# Validation of the Alberta Pediatric Obstructive Sleep Apnea (APOSA) Index for Orthodontic Treatment Need in Pediatric Patients with Obstructive Sleep Apnea Symptoms

by

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## ABSTRACT

*Objective:* To determine the predictive ability of the Alberta Pediatric Obstructive Sleep Apnea (APOSA) Index for orthodontic treatment need in pediatric patients with obstructive sleep apnea symptoms.

*Methods:* Thirty orthodontic records, representing a spectrum of craniofacial and oral features and severity, were evaluated for orthodontic treatment need using the APOSA index. The results were compared to treatment decisions made by ten expert orthodontists.

*Results:* Receiver operating characteristic (ROC) curve demonstrated a cutoff score of 6.5 with a sensitivity of 94.1% and specificity of 99%.

*Conclusions:* The APOSA index is a useful and predictive tool to determine orthodontic treatment need in pediatric patients with OSA symptoms. A sum score of 6.5 or greater on the APOSA index suggests that the patient may benefit from referral to an orthodontist. Our findings indicate that the APOSA index is a useful and predictive tool for orthodontic treatment need in pediatric patients with OSA symptoms.

## PREFACE

This thesis is an original work by Natasha Nazarali. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Validation of the Index for Facial and Oral Assessment of Orthodontic Treatment Need in Pediatric Patients with Obstructive Sleep Apnea Symptoms", No. Pro00050143, October 14, 2014.

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APOSA: Alberta Pediatric Obstructive Sleep Apnea

MAA: Mandibular advancement appliance

OSA: Obstructive Sleep Apnea

SDB: Sleep disordered breathing

ROC: Receiver Operating Characteristic

# Chapter 1: Introduction

## 1.1 Pediatric Obstructive Sleep Apnea

Sleep disordered breathing (SDB) represents a spectrum of respiratory disorders ranging from primary snoring to obstructive sleep apnea (OSA). OSA, the most common form of SDB, is characterized by repeated episodes of partial or complete airway obstruction while sleeping. The prevalence of pediatric OSA is estimated to be between 1% to 4% (1,2). Common symptoms of pediatric OSA include snoring, daytime fatigue, irritability, and behavioural problems (3). These symptoms may manifest as poor performance at school and withdrawal among peer groups (3).

The most common cause of OSA in children is adenotonsillar hypertrophy (4). Enlargement of the adenoids is normally found in children between the ages of 18 months to 6 years, which corresponds to the age of highest incidence of OSA in children (4). Other factors associated with OSA in childhood include asthma (5), obesity (6), pre-term birth (7), and chronic sinusitis (2). Pediatric OSA has numerous craniofacial correlates including mandibular retrognathism, midface dysplasia, maxillary constriction, and increased vertical growth (8).

## 1.2 Diagnosis of Obstructive Sleep Apnea

The gold standard for diagnosis of OSA is overnight polysomnography (PSG). Although the gold standard for diagnosis, there is limited access to PSG for children in many parts of Canada (9). Further,

PSG is done in unfamiliar surroundings and may not be reflective of normal sleep patterns at home. As a result, early identification and diagnosis of OSA in children is challenging. While history and clinical examination can provide some insight into signs and symptoms of altered sleep patterns, a systematic review found that history and clinical examination do not reliably identify OSA compared to PSG (10). Other diagnostic tests include videotaping, nocturnal pulse oximetry or daytime nap studies, all of which have variable positive and negative predictive values compared to overnight PSG (11).

Initial screening of pediatric OSA involves detailed clinical history and physical examination with particular attention to snoring, restless sleep, and mouth breathing. In addition, visual examination of tonsils is important. Presence of mandibular retrognathia, midface hypoplasia, maxillary constriction, and high-arched palate are potentially important craniofacial features. Pre-term birth, hypotonia (cerebral palsy, Down syndrome) and other craniofacial anomalies have increased risk for OSA (12).

Questionnaires have also been developed to help in initial screening. The Pediatric Sleep Questionnaire (PSQ) is a 22-item scale, which evaluates snoring, excessive sleepiness, and behavior. It has a sensitivity of 0.85 and a specificity of 0.87 when compared to results of overnight PSG. A score of greater than 8 of 22 questions or 33% answered positively indicates an increased risk for OSA (13). Although

clinically useful, administration of the PSQ does not eliminate the need for overnight PSG. Instead, administration of the PSQ is a helpful screening tool to identify those who may have OSA and warrants further investigation.

Despite other methods to screen for pediatric OSA, overnight PSG remains the gold standard for diagnosis and evaluation of treatment outcomes.

### 1.3 Obstructive Sleep Apnea and Craniofacial Growth

Understanding the relationship between form and function of the upper airway is important in understanding the primary etiology of OSA. From a cause-effect perspective, there are currently 2 hypotheses. Linder-Aronson suggested that nasopharyngeal airway obstruction caused by adenoid hypertrophy or other etiology, leads to mouth breathing (14). The presence of mouth breathing has been known to alter the musculo-skeletal equilibrium, and can result in altered craniofacial growth (14). The resulting growth pattern is seen as a long lower face, anterior open bite, lip incompetency, transverse maxillary constriction, posterior crossbite, and vertical direction of growth. This growth pattern is known as “adenoid faces.” The extent to which this altered balance of pressure contributes to skeletal and dental abnormalities is unclear.

The second hypothesis is that unfavourable craniofacial growth patterns are a predisposing etiologic factor to upper airway resistance.

This view states that the characteristic craniofacial morphology seen in individuals with upper airway resistance is an expression of genetically determined growth instead of a change caused by mode of breathing (15,16).

Two systematic reviews have evaluated craniofacial form in children with OSA using lateral cephalograms. Katyal et al found that children with primary snoring had an increased ANB angle of 1.54° ($p<0.00001$). This was due to a decreased SNB angle by 1.4° ($p=0.02$). This systematic review also found that children with OSA had reduced upper airway width; the distance from the posterior nasal spine to adenoid tissue measured along PNS-basion was reduced by 4.17mm ($p<00001$) and the distance from the posterior nasal spine to adenoid tissue measured along a line perpendicular to sella-basion was reduced by 3.12mm ($p<0.0001$) (17). While these differences may not be clinically significant, another systematic review by Flores et al, found similar results. This review found that children with OSA had larger ANB, decreased SNB and increased SN-MP values compared to controls(18). Both studies note that there are limitations in their conclusions, mainly due to heterogeneity across studies and the fact that lateral cephalometry provides two-dimensional measurements of three-dimensional structures.

### 1.4 Treatment of Pediatric Obstructive Sleep Apnea

Untreated pediatric OSA can lead to delayed growth (19), neurocognitive abnormalities (20), and cardiovascular impairments

including hypertension (21) and ventricular hypertrophy (22). The most common treatment approach for pediatric OSA is adenotonsillectomy. The majority of patients tolerate adenotonsillectomy well, however, postoperative complications are increased in those younger than age 3, severe OSA, and obesity (23). A multicenter retrospective study that evaluated outcomes of adenotonsillectomy in children with OSA found that 27.2% of patients had complete resolution of OSA as demonstrated by a post-adenotonsillectomy AHI<1/hour total sleep time, 21.6% demonstrated persistent OSA (AHI>5/hour total sleep time), while the remaining patients demonstrated improvement, without resolution (24). In this study, persistent OSA was associated with children older than 7 years, obesity, asthma, and severity of OSA.

Medical management of OSA includes the use of nasal corticosteroids and leukotriene receptor antagonists (25). Medication management of OSA has been effective in mild cases of OSA, however, may not be sufficient in moderate cases (23).

In patients who do not demonstrate adenotonsillar hypertrophy, in those in whom it is contraindicated, or for persistent symptoms following adenotonsillectomy, continuous positive airway pressure (CPAP) may be used. CPAP provides constant pressure to the upper airway through airflow administered through a nasal or facemask to prevent airway narrowing and collapse. The CPAP device must establish a tight seal between the nasal mask and perinasal area. The fit that is required may

exert pressure on the soft tissues of the face and underlying skeleton. In growing patients using CPAP, this pressure applied to the face has been associated with midface deficiency (26). Studies evaluating this effect have been case reports and overall, evidence does not substantiate this claim.

Although adenotonsillectomy is the most common treatment approach for pediatric OSA, it is curative in only 25% to 75% of patients (27-29). This suggests that other treatment modalities, including those aimed at improving craniofacial growth patterns, may be beneficial. Since adenotonsillectomy often addresses the main etiologic factor of pediatric OSA, it will continue to be the first line surgical approach. It is important to recognize, however, that the multidisciplinary nature of OSA requires a more comprehensive treatment strategy, requiring other therapeutic methods to manage pediatric OSA.

### 1.5 Multidisciplinary Management of Pediatric Obstructive Sleep Apnea

Multidisciplinary management of pediatric OSA from a craniofacial perspective requires improved communication between medical and dental teams. Specifically, medical teams focus on physiological components of OSA, including measuring oxygen saturation, peak end-tidal CO2, and brain activity during sleep. Treatment approaches are primarily surgical or providing ventilation support. Dentists and orthodontists focus on physical and anatomic variations, with treatment approaches aimed at orthopedic or dental correction of skeletal and dental

disharmonies. Thus, improved communication and collaboration between medical and dental teams can ensure that we focus on both the physiological and physical aspects of OSA. The challenge lies in identifying the pediatric OSA patient that may benefit from orthodontic treatment and making an appropriate referral.

Each medical professional (otolaryngologist, pediatric respirologist, orthodontist) offers different approaches to management of pediatric OSA. Specifically, otolaryngology performs surgical procedures including adenotonsillectomy, pediatric respirology can provide ventilation support through CPAP, and orthodontists fabricate oral appliances to facilitate orthopedic and dental changes. Pediatrics and otolaryngology have published clinical practice guidelines on management of the pediatric OSA patient. The American Academy of Pediatrics updated its guidelines for the diagnosis and management of pediatric OSA in 2012 (23). These guidelines indicate that all routine clinical visits should determine whether a child snores. If a child snores regularly or demonstrates signs and symptoms of OSA, an overnight polysomnogram is indicated. The patient should also be referred to a sleep specialist or otolaryngologist for further evaluation. The recommended first-line treatment of children with OSA and primary etiology of adenotonsillar hypertrophy is adenotonsillectomy. Following surgical treatment, patients should be seen for follow-up and reassessed for residual signs and symptoms of OSA. If OSA persists or if adenotonsillectomy is not indicated, CPAP management is indicated. In

patients who are obese, weight loss and dietary management is recommended. For mild cases of OSA or mild residual OSA, medical management involving nasal corticosteroids are recommended (23). The American Academy of Otolaryngology has published clinical practice guidelines on polysomnography prior to tonsillectomy in children with sleep-disordered breathing (30). These guidelines indicate that children with sleep disordered breathing and complex medical conditions (obesity, Down syndrome, neuromuscular disorders) should receive polysomnography. Polysomnography is also recommended for patients in whom tonsillectomy is unclear or when there is discordance between physical examination of tonsils and reported severity of sleep disordered breathing (30).

While these guidelines highlight each specialist's knowledge and skill set in OSA, they also create a division in the management of pediatric OSA. What is needed is a unified set of guidelines, which draw on the expertise of all medical professionals involved. This need for a common language will improve communication and patient management among colleagues, ultimately enhancing patient care.

Currently, there are no clinical practice guidelines in dentistry on management of pediatric patients with OSA. Orthodontic treatment modalities that have been reported in the literature to improve symptoms of OSA include rapid maxillary expansion (31), mandibular advancing appliances (32) and orthopedic maxillary protraction (33). Case selection

for orthodontic treatment in pediatric OSA is critical. For example, a patient with primary adenotonsillar hypertrophy may not benefit from orthodontic intervention, while a patient with a moderately retrusive mandible may benefit from an orthodontic mandibular advancing appliance. Orthodontic treatment, if initiated during a patient's growth spurt, has the potential to improve one of the etiologic factors of OSA, while improving the pattern of growth. Improvement is seen across two domains: improvement of sleep parameters, as well as improved dento-facial appearance. Further, timely referral to an orthodontist ensures that treatment begins at an appropriate stage of development to prevent malocclusion and altered growth. In order to consolidate the evidence on mandibular advancement appliances in pediatric OSA, our team completed a comprehensive review of the literature (chapter 2).

Orthodontic treatment combined with traditional surgical management of pediatric OSA has the potential to improve dento-facial appearance and improve overall quality of life.

### 1.6 Development of a Communication Tool for Orthodontic Referral of Pediatric Patients with Symptoms of Obstructive Sleep Apnea

Collaborative management of patients between medical and dental teams is challenging. Differences in training, accessibility of professionals, and communication have contributed to these challenges. Until recently, there was no tool or set of criteria to help medical teams identify patients who may benefit from orthodontic referral and treatment for their OSA

symptoms. In patients who show altered craniofacial or oral characteristics that contribute to OSA symptoms, timely orthodontic referral and treatment is important. This is due to the fact that there is a limited window of opportunity available to intervene in altered craniofacial growth. Further, without intervention, growth abnormalities continue in the same pattern, potentially worsening over time. Our team at the University of Alberta recently developed a novel index termed Alberta Pediatric Obstructive Sleep Apnea (APOSA) Index for Orthodontic Treatment Need that assists physicians and other medically trained professionals identify craniofacial and oral characteristics that may benefit from orthodontic treatment as part of their management of OSA symptoms (34). The APOSA index was developed using WHO index development guidelines as well as available literature. Shaw et al (35) has described the properties of an ideal orthodontic index as:

1. Reliable in use
2. Valid
3. Sensitive to the needs of the patient
4. Acceptable to both the public and profession
5. Administratively simple to use
6. Sensitive throughout the scale
7. Amenable to statistical analysis
8. Examination which should require minimum judgment
9. Able to detect a shift in group conditions

Development of the APOSA index involved a rigorous protocol with discussions and input from various expert teams including the index development group, external review group, and the steering committee (34). Each group had a specific role in the development process. The steering committee consisted of an orthodontist, pediatric respirologist and sleep medicine specialist, and a methodologist specializing in psychometric property analysis. The development group consisted of multidisciplinary health care professionals with expert knowledge in pediatric OSA. The external review group consisted of end-users and interested parties. The APOSA index provides a visual representation of eight features with varying levels of severity that are important in the oral and craniofacial assessment of pediatric patients with OSA symptoms. The index also underwent reliability testing. The index was determined to have fair to substantial inter-rater reliability and moderate to almost perfect intra-rater reliability. Application of the APOSA index was found to take approximately 1 minute, 10 seconds per case.

The APOSA Index for Orthodontic Treatment Need is a reliable and easy to use tool that has been subject to rigorous development protocols and revisions such that it appropriately represents the most important facial and oral features that may manifest in those with OSA symptoms. The APOSA index draws attention to the multifactorial nature of OSA and the need for an integrated communication and treatment approach, which considers craniofacial and oral features characteristic of pediatric OSA.

The objective of the APOSA index is to provide a simple and easy-to-use tool that can help prioritize patients who may benefit from orthodontic treatment as part of their OSA management.

### 1.7 Validation of the APOSA Index

The APOSA index is comprised of 8 craniofacial and oral features with 2-3 levels of severity. Each feature is represented by a visual scale, allowing the medical professional to make a direct comparison between the graphic representation of craniofacial and oral features and individual patient features. The features and severity assign a final index score for each patient, summarizing their craniofacial and oral characteristics. A higher score would support a greater need for orthodontic referral and subsequent orthodontic treatment. A statistical analysis has not been applied to the APOSA index to determine the score where referral to an orthodontist is recommended.

This study aims to apply statistical methods and validate the APOSA index. Our primary goal is to determine whether application of the APOSA index identifies patients that may benefit from orthodontic treatment as part of their OSA management protocol. Secondary objectives are to provide meaning to the scoring system of the index and determine a cut off score that will prioritize orthodontic referral and treatment for those that may benefit from it.

## 1.8 Validation of an Index

Numerous indices exist in orthodontic literature. The most common indices in orthodontics are occlusal and esthetic indices (36,37). Development of a new index is based on the fact that no index currently exists or that the previous index does not serve the desired purpose. Prior to the widespread use of an index, reliability and validation of the tool is necessary.

Reliability refers to the ability of a tool to measure something in a reproducible manner. Thus, measurements by the same individual on different occasions (intra-rater reliability) and by different individuals (inter-rater reliability) must yield similar results. Reliability is expressed between 0 and 1. A value of 0 indicates no reliability, whereas 1 indicates ideal reliability. Thus, reliability indicates that a tool is measuring *something*.

The premise of validation is to determine whether the index appropriately measures *what* it is intended to measure. In other words, can the index make appropriate conclusions? Validity testing is an important step following the development of an index, which serves the purpose of identifying whether the index performs to the same level as a 'gold standard.'

There are four types validity testing that can be applied: (1) Face Validity, (2) Content Validity, (3) Criterion Validity, and (4) Construct Validity. Face and content validity are based on a judgment that an

instrument appears reasonable and are taken into account during the development of an index (38).

(1) Face validation refers to a judgment that a tool appears to be measuring what it is intended to. This form of validity is a subjective judgment made by an expert. Empirical methods are not commonly used to assess face validity.

(2) Content validation refers to a judgment that all relevant information has been covered in the index. Content validity is achieved by adequate literature review and consultation with experts when developing an index.

(3) Criterion validation refers to how well scores of a tool match what it is intended to predict. Traditionally, criterion validation involves comparison of the tool with the current gold standard. Criterion validation can be divided into 2 different forms: concurrent validation and predictive validation. In concurrent validation, the new index is correlated with the gold standard. Both these indices are applied at the same time. In predictive validation, the gold standard criterion requires time for comparison. For example, using DAT scores to correlate a dental student's graduation in 4 years requires 4 years of dental school before analyzing predictions/hypotheses.

(4) Construct validation refers to a series of hypothesis testing formulated based on current knowledge.

Guilford (39) has described face and content validation as “validity by assumption.” However, the assumption that an instrument appears valid is not enough for the acceptance of an index. Empirical evidence is required to demonstrate that an index is measuring what it was developed to measure.

In health measurement indices, there are two methods to validate an index:

(1) Comparison to other indices. In the scenario where a similar index exists, the existing gold standard index and the new index would be applied to a sample of patients to determine whether there is a correlation between the two. This approach has been described as convergent validation or concurrent validation. It has been argued that if a current gold standard already exists, it is difficult to justify the development of another index, unless it is cost effective or better than the previous. When an index is compared to a previous gold standard, correlations of 0.4-0.8 should be expected. If the correlation is lower, it suggests that the reliability of one of the tools is particularly low or that they are measuring different things. An argument against this approach is that if it is believed that the new index or tool is better than the previous, then why compare them at all? Further, if the correlation between the two tools is less than adequate, which tool is at fault? (38). Thus, there are many factors to

consider in the validation of an index when a current gold standard exists.

(2) Validation of a New Index. Validation of a new index is based on the premise of construct validity. Essentially, we link what we are measuring with the index to an outcome by a construct/hypothesis. The hypothesis will evaluate the difference between two groups (that would be expected to have different values) based on the application of the index. The hypothesis and the index are deemed to be appropriate when the expected relationship is found. If no relationship exists, there are underlying problems with the index or hypothesis. The process of construct validity is ongoing, with different hypotheses being tested each time. More recently, the emphasis on validation has been on the level of certainty that we can attribute to the inferences we make based on our index (40,41). That is, when a validation study is conducted, a scale can be deemed to be valid in a particular circumstance and context. This means that in a different set of circumstances, the scale may not be valid (38). For example, when a validation study for a diagnostic tool is carried out in North America, parameters of the study are based on common practices, training, and clinical guidelines in North America. As a result, the tool is valid for use in North America, but may not be valid in Europe.

The applications of these concepts in health is very interesting. From the clinician's standpoint, use of an index needs to have clinical applicability and therefore, must be useful in either diagnosis or clinical decision-making. From a psychometric point of view, indices and tools require appropriate development and testing methods.

More recent literature in validity describes validity testing as a holistic and continuous process. It has shifted from the "holy trinity" of validity (content, criterion, and construct) described by Guion (42) and has moved toward establishing appropriate interpretations of test results. It was Messick's (43) work that described validity as a unified concept. As a result, the *Standards for Educational and Psychological Testing* (44) describes aspects of validity which are conceptually different, but which holistically gather evidence for the interpretation of a test/tool. Shepard described Messick's work as solidifying the understanding that construct validity is the unifying aspect of validity and that validity not only includes meaning of test scores, but relevance and utilization (45).

## 1.9 Indices and Validity in Orthodontics

The question may arise of why certain tools in orthodontics must be validated whereas others are not. Quantitative measurements such overjet and overbite are effectively measured using a periodontal probe. Treatment decisions, on the other hand, take into account numerous factors with some factors being more important than others. The 'true

answer' is therefore difficult to determine and an index used for this purpose should be validated. Further, validation of an index allows us to determine the interaction that exists between the findings and what this actually represents. An index/tool can be developed with a scoring system, but this process in itself does not tell us what the score represents or whether the score is representative of what it was intended to measure.

Validation of indices in orthodontics have utilized methods of criterion validation. In this form of validation, the index is has been compared with expert orthodontic opinion (36,46,47). Validation using expert opinion of orthodontists is particularly important when an index evaluates various attributes of malocclusion. Since treatment decisions are based on a variety of factors, some being more important than others, the validation process allows determination of the relative importance that is applied to each attribute. For an index to be valid, it should be determined that it is an appropriate substitute for the average opinion of experts. Logistic regression techniques are used to determine whether items of the index appropriately predict the opinion of experts. Further, logistic regression determines the relative weightings or 'importance value' of each item on the index.

From a clinical perspective, a tool or index must have appropriate sensitivity and specificity to justify its use. Receiver operating characteristic (ROC) curves are plotted to determine the cutoff score

where sensitivity and specificity is maximized. This process provides meaning and relevance to a previously arbitrary scoring process.

