 2 dimensional and 3 dimensional analysis

There is limited literature with regard to obesity and craniofacial shape. Ferrario et. al analyzed the 3 dimensional anthropometric characteristics via a digital face recorder in 25 obese subjects (F=56%, M=44%, mean age = 15.4 yrs, range = 13-17 yrs) of Caucasian northern Italian descent, matched with normal weight controls. It was found that obese females had larger skull base widths and a longer mandibular corpus length. Obese adolescent males had smaller mouths in the transverse dimension and a smaller upper face height (soft tissue Nasion to Subnasale). The authors concluded that obese adolescents were found to be wider in the transverse dimension, longer in the sagittal dimension and shorter in the vertical dimension or more brachycephalic facial types compared to their normal weight adolescent counterparts (Ferrario, Dellavia, Tartaglia, Turci, & Sforza, 2004).

In a study by Windhager et. al looking into facial shape dimensions of 22 female adolescents (mean age = 16 yrs, range = 10-20 yrs) using a body fat scale, the body fat percentage was determined with 5 subjects being under weight, 14 subjects normal weight, 2 subjects overweight and 1 subject obese. The authors used facial photographs with 72 landmarks placed and subsequent GM analysis and Procrustes superimposition finding that the females with overweight and obese body fat percentages had a larger lower face in the transverse dimension, shorter and wider noses, and fuller lips with downturned corners of the mouth (Windhager, Patocka, & Schaefer, 2013).

Orhn et. al compared a sample of 39 obese and 39 non-obese adolescents (F = 64%, M = 36% male, mean age F = 15.7 yrs, mean age M = 14.6 yrs) of Swedish ethnicity in measurements from lateral Cephalometric radiographs. The authors found that obese adolescents have a larger mandibular length (Condylion-Pogonion), more maxillomandibular prognathism and longer anterior cranial base (Sella-Nasion). Obese females were found to have a smaller upper anterior face height and a low mandibular plane angle (Figure 1.2). The authors speculate that in the obese group there may be higher free circulating serum insulin like growth factor-1 (IGF-1) which is possibly responsible for the increased craniofacial growth (Ohrn et al., 2002).

Sadeghianrizi et. al compared the craniofacial morphology of 50 obese adolescents (F = 54%, M = 46%, mean age 15.6 yrs) matched for age and sex to a control group. The authors found that the obese adolescent group had a larger anterior cranial base (Sella-Nasion), mandibular length (Condylion-Pogonion), corpus length (Gonion-Pogonion), maxillary length (PNS-A point), and mandibular prognathism (described as SNA, SNB, Sella-Nasion-Pogonion, which also contributed to more straight profiles) and maxillary dentoalveolar height (ANS-Prosthion). The obese adolescents also had a smaller lower anterior (ANS-Gnathion) and posterior (Sella-Gonion) face height, and mandibular plane angle (Gonion-Gnathion to Sella-Nasion). The authors also emphasized that obese female adolescents had greater upper and lower incisor proclination (UI-SN) and (LI-MP) and mandibular prognathism (Gonion-Gnathion to Nasion-Pogonion) (Figure 1.2). In general, obese adolescents were found to have larger facial dimensions compared to the normal control growth study group (Sadeghianrizi, Forsberg, Marcus, & Dahllof, 2005).

In another study by Giuca et. al, the authors looked at conventional lateral cephalometric analysis and enzyme parameters in the blood of obese adolescents. The BMI was determined by calculation of height (m)/weight (kg)^2 with the control and obese groups (n = 25 each) age and sex matched. With a group of 50 Caucasian (F = 44%, M = 56%, mean age = 10 yrs) patients, the authors found a larger anterior cranial base (Sella-Nasion), longer Maxillary length (Pterygomaxillary fissure-A Point), and shorter inter-maxillary angle (Maxillary plane to mandibular plane angle) supporting a more brachycephalic facial type (Figure 1.2). There was also found to be reduced levels of follicle stimulating hormone (FSH), Luteinizing hormone (LH), and Insulin growth factor-1 (IGF-1) and increased levels of Leptin and Insulin (Giuca, Giannotti, Saggese, Vanni, & Pasini, 2013).

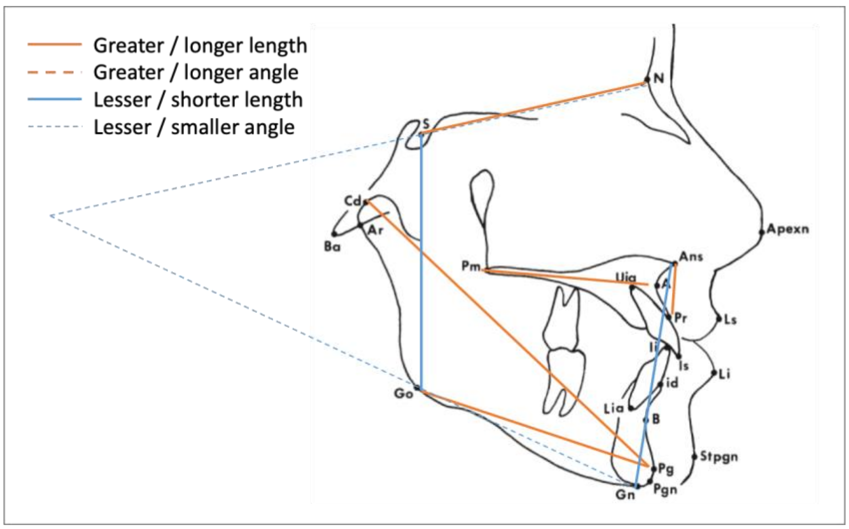


Figure 1.2 Example of cephalometric analysis and findings from Giuca et al. (2013), Sadeghianrizi et al. (2005), Orhn et al. (2002)

1.4 Medical trends seen with overweight and obese children and adolescents

When evaluating overweight children and adolescents' risk of continuing that trend into the adulthood, there is strong support for a high risk for progression. Hesketh et. al examined the prevalence and incidence of overweight and obesity rates using BMI in 1569 Australian children aged 5-10 years old with follow-up measurements taken 3 years later. The authors found that

68% of children moved to a higher BMI category (from non-overweight to overweight and overweight to obese) showing a larger progression and trend from overweight and obese BMI's than to lower BMI's, supporting that the majority of children carry and worsen their weight problems from childhood to adolescence (Hesketh, Wake, Waters, Carlin, & Crawford, 2004).

Nader et. al also looked at the predictive value of BMI status on the future risk of overweight and obesity during childhood and adolescent years. The study was conducted out of 10 hospitals in the USA looking at full records of 910 subjects with data collected for 13 years (from 24 months to 12 years old), including 31 subjects classified as overweight (F = 55%, M = 45%) and 36 obese (F = 42%, M = 58%). Overall, the authors found an increasing likelihood for children with higher weights (≥50th percentile in weight) to become overweight and obese. For example, children in preschool who were overweight were >5X more likely to be overweight at age 12 and 40% of children whose BMI's were ≥50th percentile by 3 years of age were overweight by the time they were 12 years old. From the results, the authors recommend that medical intervention is needed any time a child reaches the 85th percentile being in the overweight status for BMI (Nader et al., 2006).

