Pediatric sleep disordered breathing in the orthodontic population: Prevalence and associations with cranial base length

By

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ABSTRACT

Objective: To determine the prevalence of pediatric SDB and associated co-morbidities in the orthodontic population; to explore the relationship between cranial base length (CBL) and risk of pediatric sleep disordered breathing (SDB) in the orthodontic population,

Methods: Cone beam generated lateral cephalograms and Pediatric Sleep Questionnaires (PSQ) were collected retrospectively from 320 orthodontic patients between the ages of 5-16. PSQ scores of 390 orthodontic patients were used to determine prevalence of SDB among the orthodontic population; additional health history information obtained from 130 patients was used to assess the prevalence of associated co-morbidities. Relationship between CBL and PSQ score and associated snoring, sleepiness and behavior scores was determined using multivariate regression, from a continuous perspective and ANOVA from a categorical perspective.

Results: At 10.8%, prevalence of SDB risk was found to be higher in the orthodontic population than a general healthy population; those at higher risk for SDB showed higher prevalence of nocturnal enuresis, being overweight and having ADHD. Total PSQ score was higher in both sexes with shorter CBL (R^2=0.035, P=0.007). Snoring score was higher in patients with shorter CBL irrespective of age and sex (R^2=0.042, P<0.001). Sleepiness score was higher in older children and those with shorter CBL (P<0.001 for age, P=0.006 for CBL). Behaviour score had no significant associations with CBL. A significant difference in SDB risk was not noted in the group of patients that had cranial base lengths below average of the population.

Conclusions: The prevalence of the risk of pediatric SDB in the orthodontic population is higher than the general pediatric population, and can be associated with other co-morbidities. Associations between CBL and risk of pediatric SDB, while statistically significant, are too small in magnitude to be clinically relevant in a routine orthodontic practice. The number of patients with cranial base lengths significantly below the average were too few in our population to be able to draw meaningful conclusions regarding this sample subset and SDB risk.

PREFACE

This thesis is an original work by Sahar Abtahi. The research project, of which this thesis is a part of, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Prevalence of Children at Risk of SDB in the Orthodontic Population", No. Pro00063226 "May 17, 2016, and "Associations Between Cranial Base Length & Children at Risk of Sleep Disordered Breathing in an Orthodontic Population", No. Pro00068507, January 6, 2017.

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Dedication

This thesis is dedicated to my husband, for all his patience, love and support that have made the past 3 years possible.

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Chapter 1: Introduction

1.1 Background:

The International Classification of Sleep Disorders (ICSD-3) has categorized all sleep disorders into 8 major categories, one of which is "Sleep Related Breathing Disorders," characterized by disordered ventilation during sleep. The cause of this "disordered ventilation" may be central or obstructive in origin and is diagnosed and treated differently in adults and children[1]. Adult criteria for identifying obstructive sleep apnea often fails to identify children affected by upper airway obstruction during sleep, possibly because episodes of complete obstructive apneas are not present as often in children with sleep disordered breathing[2]. Rather, pediatric sleep-disordered breathing (SDB) describes a spectrum of symptoms and conditions, including snoring, upper airway resistance syndrome, and obstructive sleep apnea (OSA) that result in disruption of pulmonary ventilation and oxygenation, affecting sleep quality [3]. The prevalence of pediatric obstructive sleep apnea can be as high as 5.7%[4], and the associated morbidity with obstructive sleep apnea across physical, psychological and behavioral domains are significant resulting in increased health care costs; hence it is imperative that these children be identified.

Currently, laboratory-based nocturnal polysomnography (PSG) is considered the reference standard for diagnosing SDB as it monitors various physiological parameters related to sleep and wakefulness. However, PSG is expensive, labor intensive, cumbersome and often limited to tertiary care centres, which may be a reason why a large number of suspected pediatric SDB patients remain undiagnosed[5]. The

American Academy of Pediatrics recommends that all children be screened with an appropriate history and physical examination for symptoms and signs suggestive of OSA[6].Therefore, it is important to have an understanding of the epidemiology, and associated risk factors of pediatric SDB so that more efficient and targeted screening can be performed in different clinical settings.

Tonsil and/or adenoid hypertrophy have been generally considered as the most common etiology of SDB in children[7]. Factors such as upper airway soft tissue inflammation and altered neurological reflexes involving muscles of the upper airway are other common factors leading to increased upper airway collapsibility (Pcrit) and likely resulting in SDB[7,8]. These factors may be increased in cases with asthma, continuous allergies, chronic rhinosinusitis and/or Gastroesophageal Reflux Disease (GERD). Childhood obesity is another factor that is implicated in childhood sleep apnea[9] but the mechanisms may be multifactorial. In addition to the ventilatory factors that may influence sleep disordered breathing, anatomical relationships are an important consideration beyond enlarged tonsils and adenoids. Anatomical factors associated with upper airway narrowing include macroglossia, midface hypoplasia, maxillary and mandibular retrognathia, and maxillary constriction, which can influence the severity of sleep disordered breathing [8],[10]. Many of the noted anatomical features are commonly shared in patients with orthodontic malocclusions and are regularly assessed and analyzed during routine orthodontic examinations. The cranial base, for example, being at the junction between the cranium and the face has an early and influential role in craniofacial skeletal growth patterns[11]. It has been shown that a short cranial base can result in a short maxillary length and resulting midface deficiency in children and adolescents[12–14], which along with maxillary constriction and

retrusion are often seen in children suffering from SDB [8,10,15]. Since the cranial base is one of the earliest developed and most commonly assessed landmarks in orthodontics which can influence other craniofacial features, we will assess its role as a potential screening tool for pediatric sleep disordered breathing.

We should also aim to understand the epidemiology of pediatric SDB in the orthodontic population, so practitioners have a better understanding of their population demographics and be more prepared to identify risk factors and incorporate their assessment as a routine part of their practice.

The prevalence in the general pediatric population has been noted to be 1-4% for obstructive sleep apnea[16] (with some studies reporting prevalence as high as 5.7%[4]), 1.5-14.8% for habitual snoring, and a range of 4-11% for pediatric SDB [16]. The use of various methodology and questionnaires for assessing prevalence of sleep disordered breathing explains the wide range of reported prevalence. These include full sleep laboratory–based PSG, home cardiorespiratory sleep study, self-reported snoring among adolescents, and parent reported snoring or apneic events that are answered as part of many different kinds of validated and non-validated questionnaires. Different definitions of "habitual snoring" among various studies has also contributed to the large range of reported prevalence[16]. Fewer studies have looked at the epidemiology of SDB in the orthodontic population, and those that have, are mainly focused on snoring as their criteria of assessment. In our study, we aim to use comprehensive means of assessing SDB risk among the orthodontic population, and use consistent means to compare the prevalence to the general population. Given the shared anatomical features

that exist among children with SDB and those seeking orthodontic treatment, a higher prevalence of children with SDB may exist in the orthodontic population.

Assessing the role of the cranial base as a potential associating risk factor for pediatric SDB, and determining the prevalence of pediatric SDB in the orthodontic population will provide orthodontists with potentially valuable information that can be integrated into their practice for screening children for SDB. This can potentially lead to earlier diagnosis, more timely referrals and better potential comprehensive treatment options for the affected patients which includes interdisciplinary professional collaboration.

1. 2 Research Questions

The first research question of our study is focused on determining the prevalence of pediatric sleep disordered breathing in the orthodontic population, and comparing it to what is reported in the general population. We also continue to assess the prevalence of other co-morbidities among the higher risk patients in the orthodontic population. The specific questions we aim to answer are:

1a) What is the prevalence of pediatric sleep disordered breathing in the orthodontic population?

1b) How is this observed prevalence different than the prevalence of pediatric SDB in the general population?

2) What is the prevalence of certain co-morbidities among the higher risk SDB patients in the orthodontic population?

The second research question of our study is focused on the relationship between cranial base length and risk of sleep disordered breathing in the orthodontic population. The specific questions we aim to answer are:

1a) Is there an association between cranial base length and risk of sleep disordered breathing in the orthodontic population?

1b) If so, what is this association and how is it clinically relevant?

2) Are patients with significantly shorter cranial base lengths at a higher risk for SDB?

3) Can the cranial base length be a predictive risk factor in the development of pediatric sleep disordered breathing?

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Chapter 2: Cranial base length in pediatric populations with sleep disordered breathing: a systematic review

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2.1 Introduction

Sleep disordered breathing (SDB) is a disorder that is often characterized by prolonged increased upper airway resistance and partial or complete upper airway obstruction. It may lead to a disruption in pulmonary ventilation and oxygenation which may affect sleep quality[1]. SDB describes a continuum of symptoms and conditions, which may include snoring, upper airway resistance syndrome, and complete upper airway obstruction leading to obstructive sleep apnea (OSA)[2]. Of these, habitual snoring and obstructive sleep apnea are the most noted symptoms of SDB in children and have been associated with vast array of health consequences including neuro-cognitive and behavioral impairments, which can affect memory, attention, social interactions, and overall cognitive performance[3,4].

SDB remains a disease with multi-factorial etiology. Tonsil and/or adenoid hypertrophy have been generally considered as the most common etiology of SDB in children[5]. Factors such as upper airway soft tissue inflammation and altered neurological reflexes involving muscles of the upper airway are other common factors leading to increased upper airway collapsibility and likely a resulting SDB[5,6]. These factors may be increased in cases with asthma, continuous allergies, chronic rhinosinusitis and/or Gastroesophageal Reflux Disease (GERD). Anatomical factors associated with upper airway narrowing include macroglossia, micrognathia, midface hypoplasia, and childhood obesity[6].

Currently, laboratory-based nocturnal polysomnography (PSG) is considered the reference standard for diagnosing SDB as it monitors various physiological parameters related to sleep and wakefulness. However, PSG is expensive and not easily available, which may be a reason why a large number of suspected SDB pediatric patients remain undiagnosed[7].

Certain craniofacial patterns such as mandibular and maxillary retrognathia, maxillary constriction and short cranial base have been linked to pediatric SDB[8]. Studies have shown that children with obstructive sleep apnea syndrome present an increase in total and lower anterior facial heights and a more anterior and inferior position of the hyoid bone when compared to full-time nasal breathers [9]. A systematic review on the most common cephalometric variables in pediatric obstructive sleep apnea cases suggested positive association with altered reduced SNB (sella-nasion-B point) and ANB (A point-nasion-B point) angles, in addition to increased MP-SN (mandibular plane-sella-nasion) angle[10]. It is therefore important to recognize facial and craniofacial features that could be associated with SDB, as these are features routinely evaluated in dental and orthodontic practices and could be used to improve possible screening, diagnosis and treatment in pediatric SDB.

The cranial base, being at the junction between the cranium and the face clearly influences craniofacial skeletal growth patterns[11]. Development of the cranial base plays an important role in pushing the maxilla forward during its growth and failure of the cranial base to lengthen normally can result in characteristic midface deficiency as seen in congenital syndrome such as achondroplasia [12]. Hence, class III malocclusions, that are characterized by a degree of maxillary deficiency, are often

associated with a shorter cranial base and a more acute cranial base angle compared to class I and II malocclusions[13]. A short cranial base has also been suggested in patients with vertical growth pattern and skeletal open bites[14]. Hence, the development of the cranial base can greatly affect the growth of the head and face regions and could very well play a role in pediatric SDB as a craniofacial landmark. It has already been shown that premature fusion of cranial sutures leads to facial and cranial dysmorphism, which is associated with upper airway compromise and a high incidence of obstructive sleep apnea[15]. The distance between *Sella* and *Nasion* (SN), which represents the two-dimensional anterio-posterior measurement of the anterior cranial base, is a reference plane for many commonly used cephalometric measurements. During a recent study that investigated craniofacial morphology in children with OSA with and without PAP (positive airway pressure) therapy, it was observed that children with residual OSA after adenotonsillectomy treatment had anterior cranial bases that were significantly shorter in length (between 9 and 13%) than the expected normal values[8]. The data implied that the more severe the OSA, the smaller the anterior cranial base. This observation could also indicate that a reduced anterior cranial base length may be a risk factor in a subset of pediatric OSA patients that do not have adenotonsillar hypertrophy.

Current literature reviews have evaluated many of the SN derived values in pediatric SDB, however there have not been any systematic reviews that explored the cranial base length value itself in children with SDB. The goal of this systematic review is therefore to evaluate the existing literature[16–21] regarding cranial base length in children with SDB presented both in the form of OSA as well as other identifying symptoms. A potential association between pediatric SDB and cranial base length could

guide the path for future research in assessing cranial base deficiencies as a possible risk factor in disease progression or severity in cases of pediatric obstructive sleep apnea, and other forms of sleep disordered breathing. This could aid in better directing treatment for each individual pediatric patient suffering from this condition.

2.2 Materials and Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[22].

2.2.1 Eligibility criteria

Cross-sectional studies or cross-sectional data from longitudinal studies were included if they evaluated the association between cranial base length and sleep disordered breathing (SDB) in children or adolescents. The full range of pediatric SDB, from habitual snoring to OSA, were included. No restrictions were applied regarding language, ethnicity or sex. Studies were excluded if they assessed only the angles related to the cranial base or if they assessed sleep disorders not related to breathing parameters in children.

