

**CRANIOFACIAL FEATURES OF OBESE OBSTRUCTIVE SLEEP APNEA (OSA)  
PATIENTS IN RELATION TO THE OBESITY ONSET**

by

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## **Abstract**

**Objectives:** Obstructive Sleep Apnea prevalence is substantially higher in men and subjects with higher body mass indexed. OSA is present in 41% of individuals with a BMI>28 kg/m<sup>2</sup>, and in up to 78% in morbidly obese patients. Obesity alone is not the sole cause of OSA and craniofacial morphology is also a key determinant of the predisposition to airway collapse. There is still controversial data on the craniofacial characteristics of obese OSA patients and we hypothesize that the age when individuals become obese, can affect the craniofacial features of obese OSA patients.

**Methods:** The prospective sample consisted of 39 obese and 43 non-obese OSA adults matched for age and OSA severity from a retrospective cohort. The age of obesity onset was determined through a questionnaire and diagnosis of craniofacial and airway morphology was made from standard cephalometric radiographs.

**Result:** Twelve early obese, 21 late obese and 29 non-obese OSA patients were deemed eligible for this study. The mean age was 45.6, 50.9 and 48.1 years for early, late and non-obese groups, respectively. Non-obese OSA, compared to obese subjects, showed a significantly more retrognathic mandible, larger maxillo-mandibular discrepancy, shorter lower facial height, deeper overbite, less upper incisors proclination and protrusion, longer soft palate, higher position of hyoid bone, narrower inferior airway space, longer airway length and less obtuse head posture. The early obesity group, compared to non-obese, showed a prognathic mandible, longer lower facial height, more proclined upper incisors, caudally positioned hyoid bone, wider

inferior airway space and shorter airway length. The late obesity group, compared to non-obese group, showed a proclined and protrusive upper incisors, shallower overbite, inferiorly positioned hyoid bone, shorter airway length and obtuse cranio-cervical angle. There was no significant difference between early and late obesity groups.

**Conclusion:** Obese OSA patients have more developed craniofacial skeletons with less bony and airway constriction than their non-obese counterparts; and early and late obesity groups showed discrepancies in their characteristics which were different from non-obese subjects, suggesting a possible impact of obesity onset on craniofacial characteristics. Further studies are still needed to determine the effect of obesity onset on craniofacial development.

## **Lay Summary**

Obstructive sleep apnea (OSA) is a disease characterized by repetitive complete or partial obstructions of airflow during sleep. OSA results in sleep fragmentation, excessive daytime sleepiness and serious health complications. Obesity, facial bone structure and airway morphology are among the most important risk factors for OSA. This study showed that obese individuals presented with different craniofacial risk factors than their non-obese counterparts. We found that non-obese sleep apnea patients presented with constricted facial skeletons and airway passages, while obese sleep apnea patients had a better skeletal development, which indicated the presence of other contributing factors to their disease. Knowing the specific risk factors may help clinicians tailor their treatments to address the patient's specific problems. Additionally, knowing at what stage of life the patient became obese might explain the interaction between the obesity and facial skeletal development. This specific area requires further investigation through clinical research.

## **Preface**

The research topic was suggested by Dr. Fernanda Almeida and together Drs. Fernanda Almeida and Iqbal Ahmed identified the research question. Samah Al Furiiji designed the project, collected and analyzed the data. Manuscript was prepared by Samah Al Furiiji with content edited by Drs. Fernanda Almeida, Iqbal Ahmed, Edwin Yen and Benjamin Pliska.

The study was approved by the University of British Columbia Office of Research Services, Clinical Research Ethics Board (Certificate Number: H12-03085-006).

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## List of Abbreviations

<b>SA</b>	Sleep Apnea	<b>UA</b>	Upper Airway
<b>OSA</b>	Obstructive Sleep Apnea	<b>ESS</b>	Epworth Sleepiness Scale
<b>AASM</b>	American Academy of Sleep Medicine	<b>SD</b>	Standard Deviation
<b>AHI</b>	Apnea-Hypopnea Index	<b>CPAP</b>	Continuous Positive Airway Pressure
<b>BMI</b>	Body Mass Index	<b>UPPP</b>	Uvulopalatopharyngoplasty
<b>FOSQ</b>	Functional Outcome of Sleep Questionnaire	<b>WHO</b>	World Health Organization
<b>STOP</b>	Snoring, Tiredness, Observed apnea, Blood pressure	<b>CDC</b>	Centers for Disease Control and Prevention
<b>STOP- BANG</b>	Snoring, Tiredness, Observed apnea, Blood pressure, Body mass index, Age, Neck circumference and Gender	<b>GHO</b>	Global Health Observatory
<b>PSG</b>	Polysomnography	<b>NHANES</b>	National Health And Nutrition Examination Survey
<b>PM</b>	Portable Monitors	<b>TNF</b>	Tumor Necrosis Factor
<b>EEG</b>	Electroencephalography	<b>IL</b>	Interleukin
<b>EOG</b>	Electrooculography	<b>GH</b>	Growth Hormones
<b>ECG</b>	Electrocardiography	<b>LAFH</b>	Lower Anterior Facial Height
<b>EMG</b>	Electromyography	<b>LPFH</b>	Lower Posterior Facial Height
<b>RDI</b>	Respiratory Disturbance Index	<b>UBC</b>	University of British Columbia
<b>CT</b>	Computerized Tomography	<b>ODI</b>	Oxygen Desaturation Index
<b>MRI</b>	Magnetic Resonance Imaging	<b>ANOVA</b>	One Way Analysis of Variance
<b>REM</b>	Rapid Eye Movement	<b>ICC</b>	Intra-Class Correlation
		<b>IRR</b>	Intra-Rater Reliability

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## **Dedication**

*To my great family, thank you for all the support, trust and prayers.*

## Chapter 1: Introduction

The description of Sleep Apnea (SA) as a disease by Jung and Kuhlo, in 1965, has been one of the most important evolutions in the science of sleep medicine. In a study involving 3 patients with “Pickwickan Syndrome”, it was found that the patients had frequent apnea attacks during their sleep. The term “Pickwickan Syndrome” was derived from the eighteenth century novelist’s, Charles Dicken’s, lively description in his *Pickwick Papers*, of a “fat boy”, and his frequent naps (1). It formally came to be known as Obstructive Sleep Apnea.

Obstructive Sleep Apnea (OSA), as described by the American Academy of Sleep Medicine (AASM), is a sleep breathing disorder that involves a decrease, or complete halt in airflow, despite an ongoing effort to breathe (2). It occurs as a result of an obstruction to the upper airway, due to inadequate motor tone of the tongue, and/or airway dilator muscles during sleep (3). It leads to partial reductions (hypopneas), and complete pauses (apneas) in breathing, that each last at least 10 seconds during sleep. This, in turn, can result in a disturbance in gas exchange, blood oxygen desaturation and hypercapnia, with oxygen levels falling as much as 40% or more in severe cases (2).

Patients with OSA cycle multiple times between wakefulness and sleep (4), experience sleep fragmentation that often produces an excessive level of daytime sleepiness as well as other cardiovascular, metabolic, and neurocognitive effects (2, 5). A common measurement of sleep apnea is the *Apnea-Hypopnea Index* (AHI) which represents the number of apnea and hypopnea episodes, per hour of sleep (2). OSA syndrome is defined as an AHI of 5 or greater, with associated symptoms (e.g., excessive daytime sleepiness, fatigue, or impaired cognition), or an AHI of 15 or greater, regardless of associated symptoms, and can be of varying severity

(2).

## 1.1 Epidemiology

Obstructive Sleep Apnea is a disorder that has been increasingly recognized by the general population (6). The three most important factors influencing OSA prevalence, in US populations, are: sex, age group, and weight (7). In addition, its prevalence depends upon other factors, such as ethnicity, craniofacial morphology and life style related factors - like smoking, and alcohol consumption and other neuromuscular factors which are not as well known.

The Wisconsin Sleep Cohort Study, conducted in various times between 1988 and 2011, included one of the most famous studies to investigate the OSA occurrence among middle-aged adults (30-60 years) (8). They defined the OSA as  $AHI > 5$ /hour of sleep; the prevalence of OSA with excessive daytime sleepiness was 4% in men and 2% in women, while OSA alone presented in 24% of men and 9% of women, regardless of daytime sleepiness (5, 8). The prevalence of an  $AHI > 15$  was 9% for men, and 4% for women (9). According to the cohort studies (Wisconsin, 1988–2011), the prevalence of OSA was essentially higher in men, older subjects and subjects with higher body mass indexes (BMI) (9).

There has been an increase in the prevalence of OSA in recent decades, especially among middle-aged adults. A recent study by Peppard (2013), determined the prevalence among people between the ages of 30 and 70, in a study conducted from 2007 to 2010. Twenty six percent of the participants appeared to have mild to severe OSA ( $AHI \geq 5$ ), and 10% suffered from moderate to severe OSA ( $AHI \geq 15$ ) (10).

Significant gender differences were also noted. Men (13%) appeared to be more affected than women (6%), in the moderate to severe OSA subgroup ( $AHI \geq 15$ ). Fourteen percent of the

men and 5% of the women, were also found to have an OSA (AHI  $\geq$  5) in association with daytime sleepiness (10).

Despite extensive research in the investigation of its prevalence, OSA remains largely undiagnosed (11, 12). Young et al. looked at undiagnosed OSA using the same Wisconsin Sleep Study sample, and found that up to 93% of the women, and 82% of the men may have had undiagnosed moderate to severe OSA. The percentage was even higher for participants with a less severe OSA (13).

A recent multi-racial study concluded that only 7.4% to 16.2% of patients with an AHI  $\geq$  15 were diagnosed with sleep apnea (14). Thus, raising the issue of the under-diagnosis of a clinically significant health disorder.

## **1.2 OSA Diagnosis**

### **1.2.1 History:**

For the diagnosis of OSA in patients with a suspected disease, it is important to obtain a comprehensive general and sleep history in order to determine the signs and symptoms. Individuals with OSA have been found to present with daytime as well as nocturnal symptoms. Daytime symptoms include excessive daytime sleepiness, fatigue or tiredness, morning headaches (11, 15, 16), impaired concentration, decreased libido, irritability and depression (17, 18). Snoring, choking, gasping, witnessed apneas, restless sleep, insomnia, and nocturia are nighttime symptoms frequently reported by patients with OSA (5, 16, 17). The presenting symptoms are usually combined with a family history, obesity or other risk factors.

These signs and symptoms, along with repetitive cycles of hypoxia, airway collapse, and sleep fragmentation, were found to lead to a higher incidences of serious health issues,

including hypertension (19), myocardial infarction, congestive heart failures, strokes (20), diabetes mellitus (5), a seven-fold increase in motor vehicle accidents (21) and a poorer quality of life (18).

Not all patients complain about the symptoms due to lack of awareness; they believe that these symptoms are normal for their age, present with comorbid issues, have differences in the disease presentation, or are asymptomatic. Obtaining a good medical history and detailed sleep history from the patient and the bed partner appears to be important for an OSA diagnosis (3).

In addition, OSA screening tools and sleepiness assessment questionnaires such as Epworth Sleepiness Scale (ESS) (22), FOSQ (23, 24), Berlin Questionnaire (25), STOP Questionnaire (26) and STOP-BANG Questionnaire (27), have proven to be useful aides in the screening and diagnosis of OSA.

### **1.2.2 Physical Examination:**

Clinical examinations include general and orofacial assessments. General examinations for major body systems encompass the cardiovascular, respiratory, and neurological systems (28), followed by assessments to investigate the presence of common OSA predictors like obesity ( $BMI \geq 30 \text{ kg/m}^2$ ) (6), large neck circumference (men  $> 17$  inches, women  $> 16$  inches), modified Mallampati score  $\geq 3$ , adenoid and tonsillar hypertrophy (29, 30), enlarged tongue and uvula (30), high arched and narrow palate, small retrognathic mandible (18), increased overjet, nasal obstruction (6) and deviated nasal septum (18). These factors were found to contribute to the upper airway narrowing but they were not always present.

However, subjective assessments, (history and physical examinations) alone, are not sufficient for a definitive OSA diagnosis. Approximately half of the cases were found to be

wrongly diagnosed by sleep experts, when no further investigations had been conducted (31). Therefore, objective testing must be performed in order to diagnose OSA more accurately.

### **1.2.3 Objective Testing:**

There are two accepted methods for OSA objective testing; the in-laboratory overnight polysomnography (PSG), and home testing with portable monitors (PM) (6). PSG is the gold standard for OSA diagnosis.

**Level I sleep study or in laboratory polysomnography (PSG)** is a laboratory sleep study performed in a hospital setting with attending sleep technicians, utilizing a minimum of seven physiological signals. These include electroencephalography (EEG), electrooculography (EOG), electrocardiography (ECG), chin electromyography (EMG), nasal sensor for airflow, respiratory effort, ventilation, oxygen saturation measurements, body position and leg EMG derivations (5, 32).

The setting for the sleep study and scoring of events should be done according to the AASM manual for scoring of sleep and associated events (32). The total number of obstructive sleep events is reported using an apnea hypopnea index AHI (apnea and hypopnea/ hour of sleep), or respiratory disturbance index (RDI= AHI+ respiratory event related arousals). OSA diagnosis is confirmed if an AHI  $\geq 15$  events/hour or 5 events/hour with symptoms such as daytime sleepiness, fatigue, insomnia, gasping, choking or loud snoring. OSA severity is classified as mild for AHI  $\geq 5$  and  $< 15$ , moderate for AHI  $\geq 15$  and  $\leq 30$ , and severe for AHI  $> 30$ /hr (33).

Although PSG is the gold standard for an OSA diagnosis, the drawbacks of the procedure include, cost, it's time consuming, and the risk of not replicating the regular sleep pattern due to the unnatural setting of the sleep lab (34).

**Level II sleep study** is similar to Level I sleep study but without the presence of the sleep technician, where all the channels are the same, but done many times at the patient's home. It is utilized primarily for research purposes (35).

**Level III sleep study, Portable Monitors (PMs)** consists of a portable device used by the patient in their home setting, with a minimum of four signals to record the chest movement through chest belt, airflow with nasal cannula, respiratory effort with the abdominal belt, and oxygen saturation with an SpO<sub>2</sub> sensor. AASM recommends using PMs as an alternative to a PSG for an OSA diagnosis in patients with a high probability of moderate to severe OSA, without comorbid conditions (36). The scoring system should follow the AASM manual as in the PSG study. The obstructive events reported using the RDI, which is defined differently than when used with a PSG. RDI in PMs is the number of apneas + hypopneas / total recording time rather than the total sleep time, where the recording time is usually longer than the actual sleep time (37). Therefore, using RDI in PMs tends to underestimate the severity of OSA, as opposed to the AHI used in PSG (3).

