Craniofacial Morphology in Children With Obesity or Down Syndrome With and Without Obstructive Sleep Apnea

by

Dr. Corey Hoy Bok Ng

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Faculty of Dentistry
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Abstract

Introduction: Obstructive Sleep Apnea (OSA) is common in children. Risk factors include adenotonsillar hypertrophy, obesity, and craniofacial abnormalities (e.g. Down Syndrome, DS). The aim was to describe the craniofacial morphology in children with suspected OSA referred for polysomnography (PSG) in 2 cohorts: DS and obesity.

Methods: Cross-sectional study of children with DS or obesity referred for PSG at SickKids, Toronto. Orthodontic examinations, PSG, lateral cephalograms, and sleep questionnaires were completed.

Results: 42 children (20 DS, 22 obese) aged 5-18 (11.9 $\pm$3.6) were included. DS with OSA (Obstructive-Apnea-Hypopnea-Index (OAHI) >1) had increased palatal depth (p=0.04); OAHI was correlated with intercanine distance (r=0.48, p=0.03). ANB angle was increased in Obesity with OSA (p=0.03); OAHI was correlated with ANB (r=0.58, p<0.01) and upper incisor retrusion (r= -0.53, p=0.01).

Conclusions: OSA in children with DS is associated with maxillary dimensions. Upper incisor position and maxillo-mandibular relationships are associated with OSA in children with Obesity.

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List of Abbreviations

SDB: Sleep Disordered Breathing
AAP: American Academy of Pediatrics
OSA: Obstructive Sleep Apnea
PSG: Polysomnography
ICSD: International Classification of Sleep Disorders
AHI: Apnea-Hypopnea Index
OAHI: Obstructive Apnea-Hypopnea Index
BMI: Body Mass Index
GH: Growth Hormone
DS: Down Syndrome
CT: Computerized Tomography
MRI: Magnetic Resonance Imaging
AT: Adenotonsillectomy
Pcrit: Pharyngeal Critical Pressure
EMG: Electromyography
CysLTs: Cysteinyl Leukotrienes
CRP: C-Reactive Protein
CHAT: Childhood Adenotonsillectomy Trial
CPAP: Continuous Positive Airway Pressure
ADHD: Attention Deficit Hyperactivity Disorder
PPV: Positive Predictive Value
NPV: Negative Predictive Value
PSQ: Pediatric Sleep Questionnaire
SRBD: Sleep-Related Breathing Disorders
EEG: Electroencephalography
EOG: Electrooculography
PAP: Positive Airway Pressure
FMA: Frankfort Mandibular Plane Angle
BPAP: Bi-level Positive Airway Pressure
RME: Rapid Maxillary Expansion
CBCT: Cone-Beam Computed Tomography
IOTN: Index of Orthodontic Treatment Need
SaO_2: Oxygen Saturation
$TcCO_2$: Transcutaneous Carbon Dioxide
$EtCO_2$: End-tidal Carbon Dioxide
AASM: American Academy of Sleep Medicine
REM: Rapid Eye Movement
ICC: Intra-Class Correlation Coefficient

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Chapter 1: Background & Introduction

Sleep disordered breathing (SDB) is a broad term describing a spectrum of clinical abnormalities in gas exchange, respiratory pattern, and sleep architecture during sleep of varying severity.[1] The mildest form of SDB is habitual or primary snoring which is defined by the American Academy of Pediatrics (AAP) as "snoring without obstructive apnea (see definition below), frequent arousals from sleep, or gas exchange abnormalities".[2] On the other end of the spectrum, the most severe form of SDB is obstructive sleep apnea (OSA). OSA is the most common form of SDB, affecting 1.2-5.7% of healthy children.[3]

1.1 Obstructive Sleep Apnea

The American Thoracic Society defines OSA as a "disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns".[4] OSA in children was first described by Guilleminault in 1976 using polysomnography (PSG) and clinical symptoms.[5] Subsequent research has led to an increased recognition of abnormal breathing during sleep and the development of many classification systems including the International Classification of Sleep Disorders (ICSD), which was first published in 1990.[6] The ICSD was further revised in 2005 (Second Edition) and 2014 (Third Edition).[7,8] The understanding of OSA and its pathophysiology in children has improved and the relationship between respiratory abnormalities and adverse consequences will be further discussed, highlighting the importance of early diagnosis.

OSA is a common condition in children of all ages and can result in severe complications and morbidity if left untreated, which include cardiovascular disease, neurocognitive deficits, behavioural problems, and growth disturbances. The gold standard for diagnosis of OSA in adults and children is an overnight PSG, which records sleep architecture, respiratory events, cardiac rhythm, muscle activity, gas exchange, and snoring.[9] One of the more important measurements from a PSG montage which is used to define the presence and severity of OSA is the apnea-hypopnea index (AHI), which is defined as the number of apneas and hypopneas per hour of total sleep time. Another important measurement is the obstructive apnea-hypopnea index (OAHI). An obstructive apnea in children is scored when there is a drop in the peak airflow $\geq$ 90% of baseline, with the drop lasting at least the duration of two breaths during baseline breathing and is associated with the presence of respiratory effort throughout the entire period of absent airflow.[10] An obstructive hypopnea is scored in children when the drop in peak airflow is $\geq$ 30% of pre-event baseline, for the duration of at least two breaths in association with either $\geq$ 3% oxygen desaturation or an arousal.[10]

Diagnostic criteria for OSA among adults (individuals $\geq$ 13 years of age) is defined as having an AHI $\geq$ 5 on nocturnal PSG and evidence of disturbed sleep, daytime sleepiness, or other daytime symptoms.[11] The diagnostic criteria for childhood OSA is inconsistent across studies, however, an AHI threshold value of more than 1 to 5 per hour is commonly used to define the presence OSA in children.[11] The International Classification of Sleep Disorders - Version 3 (ICSD-3) classifies pediatric OSA as the presence of an OAHI > 1/hour.[8]

1.2 Epidemiology of OSA

Depending on the specific OAHI threshold used for diagnosis of OSA, the estimated prevalence rates of OSA in healthy children range from 1.2% to 5.7%.[12-14] According to these prevalence rates, it can be estimated from the 2016 Census of Canada population counts that between 94,389 and 448,346 Canadian children aged 0-19 years are affected by OSA.

It is likely that both genetic and environmental factors play a role in the development of OSA. Children between the age of 2 and 8 years are at an increased risk of OSA because of the peak in adenotonsillar hypertrophy.[13] Children outside of this age range are likely to have additional or other underlying etiologic factors such as obesity and/or craniofacial anomalies that predispose them to the development of OSA.[12-15] Craniofacial anomalies that can increase the risk of OSA include syndromes that involve midface hypoplasia (Pierre-Robin Sequence, Crouzon syndrome, Down syndrome), increased body-mass index (Prader-Willi syndrome), and absolute or relative macroglossia (Beckwith-Wiedemann syndrome, Down syndrome).[16] Obesity results in fat deposition in the upper airway resulting in upper airway narrowing and increased collapsibility; in addition, truncal obesity decreases chest wall compliance and functional residual capacity.[17]

OSA is more common in men than women in adult populations. In contrast, childhood OSA has been reported to occur equally between boys and girls.[15,18,19] However, Lumeng and Chervin reported that SDB is more common among boys and overweight/obese children.[11] It has been described that OSA is more prevalent among African American children compared to Caucasian children and may be due to underlying low socio-economic status.[11,16] Furthermore, Asians have been shown to have more severe OSA compared to matched Caucasians due to

increased esophageal pressures and certain craniofacial features such as micrognathia, retrognathia, and long face syndrome .[20]

1.3 Obesity

An overweight child is defined as having a Body Mass Index (BMI) that is at or above the age and sex specific 85th percentile but below the 95th percentile, based on the 2000 Centers for Disease Control and Prevention growth charts.[21] Obesity is defined as a BMI at or above the age and sex specific 95th percentile based on the same growth charts.[21] There is an increasing trend in childhood obesity and the condition is becoming more prevalent worldwide. The prevalence of childhood obesity among Canadian children and adolescents aged 3-19 years increased from 5% in 1978 to 13.5% in 2004.[22,23] The most recent report of the prevalence of overweight and obese Canadian children has shown a decrease between 2004 and 2013 from 31% to 27%.[23] However, there has been an increase in prevalence of severe obesity among American children and adolescents between 1999 and 2016.[24]