In a study by Reilly et. al, authors looked into quantifying the progression of overweight to obesity. The study had a sample size of 459 children (F = 55%, M = 45%) who were overweight at 7 years old and followed their weight trend 6 years later when they were 13 years old, and found that 38% of boys (78 boys) and 30% (74 girls) of girls progressed from overweight to obesity. The author also mentioned that risk of obesity for overweight children was 18-20x higher than children at a healthy weight, clearly showing that overweight children have a high risk of developing into obese adolescents. This emphasizes the value of monitoring weight status in children that are overweight (Reilly et al., 2011).

In a study conducted by Cunningham et. al, the authors reported the incidence and prevalence of obesity according to data from a large nationally representative longitudinal study of children in the USA. The data was collected by the Department of Education's National Center for Education Statistics following 9358 children from Kindergarten to the end of 8th grade, and collecting their measurements at 7 time points from 1998-2007. The authors reported that the prevalence of obesity increased with age and the incidence of obesity was highest at the youngest ages. The incidence of obesity was 45.3% for children entering Kindergarten overweight. Incidence for obesity was 10X higher for children entering Kindergarten overweight compared to children entering Kindergarten at normal weight. Overweight Kindergartners had 4X the risk of becoming obese compared to normal weight Kindergarteners. For overweight 5 year olds, the probability to become obese increased to 25% at the 85th percentile and 47% at the 95th percentile compared to 6% at the 50th percentile. The authors also reported that 50% or half of childhood obesity occurred among children who became overweight during preschool. Thus, there is evidence that higher body weight at an early age is strongly linked to obesity, and that obesity incidence occurred at higher rates at younger ages from 5-10 years of age. The authors recommended that targeting overweight children by the age 5 can help children most susceptible to becoming obese (Cunningham, Kramer, & Narayan, 2014).

In a systematic review and meta-analysis by Simmonds et. al, the authors examined whether childhood and adolescent obesity and overweight classifications are predictive of obesity and overweight classification into adulthood. The author selected studies that were longitudinal cohort studies with at least 1000 subjects with obesity measurements followed from childhood (age 7-12 years old) and its association with obesity into adolescence (aged 12-18 years old) and then on to adulthood (aged 20 years and older). In all of the 15 studies selected, BMI was classified as overweight if BMI ≥85th percentile but less than the 95th percentile and obese if BMI ≥95th percentile. The authors found that there is a strong association between childhood and adolescent obesity with a strong progression into adulthood. The author also stated that childhood overweight and obesity is a reasonable predictor of adolescent obesity in that 90% of obese adolescents were previously overweight or obese during childhood (Simmonds, Llewellyn, Owen, & Woolacott, 2016).

In a longitudinal population-based study by Gererick et. Al, the authors followed 51,505 patients analyzing BMI trends at 1-year interval time points from birth to 18 years old. The authors found that the most rapid acceleration in BMI occurred between ages 2-6 years old, supporting that early childhood is a critical age for the development of sustained overweight and obese individuals throughout life. Additionally, children who were large for their gestational age and whose mothers were obese had a high risk of obesity and just under 90% of children who were obese as early as 3 years old were overweight and obese into adolescence (Geserick et al., 2018).

1.5 Problems with 2D Cephalometric Analysis and Strength of Geometric Morphometric Craniofacial Analysis

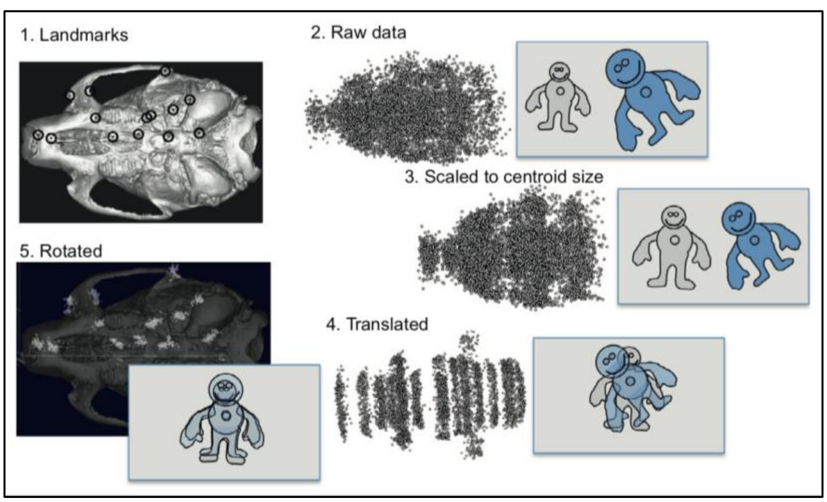
There have been critiques of two dimensional cephalometic analysis pointed out by Moyers and Bookstein et. al based on the very foundation of Cephalography, which is that its landmarks are found either within bony structures of the skull (ex. Sella, constructed Gonion) or in historically established and accepted curves of the skull that do not actually exist (ex. Orbitale, Pterygomaxillary fissure). (Bookstein, 2016; Moyers & Bookstein, 1979) With this fundamental issue, it is of interest to note within the 45 landmarks noted in the “Atlas of Craniofacial growth”

(Riolo, 1974) only 7 points are technically craniometrically valid, bringing forth the problem of human artifact in this analysis. (Bookstein, 2016) As such, cephalometrics historically has proved to be a somewhat subjective method of determining craniofacial form (along with its subtle differences) through linear and angular measurements which are dependent on landmarks with inconsistent craniofacial structural superimpositions while introducing human artifact as opposed to an unbiased, statistical and mathematical approach for craniofacial form analysis. However, there has been limited motivation for the clinician to move away from traditional cephalometric analysis due to a lack of or limited direct effect of alternative methods with regard to their diagnosis, treatment modality and treatment assessments. (Bookstein, 2016; Moyers & Bookstein, 1979)

With the goal of analyzing general and specific differences and similarities in craniofacial form, geometric morphometrics (GM) serves as an alternative to 2D cephalometric analysis. Halgrimmsson et. al defined GM as the mathematical analysis of *form* : the combination of size and shape. Shape in GM analysis is the geometry of the craniofacial complex with cephalograms standardized for size. In the analysis of the craniofacial shapes of different individuals, a map or morphospace (with X and Y axes of measurable units) is used to quantitatively compare craniofacial shape between subjects. Relative positions and distances of landmarks which have similar phenotypes cluster in the morphospace, while those that are different tend to be farther apart. Therefore the superimposition of landmark coordinate data, places individuals in their corresponding morphospace. (Hallgrimsson et al., 2015)

The most common used form for superimposition in GM is a Generalized Procrustes Analysis (GPA) which places individuals into their respective morphospace by scaling, translating and rotating the landmark coordinates (Figure 1.3). First, GPA uses a mathematical centroid (center point of the object based on the raw landmarks), then undergoes translation of the objects to share a common centroid, followed by scaling of the objects to the same centroid size. The final superimposition step is performed by the iterative rotation of the 2 objects/specimens so as to minimize the sum of squared distances between landmark configurations, creating Procrustes shape coordinates. (P. Mitteroecker & Gunz, 2009). This step is performed with each additional object/specimen. The advantages as cited by Hallgrimsson et. al for GM analyses include the ability to mathematically and visually represent variation within individuals and between groups (ie. obese and control groups) due to differences in displacements of the same landmarks and amongst different landmarks with consistency in size and stringency in shape. (Hallgrimsson et al., 2015)