**Level IV sleep study or Pulse Oximetry** is used by the patient in their home setting, records one or two parameters, such as oxygen saturation, and airflow or chest movement. It is mainly used as a screening or follow-up, rather than a diagnosis tool due to its limited assessment and low specificity (37).

### **1.3 OSA Pathophysiology**

Several factors have been found to contribute to the pathophysiology of OSA as reviewed by Eckert (4), including dilator muscle activity and reflexes, upper airway anatomical factors, lung volume, ventilatory control stability, arousal from sleep, rostral fluid shifts, and genetics. The contributions of each factor varied between individuals and between ethnic groups, which, in turn, affect the treatment modality for the individuals (17). Repetitive collapse and reopening of the upper airway in OSA patients resulted in disturbance of ventilation, hypoxia, and hypercapnia, followed by an increase in respiratory effort and sleep disruption (arousal) (4).

Dilator muscles appear to have an important role in maintaining a patent upper airway. In healthy individuals, it was found that the muscle activity for genioglossus muscles decreases during sleep (38), whereas in OSA individuals, the muscle activity is modified and activated in response to both central stimuli from brain input, respiratory drive, and local stimuli from mechanoreceptors of negative pharyngeal pressure (4).

In addition, several local anatomical factors can lead to the narrowing of the upper airway passages. Computerized tomography (CT), and Magnetic Resonance Imaging (MRI) studies showed reduced upper airway measurements in OSA patients during wakefulness (39, 40). OSA patients usually had enlarged soft tissue structures (soft palates and tongues), in addition to some skeletal characteristics, like a small maxilla and mandible, which compromise the airway and increase risk of collapsibility.

Another mechanism is lung volume which has an important interaction with the pharyngeal airway. Upper airway muscles respond to changes in lung volume; as the end-expiratory lung volume decreases, the upper airway collapsibility increases (41). Also, it is found that OSA patients usually have a higher loop gain due to premature arousal events, which then

leads to unstable ventilatory control, fluctuation in muscle activity, sleep disruption (42), and hyperventilation, leading to airway collapse (4, 43, 44).

## **1.4 OSA Risk Factors**

### **1.4.1 Gender:**

Males are usually more affected than females, with a male: female ratio of approximately 3:1 (8, 11). There are several variations that can explain these gender differences; inconsistency in reports of classical symptoms by women, (45), under-reporting of symptoms by the bed-partner (11), lower suspicion by health care providers (11) and less severe OSA in women (46).

In addition, women have different AHI and breathing characteristics than men do, as they tend to have shorter breath duration, associated with less oxyhemoglobin desaturation. Women also tend to have a lower AHI in non-rapid eye movement (non-REM) sleep, but have a similar AHI in REM sleep (11, 47).

The male predominance has also been attributed to gender differences in the upper airway (UA) anatomy, function (11, 46), and the ventilatory response (46), (11), (48, 49). In 2001, Bixler highlighted the hormonal differences during pre and post-menopause, as a factor effecting OSA pathology. OSA is higher in post-menopausal women and there was an association found between hormone replacement therapy and low OSA prevalence (50), however, short term hormonal replacement alone was not found to improve the disease to levels where it was deemed to be a beneficial therapy (51).

Male predominance could be associated with sex-related differences in UA anatomy and function, obesity and fat distribution, ventilatory control, and hormonal status. Moreover, sex differences in clinical manifestation, including less severe OSA, more frequent reports of non-

specific symptoms, and the presentation with more coexisting problems in women, may lead clinicians to consider other diagnoses (46).

Another explanation to the increased risk in men is the pattern of fat deposition (52, 53). Men tend to have a larger neck circumference (54), and more central adipose tissue around the neck, trunk and abdomen (52, 55, 56).

Additionally, the difference in bone and airway soft tissue anatomy might affect the airway collapsibility in persons with OSA (53). Studies have shown that there is a difference in upper airway anatomy between males and females. A study by Martin, in 1997, compared the UA anatomy between 60 healthy men, and 54 healthy women, with a mean age of 35 years. The study revealed a decrease in the dimensions of the UA with increasing age, in both genders, and a greater upper airway collapse in the oropharyngeal junction in the male gender (57).

#### **1.4.2 Age:**

OSA can occur in any age group, but there is an increase in prevalence in middle and older ages (14). Ancoli-Israel et al., in 1991, reported that the prevalence was higher in elderly people (65 to 99 years of age) where 70% of men, and 56% of women had an OSA (AHI>10/hr).

When analyzing 433 patients with an OSA by age range (<43, 43-52, and >52 years), Montoya et al. (58) found that patients older than 52 years were 3.8 times more likely to have OSA than younger individuals.

As previously confirmed and confirmed by the Wisconsin Sleep Cohort Study (9), older men had a higher prevalence of OSA. The relationship between age and OSA was stronger in

women than in men. Among overweight men (BMI 25–29.9), the prevalence of OSA was two-fold higher in older men than in younger men (37% vs. 18%, respectively); while it was five-fold higher in older women versus younger women (20% vs. 4%, respectively) (10).

An explanation of the age relation includes – increased fat deposition in the parapharyngeal area, increased length of soft palate and structural changes around the pharynx (59, 60). A reduction of the oropharynx dimension with increasing age, due to an increase in soft palate length, was also reported by Johnston and Richardson (61), using cephalometric radiographs.

In addition, increased age is associated with a decrease in the elastic recoil of the lung, a reduction in lung volume, leading to a decrease in tracheal tug, as well as increased collapsibility and decreased arousal threshold (62).

The position of the hyoid bone changes in older individuals. Maltais et al. (63) reported an increase in the mandibular plane-hyoid distance in older patients. Another study reported a change in the hyoid bone position with age (64). Yet, another study, by Mayer et al., observed different features in different age groups. In young and slim patients, upper airway abnormalities were the significant reason for OSA severity (AHI), while old, obese patients had less airway abnormalities suggesting the influence of a different mechanism for OSA (65).

### **1.4.3 Ethnicity:**

OSA is a disease commonly prevalent in both developed and developing countries (11). Epidemiological studies show a variation in prevalence with the characteristics and risk factors being different among different ethnic groups.

Some studies found no difference in the prevalence (10), but this could be due to the small sample size, or lack of ethnicity variation in their sample. On the other hand, other studies reported a difference in the OSA among different racial groups.

The studies involving a comparison between Caucasian and Chinese populations revealed a relatively similar prevalence, but had different risk factors. Chinese patients appeared to have more severe OSA (66) at a lower BMI compared to their Caucasian counterparts (8, 67, 68). The Chinese also appeared to have more craniofacial abnormalities (66).

A large variation between studies exists, including variations in methodology, sleep study techniques used and the definition of OSA, which might affect the true prevalence of the disease in specific populations or ethnic groups.

Income may also influence the prevalence of OSA. In one study, there was a higher prevalence in high-income countries (10% in women and 20% in men) (5, 7). Conversely, despite less overall obesity, Brazil, and some Asian countries, had the same, if not higher prevalence, as high-income countries (68, 69).

In conclusion, the prevalence of OSA is different between different ethnic groups, and the contribution of risk factors, like obesity and craniofacial features, also differs between ethnic groups (67, 70).

#### **1.4.4 Obesity:**

Obesity is considered a strong and significant risk factor in sleep apnea (7) (71) (72) (54) (52). The current increase in the obesity epidemic has resulted in an increase in obesity-related conditions, including the OSA (8, 10).

Several studies have highlighted the direct positive relationship between obesity increase

and undiagnosed sleep disordered breathing (71, 73, 74). According to Young et al. 1993, an increase of 1 SD in any measure of body habitus, was related to a three-fold increase in the risk of AHI of 5 or higher (8). The Wisconsin Sleep Cohort study found that a 10% weight gain predicted an approximately 32% increase in the AHI (weight gain: OSA severity = 1%: 3%). A 10% increase in weight predicted a six-fold increase in the odds of developing moderate-to-severe OSA (74). On the other hand, Serafini found no correlation between OSA severity and the degree of obesity, as assessed by the Body Mass Index (BMI) in severely obese patients presenting for bariatric surgery (75). However, this could be explained by the small sample size and especially by the lack of PSG studies for all the subjects in their study.

The increase in body mass index of greater than  $28 \text{ kg/m}^2$  is associated with an increase in OSA prevalence up to 41%, as evaluated by overnight polysomnography (PSG) (76). In another study, 58% of the moderate to severe OSA was related to a  $\text{BMI} \geq 25 \text{ kg/m}^2$  (71). In a group of patients presents for bariatric surgery, Lopez et al. in 2008, investigated the presence of OSA in morbidly obese patients with a mean age of 43 years, and a mean BMI of  $52 \text{ kg/m}^2$ . He concluded that the incidence of OSA had been underestimated in this group of patients and the prevalence of OSA could be as high as 78% in morbidly obese patients, who presented for bariatric surgery. The percentage was even higher (up to 95%) in those with a BMI of  $60 \text{ Kg/m}^2$ . Furthermore, the study confirmed the proportional relationship between the BMI and OSA severity, and recommended an OSA screening for those patients before they undergo bariatric surgery (77).

Similarly, Schwartz et al. conducted a study to determine the OSA prevalence and severity in bariatric surgery patients ( $n = 114$ ), with overnight sleep studies, at the John Hopkins Sleep Disorders Center. The study revealed that a high percentage of patients had mild

to moderate OSA (95.7% of men and 65.9% of women with AHI > 10 events/hour), and moderate to severe OSA was present in 65.2% of the men, and 23.1% of the women at an AHI > 30/hour, with the central obesity markedly higher in men than in women (52).

In conclusion, it is recommended that a preoperative clinical sleep evaluation be performed, preferably a PSG, to assess the presence of OSA in pre-bariatric patients, due to a high prevalence of OSA in these populations (6).

#### **1.4.5 Craniofacial Anatomy:**

The mechanisms of craniofacial morphological development are complex as a result of several interactions between genes, hormones, nutritional, and environmental factors (78). There are several craniofacial characteristics which can lead to narrow upper airway, and predispose the patient to OSA, which include, but are not limited to retrognathic maxilla and mandible, tonsillar hypertrophy, enlarged tongue and soft palate, and a lower position of the hyoid bone (79). In order to determine the craniofacial risk factors in the OSA, a meta-analysis showed that a decrease in mandibular body length had a strong association with increased risk of OSA (80).

Different ethnic groups present with different craniofacial features and hence risk factors for OSA. Anthropological measurements found that the short wide face pattern (brachycephalic) was common among Caucasians (81), the long narrow face pattern (dolicocephalic) was common among Japanese men (82), the large tongue and soft palate were features present in African Americans (83) and Chinese patients had more craniofacial abnormalities. The abnormalities of the Chinese population included a short cranial base, acute

cranial base angle, narrow upper airway, and retrognathic mandible, which increased their OSA susceptibility (66, 70).

#### **1.4.6 Familial and Genetic Predisposition:**

Genetics plays a major role in an individual's susceptibility to OSA. Both OSA and its risk factors can be genetically inherited. Although obesity, patterns of fat deposition, muscle activity, respiratory control, and craniofacial structure are genetically determined, and can interact and lead to OSA pathogenesis, a specific gene is yet to be determined as the cause factor for OSA (84).

In the 1970s, Strohl et al. studied the familial genetic contribution of hypersomnia and OSA, in a family with two sudden deaths of individuals, due to sleep apnea (85). Segregation analyses for the Cleveland Family Study concluded that genetics accounted for 35% of the OSA severity (i.e., AHI) independent of the BMI contribution. Different racial backgrounds presented with different modes of inheritance, and different risk factors (86). The familial and genetic factors contributed to the heritability of craniofacial abnormalities, such as retroposition of the maxilla and mandible, a longer soft palate, and a wider uvulae (87, 88). In addition, a volumetric MRI study showed that the size of the upper airway, including the size of the tongue, lateral pharyngeal wall, and total soft tissue, demonstrated family aggregation (89).

All of these factors resulted in a compromised upper airway, and tended to run in the family. Moreover, research also showed a familial abnormality in ventilatory control and respiratory response during sleep (90, 91).

#### **1.4.7 Smoking:**

Epidemiological investigations highlighted the association between smoking and the prevalence of snoring and OSA (11, 92). Smoking has been found to affect the respiratory response through several aspects: nasal stuffiness, upper airway irritation and inflammation, mucosal edema and secretion, reduced airway sensations and arousal thresholds due to disturbed sleep (5, 93). Smoking has also been known to change the mechanical and neural mechanisms of the upper airway and increase their collapsibility (11). Smoking is a modifiable risk factor and patients need to be aware and advised on smoking risks.

#### **1.4.8 Alcohol:**

Similar to smoking, alcohol consumption has also been found to increase upper airway collapsibility (11). Alcohol consumption on asymptomatic men was associated with snoring during sleep, significant increases in the arterial oxygen desaturation events, and the number of apneic events (94). Another study used an overnight polysomnography to assist in the sleep of asymptomatic patients after drinking alcohol; the results revealed a lower oxygen saturation, more nocturnal oxygen desaturation episodes, and more hypopnea (95). Furthermore, alcohol was found to decrease the respiratory output of the upper airway which leads to hypotonia in oropharyngeal muscles (96). OSA patients are generally advised not to drink and/or to keep consumption to a minimum.

## **1.5 OSA Management**

OSA diagnosis and etiology identification allow the treatment to be targeted towards the patient's specific condition in an efficient way. The different pathophysiology pathways are not yet fully understood and specific target treatments are under investigation. Several treatment options are available to address the patient's upper airway collapse.

### **1.5.1 Nasal Continuous Positive Airway Pressure (CPAP):**

CPAP was introduced in 1981 for OSA treatment (97). It is considered the treatment of choice for adults with moderate to severe OSA (98). CPAP acts by providing pressurized air through a mask during sleep. This air stream helps to keep an open airway, restore the oxygen level, maintain a positive pharyngeal pressure, and increase end-expiratory lung volume (99). The disadvantage of CPAP is that it has a low adherence rate of approximately 40%–70% (5) depending on the follow-up length.

### **1.5.2 Oral Appliances:**

Oral appliances (OAs) are an effective and alternative treatment for OSA. OAs maintain the mandible and/or the tongue in a protruded position, to allow for an unobstructed airway, and prevent retroglossal collapse (5). It is available in many types; there are custom and non-custom, and titratable and non-titratable appliances (98). When the effectiveness of CPAP was compared to OAs, there was no statistically significant difference in the improvement of symptoms and cardiovascular markers in patients with mild, moderate and severe OSA, despite CPAP being more successful in AHI reduction (98).

Disadvantages of OAs included costs with the need for the device to be fitted by trained dentists (98), frequent dental follow up for device titration, (5) and possible dental side effects (98). On the other hand, OAs are well tolerated by the patients, have better compliance than CPAP, are less strenuous, and they do not require an electrical source(100). Oral appliances are the second line therapy for OSA.