## 1.10 Statement of the Problem

Diagnosis and treatment of pediatric OSA is challenging. Recent evidence has drawn attention to craniofacial and oral attributes that may contribute to reduced airflow. Orthodontic treatment modalities may improve symptoms of OSA and at the same time, correct the underlying facial and oral abnormalities. Effective integration of orthodontic treatment as part of a patient's management of OSA requires improved collaboration between medical and dental teams. The APOSA index aims to improve communication between medical and dental teams in order to ensure timely recognition and treatment of abnormal facial and oral characteristics. This study aims to validate the APOSA index through statistical techniques in order to provide meaning and relevance to the index. The APOSA index will be validated against the gold standard treatment decision of orthodontists. This will ensure that conclusions drawn from use of the APOSA index are appropriate and accurate. This study aims to be the first step in engagement of the APOSA index between medical and dental professionals.

## 1.11 Research Hypothesis

The primary objective of this study is to determine the ability of the APOSA index to predict need for orthodontic treatment. Secondary objectives are

to provide meaning to the scoring system of the index and determine a cut off score that will prioritize orthodontic referral and treatment for those that may benefit from it. Our research hypothesis is: The APOSA index accurately predicts need for orthodontic treatment.

## 1.12 References


(1) Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc 2008 Feb 15;5(2):242-252.

(2) Bixler EO, Vgontzas AN, Lin HM, Liao D, Calhoun S, Vela-Bueno A, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. Sleep 2009 Jun;32(6):731-736.

(3) Schwengel DA, Dalesio NM, Stierer TL. Pediatric obstructive sleep apnea. Anesthesiol Clin 2014 Mar;32(1):237-261.

(4) Marcus CL. Pathophysiology of childhood obstructive sleep apnea: current concepts. Respir Physiol 2000 Feb;119(2-3):143-154.

(5) Kaditis AG, Kalampouka E, Hatzinikolaou S, Lianou L, Papaefthimiou M, Gartagani-Panagiotopoulou P, et al. Associations of tonsillar hypertrophy and snoring with history of wheezing in childhood. Pediatr Pulmonol 2010 Mar;45(3):275-280.

(6) O'Brien LM, Sitha S, Baur LA, Waters KA. Obesity increases the risk for persisting obstructive sleep apnea after treatment in children. Int J Pediatr Otorhinolaryngol 2006 Sep;70(9):1555-1560.

(7) Rosen CL, Larkin EK, Kirchner HL, Emancipator JL, Bivins SF, Surovec SA, et al. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. J Pediatr 2003 Apr;142(4):383-389.

(8) Huynh NT, Morton PD, Rompre PH, Papadakis A, Remise C. Associations between sleep-disordered breathing symptoms and facial and dental morphometry, assessed with screening examinations. Am J Orthod Dentofacial Orthop 2011 Dec;140(6):762-770.

(9) Katz SL, Witmans M, Barrowman N, Hoey L, Su S, Reddy D, et al. Paediatric sleep resources in Canada: The scope of the problem. Paediatr Child Health 2014 Aug;19(7):367-372.

(10) Brietzke SE, Katz ES, Roberson DW. Can history and physical examination reliably diagnose pediatric obstructive sleep apnea/hypopnea syndrome? A systematic review of the literature. Otolaryngol Head Neck Surg 2004 Dec;131(6):827-832.

(11) Roland PS, Rosenfeld RM, Brooks LJ, Friedman NR, Jones J, Kim TW, et al. Clinical practice guideline: Polysomnography for sleep-disordered breathing prior to tonsillectomy in children. Otolaryngol Head Neck Surg 2011 Jul;145(1 Suppl):S1-15.

(12) Beck SE, Marcus CL. Pediatric Polysomnography. Sleep Med Clin 2009 Sep;4(3):393-406.

(13) Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. Sleep Med 2000 Feb 1;1(1):21-32.

(14) Linder-Aronson S. Adenoids. Their effect on mode of breathing and nasal airflow and their relationship to characteristics of the facial skeleton and the denition. A biometric, rhino-manometric and cephalometro-radiographic study on children with and without adenoids. Acta Otolaryngol Suppl 1970;265:1-132.

(15) Miles PG, Vig PS, Weyant RJ, Forrest TD, Rockette HE,Jr. Craniofacial structure and obstructive sleep apnea syndrome--a qualitative analysis and meta-analysis of the literature. Am J Orthod Dentofacial Orthop 1996 Feb;109(2):163-172.

(16) Vig KW. Nasal obstruction and facial growth: the strength of evidence for clinical assumptions. Am J Orthod Dentofacial Orthop 1998 Jun;113(6):603-611.

(17) Katyal V, Pamula Y, Martin AJ, Daynes CN, Kennedy JD, Sampson WJ. Craniofacial and upper airway morphology in pediatric sleep-disordered breathing: Systematic review and meta-analysis. Am J Orthod Dentofacial Orthop 2013 Jan;143(1):20-30.e3.

(18) Flores-Mir C, Korayem M, Heo G, Witmans M, Major MP, Major PW. Craniofacial morphological characteristics in children with obstructive sleep apnea syndrome: a systematic review and meta-analysis. J Am Dent Assoc 2013 Mar;144(3):269-277.

(19) Bar A, Tarasiuk A, Segev Y, Phillip M, Tal A. The effect of adenotonsillectomy on serum insulin-like growth factor-I and growth in

children with obstructive sleep apnea syndrome. J Pediatr 1999 Jul;135(1):76-80.

(20) Chervin RD, Archbold KH, Dillon JE, Panahi P, Pituch KJ, Dahl RE, et al. Inattention, hyperactivity, and symptoms of sleep-disordered breathing. Pediatrics 2002 Mar;109(3):449-456.

(21) Marcus CL, Greene MG, Carroll JL. Blood pressure in children with obstructive sleep apnea. Am J Respir Crit Care Med 1998 Apr;157(4 Pt 1):1098-1103.

(22) Amin RS, Kimball TR, Bean JA, Jeffries JL, Willging JP, Cotton RT, et al. Left ventricular hypertrophy and abnormal ventricular geometry in children and adolescents with obstructive sleep apnea. Am J Respir Crit Care Med 2002 May 15;165(10):1395-1399.

(23) Marcus CL, Brooks LJ, Draper KA, Gozal D, Halbower AC, Jones J, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2012 Sep;130(3):576-584.

(24) Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, Mitchell RB, Promchiarak J, Simakajornboon N, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. Am J Respir Crit Care Med 2010 Sep 1;182(5):676-683.

(25) Brouillette RT, Manoukian JJ, Ducharme FM, Oudjhane K, Earle LG, Ladan S, et al. Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea. J Pediatr 2001 Jun;138(6):838-844.

(26) Li KK, Riley RW, Guilleminault C. An unreported risk in the use of home nasal continuous positive airway pressure and home nasal ventilation in children: mid-face hypoplasia. Chest 2000 Mar;117(3):916-918.

(27) Tauman R, Gulliver TE, Krishna J, Montgomery-Downs HE, O'Brien LM, Ivanenko A, et al. Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. J Pediatr 2006 Dec;149(6):803-808.

(28) Brietzke SE, Gallagher D. The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: a meta-analysis. Otolaryngol Head Neck Surg 2006 Jun;134(6):979-984.

(29) Friedman M, Wilson M, Lin HC, Chang HW. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric

obstructive sleep apnea/hypopnea syndrome. Otolaryngol Head Neck Surg 2009 Jun;140(6):800-808.

(30) Roland PS, Rosenfeld RM, Brooks LJ, Friedman NR, Jones J, Kim TW, et al. Clinical practice guideline: Polysomnography for sleep-disordered breathing prior to tonsillectomy in children. Otolaryngol Head Neck Surg 2011 Jul;145(1 Suppl):S1-15.

(31) Pirelli P, Saponara M, Guilleminault C. Rapid maxillary expansion in children with obstructive sleep apnea syndrome. Sleep 2004 Jun 15;27(4):761-766.

(32) Nazarali N, Altalibi M, Nazarali S, Major MP, Flores-Mir C, Major PW. Mandibular advancement appliances for the treatment of paediatric obstructive sleep apnea: a systematic review. Eur J Orthod 2015 Feb 12.

(33) Hiyama S, Suda N, Ishii-Suzuki M, Tsuiki S, Ogawa M, Suzuki S, et al. Effects of maxillary protraction on craniofacial structures and upper-airway dimension. Angle Orthod 2002 Feb;72(1):43-47.

(34) Altalibi M, Saltaji H, Roduta Roberts M, Major MP, MacLean J, Major PW. Developing an index for the orthodontic treatment need in paediatric patients with obstructive sleep apnoea: a protocol for a novel communication tool between physicians and orthodontists. BMJ Open 2014 Sep 18;4(9):e005680-2014-005680.

(35) Shaw WC, Richmond S, O'Brien KD, Brook P, Stephens CD. Quality control in orthodontics: indices of treatment need and treatment standards. Br Dent J 1991 Feb 9;170(3):107-112.

(36) Summers CJ. The occlusal index: a system for identifying and scoring occlusal disorders. Am J Orthod 1971 Jun;59(6):552-567.

(37) Daniels C, Richmond S. The development of the index of complexity, outcome and need (ICON). J Orthod 2000 Jun;27(2):149-162.

(38) Streiner DL, Norman GR, Cairney J. Health measurement scales: a practical guide to their development and use. : Oxford university press; 2014.

(39) Guilford JP. Psychometric methods (2nd ed.). New York, NY, US: McGraw-Hill; 1954.

(40) Cronbach L. Test validation||  in Thorndike, RL (ed) Educational Measurement, Washington, DC: American Council on Education. 1971.

(41) Landy FJ. Stamp Collecting Versus Science: Validation as Hypothesis Testing. Am Psychol 1986 November;41(11):1183-1192.

(42) Guion RM. On Trinitarian doctrines of validity. Professional Psychology 1980;11(3):385.

(43) Messick S. Standards of validity and the validity of standards in performance asessment. Educational measurement: Issues and practice 1995;14(4):5-8.

(44) American educational Research Association, American Psychological Association, National Council on Measurement in Education. Standards for educational and psychological testing. : American Educational Research Association; 1999.

(45) Shepard LA. Evaluating test validity. Review of research in education 1993:405-450.

(46) Jenny J, Cons NC, Kohout FJ. Comparison of SASOC, a measure of dental aesthetics, with three orthodontic indices and orthodontist judgment. Community Dent Oral Epidemiol 1983;11(4):236-241.

(47) Salzmann J. Handicapping malocclusion assessment to establish treatment priority. Am J Orthod 1968;54(10):749-765.

# Chapter 2 - Mandibular Advancement Appliances for the Treatment of Pediatric Obstructive Sleep Apnea: A Systematic Review

Nazarali N, Altalibi M, Nazarali S, Major MP, Flores-Mir C, Major PW. Mandibular advancement appliances for the treatment of paediatric obstructive sleep apnea: a systematic review. Eur J Orthod 2015 Feb 12

## 2.1 Abstract

*Objective*: To evaluate the effectiveness of mandibular advancement appliances (MAAs) for treatment of pediatric obstructive sleep apnea (OSA).

*Methods*: A systematic search of several electronic databases (PubMed, EMBASE (OvidSP), MEDLINE (OvidSP), Healthstar (OvidSP)), limited grey literature, and manual searches was completed with the help of a health sciences librarian. Studies evaluating the effects of MAAs in children with OSA were sought.

*Results:* A total of 71 original articles were identified from the searches. Once selection criteria were applied, only 4 articles satisfied all inclusion criteria. Only one study was a quasi-randomized clinical trial. The remaining studies were of retrospective nature. All the included studies had high risk of bias. Absence of control groups and small sample sizes were the most limiting characteristics across selected studies. The limited available evidence may be suggestive that MAAs result in improvements in AHI scores; however they do not normalize AHI scores. No medium- to long-term conclusions could be made as the studies only evaluated immediate changes. A meta-analysis was not possible due to the heterogeneity in study designs and collected information.

*Limitations:* There are significant weaknesses in the existing evidence due primarily to absence of control groups, small sample sizes, lack of randomization and short-term results.

*Conclusions:* Based on current limited evidence, it is not possible to conclude that MMAs are effective to treat pediatric OSA.

## 2.2 Introduction

Sleep-disordered breathing (SDB) represents a continuum of respiratory disorders from snoring to obstructive sleep apnea (OSA). It is characterized by increased upper airway resistance, which temporarily interrupts pulmonary ventilation, oxygenation, and sleep quality (1). The prevalence of pediatric OSA is estimated to be between 1% to 4% (2,3).

The most common cause of pediatric OSA is adenotonsillar hypertrophy (4). Pediatric OSA has numerous craniofacial correlates including mandibular retrognathism, midface dysplasia, maxillary constriction, and increased vertical growth (5).

If pediatric OSA is left untreated, it can lead to problems in physical growth (6), neurocognitive abnormalities (7), and impairments in cardiovascular function (8). Currently, there is no consensus on the best method to treat pediatric OSA (9). The most common treatment approach is adenotonsillectomy and is curative in only 25% to 75% of patients (10-12). Since many patients demonstrate persistent disease, other treatment approaches have been explored and indicated.

There are a number of orthodontic treatment modalities that have been suggested to reduce symptoms of pediatric OSA, and, at the same

time, improve the associated craniofacial abnormalities. These include rapid maxillary expansion (13), mandibular advancement appliances (14), and orthopedic maxillary protraction (15). The success of orthodontic appliances in improving symptoms of OSA has been attributed to enlarging the airway.

Mandibular advancement appliances (MAAs) can increase the lateral dimension of the velopharyngeal airway. This is accomplished as a result of forward positioning of the mandible and reduced collapsibility of the airway (16). Stimulation of upper airway dilator muscles (genioglossus) with advancement appliances has also been suggested to improve upper airway stabilization (17). From an orthodontic perspective, MAAs alter the neuromuscular forces on the craniofacial skeleton and dentition, promoting a combination of dentoalveolar changes and skeletal growth.

A 2007 Cochrane Review investigated functional orthopedic appliances in pediatric patients with OSA (18). This review found one article that met inclusion criteria (14) and concluded that functional orthopedic appliances may be effective in patients with pediatric OSA; however, strong and conclusive evidence was missing. Since this systematic review, recent articles have been published on the effectiveness of MAAs in patients with pediatric OSA. Therefore, the objective of this study is to evaluate the effectiveness of MAAs in pediatric OSA and update the previous related conclusions.

## 2.3 Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist was used as a template (19).

*Protocol and Registration*

Protocol and registration were not available.

### *2.3.1 Eligibility Criteria*

The PICOS (population, intervention, comparison, outcome, study design) question format was used to formulate a clinical question and well defined inclusion criteria.

*Population:* Children and adolescents (up to age 16) with sleep apnea.

*Intervention:* Treatment with a MAA.

*Comparison:* Treatment vs control or before and after treatment.

*Outcome:* Primary outcome was change in AHI as measured by PSG. Secondary outcomes of interest include oxygen desaturation, daytime and nocturnal symptoms, and dental and skeletal changes.

*Study Design:* Randomized or non-randomized clinical trials, either prospective or retrospective.

### *2.3.2 Exclusion Criteria*

Patients with craniofacial syndromes, studies with concomitant interventions (i.e., continuous positive airway pressure (CPAP), surgical mandibular advancement, or adenotonsillectomy), and patients older than 16 years were excluded. Patients older than 16 years were excluded as this is the upper age limit at which growth modification appliances are usually effective in children.

### *2.3.3 Information Sources and search strategy*

With the assistance of a senior health sciences librarian, a systematic search of electronic databases was completed using PubMed, EMBASE (OvidSP), MEDLINE (OvidSP), Healthstar (OvidSP), Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews from their inception to the third week of August 2014. The search was conducted using Medical Subject Headings (MeSH), key words, and combinations of key words with truncations to account for any differences in controlled terminology in the different databases. The specific search strategies for each database are shown in Table 2-1.

Hand searches of the reference lists of relevant articles were completed to identify other pertinent articles. Limited grey-literature and Google Scholar searches were completed to identify relevant publications that may have been missed by the electronic database search. No limits were applied to any of the search strategies.

### *2.3.4 Study Selection*

In the first step of the review process, two reviewers independently reviewed article titles and available abstracts of the electronic search results. When an abstract was not available or inadequate information was provided in the abstract, the full text was obtained and reviewed. Any article that evaluated MAAs in pediatric OSA patients was considered for phase 1 inclusion. Discrepancies were resolved by a third reviewer. Full text articles were then obtained for those meeting phase 1 inclusion criteria. In phase 2 of the review process, the same two reviewers evaluated the full text articles independently by applying the remaining inclusion/exclusion criteria listed above. A third investigator again resolved discrepancies in the selection of articles. Reference lists of the selected articles were reviewed to identify any articles that may have been missed. Study authors were contacted if any important information was unclear following detailed review of the full article.

### *2.3.5 Data Items*

The data extracted from the studies that met the inclusion criteria were study design, sample size, mean age, type of MAA, treatment duration with the advancement appliance, change in AHI, and secondary outcomes of interest, if available.

### *2.3.6 Data Collection Process*

Two reviewers extracted data independently, in duplicate. Extracted data was combined and compared for accuracy. Discrepancies were resolved by a third reviewer.

### *2.3.7 Risk of Bias in Individual Studies*

The selected studies were methodologically appraised according to The Cochrane Risk of Bias criteria (20) for assessing individual studies. Two reviewers assessed the quality of the studies independently, in duplicate. Discrepancies were resolved by a third reviewer.

### *2.3.8 Data Synthesis*

If the available collected information was found to be adequate, a meta-analysis was considered.

## 2.4 Results

### *2.4.1 Study Selection*

The methodological flow chart for the selection process is outlined in Figure 2-1. The specific reasons for exclusion of articles in phase 2 are detailed in Table 2- 2. Four articles (14, 21-23) satisfied the selection criteria.

### *2.4.2 Study Characteristics*

A summary of key methodological data and study results is found in Table 2-3. Included articles were all in English language, published between 2002 and 2013. The MAA design varied among all studies. Three articles were non-randomized prospective studies (21-23) and one article was a randomized control trial (14).

### *2.4.3 Risk of Bias*

Risk of Bias assessment of the individual included studies is detailed in Table 2-4. All included studies were found to have high risk of bias potential. Common weaknesses identified were non-randomized allocation and small sample sizes. Further, two studies did not include a non-treated control group (22,23).

### *2.4.4 Synthesis of Results*

A meta-analysis was not possible due to the heterogeneity in study designs and collected information. Therefore, assessment of the risk of bias across studies was not feasible (GRADE framework). The reported results are descriptive in nature.

## 2.5 Discussion

### *2.5.1 Summary of Evidence*

This systematic review aimed to analyze the literature to evaluate whether MAAs are effective in treating pediatric OSA. Following rigorous database searches, it was determined that available literature is scarce and of limited quality. This systematic review included four studies (14,21-23). The selected studies are the best level of evidence available to answer the clinical question posed in this systematic review. Limited available evidence suggests that MAAs reduce AHI values in pediatric OSA patients with mandibular retrognathism. This evidence also suggests that MAAs alone cannot normalize AHI values.

It has been hypothesized that appliances that advance the mandible have a therapeutic effect by enlarging the upper airway (velopharynx). In adults, the mandibular advancement device (MAD) is the most common non-CPAP appliance used to treat OSA (24). Studies in adult populations have found that a MAD has a diminished or similar effect on OSA signs and symptoms compared to a CPAP, but with improved tolerance and compliance to the device (25,26). MADs have therefore been suggested for adult patients with mild to moderate OSA or for those patients who cannot tolerate CPAP (24). Specifically, those with mild OSA, younger age, lower body mass indices, and females have been reported to benefit from MADs (27).

In contrast, treatment of children with OSA remains a challenge. Although adenotonsillectomy is the most common treatment for patients with pediatric OSA, a study found that 47% of patients still had abnormal sleep parameters (28) thereafter. This was likely due to the multifactorial nature of pediatric OSA. Compared to watchful waiting, adenotonsillectomy does appear to reduce symptoms and improve quality of life (29). Unlike adults, the use of CPAP in children that do not have severe signs and symptoms has not been advocated due to poor compliance and undesired craniofacial changes that may follow its prolonged use.

The accompanying craniofacial abnormalities often seen in pediatric OSA patients are suggestive of the pertinence for interceptive orthodontic treatment, while simultaneously managing some symptoms of pediatric OSA. In patients with mandibular retrognathia, MAAs have been suggested to improve symptoms associated with OSA.

The studies included in this review used different appliances to achieve mandibular advancement. Most studies utilized a removable appliance to achieve mandibular changes (14,21,23). In addition to advancing the mandible, two studies incorporated a tongue retainer (to stimulate the tongue to rest directly behind upper incisors and improve habitual position of the tongue) in their appliance (14,21) and one of those studies also included a maxillary expansion screw (21). For this study, the protocol did not specify if and how much the maxillary expansion screw

was activated. The only study using a fixed MAA also incorporated a rapid palatal expander in the appliance, achieving an average expansion of 3.2mm over 15 days (22). All of the studies reported that included patients had a BMI within the normal range.

Two studies were 6 months in length, however differed drastically in their protocol for appliance wear. One study required patients to wear the appliance full time for one week, then nights only (21), while the other required full time wear except meals (14). Assuming that the nights only patients wore their appliance for 8 hours, while the full time patients wore their appliance for 22 hours, there is a 14-hour difference in appliance wear per day between both studies. Both studies reported improved changes in AHI. The other two included studies (22,23) were longer in duration (around 1 year) and required full time wear of the MAA. Both these studies also demonstrated improvement in some PSG parameters following treatment.

A key factor that influences response to MAA is compliance. Only one of the studies used a fixed MAA (22) while the others required patient compliance for the MAA (14,21,23). While these studies indicated the protocol for wear of the MAA, none of them evaluated the level of compliance that was achieved.

If one of the goals of treatment with a MAA is to achieve permanent changes in skeletal and dental relationships, treatment duration longer

than 6 months is likely required. Thus, while both of the 6-month studies reported improvement in OSA symptoms, neither reported that ideal mandibular position had been achieved (14,21). Further, in both studies, the final PSG was done immediately following the 6-month treatment period. Neither study indicated if there was any retention or follow-up protocol post appliance removal and if any additional interventions were needed to manage either OSA or the craniofacial anomaly. In contrast, the studies that were longer in duration indicated improvement in skeletal relationships or facial profile following treatment (22,23). This improvement may also be attributed to the fact that both these studies evaluated patients who were at their peak growth period.