Figure 1.3 The 5 Steps of Procrustes Superimposition (Hallgrimsson et al., 2015)



Within the umbrella of GM analysis are additional methods to mathematically calculate and represent variation between samples such as principal component analysis (PCA) and linear discriminant analysis (LDA). LDA allows for ease of interpretation of group memberships, by using a mathematically determined plane or line used as a boundary to discriminate and allocate subjects into a given group. Therefore as subjects fall on a particular side of the discriminant line they are allocated to a specific group (McLachlan, 2004). More specifically our study analyzes morphometric data of obese and non-obese groups in order to provide an additional method of classification and visual representation of shape difference based on morphometric measurements (McLachlan, 2004; Philipp Mitteroecker & Bookstein, 2011)

Another commonly employed analytical method is principal component analysis (PCA). At its core, PCA is used to produce an additional and simplified representation to visualize and measure variation within a sample (in our case identifying which variables contribute most to shape variation) (Parsons et al., 2011; Zelditch, Swiderski, Sheets, & Fink, 2004). PCA is carried out by replacing variables with mathematically calculated new values called principal components. It is within these principal components or newly calculated values (eigenvalues) that we can give order to the variables as well as a visual representation of the variables' values along an X and Y axis to determine if there are patterns seen within these variables. PCA's value also lies in its ability to identify which variable(s) or principal component(s) (PC's) out of a myriad of PC's contributes most to variation in the sample. (Hallgrimsson et al., 2015; Zelditch et al., 2004) This value is intertwined in the benefits of PCA, which is a simplified method of representing the majority of variation where for example 3 variables or PC's could represent 90% of the variation out of the 30 variables with calculated PC scores or that were mathematically analyzed in the sample. It is then of additional benefit to focus on those variables (ie. in our case BMI, Angle classification, Gender etc...) that represent or play a crucial role in the variability or more specifically shape variation within our study. (Zelditch et al., 2004)

Objectives

Currently for two dimensional cephalometric analysis of craniofacial form for obese children and adolescents, there exists only one study that has looked at a younger age cohort with a mean age of 10 years old (Giuca et al., 2013). The other 2 studies that had examined craniofacial form had older mean ages of 15.6 years old (Sadeghianrizi et al., 2005) and 15.7 years old (Ohrn et al., 2002). Additionally, none of the previous studies utilized geometric morphometrics in their analysis. Therefore, one objective of this study is to focus on a younger age cohort of children and adolescents comparable to the Guica 2013 study to continue to establish cephalometric norms and analyses for a younger obese and control population groups and compare the findings between the 2 groups. This will help to shed further light on what was found in the previous studies. Another objective is to discuss the Cephalometric differences between younger patients seen within my study and see how it may be similar or different to the differences in older obese patients seen in previous studies (Ohrn et al., 2002; Sadeghianrizi et al., 2005) to speculate if there is an altered growth trend compared to controls as they progress with age. Finally, to our knowledge, there have been no previous studies that have included GM analysis looking specifically into differences in craniofacial shape in the 2 dimensional cephalometric images (Klingenberg, 2011).

1.5.1 Null Hypothesis

There is no difference between the craniofacial form of obese and non-obese adolescent patients (~7-16 years old).

1.5.2 Study Hypothesis

Obese patients have craniofacial form characteristics that differ from non-obese or normal population groups at a younger age (7-16 years old).

Chapter 2: Materials and Methods

2.1 Participants

A total of 277 children and adolescent patients (aged 7-16 years old) with orthodontic records (ex. Lateral cephalogram, Panoramic radiograph, composite 8 photos, models) were retrospectively reviewed with height and weight gathered prior to undergoing orthodontic treatment at the University of British Columbia. A group of 24 obese patients were identified (see below for criteria) and matched with 24 normal weight control group subjects for age, gender, and Angle-classification of malocclusion.

	Cohort		
Characteristic:	Control Group	Obese Subjects	P-value
Numbers of Patients	24	24	
Mean Age (Yrs) (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 (kgs) (+/-)	40.7 (+/- 11.9)	57.8 (+/- 20.3)	0.001*
Mean Height (meter) (+/-)	1.49 (+/- 0.16)	1.48 (+/- 0.17)	0.965
Sex			
- Male	16 (67%)	16 (67%)	
- Female	8 (33%)	8 (33%)	
Angle Class			
- Class I	11 (46%)	11 (46%)	
- Class II Div. I	8 (33%)	5 (21%)	
- Class II Div. II	1 (4%)	1 (4%)	
- Class III	4 (17%)	7 (29%)	

*Difference is statistically significant (p<.005); other characteristics not different

Table 2.1 Study patient characteristics comparing Obese and Non-obese cohorts

2.2 Power Calculation

Based on the prior recent studies (Giuca et al., 2013; Sadeghianrizi et al., 2005), a power calculation was carried out to estimate the sample size required for each group to achieve a desired power of 0.80. Using a value of 0.05 for alpha and a 2-sided test for comparing two independent samples, estimated sample sizes were calculated for selected cephalometric landmark variables from the two studies. Based on the common variable of maxillary length (Pm-A point) difference, a sample size of 15 subjects for a total of 30 subjects would be estimated as sufficient to see a difference for the total population. This sample size calculation indicates that our sample of 24 subjects in each group for a total of 48 subjects will be sufficient to detect a similar difference.

Variable	Mean 1	SD 1	Mean 2	SD 2	Effect Size	Power	Alpha	Sample Size (Total w/ Controls)
PM-A point (All) [Giuca 2013]	48.5	2.5	46.1	1.9	1.08	.80	0.05	15 (30)
PM- A point (Male) [Sadeghianrizi 2005]	50.2	2.6	46.7	2.7	1.32	.80	0.05	11 (22)
PM- A point (Female) [Sadeghianrizi 2005]	48.2	2.4	45.2	1.9	1.39	.80	0.05	10 (20)
SN-ML (Male) [Sadeghianrizi 2005]	28.8	4.7	32.8	5.9	0.75	.80	0.05	29 (58)
SN-ML (Female) [Sadeghianrizi 2005]	28.5	6.1	31.8	6.6	0.52	.80	0.05	60 (120)
ANS-Gn (Male) [Sadeghianrizi 2005]	67.3	5.6	63.3	5.1	0.75	.80	0.05	60 (120)
ANS-Gn (Female) [Sadeghianrizi 2005]	65.6	5.4	61.8	5.3	0.71	.80	0.05	33 (66)

Table 2.2 Sample size calculations based on select cephalometric endpoints from Guica (2013) and Sadeghianrizi (2005)

2.2.1 Inclusion and Exclusion Criteria

Inclusion criteria consisted of pre-orthodontic treated patients aged 7-16 years old with height and weight recorded within 1 month of when complete pre-orthodontic records were taken. Cephalometric images were also required to be clear, with subjects standing with teeth occluded and lips in a relaxed position.

Exclusion criteria consisted of subjects with craniofacial syndromes, those who received any prior orthodontic treatment, were affected by any systemic disease or were taking any medications that would affect craniofacial growth, or those who had incomplete orthodontic records.