### **1.5.3 Surgery:**

Several surgical procedures are available to address a patient's specific problem. It is an option for OSA treatment when other non-invasive approaches have failed to solve the problem and when anatomical deformities are present (6). Surgical treatment involves a wide variety of surgeries including uvulopalatopharyngoplasty (UPPP) (5), genial advancement, hyoid suspension or both (101), maxilla-mandibular advancement, tracheostomy (5), and hypoglossal nerve stimulation (102).

Today, the surgery with the highest success rates is bariatric surgery. A surgical approach for weight loss in morbidly obese patients through bariatric surgery has been shown to be effective in improving OSA symptoms. Two controlled studies, conducted by Smith et al. and Schwartz and colleagues (103, 104), concluded that the reduction of weight by 10-15% results in a 50% reduction in OSA severity as measured by the AHI. A meta-analysis by Greenburg, in 2007, involved 342 patients who underwent bariatric surgery and he evaluated the changes in OSA symptoms using PSG sleep study before and at least three months after the surgery. The result revealed that the mean AHI decreased from 45.7 events/hour to 15.8 events/hour and they concluded that the bariatric surgery significantly reduced AHI, however the OSA was not completely eliminated (105).

#### **1.5.4 Conservative Measures:**

Behavioral changes and conservative measures can be helpful, such as an adequate amount of sleep for 7-8 hours and changing from the supine position to side sleeping in position dependent OSA cases (106). In addition, avoidance of substances, like alcohol, that worsen the symptoms, is also recommended (5).

Diet and exercise to lose weight are also advisable (107). Weight loss has been found to reduce, and in some cases, eliminate OSA (7, 108, 109). In 2008, Punjabi and colleagues found that a 10% decrease in weight was associated with a 26% decrease in OSA severity, as measured by AHI, while changes in other body measures (neck and waist circumference) had no relation to changes in AHI (11). A randomized control trial showed the positive effects of weight loss on the improvement of OSA symptoms. It was found that a 10 kg reduction in weight could reduce the AHI by five events/hour (107). Also, exercise, alone, without weight loss, has proven to improve OSA (110).

Therefore, it is important to state that this approach may not be enough to eliminate OSA, and must be combined with other measures like continuous positive airway pressure (CPAP) (10, 111). The lack of complete resolution of OSA in response to weight loss can be attributed to different aspects, such as craniofacial characteristics or changes of upper airway functioning.

Since obesity and weight change are modifiable risk factors which can play a role in disease progression and regression, further investigation and research are required in this field. (8, 10, 74).

## **1.6 Obesity and OSA**

### **1.6.1 Obesity Epidemic:**

Obesity is one of the most important factors in the pathophysiology of OSA. Body mass index (BMI) is a simple calculation that uses a person's weight and height to measure obesity in both sexes in individuals 18 years and older. BMI is calculated as a person's weight in kilograms, divided by the square of his height in meters ( $\text{kg}/\text{m}^2$ ) (112). According to the World Health Organization (WHO); a BMI  $\geq 25 \text{ kg}/\text{m}^2$  is overweight, and a BMI  $\geq 30 \text{ kg}/\text{m}^2$  is obese (113).

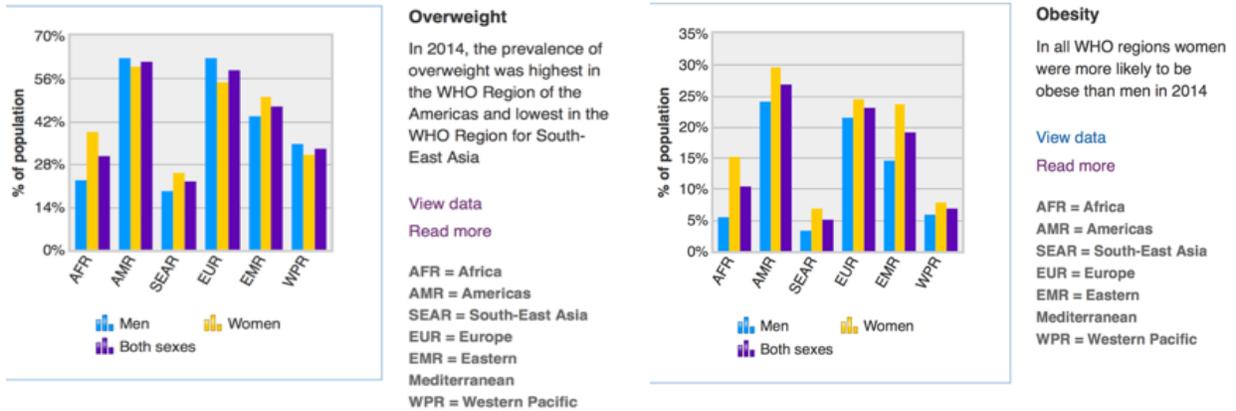
In 2014, the Centers for Disease Control and Prevention (CDC) revealed that no American state had a prevalence of obesity less than 20%. The Midwest had the highest prevalence of obesity (30.7%), followed by the South (30.6%), the Northeast (27.3%), and the West (25.7%) (114). According to Odgen, Carroll et al. (2014), more than one-third (34.9% or 78.6 millions) of U.S. adults were obese by the year 2013 (115).

As per the WHO fact sheet, updated in June 2016, worldwide obesity has more than doubled since 1980. In 2014, global statistics showed that 39% (38% men, 40% women) of adults were overweight, and 13% (11% men, 15% women) were obese. In Canada, 64.4% of adults were overweight compared to 62.6% in 2010 and 28% were obese compared to 25.9% in 2010 (113).

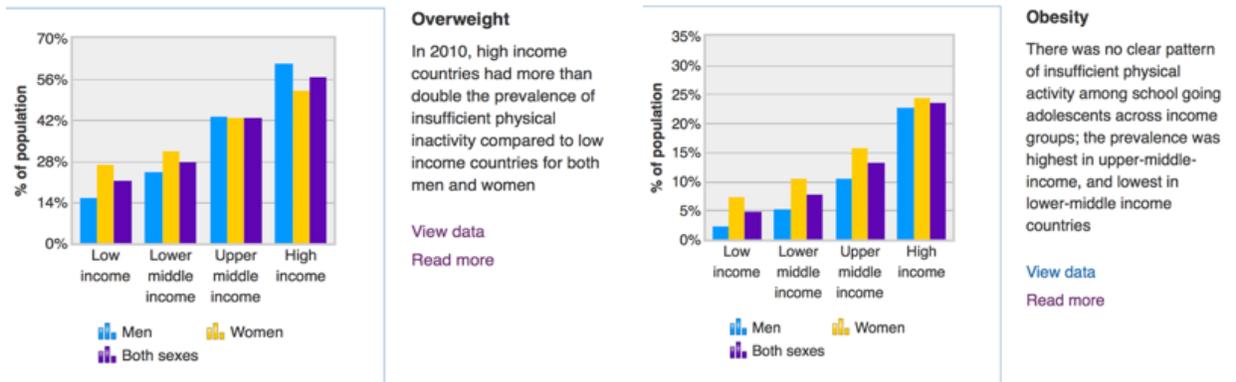
Obesity prevalence differs according to the region, ethnic background, and income level. In 2014, the Global Health Observatory (GHO) data estimated obesity according to WHO regions, which was highest in the WHO Regions of the Americas (61% overweight, 27% obese) and lowest in the WHO Region for South East Asia (22% overweight, 5% obese). In all WHO regions, women were more likely to be obese than men (116). An increase in BMI had a proportional relationship with the income level of countries, where the prevalence of obesity in

high income countries was more than double that of low and lower middle income countries (113).

**Figure 1- 1 WHO Overweight and Obesity Prevalence According to WHO Region (113)**



**Figure 1- 2 WHO Overweight and Obesity Prevalence According to World Bank Income Group (113)**



The National Health and Nutrition Examination Survey (NHANES) revealed that severe obesity (BMI > 40 kg/m<sup>2</sup>) rose to epidemic proportions in the U.S adult population from 2.9% in 1988–1994 to 5.7% in 2008 (117). Today, it is estimated that up to 16% and 27% of all-cause mortality in men and women respectively is somewhat associated with overweight and obesity in the US (118).

### **1.6.2 Relationship Between Obesity and OSA:**

The association between obesity and OSA development can be explained through several mechanisms (52):

- 1- Genetics: the heritability factors in sleep apnea and obesity were demonstrated in the Cleveland Family Study cohort (119), so both AHI and BMI co-segregate. Other studies mentioned that obesity contributed to the heritability of the OSA (120, 121), and played a major role in the associations between sleep apnea and specific genetic loci (122).
- 2- Mechanical compensatory factors: mechanical factors are related to excess local fat accumulation, which has been found to result in a reduction of the airway size (52). In obese individuals, there is an increase in abdominal fat deposition, resulting in a smaller lung volume accompanied by higher pharyngeal collapsibility (5, 123). In addition, changes in lung volume are well known to affect the upper airway size and stiffness, this happens due to a caudal traction on the trachea (124). Furthermore, reduction in lung volume and oxygen stores increases the ventilatory metabolic demand and effort of breathing (52, 123, 125).

- 3- Neural compensatory factors: the molecular signaling pathway in adipose tissue has a different activity that can produce alterations in the neural compensatory factors. Neural factors include impaired upper airway neuromuscular control regulated by signaling protein (adipokines) (52), and instability of the respiratory control system which has been found to lead to a decrease in the functional residual capacity of the upper airway caudal traction (126).
- 4- Obesity has been known to directly produce an inflammatory condition through pro-inflammatory cytokines in adipose tissue, such as the tumor necrosis factor (TNF)- $\alpha$ , and interleukin 6 (IL-6) (127).

## **1.7 Interaction Between Obesity, Craniofacial Structures and OSA**

### **1.7.1 Craniofacial Morphological Features of Obese Non-OSA Patients:**

In a study that compared the facial features of obese individuals (mean BMI= 31.67 kg/m<sup>2</sup>, SD= 1.58) with non-obese, normal controls matched for age, ethnicity and gender, it was found that obese individuals had larger skull dimensions, an increased skull width, an increased lower face depth and a mandibular corpus length and decreased upper facial height (UFH) (128).

Another study by Ohrn and collaborators in 2002, described the craniofacial morphology in obese adolescents (BMI= 32.08 to 45.12 kg/m<sup>2</sup>) using lateral cephalometric radiographs and concluded that despite low growth hormones (GH), obese subjects showed more advanced craniofacial development with increased mandibular length, prognathic maxilla and mandible, reduced UFH and a larger nasopharyngeal airway (129).

Sadeghianrizi in 2005 investigated craniofacial development in 50 obese adolescents through several measurements on lateral cephalometric radiographs and compared them to

normal control matched with age and sex, although the BMI was not given in both groups. The result of this study agreed with the previous one in terms of greater craniofacial measurements in obese individuals. It was found that obese adolescents had an increased anterior cranial base length, a larger maxilla and mandible length and a more prognathic maxilla and a mandible which resulted in a reduced facial convexity. Vertically, both the lower anterior facial height (LAFH) and lower posterior facial height (LPFH) increased, and the mandibular plane angle decreased in obese patients compared to their non-obese counterparts. Also, there was an increase in upper incisor proclination in female obese patients (78), similar findings were found by a previous study by Paoli et al. in 2001 (130).

In general, obese individuals ( $\text{BMI} > 30 \text{ kg/m}^2$ ) had more advanced and forward craniofacial development than their non-obese counterparts.

### **1.7.2 Craniofacial Morphological Features of Non-Obese OSA Patients:**

The craniofacial features of OSA patients with normal weight were investigated in several studies. Ang et al., in 2004, measured craniofacial characteristics and the head posture of 61 male non-obese OSA Chinese subjects diagnosed with PSG studies. He found that moderate to severe OSA subjects had a smaller anterior cranial base length, an acute cranial base angle, an increased gonial angle and a retrognathic mandible, however, none of these differences were significant. In addition, the moderate to severe OSA groups had more caudal hyoid bone position in relation to the mandibular border. No comparison with non-OSA subjects was made due to ethical reasons. For the head posture, no difference was found between the mild and moderate and the severe group, but when the postural variables were compared to normal published control subjects it was found that the OSA group had increased craniocervical, craniovertical and

craniohorizontal angulations. These changes in head extension and increased craniocervical angulation might reflect the compensatory mechanisms to maintain a patent airway (131).

Another study determined the cephalometric morphology in 35 Caucasian male patients with OSA by analyzing the lateral cephalometric radiographs and comparing the measurements with 24 control subjects with no history of a respiratory conditions. The study showed that OSA patients had a shorter cranial base, a smaller cranial base angle and a shorter mandibular body length. For the soft tissue, it was found that OSA patients had a narrower oropharynx, a larger soft palate area, and decreased inter-maxillary space for the tongue (the distance between the posterior pharyngeal wall and the tip of the lower incisor) (132).

Lowe et al. had several studies in 1986, 1995 and 1996 investigating the craniofacial morphology of OSA patients using both cephalometric and computerized tomography (CT). His studies showed that OSA patients had a retrognathic maxilla and mandible, an increased ANB angle, a steep mandibular plane angle, an increased gonial angle, increased upper and lower facial height, overeruption of the upper and lower teeth, proclined incisors and an anterior openbite. In addition, OSA subjects had larger tongues and soft palates (133-135).

To summarize, most of the studies agreed upon common cephalometric craniofacial and dental features of non-obese OSA subjects including short anterior cranial base (132, 136, 137), acute cranial base angle (131, 132, 138), retrognathic mandible (133, 134, 136, 139), larger ANB angle (134, 140), shorter mandibular body length (132, 141), increased lower facial height (133, 134, 136, 139-141), increased mandibular plane angle (133, 136, 139, 140, 142), more obtuse gonial angle, elongated maxillary and mandibular teeth (133, 134), proclined incisors, increased anterior openbite, increased in the length and thickness of the soft palate (132, 134, 137, 138, 140, 141, 143-145), large tongue (133, 141), narrower upper airway (132, 141), inferiorly

positioned hyoid bone which directly influences the position of the tongue and airway space (133, 134, 136, 138, 139, 141, 145, 146), and an increased cranio-cervical angle (131, 147, 148).

As seen in a recent systematic review and a meta-analysis, the most significantly affected variables in OSA patients are increased anterior facial height, reduced pharyngeal airway space and the inferiorly positioned hyoid bone. The studies were inconclusive regarding other craniofacial parameters due to significant heterogeneity (149).