A key consideration in determining whether MAAs produce long-term effects is whether the final PSG was done with the appliance *in situ*. This information would clarify whether use of the MAA produced skeletal changes or merely repositioned the mandible momentarily to a more forward position when the PSG was conducted. Since positioning the mandible forward normally enlarges the oropharynx, improvement in sleep parameters may not be the result of permanent skeletal changes or improvement in craniofacial abnormalities but just the fact that the mandible was repositioned forward. The included studies varied widely in this regard. Two studies completed the post-treatment PSG without the MAA in place (22,23), while one study completed the PSG with the

appliance *in situ* (21). The other included study did not indicate whether the appliance *was in situ* for the post-treatment PSG (14).

It is of value to note that only one of the included studies indicated the pre-treatment severity of mandibular retrognathism (22). This is important in patient selection as well as patient education as it is important to know which patients will benefit most from a MAA as well as which patients may still require additional treatment for jaw disproportions.

### *2.5.2 Limitations*

Although the studies reported improvement in some PSG values with the MAA, none of the respiratory variables returned to normal pediatric reference values. This is likely reflective that other etiologic factors, not just an anatomical problem, play a role in this pediatric OSA population. Thus, even if treatment using a MAA appears successful, patients will likely still require follow-up and long-term monitoring from their physician. The multidisciplinary nature of OSA, requiring management and interaction of many members of the health care team, cannot be emphasized enough.

The included studies were found to have a high risk of potential bias. Although one study was a quasi-RCT, the method of allocation (alphabetically by surname) was inadequate (14). In this study, the number of patients randomized was different from the number of patients analyzed due to a large number of patients lost to follow-up. Other

methodological problems across studies include no allocation concealment, no blinding, and failure to calculate and justify sample size. Two of the included studies did not include a control group (22,23). While both authors indicate that a control group was purposely left out due to the fact that it would be unethical to withhold treatment in mandibular retrognathic patients during peak growth, we cannot rule out the effects of normal growth in either of these studies. Among the studies that did include a control, both control groups varied. In one study, controls were healthy patients without OSA (21), while in another study, controls had OSA (14). Neither of the control groups received any type of treatment. While it would have been ideal for all studies to include a control group, the studies without controls provide valuable information (22,23). Both these studies demonstrated that ideal mandibular position had been achieved post-treatment. Additionally, both these studies were longer in duration and included patients who were in their pubertal growth spurt.

It is important to note that any oral appliance that repositions the mandible forward will immediately enlarge the upper airway space. Thus, a PSG while the appliance is in the mouth may result in improved outcomes. This does not, however, demonstrate that the etiology of the problem has been resolved. If the etiology of pediatric OSA is mandibular retrognathia, permanent skeletal and dentoalveolar changes are required. These changes require treatment of longer duration than one year. Thus, without long-term studies and without knowing whether the appliance was

in situ for the final PSG, we cannot determine if the effects of oral appliances are short-lived.

Recent evidence sheds light on the role of maxillary transverse constriction in pediatric SDB (30). This study found that palatal crossbite involving at least 3 teeth was significantly higher in patients at high-risk for SDB (68%) compared to those at low-risk (23.2%). Further, treatment with rapid maxillary expansion (RME) demonstrated a 14% improvement in quality of life scores in the high-risk SDB group. Thus, in the short-term, RME may be a successful treatment modality for improvement of quality of life in children with mild SDB who are also maxillary transverse deficient.

In summary, our findings are consistent with the conclusions of a previous systematic review (18). Our review found three additional relevant articles that we considered pertinent (21-23) which show some support for the use of MAA in a selective group of pediatric OSA patients.

If treatment with a MAA does in fact demonstrate long-term stability, the showcased effects are promising. Not only will treatment have the ability to improve symptoms of pediatric OSA, it also takes advantage of the adolescent growth spurt and may produce permanent skeletal and dentoalveolar changes to improve the malocclusion. Additionally, if permanent change is demonstrated, children may not need to wear the MAA permanently thereafter as skeletal growth may have resolved one of

the main contributing factors of pediatric OSA. The multifactorial etiology of pediatric OSA has to be considered.

## 2.6 Conclusions

- Based on current limited evidence, it is not possible to conclude that MMAs are effective to treat pediatric OSA.
- There are significant weaknesses in the existing evidence due primarily to absence of control groups, small sample sizes, lack of randomization and short-term results.

## 2.7 Tables

Table 2-1: Search Strategy

| Database | Keywords | Results |
|---|---|---|
| PubMed<br><br>Limits: None<br><br>1950 to 28 April 2014 | ((orthodontic appliances OR class ii functional OR class ii orthop* OR mandibular functional OR mandibular orthop* OR mandibular advance* OR mandibular device* OR mandibular appliance* OR MAA OR herbst OR frankel OR bionator* OR twin block* OR bite block* OR activator*)) AND (sleep apnea OR sleep apnoea) | 1109 |
| EMBASE (OvidSP)<br><br>Limits: None<br><br>1974 to 28 April 2014 | ((exp orthodontic device/ OR class ii functional.mp. OR class ii orthop*.mp. OR mandibular functional.mp. OR mandibular orthop*.mp. OR mandibular advance*.mp. OR mandibular device*.mp. OR mandibular appliance*.mp. OR MAA.mp. OR herbst.mp. OR frankel.mp. OR bionator*.mp. OR twin block*.mp. OR bite block*.mp. OR activator*.mp.)) AND (exp sleep disordered breathing/ OR sleep apnea.mp. OR sleep apnoea.mp.) | 950 |
| MEDLINE (OvidSP)<br><br>Limits: None<br><br>1946 to 28 April 2014 | ((exp orthodontic appliances/ OR class ii functional.mp. OR class ii orthop*.mp. OR mandibular functional.mp. OR mandibular orthop*.mp. OR mandibular advance*.mp. OR mandibular device*.mp. OR mandibular appliance*.mp. OR MAA.mp. OR herbst.mp. OR frankel.mp. OR bionator*.mp. OR twin block*.mp. OR bite block*.mp. OR activator*.mp.)) AND (exp sleep disordered breathing/ OR sleep apnea.mp. OR sleep apnoea.mp.) | 720 |
| Healthstar (OvidSP)<br><br>Limits: None<br><br>1966 to 28 April 2014 | ((exp orthodontic appliances/ OR class ii functional.mp. OR class ii orthop*.mp. OR mandibular functional.mp. OR mandibular orthop*.mp. OR mandibular advance*.mp. OR mandibular device*.mp. OR mandibular appliance*.mp. OR MAA.mp. OR herbst.mp. OR frankel.mp. OR bionator*.mp. OR twin block*.mp. OR bite block*.mp. OR activator*.mp.)) AND (exp sleep disordered breathing/ OR sleep apnea.mp. OR sleep apnoea.mp.) | 625 |
| EBM Reviews – Cochrane Central Register of Controlled Trials (OvidSP)<br><br>Limits: None<br><br>January 2014 to 28 April 2014 | ((exp orthodontic appliances/ OR class ii functional.mp. OR class ii orthop*.mp. OR mandibular functional.mp. OR mandibular orthop*.mp. OR mandibular advance*.mp. OR mandibular device*.mp. OR mandibular appliance*.mp. OR MAA.mp. OR herbst.mp. OR frankel.mp. OR bionator*.mp. OR twin block*.mp. OR bite block*.mp. OR activator*.mp.)) AND (exp sleep disordered breathing/ OR sleep apnea.mp. OR sleep apnoea.mp.) | 99 |
| EBM Reviews - Cochrane Database of Systematic Reviews (OvidSP)<br><br>Limits: None<br><br>2005 to 28 April 2014 | ((class ii functional.mp. OR class ii orthop*.mp. OR mandibular functional.mp. OR mandibular orthop*.mp. OR mandibular advance*.mp. OR mandibular device*.mp. OR mandibular appliance*.mp. OR MAA.mp. OR herbst.mp. OR frankel.mp. OR bionator*.mp. OR twin block*.mp. OR bite block*.mp. OR activator*.mp.)) AND (sleep apnea.mp. OR sleep apnoea.mp.) | 10 |
| Total electronic databases searches | | 3513 |
| Duplicates | | 1754 |
| Final | | 1759 |

Table 2-2: Reasons for Exclusion

| | Study | Reason for Exclusion |
|---|---|---|
| 1 | Amoric, 2013 (31) | Review Article |
| 2 | Ash et al., 2004 (32) | Review Article |
| 3 | Ayas et al., 1998 (33) | Review Article |
| 4 | Bacon et al., 2000 (34) | Adult Participants |
| 5 | Barewal et al., 2014 (35) | Review Article |
| 6 | Barnes et al., 2004 (36) | Adult participants |
| 7 | Bloch et al., 2000 (37) | Adult participants |
| 8 | Bonham et al., 1988 (38) | Adult participants |
| 9 | Carvalho et al., 2007 (18) | Systematic review |
| 10 | Chan et al., 2010 (16) | Adult participants |
| 11 | Chan et al., 2010 (39) | Adult participants |
| 12 | Choudhury et al., 2012 (40) | Adult participants |
| 13 | Clark et al., 1993 (41) | Adult participants |
| 14 | Clark et al., 1996 (42) | Adult participants |
| 15 | Cohen, 1998 (43) | Adult participants |
| 16 | Doff et al., 2013 (44) | Adult participants |
| 17 | Doff et al., 2010 (45) | Adult participants |
| 18 | Doff et al., 2009 (46) | Adult participants |
| 19 | El-Solh et al., 2011 (47) | Adult participants |
| 20 | Eveloff et al., 1994 (48) | Adult participants |
| 21 | Faber et al., 2003 (49) | Adult participants |
| 22 | Ferguson et al., 1996 (50) | Adult participants |
| 23 | Fransson et al., 2002 (51) | Adult participants |
| 24 | Fransson et al., 2002 (52) | Adult participants |
| 25 | George, 1987 (53) | Adult participants |
| 26 | George, 1993 (54) | Adult participants |
| 27 | Ghazal et al., 2009 (55) | Adult participants |
| 28 | Gindre et al., 2008 (56) | Adult participants |
| 29 | Hammond et al., 2007 (57) | Adult participants |

| | | |
|---|---|---|
| 30 | Hanggi et al., 2008 (58) | No OSA |
| 31 | Holley et al., 2011 (59) | Adult participants |
| 32 | Horihata et al., 2011 (60) | No OSA |
| 33 | Ishida et al., 2011 (61) | Adult participants |
| 34 | Isono et al., 1995 (62) | Adult participants |
| 35 | Jia et al., 2005 (63) | Adult participants |
| 36 | Johal et al., 1999 (64) | Adult participants |
| 37 | Johnston et al., 2002 (65) | Adult participants |
| 38 | Kyung et al., 2005 (66) | Adult participants |
| 39 | Lam et al., 2011 (67) | Adult participants |
| 40 | Lamont et al., 1998 (68) | Adult participants |
| 41 | Lee et al., 2012 (69) | Adult participants |
| 42 | Lekerud et al., 2012 (70) | Adult participants |
| 43 | Marklund et al., 1998 (71) | Adult participants |
| 44 | Marklund et al., 2001 (72) | Adult participants |
| 45 | Mehta et al., 2001 (73) | Adult participants |
| 46 | Menn et al., 1996 (74) | Adult participants |
| 47 | Millman et al., 1998 (75) | Adult participants |
| 48 | Miyao et al., 2007 (76) | Case Report |
| 49 | Nakazawa et al., 1992 (77) | Adult participants |
| 50 | Nunes et al., 2009 (78) | Full article not available |
| 51 | O'Sullivan et al., 1995 (79) | Adult participants |
| 52 | Pancer et al., 1999 (80) | Adult participants |
| 53 | Petri et al., 2008 (81) | Adult participants |
| 54 | Poon et al., 2008 (82) | Adult participants |
| 55 | Prathibha et al., 2003 (83) | Adult participants |
| 56 | Ringqvist et al., 2003 (84) | Adult participants |
| 57 | Rose et al., 2006 (85) | Case Report |
| 58 | Schessl et al., 2008 (86) | Case Report |
| 59 | Shadaba et al., 2000 (87) | Adult participants |
| 60 | Singh et al., 2007(88) | No OSA |
| 61 | Sjoholm et al., 1994 (89) | Adult participants |

| | | |
|---|---|---|
| 62 | Tegelberg et al., 2003 (90) | Adult participants |
| 63 | Trang, 2006 (91) | Review Article |
| 64 | Tsuiki et al., 2004 (92) | Adult participants |
| 65 | Vestling, 2001 (93) | Adult participants |
| 66 | Wade, 2003 (94) | Adult participants |
| 67 | Walker-Engstrom, 2003 (95) | Adult participants |

Table 2-3: Summary of Study Characteristics of Included Articles

| Study | Study Design | Sample Size | Mean Age (years) | Type of Mandibular Advancement Appliance | Duration of Advancement Appliance | Study Results |
|---|---|---|---|---|---|---|
| Zhang *et al* (2013) | Non-randomized clinical trial (prospective study) | Treatment group: 46 (31 males, 15 females)<br><br>No control group | 9.7 years ± 1.5 years | Twin Block<br><br>(Mandible was advanced to the point that the lower incisors reached an edge-to-edge relationship with the upper incisors) | Full time wear (except during meals) for 10.8 months<br><br>Patients were seen each month for follow-up<br><br>Treatment with appliance ended 1 month after mandible reached desired position | Average AHI index decreased from 14.08 ± 4.25 to 3.39 ± 1.86 ($p<0.01$)<br><br>Lowest $SaO_2$ increased from 77.78 ± 3.38 to 93.63 ± 2.66 ($p<0.01$)<br><br>Apnea was defined as complete interruption of airflow that lasts at least two breaths. Hypopnea was defined as ≥ 50% reduction of airflow with arousal and/or >3% drop in Sa $O_2$<br><br>Mean $SaO_2$ did not change significantly ($p>0.05$) from 96.22 ± 1.11 to 96.52 ± 1.07<br><br>Cephalometric data demonstrated a significant increase in superior posterior airway space, middle airway space, SNB angle and facial convexity ($p<0.01$) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Schutz *et al* (2011) | Non-randomized clinical trial (prospective study) | Treatment group: 16<br><br>No control group | 12.6 years ± 11.5 months | Herbst appliance and maxillary expander<br><br>Mandible was advanced 6mm and opened 4mm vertically. Stepwise activations were completed<br><br>Rapid palatal expander was adapted to the Herbst appliance and expanded for 15 days. Mean maxillary expansion was 3.19mm. | 12 months (fixed herbst appliance for 24 hours/day) | Significant reduction in respiratory effort related arousals 7.06 ± 5.37 to 1.31 ± 1.45 ($p<0.05$) due to a total increase in airway volume ($p<0.01$).<br><br>Significant reduction in respiratory disturbance index 7.3 ± 5.6 to 1.3 ±1.8 ($p<0.05$)<br><br>Length of the mandible (Co-Gn) increased by 6.1mm |
| Cozza *et al* (2004) | Non-randomized clinical trial (prospective study) | Treatment group: 20 (10 males, 10 females)<br><br>Control group (healthy): 20 (10 males, 10 females). Control group had no treatment | Treatment group: 5.91 years (range 4 to 8 years)<br><br>Control group: 6 years (range 5 to 7 years) | Modified monobloc (full occlusal coverage with maxillary expansion screw and tongue retainer). A Tucat's pearl on a sliding wire was used to determine the reference point for the tip of the tongue.<br><br>Appliance placed the mandible in an edge-to-edge incisor relationship<br><br>Occlusal coverage prevented maxillary posterior teeth from erupting, however eruption of posterior mandibular teeth was | 6 months<br><br>Appliance worn full time for the first week then nights only | Significant reduction in apnoea-hypopnoea index from 7.88 to 3.66 ($p= 0.0003$)<br><br>Apnoea was defined as cessation of airflow for at least 10 seconds<br><br>Hypopnoea was defined as reduction in the amplitude of airflow or thoraco-abdominal wall movement greater than 50% of baseline for more than 10 seconds (oxygen desaturation did not need to occur) or the same reduction with oxygen |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | encouraged by trimming acrylic from the occlusal surface<br><br>Lingual arch soldered to lower primary molars was used to provide anchorage and prevent jaw opening during sleep. Class II intermaxillary elastics were used at night from the monobloc to the lower lingual arch | | desaturation of at least 3% and associated with arousal<br><br>Daytime sleepiness and sleep quality improved in treated patients (Epworth sleepiness scale decreased from 15.2 ± 4.9 to 7.1 ± 2)<br><br>No significant difference in the minimum arterial oxygen saturation |
| Villa *et al*<br><br>(2002) | Randomized Clinical Trial | Treatment group: 19 (10 males, 9 females)<br><br>Control group (OSA): 13 (10 males, 3 females). Control group had no treatment<br><br>5 patients in treated group (26%) and 4 patients in control group (31%) were lost to follow-up | Treatment group: 6.86 years ± 2.34 years<br><br>Control group: 7.34 years ± 3.1 years | Acrylic bite plate for mandibular positioning. Each appliance had a lingual "target" which was an acrylic ring to stimulate the tongue into proper position<br><br>Appliance was uniquely designed to correct each patient's mandibular malposition (Retrognathic mandibles were advanced, deep bites were raised, and cross-bites were recentred) | 6 months<br><br>Full time wear except mealtimes<br><br>Patients wearing the oral appliance were seen monthly to ensure proper functioning of the appliance | Significant reduction in apnoea-hypoponea index from 7.1 ± 4.6 to 2.6 ± 2.2 ($p<0.001$) vs control group which did not show any reduction<br><br>Authors considered at least a 50% reduction in the AHI as successful treatment with an oral appliance. AHI fell 50% in 9/14 treated patients (64.2%) |

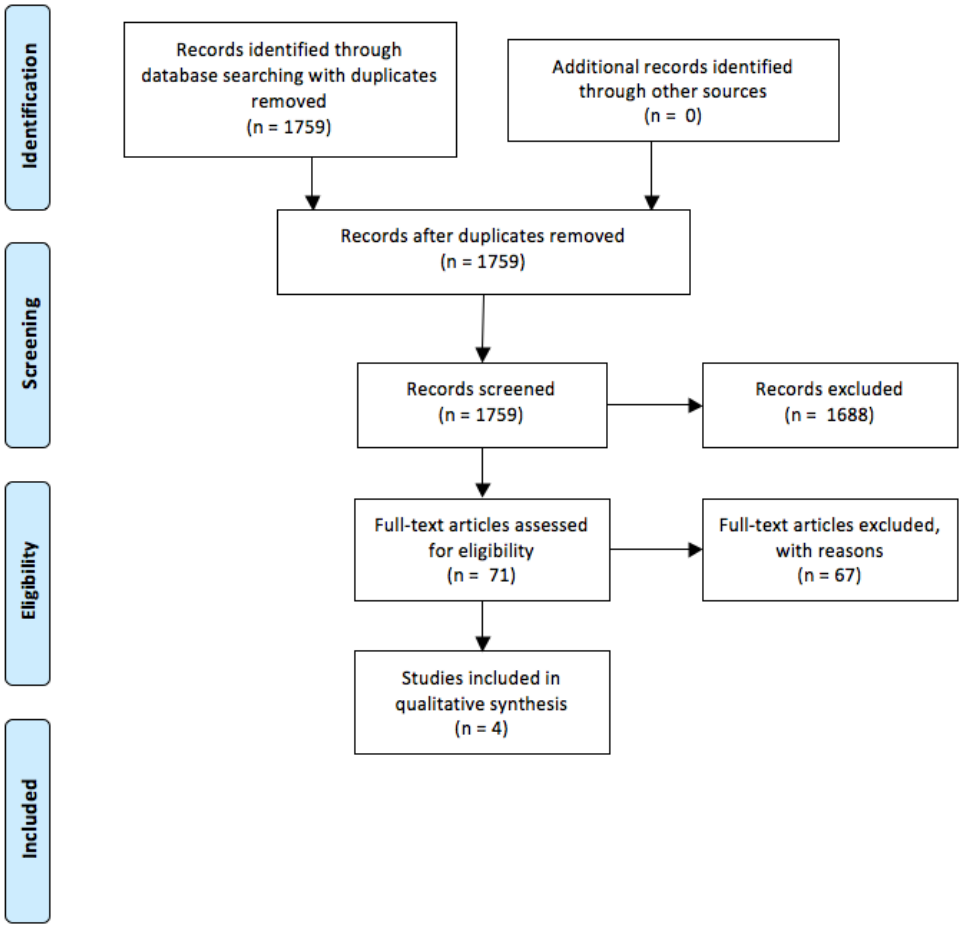
| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | Respiratory symptoms in all treated patients improved and completely regressed in 50% of patients, (as determined by a modified version of the Brouillette questionnaire)<br><br>Desaturation index decreased in treated patients but was not significant |

Table 2-4: Risk of Bias Assessment

| **Characteristic** | **Study** | | | |
|---|---|---|---|---|
| | Zhang *et al*<br><br>(2013) | Schutz *et al*<br><br>(2011) | Cozza *et al*<br><br>(2004) | Villa *et al*<br><br>(2002) |
| Sequence Generation<br><br>(Selection Bias) | **High** – Inadequate generation of a random sequence for selection | **High** – Inadequate generation of a random sequence for selection | **High** – Inadequate generation of a random sequence for selection | **Moderate –** Randomization assigned alphabetically by surname |
| Allocation Concealment (Selection Bias) | **High** - Inadequate concealment of allocations | **High** - Inadequate concealment of allocations | **High** - Inadequate concealment of allocations | **High** - Inadequate concealment of allocations |
| Blinding of Participants and Personnel (Performance Bias) | **High** - Performance bias due to knowledge of the allocated intervention by participants and personnel during study | **High** - Performance bias due to knowledge of the allocated intervention by participants and personnel during study | **High** - Performance bias due to knowledge of the allocated intervention by participants and personnel during study | **High** – Performance bias due to knowledge of the allocated intervention by participants and personnel during study |
| Blinding of Outcome Assessment (Detection Bias) | **Unclear** – Unclear if outcome assessor was blinded | **Unclear** – Unclear if outcome assessor was blinded | **Unclear** – Unclear if outcome assessor was blinded | **Unclear** – Unclear if outcome assessor was blinded |
| Incomplete Outcome Data (Attrition Bias) | **Low** – No missing outcome data | **Low** – No missing outcome data | **Low** – No missing outcome data | **High –** Large number of patients lost to follow up (26% in treatment group, 31% in control group) |
| Selective Outcome Reporting (Reporting Bias) | **Low** – Pre-specified outcomes were reported | **Low** – Pre-specified outcomes were reported | **Low** – Pre-specified outcomes were reported | **Low** – Pre-specified outcomes were reported |
| Other Sources of Bias | **High** – No control group | **High** – No control group | **Unclear** | **Unclear** |
| Overall Risk of Bias | **High** | **High** | **High** | **High** |

## 2.8 Figures

Figure 2-1: Flow chart of study selection process




*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

## 2.9 References

(1) Carroll JL. Obstructive sleep-disordered breathing in children: new controversies, new directions. Clin Chest Med 2003 Jun;24(2):261-282.