Obesity in children and adolescents is becoming more recognized as a serious medical condition and public health problem that affects nearly every major organ system.[22] Many hospitals are implementing programs that focus on education, healthy living, and weight management services to combat both the short-term and long-term effects on physical and mental health. Despite considerable clinical and policy efforts, there is no evidence of a statistically significant change in obesity prevalence in any age group.[25]

Children with obesity aged 5-17 years are more likely to have risk factors for cardiovascular disease as compared to non-obese matched controls, with 70% having at least one risk factor, such as high cholesterol or high blood pressure.[26] Furthermore, children and

adolescents with obesity are at greater risk for OSA, bone and joint problems, and social and psychological problems.[27] Children with obesity are more likely to be obese as adults with higher risk of developing cardiovascular disease, Type 2 diabetes, stroke, several types of cancer, and osteoarthritis.[28-30]

Craniofacial morphology differs between obese and non-obese adolescents as shown on lateral cephalometric radiographs.[31] Growth hormone (GH) secretion is reduced in obese individuals but despite this reduction, pre-pubertal obese children exhibit normal or increased height.[31,32] The factors that regulate craniofacial growth and development include genetics, hormones, environmental pressures, and epigenetic factors and any disturbance can cause a change in normal craniofacial growth.[33,34] Past cephalometric studies have shown that patients with GH deficiency have a small anterior and posterior cranial base size, a small posterior face height, and a small posterior mandibular height. However, more recent studies have shown that obese adolescents have increased craniofacial growth, resulting in significantly larger mandibular and maxillary dimensions compared to non-obese adolescents.[31,35] Obesity was also associated with bimaxillary prognathism and relatively greater facial measurements.[31]

1.4 Down Syndrome

Down Syndrome (DS) or Trisomy 21 is a genetic disorder that was first described by John Langdon Down in 1866.[36] DS is the most common aneuploidy of autosomal chromosomes, which involves chromosome number 21, and occurs in approximately 1 in 1000 births.[37] Individuals with DS present with a number of comorbidities affecting the respiratory, cardiovascular, gastrointestinal, hematological, immune, endocrine, musculoskeletal, renal and genitourinary, and neurological systems.[36] Although clinical anomalies affect many of these

systems, the most common reasons for hospitalization of children with DS are respiratory disorders and congenital heart malformations.[37]

DS individuals have many characteristic craniofacial and physical abnormalities. DS children are commonly brachycephalic, have downward slant of the eye lids medially, epicanthal folds, hypertelorism, and a flat nasal bridge.[36,38] Conductive hearing loss and chronic otitis media are common in this population.[39] Intraorally, features commonly found in DS individuals include a fissured tongue, relative macroglossia, microdontia, hypodontia, anterior open bite, periodontitis, negative overjet, delayed eruption of teeth, angular cheilitis, and ankyloglossia.[38,40,41]

Based on lateral cephalograms, Suri *et al.* reported that when compared to controls, DS children had altered craniofacial morphology and dental relationships. Skeletally, DS children had a more obtuse cranial base angle, reduced alveolar height in the maxilla and mandible, decreased maxillary length and anterior maxillary dimensions, maxillary retrusion, decreased mandibular ramus, body, and symphyseal dimensions.[42] Dentally and facially, DS children were found to have more proclined and undererupted maxillary incisors, undererupted lower incisors, increased tendency for anterior open bite, forward rotation of maxillary and mandibular planes, overclosure, and relative mandibular prognathism.[42]

1.5 Pathophysiology of OSA

An obstructive apnea or hypopnea occurs when the patency of the upper airway is partially or completely obstructed, resulting in partial or complete collapse of the upper airway.[43] OSA appears to be a result of a combination of structural as well as functional factors. The patency of the upper airway is determined by a balance between the collapsing forces from the

intraluminal negative pressure of the airway and the dilating forces from the soft tissue structures that provide support for the upper airway.[16,44] These forces are affected by factors such as upper airway anatomy, neuromuscular tone and collapsibility, and upper airway inflammation.[45]

1.5.1 Upper Airway Anatomy

The upper airway is comprised of muscles and soft tissues, but it lacks any rigid or bony support. As a result, the cross-sectional area of the upper airway is dependent on the luminal pressure and the activity of the pharyngeal dilator muscles.[43] The upper airway contains a collapsible portion that extends from the hard palate to the larynx. To allow for normal function and everyday tasks such as swallowing and speaking, the upper airway is able to change its shape and temporarily close. However, due to the lack of rigid support, the upper airway is vulnerable to collapse during sleep.

Studies using computerized tomography (CT) on awake patients with OSA showed that there was reduced cross-sectional area in the nasopharynx, oropharynx, and/or hypopharynx.[46] More recently, magnetic resonance imaging (MRI) has been used to describe structural risk factors for OSA in children.[47] Children with OSA have a smaller oropharynx, larger adenoids, tonsils, and retropharyngeal nodes compared to control subjects.[48] In terms of the dimensions of the mandible as determined by MRI, Schiffman *et al.* showed that a smaller mandible is not a feature in children with OSA.[49] Furthermore, analysis of MRIs have revealed that the upper airway in children with OSA is the most restricted where the adenoids and tonsils overlap and that the upper airway is most restricted throughout the initial two-thirds of its length.[50] The tonsils and adenoids grow progressively during childhood and are largest in relative size at the age of 12, but then gradually involute by adolescence and adulthood.[3] In addition to enlarged

adenoids and tonsils, the upper airway in children with OSA is further restricted by a larger soft palate.[51] The first line of treatment for children with adenotonsillar hypertrophy is surgical management which has been shown to reduce symptoms and improve quality of life and PSG findings.[52] However, adenotonsillar hypertrophy is only one of the potential anatomical determinants of OSA in children, as a high percentage of patients suffer from persistent OSA despite adenotonsillectomy (AT).[53]

In addition to adenotonsillar hypertrophy, reduction in size of craniofacial structures can compromise the pharyngeal space and contribute to the development of OSA.[43] Cephalometric studies frequently report that a narrower maxilla, mandibular retrognathia, longer lower face height, and caudal placement of the hyoid bone are characteristics seen in children with OSA.[54-58] On lateral cephalometric radiographs, the distance measured between the posterior nasal spine and adenoids was found to be reduced by 2.6-5.6 mm in children with OSA compared to healthy controls.[59] Other studies did not find any differences in maxillary and mandibular width, length, or volume measurements between patients with OSA and normal controls.[48]

Huynh *et al.* found that SDB symptoms as assessed through screening exams were primarily associated with adenotonsillar hypertrophy, allergies, frequent colds, habitual mouth breathing, and certain dentofacial morphological features. These morphological features were related to a long and narrow face (dolichocephaly), high mandibular plane angle, narrow palate, and severe crowding in the maxilla and mandible.[60] Flores-Mir *et al.* conducted a systematic review and meta-analysis in 2013 on the craniofacial morphological characteristics in children with OSA.[61] Nine articles were included in this review with all using PSG to determine the presence and severity of OSA. They found that three variables were significantly different between children with and without OSA. Children with OSA had a steeper mandibular plane

angle (MP-SN = +4.2°), a more retrusive mandible (SNB = -1.79°), and were more likely to show a Class II skeletal pattern (ANB = +1.38°).[61] Similar findings were reported in a systematic review and meta-analysis by Katyal *et al.*[59] Compared with controls, children with OSA and primary snoring showed increased weighted mean differences in ANB angle of 1.64° and 1.54°, respectively. They found that the increased ANB angle was primarily due to a decreased SNB angle in children with primary snoring by 1.4°.[59]

1.5.2 Upper Airway Collapsibility

Although anatomical differences and the structure of the upper airway have been shown to play a critical role in the development of OSA, they are not solely responsible for the pattern of SDB.[53] Obstructive apnea or hypopnea can occur when the collapsing forces are large enough to overcome the dilating forces and obstruct the airway. The pharyngeal critical pressure (Pcrit) is the airway pressure below which the flow-limiting site collapses and has been used as an index of upper airway collapsibility.[62] A higher value of Pcrit implies a more collapsible upper airway, and subjects with OSA were shown to have higher Pcrit thresholds compared to normal subjects and those with primary snoring.[63] Patients with OSA have been shown to have increased upper airway collapsibility when awake as well as having an anatomically small upper airway.[45]