### **1.7.3 Craniofacial Morphological Features of Obese OSA Patients:**

Obesity is one of the most important risk factors in OSA pathology. Studies comparing obese and non-obese OSA individuals revealed some different craniofacial morphologies. Battagel and Johal, in 2000, compared the lateral cephalograms between 28 obese and 20 normal weight patients and found that normal weight OSA subjects had a retruded maxilla, a smaller mandible, a short inter-maxillary space and uprighted incisors, while obese OSA subjects had a normal position of the maxilla, increased LAFH, normally inclined incisors and more inferiorly positioned hyoid bones (150). Similarly, Ferguson et al. in 1995, found that obese OSA patients had less craniofacial abnormalities, while their non-obese counterparts had craniofacial abnormalities such as small mandible and maxilla and a retrognathic mandible (151).

Thapa et al. in 2014 investigated the difference in craniofacial and airway features between obese, non-obese patients, and the healthy control group, while all the study subjects underwent PSG sleep study and lateral cephalometrics. They found that obese OSA patients had a prognathic mandible, an increased soft palate thickness and length, an inferior and anterior displacement of the hyoid bone and a decrease in the superior pharyngeal airway dimension when compared to the control group (152). In addition, a comparison among obese and non-

obese patients showed that non-obese patients had a retrognathic maxilla and mandible, a shorter maxilla, a narrower pharynx, a shorter palatal length and a narrower superior airway dimension (152).

Sakakibara et al. in 1999 investigated the cephalometric abnormalities in non-obese and obese OSA patients and compared them to the matched control. They determined that non-obese OSA subjects had more skeletal abnormalities such as a decreased cranial base length, a shorter maxilla and mandible, an inferiorly displaced hyoid bone, an enlarged tongue and soft palate and narrower upper airway compared to normal subjects whereas obese OSA subjects had less bony constriction and more soft tissue abnormalities. They concluded that obese and non-obese OSA patients had different etiological factors contributing to their OSA development; in obese OSA the soft tissue enlargement had an important role in OSA development, while in non-obese OSA the craniofacial discrepancies may have been the primary contributing factor in OSA (153).

Moreover, Yu et al., in 2003, analyzed the cephalometric radiographs of obese and non-obese OSA patients and compared them to non OSA patients. The results agreed with the previous studies, it was found that both OSA patients (obese and non-obese) showed an inferior position of the hyoid bone, a larger soft palate, and a narrower upper airway width. The non-obese patients had more anteroposterior bony discrepancy than their obese counterparts and non-OA patients. On the other hand, obese OSA patients had an increased A-P maxillary bone length, a mandibular prognathism, an anteriorly displaced hyoid bone and more severe soft tissue enlargement such as a larger soft palate and tongue (154).

In addition, the effect of obesity on craniofacial features was reported in a systematic review by (155) and another review by Sutherland et al. in 2012. Both studies concluded that all the selected studies reached a common conclusion; namely, that non-obese OSA subjects had

more craniofacial skeletal constriction, whereas obese OSA subjects displayed less skeletal constriction and more soft tissue abnormalities (156).

## **1.8 Obesity Onset and Craniofacial Characteristics**

From the previous studies, it appears that the craniofacial characteristics of obese OSA adults had different expression than the craniofacial characteristics of non-obese OSA. Although limited literature is present, in orthodontics literature, there is some evidence that an individual's craniofacial characteristics can be modified by the presence of obesity.

The increase in obesity has been observed in the last 50 years. Although initially observed only in adults, many studies have shown that the rate of obesity has increase in all ages. Onis and collaborators have shown that overweight and obesity in pre-school ages (2 – 5 years old) has increased in developed countries from 6.9% in 1990 to 12.9% in 2015; and globally these numbers have also increased from 4.2% to 7.9% in the same period (157). A study based on NHANES surveys for children aged 2 to 10 years old, the obesity prevalence has increased from 5% to 15.8% in the period of 1971 to 2003 and these numbers are higher in older children (10-19years old) with the prevalence moving from 6.3% to 19.8% for the same period (158). Absolute obesity prevalence was higher for female cohorts compared with male cohorts, and for black cohorts compared with white cohorts.

Recent birth cohorts are generally becoming obese in greater numbers at a given age and are experiencing a greater duration of obesity over their lifetime. This can have a major impact on this new generation health, as obesity has been associated with increased rates of cardiovascular disease and type II diabetes amongst other health issues. Experts have, therefore,

suggested that there will be profound generational consequences of the obesity epidemic in the United States (159).

There are three-critical period for obesity development during childhood and it includes the pre-natal period, the period of adiposity rebound (between 4 and 6 years of age) and adolescence. Development of obesity at any of these periods might impact the craniofacial growth (160). However, there are no studies evaluating the timing of obesity onset and craniofacial characteristics of OSA patients. If there is a difference, this could explain the heterogeneity in the findings of previous studies evaluating the craniofacial characteristics of obese OSA individuals.

## **1.9 Hypothesis**

Craniofacial anomalies among OSA patients have been investigated in several studies, but firm conclusions could not be derived as there is still a wide range of variability between different studies. One explanation could be the effect of the obesity onset on the craniofacial development and growth of obese OSA subjects. This has not been reported in any previous studies. The orthodontists have an important role in the diagnosis and treatment of these craniofacial abnormalities, hence, knowing at what point in time the patients became obese and whether this influenced their skeletal, dental and airway development would be important factors in selecting the patient's ideal treatment. Therefore, we are interested in finding out how the obesity onset is related to craniofacial abnormalities. Also, in the search for a better understanding of the pathophysiology of OSA, craniofacial characteristics may be the main component for a subset of patients, but this is poorly understood due to a wide variability between studies.

The null hypothesis of the current study is that the craniofacial features are the same between OSA subjects with an early onset of obesity and OSA subjects with a late onset.

### **1.10 Objectives**

The objective of this study was to assess the craniofacial features including the skeletal, dental, airway and head posture in obese adult OSA patients in relation to their obesity onset.

The following topics are the specific aims of the study:

- To determine the relation between the obesity onset and craniofacial morphology in obese OSA patients (evaluate if the obesity onset influences the development of craniofacial structure).
- To compare the craniofacial morphological features of obese and non-obese OSA patients.

## Chapter 2: Material and Methods

### 2.1 Subjects

Consecutive patients were referred for assessment from the bariatric program waiting list at the Department of Respiratory Medicine of the Richmond Hospital, in Richmond, British Columbia, Canada, prior to the bariatric surgery from the period of February 2016 to March 2017, and they were included in the study. Thirty nine OSA adults were recruited prospectively to the study.

Subjects with available sleep study results were eligible to be enrolled and were invited to participate in this study. The subjects were selected according to the inclusion and exclusion criteria listed in Table 2-1.

**Table 2- 1 Inclusion and Exclusion Criteria**

<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
<ul style="list-style-type: none"><li>• Adult patient (18-80 years).</li><li>• Obese (BMI&gt;30) OSA patient (indicated for bariatric surgery)</li><li>• Baseline sleep study (PSG, Level III, pulse oximetry).</li></ul>	<ul style="list-style-type: none"><li>• Completely edentulous patients</li><li>• Any patient under CPAP/oral appliance therapy for more than 2 years.</li><li>• Post-bariatric surgery patients.</li></ul>

Informed consent was obtained from all patients, and diagnosis of craniofacial morphology was made from standard cephalometric radiographs. On the basis of obesity onset, the obese OSA subjects were further divided into early (before puberty) or late obesity onset (after puberty) groups by asking the patient to answer a new questionnaire developed for this

study and illustrated in Table 2-2. The cephalometric measurements of both obese groups patients were compared with 43 non-obese OSA patients matched for age and gender. The non-obese OSA patients' data was obtained retrospectively from the University of British Columbia (UBC) database.

**Table 2- 2 Obesity Onset Questionnaire**

<input type="checkbox"/> Before puberty	<input type="checkbox"/> After puberty
<input type="checkbox"/> Before 20 years old	<input type="checkbox"/> After 20 years old
<input type="checkbox"/> Pre-school (2-5 years) <input type="checkbox"/> Elementary school, Kindergarten(6-11 yeas) <input type="checkbox"/> Middle and High school (12-19 years)	<input type="checkbox"/> University (20-25 years) <input type="checkbox"/> 26-44 years <input type="checkbox"/> 45-64 years <input type="checkbox"/> 65+ years

The study was conducted in accordance with the ethical standards of the University of British Columbia's Clinical Research Ethics Board (ethical approval # H12-03085-006).

## 2.2 Methods

### 2.2.1 Demographic Data:

Data regarding the patient's gender, age, ethnicity, weight, height and BMI were collected from each of the three groups.

### **2.2.2 Questionnaire:**

After obtaining the patients' informed consent, they were asked to complete a questionnaire about obesity onset and the history of CPAP usage. The obesity questionnaire had two options of either early obesity (before puberty, until age 20 years) or late obesity (after puberty, after age 20 years). A CPAP questionnaire was used to assess the history of CPAP use, and, if positive, to determine for how long the patients had used this type of therapy. The ethnicity question was comprised of the following eight options: Aboriginal, Hispanic or Latino, Caucasian, Asian, Black, Middle Eastern, South Asian and other.

### **2.2.3 Sleep study:**

The diagnosis of OSA was made from a sleep study using overnight PSG or Level III or IV (pulse oximetry) sleep studies. The AHI was used as the parameter for OSA diagnosis with PSG, whereas ODI (oxygen desaturation index) was used as the parameter for OSA diagnosis with Level III and pulse oximetry studies.

## **2.3 Cephalometric Analysis**

After obtaining a sleep study and a having a diagnosis of OSA being made, the patient was sent to an orthodontist office at the Richmond Health Science Center to obtain a cephalometric radiograph.

The cephalometric radiograph of an obese OSA patient were taken in the natural head position by looking straight into a mirror (161), the patient was asked to bite into a maximum intercuspation with the lips relaxed and lightly touching. The exposure was done at the end of the expiration phase while they were holding their breath. The patients practiced their breathing for

two to three times before exposure, to maintain the hyoid bone in a consistent position. A Rayscan  $\alpha$ -sc, Samsung machine was used and the parameter was adjusted to optimize the hard and soft tissue contrast with a Kvp of 85, mA of 12 and 5.2 seconds.

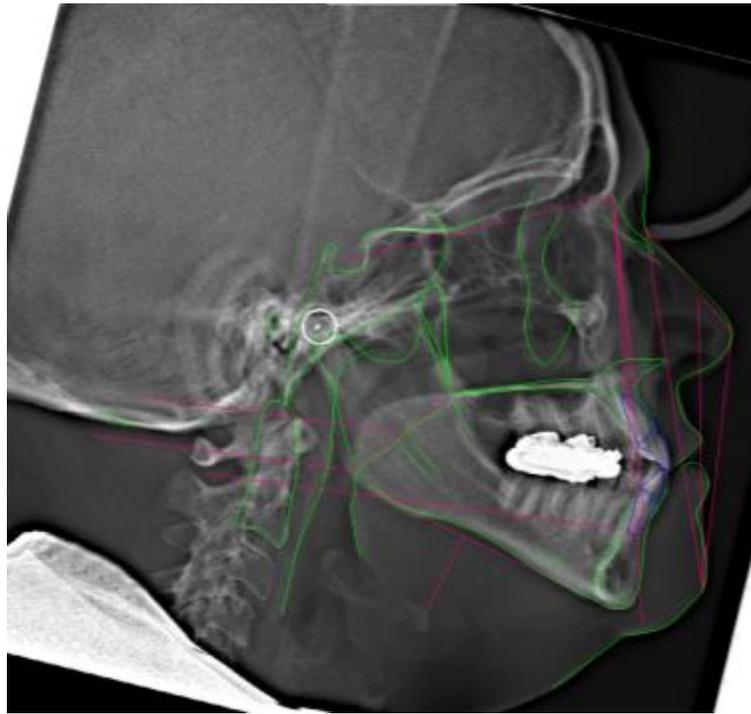
The cephalometric radiographs of control non-obese OSA patients were obtained from the UBC database, the radiographs were digitally scanned using an EPSON PERFECTION V500 PHOTO scanner at 1200 dpi and 16-bit grayscale, and the scans were saved as JPEG files. The radiographs were then imported into the Dolphin Imaging Software (version 11.7 Premium).

All radiographs were traced in a random order by one operator (SAF) to reduce the inter-examiner reliability. The patient names and demographic data were masked to eliminate possible bias.

All tracings were performed digitally using Dolphin imaging software version 11.7 Premium. A customized analysis was created in the software which contained 27 linear, 15 angular and two proportional measurements as described in Figure 2-1, and itemized in Table 2-3, 2-4, 2-5 and 2-6. In cases where there was a double image of the landmark, the average distance between the two was selected. Twenty one skeletal, 7 dental, 3 facial, 2 soft palate, 5 hyoid, 4 airway and 2 head postures variables were measured for the three groups (early obese, late obese, non-obese). Since the radiographs of obese and non-obese patients were from different machines, the magnification of linear measurements was different and it was compensated and taken into account during cephalometric tracing in order for the variables to be comparable.

To determine the intra-examiner reliability, as recommended by Houston in 1983, eleven randomly selected cephalometric radiographs were retraced under identical conditions, two weeks apart (162).

**Figure 2- 1 Cephalometric Reference Points and Lines**



### **2.3.1 Skeletal Cephalometric Analysis:**

Several skeletal measurements including an anterior cranial base length (ACBL) and angle (CBA), an anteroposterior position of the maxilla in relation to the cranial base (SNA), a maxillary length (MXL), anteroposterior position of the mandible in relation to the cranial base (SNB), a mandibular body length (MDL), a mandibular corpus length (MCL), a mandibular ramus height (MRH), a gonial angle (GOA) and a mandibular plane angle in relation to the cranial base (MPA) and Frankfort horizontal (FMA). Maxillo-mandibular discrepancy was detected using an ANB angle, Mx/Md difference (MXMD) and Wits appraisal. Moreover, vertical relationships were evaluated by measuring the upper anterior facial height (UAFH), lower anterior facial height (LAFH), total anterior facial height (TAFH), posterior facial height (PFH), the proportion of upper to lower facial height (UFH:LFH) and the Jarabak ratio of

posterior to anterior facial height (PFH:AFH). These measurements are summarized in Table 2-3.

### **2.3.2 Dental Cephalometric Analysis:**

Dental variables assessed included overbite (OB), overjet (OJ), proclination and protrusion of the upper and lower incisors (U1SN, U1NA, IMPA, L1NB, respectively), and the interincisal angle (U1L1) when applicable, as described in Table 2-4.

### **2.3.3 Facial Cephalometric Analysis:**

Facial soft tissue measurements of the upper and lower lips (ULEP, LLEP, respectively), the nasolabial angle (NLA), the soft palate length (SPL) and thickness (MAXSP) were recorded and can be seen in Table 2-5.