(2) Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc 2008 Feb 15;5(2):242-252.

(3) Bixler EO, Vgontzas AN, Lin HM, Liao D, Calhoun S, Vela-Bueno A, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. Sleep 2009 Jun;32(6):731-736.

(4) Marcus CL. Pathophysiology of childhood obstructive sleep apnea: current concepts. Respir Physiol 2000 Feb;119(2-3):143-154.

(5) Huynh NT, Morton PD, Rompre PH, Papadakis A, Remise C. Associations between sleep-disordered breathing symptoms and facial and dental morphometry, assessed with screening examinations. Am J Orthod Dentofacial Orthop 2011 Dec;140(6):762-770.

(6) Bar A, Tarasiuk A, Segev Y, Phillip M, Tal A. The effect of adenotonsillectomy on serum insulin-like growth factor-I and growth in children with obstructive sleep apnea syndrome. J Pediatr 1999 Jul;135(1):76-80.

(7) Chervin RD, Archbold KH, Dillon JE, Panahi P, Pituch KJ, Dahl RE, et al. Inattention, hyperactivity, and symptoms of sleep-disordered breathing. Pediatrics 2002 Mar;109(3):449-456.

(8) Marcus CL, Greene MG, Carroll JL. Blood pressure in children with obstructive sleep apnea. Am J Respir Crit Care Med 1998 Apr;157(4 Pt 1):1098-1103.

(9) Kaditis A, Kheirandish-Gozal L, Gozal D. Algorithm for the diagnosis and treatment of pediatric OSA: a proposal of two pediatric sleep centers. Sleep Med 2012 Mar;13(3):217-227.

(10) Tauman R, Gulliver TE, Krishna J, Montgomery-Downs HE, O'Brien LM, Ivanenko A, et al. Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. J Pediatr 2006 Dec;149(6):803-808.

(11) Brietzke SE, Gallagher D. The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: a meta-analysis. Otolaryngol Head Neck Surg 2006 Jun;134(6):979-984.

(12) Friedman M, Wilson M, Lin HC, Chang HW. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. Otolaryngol Head Neck Surg 2009 Jun;140(6):800-808.

(13) Pirelli P, Saponara M, Guilleminault C. Rapid maxillary expansion in children with obstructive sleep apnea syndrome. Sleep 2004 Jun 15;27(4):761-766.

(14) Villa MP, Bernkopf E, Pagani J, Broia V, Montesano M, Ronchetti R. Randomized controlled study of an oral jaw-positioning appliance for the treatment of obstructive sleep apnea in children with malocclusion. Am J Respir Crit Care Med 2002 Jan 1;165(1):123-127.

(15) Hiyama S, Suda N, Ishii-Suzuki M, Tsuiki S, Ogawa M, Suzuki S, et al. Effects of maxillary protraction on craniofacial structures and upper-airway dimension. Angle Orthod 2002 Feb;72(1):43-47.

(16) Chan AS, Sutherland K, Schwab RJ, Zeng B, Petocz P, Lee RW, et al. The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. Thorax 2010 Aug;65(8):726-732.

(17) Tsuiki S, Ono T, Kuroda T. Mandibular Advancement Modulates Respiratory-Related Genioglossus Electromyographic Activity. Sleep Breath 2000;4(2):53-58.

(18) Carvalho FR, Lentini-Oliveira D, Machado MA, Prado GF, Prado LB, Saconato H. Oral appliances and functional orthopaedic appliances for obstructive sleep apnoea in children. Cochrane Database Syst Rev 2007 Apr 18;(2)(2):CD005520.

(19) Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009 Oct;62(10):1006-1012.

(20) Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011 Oct 18;343:d5928.

(21) Cozza P, Polimeni A, Ballanti F. A modified monobloc for the treatment of obstructive sleep apnoea in paediatric patients. Eur J Orthod 2004 Oct;26(5):523-530.

(22) Schutz TC, Dominguez GC, Hallinan MP, Cunha TC, Tufik S. Class II correction improves nocturnal breathing in adolescents. Angle Orthod 2011 Mar;81(2):222-228.

(23) Zhang C, He H, Ngan P. Effects of twin block appliance on obstructive sleep apnea in children: a preliminary study. Sleep Breath 2013 Dec;17(4):1309-1314.

(24) Marklund M, Verbraecken J, Randerath W. Non-CPAP therapies in obstructive sleep apnoea: mandibular advancement device therapy. Eur Respir J 2012 May;39(5):1241-1247.

(25) Ahrens A, McGrath C, Hagg U. A systematic review of the efficacy of oral appliance design in the management of obstructive sleep apnoea. Eur J Orthod 2011 Jun;33(3):318-324.

(26) Phillips CL, Grunstein RR, Darendeliler MA, Mihailidou AS, Srinivasan VK, Yee BJ, et al. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med 2013 Apr 15;187(8):879-887.

(27) Sutherland K, Vanderveken OM, Tsuda H, Marklund M, Gagnadoux F, Kushida CA, et al. Oral appliance treatment for obstructive sleep apnea: an update. J Clin Sleep Med 2014 Feb 15;10(2):215-227.

(28) Guilleminault C, Huang YS, Glamann C, Li K, Chan A. Adenotonsillectomy and obstructive sleep apnea in children: a prospective survey. Otolaryngol Head Neck Surg 2007 Feb;136(2):169-175.

(29) Marcus CL, Moore RH, Rosen CL, Giordani B, Garetz SL, Taylor HG, et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. N Engl J Med 2013 Jun 20;368(25):2366-2376.

(30) Katyal V, Pamula Y, Daynes CN, Martin J, Dreyer CW, Kennedy D, et al. Craniofacial and upper airway morphology in pediatric sleep-disordered breathing and changes in quality of life with rapid maxillary expansion. Am J Orthod Dentofacial Orthop 2013 Dec;144(6):860-871.

(31) Amoric M. Efficacy and compliance in treatment of sleep apnea with Herbst mandibular advancement splints (OHA version). Int Orthod 2013 Jun;11(2):193-209.

(32) Ash SP, Smith AM. Chrome cobalt mandibular advancement appliances for managing snoring and obstructive sleep apnea. J Orthod 2004 Dec;31(4):295-299.

(33) Ayas NT, Epstein LJ. Oral appliances in the treatment of obstructive sleep apnea and snoring. Curr Opin Pulm Med 1998 Nov;4(6):355-360.

(34) Bacon W, Tschill P, Sforza E, Krieger J. A device for mandibular advancement in respiratory disorders of sleep. Clinical study. Orthod Fr 2000 Dec;71(4):295-302.

(35) Barewal RM, Hagen CC. Management of snoring and obstructive sleep apnea with mandibular repositioning appliances: a prosthodontic approach. Dent Clin North Am 2014 Jan;58(1):159-180.

(36) Barnes M, McEvoy RD, Banks S, Tarquinio N, Murray CG, Vowles N, et al. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. Am J Respir Crit Care Med 2004 Sep 15;170(6):656-664.

(37) Bloch KE, Iseli A, Zhang JN, Xie X, Kaplan V, Stoeckli PW, et al. A randomized, controlled crossover trial of two oral appliances for sleep apnea treatment. Am J Respir Crit Care Med 2000 Jul;162(1):246-251.

(38) Bonham PE, Currier GF, Orr WC, Othman J, Nanda RS. The effect of a modified functional appliance on obstructive sleep apnea. Am J Orthod Dentofacial Orthop 1988 Nov;94(5):384-392.

(39) Chan AS, Phillips CL, Cistulli PA. Obstructive sleep apnoea--an update. Intern Med J 2010 Feb;40(2):102-106.

(40) Choudhury M, Padmanabhan TV. A preliminary report on the effect of a mandibular advancement device on obstructive sleep apnea using magnetic resonance imaging and polysomnography. Int J Prosthodont 2012 Nov-Dec;25(6):613-618.

(41) Clark GT, Arand D, Chung E, Tong D. Effect of anterior mandibular positioning on obstructive sleep apnea. Am Rev Respir Dis 1993 Mar;147(3):624-629.

(42) Clark GT, Blumenfeld I, Yoffe N, Peled E, Lavie P. A crossover study comparing the efficacy of continuous positive airway pressure with anterior mandibular positioning devices on patients with obstructive sleep apnea. Chest 1996 Jun;109(6):1477-1483.

(43) Cohen R. Obstructive sleep apnea: oral appliance therapy and severity of condition. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998 Apr;85(4):388-392.

(44) Doff MH, Hoekema A, Wijkstra PJ, van der Hoeven JH, Huddleston Slater JJ, de Bont LG, et al. Oral appliance versus continuous positive airway pressure in obstructive sleep apnea syndrome: a 2-year follow-up. Sleep 2013 Sep 1;36(9):1289-1296.

(45) Doff MH, Hoekema A, Pruim GJ, Huddleston Slater JJ, Stegenga B. Long-term oral-appliance therapy in obstructive sleep apnea: a cephalometric study of craniofacial changes. J Dent 2010 Dec;38(12):1010-1018.

(46) Doff MH, Hoekema A, Pruim GJ, van der Hoeven JH, de Bont LG, Stegenga B. Effects of a mandibular advancement device on the upper airway morphology: a cephalometric analysis. J Oral Rehabil 2009 May;36(5):330-337.

(47) El-Solh AA, Moitheennazima B, Akinnusi ME, Churder PM, Lafornara AM. Combined oral appliance and positive airway pressure therapy for obstructive sleep apnea: a pilot study. Sleep Breath 2011 May;15(2):203-208.

(48) Eveloff SE, Rosenberg CL, Carlisle CC, Millman RP. Efficacy of a Herbst mandibular advancement device in obstructive sleep apnea. Am J Respir Crit Care Med 1994 Apr;149(4 Pt 1):905-909.

(49) Faber CE, Grymer L, Hjorth T. Anterior mandibular positioning device for treatment of snoring and obstructive sleep apnoea. Rhinology 2003 Sep;41(3):175-181.

(50) Ferguson KA, Ono T, Lowe AA, Keenan SP, Fleetham JA. A randomized crossover study of an oral appliance vs nasal-continuous positive airway pressure in the treatment of mild-moderate obstructive sleep apnea. Chest 1996 May;109(5):1269-1275.

(51) Fransson AM, Tegelberg A, Svenson BA, Lennartsson B, Isacsson G. Influence of mandibular protruding device on airway passages and dentofacial characteristics in obstructive sleep apnea and snoring. Am J Orthod Dentofacial Orthop 2002 Oct;122(4):371-379.

(52) Fransson AM, Svenson BA, Isacsson G. The effect of posture and a mandibular protruding device on pharyngeal dimensions: a cephalometric study. Sleep Breath 2002 Jun;6(2):55-68.

(53) George PT. A modified functional appliance for treatment of obstructive sleep apnea. J Clin Orthod 1987 Mar;21(3):171-175.

(54) George PT. Treatment of snoring and obstructive sleep apnea with a dental device. Gen Dent 1993 Jul-Aug;41(4):294-298.

(55) Ghazal A, Sorichter S, Jonas I, Rose EC. A randomized prospective long-term study of two oral appliances for sleep apnoea treatment. J Sleep Res 2009 Sep;18(3):321-328.

(56) Gindre L, Gagnadoux F, Meslier N, Gustin JM, Racineux JL. Mandibular advancement for obstructive sleep apnea: dose effect on apnea, long-term use and tolerance. Respiration 2008;76(4):386-392.

(57) Hammond RJ, Gotsopoulos H, Shen G, Petocz P, Cistulli PA, Darendeliler MA. A follow-up study of dental and skeletal changes associated with mandibular advancement splint use in obstructive sleep apnea. Am J Orthod Dentofacial Orthop 2007 Dec;132(6):806-814.

(58) Hanggi MP, Teuscher UM, Roos M, Peltomaki TA. Long-term changes in pharyngeal airway dimensions following activator-headgear and fixed appliance treatment. Eur J Orthod 2008 Dec;30(6):598-605.

(59) Holley AB, Lettieri CJ, Shah AA. Efficacy of an adjustable oral appliance and comparison with continuous positive airway pressure for the treatment of obstructive sleep apnea syndrome. Chest 2011 Dec;140(6):1511-1516.

(60) Horihata A, Ueda H, Koh M, Watanabe G, Tanne K. Enhanced increase in pharyngeal airway size in Japanese class II children following a 1-year treatment with an activator appliance. Int J Orthod Milwaukee 2013 Winter;24(4):35-40.

(61) Ishida M, Inoue Y, Kawahara R, Ryoke K. An investigation of therapeutic effectiveness and the mechanism of oral appliance therapy on obstructive sleep apnea syndrome. Nihon Kokyuki Gakkai Zasshi 2001 Aug;39(8):559-566.

(62) Isono S, Tanaka A, Sho Y, Konno A, Nishino T. Advancement of the mandible improves velopharyngeal airway patency. J Appl Physiol (1985) 1995 Dec;79(6):2132-2138.

(63) Jia PZ, Fu MK, Zeng XL. Treatment of OSAS with modified twin-block advancement appliances. Zhonghua Kou Qiang Yi Xue Za Zhi 2005 Jan;40(1):42-45.

(64) Johal A, Battagel JM. An investigation into the changes in airway dimension and the efficacy of mandibular advancement appliances in subjects with obstructive sleep apnoea. Br J Orthod 1999 Sep;26(3):205-210.

(65) Johnston CD, Gleadhill IC, Cinnamond MJ, Gabbey J, Burden DJ. Mandibular advancement appliances and obstructive sleep apnoea: a randomized clinical trial. Eur J Orthod 2002 Jun;24(3):251-262.

(66) Kyung SH, Park YC, Pae EK. Obstructive sleep apnea patients with the oral appliance experience pharyngeal size and shape changes in three dimensions. Angle Orthod 2005 Jan;75(1):15-22.

(67) Lam B, Sam K, Lam JC, Lai AY, Lam CL, Ip MS. The efficacy of oral appliances in the treatment of severe obstructive sleep apnea. Sleep Breath 2011 May;15(2):195-201.

(68) Lamont J, Baldwin DR, Hay KD, Veale AG. Effect of two types of mandibular advancement splints on snoring and obstructive sleep apnoea. Eur J Orthod 1998 Jun;20(3):293-297.

(69) Lee CH, Jung HJ, Lee WH, Rhee CS, Yoon IY, Yun PY, et al. The effect of positional dependency on outcomes of treatment with a mandibular advancement device. Arch Otolaryngol Head Neck Surg 2012 May;138(5):479-483.

(70) Lekerud AK, Sand L, Englund AK, Hirsch JM. Treatment of sleep apnoea using a mandibular advancement splint--an open prospective study. In Vivo 2012 Sep-Oct;26(5):841-845.

(71) Marklund M, Franklin KA, Sahlin C, Lundgren R. The effect of a mandibular advancement device on apneas and sleep in patients with obstructive sleep apnea. Chest 1998 Mar;113(3):707-713.

(72) Marklund M, Sahlin C, Stenlund H, Persson M, Franklin KA. Mandibular advancement device in patients with obstructive sleep apnea : long-term effects on apnea and sleep. Chest 2001 Jul;120(1):162-169.

(73) Mehta A, Qian J, Petocz P, Darendeliler MA, Cistulli PA. A randomized, controlled study of a mandibular advancement splint for obstructive sleep apnea. Am J Respir Crit Care Med 2001 May;163(6):1457-1461.

(74) Menn SJ, Loube DI, Morgan TD, Mitler MM, Berger JS, Erman MK. The mandibular repositioning device: role in the treatment of obstructive sleep apnea. Sleep 1996 Dec;19(10):794-800.

(75) Millman RP, Rosenberg CL, Carlisle CC, Kramer NR, Kahn DM, Bonitati AE. The efficacy of oral appliances in the treatment of persistent sleep apnea after uvulopalatopharyngoplasty. Chest 1998 Apr;113(4):992-996.

(76) Miyao E, Nakayama M, Noda A, Miyao M, Arasaki H. Oral appliance therapy for a child with sleep apnea syndrome due to palatine tonsil hypertrophy. Sleep and Biological Rhythms 2007;5(4):288-290.

(77) Nakazawa Y, Sakamoto T, Yasutake R, Yamaga K, Kotorii T, Miyahara Y, et al. Treatment of sleep apnea with prosthetic mandibular advancement (PMA). Sleep 1992 Dec;15(6):499-504.

(78) Nunes W, Francesco-Mion R. 151 EARLY TREATMENT AND PREVENTIVE STRATEGIES FOR OBSTRUCTIVE SLEEP APNEA AND HYPOPNEA WITH THE BIOAJUSTA X ORTHODONTIC-ORTHOPEDIC TREATMENT. Sleep Med 2009;10:S41-S42.

(79) O'Sullivan RA, Hillman DR, Mateljan R, Pantin C, Finucane KE. Mandibular advancement splint: an appliance to treat snoring and obstructive sleep apnea. Am J Respir Crit Care Med 1995 Jan;151(1):194-198.

(80) Pancer J, Al-Faifi S, Al-Faifi M, Hoffstein V. Evaluation of variable mandibular advancement appliance for treatment of snoring and sleep apnea. Chest 1999 Dec;116(6):1511-1518.

(81) Petri N, Svanholt P, Solow B, Wildschiodtz G, Winkel P. Mandibular advancement appliance for obstructive sleep apnoea: results of a randomised placebo controlled trial using parallel group design. J Sleep Res 2008 Jun;17(2):221-229.

(82) Poon KH, Chay SH, Chiong KF. Airway and craniofacial changes with mandibular advancement device in Chinese with obstructive sleep apnoea. Ann Acad Med Singapore 2008 Aug;37(8):637-644.

(83) Prathibha BN, Jagger RG, Saunders M, Smith AP. Use of a mandibular advancement device in obstructive sleep apnoea. J Oral Rehabil 2003 May;30(5):507-509.

(84) Ringqvist M, Walker-Engstrom ML, Tegelberg A, Ringqvist I. Dental and skeletal changes after 4 years of obstructive sleep apnea treatment with a mandibular advancement device: a prospective, randomized study. Am J Orthod Dentofacial Orthop 2003 Jul;124(1):53-60.

(85) Rose E, Schessl J. Orthodontic procedures in the treatment of obstructive sleep apnea in children. J Orofac Orthop 2006 Jan;67(1):58-67.

(86) Schessl J, Rose E, Korinthenberg R, Henschen M. Severe obstructive sleep apnea alleviated by oral appliance in a three-year-old boy. Respiration 2008;76(1):112-116.

(87) Shadaba A, Battagel JM, Owa A, Croft CB, Kotecha BT. Evaluation of the Herbst Mandibular Advancement Splint in the management of patients with sleep-related breathing disorders. Clin Otolaryngol Allied Sci 2000 Oct;25(5):404-412.

(88) Singh GD, Garcia-Motta AV, Hang WM. Evaluation of the posterior airway space following Biobloc therapy: geometric morphometrics. Cranio 2007 Apr;25(2):84-89.

(89) Sjoholm TT, Polo OJ, Rauhala ER, Vuoriluoto J, Helenius HY. Mandibular advancement with dental appliances in obstructive sleep apnoea. J Oral Rehabil 1994 Sep;21(5):595-603.

(90) Tegelberg A, Walker-Engstrom ML, Vestling O, Wilhelmsson B. Two different degrees of mandibular advancement with a dental appliance in treatment of patients with mild to moderate obstructive sleep apnea. Acta Odontol Scand 2003 Dec;61(6):356-362.

(91) Trang H. Obstructive sleep apnea treatment in children. Rev Mal Respir 2006 Jun;23 Spec No 2:7S128-7S130.

(92) Tsuiki S, Lowe AA, Almeida FR, Kawahata N, Fleetham JA. Effects of mandibular advancement on airway curvature and obstructive sleep apnoea severity. Eur Respir J 2004 Feb;23(2):263-268.

(93) Vestling O, Walker-Engström WB, Tegelberg A. Treatment of obstructive sleep apnea (OSA) with two different degrees of mandibular advancement of dental appliance-a prospective and randomised study. Swed Dent J 2001;25(4):180.

(94) Wade PS. Oral appliance therapy for snoring and sleep apnea: preliminary report on 86 patients fitted with an anterior mandibular positioning device, the Silencer. J Otolaryngol 2003 Apr;32(2):110-113.

(95) Walker-Engstrom ML, Ringqvist I, Vestling O, Wilhelmsson B, Tegelberg A. A prospective randomized study comparing two different degrees of mandibular advancement with a dental appliance in treatment of severe obstructive sleep apnea. Sleep Breath 2003 Sep;7(3):119-130.

# Chapter 3 – Validation of the Alberta Pediatric Obstructive Sleep Apnea (APOSA) Index for Orthodontic Treatment Need in Pediatric Patients with Obstructive Sleep Apnea Symptoms

## 3.1 Overview

The Alberta Pediatric Obstructive Sleep Apnea (APOSA) index is a novel tool developed to evaluate orthodontic treatment need in pediatric patients with obstructive sleep apnea (OSA) symptoms (1). The objective of this study is to determine the predictive ability of the APOSA index as a tool for orthodontic treatment need compared to the perception of treatment need determined by a sample of North American orthodontists with special expertise in pediatric OSA. Thirty orthodontic records, representing a spectrum of craniofacial and oral features and severity, were evaluated for orthodontic treatment need using the APOSA index. The results were compared to treatment decisions made by ten expert orthodontists. Receiver operating characteristic (ROC) curve demonstrated a cutoff score of 6.5 with a sensitivity of 94.1% and specificity of 99%. Our findings indicate that the APOSA index is a useful and predictive tool for orthodontic treatment need in pediatric patients with OSA symptoms.