2.2.2 Data sources and search strategy

Comprehensive searches up to January 20, 2017 were carried out using the following electronic bibliographic databases: Ovid MEDLINE (1946 to Jan 20, 2017); EMBASE (1974 to Jan 20, 2017); and Science Citation Index (1900 to Jan 20, 2017).

The search strategy was designed with the assistance of a librarian specialized in health sciences. Search terms were first designed and implemented in Medline and then adapted to run the search in other databases. The identified terms included: "Cephalometry", "Morphology", "Dimensions", "Cranial Base", "Skull base", "Sleep disorders", "Sleep apnea". No restrictions were applied regarding language or publication year. Search was limited to

pediatric population aged 0-18 years. Table 1A and 1B provide more detail regarding the specific combination of terms used in the selected electronic databases. The reference lists of any of the finally selected articles were further explored for any potential papers not identified through the electronic search.

2.2.3 Study selection

The primary author (S.A) and a second reviewer (A.P) reviewed the titles and abstracts of all identified citations. Any studies, based on abstracts and titles, not fulfilling the inclusion criteria were excluded from further evaluation. Full-text articles were retrieved for those meeting the criteria. The same authors reviewed all full texts and re-applied the inclusion and exclusion criteria in the final selection. Any discrepancies in opinions were discussed between the two authors until a unanimous conclusion was reached.

2.2.4 Data collection process and data items

Data was extracted from each of the selected articles considering the following items: presence/type of SDB in a pediatric population and assessment of cranial base length. For each of the included studies, authors, year of publication, country, size and demographic features of the sample (age range and mean), means of assessing cranial base length, results and conclusions that were pertinent to the review were recorded.

2.2.5 Risk of bias in individual studies

The methodology of selected studies was evaluated by using a modified version of NIH (National Institute of Health) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [23]. The quality of each selected study was assessed independently. The criteria were based on: research question, study population, groups recruited from the same population and uniform eligibility criteria, sample size, varying levels of exposure,

exposure assessment, outcome assessment, and statistical analysis. Results were summarized using a modified Cochrane version of a risk of bias summary table indicating low risk, high risk, and unclear risk according to the responses in the noted criteria [24,25].

2.2.6 Synthesis of the results

Findings were evaluated in a descriptive manner based on the information provided by each of the included studies. A meta-analysis was planned if appropriate.

2.2.7 Risk of bias across studies

A summary of the overall strength of evidence was presented using "Grading of recommendations, assessment, development and evaluation" (GRADE) Summary of Findings tables [26,27].

2.3 Results

2.3.1 Study selection

The numbers of abstracts and titles obtained from each database are outlined in Table 1B. The PRISMA flow diagram shows the selection process of articles included in this study (Figure 1). The search yielded 56 articles after removal of duplicates, out of which 40 were excluded based on the abstracts. After reviewing the full texts of the 16 selected articles, 10 of the articles were excluded from our study based on the reasons outlined in Table 2. Therefore, only 6 articles were selected as the final studies matching our inclusion and exclusion criteria and were reviewed qualitatively (Table 3). A meta-analysis of the results was not possible because the included studies all used different landmarks for defining cranial base length and were too different methodologically for their results to be properly combined quantitatively (meta-analysis).

2.3.2 Study characteristics

Four of the selected studies were cross sectionals [16–18,20]. One of them had identified itself as a case-control, but data was collected in a cross-sectional manner [19]. The other article was a longitudinal cohort study that looked at cephalometric landmarks before and after adeno-tonsillectomy treatment [21]. For our review purposes, only the results at baseline where no treatment was yet provided was considered. All studies were published between 2000 to 2014. All studies were in English, except one, which was translated from Chinese [20].

2.3.3 Study population characteristics

- Five of the selected studies looked at pediatric populations with obstructive sleep apnea [16–18,20,21]. The remaining study looked at pediatric population of patients with habitual snoring, confirmed by history and clinical evaluation [19].
- Four of the studies [16,17,19,20]did not report *where* their test subjects were obtained from. One of the studies noted selecting their OSA population of patients from a group planned to undergo adeno-tonsillectomy[21]. Only one of the studies specifically reported the hospital and department where both the subject and control groups were selected from [18]. The pediatric population assessed in all six of these studies ranged from 3-16 years of age and all included both males and females, except for one study that included only males [20].
- Five of the six studies [17–21] included a control group of patients without any sleeping or breathing disorder to serve as comparison for the study group. Other than lack of clinical history, none of these studies mention an assessment tool to ensure the absence of sleeping or breathing disorder for their control subjects. These control groups were age and gender matched in two of these studies [18,21], age-matched in

one of the studies [19] and undefined [17] or mis-matched [20] in the other two. The remaining article [16] did not have a control group and looked at correlation of cephalometric landmarks with severity of OSA based on the AHI (Apnea-Hypoapnea Index). This was also the only study where degree of disease was assessed instead of presence of disease.

2.3.4 Sleep disordered breathing

In one study, the diagnosis of sleep apnea for the study subjects were based on clinical and medical history, sleep questionnaires and polysomnography [18]. Three of the other studies also mentioned polysomnography as the mode of diagnosis for OSA in the study subjects [16,20,21]. One of the studies mentioned fulfilling diagnostic criteria of the American Academy of Sleep Medicine as means of their OSA diagnosis [17]. The last study that looked at habitual snorers as subjects, used history and clinical evaluation [19].

2.3.5 Cranial base dimension (length)

All six selected articles used cephalometric landmarks on cephalograms as a way to assess craniofacial parameters, including cranial base length. Although in all the studies, other parameters of craniofacial morphology were evaluated, only those parameters relating to cranial base length were analyzed for the purpose of this systematic review. Five of the six studies [16–20]explained their technique of obtaining the lateral cephalograms and one study appeared to have obtained them retrospectively from the patients' charts [21]. All cephalometric points and landmarks used in each study were defined within the studies using either descriptions or figures. Two of the studies used cephalometric landmarks proposed by Ricketts [16,17]and one used the landmarks proposed by Bjork [21]. Another study [18] selected landmarks through two teams of radiologists and dentists. Two of the studies did not explain their means of landmark selection [19,20]. The landmarks were

measured 3 times by a single author in two of the studies and the means were used [16,20]. The landmarks were measured by the same operator [19] and by two teams of radiologists and dentists [18] in other studies. Two of the studies do not mention who had measured the landmarks [17,21]. Each of the six studies used different landmarks to define cranial base length, which are outlined in detail in Table 3.

2.3.6 Confounding variables

Five of the six studies discussed controlling for certain possible confounding factors. One study [18] excluded overweight children, as well as children affected by craniofacial syndromes or systemic diseases or deformities of the splanchnocranium bones to minimize bias on respiratory performance. Another study included only children with BMI (Body Mass Index) in the range of 14-19 in their study sample, but did not report the BMI in their control group [17]. One study set age and BMI as covariance to exclude their effect on severity of sleep apnea (AHI) [16]. One study excluded mouth breathers, those with chronic diseases of the nasopharynx and those receiving orthodontic treatment from their control group [20]. Another study excluded patients with previous adenoidectomy or ENT surgery or those using topical or systemic nasal medication from their test subjects [19].

2.3.7 Noted associations

Kawashima et al. [17], did not report a method of statistical analysis or calculating statistical significance. The investigators in this study did not note a significant difference in the length of the anterior cranial base between the pediatric group diagnosed by obstructive sleep apnea and the control group.

Similarly, Chiang et al. [16] found no significant correlation between the length of the cranial base (in the anterior or posterior segment) and the severity of OSA as indicated by Apnea/Hypopnea Index. This study used partial correlations to determine associations.

Zetterngren-Wejk et al. [21] found the length of anterior cranial base to be significantly shorter by about 2.5% in the group of patients diagnosed with OSA compared to the control group. This study used a paired t-test to compare means.

Perillo et al. [18] used student t-test to compare means and found the anterior cranial length (by 4.2%), posterior cranial length (by 3.1%) and the entire depth of the basicrainium (by 2.4%) to be shorter in pediatric patients with OSA compared to the control group. They reported this difference to be "significant" for the anterior cranial base length and "probably significant" for the posterior and total cranial base length.

Tanon-Anoh et al. [19] used student's t-test and Pearson's correlation to compare means and they found the total length of the cranial base to be significantly shorter by 4.1% in their subjects with chronic retronasal obstruction that habitually snore, compared to the controls.

Finally, Yong-Hua et al. [20] also used the t test to compare means and found the anterior cranial base length (by 5.4%) and the total cranial base length (by 4.1%) to be *longer* in boys with OSA. They noted this difference to be significant for only the total cranial base length.

2.3.8 Risk of bias within studies

The eight criteria used to assess each individual paper for observational cohort/cross-sectional studies is outlined in Table 4A. The criteria are based on: research question, study population, groups recruited from the same population and uniform eligibility criteria, sample size, varying levels of exposure, exposure assessment, outcome assessment, and statistical analysis. The labels low risk, high risk, and unclear risk in Table 4B refer to responses to these criteria. All the studies carried a low risk of bias regarding their research question, study population or outcome assessment and

only one [19] of the six carried a high risk of bias regarding exposure assessment. All the studies had a high risk of bias in their sample size determination and four of the six [16,17,20,21] studies had a high or unclear risk of bias in the recruitment of their subjects. Four [17,19–21] of the studies also had high or unclear risk of bias in their statistical calculations.

2.3.9 Risk of bias across studies

The overall quality of evidence was rated low to very low among the studies using the GRADE approach, based on the study design, risk of bias, effect of bias on results, and lack of precision. The summary of findings can be found in Table 5.

2.4 Discussion

To date, the existing literature has shown a positive association between pediatric sleep disordered breathing and craniofacial features such as retrusive mandible, steep mandibular plane, and vertical direction of growth [10]. Although many of these features are affected by the cranial base, not many studies have examined cranial base characteristic in pediatric SDB. This systematic review collected and evaluated the existing literature on the association of cranial base length with pediatric sleep disordered breathing.

2.4.1 Summary of evidence

In the current systematic review, two of the identified studies [16,17] *did not* find a significant correlation between pediatric OSA (presence or severity) and cranial base length in both the anterior and posterior segments. One of these studies [17] purely looked at cranial base dimensions in OSA vs. healthy pediatric population, while the other [16] looked at the severity of OSA correlating with cranial base dimensions. As

such, the two studies were too different in design, for the results to be compared or combined. In assessing risk of bias, neither of the studies had a justification for their sample size nor had clear selection criteria for their subjects. The study by Kawashima et al. [17] had further failed to match the characteristics of their control group with their sample population, had failed to account for any confounding variables and had made a conclusion based on only 15 individuals.

Three of the identified studies [18,19,21] *did* find that the cranial base lengths in the SDB affected pediatric population are shorter than those in the healthy population. None of these studies had justified their sample size, only two [19,21] had outlined their subject selection criteria and unlike the other studies that used objective tools for OSA diagnosis, the study by Tanon-Anoh et al. [19], relied on clinical history and examination. Nevertheless, these three studies had all tried to match their control groups' characteristics to their study subjects.

Only one of the studies [20] showed that the cranial base is longer in subjects affected by OSA compared to healthy controls. This study carried a high risk of bias in its sample size determination, eligibility criteria, level of exposure and statistical analysis. Furthermore, the authors had compared only 7 study subjects with an average age of 9.5 to 29 control subjects with an average age of 11 in an all-male population, which significantly added to the methodological shortcomings.

2.4.2 Limitations and future direction

When using GRADE to assess the outcome across studies, it is seen that while all the included studies were low to very low in quality due to their cross-sectional design and inherent risks of bias, the three studies that show a shorter cranial base with

positive pediatric SDB were graded as low quality of evidence compared to the other three that were graded as very low. The studies that are showing a longer cranial base in positive SDB patients or are not showing an association fall under the very low quality of evidence mainly due to their inability to match their control and subject populations. In particular, Kawashima et al. [17] had used double the number of their subjects in their control group without providing the age and sex in their control population. Similarly, Yong-Hua et al. [20] had a study population of 7 vs. a control of 29, with the control group having a higher average age. "Age," therefore could have been a confounding factor affecting cranial base length that was not accounted for. Given this difference in evidence quality, there appears to be slightly stronger evidence supporting the presence of a shorter cranial base length in the pediatric population affected by SDB. In other words, although significant deficiencies were identified in all the included studies, those that suggested shorter cranial bases have a lower risk of bias which can be interpreted as more likely to showcase values closer to the truth. In any event, caution has to be exercised as based on the current reported evidence, no categorical conclusions can be supported.

The idea that a short cranial base and pediatric SDB are correlated is a plausible hypothesis, given the fact that a short cranial base will generate a smaller maxillary complex, which is a characteristic feature of children with SDB. it has been shown that a short cranial base can result in a short maxillary length and resulting midface deficiency in children and adolescents[13,28,29]. Similarly, maxillary constriction and retrusion are often seen in children suffering from SDB[6,8,30]. Furthermore, a steeper gonial angle representative of a vertical growth pattern, anterior open bite tendency and lip incompetence have been reported as common findings among children with OSA[10];

this same vertical pattern has been associated with short cranial base[14]. More specifically, significantly shorter posterior cranial base lengths have been observed in high angle (vertical) class II division I patients[31] Nevertheless, based on the GRADE approach, given the range from low to very low quality of evidence that exists on the relationship between cranial base length and pediatric SDB, their true association is likely to be somehow different than what is noted in the existing studies and hence more research in the area is warranted. The direction and magnitude of the potential difference is also unknown.