### **2.3.4 Hyoid, Airway and Head Posture Cephalometric Analysis:**

Table 2-5 summarizes the hyoid bone position with both vertical (HYMP, HYRGN) and horizontal (HYC3) positions being determined by linear and angular measurements (HYA, HYMEMP). The upper airway region was divided into three parts, the superior airway space (SPAS), the middle airway space (MAS), and the inferior airway space (IAS); in addition, the vertical airway length (VAL) was measured, and the variables are described in Table 2-6.

Head posture was an important variable in previous studies, therefore we have measured head posture in relation to the cervical vertebra with the cranial base (CVSN) and the maxilla (CVPP) as described in Table 2-6.

**Table 2- 3 Skeletal Measurements**

<b>Variable</b>	<b>Abbreviation</b>	<b>Definition</b>
<b>Cranial base:</b>		
Anterior cranial base length (mm)	ACBL	Linear distance between S and N
Cranial base angle (°)	CBA	Angle Between S-N-Ba
<b>Maxilla:</b>		
Maxilla to cranial base (°)	SNA	Angle between S-N-A
Midface length (mm)	MFL	Linear distance between Co and A
Maxillary length (mm)	MXL	Linear distance between ANS and PNS
<b>Mandible:</b>		
Mandible to cranial base (°)	SNB	Angle between S-N-B
Mandibular length (mm)	MDL	Linear distance between Co and Gn
Mandibular corpus length (mm)	MCL	Linear distance between Go and Gn
Mandibular ramus height (mm)	MRH	Linear distance between Ar and Go
Gonial angle (°)	GOA	Angle between Ar-Go-Me
Mandibular plane angle (°)	MPA	Angle between MP and S-N line
Frankfort to mandibular plane angle (°)	FMA	Angle between MP and FH
<b>Maxilla to Mandible:</b>		
Maxillomandibular relationship (°)	ANB	Angle between A-N-B
Mx/Md difference (mm)	MXMD	Difference between Co-Gn and Co-A
Wits Appraisal (mm)	WITS	Linear distance between Ao and Bo
<b>Vertical relation:</b>		
Upper anterior facial height (mm)	UAFH	Linear distance between N and ANS
Lower anterior facial height (mm)	LAFH	Linear distance between ANS and Me
Total anterior facial height (mm)	TAFH	Linear distance between N and Me
Posterior facial height (mm)	PFH	Linear distance between S and Go
Upper facial height to lower facial height (%)	UFH:LFH	N-ANS / ANS-Me
Posterior facial height to anterior facial height (%)	PFH:AFH	S-Go / N-Me
<p><u>Landmarks:</u> S= Sella, N= Nasion, Ba= Basion, A= point-A, Co= condylion, ANS= Anterior Nasal Spine, PNS= Posterior Nasal Spine, B= point-B, Gn= Gnathion, Go= Gonion, Ar= Articulare, Me= Menton, MP= Mandibular Plane, FH= Frankfort Horizontal, Mx= Maxilla, Md= Mandible, Ao= point A perpendicular to occlusal plane, Bo= point B perpendicular to occlusal plane.</p>		

**Table 2- 4 Dental Measurements**

<b>Variable</b>	<b>Abbreviation</b>	<b>Definition</b>
Overbite (mm)	OB	Vertical overlap of U1 and L1
Overjet (mm)	OJ	Horizontal overlap of U1 and L1
Upper incisor inclination (°)	U1SN	Angle between U1 and S-N line
Upper incisor position (mm)	U1NA	Linear distance between U1 and N-A line
Lower incisor inclination (°)	IMPA (LIMP)	Angle between L1 and MP
Lower incisor position (mm)	L1NB	Linear distance between L1 and N-B line
Interincisal angle (°)	U1L1	Angle between U1 long axis and L1 long axis
<u>Landmarks:</u> U1= Upper incisor, L1= Lower incisor.		

**Table 2- 5 Facial Soft Tissue, Soft Palate and Hyoid Measurements**

<b>Variable</b>	<b>Abbreviation</b>	<b>Definition</b>
<b>Facial</b>		
Upper lip-E plane (mm)	ULEP	Linear distance between UL and E-plane
Lower lip-E plane (mm)	LLEP	Linear distance between LL and E-plane
Nasolabial angle (°)	NLA	Angle between UL, Col and Sn
<b>Soft Palate</b>		
Soft palate length (mm)	SPL	Linear distance between PNS and Pa
Max soft palate thickness (mm)	MAXSP	Linear distance between SP superior and SP inferior point
<b>Hyoid Bone</b>		
Vertical hyoid position (mm)	HYMP	Linear distance between Hy perpendicular to MP
Vertical hyoid position (mm)	HYRGN	Linear distance between Hy and RGN
Horizontal hyoid position (mm)	HYC3	Linear distance between Hy and C3
Hyoid angle (°)	HYA	Angle between Hy-Go and Hy-Me
Hyoid to MP (°)	HYMEMP	Angle between Hy-Me-Go
<u>Landmarks:</u> UL= Upper Lip, LL= Lower Lip, E-plane: tip of nose to soft tissue pogonion, Col= Columella, Sn= Subnasale, Pa= tip of uvula, SP= Soft Palate, Hy= Hyoid, RGN= Retrognathion, C3= Cervical vertebrae 3.		

**Table 2- 6 Airway and Head Postures Measurements**

<b>Variable</b>	<b>Abbreviation</b>	<b>Definition</b>
<b>Airway</b>		
Superior posterior airway space (mm)	SPAS	Width of airway along line parallel to Go-B line through middle of SP
Middle airway space (mm)	MAS	Width of airway along line parallel to Go-B line through Pa
Inferior airway space (mm)	IAS	Width of airway along Go-B line
Vertical airway length (mm)	VAL	Linear distance between PNS and V
<b>Head posture</b>		
Cervical vertebrae to cranial base (°)	CVSN	Angle between C2 superior posterior (CV2 sp)-C4 inferior posterior (CV4 ip) and SN line
Cervical vertebrae to maxilla (°)	CVPP	Angle between C2 superior posterior (CV2 sp)-C4 inferior posterior (CV4 ip) and PP (ANS-PNS)
<u>Landmarks:</u> V= Epiglottic fold, C2= Cervical vertebrae 2, C4= Cervical vertebrae 4, PP= palatal plane.		

## 2.4 Statistical Analysis

The intra-examiner reliability for cephalometric tracing and measurements was determined through eleven randomly traced and measured cephalometric radiographs with an interval of two weeks. The reliability between the measurements was determined using the intra class correlation coefficient (163).

Descriptive data regarding the patient's age, BMI and AHI/ODI is presented as mean, standard deviation and range.

Comparison of the craniofacial characteristics between the groups (non-obese, early obese, late obese) were conducted for variables with excellent reliability. For parametric variables, a One-Way Analysis of Variance (ANOVA), followed by a Tukey post-hoc analysis, was used to determine in which group the difference was. Similarly, non-parametric variables

were analyzed using a Kruskal Wallis followed by Mann-Whitney U test to determine between group differences.

Parametric variables included the SNA angle, the MXL, the SNB angle, the MPA, the ANB angle, the LAFH, UFH:LFH, PFH:AFH, the U1SN, the U1NA, IMPA, L1NB, U1L1, soft tissue variables including the ULEP, LLEP, NLA, MAXSP, and the hyoid bone measurements in relation to the mandibular plane HYMP, HYA and CVSN. Non-parametric variables included WITS appraisal, OB, OJ, SPL, HYRGN, IAS and VAL.

All statistical analyses were conducted using IBM SPSS Statistics version 24 (SPSS Inc., Chicago, IL, USA).

## Chapter 3: Results

### 3.1 Error Analysis

An intra-class correlation (ICC) analysis for the eleven repeated cephalometric radiograph measurements revealed that the intra-rater reliability (IRR) was poor ( $ICC < 0.4$ ) for the cranial base angle (CBA), the mandibular corpus length (MCL), the upper anterior facial height (UAFH) and the superior posterior airway space (SPAS). A fair IRR ( $ICC = 0.4 - 0.59$ ) was seen for the anterior cranial base length (ACBL), the midface length (MFL), the mandibular length (MDL), the mandibular plane angle in relation to the Frankfort horizontal (FMA), the total anterior facial height (TAFH), and the position of the hyoid to C3 (HYC3). In addition, a good IRR ( $ICC = 0.6 - 0.74$ ) was found for the following variables, the mandibular ramus height (MRH), the gonial angle (GOA), the Mx/Md difference (MXMD), the posterior facial height (PFH), the middle airway space (MAS) and the head posture related to the palatal plane (CVPP). The remaining variables showed an excellent IRR ( $ICC = 0.75 - 1$ ) and included the variables SNA angle, maxillary length (MXL), SNB angle, mandibular plane angle (MPA), ANB angle, Wits appraisal, lower anterior facial height (LAFH), upper to lower facial height (UFH:LFH), posterior to anterior facial height (PFH:AFH), all the dental measurements of an overbite (OB), overjet (OJ), upper incisor inclination and position (U1SN, U1NA, respectively), lower incisor inclination and position (IMPA, L1NB, respectively) and the interincisal angle (U1L1). Moreover, all of the soft tissue variables appeared to have an excellent reliability including the upper and lower lips in relation to the esthetic plane (ULEP, LLEP, respectively), nasolabial angle (NLA), soft palate length (SPL) and thickness (MAXSP). Similarly, the hyoid bone measurements in relation to the mandibular plane (HYMP), retrognathion (HYRGN), hyoid angle (HYA), hyoid to mandibular plane angle (HYMEMP), inferior airway space (IAS), vertical

airway length (VAL) and the head posture in relation to the cranial base (CVSN) all had an excellent IRR with an ICC higher than 0.86 (Table 3-1). All bolded variables in Table 3-1 showed an excellent ICC and were considered for statistical analysis.

**Table 3- 1 Reliability of Repeated Cephalometric Measurements Recorded 2 Weeks Apart Divided by Skeletal, Dental, Facial Soft Tissue, Soft Palate, Hyoid, Airway and Head Posture Measurement**

Variables		N	ICC
<b>Skeletal</b>			
Anterior cranial base length (mm)	ACBL: S-N	11	0.476
Cranial base angle (°)	CBA: S-N-Ba	11	0.000
<b>Maxilla to cranial base (°)</b>	<b>SNA</b>	<b>11</b>	<b>0.955</b>
Midface length (mm)	MFL: Co-A	11	0.585
<b>Maxillary length (mm)</b>	<b>MXL: ANS-PNS</b>	<b>11</b>	<b>0.767</b>
<b>Mandible to cranial base (°)</b>	<b>SNB</b>	<b>11</b>	<b>0.930</b>
Mandibular length (mm)	MDL: Co-Gn	11	0.441
Mandibular corpus length (mm)	MCL: Go-Gn	11	0.105
Mandibular ramus height (mm)	MRH: Ar-Go	11	0.695
Gonial angle (°)	GOA: Ar-Go-Me	11	0.653
Mandibular plane angle (°)	MPA: MP-SN	11	0.806
Frankfort to mandibular plane angle (°)	FMA: MP-FH	11	0.520
<b>Maxillomandibular relationship (°)</b>	<b>ANB</b>	<b>11</b>	<b>0.766</b>
Mx/Md difference (mm)	MXMD: Co-Gn _ Co-A	11	0.696
<b>Wits Appraisal (mm)</b>	<b>WITS: Ao-Bo</b>	<b>10</b>	<b>0.799</b>
Upper anterior facial height (mm)	UAFH: N-ANS	11	0.158
<b>Lower anterior facial height (mm)</b>	<b>LAFH: ANS-Me</b>	<b>11</b>	<b>0.942</b>
Total anterior facial height (mm)	TAFH: N-Me	11	0.577
Posterior facial height (mm)	PFH: S-Go	11	0.656
<b>Upper to lower facial height (%)</b>	<b>UFH:LFH</b>	<b>11</b>	<b>0.751</b>
<b>Posterior to anterior facial height (%)</b>	<b>PFH:AFH</b>	<b>11</b>	<b>0.941</b>
<b>Dental</b>			
<b>Overbite (mm)</b>	<b>OB</b>	<b>10</b>	<b>0.836</b>
<b>Overjet (mm)</b>	<b>OJ</b>	<b>10</b>	<b>0.865</b>

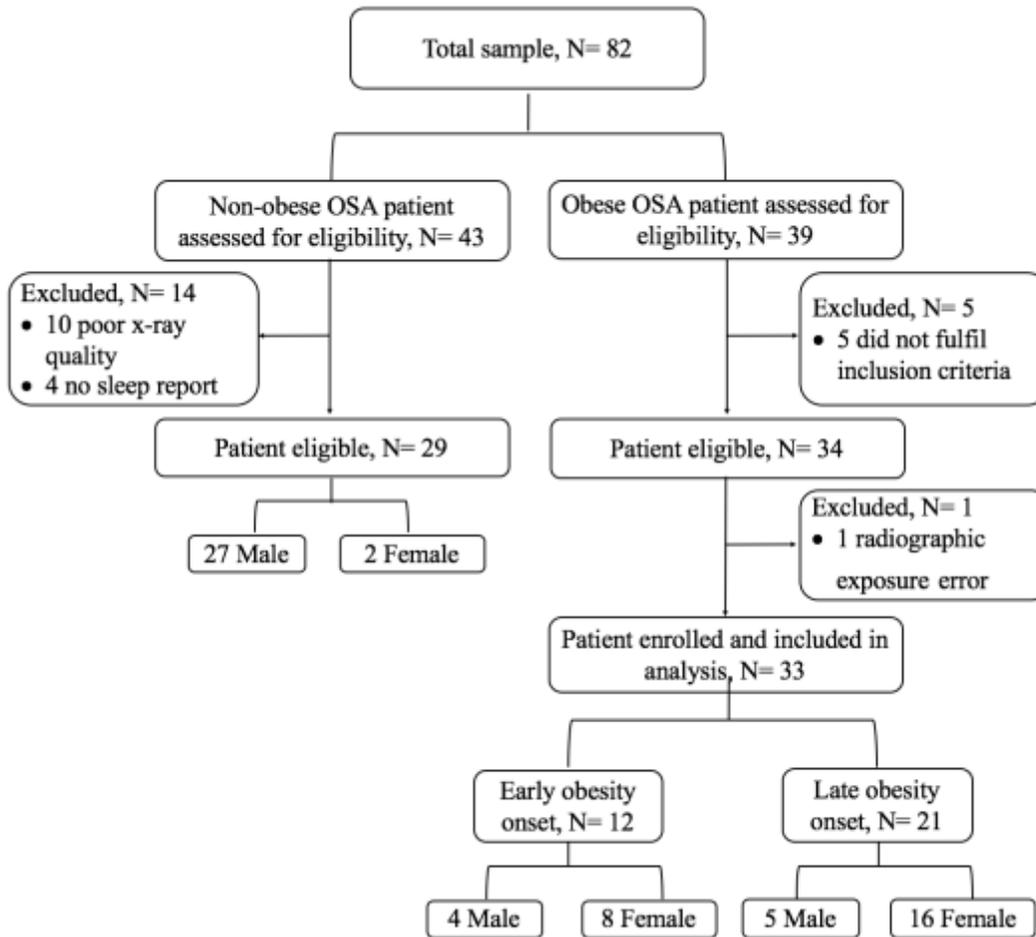
<b>Variables</b>		<b>N</b>	<b>ICC</b>
Upper incisor inclination (°)	U1SN	11	0.924
Upper incisor position (mm)	U1NA	11	0.824
Lower incisor inclination (°)	IMPA	11	0.949
Lower incisor position (mm)	L1NB	11	0.936
Interincisal angle (°)	U1LI	11	0.946
<b>Facial Soft Tissue</b>			
Upper lip-E plane (mm)	ULEP	8	0.988
Lower lip-E plane (mm)	LLEP	8	0.982
Nasolabial angle (°)	NLA: Col-Sn-UL	8	0.940
<b>Soft Palate</b>			
PNS-Pa (mm)	SPL: PANS-Pa	11	0.869
Max soft palate thickness (mm)	MAXSP	10	0.960
<b>Hyoid</b>			
Horizontal hyoid position (mm)	HYMP: Hy-MP prep	10	0.991
Horizontal hyoid position (mm)	HYRGN: Hy- RGN	10	0.980
Horizontal hyoid position (mm)	HYC3: Hy-C3	10	0.477
Hyoid angle (°)	HYA: Hy-Go to Hy-Me	10	0.992
Hyoid to MP (°)	HYMEMP: Hy-Me-MP	10	0.970
<b>Airway</b>			
Superior posterior airway space (mm)	SPAS	11	0.000
Middle airway space (mm)	MAS	11	0.722
Inferior airway space (mm)	IAS	11	0.864
Vertical airway length (mm)	VAL: PNS-V	7	0.901
<b>Head posture</b>			
Cervical vertebrae to cranial base (°)	CVSN: CV2sp-CV4ip- SN	10	0.893
Cervical vertebrae to maxilla (°)	CVPP: CV2sp-CV4ip- SN	10	0.686