## 3.2 Introduction

Sleep disordered breathing (SDB) represents a spectrum of respiratory disorders ranging from primary snoring to obstructive sleep apnea (OSA). OSA is characterized by repeated episodes of partial or complete airway obstruction during sleep. The prevalence of pediatric OSA is estimated to be between 1% - 4% (2,3). Common symptoms of

pediatric OSA include snoring, daytime fatigue, irritability, and behavioural problems (4). These symptoms may manifest as poor performance at school and withdrawal among peer groups(4).

The most common cause of OSA in children is adenotonsillar hypertrophy (5). The first-line surgical treatment approach in children with OSA is adenotonsillectomy and is curative in only 25%-75% of patients (6-8). While adenotonsillectomy remains the mainstay first-line treatment approach, it is important to consider other etiologic factors and a multidisciplinary approach to diagnosis and management of pediatric OSA.

Pediatric OSA has numerous craniofacial correlates including mandibular retrognathism, midface dysplasia, maxillary constriction, and increased vertical growth (9). Improving these craniofacial abnormalities through orthodontic treatment can be a useful adjunct for management of the pediatric patient with OSA symptoms. Orthodontic treatment modalities that have been reported in the literature for pediatric OSA include rapid maxillary expansion (10), mandibular advancement appliances (11), and orthopedic maxillary protraction (12). These findings highlight the importance of multidisciplinary evaluation and management of pediatric OSA. While orthodontic treatment alone cannot resolve OSA, it can improve symptoms and quality of life in children who demonstrate the associated craniofacial abnormalities. Further, orthodontic treatment during a child's peak growth may also provide skeletal and dental improvements of craniofacial anomalies.

One of the challenges in developing a streamlined and multidisciplinary approach to management lie in barriers of communication between medical and dental teams. Specifically, medical teams have advanced training in physiological components of sleep disordered breathing including oxygen saturation, peak end-tidal $CO_2$, and brain activity during sleep. Treatment approaches are primarily surgical or providing ventilation support. Dentists and orthodontists focus on physical and anatomic variations, with treatment approaches aimed at orthopedic or dental correction of skeletal and dental disharmonies. Tools to improve communication and collaboration between medical and dental teams will enhance the multi-disciplinary care for pediatric OSA.

In patients who demonstrate altered craniofacial or oral characteristics that may contribute to OSA symptoms, timely orthodontic referral and treatment is necessary. This is due to the fact that there is a limited window of opportunity to intervene in altered craniofacial growth. Further, without any intervention, growth abnormalities continue in the same pattern, becoming more severe with time. As a result, timely identification and orthodontic referral of the pediatric OSA patient is essential.

Our research team at the University of Alberta developed a novel index in close concordance with World Health Organization's (WHO) recommendations for index development (13). This index allows medical professionals to identify patients who may have a craniofacial component

to their OSA and who may benefit from orthodontic treatment (1). Consistent with WHO recommendations, the following steps were followed in the development of the Alberta Pediatric Obstructive Sleep Apnea (APOSA) index:

1. Establishing a Steering Committee
2. Scoping the Index
3. Reviewing the Literature
4. Drafting the Index
5. Organizing an Index Development Group
6. Organizing an External Review Group

Currently, the APOSA index provides a visual representation of 8 craniofacial and oral features with 2-3 levels of severity for each feature (Appendix A). Specifically, the index evaluates profile, midface deficiency, lower face height, lip strain to close, palate, overjet, overbite, and posterior crossbites. Application of the index results in a score that summarizes craniofacial and oral characteristics for the patient being evaluated. Ultimately, this score will determine whether the patient would benefit from orthodontic referral. Reliability testing of the APOSA index demonstrated fair to substantial inter-rater reliability and moderate to almost perfect intra-rater reliability.

The objective of the APOSA index is to facilitate an integrated communication and management approach that considers craniofacial and oral features characteristic of pediatric OSA. This study aims to determine

the predictive ability of the APOSA index through statistical techniques in order to provide meaning and relevance to the index. Through this process, we aim to determine a cut-off score that will prioritize orthodontic referral and treatment for patients that would benefit from it.

The primary objective of this study is to determine the predictive ability of the APOSA index in determining orthodontic treatment need. Secondary objectives include determining a cut-off score required for referral as well as determining the sensitivity and specificity of the APOSA index. Our research hypothesis is that the APOSA index accurately predicts need for orthodontic treatment.

## 3.3 Methods

Predictive ability of the APOSA index was evaluated with a prospective/retrospective study. Protocol was approved by the University of Alberta Health Research Ethics Board (Pro00050143). A sample of thirty pre-existing initial orthodontic records from the University of Alberta Multi-disciplinary Upper Airway Research Clinic was used to establish the data set to be reviewed by orthodontists. Inclusion criteria for the records were:

1) Patients aged 6 to 16. This age range was chosen as it is in this age group that orthodontic intervention (orthopedic) may improve craniofacial abnormalities.

2) Symptoms of pediatric OSA confirmed by a specialist physician (pediatric respirologist, sleep medicine specialist, otolaryngologist).
3) Presence of three-dimensional facial imaging (3dMD, Atlanta, Ga).

At the time of record selection, the total patients seen in the University of Alberta Upper Airway Research Clinic was 169. Total patients with 3dMD imaging was 130. Records were screened to include only those patients who had physician confirmed diagnosis of sleep disordered breathing. Of the remaining 50 records, 5 were removed due to initial records showing that the patient had already started orthodontic treatment, 11 were removed due to poor quality or missing records, and 1 was removed for not having any records. Of the remaining 33 patient records, 30 were selected. All identifying features were removed and patients were coded by number. The mean age of patients in our data set was 11.7 years +/- 2.5 years. A complete set of records for each patient included three-dimensional facial imaging, extraoral and intraoral photos, panorex, and cephalogram. Coded records and Vultus Viewer (3dMD) software were placed on a password protected CD.

Ten practicing orthodontists in North America with expert knowledge in pediatric OSA were sought. Expert knowledge was considered as research in the area or further education/training in OSA and its relevance to orthodontic practice. Orthodontists were contacted by

email with an invitation to participate in our study (Appendix B). Orthodontists who responded with interest to participate were mailed a package consisting of a consent form, pre-addressed and stamped envelope to return signed consent, password protected CD including orthodontic records and Vultus Viewer (3dMD) software, and instruction sheet. The instruction sheet (Appendix C) outlined use of Vultus Viewer (3dMD) software and the data collection form. Orthodontists were sent a separate email containing the password for the CD and online link for the data collection form. Participant orthodontists were asked to review the entire set of orthodontic records and make a dichotomous yes or no decision on whether orthodontic treatment was recommended to improve symptoms of OSA. It was emphasized that their yes or no decision should be based on potential improvement in OSA symptoms rather than other reasons for orthodontic treatment (ex. crowding, esthetics). There was no time limit to review the records. Along with the complete set of records, orthodontists were provided with the age and gender of the patient. No information was provided on chief complaint, severity of OSA symptoms, or previous/current orthodontic treatment. The majority consensus treatment decision of orthodontists represented the gold standard treatment decision. Majority was considered greater than 6 out of 10 orthodontists making a particular treatment decision. Our team of expert orthodontists consisted of 6 orthodontists from Alberta, 1 from British Columbia, 1 from Ontario, 1 from Quebec, and 1 from California.

The principal investigator reviewed the same set of orthodontic records and applied the APOSA index for each patient. The sum score on the APOSA index was calculated for each patient. The level of significance (p-value) was set at 0.05.

## 3.4 Statistical Analysis

SPSS for Mac (Version 21) and SAS University Edition were used for all statistical analyses. The orthodontists' treatment decision (ex. Yes or No) was related to the scores on the APOSA index using regression analysis. Binary logistic regression was used to evaluate the predictive ability of the APOSA index. Cut-off score, sensitivity, and specificity of the APOSA index was analyzed using Receiver Operating Characteristic (ROC) curves. The ROC curve of the sum score on the APOSA index allows visual determination of optimal cutoff scores that maximize correct treatment decisions. The ROC curve represents a plot of sensitivity on the y-axis versus 1-specificity (false positives) on the x-axis. Sensitivity is the true positives while specificity is the true negatives. In any diagnostic test, we aim to maximize both sensitivity and specificity. The optimum cutoff score for a test is generally a trade-off between sensitivity and specificity. The ROC curve facilitates the determination of a cutoff as it illustrates a plot for the trade-offs that occur at each cutoff score. The optimum cutoff score for a test has the highest sensitivity and specificity and is found on the ROC curve by locating the highest point on the vertical axis (true positives) and the lowest point on the horizontal axis (false positives).

## 3.5 Results

Participant orthodontists and the principal investigator reviewed thirty initial orthodontic records of pediatric patients with OSA symptoms. Of the thirty patients in our sample, twenty-six had a positive history for snoring. Majority consensus decision of orthodontists determined that 17 patients would benefit from orthodontic treatment to improve symptoms of OSA, while 13 patients would not benefit from orthodontic treatment.

Logistic regression analysis was used to determine the predictive ability of the APOSA index for determining whether orthodontic treatment was indicated to manage OSA symptoms. The logistic regression model was statistically significant, using the eight items of the APOSA index as predictors. This means that the eight items as a set distinguished between patients who would benefit from orthodontic treatment for their OSA symptoms from those who would not (chi-square = 41.054, $p<0.001$ with df=8). The model explained 100% of the variance in treatment need (Nagelkerke's $R^{2 = 1.00}$) and correctly classified 100% of cases (Tables 3-1 – Table 3-3). Individually, the 8 craniofacial and oral features were not significant in the model (Table 3-4). This is likely due to high intercorrelations that were found among predictor variables (Table 3-5).

In order to determine the cutoff score required to refer a patient to an orthodontist, an ROC curve was plotted with the total score taken across the eight items of the APOSA index. The area under the curve

(AUC) and 95% confidence interval was calculated. The AUC was 0.998 (95% CI = 0.988, 1), indicating near perfect discriminatory ability for orthodontic treatment need (Table 3-6).

Overall, the combination of eight craniofacial and oral features of the APOSA index predict with near perfect ability, the gold standard treatment decision of the orthodontists. The optimum score on the APOSA index to refer a patient to an orthodontist is 6.5 (sensitivity: 94.1%, specificity: 99%). The optimum cutoff was determined by locating the point on the ROC curve that maximized sensitivity and specificity (Table 3-7). This point is generally found on the upper left corner of the ROC curve. Any increase in sensitivity or specificity by changing the cutoff score will result in a decrease in the other factor (Figure 3-1).

The high correlations (ex. Correlations of 0.8 or higher) observed in the regression analysis indicate that the craniofacial and oral features being evaluated with the APOSA index have statistical redundancy. Statistical redundancy in this context refers to the fact that our analysis indicates that we are measuring the same feature multiple times. From an orthodontic perspective, this provides evidence that patients with OSA symptoms often have numerous craniofacial and oral characteristics. This multicollinearity suggests that the index may be modified in the future by removing items that are highly correlated. From a non-dental clinical perspective, the APOSA index would be further simplified and promote time efficiency if it were reduced to only extraoral features (i.e., profile,

midface deficiency, lower face height, and lip strain). Logistic regression analysis and ROC curve was completed using extraoral features for comparison.

The logistic regression model was statistically significant, indicating that the extraoral features of the APOSA index distinguished between patients who would benefit from orthodontic treatment for their OSA symptoms from those who would not (chi-square = 26.205, $p<0.001$ with df=4). The model explained 78.1% (Nagelkerke's $R^2$) of the variance in treatment need and correctly classified 93.3% of cases (Table 3-8 - Table 3-10). Individually, the 4 extraoral features were not significant (Table 3-11). This is likely due to high intercorrelations that were found among predictor variables (Table 3-12).

To determine the cutoff score required for referral when only extraoral features of the APOSA index are considered, an ROC curve was plotted with the sum of the item scores obtained from the extraoral variables. The AUC and 95% confidence interval was calculated. The AUC was 0.941 (95% CI = 0.828, 1), indicating near perfect discriminatory ability for orthodontic treatment need (Table 3-13). The optimum cutoff score is 2.5 (sensitivity: 94.1%, specificity: 92.3%). The optimum cutoff was determined by locating the point on the ROC curve that maximized sensitivity and specificity (Table 3-14). Compared to administration of the complete APOSA index, specificity was decreased while sensitivity remained the same. This decrease is expected when moving from an 8-

item to 4-item index. The decreased specificity of the 4-item index is unlikely to have any clinical significance as a false positive would result in an orthodontic referral that may not help manage sleep apnea, however, may be beneficial for other reasons (ex. Ectopic eruption, functional shift, etc). From a clinical perspective, a modified APOSA index with fewer items would save time in administration, however is associated with a decreased specificity.

The decision to repeat logistic regression analysis and ROC curves with extraoral features was based on the finding that all eight craniofacial and oral features are highly interrelated. Currently, no evidence exists on which craniofacial and oral features are more important than others in pediatric OSA. Thus, our decision to evaluate extraoral features was based on analysis of statistical results and ease of administration of the APOSA index by end-users. Ideally, if the APOSA index is to be modified in the future, the decision of which craniofacial and oral features to be removed must be guided by theory or empirical evidence supported by studies with larger sample sizes.

The data was further analyzed using only those patients who scored eight or above on the Pediatric Sleep Questionnaire (PSQ). This was done in order to examine only those patients who require additional medical assessment for OSA. From the initial sample of thirty patient records, thirteen records were removed and seventeen patients were further analyzed. Of the thirteen records removed, six patients had a PSQ

score less than eight and seven did not have a PSQ score reported. Logistic regression and ROC analysis could not be replicated with this data set due to complete and quasi-complete separation of the outcome variable (treatment or no treatment) by 2 predictor variables. In binary logistic regression, separation occurs when a predictor variable can perfectly predict the outcome variable, therefore removing the need for other predictors in the model. Separation and quasi-separation are more likely in smaller data sets where variance of the sample on a variable of interest is reduced, in situations where predictor variables are highly related to the outcome variable and when the event is rare. From this analysis, it was determined that lip strain is a perfect predictor of treatment need while midface deficiency is an almost-perfect predictor of treatment need. Thus, with perfect and near-perfect prediction of lip strain and midface deficiency for treatment need, a model of fit using other predictors was not necessary. In this analysis, we evaluated extremes of our already specific sample. The population of pediatric patients with symptoms of OSA is limited, and by evaluating patients scoring 8 or greater on PSQ, we further restricted our sample to those patients requiring further medical assessment for possible OSA. This restriction of range resulted in decreased variability in lip strain and midface deficiency. Overall, the effect or association between variables was masked. Separation may be overcome by increasing the sample size, thereby increasing the variability within the sample. Another option may be to combine categories of

predictors that are related. For example, when the transverse dimension is being evaluated in the model and “crossbite” has no event because of a small number of trials, it may make sense to combine “crossbite” and “palate” into a category called transverse.

Overall, the eight craniofacial and oral features of the APOSA index as a set have excellent ability to predict need for orthodontic treatment. The relative importance or contribution of each feature cannot be determined reliably due to the fact that the features, particularly intraoral, are highly correlated. The predictive ability of the model was better when all eight craniofacial and oral features were evaluated compared to only extraoral features as predictors.

## 3.6 Discussion

The APOSA index has been developed to identify pediatric patients with OSA symptoms that may benefit from orthodontic treatment as part of their management protocol. This study aimed to produce criterion validity evidence, specifically the predictive ability of the APOSA index, and subsequently determine the optimum cutoff score required for referral to an orthodontist. The results of our study demonstrate that a score of 6.5 or greater on the APOSA index indicates the patient would benefit from a referral to an orthodontist. The optimum cutoff score was determined by locating the point on the ROC curve that maximized sensitivity and specificity. At a cutoff score of 6.5, the APOSA index has a sensitivity of

94.1% and specificity of 99%. These findings indicate that the APOSA index is a useful tool, which demonstrates near perfect discriminatory ability in identifying patients that may benefit from orthodontic treatment as part of their OSA management protocol.

While adenotonsillectomy remains the most common treatment approach, it is important to consider the multidisciplinary nature of pediatric OSA. The craniofacial and oral correlates of pediatric OSA draw attention to various orthodontic treatment modalities that may help improve quality of life and symptoms of OSA. Appropriate case selection and timing of orthodontic treatment is critical. It is important to be able to recognize the craniofacial and oral characteristics associated with OSA and make a timely referral to an orthodontist, when indicated. While two hypotheses can explain the relationship between obstructive sleep apnea and craniofacial growth, the exact etiology of the abnormal craniofacial growth does not influence whether the patient should be treated. Instead, the presenting craniofacial abnormality, particularly maxillary constriction and mandibular retrognathism, should be treated early.

Traditionally, medical and dental teams have worked independently with little communication. It is important to acknowledge the multifactorial nature of pediatric OSA and develop ways of improving communication and collaboration amongst colleagues. The APOSA index aims to be part of this process by summarizing craniofacial and oral features that identify

patients who may benefit from orthodontic treatment for their OSA symptoms.

Ultimately, orthodontic treatment will benefit a small cohort of patients who demonstrate moderate to severe craniofacial and oral anomalies. Orthodontic treatment modalities that have been suggested as part of OSA management have a limited window of potential in growing individuals. It must be acknowledged that any orthodontic treatment rendered will not resolve pediatric OSA, however, it can be a useful adjunct to traditional treatment approaches. Orthodontic treatment aimed at improving craniofacial anomalies associated with obstructive sleep apnea has minimal risk compared to the potential advantages of growth modification or maxillary transverse development. Further, burden of treatment associated with orthodontic treatment is minimal in comparison to that of other treatment approaches, including adenotonsillectomy and CPAP. Burden of treatment associated with orthodontic treatment is primarily time and cost, whereas other treatment approaches involve surgical risks or long-term dependence on an appliance.

While the APOSA index was determined to have near perfect discriminatory ability of orthodontic treatment need, there are limitations in our study. Sample size in our study was limited due to the number of appropriate patients in our patient pool satisfying inclusion criteria. Since the objective of the APOSA index is to identify patients with OSA symptoms who may benefit from orthodontic treatment, all included

patients were required to have symptoms of OSA diagnosed by a specialist physician. Further, since the gold standard treatment decision made by orthodontists was based on records alone, rather than clinical evaluation, it was necessary to use records of excellent diagnostic quality. To improve assessment of craniofacial form and features, 3dMD images were required for all patients. Given that the prevalence of pediatric OSA is between 1-4%, all of the above factors limited our sample size. Further, our patient pool was limited to those presenting for initial assessment at the University of Alberta Upper Airway Research Clinic. The fact that these patients had already been referred for orthodontic assessment suggests that our patients may represent those demonstrating extreme variations of craniofacial anomalies. In a future study, patients can be recruited from a pediatric sleep clinic, thus obtaining a patient pool demonstrating a wider range of craniofacial characteristics.

In our sample of patients, the APOSA index demonstrated near perfect discriminatory ability and an optimum cutoff score of 6.5. In a similar sample of patients, a summed score of 6.5 or greater on the APOSA index indicates that the patient would benefit from orthodontic assessment. Thus, while the APOSA index is predictive of treatment need, we cannot conclude that it is valid across all settings. Further studies can prospectively follow patients scoring 6.5 or greater on the APOSA index and determine whether orthodontic treatment impacted signs or symptoms of pediatric OSA.

From our set of thirty patient records, orthodontists identified that seventeen patients would benefit from orthodontic treatment for their OSA symptoms, while thirteen would not. Given that orthodontic treatment does not resolve OSA and that most studies evaluating the effect of orthodontic appliances for OSA are short in duration, it is surprising that experts recommended treatment for the majority of patients. Although expert orthodontists were asked to make treatment decisions solely on perceived improvement in OSA symptoms, the tendency for treatment may have been influenced by other factors of malocclusion (crowding, ectopic teeth, esthetics, etc).

While most of our discussion has focused on referral to an orthodontist, it is important for dentists and orthodontists to be aware of common symptoms of OSA such that appropriate medical referral can be made when indicated. Detailed medical history and patient evaluation can gather information on snoring, daytime fatigue, and attention deficit (14). Risk factors including asthma (15), obesity (16), chronic sinusitis (17), and pre-term birth (18) should also be evaluated. Administration of the Pediatric Sleep Questionnaire (PSQ) is a helpful screening tool to identify patients who may benefit from further medical investigation (19).

Overall, the APOSA index is a useful and predictive tool to determine orthodontic treatment need in pediatric patients with OSA symptoms. The APOSA index is valid for identifying pediatric patients with

OSA symptoms who would benefit from orthodontic treatment at a cutoff score of 6.5.

A future study may use the recommended cutoff score on a sample of patients and prospectively examine whether orthodontic treatment improved symptoms of pediatric OSA.

## 3.7 Conclusion

The APOSA index is a predictive tool to determine orthodontic treatment need in pediatric patients with OSA symptoms. A summed score of 6.5 or greater on the index indicates that orthodontic referral and treatment may be a beneficial adjunct for management of pediatric OSA. Application of the APOSA index and its cutoff score appropriately predicts and substitutes for the consensus decision of orthodontic experts in North America. Overall, the APOSA index is a simple and easy to use tool to help identify those patients who may benefit from orthodontic treatment for their OSA symptoms.