Given the moderate number of studies that were excluded from this systematic review based on the lack of information on cranial bases length, it is recommended that future studies include an assessment of the length of the cranial base. Furthermore, five of the studies that were evaluated were cross-sectional in design and one was longitudinal with a cross sectional component. As a result, we cannot infer a cause and effect relationship. To establish casualty or to determine the role of cranial base in the possible development of pediatric SDB, longitudinal studies are needed.

In all six studies, 2-D cephalograms were used to assess cranial base length. Therefore, any conclusions made would only relate to the "sagittal" length of the cranial base. In general, any linear measurements (including S-N or any of the other defined parameters in the noted studies) obtained from 2-D cephalograms lack in accuracy due to superimpositions, geometric distortions, shadowing and obscured landmarks [32] . As well, the pneumatization of the frontal sinus extends throughout childhood and a final stable position is reached after puberty [33]; this may impact the nasion (N), which is the anterior landmark for 2-D measurements of the cranial base. As there are no

studies that measure cranial base length in 3-dimentions, an accurate measurement of this dimension is difficult to obtain and any measured dimensions in these studies can be inferred as "approximations." Ideally 3-D measurements should be the aim of future research, however, out of the chosen landmarks in the studies, S-N is the most clinically relevant as it is the one often traced and assessed by orthodontists.

Further research should also aim at establishing clinical relevance and implications. For example, while PSG is the true diagnostic tool for SDB, its high costs and need for hospitalization, prevent it from being readily available to practitioners. As such, questionnaires and/or clinical exam may provide a possible alternative. In the study by Tanon-Anoh et al. [19], which was analyzed in this review, patient's history and clinical exam were used to select study subjects with habitual snoring. While this selection technique held a higher risk of bias compared to PSG testing, it was a more clinically feasible approach that still showed a significantly shorter cranial base length in habitual snorers. Currently, the PSQ is the only questionnaire that has a diagnostic accuracy good enough to be used as a screening method for SDB [34] and may hence be considered as a more practical risk assessment tool in future research.

Enhancing the methodology and the clinical relevance of future studies can help identify additional risk factors in pediatric sleep disordered breathing, which can provide clinicians with additional diagnostic tools and more customizable treatment options.

2.5 Conclusions

Although studies with slightly lower risk of bias may indicate shorter cranial base lengths in pediatric patients with SDB, neither an association nor a lack thereof between cranial base length and pediatric SDB can be supported or refuted due to low to very low quality of included studies.

Practice Points:

1. Few studies with high risk of bias exist assessing the potential association between cranial base length and pediatric sleep disordered breathing.
2. A categorical association between the cranial base length and pediatric sleep disordered breathing cannot be fully supported or refuted based on the existing evidence.
3. A trend in the identified evidence suggests that some children with sleep disordered breathing may have associated shorter cranial base lengths.

Research Agenda:

1. Increased number and higher quality studies to clarify a potential association between cranial base length and pediatric sleep disordered breathing are needed.
2. Longitudinal studies are needed to support any potential cause and effect relationship between cranial base length and sleep disordered breathing in children.
3. 3-D imaging may enhance our understanding of any identified cranial base alteration in children with sleep disordered breathing.

Table 1A: Search strategy (in Medline through Ovid)
#1 "Cephalometry/"OR "cephalometr*.mp." OR "(morpholog* or anatomy or dimension*).mp." OR "head size.mp."
#2 "exp Skull Base/" OR "((cranial or skull) adj base).mp."
#3 "exp sleep disorders/ or exp sleep apnea, obstructive/" OR "(sleep adj disorder*).mp."
#4 #1 AND #2 AND #3
#5 exp child/ or exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or exp infant/ or adolescent/ or exp pediatrics/ or child, abandoned/ or exp child, exceptional/ or child, orphaned/ or child, unwanted/ or minors/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn. [17]
#6 #5 AND #4

Table 1B- Search strategies and results from different electronic databases		
Database	**Keywords**	**Results**
Ovid MEDLINE(R) (1946 to May 2016)	"Cephalometry/"OR "cephalometr*.mp." OR "(morpholog* or anatomy or dimension*).mp." OR "head size.mp." AND "exp Skull Base/" OR "((cranial or skull) adj base).mp." AND "exp sleep disorders/ or exp sleep apnea, obstructive/" OR "(sleep adj disorder*).mp." (exp child/ or exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or exp infant/ or adolescent/ or exp pediatrics/ or child, abandoned/ or exp child, exceptional/ or child, orphaned/ or child, unwanted/ or minors/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn.) [18]	45
Science Citation Index (1900 to May 2016)	TS=(skull base OR cranial base) AND TS=(cephalometry) AND TS=(sleep apnea OR sleep disorders) AND TS=(Pediatric OR Children) Indexes=SCI-EXPANDED Timespan=All years	5

Table 1B- **Search strategies and results from different electronic databases (cont.)**		
Database	**Keywords**	**Results**
EMBASE (1974-May 2016)	"Cephalometry/"OR "cephalometr*.mp." OR "(morpholog* or anatomy or dimension*).mp." OR "head size.mp." AND "exp Skull Base/" OR "((cranial or skull) adj base).mp." AND "exp sleep disorders/ or exp sleep apnea, obstructive/" OR "(sleep adj disorder*).mp." (exp child/ or exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or exp infant/ or adolescent/ or exp pediatrics/ or child, abandoned/ or exp child, exceptional/ or child, orphaned/ or child, unwanted/ or minors/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn.) [18]	22
Total database searches		72
Duplicates		16
Final		56

Table 2: Excluded articles and the reasons for their exclusion

	Authors/ Year	***Resason for exclusion***
1	Finkelstein et al., 2000[35]	1
2	Flores-Mir et al., 2013[10]	2
3	Juliano et al., 2009[36]	1
4	Korayem M., 2013[8]	3
5	Lofstrand-Tiderstrom et al., 1999[37]	1
6	Marino A., et al, 2009[38]	1
7	Ozdemir et al., 2004[39]	1
8	Parkkinin et al., 2010[40]	1
9	Predrag et al., 2012[41]	1
10	Zicari et al, 2014[42]	1

1) Inclusion criteria was not met

-*Length* of cranial base not assessed

2)Article is a review study*(reference list was reviewed)*

3)No healthy controls used for comparison (results based on undefined normative values)

Table 3: Summary of descriptive characteristics of finally selected studies

Study author, Date	*Study design*	*Study group*	*Control group*	*Method of assessment*	*Result*
Chiang et al., 2012[16]	**Cross-sectional evaluation of correlations between Cephalometric Variables (i.e. cranial base length) and severity of OSA in pediatric patients**	**N=56 (36 males and 20 females)** **Age: 3-13 (mean: 7.6 yrs)** **Country: Taiwan**	**none**	**Lateral Cephalogram** **Cephalometric landmarks proposed by Rickett's were used** **Cranial base length determinants noted:** **BA-S (posterior length)** **S-N (anterior length)** **Ba-N (total length)**	**Parameters of BA-S, S-N and Ba-N were not significantly correlated with AHI in the studied population**
Kawashima et. al.2000[17]	**Cross sectional comparison of children with OSA and healthy children**	**N=15 (11 boys, 4 girls)** **Age: 3-5 (mean=4.7)** **Country: Japan**	**N=30 (No detail provided on age or gender)**	**Lateral Cephalogram** **Use of landmarks proposed by Rickets on cephalometric analysis** **Anterior Cranial length: distance of line between NA and CC**	**Anterior cranial length in OSA group: 51.9 ± 4.2 mm** **Anterior cranial length in control group: 51.9 ± 3.0 mm**

Study author, Date	*Study design*	*Study group*	*Control group*	*Method of assessment*	*Result*
Perillo et. al., 2012[18]	**Cross-sectional comparison of children with OSA and healthy children**	**N=40 (20 boys, 20 girls)** **Age: 4-14 (mean=8.95)** **Country: Italy**	**N=40(20 boys,20 girls)** **Age:5-15 (mean: 9.4)**	**Lateral cephalograms** **16 craniometric landmarks selected by radiologist and odontologist on research team** **Determinants of cranial base length:** **BA-N: entire depth of basicranium** **N-S: Anterior cranial length** **S-BA: Posterior cranial length**	***BA-N*** **OSA group: 97.5±1.6mm** **Control group: 99.9±1.9mm** **Significance: P<0.05*** ***N-S*** **OSA group: 71.1±3.8mm** **Control group: 74.2±3.1mm** **Significance: P<0.01*** ***S-BA*** **OSA group: 37.3±1.2mm** **Control group: 38.5±1.6mm** **Significance: P<0.05***
Tanon-Anoh et al., 2014[19]	**Observational study of cephalometric variables between habitual snorers and controls**	**N=29 (16 M, 13 F)** **Age: 3-6 yrs** **Population: Ivorian melanoderm**	**N=29 (15 M, 14 F)** **Age matched**	**Lateral Cephalograms** **16 landmarks selected by author** **Determinant of cranial base length: N-Ba (total length)**	**N-BA** **Habitual snorers: 92.82±7.37** **Controls: 96.8±4.93mm** **Significance: P=0.019***

Study author, Date	*Study design*	*Study group*	*Control group*	*Method of assessment*	*Result*
Yong-hua et al., 2003[20]	**Cross sectional evaluation of Cephalometric variables in mixed-dentition boys with and without OSA**	**N=7 (all male)** **Age: 8-11 (mean: 9.5 yrs)** **Country: China**	**N=29 (all male)** **Age: mean of 11 yrs**	**Lateral Cephalogram** **25 landmarks assessed by the author** **Determinants of cranial base length:** **S-N (anterior length)** **BA-N (total length)**	**S-N** **OSAS group: 64.83±3.67mm** **Control group:61.33±5.23mm** **Significance: P=0.1055** **BA-N** **OSAS group: 96.10±3.04mm** **Control: 100.17±3.57mm** **Significance: P=0.0041***
Zetterngren-Wejk et al., 2006[21]	**Prospective cohort study comparing children with OSA with healthy controls at baseline and after treatment.** **Cross-sectional data from T_0 (before treatment) were assessed**	**N=17 (10 boys, 7 girls)** **Age: 5.6±1.34** **Country: Sweden**	**N=17 (age & gender matched)** **Age: 5.8±1.4**	**Lateral cephalogram taken at various time points after adeno-tonsillectomy procedure as treatment for OSA.** **Landmarks based on Bjork** **Determinant of anterior cranial base length: N-FHP**	**Baseline(T0)** **N-FHP measurements:** **OSA group: 58.1 ± 2.49mm** **Control group: 59.6±2.26mm** **Difference: -1.5 ± 2.17** **Significance: P=0.009 ***

***AHI-Apnea/Hypo-apnea Index**

***BA-most inferior posterior point of the occipital bone at the anterior margin of the occipital foramen**

***CC- intersection point of BA-NA line and the facial axis plane**

***FHP-the perpendicular line to Frankfort Horizontal passing through the sella point**

***OSA(S)- Obstructive Sleep Apnea (Syndrome)**

***NA(N)- nasion- most anterior point of the frontonasal suture**

***S- Centre of Sella Tursica**

Table 4A: Quality assessment tool for observation cohort and cross sectional studies

Criteria	Chiang et al., 2012[16]	Kawashima et. al. 2000[17]	Perillo et. al., 2012[18]	Tanon-Anoh et al., 2014[19]	Yong-hua et al., 2003[20]	Zetterngren-Wejk et al., 2006[21]
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes
3. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?	NR	NR	Yes	Yes	No	No
4. Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	No	No	No
5. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Yes	No	No	No	No	No
6. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	No	Yes	Yes

7. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
8. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	**Yes**	**No**	**Yes**	**NR**	**NR**	**NR**
NR: Not Reported						

Table 4B: Summary tool for observation cohort and cross sectional studies

First Author, Date of Publication	Chiang et al., 2012[16]	Kawashima et. al. 2000[17]	Perillo et. al., 2012[18]	Tanon-Anoh et al., 2014[19]	Yong-hua et al., 2003[20]	Zetterngren-Wejket al., 2006[21]
Research question						
Study population						
Groups recruited from the same population and uniform eligibility criteria						
Sample size						
Varying levels of exposure (independent variable)						
Exposure measurement and assessment						
Outcome measurement and assessment						
Statistical analysis						

High risk	Low risk	Unclear risk

Table 5: GRADE's Summary of findings

Is there an association between cranial base length and sleep disordered breathing in the pediatric population?