### **3.2 Sample Characteristics**

Thirty nine obese OSA patients who were waiting for bariatric surgery at the Richmond Hospital were prospectively recruited from the period of February 2016 to March 2017. Six patients were excluded, 4 due to prolonged CPAP use, one was edentulous, and one due to a radiographic exposure error. The final sample consisted of 33 patients, 12 with early obesity onset and 21 with late obesity onset. The majority of patients in this sample were female (72.7% female vs. 27.3% male).

For the non-obese OSA patients, retrospective data was obtained from a UBC database, and 43 patients were identified as eligible; 14 of the them were excluded, 10 due to poor radiographic quality and 4 had no sleep reports, thus, the final sample of this group consisted of 29 patients including 27 males and two females. Figures 3-1 and Table 3-2 summarizes the sample selection process and gender distribution.

**Figure 3- 1 Sample Selection Process**



**Table 3- 2 Sample Gender Distribution**

		Non-obese	Early obese	Late obese	Total
Gender	Male	27	4	5	36
	Female	2	8	16	26
Total		29	12	21	62

Data regarding ethnicity of obese OSA subjects were reported if available. It comprised of two Aboriginal patients, fifteen Caucasian, eight South Asian, two Middle Eastern and six of unknown backgrounds.

Furthermore, the age, the body mass index (BMI) and the OSA characteristics (AHI or ODI) were recorded and are described as a mean, standard deviation and range for the three groups in Table 3-3. There was no statistically significant difference in age distribution between the three groups. Similarly, the BMI had no statistically significant difference between early and late obese groups, whereas both of them had a significantly higher BMI than non-obese subjects.

There were different types of sleep studies available for the obese OSA patients, 16 subjects had an overnight PSG study and the AHI was used as the diagnostic parameter, 10 subjects had a Level III sleep study and 7 subjects had an oximetry study with the ODI used as the diagnostic parameter. All non-obese OSA subjects had an overnight PSG sleep study, therefore, the AHI was obtained. As these variables were taken from different types of sleep studies, no statistical analysis other than the mean and SD was performed. Table 3-3 shows each group average AHI/ODI, all patients had OSA and the majority of the patients had severe OSA.

**Table 3- 3 Sample Characteristics**

		<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>Range (Min-Max)</b>	<b>P-value</b>
<b>AGE (year)</b>	Non-obese	29	48.1	11.4	(31.1 – 72.7)	0.48
	Early obese	12	45.6	14.7	(19.5 – 60.3)	
	Late obese	21	50.9	12.1	(32.1 – 70.9)	
<b>BMI (kg/m<sup>2</sup>)</b>	Non-obese	29	25.6*	2.7	(17.59 – 29.38)	0.00
	Early obese	12	52.3*	9.8	(43.30 – 76.34)	
	Late obese	21	48.1	6.8	(33.90 – 59.63)	
<b>AHI or ODI (events/hour)</b>	Non-obese	29	45.7	12	(31 – 68.6)	
	Early obese	12	39.4	23.2	(13.6 - 79)	
	Late obese	21	41	25.6	(11.8 – 121.8)	

\* Statistically significant difference between non-obese and early obese groups (P-value= 0.00).

┘ Statistically significant difference between non-obese and late obese groups (P-value= 0.00).

### **3.3 Cephalometric Analysis**

Cephalometric variables with excellent ICC ( $ICC \geq 0.75$ ) were reported and described as a mean and standard deviation for all three groups and illustrated in table 3-4, 3-5 and 3-6.

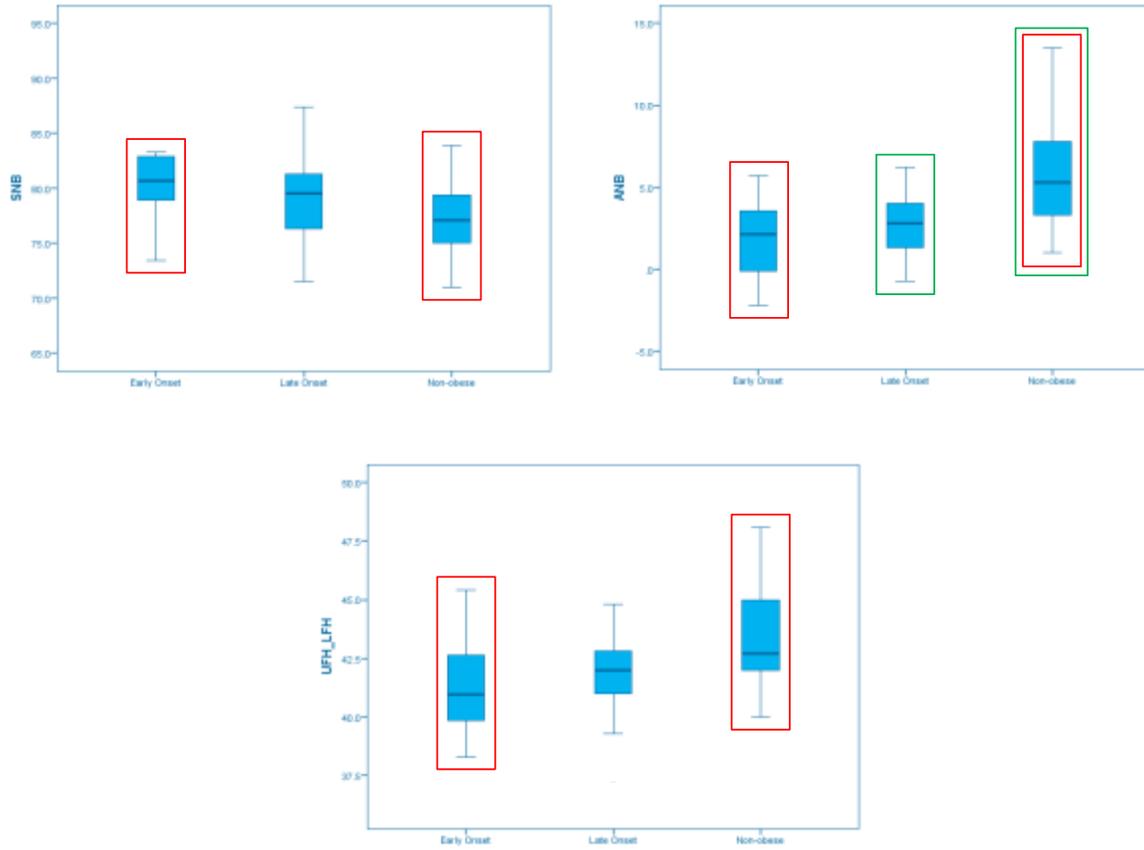
#### **3.3.1 Early Obesity Onset Versus Non-Obese:**

An early obese onset group was significantly different than the non-obese group for several variables. For skeletal analysis, the early obese group expressed a more prognathic mandible than non-obese patients ( $p= 0.038$ ) with a larger maxillo-mandibular discrepancy (ANB angle) present in non-obese patients ( $p< 0.001$ ). The upper to lower facial height ratio was significantly shorter in the early obesity group compared to non-obese patients ( $p= 0.015$ ). In the evaluation of dental characteristics, the upper incisors were significantly more protrusive in early obese patients compared to non-obese subjects ( $p= 0.019$ ), and these skeletal and dental differences are illustrated in Tables 3-4 and 3-5 and Figures 3-2 and 3-3.

In the assessment of the soft palate, the hyoid bone and the upper airway, early obese subjects had a more caudally positioned hyoid bone in relation to the retrognathion ( $p= 0.003$ ) and smaller hyoid bone mandibular plane angle compared to the non-obese subjects ( $p< 0.001$ ). Furthermore, there was a statistically significant difference in the lower airway width between early obese and non-obese patients with the inferior airway space wider in early obese patients ( $p= 0.006$ ). The vertical airway length was significantly shorter in the early obese group than non-obese group ( $p= 0.002$ ), the hyoid bone and the airway differences are presented in Table 3-6, Figures 3-4 and 3-5.

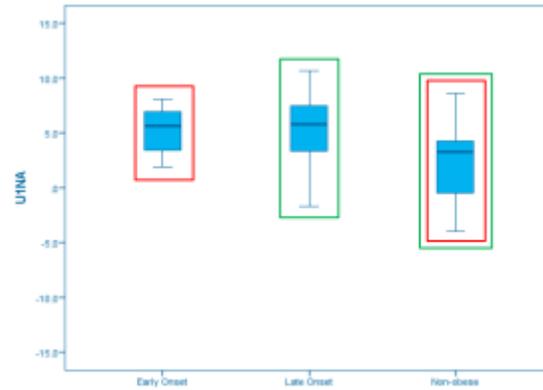
All other variables showed no statistically significant difference, variables are shown in Tables 3-4, 3-5 and 3-6.

**Figure 3- 2 Skeletal Differences between Early Obesity Onset, Late Obesity Onset and Non-Obese Patients: SNB (°), ANB (°), UFH:LFH(%)**



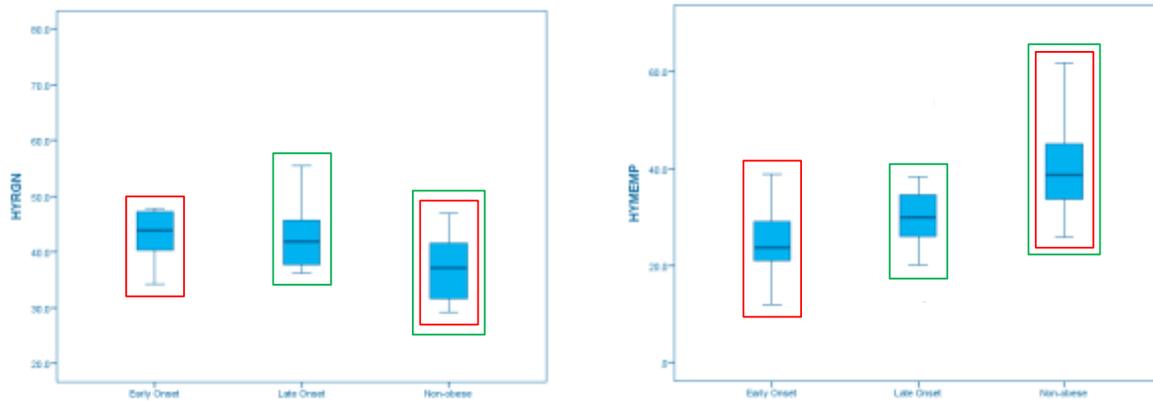
- Significant difference between early obesity and non-obese.
- Significant difference between late obesity and non-obese (to be further discussed below).

**Figure 3- 3 Dental Differences between Early Obesity Onset, Late Obesity Onset and Non-Obese Patients: U1-NA (mm)**



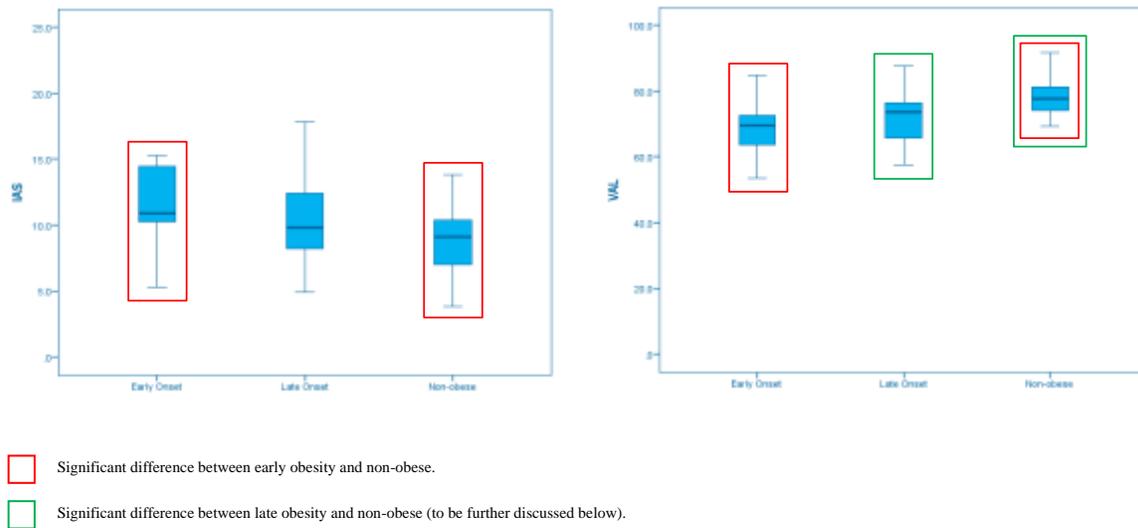
- Significant difference between early obesity and non-obese.
- Significant difference between late obesity and non-obese (to be further discussed below).