During sleep, children with severe OSA may experience obstructive apneic episodes but can maintain normal sleep state distribution.[64] This suggests that during obstructive episodes, a compensatory mechanism is able to maintain airway patency via neuromuscular activation, ventilatory control, and arousal threshold.[53]

The genioglossus, hyoglossus, and styloglossus are muscles that help to dilate the pharynx and maintain patency of the upper airway during respiration. These muscles produce

forward movement of the tongue and increase oropharyngeal airway size and stiffness.[53] These muscles experience inspiratory phasic activation approximately 200 ms prior to the diaphragm which act to prepare the airway so it can resist negative intraluminal pressure during inspiration. The coordination between the upper airway muscles and diaphragm acts at the level of the central nervous system (CNS).[45,65]

During wakefulness, children have stable ventilation patterns with strong activation of the pharyngeal dilator muscles, specifically the genioglossus.[66] Children with OSA have increased genioglossus electromyography (EMG) recording levels compared with non-OSA controls.[66] The genioglossus stabilizes and enlarges the portion of the upper airway that is most vulnerable to collapse. Increase of genioglossus EMG levels suggests reflex activation of the genioglossus via mucosal mechanoreceptors to negative airway pressure. In the initial stages of sleep, the genioglossus EMG activity decreases in both OSA children and normal control children with a subsequent increase in airway resistance and collapsibility of the airway. Normal children with a mechanically stable airway have EMG activity that remains below the wakeful baseline during stage 2 of sleep. However, a greater reduction of EMG activity in OSA patients during sleep onset results in increased airway resistance to the point where reflex activation of the pharyngeal dilator muscles is necessary to maintain airway patency.[67]

During collapse of the upper airway, minute ventilation decreases, inducing a compensatory increase in respiratory effort during inspiration that results in a large negative luminal pressure. Mucosal mechanoreceptors detect large negative luminal pressure changes, initiating a negative pressure reflex. This reflex induces the activation of pharyngeal dilator muscles and respiratory effort to decrease airway collapsibility and increase minute ventilation.[53] Marcus *et al.* observed that normal children are able to perform a negative pressure reflex and

restore minute ventilation without arousal when subjected to inspiratory resistance loading.[68] This negative pressure reflex is substantially diminished or completely lost in patients with OSA.[53] Therefore, patients with OSA must depend on arousal mechanisms to sustain minute ventilation.[68]

1.5.3 Inflammation

It is hypothesized that snoring can induce a mucosal inflammatory response and swelling, which ultimately affects upper airway resistance and collapsibility. In children, OSA has been found to be associated with both systemic and local inflammation in the upper airway.[69] OSA can induce a systemic proinflammatory response which can result in end-organ dysfuction.[70]

In children with SDB, higher levels of cysteinyl leukotrienes (CysLTs) have been found in upper airway samples.[69] CysLTs are major inflammatory mediators and potent neutrophil chemoattractants and activators. The expression of their receptors has been shown to be higher in children with OSA compared to children with recurrent tonsillitis, suggesting an inflammatory process involving leukotriene expression and regulation occurs in children with OSA. Local mucosal inflammation and edema could possibly impair the afferent limb of the negative pressure reflex.[16,71] Goldbart *et al.* also found that there was upregulation of glucocorticoid receptor gene expression in adenoid and tonsillar tissues from children with OSA compared to tissues from children with recurrent throat infections.[72] OSA severity has been shown to be reduced with the use of intranasal corticosteroid sprays and/or oral leukotriene antagonists when used in children with mild OSA or as an adjunct with other interventions.[73-75] Treatment effects were shown to be effective at normalizing PSG findings and have lasting effects in 62% of

children with mild OSA when given a combination of intranasal corticosteroid and oral montekulast for 12 weeks.[76]

Systemic inflammation can be reflected by C-reactive protein (CRP) plasma levels, which has been shown to be elevated in children with OSA.[77] Furthermore, CRP levels were found to decrease in children with OSA three months after AT, with a significant correlation between the changes in CRP and reduction in the severity of OSA.[78] Increased systemic inflammation is thought to be triggered by sleep fragmentation and episodic hypoxia that is common to OSA, which may lead to endothelial dysfunction, increased blood pressure, and insulin resistance.[79-81] However, systemic steroids have been shown to be ineffective at treating OSA.[82]

1.6 Obesity and OSA

Obesity is a known risk factor for OSA in adults and the prevalence of OSA is tripled for every standard deviation increase of BMI.[83,84] The increasing epidemic of childhood obesity has unfortunately made it an important risk factor for modern childhood OSA. Compared to an estimated prevalence of OSA in 3% of healthy 2-8 year old children, obesity greatly increases the risk of OSA in children with an estimated prevalence ranging from 19% to 61% depending on age, degree of obesity, and definition of OSA.[11,85] A vicious cycle can be initiated in children with both obesity and OSA, whereby the presence of OSA affects insulin resistance and leptin levels which continue the predisposition towards obesity.[86] Additionally, sleepiness can reduce a child's likelihood of engaging in physical activity and enhance eating habits that favour calorie-dense foods.[87] It was found that compared to controls, children with OSA have increased plasma ghrelin levels, resulting in hunger stimulation and increase in food intake.[88] Clinical and

epidemiological studies have established that obesity is one of the strongest predictors of OSA in both adults and children.[89,90] Redline *et al*. found that the risk of OSA in 399 children aged 2-18 years was 4.5 times higher in obese children.[17]

The pathophysiology of OSA in obese children involves anatomical and functional factors that restrict the upper airway, alterations in chest wall mechanics affecting upper airway collapsibility and lung volumes, and inflammatory and metabolic factors that further contribute to the disorder.[91] Obesity related anatomic risk factors specific to the upper airway soft tissues include the size of the parapharyngeal fat pads, lateral pharyngeal walls, soft palate, tongue, and amount of fat deposition in the tongue.[47] Increased size of pharyngeal lymphoid tissue has been shown to be the primary risk factor for OSA in obese adolescents.[47]

Arens *et al*. performed volumetric analysis of the upper airway and noted larger adenoids, tonsils, and retropharyngeal nodes in obese children with OSA compared to matched controls.[92] The size of the lymphoid tissue correlated with the severity of OSA but the effect was not modified by BMI.[92] Parapharyngeal fat pads and abdominal visceral fat are also significantly increased in obese subjects, but their size were not correlated with the severity of OSA.[92] Residual OSA exists after AT in 54-76% of obese children compared to about 15-20% in children without obesity.[93,94] The Childhood Adenotonsillectomy Trial (CHAT), a multi-center randomized controlled trial of adenotonsillectomy versus watchful waiting found that only 33% of obese children had residual OSA, however, this finding was limited to a pre-adolescent sample that excluded extremely obese patients.[52] After AT in obese children with OSA, it was found that AT increased the volume of the nasopharynx and oropharynx.[95] However, there was significant residual adenoid tissue, either from incomplete removal or regrowth, and an increase in the volume of the tongue and soft palate may have contributed to the lower success rate of AT

in obese children with OSA.[95] In this population, deposition of adipose tissue around the pharyngeal muscles and tissues and within the base of the tongue results in decreased airway size and an increase in airway resistance.[96] Furthermore, obese children may have altered chest wall mechanics and reduced lung volumes due to displacement of the diaphragm by the abdomen and decreased central ventilatory drive.[91]

A recent study on 210 Canadian children with obesity demonstrated that the prevalence of OSA as determined by PSG findings was 44% of which 28% were classified as having moderate or severe OSA.[97] The predictive factors of OSA were mouth breathing/nasal congestion (odds ratio = 0.33), presence of syndrome or multiple anomalies (odds ratio = 2.4), family history of OSA (odds ratio = 2.7), and sleep problems (odds ratio = 12.4).[97] Obese children with OSA were more likely to desaturate and they showed that a desaturation index of less than 6 events per hour was predictive of the absence of OSA (odds ratio = 4.96).[97]