A qualitative descriptive analysis of the results was performed; meta-analysis was not performed due to differences in methodology

Outcome	***Number of studies/study design***	***Number of participants***	***Quality of Evidence (GRADE)***
Shorter cranial base length with SDB	3 observational studies	86 test subject 86 controls	⊕⊕⊖⊖ Low[a,b]
No change in cranial base length with SDB	2 observational studies	71 test subjects 30 controls	⊕⊖⊖⊖ Very Low[a,c]
Longer cranial base length with SDB	1 observational study	7 test subjects 29 controls	⊕⊖⊖⊖ Very Low[a,c,d]

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are *moderately* confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a) Observational study design-Low quality evidence

b) Risks of bias exist but potential limitations are unlikely to change study results (not downgraded)

c) High risk of bias due to failure to properly match subjects and controls

d) Lack of precision due to low sample size

} -1

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Chapter 3: Prevalence of the risk of pediatric sleep disordered breathing and its associated symptoms in the orthodontic population

3.1 Introduction

Classically, Pediatric sleep-disordered breathing (SDB) was characterized as obstructive sleep apnea syndrome (OSAS), which was defined as partial or complete upper airway obstruction during sleep, associated with sleep disruption, hypoxemia, hypercapnia, or daytime symptoms attributable to the sleep-related airway obstruction. Today, pediatric SDB encompasses a wide spectrum of symptoms that include snoring, upper airway resistance syndrome, and obstructive sleep apnea (OSA) [1]. Habitual snoring and obstructive sleep apnea are the most noted symptoms of SDB in children and have been associated with neuro-cognitive and behavioral impairments, associated with deficits in memory, attention, social interactions, and overall cognitive performance[2,3]. The prevalence of pediatric OSA is estimated to be 1-4%, while for SDB and habitual snoring, a wider range of 4-11% and 1.5-14.8% respectively have been reported [4]. This is mainly due to the wide variety of methodology that different studies have used in diagnosing OSA and SDB, which may include overnight polysomnography (PSG), home cardiorespiratory sleep study, and various self-reported, and parent reported questionnaires [4]. Currently, overnight polysomnography (PSG) is considered the gold standard in SDB diagnosis as it monitors various physiological parameters related to sleep and wakefulness. However, the time, effort, and expense of the procedure has limited many research and epidemiological studies from using it as their means of assessment [5]. For clinicians, recognizing the prevalence of SDB and its associated symptoms can prompt a more regular, thorough, and targeted screening, and determine the possible need for additional diagnostic workup[4].

Pediatric SDB is most often associated with enlarged tonsil and/or adenoids [6], however factors such as obesity, upper airway inflammation in asthma and allergic rhinitis and altered neurological reflexes involving muscles of the upper airway in cerebral palsy and neuromuscular disorders can also lead to SDB symptoms[7,8]. Other risk factors associated with pediatric SDB may include preterm birth, nocturnal enuresis, and African American descent[9–13]. Craniofacial disharmony can also often be associated with pediatric SDB. Anatomical and craniofacial features that have been associated with upper airway narrowing and SDB in children include macroglossia, midface hypoplasia, mandibular and maxillary retrognathia, maxillary constriction, short cranial base, increased total and lower anterior facial heights and a more anterior and inferior position of the hyoid bone[8,14,15]. These anatomical features are clinically and radiographically assessed during a routine orthodontic exam and often become the target of orthodontic treatment. Hence, understanding the presence and prevalence of SDB, its associated symptoms and potential risk factors in the orthodontic population can help practitioners make timely decisions regarding treatment options and necessary referrals.

The few studies that have looked into the prevalence of SDB in the orthodontic population have mainly focused on snoring as their criteria of assessment. Snoring prevalence in the orthodontic population have had variable results with one article reporting 10.8% of the patients "usually snore," and 2.9% "always snore," with a reported prevalence of 1.8% for apneas[16]. Another article has reported 17% of the orthodontic patients "often snore"[17] and there is another report of 53% snorers in the orthodontic population, which the authors attribute to lack of question specificity[18]. One study[19] has reported the overall SDB prevalence in the orthodontic population to

be 18% but has used a small sample size exclusively obtained from a single university-based orthodontic clinic, which is subject to selection bias. The use of various questionnaires with different definitions of "habitual snoring" has resulted in a wide range of reported snoring prevalence in the orthodontic population that is difficult to compare with the general pediatric population.

The current study aims to determine the prevalence of positive risk for sleep disordered breathing in the pediatric orthodontic population using a large and randomized sample selected from various clinics in Alberta, Canada. More specifically, pediatric sleep questionnaire (PSQ) with a sensitivity of 0.85 and specificity of 0.87 for SDB diagnosis[5] has been used to determine the prevalence of overall SDB risk, habitual snoring and sleepiness prevalence in the orthodontic population, and the numbers are compared to those obtained by identical means from the general pediatric population. Furthermore, an additional health history questionnaire has been used to compare the existence of certain co-morbidities and environmental conditions among the high and low risk SDB population in our sample.

3.2 Materials and Methods

3.2.1 Study Population

Ethics approval was obtained from the University of Alberta's Health Research Ethics Board. Data was collected from 390 patients between the age of 5-16 who were seeking orthodontic treatment at the University of Alberta clinic and several other private practices in Alberta. The patients either had already completed the Pediatric Sleep Questionnaire (PSQ) as part of their initial orthodontic records by their treating clinician or were asked to fill out a questionnaire during their initial records appointment. The patients who were recruited prospectively (n=130) completed the

appropriate consent forms and were also asked to fill out an additional health history questionnaire.

3.2.2 Pediatric sleep questionnaire (PSQ)

In this study, Pediatric Sleep Questionnaire (PSQ) was used to assess risk of sleep disordered breathing as it is currently the only questionnaire with a diagnostic accuracy good enough to be used as a screening method for SDB[20]. PSQ responses were obtained from 390 subjects as previously noted. This 22-item questionnaire contains questions on snoring frequency, loud snoring, observed apneas, difficulty breathing, daytime sleepiness, inattentive and hyperactive behavior. Possible responses are yes=1, no=0 and I don't know=missing item, and the score is calculated by determining the mean response on non-missing items. In our study, any question, that had been answered with "sometimes," was taken to indicate a positive response. The optimal score cut off to indicate presence of SDB has been noted to be 0.33 (33% positive responses) with greater values suggesting the diagnosis[5]. Hence, for the purposes of our study, any patient scoring positive on more than 33% on the questionnaire was categorized as high risk for SDB. Habitual snoring (defined as snoring more than half the time while sleep), and excessive daytime sleepiness (defined as presence of 2 or more symptoms of 4 of the items in the questionnaire) were also assessed as per Archbold, et al[21].

3.2.3 Additional health history questionnaire

An additional health history questionnaire was formulated based on the known associated health and environmental factors related to pediatric SDB and modeled after the I-ARC clinical checklist for identifying pediatric sleep disordered breathing[22]. This

additional questionnaire was given prospectively to 130 of the patients and their parents to assess the presence of additional symptoms and/or conditions. These included the presence or absence of nocturnal enuresis, ADHD, GERD, asthma, environmental allergies, indoor pets, smoking environment, preterm labour, family history of sleep apnea, and being overweight.

3.2.4 Data analysis

The PSQ responses collected from the 390 patients were quantified based on total score, habitual snoring and sleepiness and were compared with the same numbers collected by the same means from the general pediatric clinics by Archbold et al.[21]. Of these, 130 patients were further assessed for additional symptoms based on the added health questionnaire, and the results were compared between the high SDB risk and low SDB risk patients among our collected sample. Chi-square test was used to assess any significant difference between SDB symptoms in our orthodontic sample vs. Archbold et al.'s general pediatric population. Fisher's exact test was used to compare the presence and absence of certain health/environmental conditions among the high risk vs. low risk population in our sample. Statistical Package for Social Sciences (version 22; SPSS, Chicago, IL) was used to carry out all statistical analyses and statistical significance was set at $p \leq 0.05$.

3.3 Results

3.3.1 Demographics

Our collected sample of 390 patients compromised of 173(44%) male patients, and 217 female patients (56%). The average age of our sample was 10.3 years.

3.3.2 Sleep disordered breathing (based on PSQ)

A score suggestive of high risk for SDB (≥ 0.33) was found in 42/390 (10.8%) of the patients. Habitual snoring, defined as snoring more than half the time, was present in 52 (13.3%) of our patients and sleepiness was present in 70 (17.9%) of our patients. The noted prevalence and their sex distribution are outlined in Table 3-1. Chi-square test did not indicate a significant difference between the frequencies of these symptoms among the sexes.

Table 3 -1: Prevalence of SDB risk and associated symptoms in the orthodontic population

	# of patients (%) N=390	# of males (%) N=173	# of females (%) N=217
PSQ score ≥0.33	42 (10.8%)	21 (12.1%)	21 (9.7%)
Snores more than half the time	52 (13.3%)	20 (11.6%)	32 (14.7%)
Sleepiness ≥2	70 (17.9%)	36 (20.8%)	34 (15.7%)

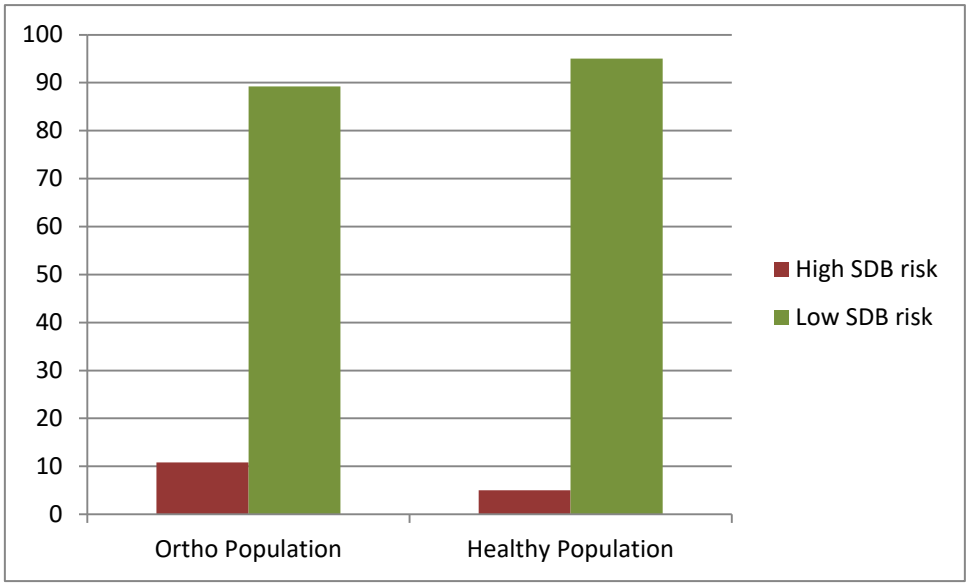
As there is no significant difference among the sexes with regards to risk of SDB and associated symptoms, the prevalence of SDB risk and its associated symptoms in our total orthodontic population was compared with that in Archbold et al.'s[21] study who uses identical means for determining SDB prevalence in general pediatric clinics. Table 3-2 shows the prevalence of SDB risk and associated symptoms in Archbold et al.'s total population which compromises all patients seen in general pediatric clinics as well as in their sub-population of healthy children seen for immunization[21]. Frequencies of

patients in each of the symptom categories were compared between the orthodontic population and the general pediatric population, and between the orthodontic population and the healthy sub-population in Archbold et al.'s study. Chi-square test did not show a significant difference in any of the symptom categories between our orthodontic population and the general pediatric clinic population. However, the orthodontic population did seem to have a significantly higher number of patients in the high SDB risk category compared to the healthy sub-population (P=0.018). This difference is indicated in Figure 3-1. The orthodontic population also had a higher percentage of patients in the sleepiness category compared to the healthy sub-population, although this difference was not statistically significant (P=0.084).

Table 3 -2: Prevalence of SDB risk and associated symptoms in the orthodontic population compared to Archbold et al.'s total and healthy sub-population at a general pediatric clinic

Population	PSQ score ≥0.33 (high SDB risk) # of patients (%)	Snores more than half the time # of patients (%)	Sleepiness ≥2 # of patients (%)
Orthodontic (n=390)	**42 (10.8%)***	52 (13.3%)	70 (17.9%)
General Pediatric Clinic (n=1038)	115 (11.1%)	176 (17%)	162 (15.6%)
Healthy child in pediatric clinic (n=201)	**10 (5%)**	Not reported	25 (12.4%)
* Significant difference (chi-square, P=0.018) between frequency of high SDB risk patient in the orthodontic population vs. the healthy sub-population in general pediatric clinic			

Figure 3 -1: Prevalence of high SDB risk patients among the orthodontic and healthy pediatric population (in %))



3.3.3 Additional health questionnaire

130 of our orthodontic patients were asked to complete an additional health history questionnaire to determine the prevalence of certain environmental conditions and co-morbidities in the high risk vs. low risk SDB groups. This group consisted of 71 females and 59 males with an average age of 12 years. Table 3-3 show the prevalence of associated environmental and health conditions in the low vs. high SDB risk groups.

Table 3-3: Prevalence of associated environmental and health conditions in high risk SDB vs. low risk SDB groups of patients in the orthodontic population

Associated Health History	Selected pediatric orthodontic population & additional health history information (n=130)			
	Low risk of SDB (108)		High risk of SDB (22)	
	M: 45	F: 63	M: 14	F: 8
Bed wetting	0 (0%)		3 (13.6%)*	
Overweight	3 (2.7%)		4 (18.2%)*	
ADHD	4 (3.7%)		7 (31.8%)*	
GERD	2 (1.9%)		0 (0%)	
Asthma	7 (6.5%)		1 (4.5%)	
Environmental Allergies	17 (15.7%)		5 (22.7%)	
Indoor pets with hair	55 (50.9%)		16 (72.7%)	
Someone who smokes	11 (10.2%)		5 (22.7%)	
Pre-term child	6 (5.6%)		1 (4.5%)	
Family history of sleep apnea	24 (22.2%)		4 (18.2%)	

* Fisher's exact test: $P<0.05$

Among the associated health and environmental conditions, there is a significant difference in the presence of nocturnal enuresis ($P= 0.004$), being overweight

(P=0.016), and having ADHD (P<0.001) between the high risk and low risk SDB groups as per the fisher's exact test (Figures 3-2 to 3-4), with a higher percentage of patients in the high risk SDB group experiencing the noted conditions.