2.2.2 Control Matching Protocol

Control group matching was carried out by prioritizing age (within 6 mo. of the obese subject), gender, and then Angle-classification of malocclusion and BMI determined by the CDC BMI growth charts for youth aged 2-20 years for age and sex (Figure 1.1). The obese group was defined as having BMI ≥95th percentile for age and sex specific CDC growth charts and the control group was determined by matching a subject in the sample closest to the 50th percentile (with a range of 42-75%) which fulfilled the requirement of being all within the normal weight classification according to CDC. The Angle-classification of malocclusion was separated into 4 groups (Class I, Class II div. I, Class II div. II, Class III) and was ideally matched for all except for 3 subjects.

2.3 Morphometric methods and dental/skeletal maturation analyses

2.3.1 Conventional cephalometric analysis

Cephalometric radiographs were traced and annotated with landmarks listed in Table 2.2 using Dolphin Imaging Software (Dolphin Imaging, Chatsworth, Calif). Intra-examiner error analysis was performed for 10 randomly selected subjects (both obese and control) by repeating measurements 2 weeks part. Error across landmarks was found to be low, indicating good consistency of landmark identification (range from 0.06 to 1.04 millimeters). Cephalometric points with maximum error at 1.04mm were also not used in the conventional analysis (1.04mm for Porion and Articulare). Traditional linear and angular measurements were obtained from Dolphin. Additionally, X and Y coordinates of all landmarks were obtained for GM analysis.

Landmark	Measurement Error (mm)		
	Average	Max	Std Dev
A Point	0.091	0.232	0.078
ANS	0.041	0.147	0.041
Anatomical Gnathion	0.061	0.156	0.051
Articulare	0.301	1.042	0.428
B Point	0.240	0.822	0.255
Basion	0.104	0.245	0.067
Condylion	0.168	0.454	0.139
Constructed Gonion	0.161	0.604	0.178
Distal L6	0.124	0.346	0.125
Distal U6	0.107	0.336	0.119
L1 Labial Gingival Border	0.076	0.175	0.066
L1 Lingual Gingival Border	0.032	0.092	0.027
L1 Root	0.054	0.220	0.065
L1 Tip	0.031	0.059	0.017
L6 Occlusal	0.099	0.427	0.131
Menton	0.057	0.107	0.030
Mesial L6	0.104	0.301	0.121

Landmark	Measurement Error (mm)		
	Average	Max	Std Dev
Mesial U6	0.102	0.180	0.049
Mid Ramus (R1)	0.236	0.666	0.244
Nasion	0.061	0.323	0.105
Orbitale	0.069	0.369	0.114
PNS	0.043	0.117	0.034
PRO-prosthlion	0.096	0.332	0.105
PT Point	0.106	0.432	0.125
Pogonion	0.093	0.270	0.100
Porion	0.170	1.043	0.317
Ramus Point	0.361	0.885	0.348
Sella	0.032	0.074	0.023
Sigmoid Notch (R3)	0.114	0.292	0.089
U1 Labial Gingival Border	0.131	0.484	0.143
U1 Lingual Gingival Border	0.045	0.175	0.049
U1 Root	0.070	0.396	0.117
U1 Tip	0.038	0.079	0.023
U6 Occlusal	0.082	0.305	0.095

Table 2.3 Error analysis for cephalometric tracings

2.3.2 Geometric morphometric cephalometric analysis

Geometric Morphometric (GM) analyses was performed using R Studio Package. As opposed to traditional morphometrics (linear distances and angles), GM analyses utilize all landmarks belonging to a configuration and hence assesses shape as a whole. To study cranioskeletal form, we excluded soft tissue landmarks, since these can be differentially affected by the patient's obesity status. We also chose to exclude landmarks identifying maxillary and mandibular molars, since their inclusion in the GM analysis could emphasize difference driven by Angle's classification as opposed to differences driven by BMI. Briefly, all X, Y coordinates were first subjected to a generalized Procrustes analysis (GPA) to account for position, rotation and scale. Following this, new Procrustes coordinates for each landmark were obtained and subjected to Principle Component Analysis (PCA). Next, a linear discriminate function analysis was performed to evaluate the differences in landmark configuration driven by obesity status in our sample. To visualize these differences, the shift in landmarks driven by the discriminate analysis was interpolated onto an average cephalogram. The positive and negative maxima of this interpolation representing the obese and control populations extremes, are reported here. Additionally, we performed canonical variate analysis (CVA) to confirm that our analyses can distinguish recognizable craniofacial forms (i.e. as per Angle's classification of malocclusion).

2.3.3 Dental maturation analysis

Dental maturation index scores were obtained from panoramic radiographs using the Demerijian method (Demirjian et al., 1973) with dental maturation compared between the obese and control samples. The Demerijian method is the most widely used dental maturity method, which assesses and calculates dental age compared to chronological age based on the formation of seven mandibular permanent teeth (1^{st} and 2^{nd} molar, 1^{st} and 2^{nd} pre-molar, canine, central and lateral incisor). Each of the seven teeth are rated according to tooth follicle shape, pulp chamber, dentin deposit and root formation on a 7-point scale from A-H.

2.3.4 Skeletal maturation analysis

Cervical vertebral maturation (CVM) scores were obtained from lateral cephalograms using the CVM method (Baccetti et al., 2005) with skeletal maturation compared between the obese and control samples. Bacetti's CVM method is a modified version for the detection of the peak in mandibular growth, based on the analysis of the morphology of the second through fourth cervical vertebrae. There are six maturational stages (cervical stage 1 through cervical stage 6, i.e., CS1 through CS6), each based on the shape of each vertebra. CS1 and CS2 are prepeak stages; the peak in mandibular growth occurs between CS3 and CS4.

2.4 Statistical Analysis

Either SPSS version 25.0 or Excel was used for all statistical analyses and the threshold for the statistical significance was set at $P < 0.05$ for all tests. For the collected data, assumptions were made that normality of the data existed. When comparing the obese to the control group characteristics of chronologic age which consisted of 2 independent means, a paired T-test was carried out. A paired T-test was also carried out for specific 2 dimensional cephalometric linear and angular measurements to determine if differences of means across the 2 groups exist. A paired T-test was carried out for mean dental maturation scores between obese and control groups and a Pearson correlation was carried out in comparison of chronological age and dental age or dental maturation. A chi-square test was carried out for skeletal maturation since the CVM score 1 through 6 as a categorical variable.

For the GM analysis, a Procrustes ANOVA was performed to evaluate whether sex, angle classification or obesity status account for significant differences in cranioskeletal form, in our sample ($p < 0.05$)

Chapter 3: Results

There was no statistically significant difference (P < 0.895) in chronological age between the obese and control groups supporting the notion that the 2 groups were matched and controlled well for age (Table 2.1). The groups differed significantly however, in BMI, with patients in the obese group having a mean BMI of 25.4 which is comparable to the U.S. national average of adult men and women according to the CDC.

3.1 Conventional cephalometric analysis

Conventionally used linear and angular cephalometric measurements were assessed and compared between the obese and control groups in our sample. Conventional cephalometric analysis found no statistically significant differences in measurements between the obese and control groups in this study except for maxillary length (PNS-A point) and gonial angle (Ar-Go-Gn) (Table 3.1). Maxillary length was found to be greater by 2mm in the obese group and gonial angle greater by 3.7 degrees with significance in both T-test (p=0.041 maxillary length, p=0.028 gonial angle) and ANOVA (p=0.049 maxillary length, p=0.028 gonial angle) analysis. However, a post-hoc analysis using Bonferroni's correction with a new alpha of p=0.0028 for significance, indicated that neither of the differences found in the two measurements are significant.