In the presence of obesity, OSA has significant effects on glycemic regulation and affects lipid homeostasis through changes in insulin sensitivity.[69,98] Insulin resistance and high-density lipoprotein (HDL) levels improved after AT and normalized OAHI in about 25% of normal children compared to 10% of obese children.[99] Fasting glucose was not improved after AT and was most strongly associated with post-AT OAHI, suggesting that children with increased insulin resistance were more likely to have residual OSA.[99] Koren *et al*. also found that sleep duration was inversely associated with glucose levels and that sleep fragmentation was positively associated with insulin resistance, suggesting a synergistic relationship between insulin resistance and sleep fragmentation in children with obesity and OSA.[100]

1.7 Down Syndrome and OSA

Children with DS have a significantly higher risk of OSA when compared to children of the general population.[101] The prevalence of OSA in DS is much higher than in healthy children and can be upwards of 60%.[102-104] Furthermore, Shott *et al.* found that 80% of the children diagnosed with DS showed abnormal PSG results.[105] Craniofacial abnormalities which predispose these children to OSA include midface hypoplasia, mandibular hypoplasia, relative macroglossia, glossoptosis, an abnormally small upper airway with superficially positioned tonsils, relative tonsillar and adenoidal hypertrophy, hypopharyngeal collapse, tracheal stenosis, and laryngomalacia.[16,106] Low upper airway muscle tone and lymphoid hyperplasia are additional factors influencing pharyngeal airway collapse in children with DS.[107,108]

Volumetric measurements of the tongue with MRI showed that DS children had a normally sized tongue.[109] DS children have reduced space for the tongue from a hypoplastic maxilla, leading to airway volume loss and putting them at risk of OSA.[109] DS children also have increased incidence of lower respiratory tract infections, increased secretions leading to aspiration, obesity, hypothyroidism, and generalized hypotonia, which all further put this population at risk of OSA.[3,110]

Skotko *et al*. studied OSA in DS children and aimed to create a predictive model for presence of OSA as defined by PSG determined AHI > 1.[111] Their study involved an overnight PSG, physical examination, medical history, lateral cephalogram, 3D photographs, sleep questionnaires, and urine samples. The resultant predictive model included variables from sleep questionnaires, medication history, vital signs, patient's age, physical examination findings, and anthropometric measurements. Physical examination findings used in the predictive model were

presence of macroglossia, Mallampati score[112], and neck circumference. Variables from the lateral cephalograms, 3D photographs, dental examinations, and urine samples did not improve their predictive model and were not included in their final model.[111]

1.8 Complications of Pediatric OSA

Untreated OSA in children may lead to serious morbidity that affects multiple organs and systems, and these negative consequences may not be completely reversible.[1] The consequences of OSA are a result of the interactions between nocturnal episodic hypoxia, hypercapnia, and sleep fragmentation.[1] The effects of untreated SDB and OSA include behavioral disturbances, neurocognitive deficits, cardiovascular complications, inflammatory complications, growth impairment, decreased quality of life, and increased health related costs.

1.8.1 Behavioural and Neurocognitive Complications

Behavioural and neurocognitive morbidities are some of the most well-established long term consequences of pediatric OSA and behavioural dysregulation is the most commonly encountered comorbidity of OSA.[1] Numerous studies have investigated the relationship between OSA and behavioral and neurocognitive function. The majority of studies consistently report some association between OSA and hyperactivity, attention deficits, impulsivity, and attention deficit hyperactivity disorder-like symptoms.[1,3] In addition to behavioral changes, there are also reports of children with OSA demonstrating cognitive impairments that include poor school performance, impaired executive functioning, and inverse relationships with memory and learning.[1] These sequelae may lead to more extensive behavioral disturbances such as restlessness, aggressive behaviour, and excessive daytime sleepiness. More recently, studies have assessed neurocognition before and after treatment for OSA and demonstrated that there is

significant improvement in neurocognition post treatment that are sustained for more than a year.[3] The CHAT study found that for children who underwent AT, there was no improvement in attention or executive function but improvements in behaviour were reported by care givers and teachers.[52] However, the CHAT study excluded children with severe OSA which might explain the study's negative findings for neurocognition.[52]

1.8.2 Cardiovascular Complications

The early identification of cardiovascular complications associated with OSA is important such that intervention and treatment can be undertaken to reverse these processes in childhood and prevent further complications in adult life.[1] During sleep, recurrent episodes of upper airway obstruction in OSA results in intermittent hypoxia, hypercapnia, and intrathoracic pressure swings, which elicit disturbances in autonomic function. Increased urinary catecholamine levels and right ventricular dysfunction has also been demonstrated in children with OSA.[1] Most importantly, OSA is one of the leading causes of secondary hypertension, with more than 50% of OSA patients having hypertension.[113] During sleep, normal individuals experience a nocturnal decrease, or “dip”, in blood pressure.[114] However, some OSA patients do not demonstrate this normal dip during sleep, and are classified as “non-dippers”.[115] Non-dippers are at increased risk for hypertensive organ damage and subsequent cardiovascular events.[113,116,117] Continuous Positive Airway Pressure (CPAP) therapy is recommended to treat OSA patients despite only modest blood pressure responses.[118]

1.8.3 Somatic Growth Impairment

Historically, failure to thrive was one of the most common consequences of OSA and has been reported in up to 50% of children presenting for AT. However, increased awareness of this

diagnosis in recent years has led to earlier recognition and referral which has translated in fewer children presenting with failure to thrive secondary to undiagnosed OSA.[1,119] Suggested etiologies for somatic growth impairment include decreased caloric intake, increased work of breathing, and reduction in growth factors such as insulin-like growth factor-1 and growth hormone. Significant increases in insulin-like growth factor-1 and healthy weight gain without increased body fat percentage have been demonstrated six months after AT.[120,121]

1.8.4 Quality of Life and Healthcare Resource Utilization

Childhood OSA leads to significant decreases in health related quality of life. However, quality of life scores significantly improve following AT treatment.[122] Studies on children with OSA have shown that they are heavy consumers of healthcare resources, which is significantly increased several years before OSA diagnosis and usage can start as early as the first year of life.[123] The total number of hospital visits in children with OSA was 40% higher and these children required 20% more repeated hospital visits compared with matched controls. There was also a significant increase in referrals to otolaryngologists and pediatric respiratory medicine physicians, as well as increased consumption of anti-infective and respiratory system drugs in children with OSA.[123] Therefore, timely diagnosis and treatment of OSA can improve and possibly prevent serious end-organ dysfunction, as well as improve quality of life and reduce healthcare costs.

1.9 Diagnosis

The American Academy of Pediatrics (AAP) has outlined the goals for the management of OSA in their clinical practice guidelines as follows: 1) identify children who are at risk for OSA; 2) avoid unnecessary intervention in patients who are not at risk; and 3) evaluate which

patients are at risk of complications so that appropriate precautions can be taken.[2] Multiple diagnostic methods that have been evaluated include history and physical examination, audiotaping or video recording, pulse oximetry, patient questionnaires, and PSG.[2] Although, PSG is the gold standard test to diagnose OSA, due to the combination of its resource intensive nature of as well as the limited access to PSGs, other tools have been evaluated for their diagnostic accuracy to screen for pediatric OSA.

1.9.1 Signs and Symptoms

Although children with OSA may sometimes be asymptomatic, the most common signs and symptoms associated with childhood OSA are summarized in Table 1.1.

Table 1.1 Common Signs and Symptoms of Pediatric OSA[3,124]

History	Physical Examination
Daytime Symptoms • Morning headaches • Daytime sleepiness • Diagnosis of Attention Deficit Hyperactivity Disorder • Learning problems • Irritability • Hyperactivity **Nocturnal Symptoms** • Snoring • Witnessed apneas • Gasping • Paradoxical breathing • Neck hyperextension • Nocturnal diaphoresis • Nocturnal enuresis • Cyanosis	• Failure to thrive or overweight/obesity • Tonsillar hypertrophy • Adenoidal faces • Micrognathia/retrognathia • High-arched palate • Signs of cor pulmonale (shortness of breath, wheezing, cyanosis, ascites) • Systemic Hypertension

Multiple studies have been performed to evaluate the use of history alone as a screening tool for the diagnosis of OSA.[3,125-127] One study found that some of the parent's observations (observed cyanosis and loud snoring) are more frequently reported in children with OSA, however, no single or combination of observations could accurately predict the severity of OSA.[125] Sensitivities for these questions ranged from 35% to 85% and specificities ranged from 41% to 92%.[125] Although history has been shown to be poor at discriminating between primary snoring and OSA, a thorough evaluation of the child should be performed nonetheless.[2]

Snoring is the most common clinical symptom of OSA. The AAP recommends that clinicians should inquire whether a child snores as screening symptom for OSA during any routine healthcare visit.[2] Almost all children with OSA snore, thus asking about snoring is a sensitive, but not specific screening measure. If a history of snoring is confirmed, a more detailed history and physical examination for symptoms should be obtained. However, physical examinations for children with OSA are often normal. Non-specific findings related to adenotonsillar hypertrophy such as mouth breathing, nasal obstruction during wakefulness, adenoidal faces, and hyponasal speech may be present.[2] However, the presence of adenotonsillar hypertrophy has not been shown to reliably predict OSA.[128] Therefore, clinicians need to have a high index of suspicion for OSA in children at increased risk of developing OSA.