Figure 3 -2: Prevalence of nocturnal enuresis in the high risk vs. low risk SDB groups in an orthodontic population (in %)

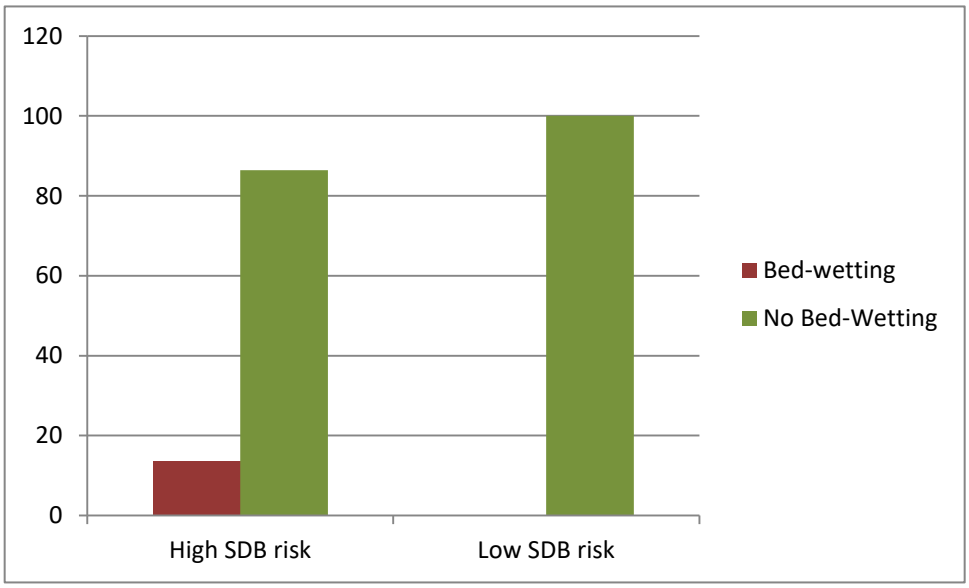


Figure 3 -3: Prevalence of being overweight in the high risk vs. low risk SDB groups in an orthodontic population (in %)

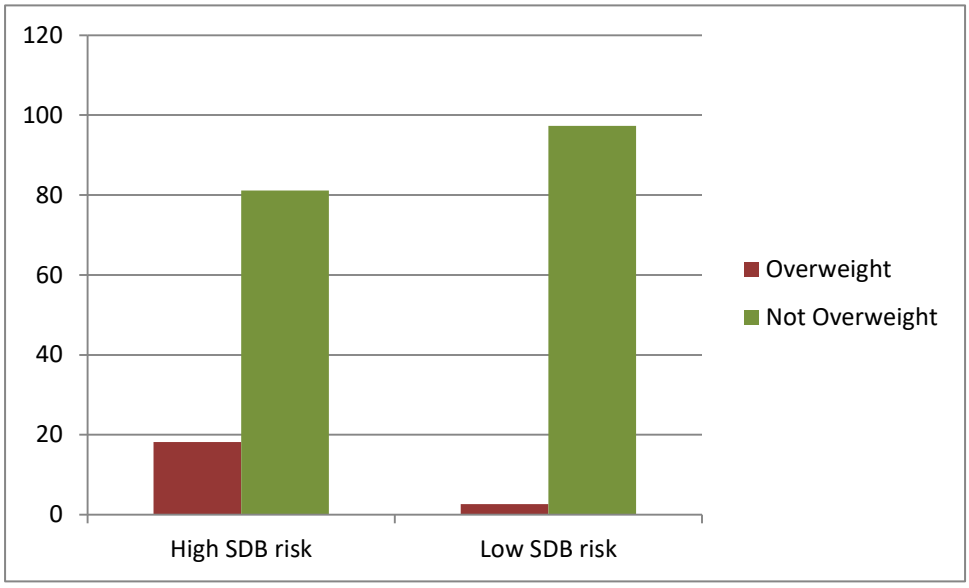
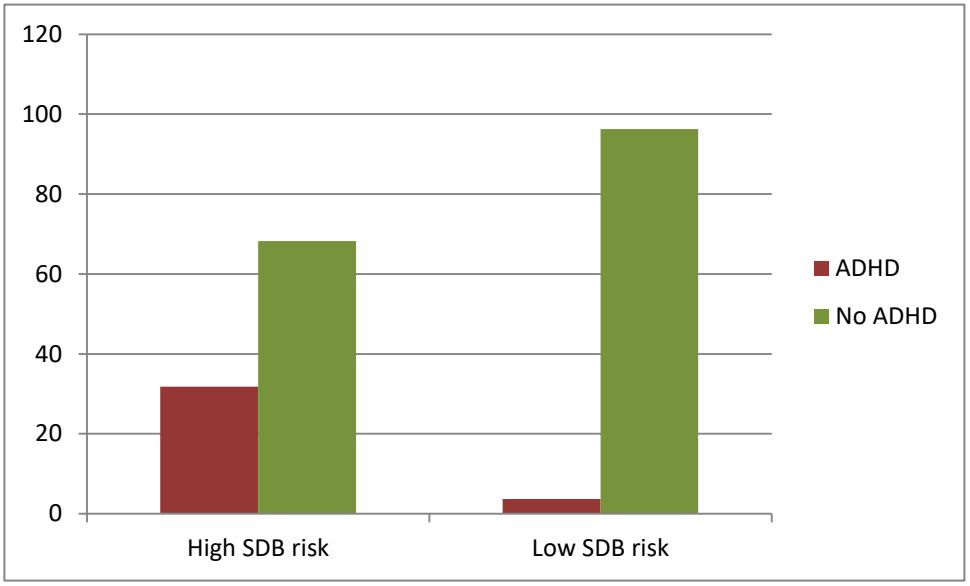


Figure 3- 4: Prevalence of ADHD in the high risk vs. low risk SDB groups in an orthodontic population (in %)



A higher percentage of patients in the high risk group also had environmental allergies, indoor pets with hair and a smoking household member, however, these were not statistically significant when compared to the low risk group. By contrast, the low risk SDB group had a higher percentage of patients who suffered from GERD, asthma, pre-mature birth and family history of sleep apnea; again the difference, when compared to the high risk SDB group was not significant in any of these categories.

3.4 Discussion

The prevalence for the risk of sleep disordered breathing among the orthodontic population in our study has been estimated to be 10.8%. It is difficult to compare this to a normal value in a healthy pediatric population as the available studies are variable in methodology and report a wide range of prevalence (4-11%) depending on the diagnostic measures, parental reports or diagnostic testing used[4]. Hence, we chose Archbold et al.'s study as our means of comparison as they use the pediatric sleep questionnaire (PSQ) and associated sleepiness and snoring scores as their means of assessing risk of

SDB[21], which is identical to our study. Our estimated SDB prevalence is very close to their reported prevalence of 11.1% and falls in the higher end of the normal spectrum among the reported SDB prevalence in other studies[4]. Nevertheless, Archbold et al. report their general pediatric population to include patients who were visiting the clinic due to respiratory problems, allergies and gastrointestinal symptoms, all of which can contribute to development of SDB symptoms. Hence, their population cannot be representative of the healthy pediatric population. Only 201 patients in their population were well-patients who were presenting for immunization and among those, the prevalence of SDB risk was significantly lower than our orthodontic population (by 5.8%). A previous thesis study that had looked at overall risk of SDB in the orthodontic population had reported a prevalence of 18%[19]. This study, however, had looked at only 100 patients who were receiving orthodontic treatment at the University of North Carolina Orthodontic Department, and were hence subject to selection bias. There is evidence that residence in a neighborhood of socioeconomic disadvantage (which is often seen in university-based patients) is a risk factor for pediatric OSA[23]; as a result, pure sample selection from such a population can exaggerate true SDB prevalence. Therefore, while a higher SDB prevalence does seem to be present in the orthodontic population, this number may not actually be too much higher than what may exist in the normal pediatric population.

The prevalence of snoring in healthy children among previous studies has also been variable due to each study's unique definition of "snoring." The studies that use the criteria of “always snoring," have a range of reported prevalence of 1.5 to 6.2%; studies that use the criteria of “often snoring” report prevalence in the range of 3.2 to 14.8%[4]. Nevertheless, a meta-analysis based on 41 studies reporting questionnaire data for

snoring prevalence, has found prevalence of habitual snoring among children to be 7.45% (95% confidence interval, 5.75–9.61)[4]. In our study, where snoring was defined as "more than half the time" based on the PSQ, prevalence was noted to be 13.3%, which is higher than the overall prevalence in the general population. Other studies that have looked at snoring prevalence in the orthodontic population have had variable results with some reporting 10.8% of the patients "usually snore"[16], 17% of the patients "often snore"[17] and a report of 53% snorers in the orthodontic population, which the authors attribute to lack of question specificity[18].

Approximately 15% to 22% of children who have not yet received orthodontic treatment have asymmetric occlusions and nearly 30% have sagittal asymmetries[16]. Given that sagittal and vertical craniofacial disharmony can be associated risk factors for pediatric SDB, it is not surprising that the prevalence of SDB or habitual snoring should be higher in the orthodontic population.

In further assessing risk factors of SDB in the orthodontic population, a positive significant association was seen between SDB and nocturnal enuresis, being overweight and having ADHD. A high prevalence of enuresis in children with suspected sleep-disordered breathing has been noted, which is likely due to the effects of obstructive sleep apnea on arousal response, bladder pressure, or urinary hormone secretion [9]. Obese children have fatty infiltrates around their upper airway structures and neck contributing to upper airway narrowing and increased pharyngeal collapsibility[8].Furthermore, being overweight and nocturnal enuresis have both been associated with presence of OSA in children, without being associated with each other[10]. Since both of these risk factors were also present in the high risk SDB patients

in our orthodontic sample, it is important to consider the possibility of OSA in patients that present clinically with both of these conditions.

Hyperactivity and aggressive daytime behavior are among the most frequent symptoms noted in children with obstructive sleep apnea syndrome, and children with habitual snoring or sleep disturbances show more behavior problems[24,25]. Six of the 22 questions on the PSQ relate to the child's behavior and the categorical score of these six questions has been shown to have a high and significant association with the diagnosis of SDB[5]. While we cannot say that every child suffering from SDB is also diagnosed with ADHD, the two conditions likely have a close association.

Other risk factors that we were expecting to be present at a higher percentage in the high risk SDB group were asthma and GERD. The presence of upper airway inflammation in conditions such as asthma and chronic rhinitis often lead to upper airway collapsibility seen in SDB. Furthermore, asthma and GERD are both inflammatory conditions, and elevation of pro-inflammatory cytokines has also been reported in pediatric OSA[8]. Both of these conditions, however, were actually less in the high risk SDB group among our orthodontic sample, although the difference was not statistically significant. A higher sample size may potentially be needed to verify the true prevalence of these conditions in the orthodontic population. Furthermore, parent reported questionnaires such as the PSQ, regardless of their reliability, are still subject to bias, and parent's level of understanding and attentiveness to the child's conditions and environment. Ideally, performing overnight polysomnography on the patients labeled as high SDB risk could verify some of our findings, however such an effort would be too time consuming and expensive for the patients to undergo.

Although the results of our study cannot confirm a definite risk in the orthodontic population, understanding that a higher prevalence of children at risk of SDB could be presenting to orthodontic practices should alert us to take a more thorough medical and social history of the patients. This will enable more effective screening and facilitate multidisciplinary approach to diagnosis and treatment for patients that need it the most.

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Chapter 4: Relationship between cranial base length and risk of pediatric sleep disordered breathing in the orthodontic population

4.1 Introduction

Sleep-disordered breathing (SDB) is characterized by prolonged increased upper airway resistance, partial or complete upper airway obstruction that disrupts pulmonary ventilation and oxygenation and hence affects sleep quality. In the pediatric population, SDB describes a range of symptoms and conditions, which include snoring, upper airway resistance syndrome, and obstructive sleep apnea[1].

SDB remains a disease with multi-factorial etiology. Obstruction of the upper airway by tonsil and/or adenoid hypertrophy is the main factor in the development of SDB in children[2,3]. Adenotonsillar hypertrophy can result in airway narrowing and a clinically significant airway obstruction during sleep[3] . Factors such as upper airway soft tissue inflammation, increase in pro-inflammatory markers and altered neurological reflexes involving muscles of the upper airway [all of which can occur in cases of asthma and chronic rhinosinusitis] are other common factors that can result in SDB[2,4,5]. Currently, adenotosillectomy is the first line of therapy in pediatric SDB, but has a variable curative rate[6]. Generally, when defining success as apnea-hypopnea index (AHI) of <1, the estimate for OSAHS (obstructive sleep apnea/hypopnea syndrome) treatment success with adenotonsillectomy was 59.8%[6]. More recent meta-analyses have reported an overall success rate of 51% for adenotonsillectomy[7] and an overall success rate of 17% for lingual tonsillectomy[8], when success was defined as postoperative AHI < 1. Craniofacial dysmorphology can also be an important etiological

factor in pediatric SDB and can hence become the target of treatment in cases where adenotosillectomy may be ineffective.