Cephalometric Measurement	**Cohort Average**				
	Obese Subjects	Non-Obese Controls	T-test P-value	ANOVA P-value	Post-hoc Significance
Linear Variables (mm)					
Posterior Facial Height (S-Go)	74.2 (+/- 7.5)	75.8 (+/- 7.8)	0.483	0.466	N
Lower Face Height (ANS-Gn)	57.5 (+/- 6.7)	57.3 (+/- 4.4)	0.923	0.876	N
Anterior Cranial Base (S-N)	64.9 (+/- 3.9)	64.7 (+/- 3.8)	0.833	0.822	N
Maxillary Length (PNS-A)	44.3	42.3	0.041	0.049	N

	(+/- 3.5)	(+/- 3.1)			
Mandibular Unit Length (Co-Pog)	98.3 (+/- 8.5)	96.0 (+/- 6.6)	0.282	0.231	N
Length of Mandibular Base (Go-Pg)	65.0 (+/- 5.3)	63.9 (+/- 3.8)	0.411	0.317	N
Maxillary Dentition (U1-NA)	3.6 (+/-2.9)	3.9 (+/-2.8)	0.725	0.694	N
Mandibular Dentition (L1-NB)	4.3 (+/-1.8)	4.4 (+/-1.7)	0.945	0.949	N
Lower Lip to E-Plane	-0.6 (+/-3.1)	0.8 (+/-2.9)	0.099	0.088	N
Upper Lip to E-Plane	-1.5 (+/-2.7)	-1.3 (+/-2.7)	0.865	0.849	N
Angular Variables (º)					
Mandible to Cranial Base (SN-MP)	32.8 (+/- 7.1)	31.2 (+/- 5.2)	0.366	0.282	N
Gonial Angle (Ar-Go-Gn)	129.7 (+/-6.0)	126.0 (+/-5.1)	0.028	0.028	N
Maxilla to Cranial Base SNA	82.1 (+/-3.3)	81.0 (+/-4.8)	0.361	0.413	N
Mandible to Cranial Base SNB	78.6 (+/-4.5)	77.7 (+/-4.9)	0.506	0.548	N
Mandible to Cranial Base FMA (MP-FH)	25.8 (+/-5.9)	27.4 (+/-4.2)	0.304	0.349	N
Maxillo-Mandibular ANB	3.8 (+/-2.1)	3.2 (+/-2.9)	0.405	0.434	N
Maxillary Dentition (U1-SN)	104.5 (+/-11.0)	102.8 (+/-10.7)	0.582	0.654	N
Mandibular Dentition (L1-MP)	91.0 (+/-8.2)	91.7 (+/-5.4)	0.729	0.628	N

Table 3.1 Comparison of cephalometric measurement means between Obese subjects and Non-obese controls

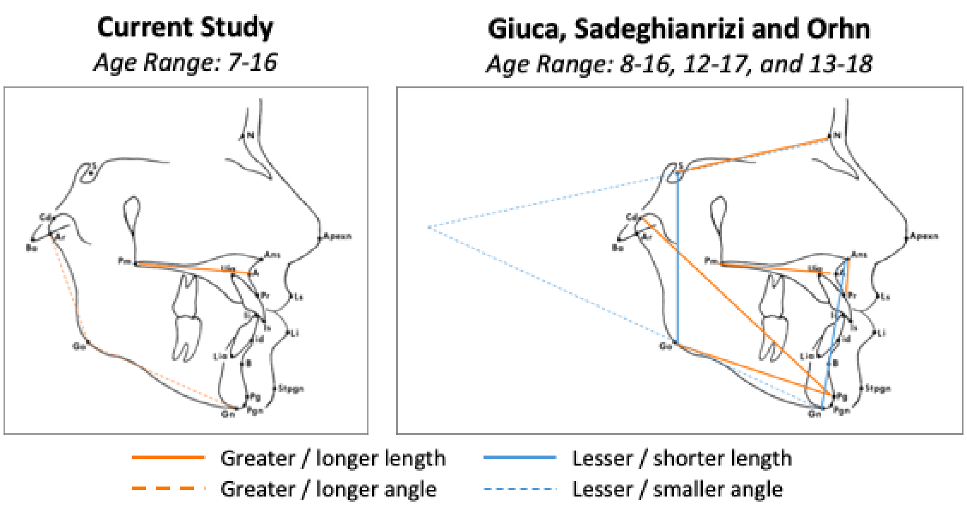


Figure 3.1 Comparison of findings between Obese subjects and Non-obese controls in current study compared to previous literature in older subjects.

3.2 Geometric morphometric cephalometric analysis

GM analysis carried out by obtaining X, Y coordinates from cephalometric tracings were subject to Procrustes superimposition to remove translational, rotational and scale differences between individual tracings, followed by iterative best fit superimposition to obtain new Procrustes coordinates for each configuration. Following this, Principal component (PC) analysis was performed. When assessing the distribution of individuals along vertical (PC1) and horizontal (PC4) axes, a segregation was found along the vertial axes with the non-obese subjects tending to cluster around the lower values and obese subjects clustering around the higher values (Figure 3.2). A multivariate ANOVA analysis was performed to evaluate whether any of the factors assessed here (BMI, sex, and angle classification) significantly contributes to the principle components of shape difference identified by our analysis. Only BMI and angle classification displayed Mean of Squares (MS) that were significantly greater than the residuals (estimation of error and biological variation, Table 3.2, p-value <0.005) confirming that individuals who differ in angle classification and BMI also display statistically significant differences in craniofacial morphology.

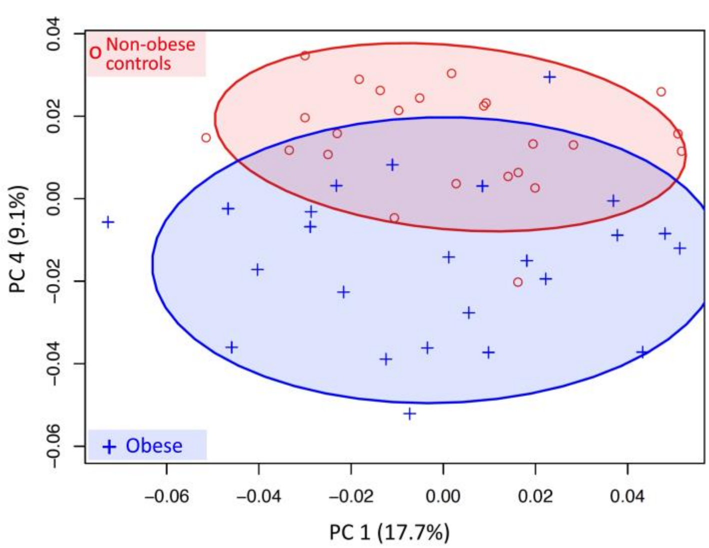


Figure 3.2 Principal component (PC) analysis showing segregation of obese (red) and control (blue) subjects along PC4

Canonical Variate Analyses (CVA) identified that axis 1 segregates the dataset based on Angle's classification of malocclusion (Figure 3.3). Notably, all our GM analyses were performed using only hard tissue landmarks and excluded the molar landmarks routinely used in cephalometric analysis (see Materials and Methods). Hence, the distribution in Figure 3.3 suggests that overall craniofacial form of Class I, II and III individuals is indeed distinct enough to be separated by a CVA, despite the exclusion of molar landmarks.