Attention deficit hyperactivity disorder (ADHD) is a common behavioral disorder in children and adolescents with its main symptoms involving inattention, hyperactivity, and impulsivity.[129] There is a high prevalence of snoring and sleep problems in children with ADHD. [129,130] In addition, untreated OSA often presents with similar symptoms of ADHD and is a common cause of misdiagnosis. Therefore, children may be incorrectly prescribed long-term methylphenidate instead of recognizing and treating their underlying sleep disorder.[131]

There is an increased prevalence of secondary nocturnal enuresis in children with OSA. There are two potential explanations for this finding. Firstly, increased secondary nocturnal enuresis may be a result of the blunting effects of OSA on the arousal response. Secondly, upper airway collapse results in increased negative intrapleural pressure which increases venous return leading to left atrial distension and resultant increases in atrial natriuretic peptide and antidiuretic hormone.[132,133]

1.9.2 Questionnaires

Parent questionnaires have been developed as screening tools for the diagnosis of pediatric OSA. One of the earliest questionnaires was developed by Brouillette *et al*. which calculated a score based on the responses to three main questions: 1) difficulty during sleep; 2) apnea observed during sleep; and 3) snoring.[134] The questionnaire was initially tested on 23 children with OSA and 46 controls. The formula used to calculate OSA score was: OSA score = 1.42D + 1.41A + 0.71S – 3.83 (where D is difficulty during sleep, A is apnea observed during sleep, and S is snoring).[134] The D and S variables were scored 0-3 based on responses of never, occasionally, frequently, and always.[134] The A variable was scored as 0 and 1 for no and yes, respectively.[134] 23 additional patients referred for possible OSA were used to test the scoring algorithm and the investigators found that an OSA score > 3.5 predicted the presence of OSA, while a score < -1 predicted the absence of PSG diagnosed OSA.[134]

Schechter *et al.* compiled a total of 4 studies that used this questionnaire and found that in a total of 765 patients, the overall sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 60%, 52%, 65% and 46%, respectively.[135] The

investigators concluded that the questionnaire developed by Brouillette *et al*. had unacceptably low sensitivity and specificity for predicting OSA.[135]

The Pediatric Sleep Questionnaire (PSQ) was published and validated by Chervin *et al*. in 2000.[127] It is a parent-reported questionnaire with 77 questions that is comprised of 4 subscales for SDB, snoring, sleepiness, and behaviour. The most commonly used subscale of the PSQ for assessing the presence of OSA is the Sleep-Related Breathing Disorders (SRBD) subscale, which consists of 22 questions (Appendix A). The questions on the SRBD scale are categorical in a Yes/No/Don't Know response format. The SRBD subscale of the PSQ was tested in Michigan on 162 children (54 with SRBDs and 108 general pediatric patients) between the ages of 2 and 18. It was able to correctly classify 86.4% of subjects with an overall sensitivity of 85% and specificity of 87% when using a cut-off score of 0.33.[127] A follow up study on 105 children from the Washtenaw County Adenotonsillectomy Cohort aged 5 to 12.9 years showed a sensitivity of 78% and specificity of 72%.[126]

Spruyt and Gozal developed a third questionnaire in 2012.[136] The questionnaire consists of a set of 6 hierarchically ordered questions with Likert-type responses for the preceding 6-month time frame (Appendix B). Questions 1-4 and 6 were scored based on the following responses: "never" (0), "rarely" (once per week; 1), "occasionally" (twice pre week; 2), "frequently" (three to four times per week; 3), and "almost always" (four or more times per week; 4). Question 5 addressed snoring and were scored for the following responses: "mildly quiet" (0), "medium loud" (1), loud (2), "very loud" (3) and "extremely loud" (4). From a sample of 1133 children from schools around Louisville that were predominantly white non-Hispanics and aged 5-9 years old, they found that their questionnaire had a sensitivity of 59.03%, a specificity of 82.85%, a PPV of 35.4, and NPV of 92.7. They concluded that their

questionnaire will aid the screening of children at high risk of SDB but cannot be used as the sole diagnostic tool.[136]

A systematic review by Schechter *et al*. evaluated the diagnostic accuracy of questionnaires for the diagnosis of pediatric OSA as compared to PSG. They concluded that questionnaires had unacceptably low sensitivity and specificity for OSA and could not be used in clinical practice.[135] More recently, a systematic review by De Luca Canto *et al*. assessed the ability of different questionnaires and clinical examinations to assess SDB in children. They concluded that the PSQ had the best diagnostic accuracy of the evaluated tests. However, they recommended that dentists should use the PSQ *only* as a screening tool for pediatric SDB because its diagnostic accuracy is not high enough to replace the current reference standard, PSG.[137]

1.9.3 Polysomnography

An overnight PSG is the gold standard for diagnosing OSA and is the only diagnostic test able to both identify SDB and quantify the respiratory and sleep abnormalities associated with OSA in children.[3] An overnight PSG is also known as a Level I study which is performed in a sleep laboratory and attended by a sleep technologist and measures several complex polygraphic signals and physiological channels.[9] It measures electroencephalography (EEG), submental and limb extremity electromyography (EMG), electrooculography (EOG), and cardiorespiratory variables such as respiratory effort, heart rate, pulse oximetry, and carbon dioxide levels. A typical recording lasts for approximately 8 to 10 hours and from the acquired information, respiratory events (flow limitation, central and obstructive events), arousals, gas exchange abnormalities, periodic limb movements and autonomic changes can be evaluated.[16] Notably, an

obstructive apnea-hypopnea index (OAHI) is derived based on the PSG data which reflects both the presence of and severity of OSA.

OAHI is defined as the number of obstructive apneas and obstructive hypopneas per hour of total sleep time. An obstructive apnea is defined as a drop in the peak airflow ≥90% of baseline, with the drop lasting at least the duration of two breaths (as determined during baseline breathing) and is associated with the presence of respiratory effort throughout the entire period of absent airflow.[10] An obstructive hypopnea is defined as a drop in the peak airflow ≥30% of baseline, for the duration of at least two breaths and associated with either a ≥3% oxygen desaturation or an arousal.[10] Unfortunately, individual sleep laboratories often establish their own thresholds for diagnosis of OSA. Beck *et al.* reported that an AHI ≤ 1.4 is statistically normal and that many centres will treat children for OSA with an AHI in the range of 2-5.[138]

However, more recently ,The International Classification of Sleep Disorders-Version 3 (ICSD-3) classified pediatric OSA as the presence of an OAHI > 1/hour.[8] Although PSGs are the gold standard test for the diagnosis of pediatric OSA, challenges related to performing an overnight PSGs include inconvenience of having to sleep away from home, expenses to the patient and their family due to missed days of work, as well as a relative shortage of pediatric sleep diagnostic facilities resulting in prolonged wait times for children. There is a lack of resources and services for pediatric SDB across Canada; Katz *et al*. estimated that there are 7.5 times more children with OSA than the current testing capacity in Canada.[139] Furthermore, there are marked provincial discrepancies across Canada with many provinces having no dedicated pediatric sleep diagnostic centers.[139] In those provinces with access to pediatric PSG, wait times ranged from less than one month up to 1.5-2 years.[139]