Anatomical and craniofacial features that have been associated with upper airway narrowing and SDB in children include macroglossia, midface hypoplasia, mandibular and maxillary retrognathia, maxillary constriction, short cranial base, increased total and lower anterior facial heights and a more anterior and inferior position of the hyoid bone[5,9,10]. Landmarks identified on cephalograms are used in orthodontics to assess anatomical relationships that help determine the direction of a child's orthodontic treatment. Among the cephalometric landmarks, a positive association with pediatric SDB has been noted with reduced SNB (sella-nasion-B point) angle, increased ANB (A point-nasion-B point) angle, and increased MP-SN (mandibular plane-sella-nasion) angle[11,12]. It is therefore important to recognize facial and craniofacial features that could be associated with SDB, as they can be potential targets for SDB treatment.

The distance between *Sella* and *Nasion* (SN), represents the two-dimensional anterio-posterior measurement of the anterior cranial base. The cranial base, being at the junction between the cranium and the face clearly influences craniofacial skeletal growth patterns[13]. Therefore, SN is a reference plane for many commonly used cephalometric measurements, including SNA, SNB, MP-SN, which have been associated with pediatric SDB[11,12]. However, very few studies have looked at the association of the cranial base itself with pediatric SDB. A recent systematic review conducted by our group[14] (Chapter 2) that looked at the association of cranial base length with sleep disordered breathing in the pediatric population showed only 6 studies of low-very low quality on the subject. Many of these studies had small sample sizes, poor selection criteria and confounding variables. The studies that had failed to show an association

between cranial base length and pediatric SDB had further failed to match their control and experimental groups by age and gender. Hence, while a trend in the reviewed evidence suggests that some children with sleep disordered breathing may have associated shorter cranial base lengths, more studies in the area are warranted. Our study, while still cross-sectional in design, will try to address some of these shortcomings through selection of a large randomized sample size and by statistically controlling for some of the confounding variables. One of the studies[10] that was excluded from our systematic review observed that children with residual OSA after adenoidectomy (with or without tonsillectomy) treatment had anterior cranial bases that were significantly shorter in length (between 9 and 13%) than the expected normal values. This observation, plus the fact that a short cranial base will generate a smaller maxillary complex, which is a characteristic feature of some children with SDB[14], makes the hypothesis that a short cranial base is associated with an increased risk of pediatric SDB a plausible one.

Given the potential role of cranial base in increasing risk of pediatric SDB and given the lack of current strong evidence in the area, this study aims to explore the possible association of cranial base length with risk of pediatric sleep disordered breathing in a way that is clinically relevant to the orthodontic practice. More specifically, this study will aim to answer the following questions:

1a) Is there an association between cranial base length and risk of sleep disordered breathing among children aged 6-16 who are receiving orthodontic treatment?

1b) If there is an association, what is the clinical significance?

2) Are patients with significantly shorter cranial base lengths at a higher risk for SDB?

3) Can the cranial base length be a predictive factor in determining risk of pediatric sleep disordered breathing?

4.2 Materials and Methods

4.2.1 Study Population

Ethics approval was obtained from the University of Alberta's Health Research Ethics Board. Data was collected retrospectively from 320 patients between the age of 5-16 who were seeking orthodontic treatment at the University of Alberta Clinic and several other Private practices in Alberta and had cone beam computed tomography (CBCT) imaging and pediatric sleep questionnaires completed as part of their initial orthodontic exam and records.

4.2.2 Cranial Base Length

All selected subjects had previously undergone 3-dimentional radiographic examination with CBCT as part of their diagnostic assessment prior to orthodontic treatment. Images had been taken using iCAT with a voxel size of 0.3, kVp of 120, and variable mAs, exposure times and fields of view depending on the patient and treating clinician. The images were obtained in the DICOM3 format and processed as per Korayem et al.[10] using Dolphin 3D to produce 2-dimensional lateral cephalometric images according to a standardized imaging protocol. The cranial base length was defined by the landmarks S-N (mm)(Appendix-Fig A) which more specifically defines the anterior cranial base and is based on the most commonly used variable for the cranial base[10]. All S-N landmark measurements were traced and measured by the same operator (S.A), who is an orthodontic resident. To take the effect of intra-operator measurement error into account, 10 of the cephalometric images were traced and

measured for S-N at 3 separate times, with each measurement taken at least a week apart and in random order. Intraoperator reliability was evaluated for cranial base length measurements using the intraclass correlation coefficient.

4.3.3 Risk of Pediatric Sleep Disordered Breathing (SDB)

Currently, laboratory-based polysomnography (PSG) is considered the gold standard for diagnosing SDB as it monitors various physiological parameters related to sleep and wakefulness; However, PSG is burdensome and is often limited to tertiary care centres which may be a reason why a large number of suspected SDB patients remain undiagnosed[15]. In this study, Pediatric Sleep Questionnaire (PSQ) was used to assess risk of sleep disordered breathing as it is currently the only questionnaire with a diagnostic accuracy good enough to be used as a screening method for SDB[16]. All selected subjects had completed the PSQ as part of their initial charting and orthodontic records. This 22-item questionnaire contains questions on snoring frequency, loud snoring, observed apneas, difficulty breathing, daytime sleepiness, inattentive and hyperactive behaviour. Possible responses are yes=1, no=0 and I don't know=missing item, and the score is calculated by determining the mean response on non-missing items. The optimal score cut off to indicate presence of SDB has been reported to be 0.33 (33% positive responses) with greater values suggesting the diagnosis[15]. Furthermore, the subscores for categories of snoring (4 items), sleepiness (4 items) and behaviour (6 items) have also been shown to be strongly associated with presence of SDB[15]. Hence, the total PSQ score and the scores of its subcategories were calculated and used on a continuous scale to reflect risk of SDB among the patient population as the primary means of analysis. Furthermore, to determine if a pattern of increased SDB may be present in cases with abnormally short cranial base lengths that may be masked

when looking at the data continuously, the cranial base lengths were also analyzed categorically. Hence, mean and standard deviation of the collected cranial base lengths were used to categorize them into very short (<59.49mm), short (59.50mm-63.88mm), average (63.89mm-72.66mm), long (72.67mm-77.05mm), and very long (>77.06mm), and risk of SDB was assessed and compared in each category.

4.3.4 Statistical analysis

The Statistical Package for Social Sciences (version 22; SPSS, Chicago, IL) was used to carry out the statistical analyses. To assess the potential relationship between cranial base length and risk of SDB, Multivariate Regression analysis was used, with cranial base length as the predictive variable, and total PSQ score, snore score, sleepiness score and behaviour score as the outcome variables. Age and sex were further set as co-variates. Multicollinearity among the 3 variables of cranial base length, age and sex was also assessed. Linear regression models were then constructed and assessed for variables showing significant associations with the cranial base length. ANOVA was used to compare SDB risk among cranial base lengths categorized based on length abnormalities. Statistical significance for all analyses was set at $p \leq 0.05$.

4.4 Results

The cranial base length (measured from CBCT acquired lateral cephalogram) and the PSQ scores (total and sub-categorical) were measured for a total of 320 patients between the age of 5-16, seeking orthodontic treatment. The population consisted of 140 male and 180 female patients and had an average age of 9.95 yrs.

4.4.1 Reliability: Intra-operator consistency

Intra-operator reliability was high for the S-N measurement with an intraclass correlation of 0.994 (CI: 0.983-0.998) (Table A-Appendix). The profile plot (Figure 4-1) shows the consistency among measurements between the 3 measurements taken for 10 randomly selected subjects.

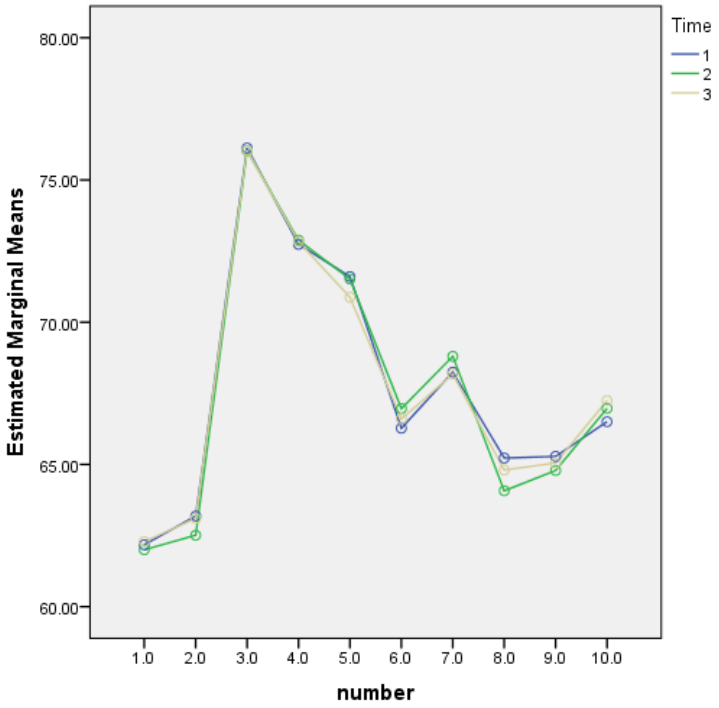

Figure 4 -1: Estimated Marginal Means of Cranial Base Length Measurements taken at 3 different time points

4.4.2 Associations between cranial base length and total PSQ score, snore score, sleepiness score and behaviour score

In order to be able to run multivariate regression analysis, and ANOVA, assumptions of independence, equal variance and linearity among pairs of outcome variables were met. Although the outcome variables had a left-skewed population distribution, MANOVA's robustness to violation of normality allowed us to carry out the analysis. One outlier was identified and removed from the dataset. The statistical

analysis was conducted with and without the outlier and as there was no change in the results, the outlier was maintained in the final analysis. Multicollinearity was assessed between the independent variable of cranial base length and the two independent co-variates of age and sex. The VIF was less than 3 for all the independent variables, indicating no collinearity among them (Table B- Appendix).

A multivariate regression analysis with cranial base length, age and sex (co-variates) as predictive variables and total PSQ score, snore score, sleepiness score and behaviour score as outcome variables were conducted. The effect of possible interactions between the predictive variables were also evaluated. Sex (P=0.041), age (P<0.001) and cranial base length (P=0.002) all showed a significant association with the outcome variables (Table C-Appendix). Hence, the follow up test of between subject effects was conducted to see the specific associations (Table D-Appendix). The cranial base length showed a significant association with total PSQ score (P=0.002), snoring score (P<0.001), and sleepiness score (P=0.006). However, the sleepiness score also showed a significant association with age (P<0.001) and sex (P=0.034), and the total PSQ score showed a significant association with sex (P=0.007). There was no significant association between cranial base length and behaviour score. The nature of the observed associations was further explored with a linear regression model.

From a categorical perspective, only 6 patients fell into the “very short cranial base” category with 2 standard deviations away from the mean; these patients had an average PSQ score of 0.24. Patients with average cranial bases had an average PSQ score of 0.13, and those with the longest cranial bases had an average PSQ score of 0.06 (Table E-Appendix). Although a pattern of decreasing PSQ score seems to be present,

comparison among the categories did not reveal a statistically significant SDB risk among the defined cranial base categories (Table F-Appendix).

4.4.2.1 Total PSQ score

Based on the result of multivariate regression, total PSQ score is being affected by cranial base length and the sex of the patients. Looking at the scatter plot (Figure 4-2) and the linear regression model (Table G-Appendix), when controlled for sex, there is a pattern of decrease in total PSQ score with increasing cranial base length in both male and female children, with males generally having a higher PSQ average at any given cranial base length compared to females. This relationship is defined by:

$$Total\ PSQ\ Score = 0.442 - 0.005 Cranialbaselength$$

in females and by:

$$Total\ PSQ\ Score = 0.483 - 0.005 Cranialbaselength$$ in males.

While statistically significant, the relationship has a R^2 of 0.035, which indicates that only 3.5% of the variations in total PSQ score can be explained by the cranial base length and sex of the patients as indicated by the noted linear equation.