	Df	SS	MS	Rsq	F	Z	Pr (>F)
BMI	1	0.013640	0.013640	0.061694	3.094142	2.942249	0.002
Sex	1	0.003990	0.003990	0.018045	0.905006	0.106975	0.454
Angle	1	0.012428	0.012428	0.056211	2.819177	2.740477	0.003
BMI:Sex	1	0.001023	0.001023	0.004627	0.232044	-2.846170	0.996
BMI:Angle	1	0.003361	0.003361	0.015200	0.762343	-0.093550	0.552
Sex:Angle	1	0.004716	0.004716	0.021328	1.069677	0.766922	0.231
BMI:Sex:Angle	1	0.005602	0.005602	0.025339	1.270813	1.337285	0.087
Residuals	40	0.176338	0.004408	NA	NA	NA	NA
Total	47	0.221097	NA	NA	NA	NA	NA

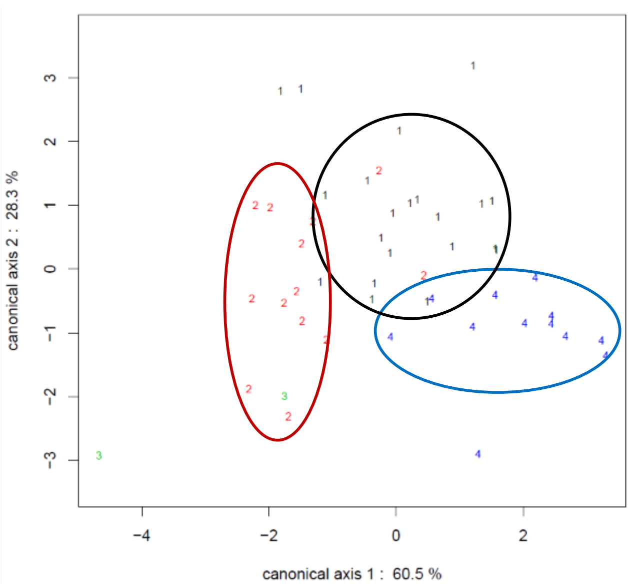


Table 3.2 Statistical comparison of obesity, sex, and angle classification on craniofacial morphology

Figure 3.3 Distribution of individuals along canonical axis 1 segregates the dataset based on Angle's classification of malocclusion (1= class I, 2= Class II Div1, 3= Class II Div 2, 4= class 3) showing segregation of angle.

3.3 Linear Discriminate Analysis (LDA)

To visualize the difference between the craniofacial form in obese and non-obese individuals, we performed a linear discriminate analysis (LDA) using BMI as a function. The results of the LDA were interpolated onto an average cephaogram and wireframe, and the extreme ends of the discriminate analysis which corespond to the obese and control patient's configurations are presented in Figure 3.4 (A=control, red; B=obese, blue; C,D= superimpositions registerd on the cranial base). These visualizations suggest that obese patients have a more protrusive pogonion / chin point, and the naso-maxillary complex was longer in the vertical dimension.

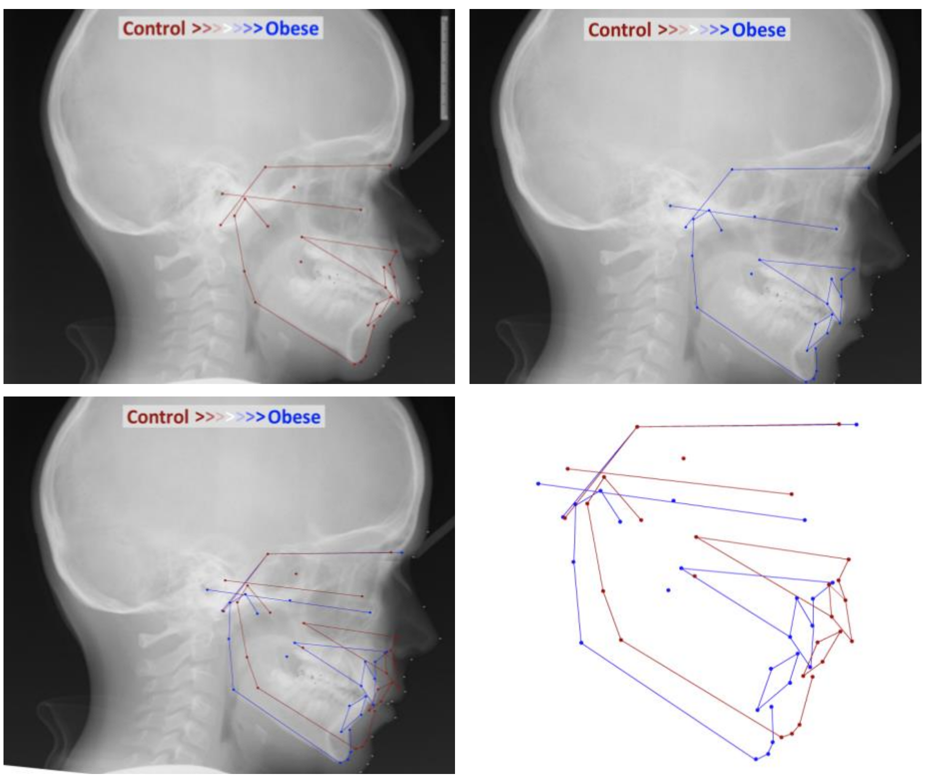


Figure 3.4 Interpolation of the LDA onto a cephalometric radiograph and wireframes showing the control (A, red) and obese (B, blue) ends of the distribution of patient in our dataset. (C and D) superimposition of the control and obese ends of the linear discriminate analysis using the cranial base (Sella-nasion-basion) for registration

We also performed a cross-validation study to assess whether individual subjects are correctly categorized into obese and non-obese groups using their coordinate shape data. Table 3.3 indicates that upon cross-validation, 88% of non-obese patients and 92% of obese patients were correctly categorized into their separate BMI groups (P < 0.001), supporting the finding that a shape difference indeed exists between the two groups.

Table 3.3 Grouping along with cross-validation of obese and non-obese patients based on linear discriminate function analysis

From Discriminant Function:			
Group	Control	Obese	Total
Control	24	0	24
Obese	0	24	24
From Cross-Validation:			
Group	Control	Obese	Total
Control	21	3	24
Obese	2	22	24
Difference Between Means			
Procrustes Distance between means		0.04008	
P Value (1000 permutation tests)		< 0.001	

3.4 Dental maturation analysis

We found a statistically significant difference (P <0.0048) in dental maturity, with the obese group having higher dental maturation scores or being further along in dental age compared to the non-obese group. As previously noted, there was no difference in chronological age (Table 2.1), indicating the well-controlled matching between the two groups.

Mean (SD)	Obese	Control	Difference	T-test
Chronological Age	11.19 (2.50)	11.28 (2.36)	0.09	p=0.8957
Dental Maturity Score	90.71 (6.07)	85.06 (6.52)	5.65	p=0.0048

Table 3.4 Comparison of Obese and control cohorts in age and dental maturity

When dental maturation was compared to chronological age for the obese and control groups after analysis with Pearson correlation, it was found that there was a statistically significant low to moderate correlation in the obese group (r = 0.61, P <0.002) but no correlation in the control group (r = 0.15, P <0.496).