1.9.4 Cephalometric Measurements and OSA

The use of cephalometry and cephalometric radiographs for orthodontic practice was first introduced in the United States by Dr. B. Holly Broadbent in 1931.[140] Since then, its use has led to the development of many detailed cephalometric analyses that assist orthodontists in everyday diagnosis and treatment planning. The Steiner, Downs, Wits, Harvold, and Tweed analyses are some of the most commonly used analyses.[141-145] In addition to diagnosis and treatment planning, cephalometric radiographs can also be used to assess growth, monitor growth by superimpositions, and to determine treatment effects.[146-148] Length and angular measurements are based on multiple cephalometric landmarks which are summarized in Table 1.2.[146]

Table 1.2 Common Cephalometric Landmarks

Cephalometric Landmark	Landmark Symbol	Definition
A point (subspinale)	A	Innermost point on the concavity of the anterior maxilla between the anterior nasal spine and upper incisor
Anterior Nasal Spine	ANS	Tip of the anterior nasal spine
Articulare	Ar	Point of intersection between the shadow of the zygomatic arch and the posterior border of the mandibular ramus
B Point (supramentale)	B	Innermost point on concavity of the mandible between the lower incisor and bony chin
Basion	Ba	Lowest point on the anterior margin of the foramen magnum
Bolton	Bo	Highest point in the upward curvature of the retrocondylar fossa of the occipital bone
Condylion	Co	Most posterior and superior point of the mandibular condyle
Glabella	G	Most prominent point of the frontal bone between the supraorbital ridges
Gnathion	Gn	The center of the inferior point on the mandibular symphysis; midpoint between pogonion and menton
Gonion	Go	Midpoint of the contour connecting the ramus and body of the mandible
Menton	Me	The most inferior point on the mandibular symphysis
Nasion	Na	Anterior point of the intersection between the nasal and frontal bones
Orbitale	Or	The lowest point on the inferior margin of the orbit
Pogonion	Pg	Most anterior point on the contour of the bony chin
Porion	Po	Midpoint of the upper contour of the external auditory canal
Posterior Nasal Spine	PNS	Tip of the posterior spin of the palatine bone at the junction of the hard and soft palates
Pterygomaxillary fissure	Ptm	The point at the base of the pterygomaxillary fissure where the anterior and posterior walls meet
PT point	PT	Point at junction between Ptm and foramen rotundum; most posterior superior point on the pterygomaxillary fissure
Sella	S	The midpoint of the cavity of sella turcica
Spheno-occipital Synchondrosis	SO	Junction between the occipital and basisphenoid tissues

Studies evaluating cephalograms in children with OSA demonstrate mixed results. Luzzi *et al*. conducted a study on 30 children between the ages of 5 and 8 years with habitual snoring who went for an overnight PSG and lateral cephalogram.[149] They found that children with increasing airflow obstruction and SDB had significantly greater Frankfurt Mandibular Plane Angles (FMA). They concluded that mandibular rotation plays an important role in the pathophysiology of upper airway patency and that cephalometric analysis provides an easily accessible early warning sign for the presence of future development of SDB.[149] However, Katyal *et al*. conducted a study on a sample of children between the ages of 8 and 18 years. These authors found that there were no saggital or vertical skeletal cephalometric predictors that were identified in children at high risk for SDB.[150] The same authors went on to conduct a meta-analysis on craniofacial and upper airway morphology in pediatric SDB and found that only the ANB angle in children with OSA versus healthy controls was increased in the OSA group by a weighted mean difference of 1.64° (95% confidence interval = 0.88 to 2.41, $p < 0.0001$).[59] In children with primary snoring versus healthy controls, primary snorers had an increased ANB angle by a weighted mean difference of 1.54° (95% confidence interval = 0.89 to 2.2, $p < 0.00001$) and was mainly due to mandibular retrusion as measured by a reduced sella-nasion-B point (SNB) angle (weighted mean difference = -1.4, 95% confidence interval = -2.58 to -0.23, $p = 0.02$).[59] They concluded that the increased ANB angle of less than two degrees may not be clinically significant and that their meta-analysis could not support a direct causal relationship between craniofacial features and pediatric SDB.[59] These features may persist into the adult years as shown by Laxmi *et al*. in a sample of OSA and control patients ranging from the ages of 25-45.[151] They found that the OSA group had a significantly increased ANB angle, increased mandibular plane angle (GoGn-SN), increased lower anterior face height, decreased posterior

airway space, increased soft palate length, and increased tongue length and thickness.[151] A meta-analysis of cephalometric studies in adult patients with OSA confirmed by PSG reinforced these conclusions and reported that those with OSA had reduced pharyngeal airway space, inferiorly positioned hyoid bone, and increased anterior face heights when compared to healthy controls.[152]

1.10 Pediatric OSA Treatment

Treatment for pediatric OSA depends on the underlying etiology, clinical assessment, as well as the severity of the disease. It should be tailored to each child based on each patient's unique clinical constellation of pathology. First line treatment for pediatric OSA is adenotonsillectomy. However, there are several other treatment options including both medical and surgical options.

1.10.1 Adenotonsillectomy

Adenotonsillar hypertrophy is the most common cause of childhood OSA. Adenotonsillar hypertrophy occurs most frequently between the ages of 2-6 years, when the pharyngeal lymphoid tissue outgrows the structures of the surrounding airway, leading to obstruction of the upper airway during sleep.[153] Adenotonsillectomy (AT) is recommended as the first line treatment of pediatric OSA as only 9% of OSA secondary to adenotonsillar hypertrophy displayed spontaneous resolution within 1 year.[153,154]

Friedman *et al*. conducted a systematic review and found that the success of AT ranges from 24-100% in the pediatric population.[155] Specifically, when cure of OSA was defined as AHI of < 1 post-operatively, AT was successful in 66.3% of the time. Furthermore, Lim *et al*. concluded that a cure rate of OSA (AHI < 5) from AT was between 78.4% and 100%.[156] However, in children with underlying airway abnormalities due to factors such as obesity,

craniofacial anomalies, and neuromuscular deficits, AT is more likely to fail as a treatment compared to AT performed on children without the abnormalities.[153]

A randomized controlled trial by Marcus *et al.* (Childhood Adenotonsillectomy Trial; CHAT) evaluated the benefits and risks of AT compared to watchful waiting for the management of pediatric OSA.[52] A total of 464 children between the ages of 5-9 years old with a diagnosis of OSA as defined by AHI score of 2 or more events per hour or obstructive apnea index (OAI) score of 1 or more events per hour were randomly assigned to early AT or watchful waiting. Children with severe OSA from PSG findings of AHI more than 30 events per hour, OAI of more than 20 events per hour, or arterial oxyhemoglobin saturation of less than 90% for 2% or more of their total sleep time were excluded. They found that surgical intervention of early AT did not significantly improve attention or executive function as measured by neuropsychological testing (Developmental Neuropsychological Assessment; NEPSY). However, early AT did reduce symptoms and improve secondary outcomes of behaviour, quality of life, and PSG findings. In the CHAT study, 79% of the children undergoing AT had normalization of their PSG findings. Interestingly, normalization also occurred in 46% of children that were observed for 6 months.[52] When obese and non-obese children were compared, obese participants were less likely to improve. PSG findings were normalized in 54% of obese children vs. 85% of non-obese children that underwent early adenotonsillectomy. As well, only 29% of obese children vs. 67% of non-obese children had improved PSG findings when no adenotonsillectomy was performed.[52]

Studies have shown that pre-pubertal adolescents that were initially considered to be cured of OSA by AT had recurrence later as teenagers.[157,158] Patients that were initially treated with AT had narrowing behind the base of the tongue and other anatomical abnormalities that

either were not identified previously or were not present during the initial exam.[157] A narrow upper airway and snoring was shown to persist 12 years after AT.[158] Complete resolution of OSA following AT was present in only 51% of non-obese pre-pubertal children when studied with a PSG 3 months post-operatively.[159] AT was also shown to lead to significant improvements in many indices of SDB in children, however, 70% of children above 7 years old or those who were obese had residual OSA.[160] Therefore, regular monitoring is necessary for patients even if they had a good response to AT.[153]

1.10.2 Noninvasive Positive Airway Pressure

Noninvasive Positive Airway Pressure (PAP) therapy is recommended for children who are not candidates for AT, who need a temporizing therapy pending a definitive surgical intervention and/or those with persistent moderate to severe OSA post AT.[153] PAP works by counteracting sleep-induced negative transmural pressure that promotes collapse and narrowing of the upper airway. Upper airway patency is maintained by delivery of pressurized air that creates a pneumatic splint to prevent partial or complete collapse of the airway during sleep.[161] The aim of PAP therapy is to normalize obstructive apnea hypopnea index (OAHI), improve sleep quality, and normalize gas exchange. There are two main types of noninvasive PAP therapy that are delivered through masks that are worn over the nose or both the nose and mouth: 1) continuous positive airway pressure (CPAP) and 2) Bi-level positive airway pressure (BPAP).