## 3.8 Figures

Figure 3-1: Receiver operating characteristic (ROC) curve for Sum of APOSA Index

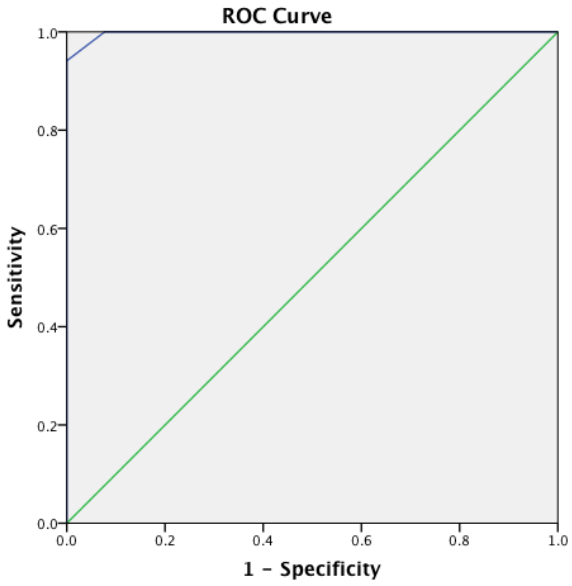
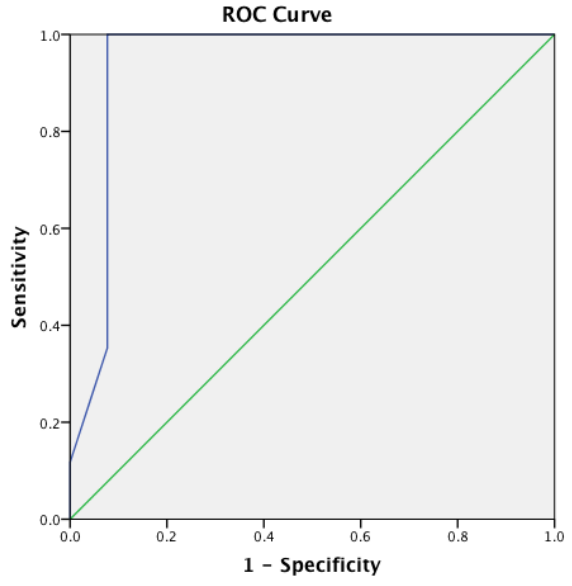



Figure 3-2: Receiver operating characteristic (ROC) curve for Sum of Extraoral Features of APOSA Index



## 3.9 Tables

Table 3-1: Logistic Regression - Test of Model Coefficients

| | Chi-Square | Degrees of Freedom | p-value |
|---|---|---|---|
| Model | 41.054 | 8 | .000 |

Table 3-2: Logistic Regression - Model Summary

| | Nagelkerke $R^2$ |
|---|---|
| Model | 1 |

Table 3-3: Logistic Regression - Prediction

| **Observed** | | **Predicted** | | |
|---|---|---|---|---|
| | | Rating | | Percentage Correct |
| | | 0 | 1 | |
| Rating | 0 | 13 | 0 | 100 |
| | 1 | 0 | 17 | 100 |
| Overall Percentage | | | | 100 |

Cut value 0.5

Table 3-4: Logistic Regression - Variables in the Equation

| | B | S.E | **Sig** | Exp (B) | 95 % Confidence Interval for Exp (B) | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| Profile | 3.8 | 9928.2 | 1.0 | 45.2 | 0 | - |
| Midface | 1.0 | 14248.1 | 1.0 | 2.8 | 0 | - |
| Lower Face Height | 13.3 | 41168.0 | 1.0 | 583677.9 | 0 | - |
| Lip Strain | 7.8 | 15971.1 | 1.0 | 2386.2 | 0 | - |
| Palate | 24.7 | 22820.4 | 1.0 | 53810196547.2 | 0 | - |
| Overjet | 21.5 | 27171.7 | 1.0 | 2274516960.0 | 0 | - |
| Overbite | 1.7 | 57112.2 | 1.0 | 5.9 | 0 | - |
| Crossbite | 2.4 | 17738.1 | 1.0 | 11.9 | 0 | - |
| Constant | -61.3 | 54479.8 | 1.0 | .0 | | |

Table 3-5: Correlation Matrix

| | Constant | Profile | Midface | LFH | Lip Strain | Palate | Overjet | Overbite | Crossbite |
|---|---|---|---|---|---|---|---|---|---|
| Constant | 1.0 | .6 | .05 | -.9 | .7 | .8 | -.9 | .9 | -.9 |
| Profile | .6 | 1.0 | -.2 | -.6 | .2 | .7 | -.6 | .7 | -.7 |
| Midface | .05 | -.2 | 1.0 | -.1 | .2 | -.05 | -.0 | -.1 | .0 |
| Lower Face Height | -.9 | -.6 | -.1 | 1.0 | -.8 | -.9 | .9 | -.9 | .8 |
| Lip Strain | .7 | .2 | .2 | -.8 | 1.0 | .7 | -.8 | .7 | -.6 |
| Palate | .8 | .7 | -.0 | -.9 | .7 | 1.0 | -.8 | .9 | -.9 |
| Overjet | -.9 | -.6 | -.0 | .9 | -.8 | -.8 | 1.0 | -.9 | .9 |
| Overbite | .9 | .7 | -.1 | -.9 | .7 | .9 | -.9 | 1.0 | -.9 |
| Crossbite | -.9 | -.7 | .0 | .8 | -.6 | -.9 | .9 | -.9 | 1.0 |

Table 3-6: ROC Curve - Area Under the Curve (AUC) for Sum of APOSA Index

| Variables | Area | Standard Error | p-value | 95% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound |
| Sum | 0.998 | 0.005 | <0.001 | 0.988 | 1.0 |

Table 3-7: ROC Curve (Sum of APOSA Index) - Determining a Cut Off Score for Optimized Sensitivity and Specificity

Coordinates of the ROC Curve

| Positive if Greater Than or Equal To | Sensitivity | 1 - Specificity |
|---|---|---|
| -1.00 | 1.000 | 1.000 |
| .50 | 1.000 | .692 |
| 1.50 | 1.000 | .462 |
| 2.50 | 1.000 | .231 |
| 3.50 | 1.000 | .154 |
| 5.00 | 1.000 | .077 |
| 6.50 | .941 | .000 |
| 7.50 | .706 | .000 |
| 8.50 | .588 | .000 |
| 9.50 | .471 | .000 |
| 10.50 | .353 | .000 |
| 11.50 | .235 | .000 |
| 13.00 | .118 | .000 |
| 14.50 | .059 | .000 |
| 16.00 | .000 | .000 |

Table 3-8: Logistic Regression - Test of Model Coefficients with Extraoral Features Only

| | Chi-Square | Degrees of Freedom | p-value |
|---|---|---|---|
| Model | 26.205 | 4 | .000 |

Table 3-9: Logistic Regression - Model Summary with Extraoral Features Only

| | Nagelkerke $R^2$ |
|---|---|
| Model | .781 |

Table 3-10: Logistic Regression - Prediction with Extraoral Features Only

| **Observed** | | **Predicted** | | |
|---|---|---|---|---|
| | | **Rating** | | **Percentage Correct** |
| | | 0 | 1 | |
| Rating | 0 | 12 | 1 | 92.3 |
| | 1 | 1 | 16 | 94.1 |
| Overall Percentage | | | | 93.3 |

Cut value 0.5

Table 3-11: Logistic Regression - Variables in the Equation with Extraoral Features Only

| | B | S.E | **Sig** | Exp (B) | 95 % Confidence Interval for Exp (B) | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| Profile | 1.3 | 0.9 | 0.16 | 3.7 | 0.5 | 24.6 |
| Midface | 3.1 | 1.7 | 0.07 | 23.1 | 0.7 | 702 |
| Lower Face Height | 0.0 | 1.1 | 0.95 | 1.0 | 0.1 | 10.0 |
| Lip Strain | 0.9 | 1.0 | 0.35 | 2.6 | 0.3 | 20.4 |
| Constant | -2.6 | 1.2 | 0.0 | 0.06 | | |

Table 3-12: Correlation Matrix with Extraoral Features Only

| | Constant | Profile | Midface Deficiency | LFH | Lip Strain |
|---|---|---|---|---|---|
| Constant | 1.0 | -.3 | -.09 | -.4 | .02 |
| Profile | -.3 | 1.0 | .2 | -.0 | -.5 |
| Midface Deficiency | -.09 | .2 | 1.0 | -.6 | .1 |
| Lower Face Height | -.4 | -.02 | -.6 | 1.0 | -.3 |
| Lip Strain | .02 | -.5 | .1 | -.3 | 1.0 |

Table 3-13: ROC Curve - Area Under the Curve (AUC) for Sum of Extraoral Features on APOSA Index

| Area | Standard Error | Asymptotic Sig. | Asymptotic 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| .941 | .058 | .000 | .828 | 1.000 |

Table 3-14: ROC Curve (Extraoral Sum of APOSA Index) - Determining a Cut Off Score for Optimized Sensitivity and Specificity with Extraoral Features Only

| Positive if Greater Than or Equal To | Sensitivity | 1 - Specificity |
|---|---|---|
| -1.00 | 1.000 | 1.000 |
| .50 | 1.000 | .615 |
| 1.50 | 1.000 | .077 |
| 2.50 | .941 | .077 |
| 3.50 | .765 | .077 |
| 4.50 | .588 | .077 |
| 5.50 | .353 | .077 |
| 6.50 | .118 | .000 |
| 7.50 | .059 | .000 |
| 9.00 | .000 | .000 |

## 3.10 References

(1) Altalibi M, Saltaji H, Roduta Roberts M, Major MP, MacLean J, Major PW. Developing an index for the orthodontic treatment need in paediatric patients with obstructive sleep apnoea: a protocol for a novel communication tool between physicians and orthodontists. BMJ Open 2014 Sep 18;4(9):e005680-2014-005680.

(2) Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc 2008 Feb 15;5(2):242-252.

(3) Bixler EO, Vgontzas AN, Lin HM, Liao D, Calhoun S, Vela-Bueno A, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. Sleep 2009 Jun;32(6):731-736.

(4) Schwengel DA, Dalesio NM, Stierer TL. Pediatric obstructive sleep apnea. Anesthesiol Clin 2014 Mar;32(1):237-261.

(5) Marcus CL. Pathophysiology of childhood obstructive sleep apnea: current concepts. Respir Physiol 2000 Feb;119(2-3):143-154.

(6) Tauman R, Gulliver TE, Krishna J, Montgomery-Downs HE, O'Brien LM, Ivanenko A, et al. Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. J Pediatr 2006 Dec;149(6):803-808.

(7) Brietzke SE, Gallagher D. The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: a meta-analysis. Otolaryngol Head Neck Surg 2006 Jun;134(6):979-984.

(8) Friedman M, Wilson M, Lin HC, Chang HW. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. Otolaryngol Head Neck Surg 2009 Jun;140(6):800-808.

(9) Huynh NT, Morton PD, Rompre PH, Papadakis A, Remise C. Associations between sleep-disordered breathing symptoms and facial and dental morphometry, assessed with screening examinations. Am J Orthod Dentofacial Orthop 2011 Dec;140(6):762-770.

(10) Pirelli P, Saponara M, Guilleminault C. Rapid maxillary expansion in children with obstructive sleep apnea syndrome. Sleep 2004 Jun 15;27(4):761-766.

(11) Nazarali N, Altalibi M, Nazarali S, Major MP, Flores-Mir C, Major PW. Mandibular advancement appliances for the treatment of paediatric obstructive sleep apnea: a systematic review. Eur J Orthod 2015 Feb 12.

(12) Hiyama S, Suda N, Ishii-Suzuki M, Tsuiki S, Ogawa M, Suzuki S, et al. Effects of maxillary protraction on craniofacial structures and upper-airway dimension. Angle Orthod 2002 Feb;72(1):43-47.

(13) World Health Organization. WHO Handbook for guideline development. : World Health Organization; 2014.

(14) Schwengel DA, Dalesio NM, Stierer TL. Pediatric obstructive sleep apnea. Anesthesiol Clin 2014 Mar;32(1):237-261.

(15) Kaditis AG, Kalampouka E, Hatzinikolaou S, Lianou L, Papaefthimiou M, Gartagani-Panagiotopoulou P, et al. Associations of tonsillar hypertrophy and snoring with history of wheezing in childhood. Pediatr Pulmonol 2010 Mar;45(3):275-280.

(16) O'Brien LM, Sitha S, Baur LA, Waters KA. Obesity increases the risk for persisting obstructive sleep apnea after treatment in children. Int J Pediatr Otorhinolaryngol 2006 Sep;70(9):1555-1560.

(17) Bixler EO, Vgontzas AN, Lin HM, Liao D, Calhoun S, Vela-Bueno A, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. Sleep 2009 Jun;32(6):731-736.

(18) Rosen CL, Larkin EK, Kirchner HL, Emancipator JL, Bivins SF, Surovec SA, et al. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. J Pediatr 2003 Apr;142(4):383-389.

(19) Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. Sleep Med 2000 Feb 1;1(1):21-32.

# Chapter 4: General Discussion

## 4.1 Evaluation of Research Hypothesis

The primary objective of this study was to determine the ability of the APOSA index to predict orthodontic treatment need. Our research hypothesis was that the APOSA index accurately predicts need for orthodontic treatment in pediatric patients with OSA symptoms. In addition to determining predictive ability, we aimed to provide relevance and interpretation to the scoring of the index.

Our study demonstrated that the APOSA index is an excellent predictor of orthodontic treatment need. That is, application of the APOSA index is an appropriate substitution for the gold standard treatment decision made by expert orthodontists in North America. A sum score of 6.5 or greater on the APOSA index suggests that the patient may benefit from referral to an orthodontist. The sensitivity of the APOSA index is 94.1% and specificity is 99%.

## 4.2 Clinical Significance and Implications

The multifactorial nature of pediatric OSA draws attention to the need for improved multidisciplinary collaboration and management of pediatric OSA patients. Routine orthodontic examinations should involve a thorough medical history and identification of common signs and symptoms of pediatric OSA. These include snoring, daytime fatigue, and attention deficit (1). The Pediatric Sleep Questionnaire (PSQ) can be

administered to those patients demonstrating risk for pediatric OSA (2). A score of 8 or greater on the PSQ indicates further medical investigation.

Similarly, it is important for physicians to evaluate craniofacial form and oral characteristics that may contribute to pediatric OSA. The APOSA Index developed at the University of Alberta aims to engage medical and dental professionals to enhance communication and collaborative management of patients (3).

The APOSA index was developed using craniofacial and oral features characteristic of pediatric OSA. These include: profile, midface deficiency, lower face height, lip strain to close, palate, overjet, overbite, and posterior crossbites. Logistic regression analysis found that while the APOSA index is predictive in determining need for orthodontic treatment, the craniofacial and oral features are highly related. As a result, there is redundancy within the index and evidence that the APOSA index may be modified in the future to remove some factors.

Currently, no evidence exists on which craniofacial and oral features are more important than others in predicting treatment need. The decision to substitute or remove index items should be based on empirical evidence supported by studies with larger sample sizes.

Since the correlations of predictor variables were especially high for intraoral variables, logistic regression analysis and ROC curve was plotted using only extraoral features. The modified index was also predictive in

determining need for orthodontic treatment. At a cutoff score of 2.5, the sensitivity was 94.1% and specificity was 92.3%. Compared to administration of the 8-item APOSA index, specificity was lower while sensitivity remained the same. The decreased specificity is unlikely to have any clinical significance. In the event of a false positive, an orthodontic assessment, while not beneficial for OSA management, may identify dental characteristics requiring treatment (i.e. ectopic teeth, functional shift).

From a physician's perspective, a modified 4-item index may be preferred due to ease and time efficiency in administration. From an orthodontic perspective, the 4-item index eliminates critical components of an examination. For example, the inclusion of palatal width is critical as transverse maxillary deficiency can be managed orthopedically when a patient is young and sutures can be manipulated. Timely referral to an orthodontist, regardless of improvement in OSA symptoms, can improve skeletal disharmonies and decrease future burden of treatment. A missed opportunity to correct transverse maxillary deficiency in childhood and adolescence may require a surgical approach if it is to be corrected in adulthood. A modified 4-item index evaluating only extraoral features would not consider transverse discrepancies and thus, may result in missed opportunities for treatment.

The 8-item APOSA index was found to have fair to substantial inter-rater reliability and moderate to almost perfect intra-rater reliability. In

addition, ROC curve analysis demonstrated excellent predictive ability in determining need for orthodontic treatment.

## 4.3 Recommendations for Future Research

Future research should continue to examine the role of craniofacial and oral features in relation to pediatric OSA. An improved understanding of the relationships and relative contributions of each predictor would provide strong evidence to modify the APOSA index. A modified APOSA index based on these relationships would save time in administration of the APOSA index while ensuring that all relevant predictors have been evaluated.

A future study may also apply the cutoff score of 6.5 on a sample of patients and prospectively determine whether orthodontic treatment improved symptoms of pediatric OSA. This would allow us to evaluate the effectiveness of our cutoff score in clinical practice as well as examine the relationship between treatment need and treatment response.

Based on the above recommendations, it is possible that the APOSA index may be modified over time to achieve the best balance between relevant predictor variables and ease of administration of the index.

## 4.4 Conclusion

The APOSA index has been designed to improve communication and collaboration among medical and dental colleagues in treating pediatric patients with OSA symptoms. The APOSA index is valid in identifying pediatric patients who may benefit from orthodontic treatment at a cutoff score of 6.5. Our study found that application of the APOSA index is an appropriate substitute for the gold standard treatment decision made by orthodontists. Case selection for orthodontic treatment in pediatric OSA is critical. Orthodontic treatment, if initiated during a patient's growth spurt, has the potential to improve one of the etiologic factors of OSA, while improving the pattern of growth. Thus improvement is across two domains: improvement of sleep parameters, as well as improved dento-facial appearance. Further, timely referral to an orthodontist ensures that treatment begins at an appropriate stage of development to prevent malocclusion and altered growth.

## 4.5 References

(1) Schwengel DA, Dalesio NM, Stierer TL. Pediatric obstructive sleep apnea. Anesthesiol Clin 2014 Mar;32(1):237-261.

(2) Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. Sleep Med 2000 Feb 1;1(1):21-32.

(3) Altalibi M, Saltaji H, Roduta Roberts M, Major MP, MacLean J, Major PW. Developing an index for the orthodontic treatment need in paediatric patients with obstructive sleep apnoea: a protocol for a novel communication tool between physicians and orthodontists. BMJ Open 2014 Sep 18;4(9):e005680-2014-005680.

## References


(1) Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc 2008 Feb 15;5(2):242-252.

(2) Bixler EO, Vgontzas AN, Lin HM, Liao D, Calhoun S, Vela-Bueno A, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. Sleep 2009 Jun;32(6):731-736.

(3) Schwengel DA, Dalesio NM, Stierer TL. Pediatric obstructive sleep apnea. Anesthesiol Clin 2014 Mar;32(1):237-261.

(4) Marcus CL. Pathophysiology of childhood obstructive sleep apnea: current concepts. Respir Physiol 2000 Feb;119(2-3):143-154.

(5) Kaditis AG, Kalampouka E, Hatzinikolaou S, Lianou L, Papaefthimiou M, Gartagani-Panagiotopoulou P, et al. Associations of tonsillar hypertrophy and snoring with history of wheezing in childhood. Pediatr Pulmonol 2010 Mar;45(3):275-280.

(6) O'Brien LM, Sitha S, Baur LA, Waters KA. Obesity increases the risk for persisting obstructive sleep apnea after treatment in children. Int J Pediatr Otorhinolaryngol 2006 Sep;70(9):1555-1560.

(7) Rosen CL, Larkin EK, Kirchner HL, Emancipator JL, Bivins SF, Surovec SA, et al. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. J Pediatr 2003 Apr;142(4):383-389.

(8) Huynh NT, Morton PD, Rompre PH, Papadakis A, Remise C. Associations between sleep-disordered breathing symptoms and facial and dental morphometry, assessed with screening examinations. Am J Orthod Dentofacial Orthop 2011 Dec;140(6):762-770.

(9) Katz SL, Witmans M, Barrowman N, Hoey L, Su S, Reddy D, et al. Paediatric sleep resources in Canada: The scope of the problem. Paediatr Child Health 2014 Aug;19(7):367-372.

(10) Brietzke SE, Katz ES, Roberson DW. Can history and physical examination reliably diagnose pediatric obstructive sleep apnea/hypopnea syndrome? A systematic review of the literature. Otolaryngol Head Neck Surg 2004 Dec;131(6):827-832.

(11) Roland PS, Rosenfeld RM, Brooks LJ, Friedman NR, Jones J, Kim TW, et al. Clinical practice guideline: Polysomnography for sleep-disordered breathing prior to tonsillectomy in children. Otolaryngol Head Neck Surg 2011 Jul;145(1 Suppl):S1-15.

(12) Beck SE, Marcus CL. Pediatric Polysomnography. Sleep Med Clin 2009 Sep;4(3):393-406.

(13) Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. Sleep Med 2000 Feb 1;1(1):21-32.

(14) Linder-Aronson S. Adenoids. Their effect on mode of breathing and nasal airflow and their relationship to characteristics of the facial skeleton and the denition. A biometric, rhino-manometric and cephalometro-radiographic study on children with and without adenoids. Acta Otolaryngol Suppl 1970;265:1-132.
Miles PG, Vig PS, Weyant RJ, Forrest TD, Rockette HE,Jr. Craniofacial structure and obstructive sleep apnea syndrome--a qualitative analysis and meta-analysis of the literature. Am J Orthod Dentofacial Orthop 1996 Feb;109(2):163-172.

(15) Vig KW. Nasal obstruction and facial growth: the strength of evidence for clinical assumptions. Am J Orthod Dentofacial Orthop 1998 Jun;113(6):603-611.

(16) Katyal V, Pamula Y, Martin AJ, Daynes CN, Kennedy JD, Sampson WJ. Craniofacial and upper airway morphology in pediatric sleep-disordered breathing: Systematic review and meta-analysis. Am J Orthod Dentofacial Orthop 2013 Jan;143(1):20-30.e3.

(17) Flores-Mir C, Korayem M, Heo G, Witmans M, Major MP, Major PW. Craniofacial morphological characteristics in children with obstructive sleep apnea syndrome: a systematic review and meta-analysis. J Am Dent Assoc 2013 Mar;144(3):269-277.

(18) Bar A, Tarasiuk A, Segev Y, Phillip M, Tal A. The effect of adenotonsillectomy on serum insulin-like growth factor-I and growth in children with obstructive sleep apnea syndrome. J Pediatr 1999 Jul;135(1):76-80.

(19) Chervin RD, Archbold KH, Dillon JE, Panahi P, Pituch KJ, Dahl RE, et al. Inattention, hyperactivity, and symptoms of sleep-disordered breathing. Pediatrics 2002 Mar;109(3):449-456.

(20) Marcus CL, Greene MG, Carroll JL. Blood pressure in children with obstructive sleep apnea. Am J Respir Crit Care Med 1998 Apr;157(4 Pt 1):1098-1103.

(21) Amin RS, Kimball TR, Bean JA, Jeffries JL, Willging JP, Cotton RT, et al. Left ventricular hypertrophy and abnormal ventricular geometry in children and adolescents with obstructive sleep apnea. Am J Respir Crit Care Med 2002 May 15;165(10):1395-1399.