**Figure 3- 4 Hyoid Bone Differences between Early Obesity Onset, Late Obesity Onset and Non-Obese Patients: HY-RGN (°), HYMEMP (°)**



- Significant difference between early obesity and non-obese.
- Significant difference between late obesity and non-obese (to be further discussed below).

**Figure 3- 5 Upper Airway Differences between Early Obesity Onset, Late Obesity Onset and Non-Obese Patients: IAS (mm), VAL (mm)**



### 3.3.2 Late Obesity Onset Versus Non-Obese:

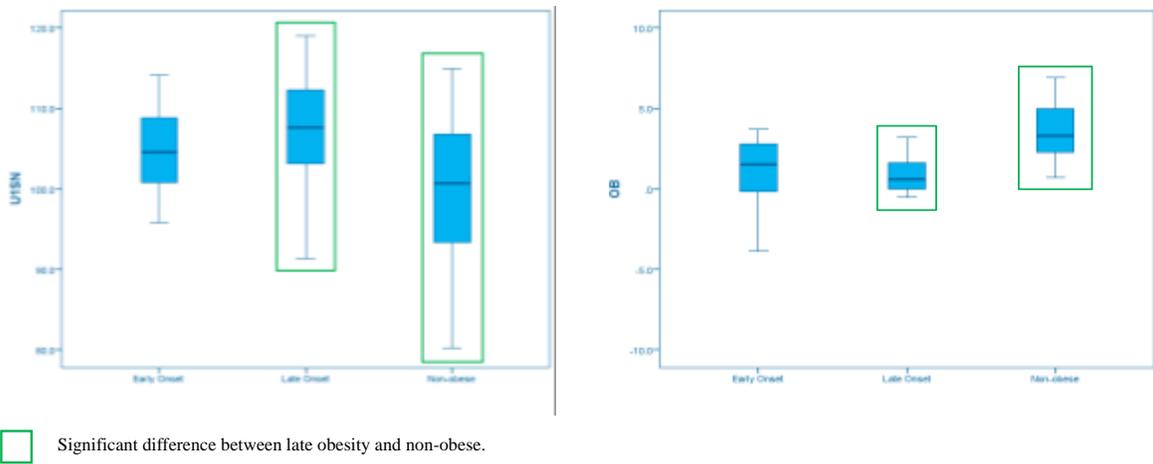
Some differences were detected among late obese versus non-obese patients. For skeletal analysis, the non-obese group had a larger maxillo-mandibular discrepancy (ANB angle) than the late obese group ( $p= 0.002$ ). In the evaluation of dental characteristics, the late obese patients showed significantly more proclined ( $p= 0.006$ ) and protrusive upper incisors ( $p= 0.041$ ) with a shallower overbite ( $p= 0.009$ ) than their non-obese counterparts. These differences are presented in Tables 3-4 and 3-5, Figures 3-2, 3-3 and 3-6.

In the assessment of the soft palate, the hyoid bone and upper airway of late obesity group, the hyoid bone was in an inferior position ( $p= 0.002$ ) with a smaller hyoid bone to the mandibular plane angle compared to non-obese subjects ( $p= 0.001$ ). Also, a statistically significant difference was found between late obese and non-obese patients in a vertical airway length, where it was found to be shorter in late obese subjects ( $p= 0.007$ ). In addition, more

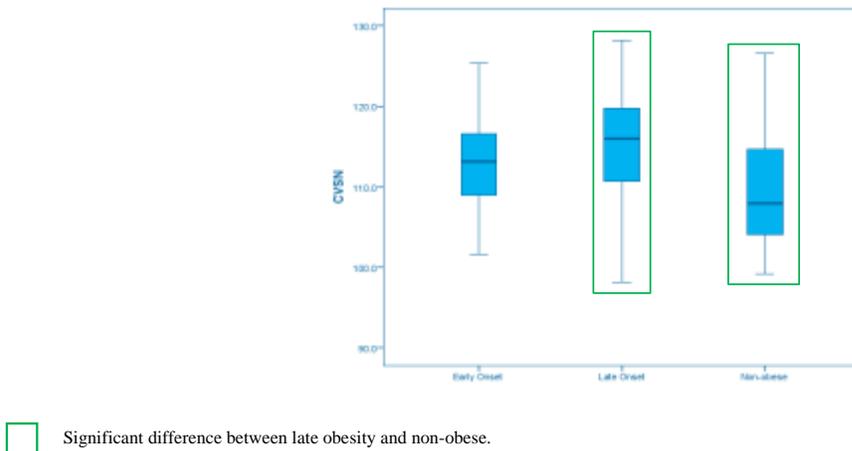
upward head posture was found in late obese subjects in comparison to non-obese subjects ( $p=0.023$ ), and these differences are presented in Table 3-6, Figures 3-4, 3-5 and 3-7.

The remaining variables showed no statistically significant difference between late obese and non-obese patients and are presented in Tables 3-4, 3-5 and 3-6.

**Figure 3- 6 Dental Differences between Late Obesity Onset and Non-Obese Patients: U1-SN ( $^{\circ}$ ), OB (mm)**



**Figure 3- 7 Head Posture Differences between Late Obesity Onset and Non-Obese Patients: CVSN ( $^{\circ}$ )**



### **3.3.3 Early Obesity Onset Versus Late Obesity Onset:**

Based on a small sample of 12 early obese and 21 late obese subjects, statistical analysis showed that none of the variables had a statistically significant difference between early and late obese subjects. It was found that early obese patients had a tendency for a hypodivergent growth pattern and deeper overbite compared to late obese patients and these findings are presented in Tables 3-4, 3-5 and 3-6 where, if there was no significant difference, the p-value represents the result from the ANOVA or Kruskal Wallis test between the 3 groups. While, if there was a significant difference with ANOVA or Kruskal Wallis, the p-value described is the result of the Turkey post-hoc or Mann Whitney U test used to identify which of the groups means were different.

This was a pilot study and there was no previous data to do a power calculation. Based on the current results, a power calculation using a post hoc test has been conducted on three variables (SNB, SNMP and U1SN) to determine the ideal sample size and understand if obesity onset has an impact on craniofacial characteristics of obese OSA individuals. We found that SNB and U1SN has a power higher than 70% and a sample of 78 individuals (39 in each group) would likely identify differences between groups. SNMP has a power of 25%, and a sample size of 282 individuals (141 in each group) would be important to determine if mandibular angle is different between early and late obesity onset groups.

**Table 3- 4 Skeletal Measurements between Non-Obese, Early and Late Obese Patients**

<b>Variables</b>	<b>Non-obese Mean ± SD</b>	<b>Early obese Mean ± SD</b>	<b>Late obese Mean ± SD</b>	<b>P-value</b>
SNA (°)	83 ± 3.5	82.6 ± 5.1	82.3 ± 4.1	0.83
MXL (mm)	54.9 ± 5.5	54.1 ± 5.5	52.1 ± 4.9	0.18
SNB (°)	77.1 ± 3.8 *	80.7 ± 4.2 *	79.3 ± 4.8	0.038
MPA (°)	33.1 ± 7.5	27.4 ± 4.6	32.6 ± 7.6	0.06
ANB (°)	5.9 ± 3.3 *┐	1.8 ± 2.3 *	3 ± 2.4┐	*= 0.000, ┐= 0.002
WITS (mm)	3.1 ± 3.9	-0.3 ± 3.3	0.2 ± 3.2	0.12
LAFH (mm)	69 ± 6.7	68.7 ± 6.7	66.3 ± 4.3	0.27
UFH_LFH (%)	43.2 ± 1.9 *	41.2 ± 2 *	42 ± 2.1	0.015
PFH_AFH (%)	67.6 ± 5.9	70.7 ± 4	66.5 ± 6.9	0.14

\* Statistically significant difference between non-obese and early obese groups.

┐ Statistically significant difference between non-obese and late obese groups.

**Table 3- 5 Dental Measurements between Non-Obese, Early and Late Obese Patients**

<b>Variables</b>	<b>Non-obese Mean ± SD</b>	<b>Early obese Mean ± SD</b>	<b>Late obese Mean ± SD</b>	<b>P-value</b>
OB (mm)	3.1 ± 2.9┐	1.5 ± 2.9	0.4 ± 2.1┐	0.009
OJ (mm)	3.8 ± 0.9	3.6 ± 1.8	4.2 ± 2.1	0.45
U1SN (°)	99.8 ± 9.4┐	104.8 ± 5.4	106.4 ± 9.1┐	0.041
U1NA (mm)	1.9 ± 4.2 *┐	5.4 ± 1.9 *	5.3 ± 3.2┐	*= 0.019, ┐= 0.006
IMPA (°)	96.9 ± 9.2	94.6 ± 7.4	94.3 ± 10.3	0.66
L1NB (mm)	6.5 ± 2.9	4.3 ± 3.8	5.6 ± 3.3	0.19
U1L1 (°)	126.8 ± 11.9	130.7 ± 14.2	124.6 ± 13.3	0.44

\* Statistically significant difference between non-obese and early obese groups.

┐ Statistically significant difference between non-obese and late obese groups.

**Table 3- 6 Facial Soft Tissue, Hyoid Bone, Airway, Head Posture Measurements between Non-Obese, Early and Late Obese Patients**

Variables	Non-obese Mean ± SD	Early obese Mean ± SD	Late obese Mean ± SD	P-value
ULEP (mm)	-4.4 ± 3.8	-7.5 ± 4.6	-4.5 ± 2.9	0.08
LLEP (mm)	-2.4 ± 4.5	-5.5 ± 6.1	-3.2 ± 3.7	0.25
NLA (°)	109 ± 12.4	103 ± 13.4	109 ± 13.3	0.40
SPL (mm)	41.2 ± 4.5	40.8 ± 6.7	37.9 ± 4.7	0.05
MAXSP (mm)	11.2 ± 1.7	10.2 ± 1.4	10.8 ± 2.2	0.25
HYMP (°)	23.8 ± 4.5	19.9 ± 8.3	22.2 ± 7.9	0.25
HYRGN (mm)	37.1 ± 5.4 *┐	45.5 ± 9.9 *	42.8 ± 6.3┐	*= 0.003, ┐ = 0.002
HYA (°)	103 ± 11.9	114.9 ± 16.9	104.2 ± 27.1	0.21
HYMEMP (°)	40.7 ± 9.4 *┐	24.7 ± 7.5 *	31.1 ± 11.8┐	*= 0.000, ┐ = 0.001
IAS (mm)	8.7 ± 2.5 *	12.2 ± 4.5 *	10.7 ± 4.3	0.006
VAL (mm)	77.6 ± 5.5 *┐	68.8 ± 8.4 *	67.7 ± 17.9┐	*= 0.002, ┐ = 0.007
CVSN (°)	109.6 ± 7.5┐	112.8 ± 7.4	115.5 ± 7.5┐	0.023

\* Statistically significant difference between non-obese and early obese groups.

┐ Statistically significant difference between non-obese and late obese groups

### 3.3.4 Obese Versus Non-Obese:

Since there were no significant difference between early and late obesity subjects, the two groups were combined into one obese group and compared to non-obese subjects. For skeletal analysis, the non-obese group expressed a more retrognathic mandible ( $p= 0.013$ ), larger anteroposterior discrepancy between the maxilla and the mandible (ANB  $p< 0.001$ ; WITS  $p= 0.040$ ), and a shorter lower facial height ( $p= 0.005$ ). In the evaluation of dental characteristics, non-obese patients showed a deeper overbite ( $p= 0.014$ ), and less upper incisors proclination ( $p= 0.014$ ) and protrusion ( $p< 0.001$ ). In the assessment of the soft palate, hyoid bone and upper airway, non-obese patients had a longer soft palate ( $p= 0.033$ ), higher (superior) position of their hyoid bone ( $p= 0.001$ ), a more obtuse HYMEMP angle ( $p= 0.000$ ), a narrower inferior airway space ( $p= 0.016$ ), a longer vertical airway length ( $p< 0.001$ ) and a less obtuse head posture ( $p=$

0.013) and the comparisons are presented in Table 3-7.

**Table 3- 7 Cephalometric Measurements between Non-Obese and Obese (Combined Early + Late Obese) Subjects**

<b>Variables</b>	<b>Non-obese Mean ± SD</b>	<b>Obese Mean ± SD</b>	<b>P-value</b>
SNA (°)	83 ± 3.5	82.4 ± 4.4	0.564
MXL (mm)	54.9 ± 5.5	52.8 ± 5.2	0.121
SNB (°)	77.1 ± 3.8 *	79.8 ± 4.6 *	0.013
MPA (°)	33.1 ± 7.5	30.7 ± 7.1	0.192
ANB (°)	5.9 ± 3.3 *	2.6 ± 2.4 *	0.000
WITS (mm)	3.1 ± 3.9 *	-0.5 ± 3.2 *	0.040
LAFH (mm)	69 ± 6.7	67.2 ± 5.3	0.241
UFH_LFH (%)	43.2 ± 1.9 *	41.7 ± 2.1 *	0.005
PFH_AFH (%)	67.6 ± 5.9	68 ± 6.3	0.811
OB (mm)	3.1 ± 2.9 *	0.8 ± 2.5 *	0.014
OJ (mm)	3.8 ± 0.9	3.9 ± 1.9	0.777
UISN (°)	99.8 ± 9.4 *	105.8 ± 7.9 *	0.014
UINA (mm)	1.9 ± 4.2 *	5.3 ± 2.8 *	0.000
IMPA (°)	96.9 ± 9.2	94.4 ± 9.2	0.363
LINB (mm)	6.5 ± 2.9	5.1 ± 3.5	0.139
UIL1 (°)	126.8 ± 11.9	126.9 ± 13.8	0.986
ULEP (mm)	-4.4 ± 3.8	-5.5 ± 3.8	0.365
LLEP (mm)	-2.4 ± 4.5	-4.1 ± 4.7	0.293
NLA (°)	109 ± 12.4	107.3 ± 13.5	0.703
SPL (mm)	41.3 ± 4.6 *	39.1 ± 5.7 *	0.033
MAXSP (mm)	11.2 ± 1.7	10.5 ± 1.9	0.164
HYMP (°)	23.8 ± 4.5	21.4 ± 7.9	0.171
HYRGN (mm)	37.1 ± 5.4 *	43.7 ± 7.7 *	0.001
HYA (°)	103 ± 11.9	107.9 ± 24.4	0.339
HYMEMP (°)	40.7 ± 9.4 *	28.9 ± 10.8 *	0.000
IAS (mm)	8.7 ± 2.5 *	11.3 ± 4.4 *	0.016
VAL (mm)	77.6 ± 5.5 *	68.2 ± 14.8 *	0.000
CVSN	109.6 ± 7.5 *	114.6 ± 7.5 *	0.013

\* Statistically significant difference between non-obese and obese groups.