PAP therapy has been shown to be an effective treatment of pediatric OSA across all age groups.[3] Marcus *et al.* showed that both CPAP and BPAP were both efficacious in reducing AHI from 27 ± 32 to 3 ± 5 per hour.[162] However, 27.6% of 29 children did not adhere for at least 6 months and for the children who did adhere to PAP use, the average nightly use was 5.3 ± 2.5

hours.[162] Furthermore, a study on 99 Australian children found that adherence (>4 hours/night for at least 70% of nights over 1 year) was higher in those that used BPAP (80%) compared to CPAP (76%).[163]

However, PAP therapy may be cumbersome to wear and the greatest barrier to effective treatment is adherence.[164] A 3 month follow up study found that maternal education was the main predictor for number of nights used and hours of PAP use per night.[165] They also found that adherence to PAP was lower in African American children compared to other races and correlated inversely with age.[165] Adherence was not correlated with severity of OSA or pressure levels.[165] The successful implementation of PAP therapy in the home for a child often involves the whole family and requires cooperation and commitment from both the patient and the parents.[153] A 3 year follow up after initiation of PAP therapy found that patients with more severe OSA, higher BMI, and subjective daytime sleepiness were more adherent to PAP therapy.[166] However, in children and adolescents, the adherence to PAP therapy appears to be primarily related to family and demographic factors rather than OSA severity or measures of psychosocial functioning.[165] Complications of PAP include skin erythema and breakdown, midface hypoplasia, gastric insufflation, aspiration risk, nosebleeds, nasal congestion, eye irritation, rebreathing CO_2, pulmonary air leaks, and cardiovascular complications (decreased venous return, right atrial filling, and left ventricular filling).[167]

There are contradictory reports regarding the long-term effects of PAP therapy on the development of the face, jaws, and teeth.[3] Some case reports suggest that early childhood long-term treatment with either CPAP or BPAP carries a high risk of facial growth impairment, particularly, midface hypoplasia and Class III malocclusions.[168,169] However, a cross-sectional study by Korayem *et al.* of 12 children (mean age of 9 years) that wore PAP for 6 months for at

least 6 hours per night, showed no statistically significant difference in midface projection compared to 11 healthy controls.[170] However, these conflicting results may be a result of differences in the ages of the children studied as well as duration of PAP therapy.

1.10.3 Orthodontic Treatment

Orthodontic appliances have been considered as potential treatment options for patients with persistent or residual OSA post AT. Craniofacial abnormalities with imbalanced development may contribute to OSA.[171] These include posterior crossbites, Class II skeletal and dental malocclusions, and anterior open bite.[172] Orthodontic treatment improves esthetic and occlusal relationships, but can also help guide facial growth to correct facial imbalances, improve swallowing, reposition tongue posture, and re-establish nasal breathing.[172] Extraction of teeth is commonly performed to aid with orthodontic treatment, however, the absence of four premolars by extraction therapy was shown to not be a significant factor in the cause of OSA.[173]

Rapid Maxillary Expansion

Rapid Maxillary Expansion (RME) is a common orthodontic procedure used to correct maxillary arch constriction and posterior crossbites by separation of the mid-palatal suture prior to its fusion.[172] It is commonly used in children and adolescents in the primary, mixed, or permanent dentition.

Maxillary constriction is common in children with OSA and many children have associated nasal obstruction due to nasal septum deviation with or without turbinate hypertrophy.[174] The exact pathophysiology of maxillary constriction in OSA is unclear, however, it is thought that maxillary constriction increases nasal resistance and alters the tongue

position. This leads to narrowing of the retroglossal airway and the subsequent development of OSA.[174]

In terms of oropharyngeal airway volume, there currently isn't any evidence to support enlargement via RME. Adolescent patients with maxillary constriction were treated with hyrax palatal expanders for routine orthodontic treatment. Compared to controls, cone-beam computed tomography (CBCT) showed no significant differences in volume, length, and minimum cross-sectional area of the oropharynx.[175]

Although RME may not affect oropharyngeal volume, it may affect the nasopharynx as RME has been shown to increase nasal width and nasal cavity dimensions and in doing so, reducing the nasal resistance to airflow.[16] Pirelli *et al.* investigated the effect of RME on 31 children with maxillary constriction, without adenoid hypertrophy, with OSA demonstrated by PSG.[176] The duration of RME treatment was between 10-20 days with 6-12 months of retention. The mean AHI fell from 12.2 to less than one event per hour, demonstrating resolution of OSA. The authors also investigated whether RME could improve patency of nasal breathing and OSA in 31 children with a history of snoring, mouth breathing, and night time apneas. Posterior-anterior cephalometric evaluations were performed before orthodontic treatment, one month after initiation of treatment, and at the end of orthodontic treatment. They concluded that in children with BMI < 24 kg/m^2 and no adenotonsillar hypertrophy, RME widens the nasal fossa and releases the septum with restoration of normal nasal airflow and a disappearance of obstructive SDB.[177] A 12 year follow up of these patients showed no significant changes in PSG findings into adulthood with stability of the maxillary base as shown by CT imaging.[178]

Functional Appliance Therapy

Functional appliances can be either removable or fixed intraoral devices that can alter muscular forces on teeth and the underlying craniofacial skeletal as well as change the resting posture of the mandible. Altered neuromuscular action can affect bony growth and the developing occlusion. Functional appliances have been used in children because they posture the mandible forward and potentially enlarge the upper airway to improve respiratory function.[179]

A 2016 Cochrane review on the effectiveness of using functional appliances for the treatment of OSA in children only identified one paper that met their inclusion criteria.[180] The authors concluded that there is insufficient evidence to support or refute the effectiveness of functional orthopaedic appliances for the treatment of OSA in children but they may be considered in specific cases as an auxiliary in the treatment of children with craniofacial abnormalities which are risk factors for OSA. Regarding, the one study that was included in the Cochrane review, this was a randomized controlled trial of an active oral appliance vs. no treatment in 32 children with OSA defined by an AHI > 1 event/hour as diagnosed by PSG. 9 participants were lost to follow up and of the remaining sample, 14 were treated with an oral appliance. Pretreatment AHI was 7.1 ± 3.6 which decreased to 2.6 ± 2.2 after 6 months of treatment ($p < 0.001$).[181]

1.11 OSA and Craniofacial and Dentofacial Development

Craniofacial structures can be defined as structures of the cranium, specifically, the skeletal and neuromuscular structures of the skull, brain, and the face.[146] Dentofacial structures refer to the skeletal and neuromuscular structures of the face, mouth, and teeth and their relationship to each other.[146] Craniofacial growth and development in children is a result of both

genetic and environmental influences.[34] There can be craniofacial and dentofacial morphological sequelae secondary to upper airway obstruction.[182]

Linder-Aronson first described the effect of the adenoids on the mode of breathing and their relationship with dentofacial characteristics in children in a series of elegant experiments.[183] Enlarged adenoids or an anatomical defect such as decreased nasal width or nasal septum deviation reduce nasal breathing and result in mouth breathing as the primary mode of respiration. Mouth breathing leads to an altered pattern of muscle recruitment in the oral and nasal capsule, ultimately resulting in skeletal changes.[184] Increased nasal resistance resulting from nasal obstruction in the first 6 months of life in baby rhesus monkeys has been shown to lead to narrowing of the dental arches, decreased maxillary length, anterior crossbite, maxillary overjet, and an increase in anterior face height.[184,185] These changes were shown to be reversible when the nasal obstruction and resistance was removed while the monkey was still in its developmental phase.[184]

Mouth breathing in children is commonly associated with an extended head posture (3-5° extended craniocervical posture), retrognathic mandible, an increased anterior face height, steeper mandibular plane, a lowered hyoid bone, anterior-inferior posture of the tongue, and high palatal vault.[186] This pattern of findings is termed the “long face syndrome” or “adenoid facies”.[55-57,183] A typical adenoid face is characterized by incompetent lips, narrow maxillary dental arch, retroclined mandibular incisors, increased anterior face height, steep mandibular plane, and retrognathic mandible.[183]

Dentofacial anomalies can be present as malocclusions which can be identified during routine intra-oral examinations. Specifically, posterior crossbite, Class II skeletal and dental

malocclusion, and anterior open bite are more prevalent in children with OSA versus controls.[187] The prevalence of posterior crossbite in children with OSA is between 16.7%-68.2% versus 2.4%-23.2% in controls.[59,188,189] The prevalence of Class II skeletal and dental patterns in children with OSA is between 29.3%-88% versus 4.9%-28% in controls.[188-190] The prevalence of anterior open bite in children with OSA is between 5%-20% versus 0% in controls.[60,188,189] However, only one study confirmed the presence of OSA with PSG[189], while the others used questionnaires to confirm OSA.