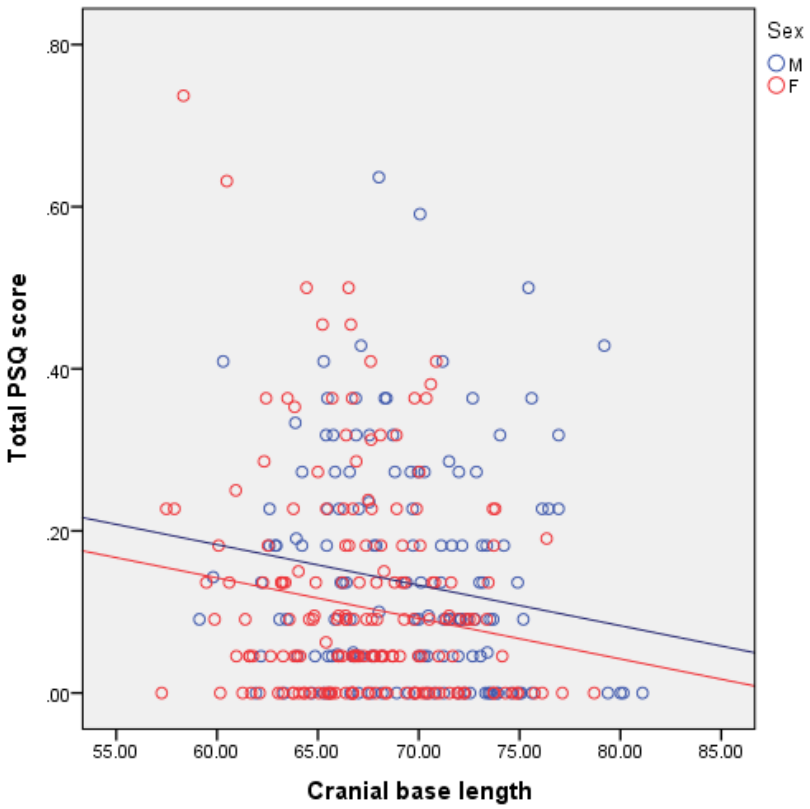

Figure 4 -2: Scatter plot of Cranial Base Length and Total PSQ Score separated by sex

4.4.2.2 Snore score

Based on the multivariate regression, snore score is the only outcome variable being exclusively affected by the cranial base length without a significant influence from age and sex of the patient. A scatter plot and linear regression analysis were used to further assess the relationship between the cranial base length and snore score. Based on the scatter plot (Figure 4-3) and the test of linear regression (Table H-Appendix), the resulting equation for a linear relationship is shown as:

$$Snoring\ scale = 0.796 - 0.010 Cranialbaselength$$

With a slope of -0.010, the line explaining the relationship between the two variables has a negative slope, indicating that as the cranial base length decreases, the snoring

scale increases. The correlation co-efficient is 0.206, and the R^2 value for the relationship in this model is 0.042, indicating that 4.2% of the variations seen in the snoring score can be explained by cranial base length. A P-value of P<0.001 provides strong evidence against the null hypothesis and can define this relationship as being statistically significant, however the correlation co-efficient is low and indicates a weak relationship.

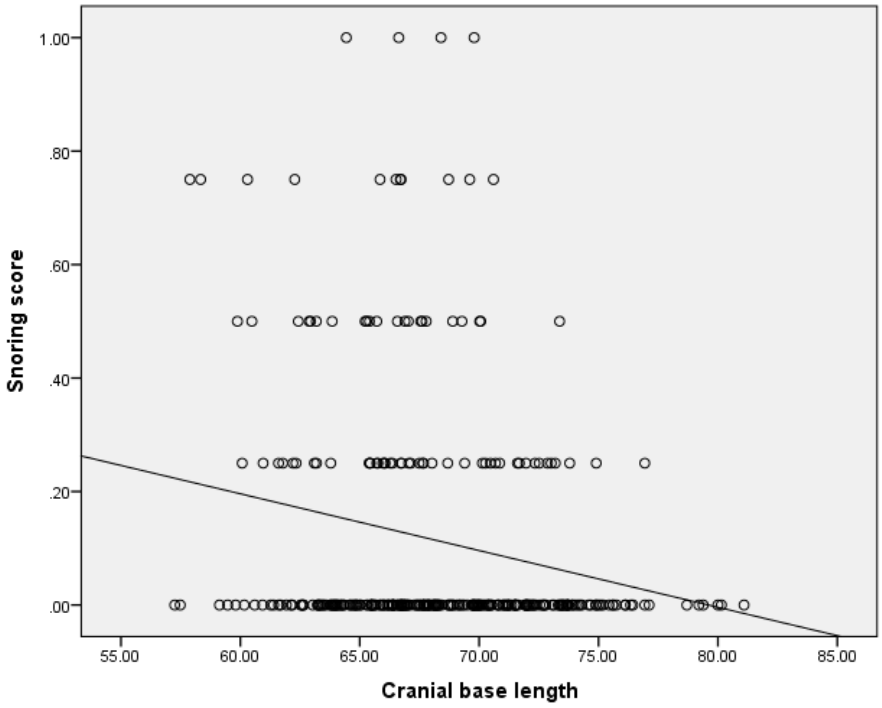

Figure 4- 3: Scatter plot of Cranial Base Length and Snoring Score

4.4.2.3 Sleepiness score

Based on the multivariate regression, sleepiness score seems to be affected by the cranial base length, the age and the sex of the child. The linear regression model (Table I-Appendix) gives the following equation:

Sleepiness score=0.523-0.008 (cranial base length)+0.021 (age)- 0.054 (sex)

This could be further simplified into:

Sleepiness score=0.523-0.008 (cranial base length)+0.021 (age)

for males and

Sleepiness score=0.469-0.008 (cranial base length)+0.021 (age)

for females.

The equations indicate that the sleepiness score increases with decreasing cranial base length and with increasing age. Both of these relationships are statistically significant ($P<0.001$ for age, $P=0.006$ for cranial base length) but age seems to have a larger effect on sleepiness score as indicated by a larger co-efficient and stronger evidence against the null. Nevertheless, in answer to our research question, the sleepiness score increases with decreasing cranial base length when age and sex are controlled.

4.4.2.4 Behaviour score

The multivariate regression analysis did not show a significant relationship between cranial base length and the behaviour score of the patients. Based on the multivariate regression, sex seems to be the factor mainly affecting the behaviour score of the child.

4.5 Discussion

The anterior cranial base is among the first structures to complete its growth in the craniofacial development[17], and has historically been used as a stable structure to assess growth through cephalometric superimpositions[18]. To date, the existing literature has shown a positive association between pediatric sleep disordered breathing and craniofacial features such as retrusive mandible, steep mandibular plane, and vertical direction of growth[11], which often use the linear measurement of cranial base as a reference plane. However, few and conflicting studies of low-very low quality exist on the relationship between pediatric SDB and the cranial base length[19]. It is therefore important to investigate such a relationship in order to provide earlier screening tools for SDB in the orthodontic population. As the Pediatric Sleep Questionnaire has been validated to show strong association with a diagnosis of pediatric SDB, it was used in this study to assess the relationship between cranial base length and *risk of* pediatric sleep disordered breathing.

Based on the 320 orthodontic patients assessed, it was observed that cranial base length was negatively correlated with risk of sleep disordered breathing in three of the four categories assessed. The total PSQ score, while affected by the patient's sex, showed a weak but significant negative correlation with the cranial base length; the sleepiness scale showed a negative correlation with cranial base length but was being more affected by the patient's age. The snoring scale had the highest association with the cranial base length, which was independent of the age and sex of the patients. The correlation, while still weak, was significant and indicated an increase in the snoring scale by 0.01 with every mm decrease in the cranial base length. Chervin et al.'s original paper on the PSQ validity indicated the snoring scale to have one of the highest and

most significant association with a SDB diagnosis among the sub-categories[15]. Hence we can infer a slightly higher risk of SDB in patients that have shorter cranial base. This association, while statistically significant, may not be clinically significant. In other words, a 25 mm reduction in cranial base length has to be present before an incremental score increase in the snoring scale can be seen; This may be seen in cases of syndromic craniosynostosis, where cranial sutures are prematurely fused, and incidence of OSA can reach 68%[20]. Another way to explore the relationship between cranial base length and pediatric SDB is to not view a short cranial base length as a possible associative factor but rather the feature of an additional subtype of pediatric SDB that may not present with the common phenotypes of enlarges adenoids/tonsils or underlying inflammation. In their paper, Korayem et al.[10] observed shorter cranial bases in a pediatric population that had adenoidectomy done as first means of OSA treatment yet had remained symptomatic and were potentially in need of PAP treatment. In their study, the measured cranial bases were 9% shorter than the norm in the patients who did not use PAP as treatment after adenotonsillectomy and 13% shorter for those patients who did use PAP. This can indicate that perhaps there may be subtypes of pediatric SDB that are not associated with the common etiologies of inflammation and adenoid hypertrophy. In our study, we attempted to isolate this subtype by categorizing patients according to their cranial base lengths and looking at the SDB risk of those with the shortest cranial bases. However, as there were only 6 patients in this category, with the smallest cranial base at 57.25mm, a significantly higher SDB risk could not be seen and a threshold cranial base length for SDB development could not be estimated. Perhaps, by exploring a population of syndromic patients or patients suffering from PAP-dependent OSA, we may be able to isolate more

of the individuals that have short cranial bases as the primary etiologic factor in SDB development. Being able to identify these individuals would enable practitioners to pursue more appropriate treatment modalities, subjecting a fewer number of patients to medications or adenotonsillectomy procedures. A low number of these individuals naturally compromise the generally healthy orthodontic population, hence, it is not a surprise to see weaker associations with SDB in our selected population. Furthermore, due to the retrospective nature of our study, there were factors that could not be accounted for; for example, we know that the risk of pediatric SDB is affected by the child's ethnicity, obesity and underlying medical conditions[21] that could not be controlled for in this study.

There was no association between the behavior scale and the cranial base length. As well, snoring scale (which had the strongest association with cranial base length in this study) has previously shown the least correlation with neurobehavioral assessments and the strongest correlation with OSA related quality of life[22]. Therefore, it is important to recognize that while the PSQ compiles multiple facets of the disease to serve as a good screening tool for SDB, craniofacial features like the cranial base are likely only increasing SDB risk through anatomical modifications of the airway and not through neurocognitive modifications. This is reasonable as snoring is a primary symptom of upper airway obstruction and symptoms of snoring and nasal patency have been shown to have significant associations with other cephalometric structures indicating anterio-posterior positioning of the jaws and patients' growth pattern[9].

Despite the anterior cranial base being considered a stable structure, the common landmarks delineating it on a cephalogram are "sella" and "nasion" which have been

shown to move with age. Nasion could potentially move upward and forward with the development of the frontal sinus and sella moves downward and backward, resulting in a longer cranial base with age[23]. Nevertheless, in the sample population studied, multicollinearity of cranial base length, age, and sex was assessed and not found to be significant. Furthermore, the potential effect of age and sex on the SDB risk assessment was taken into account as noted. Hence, while 3-D imaging could be used to identify more stable landmarks for the cranial base length, we do not feel that it would significantly change the results that we have obtained.

There is still a lot of controversy regarding a direct cause and effect relationship between the respiratory obstructions and craniofacial growth, however identifying earlier developed structures, like the cranial base, may help clarify the confusion. Based on this study, the association between the cranial base length and pediatric SDB risk is not strong enough to serve as such a tool in the orthodontic population, and there seems to be a very low number of patients in the orthodontic population with cranial bases short enough to serve as the etiologic factor for SDB. Nevertheless, the cranial base may be more significant of a factor in orthodontic hospital residency programs where a higher number of syndromic patients or patients with more compromised medical conditions are treated.

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Chapter 5: General Discussion

5.1 Summary of results

Our study aimed to assess the role of the cranial base as a potential associating risk factor for pediatric sleep disordered breathing, and determine the prevalence of pediatric SDB in the orthodontic population.

In answering our first question, we found the prevalence of overall SDB risk to be 10.8%, habitual snoring to be 13.3% and sleepiness to be 17.9% in the orthodontic population. The overall SDB risk was significantly higher than the reported prevalence of 5%[5] in a healthy pediatric population using the same assessment criteria. Comparisons with other reported numbers also place the prevalence of habitual snoring in our orthodontic population in the higher than normal spectrum. Nevertheless, defining a "healthy" pediatric population is difficult if not impossible, as many otherwise healthy children may be dealing with obesity, asthma, allergies, ADHD and other environmental and health circumstances that could increase their risk of SDB development. Even in our selected orthodontic population, a significantly higher rate of nocturnal enuresis, obesity and ADHD were seen in children that were categorized as having higher risk for SDB. With so many factors playing a role in SDB development in children, it is difficult to attribute risk to one isolated population, although the vertical and sagittal disharmonies present in the orthodontic population could be one of the contributing risk factors for the higher observed prevalence.

In answering our second question, it was determined that a shorter cranial base length was associated with a higher risk of sleep disordered breathing in the orthodontic

population, which was most clearly seen when "snoring" was used as the criteria for assessing SDB risk. However, the magnitude of this association was too small to have any clinical significance in the orthodontic practice and could potentially be seen in syndromic patients or those with severe CPAP dependent apneas. The low number of orthodontic patients that had significantly shorter than average cranial bases did not seem to carry a higher risk for SDB, either. As our study was a cross sectional observational study using retrospective data, no conclusions on a shorter cranial base "causing" pediatric SDB can be made. Nevertheless, given the early role of the cranial base in the craniofacial skeletal growth patterns[1], and its effect on the maxillary complex [2–4], the possibility of shorter cranial base predicting SDB symptoms in children remains plausible. Based on our study, this carries very little (if any) clinical significance in the orthodontic practice.