(22) Marcus CL, Brooks LJ, Draper KA, Gozal D, Halbower AC, Jones J, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2012 Sep;130(3):576-584.

(23) Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, Mitchell RB, Promchiarak J, Simakajornboon N, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. Am J Respir Crit Care Med 2010 Sep 1;182(5):676-683.

(24) Brouillette RT, Manoukian JJ, Ducharme FM, Oudjhane K, Earle LG, Ladan S, et al. Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea. J Pediatr 2001 Jun;138(6):838-844.

(25) Li KK, Riley RW, Guilleminault C. An unreported risk in the use of home nasal continuous positive airway pressure and home nasal ventilation in children: mid-face hypoplasia. Chest 2000 Mar;117(3):916-918.

(26) Tauman R, Gulliver TE, Krishna J, Montgomery-Downs HE, O'Brien LM, Ivanenko A, et al. Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. J Pediatr 2006 Dec;149(6):803-808.

(27) Brietzke SE, Gallagher D. The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: a meta-analysis. Otolaryngol Head Neck Surg 2006 Jun;134(6):979-984.

(28) Friedman M, Wilson M, Lin HC, Chang HW. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. Otolaryngol Head Neck Surg 2009 Jun;140(6):800-808.

(29) Roland PS, Rosenfeld RM, Brooks LJ, Friedman NR, Jones J, Kim TW, et al. Clinical practice guideline: Polysomnography for sleep-

disordered breathing prior to tonsillectomy in children. Otolaryngol Head Neck Surg 2011 Jul;145(1 Suppl):S1-15.

(30) Pirelli P, Saponara M, Guilleminault C. Rapid maxillary expansion in children with obstructive sleep apnea syndrome. Sleep 2004 Jun 15;27(4):761-766.

(31) Nazarali N, Altalibi M, Nazarali S, Major MP, Flores-Mir C, Major PW. Mandibular advancement appliances for the treatment of paediatric obstructive sleep apnea: a systematic review. Eur J Orthod 2015 Feb 12.

(32) Hiyama S, Suda N, Ishii-Suzuki M, Tsuiki S, Ogawa M, Suzuki S, et al. Effects of maxillary protraction on craniofacial structures and upper-airway dimension. Angle Orthod 2002 Feb;72(1):43-47.

(33) Altalibi M, Saltaji H, Roduta Roberts M, Major MP, MacLean J, Major PW. Developing an index for the orthodontic treatment need in paediatric patients with obstructive sleep apnoea: a protocol for a novel communication tool between physicians and orthodontists. BMJ Open 2014 Sep 18;4(9):e005680-2014-005680.

(34) Shaw WC, Richmond S, O'Brien KD, Brook P, Stephens CD. Quality control in orthodontics: indices of treatment need and treatment standards. Br Dent J 1991 Feb 9;170(3):107-112.

(35) Summers CJ. The occlusal index: a system for identifying and scoring occlusal disorders. Am J Orthod 1971 Jun;59(6):552-567.

(36) Daniels C, Richmond S. The development of the index of complexity, outcome and need (ICON). J Orthod 2000 Jun;27(2):149-162.

(37) Streiner DL, Norman GR, Cairney J. Health measurement scales: a practical guide to their development and use. : Oxford university press; 2014.

(38) Guilford JP. Psychometric methods (2nd ed.). New York, NY, US: McGraw-Hill; 1954.

(39) Cronbach L. Test validation|| in Thorndike, RL (ed) Educational Measurement, Washington, DC: American Council on Education. 1971.

(40) Landy FJ. Stamp Collecting Versus Science: Validation as Hypothesis Testing. Am Psychol 1986 November;41(11):1183-1192.

(41) Guion RM. On Trinitarian doctrines of validity. Professional Psychology 1980;11(3):385.

(42) Messick S. Standards of validity and the validity of standards in performance asessment. Educational measurement: Issues and practice 1995;14(4):5-8.

(43) American educational Research Association, American Psychological Association, National Council on Measurement in Education. Standards for educational and psychological testing. : American Educational Research Association; 1999.

(44) Shepard LA. Evaluating test validity. Review of research in education 1993:405-450.

(45) Jenny J, Cons NC, Kohout FJ. Comparison of SASOC, a measure of dental aesthetics, with three orthodontic indices and orthodontist judgment. Community Dent Oral Epidemiol 1983;11(4):236-241.

(46) Salzmann J. Handicapping malocclusion assessment to establish treatment priority. Am J Orthod 1968;54(10):749-765.

(47) Carroll JL. Obstructive sleep-disordered breathing in children: new controversies, new directions. Clin Chest Med 2003 Jun;24(2):261-282.

(48) Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc 2008 Feb 15;5(2):242-252.

(49) Bixler EO, Vgontzas AN, Lin HM, Liao D, Calhoun S, Vela-Bueno A, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. Sleep 2009 Jun;32(6):731-736.

(50) Marcus CL. Pathophysiology of childhood obstructive sleep apnea: current concepts. Respir Physiol 2000 Feb;119(2-3):143-154.

(51) Huynh NT, Morton PD, Rompre PH, Papadakis A, Remise C. Associations between sleep-disordered breathing symptoms and

facial and dental morphometry, assessed with screening examinations. Am J Orthod Dentofacial Orthop 2011 Dec;140(6):762-770.

(52) Bar A, Tarasiuk A, Segev Y, Phillip M, Tal A. The effect of adenotonsillectomy on serum insulin-like growth factor-I and growth in children with obstructive sleep apnea syndrome. J Pediatr 1999 Jul;135(1):76-80.

(53) Chervin RD, Archbold KH, Dillon JE, Panahi P, Pituch KJ, Dahl RE, et al. Inattention, hyperactivity, and symptoms of sleep-disordered breathing. Pediatrics 2002 Mar;109(3):449-456.

(54) Marcus CL, Greene MG, Carroll JL. Blood pressure in children with obstructive sleep apnea. Am J Respir Crit Care Med 1998 Apr;157(4 Pt 1):1098-1103.

(55) Kaditis A, Kheirandish-Gozal L, Gozal D. Algorithm for the diagnosis and treatment of pediatric OSA: a proposal of two pediatric sleep centers. Sleep Med 2012 Mar;13(3):217-227.

(56) Tauman R, Gulliver TE, Krishna J, Montgomery-Downs HE, O'Brien LM, Ivanenko A, et al. Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. J Pediatr 2006 Dec;149(6):803-808.

(57) Brietzke SE, Gallagher D. The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: a meta-analysis. Otolaryngol Head Neck Surg 2006 Jun;134(6):979-984.

(58) Friedman M, Wilson M, Lin HC, Chang HW. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. Otolaryngol Head Neck Surg 2009 Jun;140(6):800-808.

(59) Pirelli P, Saponara M, Guilleminault C. Rapid maxillary expansion in children with obstructive sleep apnea syndrome. Sleep 2004 Jun 15;27(4):761-766.

(60) Villa MP, Bernkopf E, Pagani J, Broia V, Montesano M, Ronchetti R. Randomized controlled study of an oral jaw-positioning appliance for the treatment of obstructive sleep apnea in children with malocclusion. Am J Respir Crit Care Med 2002 Jan 1;165(1):123-127.

(61) Hiyama S, Suda N, Ishii-Suzuki M, Tsuiki S, Ogawa M, Suzuki S, et al. Effects of maxillary protraction on craniofacial structures and upper-airway dimension. Angle Orthod 2002 Feb;72(1):43-47.

(62) Chan AS, Sutherland K, Schwab RJ, Zeng B, Petocz P, Lee RW, et al. The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. Thorax 2010 Aug;65(8):726-732.

(63) Tsuiki S, Ono T, Kuroda T. Mandibular Advancement Modulates Respiratory-Related Genioglossus Electromyographic Activity. Sleep Breath 2000;4(2):53-58.

(64) Carvalho FR, Lentini-Oliveira D, Machado MA, Prado GF, Prado LB, Saconato H. Oral appliances and functional orthopaedic appliances for obstructive sleep apnoea in children. Cochrane Database Syst Rev 2007 Apr 18;(2)(2):CD005520.

(65) Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009 Oct;62(10):1006-1012.

(66) Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011 Oct 18;343:d5928.

(67) Cozza P, Polimeni A, Ballanti F. A modified monobloc for the treatment of obstructive sleep apnoea in paediatric patients. Eur J Orthod 2004 Oct;26(5):523-530.

(68) Schutz TC, Dominguez GC, Hallinan MP, Cunha TC, Tufik S. Class II correction improves nocturnal breathing in adolescents. Angle Orthod 2011 Mar;81(2):222-228.

(69) Zhang C, He H, Ngan P. Effects of twin block appliance on obstructive sleep apnea in children: a preliminary study. Sleep Breath 2013 Dec;17(4):1309-1314.

(70) Marklund M, Verbraecken J, Randerath W. Non-CPAP therapies in obstructive sleep apnoea: mandibular advancement device therapy. Eur Respir J 2012 May;39(5):1241-1247.

(71) Ahrens A, McGrath C, Hagg U. A systematic review of the efficacy of oral appliance design in the management of obstructive sleep apnoea. Eur J Orthod 2011 Jun;33(3):318-324.

(72) Phillips CL, Grunstein RR, Darendeliler MA, Mihailidou AS, Srinivasan VK, Yee BJ, et al. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med 2013 Apr 15;187(8):879-887.

(73) Sutherland K, Vanderveken OM, Tsuda H, Marklund M, Gagnadoux F, Kushida CA, et al. Oral appliance treatment for obstructive sleep apnea: an update. J Clin Sleep Med 2014 Feb 15;10(2):215-227.

(74) Guilleminault C, Huang YS, Glamann C, Li K, Chan A. Adenotonsillectomy and obstructive sleep apnea in children: a prospective survey. Otolaryngol Head Neck Surg 2007 Feb;136(2):169-175.

(75) Marcus CL, Moore RH, Rosen CL, Giordani B, Garetz SL, Taylor HG, et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. N Engl J Med 2013 Jun 20;368(25):2366-2376.

(76) Katyal V, Pamula Y, Daynes CN, Martin J, Dreyer CW, Kennedy D, et al. Craniofacial and upper airway morphology in pediatric sleep-disordered breathing and changes in quality of life with rapid maxillary expansion. Am J Orthod Dentofacial Orthop 2013 Dec;144(6):860-871.

(77) Amoric M. Efficacy and compliance in treatment of sleep apnea with Herbst mandibular advancement splints (OHA version). Int Orthod 2013 Jun;11(2):193-209.

(78) Ash SP, Smith AM. Chrome cobalt mandibular advancement appliances for managing snoring and obstructive sleep apnea. J Orthod 2004 Dec;31(4):295-299.

(79) Ayas NT, Epstein LJ. Oral appliances in the treatment of obstructive sleep apnea and snoring. Curr Opin Pulm Med 1998 Nov;4(6):355-360.

(80) Bacon W, Tschill P, Sforza E, Krieger J. A device for mandibular advancement in respiratory disorders of sleep. Clinical study. Orthod Fr 2000 Dec;71(4):295-302.

(81) Barewal RM, Hagen CC. Management of snoring and obstructive sleep apnea with mandibular repositioning appliances: a prosthodontic approach. Dent Clin North Am 2014 Jan;58(1):159-180.

(82) Barnes M, McEvoy RD, Banks S, Tarquinio N, Murray CG, Vowles N, et al. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. Am J Respir Crit Care Med 2004 Sep 15;170(6):656-664.

(83) Bloch KE, Iseli A, Zhang JN, Xie X, Kaplan V, Stoeckli PW, et al. A randomized, controlled crossover trial of two oral appliances for sleep apnea treatment. Am J Respir Crit Care Med 2000 Jul;162(1):246-251.

(84) Bonham PE, Currier GF, Orr WC, Othman J, Nanda RS. The effect of a modified functional appliance on obstructive sleep apnea. Am J Orthod Dentofacial Orthop 1988 Nov;94(5):384-392.

(85) Chan AS, Phillips CL, Cistulli PA. Obstructive sleep apnoea--an update. Intern Med J 2010 Feb;40(2):102-106.

(86) Choudhury M, Padmanabhan TV. A preliminary report on the effect of a mandibular advancement device on obstructive sleep apnea using magnetic resonance imaging and polysomnography. Int J Prosthodont 2012 Nov-Dec;25(6):613-618.

(87) Clark GT, Arand D, Chung E, Tong D. Effect of anterior mandibular positioning on obstructive sleep apnea. Am Rev Respir Dis 1993 Mar;147(3):624-629.

(88) Clark GT, Blumenfeld I, Yoffe N, Peled E, Lavie P. A crossover study comparing the efficacy of continuous positive airway pressure with anterior mandibular positioning devices on patients with obstructive sleep apnea. Chest 1996 Jun;109(6):1477-1483.

(89) Cohen R. Obstructive sleep apnea: oral appliance therapy and severity of condition. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998 Apr;85(4):388-392.

(90) Doff MH, Hoekema A, Wijkstra PJ, van der Hoeven JH, Huddleston Slater JJ, de Bont LG, et al. Oral appliance versus continuous positive airway pressure in obstructive sleep apnea syndrome: a 2-year follow-up. Sleep 2013 Sep 1;36(9):1289-1296.

(91) Doff MH, Hoekema A, Pruim GJ, Huddleston Slater JJ, Stegenga B. Long-term oral-appliance therapy in obstructive sleep apnea: a cephalometric study of craniofacial changes. J Dent 2010 Dec;38(12):1010-1018.

(92) Doff MH, Hoekema A, Pruim GJ, van der Hoeven JH, de Bont LG, Stegenga B. Effects of a mandibular advancement device on the upper airway morphology: a cephalometric analysis. J Oral Rehabil 2009 May;36(5):330-337.

(93) El-Solh AA, Moitheennazima B, Akinnusi ME, Churder PM, Lafornara AM. Combined oral appliance and positive airway pressure therapy for obstructive sleep apnea: a pilot study. Sleep Breath 2011 May;15(2):203-208.

(94) Eveloff SE, Rosenberg CL, Carlisle CC, Millman RP. Efficacy of a Herbst mandibular advancement device in obstructive sleep apnea. Am J Respir Crit Care Med 1994 Apr;149(4 Pt 1):905-909.

(95) Faber CE, Grymer L, Hjorth T. Anterior mandibular positioning device for treatment of snoring and obstructive sleep apnoea. Rhinology 2003 Sep;41(3):175-181.

(96) Ferguson KA, Ono T, Lowe AA, Keenan SP, Fleetham JA. A randomized crossover study of an oral appliance vs nasal-continuous positive airway pressure in the treatment of mild-moderate obstructive sleep apnea. Chest 1996 May;109(5):1269-1275.

(97) Fransson AM, Tegelberg A, Svenson BA, Lennartsson B, Isacsson G. Influence of mandibular protruding device on airway passages and dentofacial characteristics in obstructive sleep apnea and snoring. Am J Orthod Dentofacial Orthop 2002 Oct;122(4):371-379.

(98) Fransson AM, Svenson BA, Isacsson G. The effect of posture and a mandibular protruding device on pharyngeal dimensions: a cephalometric study. Sleep Breath 2002 Jun;6(2):55-68.

(99) George PT. A modified functional appliance for treatment of obstructive sleep apnea. J Clin Orthod 1987 Mar;21(3):171-175.

(100) George PT. Treatment of snoring and obstructive sleep apnea with a dental device. Gen Dent 1993 Jul-Aug;41(4):294-298.

(101) Ghazal A, Sorichter S, Jonas I, Rose EC. A randomized prospective long-term study of two oral appliances for sleep apnoea treatment. J Sleep Res 2009 Sep;18(3):321-328.

(102) Gindre L, Gagnadoux F, Meslier N, Gustin JM, Racineux JL. Mandibular advancement for obstructive sleep apnea: dose effect

on apnea, long-term use and tolerance. Respiration 2008;76(4):386-392.

(103) Hammond RJ, Gotsopoulos H, Shen G, Petocz P, Cistulli PA, Darendeliler MA. A follow-up study of dental and skeletal changes associated with mandibular advancement splint use in obstructive sleep apnea. Am J Orthod Dentofacial Orthop 2007 Dec;132(6):806-814.

(104) Hanggi MP, Teuscher UM, Roos M, Peltomaki TA. Long-term changes in pharyngeal airway dimensions following activator-headgear and fixed appliance treatment. Eur J Orthod 2008 Dec;30(6):598-605.

(105) Holley AB, Lettieri CJ, Shah AA. Efficacy of an adjustable oral appliance and comparison with continuous positive airway pressure for the treatment of obstructive sleep apnea syndrome. Chest 2011 Dec;140(6):1511-1516.

(106) Horihata A, Ueda H, Koh M, Watanabe G, Tanne K. Enhanced increase in pharyngeal airway size in Japanese class II children following a 1-year treatment with an activator appliance. Int J Orthod Milwaukee 2013 Winter;24(4):35-40.

(107) Ishida M, Inoue Y, Kawahara R, Ryoke K. An investigation of therapeutic effectiveness and the mechanism of oral appliance therapy on obstructive sleep apnea syndrome. Nihon Kokyuki Gakkai Zasshi 2001 Aug;39(8):559-566.

(108) Isono S, Tanaka A, Sho Y, Konno A, Nishino T. Advancement of the mandible improves velopharyngeal airway patency. J Appl Physiol (1985) 1995 Dec;79(6):2132-2138.

(109) Jia PZ, Fu MK, Zeng XL. Treatment of OSAS with modified twin-block advancement appliances. Zhonghua Kou Qiang Yi Xue Za Zhi 2005 Jan;40(1):42-45.

(110) Johal A, Battagel JM. An investigation into the changes in airway dimension and the efficacy of mandibular advancement appliances in subjects with obstructive sleep apnoea. Br J Orthod 1999 Sep;26(3):205-210.

(111) Johnston CD, Gleadhill IC, Cinnamond MJ, Gabbey J, Burden DJ. Mandibular advancement appliances and obstructive sleep apnoea: a randomized clinical trial. Eur J Orthod 2002 Jun;24(3):251-262.

(112) Kyung SH, Park YC, Pae EK. Obstructive sleep apnea patients with the oral appliance experience pharyngeal size and shape changes in three dimensions. Angle Orthod 2005 Jan;75(1):15-22.

(113) Lam B, Sam K, Lam JC, Lai AY, Lam CL, Ip MS. The efficacy of oral appliances in the treatment of severe obstructive sleep apnea. Sleep Breath 2011 May;15(2):195-201.

(114) Lamont J, Baldwin DR, Hay KD, Veale AG. Effect of two types of mandibular advancement splints on snoring and obstructive sleep apnoea. Eur J Orthod 1998 Jun;20(3):293-297.

(115) Lee CH, Jung HJ, Lee WH, Rhee CS, Yoon IY, Yun PY, et al. The effect of positional dependency on outcomes of treatment with a mandibular advancement device. Arch Otolaryngol Head Neck Surg 2012 May;138(5):479-483.

(116) Lekerud AK, Sand L, Englund AK, Hirsch JM. Treatment of sleep apnoea using a mandibular advancement splint--an open prospective study. In Vivo 2012 Sep-Oct;26(5):841-845.

(117) Marklund M, Franklin KA, Sahlin C, Lundgren R. The effect of a mandibular advancement device on apneas and sleep in patients with obstructive sleep apnea. Chest 1998 Mar;113(3):707-713.

(118) Marklund M, Sahlin C, Stenlund H, Persson M, Franklin KA. Mandibular advancement device in patients with obstructive sleep apnea : long-term effects on apnea and sleep. Chest 2001 Jul;120(1):162-169.

(119) Mehta A, Qian J, Petocz P, Darendeliler MA, Cistulli PA. A randomized, controlled study of a mandibular advancement splint for obstructive sleep apnea. Am J Respir Crit Care Med 2001 May;163(6):1457-1461.

(120) Menn SJ, Loube DI, Morgan TD, Mitler MM, Berger JS, Erman MK. The mandibular repositioning device: role in the treatment of obstructive sleep apnea. Sleep 1996 Dec;19(10):794-800.

(121) Millman RP, Rosenberg CL, Carlisle CC, Kramer NR, Kahn DM, Bonitati AE. The efficacy of oral appliances in the treatment of persistent sleep apnea after uvulopalatopharyngoplasty. Chest 1998 Apr;113(4):992-996.

(122) Miyao E, Nakayama M, Noda A, Miyao M, Arasaki H. Oral appliance therapy for a child with sleep apnea syndrome due to palatine tonsil hypertrophy. Sleep and Biological Rhythms 2007;5(4):288-290.

(123) Nakazawa Y, Sakamoto T, Yasutake R, Yamaga K, Kotorii T, Miyahara Y, et al. Treatment of sleep apnea with prosthetic mandibular advancement (PMA). Sleep 1992 Dec;15(6):499-504.

(124) Nunes W, Francesco-Mion R. 151 EARLY TREATMENT AND PREVENTIVE STRATEGIES FOR OBSTRUCTIVE SLEEP APNEA AND HYPOPNEA WITH THE BIOAJUSTA X ORTHODONTIC-ORTHOPEDIC TREATMENT. Sleep Med 2009;10:S41-S42.

(125) O'Sullivan RA, Hillman DR, Mateljan R, Pantin C, Finucane KE. Mandibular advancement splint: an appliance to treat snoring and obstructive sleep apnea. Am J Respir Crit Care Med 1995 Jan;151(1):194-198.

(126) Pancer J, Al-Faifi S, Al-Faifi M, Hoffstein V. Evaluation of variable mandibular advancement appliance for treatment of snoring and sleep apnea. Chest 1999 Dec;116(6):1511-1518.

(127) Petri N, Svanholt P, Solow B, Wildschiodtz G, Winkel P. Mandibular advancement appliance for obstructive sleep apnoea: results of a randomised placebo controlled trial using parallel group design. J Sleep Res 2008 Jun;17(2):221-229.

(128) Poon KH, Chay SH, Chiong KF. Airway and craniofacial changes with mandibular advancement device in Chinese with obstructive sleep apnoea. Ann Acad Med Singapore 2008 Aug;37(8):637-644.

(129) Prathibha BN, Jagger RG, Saunders M, Smith AP. Use of a mandibular advancement device in obstructive sleep apnoea. J Oral Rehabil 2003 May;30(5):507-509.