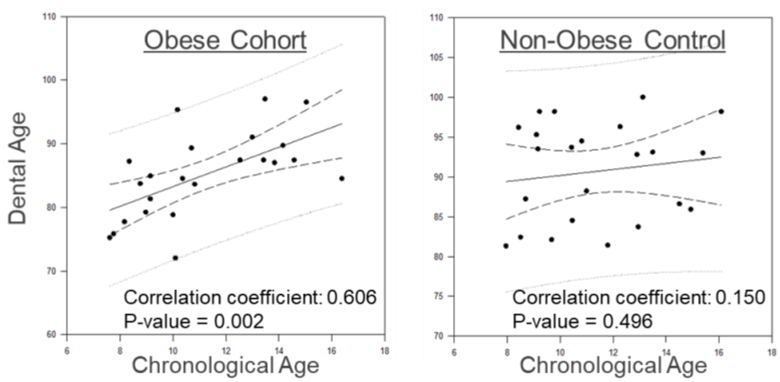


Figure 3.5 Pearson correlation of chronological age and dental age in Obese and Non-obese subjects

3.5 Skeletal maturation analysis

Assessment of skeletal maturation scores using the Cervical vertebral maturation (CVM) method (Baccetti et al., 2005) revealed no statistically significant difference between the obese and control groups (Chi-square: 34.384, DF = 20, P <0.024) with the two groups showing similar skeletal maturation stages.

CVM Stage	1	2	3	4	5	6	Avg
Obese (n=23)	7 (29%)	5 (21%)	7 (29%)	2 (8%)	3 (13%)	0 (0%)	2.54
	19 (79%)			5 (21%)			
Control (n=23)	6 (25%)	4 (17%)	7 (29%)	4 (17%)	1 (4%)	2 (8%)	2.83
	17 (71%)			7 (29%)			

Table 3.5 CVM stage assessments

	1	2	3	4	5
1 – Observed	4	1	1	0	0
1 – Expected	1.75	1.25	1.75	0.50	0.75
2 – Observed	2	2	0	0	0
2 – Expected	1.17	0.83	1.17	0.33	0.50
3 – Observed	1	2	4	0	0
3 – Expected	2.04	1.46	2.04	0.58	0.88
4 – Observed	0	0	1	2	1
4 – Expected	1.17	0.83	1.17	0.33	0.50
5 – Observed	0	0	0	0	1
5 – Expected	0.29	0.21	0.29	0.08	0.13
6 – Observed	0	0	1	0	1
6 – Expected	0.58	0.42	0.58	0.17	0.25

Table 3.6 Chi-square assessment table with 20 degrees of freedom

Chapter 4: Discussion

4.1 Methodology

Conventional cephalometry is a 2-dimensional analysis of a 3-dimensional structure and therefore its images are subject to projection, landmark identification, and measurement errors. Landmark errors depend on the quality of the radiograph, reproducibility of the landmark, and operator experience and precision. Magnification and distortion can also play a role during image acquisition and processing (Lagravere et al., 2010). In addition to the limitations inherent to cephalogram image, the most commonly used method to assess differences in craniofacial form, i.e. conventional cephalometric analyses, also has certain limitations (Bookstein, 2016; Moyers & Bookstein, 1979). Geometric morphometrics (GM) allows a method of analysis of an object or image based on landmark coordinates (X , Y) that can differentiate variability due to both size and shape while considering the overall configuration of all coordinates together, as opposed to linear distances and angles between select sets of landmarks. Shape information can be visualized by plotting landmark positions in a Procrustes superimposition, a method of optimally matching one shape to another where the Procrustes distance is a measure of the closeness in shape of superimposed images. Procrustes distances can be used to summarize variations in populations, to express the degree of similarity of individual images, means of populations, or to search for matches between images (Bush, Bush, & Sheets, 2011). Quantification of shape and size using specific multivariate statistical geometric morphometric procedures renders more accurate results than those obtained by conventional linear and angular methods (Bilfeld et al., 2013; Corti, 1993). This analysis helps to reduce confounding factors within linear and angular measurements for cephalometric shape in order to identify the more pronounced and subtle differences that exist between the comparison groups.

When examining error, it has been established in the literature that intra-examiner landmark identification errors are generally lower than inter-observer errors (Kamoen, Dermaut, & Verbeeck, 2001). Previous studies report that intra-examiner reliability for all coordinates for most landmarks on digital lateral cephalograms have an intra-class correlation coefficient greater than 0.9 with the means of landmark identification differing by approximately 1mm in most coordinates (Lagravere et al., 2010). Within this study, our intra-examiner reliability was very good showing less than 1mm of tracing error of most points between tracings with a 2 week waiting period and only 2 points (Porion, Articulare) showing greater than 1mm error.

4.2 Craniofacial morphology of obese versus non-obese adolescents

When we examine the past literature, there is strong support for the progression and increased risk of overweight children to become obese, beginning as early as 3 years of age (Geserick et al., 2018; Nader et al., 2006). With this early onset and general trend comes the possibility of increased influence over craniofacial growth and shape, as well as precocious dental and skeletal maturation. Two prior studies have compared craniofacial differences between obese and non-obese children (Giuca et al., 2012; Sindelarova et al., 2018) using control groups. Ohrn et. al (2002) performed a similar analysis, however they allowed in their inclusion criteria, adolescents with prior orthodontic treatment, potentially being a confounding factor. In the Sadeghianrizi study, there were no mentions of inclusion or exclusion criteria established. Our study aimed to examine whether facial growth and shape changes identified by others previously, would manifest in a younger age group (Giuca et al., 2013; Ohrn et al., 2002; Sadeghianrizi et al., 2005).

Our study found fewer areas in which there were craniofacial differences between obese and non-obese patients than previous studies. Some of those studies used soft tissue points which would contribute to greater variability and could explain some of the smaller differences. Additionally, our study included a younger aged cohort in the sample than previous studies. With a younger age cohort, subjects would have not yet reached their growth spurt and full skeletal maturation. There is a likelihood that after their peak pubertal growth spurt, more craniofacial form differences would potentially become evident as was found in the previous older age studies (Ohrn et al., 2002; Sadeghianrizi et al., 2005).

Our study and past literature recognizes that there is a tendency for a characteristic difference in craniofacial form in obese individuals with an increased maxillary length and brachycephalic facial form (Giuca et al., 2013). This reinforces the notion that dentists and orthodontics should keep a closer watch or observation of growth changes in younger and obese patients to initiate treatment or consider a shorter orthodontic recall schedule. Since growth modification is best used during a specific time window with precocious skeletal maturation, a child's peak pubertal growth spurt may be prematurely passed compared to their normal weight peers (Giuca et al., 2012). The fact that dental maturation and eruption are accelerated in obese individuals also supports the argument for closer monitoring of caries along with earlier orthodontic screenings (Sindelarova et al., 2018). Given what we know from past literature with changes in growth, dental and skeletal maturation in obese children and adolescents confirmed by this study, we recommend that potentially clinically relevant changes to height and weight be routinely recorded in the orthodontic medical history documentation. Hence, BMI and obesity are confounding factors to growth and maturation which can change the approach to treatment and retention for such patients.