5.2 Limitations

The biggest limitation of our study was our inability to *diagnose* SDB among our selected population. Even though the pediatric sleep questionnaire (PSQ) that was used as SDB risk assessment in our study has a sensitivity of 0.85 and specificity of 0.87 for SDB diagnosis[6] and is considered the only questionnaire with a diagnostic accuracy good enough to be used as a screening method for SDB[7], it is still a questionnaire subject to bias and misinterpretation. Chervin et al., have noted that while the PSQ scale predicts polysomnographic results to an extent useful for research, it is not reliable enough for most individual patients[8]. Obtaining polysomnographic data from a generally healthy orthodontic population would have been too costly and burdensome

for the patients to ethically justify, hence there was no option but to use the PSQ which is still considered a practical risk assessment tool in research[9].

While use of 3D landmark selection could have also enhanced the accuracy of our results in assessing cranial base length and SDB risk association, our study was meant to mimic the technique of Korayam et al., who had seen the largest change in cranial base length with the presence of SDB among the existing literature[10]. Furthermore, given the very small and clinically insignificant association seen in our study, a 3D study is not warranted.

5.3 Future studies

Focus should be placed on establishing a feasible yet consistent means for assessing SDB risk among various populations so results for either prevalence or associations with particular risk factors can be better assessed across population. Archbold et al.'s study[5] was the only study that had used means similar to ours for assessing prevalence of SDB risk in the general pediatric population. Alternatively, we can run a similar research project in a separate population outside of the orthodontic practices to provide a more realistic source of comparison. An easier way may also be using data from a population representative birth cohort such as the study of Canadian Healthy Infant Longitudinal Development (CHILD) to obtain PSQ responses in a larger healthy pediatric population.

As previously mentioned, one of our biggest limitations was our inability to diagnose SDB. Given the difficulty in obtaining PSG on patients, we may consider oximetry or level 3 home sleep testing as alternatives to PSQ for assessing SDB risk.

While the burden of participation may be higher for patients undergoing these tests, the results are likely to be more diagnostic of SDB.

Future research can also focus on anatomic and cephalometric landmarks less explored for their association with pediatric SDB. For example, while more studies have verified the association between maxillary constriction, retrusive mandible and increased vertical face height in SDB affected children[11], fewer have focused on the sagittal and vertical position of the maxillary complex and the cranial base angle. These areas can be focused on in future studies as identifying more anatomic and radiographic risk factors can aid in more efficient screenings and diagnosis for pediatric SDB.

5.4 Conclusions

The prevalence of the risk of pediatric sleep disordered breathing in the orthodontic population, at 10.8% is higher than the general pediatric population, and can be associated with a higher risk of nocturnal enuresis, ADHD, and being overweight. Hence, it is important that SDB screening become the standard of care in the routine orthodontic practice.

The cranial base length is shorter in pediatric orthodontic patients that are at higher risk of sleep disordered breathing, however the magnitude of this change is not clinically significant in the orthodontic practice and cannot be used to predict risk of SDB in children

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Appendix

Figure A) S-N (sella-nasion)-representative of anterior cranial base

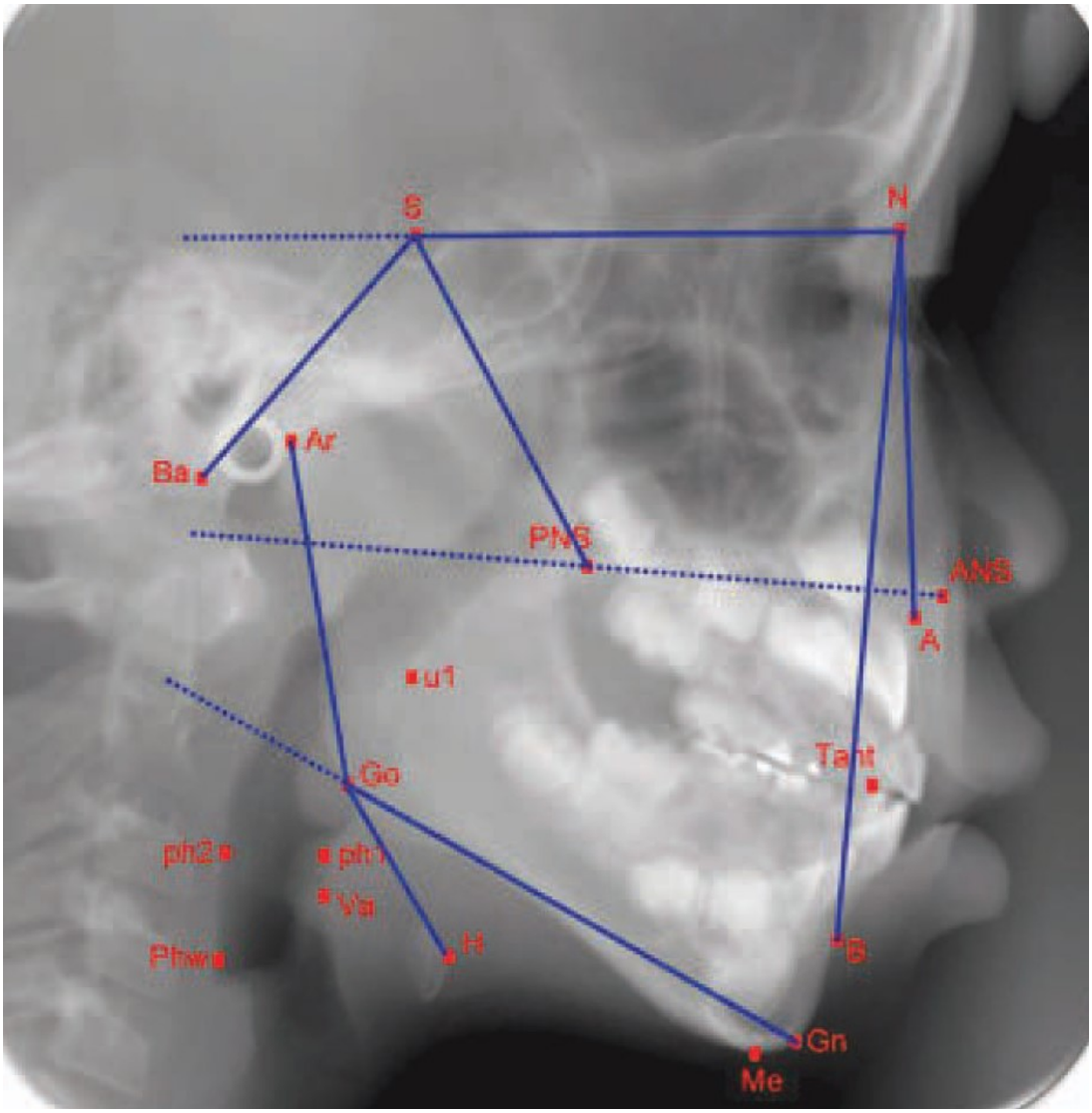

Table A) Intra-operator reliability test for cranial base length measurements

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.994[a]	.983	.998	502.265	9	18	.000
Average Measures	.998[c]	.994	.999	502.265	9	18	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition. The between-measure variance is excluded from the denominator variance.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Table B) Test of Multicollinearity with age, sex and cranial base length set as dependent variables respectively

Model		Collinearity Statistics	
		Tolerance	VIF
1	cranial base length	.933	1.071
	sex	.933	1.071

Model		Collinearity Statistics	
		Tolerance	VIF
1	cranial base length	.951	1.052
	age	.951	1.052

Model		Collinearity Statistics	
		Tolerance	VIF
1	age	1.000	1.000
	sex	1.000	1.000

Table C, D) Multivariate Regression Analysis & Test of between subjects

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
Intercept	Pillai's Trace	.064	5.323[b]	4.000	313.000	.000
	Wilks' Lambda	.936	5.323[b]	4.000	313.000	.000
	Hotelling's Trace	.068	5.323[b]	4.000	313.000	.000
	Roy's Largest Root	.068	5.323[b]	4.000	313.000	.000
cranialbaselength	Pillai's Trace	.055	4.551[b]	4.000	313.000	.001
	Wilks' Lambda	.945	4.551[b]	4.000	313.000	.001
	Hotelling's Trace	.058	4.551[b]	4.000	313.000	.001
	Roy's Largest Root	.058	4.551[b]	4.000	313.000	.001
sexcoded2	Pillai's Trace	.034	2.794[b]	4.000	313.000	.026
	Wilks' Lambda	.966	2.794[b]	4.000	313.000	.026
	Hotelling's Trace	.036	2.794[b]	4.000	313.000	.026
	Roy's Largest Root	.036	2.794[b]	4.000	313.000	.026
age	Pillai's Trace	.069	5.786[b]	4.000	313.000	.000
	Wilks' Lambda	.931	5.786[b]	4.000	313.000	.000
	Hotelling's Trace	.074	5.786[b]	4.000	313.000	.000
	Roy's Largest Root	.074	5.786[b]	4.000	313.000	.000

a. Design: Intercept + cranialbaselength + sexcoded2 + age

b. Exact statistic

Tests of Between-Subjects Effects

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	Total PSQ ratio	.257[a]	3	.086	4.742	.003
	snoring ratio	.640[b]	3	.213	4.769	.003
	sleepiness ratio	1.147[c]	3	.382	8.042	.000
	beh ratio	.799[d]	3	.266	3.463	.017
Intercept	Total PSQ ratio	.273	1	.273	15.110	.000
	snoring ratio	.774	1	.774	17.291	.000
	sleepiness ratio	.322	1	.322	6.778	.010
	beh ratio	.297	1	.297	3.864	.050
cranialbaselength	Total PSQ ratio	.168	1	.168	9.292	.002
	snoring ratio	.613	1	.613	13.699	.000
	sleepiness ratio	.368	1	.368	7.748	.006
	beh ratio	.061	1	.061	.799	.372
sexcoded2	Total PSQ ratio	.132	1	.132	7.330	.007
	snoring ratio	.003	1	.003	.077	.781
	sleepiness ratio	.216	1	.216	4.542	.034
	beh ratio	.767	1	.767	9.976	.002
age	Total PSQ ratio	.051	1	.051	2.815	.094
	snoring ratio	.013	1	.013	.292	.589
	sleepiness ratio	.884	1	.884	18.595	.000
	beh ratio	.013	1	.013	.175	.676
Error	Total PSQ ratio	5.710	316	.018		
	snoring ratio	14.140	316	.045		
	sleepiness ratio	15.025	316	.048		
	beh ratio	24.310	316	.077		
Total	Total PSQ ratio	11.273	320			
	snoring ratio	18.500	320			
	sleepiness ratio	22.500	320			
	beh ratio	36.611	320			
Corrected Total	Total PSQ ratio	5.967	319			
	snoring ratio	14.780	319			
	sleepiness ratio	16.172	319			
	beh ratio	25.110	319			

Table E) PSQ scores in patients with very short, short, average, and long and very long cranial bases and comparison of their means

Descriptives

PSQ

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
VS	6	.2383	.26088	.10650	-.0354	.5121	.00	.74
S	46	.1372	.13513	.01992	.0970	.1773	.00	.63
M	213	.1307	.13313	.00912	.1127	.1486	.00	.64
L	48	.1144	.12430	.01794	.0783	.1505	.00	.50
VL	7	.0614	.16252	.06143	-.0889	.2117	.00	.43
Total	320	.1297	.13624	.00762	.1147	.1446	.00	.74

Table F) Comparison of SDB risk among patients with varying cranial base lengths

ANOVA

PSQ

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.117	4	.029	1.594	.176
Within Groups	5.804	315	.018		
Total	5.921	319			

Table G) Linear Regression Model between Cranial Base Length and Total PSQ score

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.186[a]	.035	.028	.13481	.035	5.673	2	317	.004

a. Predictors: (Constant), sexcoded2, cranial base length

b. Dependent Variable: Total PSQ ratio

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	.206	2	.103	5.673	.004[b]
	Residual	5.761	317	.018		
	Total	5.967	319			

a. Dependent Variable: Total PSQ ratio

b. Predictors: (Constant), sexcoded2, cranial base length

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.483	.124		3.891	.000
	cranial base length	-.005	.002	-.156	-2.730	.007
	sexcoded2	-.041	.016	-.149	-2.605	.010

a. Dependent Variable: Total PSQ ratio

Table H) Linear Regression Model of Cranial Base Length and snoring score

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.206[a]	.042	.039	.21099	.042	14.029	1	318	.000

a. Predictors: (Constant), cranial base length

b. Dependent Variable: snoring ratio

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	.624	1	.624	14.029	.000[b]
	Residual	14.156	318	.045		
	Total	14.780	319			

a. Dependent Variable: snoring ratio

b. Predictors: (Constant), cranial base length

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.796	.184		4.323	.000
	cranial base length	-.010	.003	-.206	-3.745	.000

a. Dependent Variable: snoring ratio

Table I) Linear Regression Model of Cranial Base Length and sleepiness score

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.266[a]	.071	.062	.21805	.071	8.042	3	316	.000

a. Predictors: (Constant), sexcoded2, age, cranial base length

b. Dependent Variable: sleepiness ratio

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1.147	3	.382	8.042	.000[b]
	Residual	15.025	316	.048		
	Total	16.172	319			

a. Dependent Variable: sleepiness ratio

b. Predictors: (Constant), sexcoded2, age, cranial base length

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.523	.201		2.603	.010
	cranial base length	-.008	.003	-.160	-2.784	.006
	age	.021	.005	.240	4.312	.000
	sexcoded2	-.054	.025	-.120	-2.131	.034

a. Dependent Variable: sleepiness ratio