(130) Ringqvist M, Walker-Engstrom ML, Tegelberg A, Ringqvist I. Dental and skeletal changes after 4 years of obstructive sleep apnea treatment with a mandibular advancement device: a prospective, randomized study. Am J Orthod Dentofacial Orthop 2003 Jul;124(1):53-60.

(131) Rose E, Schessl J. Orthodontic procedures in the treatment of obstructive sleep apnea in children. J Orofac Orthop 2006 Jan;67(1):58-67.

(132) Schessl J, Rose E, Korinthenberg R, Henschen M. Severe obstructive sleep apnea alleviated by oral appliance in a three-year-old boy. Respiration 2008;76(1):112-116.

(133) Shadaba A, Battagel JM, Owa A, Croft CB, Kotecha BT. Evaluation of the Herbst Mandibular Advancement Splint in the management of patients with sleep-related breathing disorders. Clin Otolaryngol Allied Sci 2000 Oct;25(5):404-412.

(134) Singh GD, Garcia-Motta AV, Hang WM. Evaluation of the posterior airway space following Biobloc therapy: geometric morphometrics. Cranio 2007 Apr;25(2):84-89.

(135) Sjoholm TT, Polo OJ, Rauhala ER, Vuoriluoto J, Helenius HY. Mandibular advancement with dental appliances in obstructive sleep apnoea. J Oral Rehabil 1994 Sep;21(5):595-603.

(136) Tegelberg A, Walker-Engstrom ML, Vestling O, Wilhelmsson B. Two different degrees of mandibular advancement with a dental appliance in treatment of patients with mild to moderate obstructive sleep apnea. Acta Odontol Scand 2003 Dec;61(6):356-362.

(137) Trang H. Obstructive sleep apnea treatment in children. Rev Mal Respir 2006 Jun;23 Spec No 2:7S128-7S130.

(138) Tsuiki S, Lowe AA, Almeida FR, Kawahata N, Fleetham JA. Effects of mandibular advancement on airway curvature and obstructive sleep apnoea severity. Eur Respir J 2004 Feb;23(2):263-268.

(139) Vestling O, Walker-Engström WB, Tegelberg A. Treatment of obstructive sleep apnea (OSA) with two different degrees of mandibular advancement of dental appliance-a prospective and randomised study. Swed Dent J 2001;25(4):180.

(140) Wade PS. Oral appliance therapy for snoring and sleep apnea: preliminary report on 86 patients fitted with an anterior mandibular positioning device, the Silencer. J Otolaryngol 2003 Apr;32(2):110-113.

(141) Walker-Engstrom ML, Ringqvist I, Vestling O, Wilhelmsson B, Tegelberg A. A prospective randomized study comparing two different degrees of mandibular advancement with a dental

appliance in treatment of severe obstructive sleep apnea. Sleep Breath 2003 Sep;7(3):119-130.

(142) Altalibi M, Saltaji H, Roduta Roberts M, Major MP, MacLean J, Major PW. Developing an index for the orthodontic treatment need in paediatric patients with obstructive sleep apnoea: a protocol for a novel communication tool between physicians and orthodontists. BMJ Open 2014 Sep 18;4(9):e005680-2014-005680.

(143) Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc 2008 Feb 15;5(2):242-252.

(144) Bixler EO, Vgontzas AN, Lin HM, Liao D, Calhoun S, Vela-Bueno A, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. Sleep 2009 Jun;32(6):731-736.

(145) Schwengel DA, Dalesio NM, Stierer TL. Pediatric obstructive sleep apnea. Anesthesiol Clin 2014 Mar;32(1):237-261.

(146) Marcus CL. Pathophysiology of childhood obstructive sleep apnea: current concepts. Respir Physiol 2000 Feb;119(2-3):143-154.

(147) Tauman R, Gulliver TE, Krishna J, Montgomery-Downs HE, O'Brien LM, Ivanenko A, et al. Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. J Pediatr 2006 Dec;149(6):803-808.

(148) Brietzke SE, Gallagher D. The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: a meta-analysis. Otolaryngol Head Neck Surg 2006 Jun;134(6):979-984.

(149) Friedman M, Wilson M, Lin HC, Chang HW. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. Otolaryngol Head Neck Surg 2009 Jun;140(6):800-808.

(150) Huynh NT, Morton PD, Rompre PH, Papadakis A, Remise C. Associations between sleep-disordered breathing symptoms and facial and dental morphometry, assessed with screening examinations. Am J Orthod Dentofacial Orthop 2011 Dec;140(6):762-770

(151) Pirelli P, Saponara M, Guilleminault C. Rapid maxillary expansion in children with obstructive sleep apnea syndrome. Sleep 2004 Jun 15;27(4):761-766.

(152) Nazarali N, Altalibi M, Nazarali S, Major MP, Flores-Mir C, Major PW. Mandibular advancement appliances for the treatment of paediatric obstructive sleep apnea: a systematic review. Eur J Orthod 2015 Feb 12.

(153) Hiyama S, Suda N, Ishii-Suzuki M, Tsuiki S, Ogawa M, Suzuki S, et al. Effects of maxillary protraction on craniofacial structures and upper-airway dimension. Angle Orthod 2002 Feb;72(1):43-47.

(154) World Health Organization. WHO Handbook for guideline development. : World Health Organization; 2014.

(155) Schwengel DA, Dalesio NM, Stierer TL. Pediatric obstructive sleep apnea. Anesthesiol Clin 2014 Mar;32(1):237-261.

(156) Kaditis AG, Kalampouka E, Hatzinikolaou S, Lianou L, Papaefthimiou M, Gartagani-Panagiotopoulou P, et al. Associations of tonsillar hypertrophy and snoring with history of wheezing in childhood. Pediatr Pulmonol 2010 Mar;45(3):275-280.

(157) O'Brien LM, Sitha S, Baur LA, Waters KA. Obesity increases the risk for persisting obstructive sleep apnea after treatment in children. Int J Pediatr Otorhinolaryngol 2006 Sep;70(9):1555-1560.

(158) Bixler EO, Vgontzas AN, Lin HM, Liao D, Calhoun S, Vela-Bueno A, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. Sleep 2009 Jun;32(6):731-736.

(159) Rosen CL, Larkin EK, Kirchner HL, Emancipator JL, Bivins SF, Surovec SA, et al. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. J Pediatr 2003 Apr;142(4):383-389.

(160) Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. Sleep Med 2000 Feb 1;1(1):21-32.

(161) Schwengel DA, Dalesio NM, Stierer TL. Pediatric obstructive sleep apnea. Anesthesiol Clin 2014 Mar;32(1):237-261.

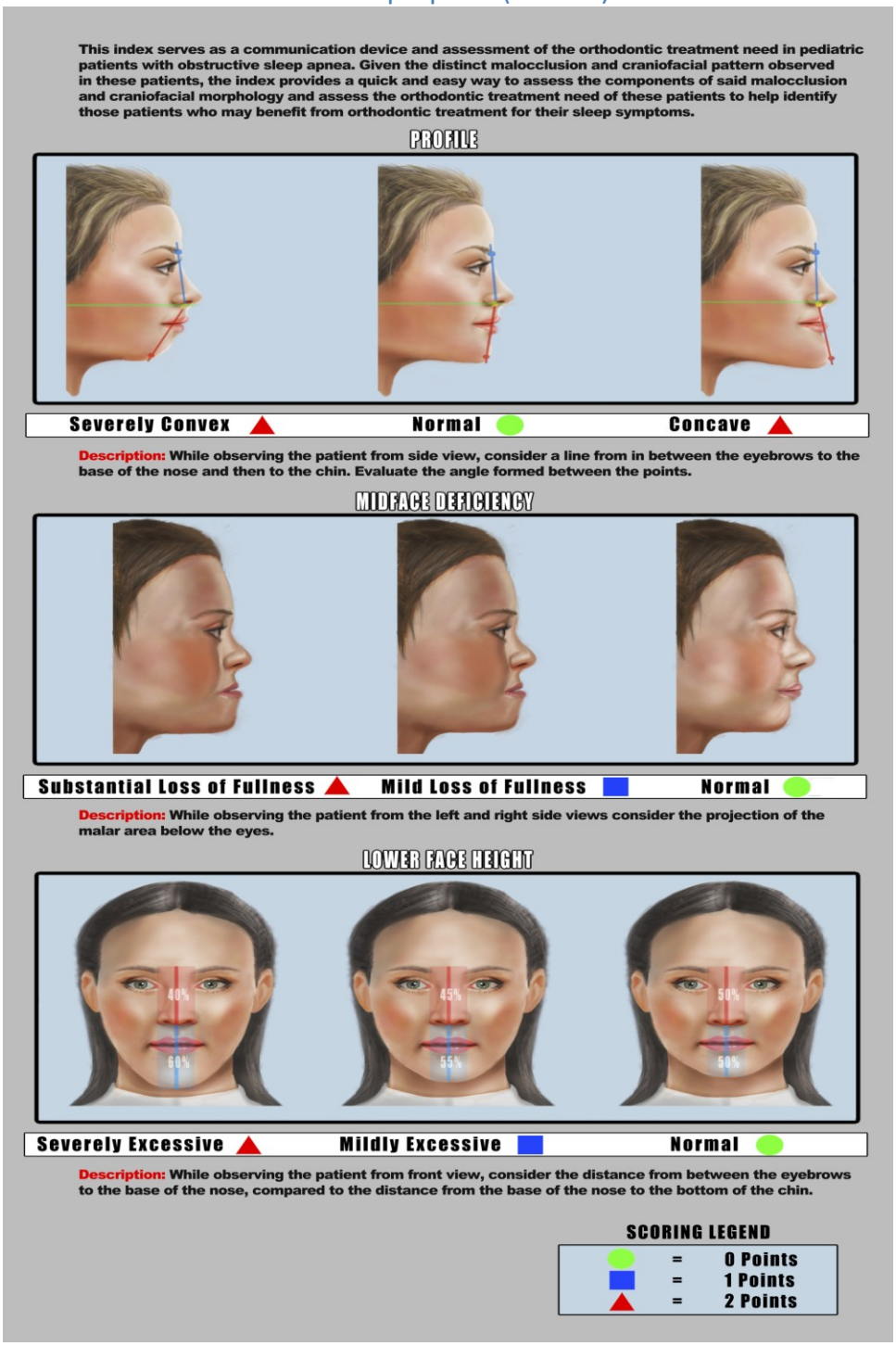
(162) Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-

disordered breathing, snoring, sleepiness, and behavioral problems. Sleep Med 2000 Feb 1;1(1):21-32.

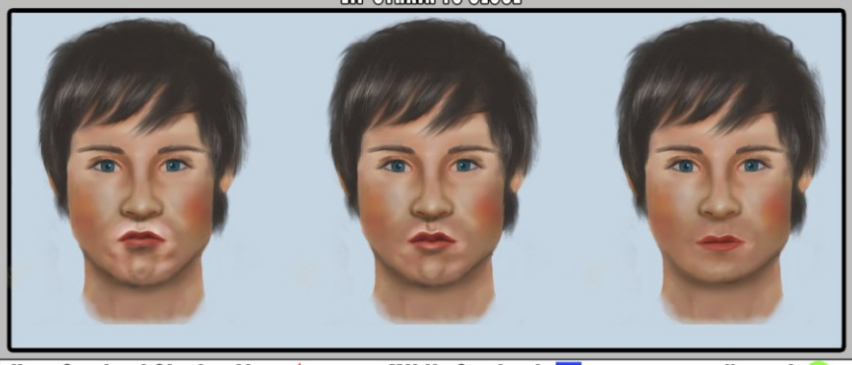
(163) Altalibi M, Saltaji H, Roduta Roberts M, Major MP, MacLean J, Major PW. Developing an index for the orthodontic treatment need in paediatric patients with obstructive sleep apnoea: a protocol for a novel communication tool between physicians and orthodontists. BMJ Open 2014 Sep 18;4(9):e005680-2014-005680.

## Appendix

### A. Alberta Pediatric Obstructive Sleep Apnea (APOSA) Index



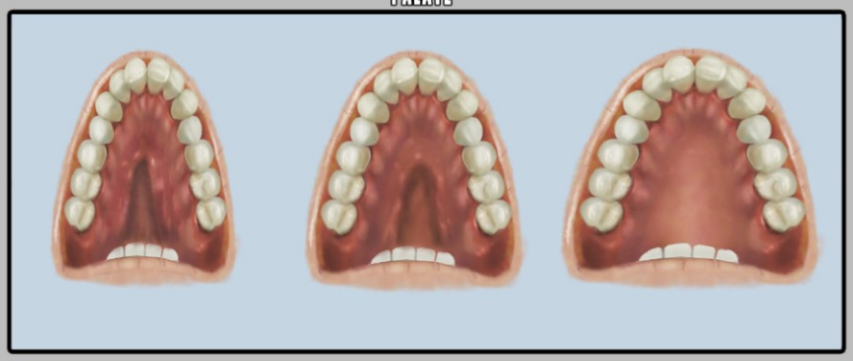
## LIP STRAIN TO CLOSE



Very Strained Closing Lips ▲ Mildly Strained ■ Normal ●

**Description:** While observing the patient from front view, and asking the patient to close their lips together, consider the amount of strain on the lip closing muscles around the mouth.

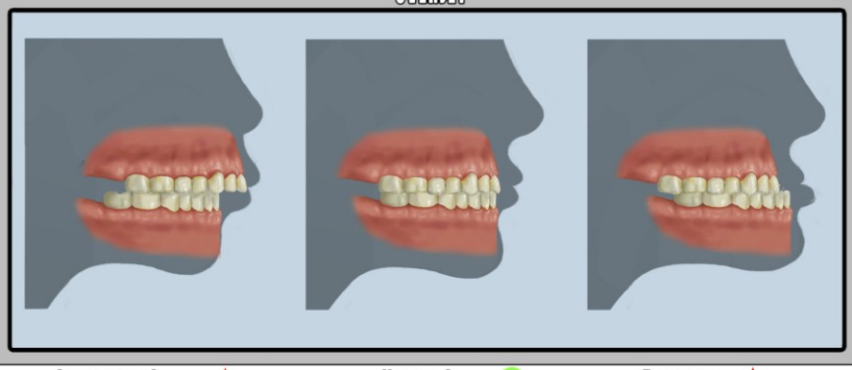
## PALATE



Severely High Arched ▲ Mildly High Arched ■ Normal ●

**Description:** When viewing the palate inside the mouth, consider the depth of the palate, and the magnitude of the arch of the palate.

## OVERJET

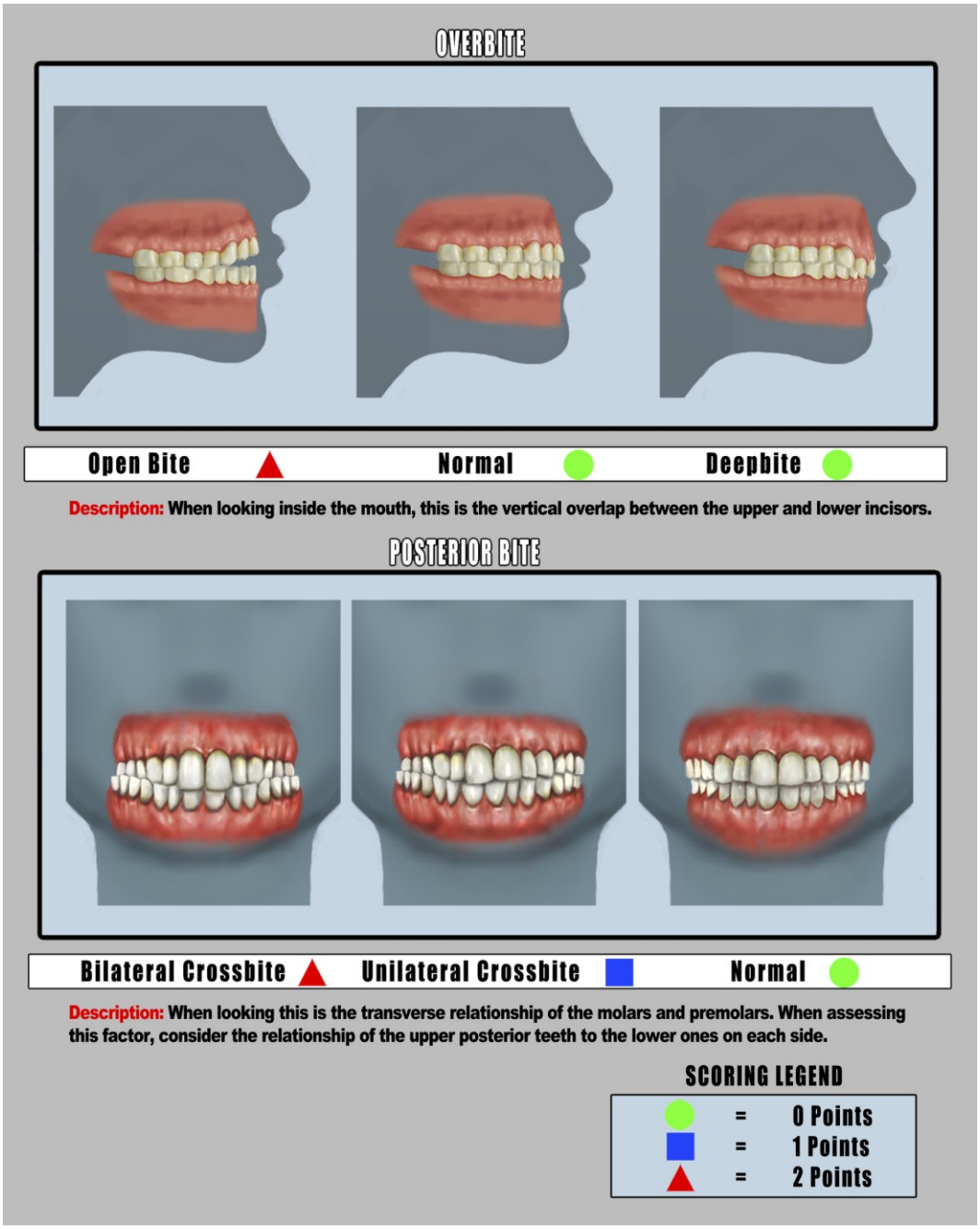


Increased ▲ Normal ● Reverse ▲

**Description:** Looking inside the mouth, this is the horizontal distance between the outside surface of upper and lower incisors. An excessive overjet is greater than 5mm.

## SCORING LEGEND

| | | |
|---|---|---|
| ● | = | 0 Points |
| ■ | = | 1 Points |
| ▲ | = | 2 Points |


OVERBITE
Open Bite
Normal
Deepbite
Description: When looking inside the mouth, this is the vertical overlap between the upper and lower incisors.
POSTERIOR BITE
Bilateral Crossbite
Unilateral Crossbite
Normal
Description: When looking this is the transverse relationship of the molars and premolars. When assessing this factor, consider the relationship of the upper posterior teeth to the lower ones on each side.
SCORING LEGEND
= 0 Points
= 1 Points
= 2 Points

## B. Recruitment email sent to orthodontists

Subject: Invitation to Participate in Study for Orthodontic Treatment Need in Patients with Pediatric OSA Symptoms

Dear Dr._____,

On behalf of Dr. Paul Major, I would like to invite you to participate in a study we are undertaking at the University of Alberta. You are receiving this email because our research team at the University of Alberta believes that you have expert knowledge in orthodontic treatment modalities for children with obstructive sleep apnea (OSA) symptoms.

Currently, there is limited communication between medical and dental teams in managing patients with OSA symptoms. This may be due to the fact that there is no protocol or index which helps physicians identify patients that may benefit from an orthodontic referral for their OSA symptoms.

Our research team at the University of Alberta has developed a novel index that will help non-dentally trained professionals identify craniofacial features, which may benefit from orthodontic referral. In order to make this index accessible, we must first validate our tool. We would like to invite you to assist us in the validation of this index.

All participants will be required to review a series of 30 initial orthodontic records and decide whether orthodontic treatment 'is' or 'is not' indicated for improvement of OSA symptoms. Total time commitment to review the records is expected to be approximately 1.5 -2 hours.

To accept or decline this invitation or if you have any other questions, please feel free to respond to this email or contact me directly.

Thank you for your time and consideration.

Natasha Nazarali
Graduate Orthodontic Resident

## C. Instruction sheet provided to participant orthodontists

**Instructions**

Thank you for your participation in our research, your time is greatly appreciated.

Enclosed you will find a number of items:

- Information sheet and consent form
- Pre-addressed and stamped envelope
- CD of records

Please review the information sheet and consent form. Should you have any further questions or require any clarification, you may contact me by email or by phone

The signed consent form should be placed in the pre-addressed and stamped envelope and mailed so that we may keep it for our records.

The enclosed CD contains 3dMD viewer software and 30 folders corresponding to 30 patient records. The CD is password protected. When you insert the CD, click on 'agent.' You will be prompted for the password. The password is: **sleepstudy**

- Please open the 3dMD viewer software by double clicking on the icon  . This will allow you to view our 3D records. Please note that the 3dMD software must be used with Windows.
- Once the 3dMD viewer software is opened, you can drag and drop the 3D **.tsb** file into the window to view the 3D image. To rotate the image, click on  located at the top left of the screen. To view another 3D image, you may drag and drop another .tsb file into the window. You will receive a message asking if you would like to "replace the existing surface?" Click 'Yes'
    - The following mouse commands may be helpful to view the 3D images:
        - Right mouse button: While pressing the right mouse button, you may translate the 3D images across the screen
        - Middle mouse button: Allows you to rotate the image in space
        - Right and left mouse button: Pressing both right and left mouse buttons at the same time will allow you to zoom in (press both buttons and move the mouse downwards) or zoom out (press both buttons and move the mouse upwards)
- Each patient is coded by number (#1-30) and should correspond to your responses on the data collection forms that were emailed to you. Please note that two data collection forms were emailed to you. This will allow you to review 15 records at a time instead of completing the entire data set at the same time.
- Please review the 3D image and corresponding intraoral photos and radiographs for each patient. For each patient, please decide whether orthodontic treatment is indicated to improve OSA symptoms. **While treatment may be required for various reasons (ex. crowding), we are focusing only on treatment that will improve OSA symptoms.**

If you have any questions or require any technical assistance, please do not hesitate to contact me.

Thank you again for your time.

Sincerely,

Natasha Nazarali
Orthodontic Graduate Resident
University of Alberta