4.3 Limitations of the Study

Some of the limitations of our study included a reduced sample size where the sample size calculations indicate that some of the variables would require a larger sample size to detect a difference (e.g., ~90 obese subjects needed for SN-ML or ANS-Gn measurements). Indeed, our power calculation had shown that we were under power for our female sample (only 8) and a post-hoc power calculation indicates that a greater sample size would have been required to find a statistical difference from our results (Table 4.1), even for variables where a difference was found such as Maxillary length and Gonial angle. Listed in table 4.1 are the variables we had analyzed showing a post-hoc power calculation of the sample size at 0.80 power. Our sample size of 24 obese and control subjects proved to be under power for all variables analyzed and therefore may be unable to detect a difference between groups for variables except for maxillary length and gonial angle. As an aside, having a smaller sample size and being under power for our post-hoc power calculations increases the risk of a type II error – concluding there is no difference in the variable when there actually is a difference (i.e., falsely accepting the null hypothesis) and furthermore helping to explain the reason for finding less differences in our traditional linear cephalometric analysis compared to those found in prior studies. (Giuca et al., 2013; Ohrn et al., 2002; Sadeghianrizi et al., 2005).

Variable	Obese Mean	Obese SD	Non-Obese Mean	Non-Obese SD	Effect Size	Power	Alpha	Sample Size per Group
Posterior Facial Height (S-Go)	74.2	7.5	75.8	7.8	0.212	0.80	0.05	357
Lower Face Height (ANS-Gn)	57.5	6.7	57.3	4.4	0.035	0.80	0.05	12,816
Anterior Cranial Base (S-N)	64.9	3.9	64.7	3.8	0.052	0.80	0.05	5,807

Maxillary Length (PNS-A)	44.3	3.5	42.3	3.1	0.454	0.80	0.05	78
Mandibular Unit Length (Co-Pog)	98.3	8.5	96.0	6.6	0.038	0.80	0.05	10,872
Length of Mandibular Base (Go-Pg)	65.0	5.3	63.9	3.8	0.239	0.80	0.05	276
Maxillary Dentition (U1-NA)	3.6	2.9	3.9	2.8	0.105	0.80	0.05	1,425
Mandibular Dentition (L1-NB)	4.3	1.8	4.4	1.7	0.057	0.80	0.05	4,833
Lower Lip to E-Plane	-0.6	3.1	0.8	2.9	0.466	0.80	0.05	74
Upper Lip to E-Plane	-1.5	2.7	-1.3	2.7	0.074	0.80	0.05	2,868
Mandible to Cranial Base (SN-MP)	32.8	7.1	31.2	5.2	0.257	0.80	0.05	239
Gonial Angle (Ar-Go-Gn)	129.7	6.0	126.0	5.1	0.664	0.80	0.05	37
Maxilla to Cranial Base SNA	82.1	3.3	81.0	4.8	0.267	0.80	0.05	222
Mandible to Cranial Base SNB	78.6	4.5	77.7	4.9	0.191	0.80	0.05	432
Mandible to Cranial Base FMA (MP-FH)	25.8	5.9	27.4	4.2	0.312	0.80	0.05	163
Maxillo-Mandibular ANB	3.8	2.1	3.2	2.9	0.237	0.80	0.05	281
Maxillary Dentition (U1-SN)	104.5	11.0	102.8	10.7	0.157	0.80	0.05	638
Mandibular Dentition (L1-MP)	91.0	8.2	91.7	5.4	0.101	0.80	0.05	1,540

Table 4.1 Post-hoc power calculation

Additionally, a larger sample size could allow us to stratify our groups by sex or by ethnicity, which has been shown to play an influential role in craniofacial shape differences (Miyajima, McNamara, Kimura, Murata, & Iizuka, 1996), to compare craniofacial shape differences of obese and control groups between and within different races. A larger sample size could also allow us to analyze subjects in smaller sub-groups by age (1-2 years difference). This would help us assess growth changes that occur at a particular age in obese individuals and should support the notion that ethnically distinct groups with higher BMI's tend to have more change in craniofacial form (DuPlessis et al., 2016; Miyajima et al., 1996). One aspect that could have played a role in the difficulty of finding differences in our sample is the diverse racial background of our overall sample (primarily a mix of Caucasians and Asians) where a more racial homogenous sample (ie. First nation aboriginals in Canada and Hispanics and African Americans in the USA) like those found in previous studies could help us to see more clearly how ethnicity plays a role in its differences of craniofacial morphology with obese and control groups in a population. Increasing sample size could either be achieved through the addition of the 45 subjects found within the overweight cohort (85^{th}- 94.9^{th} BMI percentile) or through a collaboration with another research group to add a secondary sample of obese subjects as we were only able to find 24 obese patients in the UBC sample.

Pertaining to the skeletal maturation measured by the CVM stages (Baccetti et al., 2005), although there was no difference found between the skeletal maturation between the 2 groups in our sample this could also be due to a small sample size, as well as a younger aged sample size not yet truly exhibiting the accelerated growth seen with previous studies. The CVM stage is also by nature a categorical variable with 6 stages potentially missing smaller increments of growth changes between stages.

Another limitation of the study was the potential for cephalometric error given the limitations of 2 dimensional cephalometric analysis as previously mentioned.

4.4 Future Directions

With regard to future directions of the study, one interesting element of analysis previously mentioned by Ohrn would be the role of muscle activity in growth. Therefore, an analysis of measuring the masticatory forces in obese compared to non-obese individuals could help to shed more light on the potential sources of the morphological differences identified in this and previous studies. Another future direction of this study would be to examine if there is a dose-related response in craniofacial form between overweight and obese individuals, with the same growth pattern seen but more pronounced effect in the older obese population to see if increase changes in growth manifest over a longer period of time. It would also be interesting to assess whether BMI has an influence on an individual's response to orthopedic growth modification treatment.

Additionally given the fact that our study was 2 dimensional (only examining the sagittal and vertical dimensions) it would be useful to have a database of 3 dimensional images through either cone beam computed tomography images for hard tissue or digital facial images for soft tissue records, as was previously examined by (Ferrario et al., 2004) and (Klingenberg, 2011). The various analysis in this study focused primarily on the hard tissue points to eliminate the greater variability and potential measurement errors of soft tissue points. While the raw cephalometric images could be edited to show greater clarity and definition of soft tissue points, such manipulations run the risk of introducing bias into the analysis.

Chapter 5: Conclusion

1. The only conventional cephalometric measurement that was statistically different between obese and non-obese patients in our study is an increased maxillary length (Pm-A Point) and gonial angle in obese patients.
2. Geometric Morphometric analyses not previously carried out in 2 dimensional cephalometric studies indicates that obese individuals display a statistically significant difference in overall craniofacial form, specifically a more brachycephalic craniofacial form, compared to non-obese individuals.
3. Our findings when compared to previous data help to reinforce similar findings (i.e., obese children and adolescents with longer maxillary length and brachycephalic facial form) in previous studies in younger (Giuca et al., 2013) and older (Ohrn et al., 2002; Sadeghianrizi et al., 2005) age groups as this study consisted of a majority of younger patients (~ 83% = 6-14 years old), many of whom had not yet attained and surpassed peak growth.

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