## Chapter 4: Discussion

Although the craniofacial features of obese and non-obese OSA patients have been investigated in the literature, the effect of obesity onset on craniofacial development has not been reported. Wide variability exists between the studies with divergent sample sizes, populations, methodology and results with most of them lacking a proper control sample. In addition, the criteria to determine obesity and diagnosis of OSA varied between the studies, and all of these factors makes direct comparisons between the studies complex. Therefore, more research with well-defined objectives and a clear definition of parameters is needed. Moreover, the obesity impact on craniofacial growth in OSA patients has not been investigated. Our study has shown that early obesity patients are significantly different from non-obese patients showing a more prognathic mandible, a smaller ANB angle, a longer lower facial height, protrusive incisors, a caudal position of the hyoid bone, a wider lower airway and a shorter vertical airway length. Furthermore, late obesity patients are significantly different from non-obese patients with late obese presenting with a smaller ANB angle, proclined and protrusive upper incisors, a shallower overbite, an inferiorly positioned hyoid bone, a shorter vertical airway length and an obtuse craniocervical angle. Although we found no differences between early and late obesity characteristics, the data described above, and as illustrated in the boxplots in our results, suggest that there is a tendency for discrepancy between these groups. We believe that further studies with a larger sample size may find interesting differences between those groups.

#### 4.1 Error Analysis

Digital cephalometric radiographs reliability has been investigated in several studies. We found an excellent intra-rater reliability ( $ICC > 0.75$ ) for 30 out of 44 variables (Table 3-1). Interestingly, the majority of angular measurements were reliable with unreliable variables being related to landmarks which are difficult to locate on cephalometric radiographs (164) such as articulare, orbitale, basion, gonion, porion (165-167), soft palate and its related airway measures (168).

In this study, skeletal variables that showed high reliability included the relationship of the maxilla and the mandible to the cranial base (SNA, SNB), the maxillo-mandibular relationship (ANB, WITS), the mandibular plane angle (MPA) and the lower anterior facial height (LAFH). Our findings are similar to those found by Damstra et al. who reported a strong intra-observer agreement for SNA ( $ICC= 0.96$ ), SNB ( $ICC= 0.95$ ), ANB ( $ICC= 0.87$ ), WITS ( $ICC= 0.89$ ), SN-MP ( $ICC= 0.87$ ), LAFH ( $ICC= 0.99$ ) (169). In contrast, the reliability of midface and mandibular length (Co-A= 0.58 and Co-Gn= 0.44) were fair in the current study compared to Damstra et al. who found high reliability with a large measuring error. In addition, a study from Albarakati et al. had a similar finding for the reliability of skeletal and angular measurements, however, there were different results for the anterior cranial base length, the mandibular length, the mandibular corpus length and gonial angle, which suggests good intra-examiner reliability (170). Furthermore, Ang et al. found a good agreement for the repeated measurements of the cranial base angle, cranial base length and gonial angle which contrasts the findings of our study (131). These differences could be attributed to the radiographic resolution, error in landmark identification, adjacent structures superimposition and observer experience. Our study is unique, where all obese patients were morbidly obese, and this could also have

affected reliability in the determination of cephalometric variables due to an attenuation of radiation by adipose tissues.

In general, dental variables, including the upper and lower incisors inclinations and positions, almost always have excellent reliability. This is supported by the findings of Damstra et al. who reported that U1-SN (ICC= 0.95) and L1-MP (ICC= 0.94) (169), Albarakati et al. (170) and Bates and McDonald (171) studies. This could be due to the simplicity in locating the incisors landmarks.

The landmarks used to locate the soft palate and airway are among the most variable landmarks. It was found, in our study, that the soft palate thickness and length along with the inferior airway space are reliable measurements, while the superior and middle airways are not reliable. This finding is inconsistent with Miles 1995 finding investigating the reliability of the landmarks most commonly used in OSA studies. They reported that the soft palate tip and the inferior airway space are among the most unreliable landmarks. They attributed this finding to the quality of the radiograph, difficulty of landmark identification and the dynamic nature of the soft palate (168). In our study, the resolution of the soft tissue was considered in the radiographic parameters during exposure which resulted in good resolution, that perhaps explain the difference between the studies. Miles recommended to cautiously interpret the finding of the soft palate and upper airway due to inaccuracies in identifying this dynamic three dimensional structure (168).

Moreover, most of the hyoid bone measurements and head posture in relation to the cranial base were reliable. A similar finding has been reported by Ang et al. (131) and Bates and McDonald (171).

With regards to measurement reliability, it is clear that each study has different variables

which may or may not be reliable. Therefore, it is imperative to assess and compare only the variables that show an excellent intra-examiner reliability. In the current study, we evaluated and compared only measurements with excellent intra-examiner reliability, which minimizes measurements bias in detecting the difference between the groups.

#### **4.2 Sample Characteristics**

Our study found craniofacial differences between the non-obese and obese groups. It is important to state that these groups were not equally distributed for gender. Our non-obese group consisted of 2 females and 27 males, whereas the obese groups consisted of 24 females and 9 males with the majority of the obese patients were female (72.7%) and majority of the non-obese sample was male (93%). The predominance of male subjects in non-obese OSA sample is in accordance with the well-known prevalence of OSA (8, 10, 11). This difference in gender distribution, with a higher prevalence of females in the obese group, could be due to a higher number of females seeking weight loss by bariatric surgery as compared to males. Therefore, the craniofacial differences could be attributed to gender differences only. Despite the gender differences, our results have a similar finding to the previous studies where the non-obese male subjects has a higher degree of craniofacial impairment compared to their obese counterparts (151). In the comparison between the early obese to late obese groups, the ratio female/male was 8/4 and 16/5, respectively. The prevalence of female in these two groups was not as different, and gender differences in the comparisons between these groups is unlikely to have impacted the results. Although this was not the main interest of the current study, future research is required to better understand gender difference impact on craniofacial characteristics between early and late obesity groups.

Obese OSA patients presented with different types of sleep assessment studies and recorded sleep parameters. Available data was either an AHI if the patient had a PSG study or an ODI if the patient had Level III or an oximetry study. ODI was used instead of an AHI in the Level III study because AHI scores in Level III are different than the AHI scores in PSG. AHI on a portable monitor is calculated as number of apneas and hypopneas per hour of recording, while in PSG the AHI is calculated as number of apneas and hypopneas per hour of actual sleep due to the presence of electroencephalography (EEG). Therefore, the AHI score on the Level III study might underestimate the index. The ODI (number of arterial oxygen desaturation of  $\geq 3\%$  / hour of sleep)(32) was used instead of the AHI in Level III and oximetry sleep studies because a high agreement (ICC= 0.89) had been found between the oxygen desaturation index and apnea hypopnea index (172, 173), which makes ODI more reliable than AHI in those types of sleep tests. Because of these differences, we have not attempted any further statistical analysis which involved AHI, such as correlations of craniofacial characteristics and disease severity. Still, previous studies have often used questionnaires only to assess sleep apnea patients' craniofacial characteristics. Our study has added the requirement of a sleep study, positive for OSA for participants to be enrolled in our analysis. Future studies involving only one type of sleep recording will be useful for further analysis.

### **4.3 Cephalometric Analysis**

#### **4.3.1 Skeletal Features:**

Our study investigated obesity onset and its effect on craniofacial growth. It was found that there was no significant difference in the position of the maxilla in relation to the cranial base between the three groups, while the mandible was more prognathic in the early obese

subjects compared to non-obese subjects. Non-obese patients had a larger maxillo-mandibular discrepancy (larger ANB angle) with a retrognathic mandible than both early and late obese patients. These findings agree with Ferguson et al's study and Cuccia et al's review in 2007 which reported prognathic mandible in obese OSA patients and a larger ANB angle with retrognathic mandible in non-obese OSA patients (151) (152, 155). Similarly, Lee et al. in 2010 showed that Chinese OSA patients had a lower BMI with a more bony restricted craniofacial skeletons than Caucasian OSA patients with had higher BMIs (174). In addition, it was found that early obese patients had a longer lower facial height than their non-obese counterparts. This finding agrees with Battagel and Johal's finding (175) as well as Pae and Ferguson (176). When the early and late obese groups were combined into one obese group and were compared to the non-obese OSA patients, a similar finding was found. It appears that the obese OSA patients had a different skeletal morphology than their non-obese counterparts; therefore, they have different risk factors which may require a different treatment approaches.

#### **4.3.2 Dental Features:**

The upper incisors were significantly more protrusive in both early and late obese individuals compared to non-obese subjects with more proclined upper incisors and a shallower overbite in the late obesity group. Moreover, when the combined obese were compared to non-obese subjects, the non-obese presented with a deeper overbite and less incisor proclination. This result agrees with Battagel and Johal (175) and Pae and Ferguson (176). This difference in incisor inclination could be attributed to the pressure applied by the enlarged tongue in obese patients.

#### **4.3.3 Soft Tissue Features:**

No significant difference was detected between the three groups. But, when the combined obese subjects were compared to non-obese subjects, the soft palate was longer in non-obese patients. This result is the opposite of what was found by Feguson et al. (151) , (175) and (152). This difference could be explained by the differences in sample characteristics, where our obese population presented a higher BMI than in previous studies.

#### **4.3.4 Hyoid, Airway and Head Posture Features:**

The hyoid bone position was more in the caudal position (further from retrognathion) in both early and late obese groups compared to non-obese patients. In addition, both of these obese groups had a smaller hyoid bone to mandibular plane angle compared to the non-obese subjects. Several studies reported the same finding (151, 152, 155). The change in the hyoid bone position could be a consequence of OSA rather than a cause, adaptation to tongue position or fat distribution in obese subjects (155, 177, 178).

The vertical airway length was significantly shorter in both early and late obese subjects when compared to the non-obese group. In contrast, another study found no difference in the airway length between obese and non-obese participants (176). While there were no differences in the superior and middle airway width in our study, the early obese patients had a wider lower airway width than non-obese. Our findings are in agreement with Thapa and colleagues (2015) and Yu and collaborators (2003) (152, 154).

Another interesting finding was that the late obese patients had an overextended head posture with the cranio-cervical angle being significantly more obtuse than non-obese patients. A similar result was found by Pae and Ferguson in 1999. This could be a compensatory mechanism to the narrow airway dimension (179) which may be present even while awake.

None of the variables was significant between early and late obesity groups; likely due to the small sample size in our trial. We only had 12 early obese subjects and 21 late obese subjects. Despite the small sample size, we've seen interesting differences and tendencies which indicate the possibility that these two groups do indeed have some craniofacial differences. Further studies are required to investigate the impact of the timing of obesity onset on craniofacial characteristics of OSA and non-OSA individuals.

#### **4.4 Limitation of the Study**

Several limitations were present in this study during different stages of the research. Limitation during data collection includes small sample size, the examiner was not blinded to obese and non-obese groups due to differences in the radiographs, missing data (ethnicity), subjectivity on reporting the obesity onset, presence of different sleep apnea parameters (AHI vs. ODI) and ODI definition was different between the sleep studies (3% vs. 4%). Limitations during result interpretation includes generalization of the present results to different ethnicities, different studies had different cutoffs for the AHI, ODI and BMI. Despite these limitations, we found similar results to previous studies, confirming that our analysis is valid.

Limitations during cephalometric analysis includes 2D images of a 3D object. Cephalometric radiography is influenced by the head position, by swallowing, respiration, tension, and other factors, and the control group cephalometric radiographs had low resolution which resulted in inaccuracies in landmark identification and measurements errors, missing cephalometric variables and unavailability for normative data to compare, especially for airway and hyoid measurements. Although cephalometrics has several limitations, this radiographic technique has been used since 1930s. There are several advantages of this technique, such as small radiation dosage, ease of reproduction and access to comparison to other studies, due to

frequency of use. It is also important to state that there are various standards in the literature for different age groups, races and genders. Based on the current evidence and the ethical concerns, for the current study, we feel that one cephalometric analysis for each individual was of low enough radiation and high information to be extracted.

This study has delineated and described important information on craniofacial characteristics of obese sleep apnea patients. There are differences between early obese and non-obese patients which differed from the differences between late obese and non-obese individuals, indicating that the onset of obesity requires further investigation and may have an impact on craniofacial growth or changes throughout life. In order to have an 80% power a larger sample size of approximately 39 patients/group would likely show a statistical difference in between early obesity onset and late obesity onset patients for the variables SNB and U1SN and a sample size of 141 patients/group for the mandibular plane angle (SNMP).

There were a variety of significant craniofacial characteristics differences between obese and non-obese individuals. A better understanding of craniofacial characteristics of OSA individuals may enlighten new therapy approaches and improve knowledge on the pathophysiology of OSA.

## Chapter 5: Potential Future Studies

The most important aspect for the improvement of the current study is to include a larger sample size in each obesity onset group and include samples balanced for gender and ethnicities. Increasing the sample size will not only increase the power of the study and make the differences between groups more obvious, it will also eliminate the confounding factor of gender differences and allow the comparison between different ethnic groups. Specifically, previous literature has shown patients of different ethnic backgrounds present with a wide variety of craniofacial features and risk factors.

The method of reporting the obesity onset should be improved to be more reliable. Depending on a patient's self-reporting questionnaire, there is a high chance of subjectivity. An objective method for determining obesity onset includes longitudinal follow up of the children during development and more importantly during the three-critical period of obesity onset, reviewing the patient's medical chart or contacting the physician should be used to improve the accuracy of the analysis.

In addition, selecting patients with the same sleep assessment method would make the comparison more reasonable, reduce bias and will allow for further analysis. A proper control group of obese non-OSA subjects would be appropriate to determine the specific risk factor among obese OSA patients, but that is difficult to achieve because it is limited by ethical concerns.

Additionally, the craniofacial skeleton and upper airway are three-dimensional structures that require a three-dimensional tool for evaluation. The dynamic nature and the physiologic needs might affect the position, shape and dimension of these structures. The overall volumetric

perimeter rather than the absolute dimensional value might be more important and more accurate in the evaluation of craniofacial skeletons.

## Chapter 6: Conclusion

- In the sample population of 33 obese OSA adults between the ages 18-80 who were referred to Richmond Hospital pending bariatric surgery, there were no significant differences in the craniofacial morphology between early obesity and late obesity onset patients.
- Obese OSA patients had more developed craniofacial skeletons with less bony and airway restriction than their non-obese counterparts, indicating the variability in OSA contributing factors.
- Early and late obesity patients were different than the non-obese control subjects in different aspects and further studies with these populations are required.
- A well-designed study with a larger sample size and an objective measure to determine the obesity onset is required to investigate further into the role of obesity onset on an individual's craniofacial development. This will help in the understanding of the OSA pathophysiology and in the management of OSA to address the patient's specific needs.

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