The literature is contradictory regarding the resolution versus the persistence of craniofacial and dentofacial abnormalities after treatment for OSA in children. Some studies have shown that cephalometric variables normalize after early treatment of OSA with AT, while others have shown that open bites and crossbites are still present 2 years after AT.[57,187] However, the studies greatly differed in methodology as the former had OSA confirmed by PSG pre-treatment only, while the former did not confirm OSA with PSG. It is recommended that children with OSA are diagnosed early and treatment is initiated at a young age so that sequelae of the disease are prevented and any long term craniofacial and dentofacial changes are normalized.[57,187]

Two systematic reviews by Flores-Mir *et al*. and Katyal *et al.* in 2013 compared cephalometric radiograph findings between non-syndromic healthy children and children with OSA.[59,61] Flore-Mir *et al.* identified 9 studies that met their inclusion criteria and a total of 198 children with PSG confirmed OSA were compared against age-matched controls.[61] They reported significant findings in children with OSA having a more retrusive chin (mean difference SNB = -1.79°, $p < 0.001$), steeper mandibular plane (mean difference MP-SN = 4.2°, $p < 0.001$), and a tendency towards Class II malocclusion (mean difference ANB = 1.38°, $p < 0.001$).[61]

Katyal *et al.* identified 9 studies in their review that included a total of 264 children with OSA confirmed with either PSG or questionnaires.[59] Similarly, they found that children with OSA had a steeper mandibular plane angle (mean difference MP-SN = 2.74°, $p = 0.006$) and larger ANB angle (mean difference ANB = 1.64°, $p < 0.0001$).[59]

1.13 Study Rationale

Currently, the understanding of OSA as it relates to craniofacial and dentofacial morphology is unclear due to varying methodological approaches. Almost all studies do not use the gold standard, PSG, to confirm the presence or absence of OSA. Furthermore, there is limited literature that addresses craniofacial morphology in populations that are at higher risk of OSA, including children with DS or children with obesity. Formal orthodontic clinical and radiographic examinations are not part of the clinical standard of care in most sleep medicine programs. Furthermore, the assessment of craniofacial features can be subjective resulting in significant inter-clinician variation. Therefore, it is important to establish a standard clinical examination protocol when screening these high risk populations and to be able to correlate these with objective measures of craniofacial features that may be risk factors of the presence of pediatric OSA.

1.14 Study Aim

The primary aim of this study was to describe and compare the craniofacial morphology of children with suspected OSA who have been referred for a PSG in two pediatric cohorts of patients: DS and Obesity. The secondary aim of our study was to identify clinical and/or cephalometric predictors of OSA in the two cohorts of children: DS and Obesity.

Chapter 2: Methods and Materials

2.1 Study Design

This was a cross-sectional study that took place at the Hospital for Sick Children (SickKids) in Toronto, Ontario, Canada. Ethics approval was obtained from both the University of Toronto Health Sciences Research Ethics Board (Protocol #31147) and the Hospital for Sick Children's Research Ethics Board (REB #1000047032).

2.2 Study Population and Participants

Children who were referred to the sleep laboratory at SickKids for an overnight PSG between October 2016 and February 2018 were screened to determine eligibility for participation in the study according to the inclusion and exclusion criteria listed in Table 2.1.

Table 2.1 Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Age 5 to 18 years • Diagnosis of DS or Obesity • Referred for a PSG at SickKids	• Children and/or parental caregivers who were not proficient in English

2.3 Study Procedures

After consent and enrolment into the study, each participant underwent the following study procedures:

1) Demographic and Anthropometric Measures
2) Sleep Questionnaires
    a. Sleep Related Breathing Disorders (SRBD) Scale of the PSQ
    b. Spruyt and Gozal Sleep Questionnaire
3) Clinical Orthodontic Examination

4) Polysomnogram
5) Lateral Cephalogram

Study procedures 1-4 were completed at the SickKids Sleep Laboratory on the night of their scheduled sleep study. The lateral cephalogram was taken by an x-ray technologist in the SickKids Orthodontic Clinic the morning after the PSG was completed.

2.3.1 Demographic and Anthropometric Measures

The following demographic and anthropometric information was collected for each patient: 1) date of sleep study; 2) age; 3) date of birth; 4) gender; 5) country of origin of mother; 6) country of origin of father; 7) body type; 8) height; 9) weight; and 10) BMI.

Each participant's BMI was calculated using the formula BMI = Weight (kg)/Height^2 (m^2). The resultant BMI was then converted into a percentile for the population according to the patient's age and gender using the BMI percentile calculator by the Centers for Disease Control and Prevention (CDC).[191] Charts specifically designated for DS pediatric populations were used to determine the BMI percentile for the DS group.[192]

2.3.2 Sleep Questionnaires

Sleep Related Breathing Disorders Scale of the PSQ

The parents and guardians of each patient completed the Sleep-Related Breathing Disorders (SRBD) Scale of the PSQ. There are 22 items for the SRBD scale, each with the following response options: yes, no, or don't know. The SRBD scale is scored by dividing the number of items answered positively ("yes") by the number of items answered either positively ("yes") or negatively ("no"). Items that have missing responses or are answered as "don't know"

are excluded. The resultant score could range from 0 to 1.0. Scores greater than 0.33 were considered to be positive and suggestive of pediatric SDB.[126]

Spruyt and Gozal Sleep Questionnaire

A second questionnaire completed by the parents or guardians of the participants was the Spruyt and Gozal Sleep Questionnaire.[136] This questionnaire consists of 6 questions that are answered based on the preceding 6-month time frame and use a Likert-type response scale. Questions 1-4 and 6 are scored for the following responses: “never” (0), “rarely” (1), “occasionally” (2), “frequently” (3) and “almost always” (4). Question 5 addresses snoring and are scored for the following responses: “mildly quiet” (0), “medium loud” (1), loud (2), “very loud” (3) and “extremely loud” (4). The total score for the questionnaire was calculated based on the following formula (where Q1 = raw score to question 1, Q2 = raw score to question 2, and so forth): A = (Q1 + Q2)/2; B = (A + Q3)/2; C = (B + Q4)/2; D = (C + Q5)/2; and the cumulative score = D + Q6)/2. A cumulative score that is equal to or greater than 2.72 is indicative of the child having a high risk for OSA.[136]

2.3.3 Clinical Orthodontic Examination

All study participants underwent the same comprehensive clinical examination by the same examiner, C.N. The examination consisted of measurements that addressed the dental, skeletal, functional, and esthetic features of the participant. The clinical examination was subdivided into three sections: 1) Frontal View, 2) Profile View, and 3) Intra-Oral Examination.

Frontal View

The frontal view examination began with determining the facial type as either mesocephalic (average head), brachycephalic (broad and short head), or dolichocephalic (narrow and long head). The lower face height was measured by comparing the soft tissue upper face height (soft tissue glabella to soft tissue subnasale) to the soft tissue lower face height (soft tissue subnasale to soft tissue menton). A normal face height existed if the ratio between the soft tissue upper face height to soft tissue lower face height was approximately 1:1.[146] If the lower face height was shorter than the upper face height (soft tissue face height ratio greater than 1:1), a decreased lower face height existed. Contrarily, if the lower face height was greater than the upper face height (soft tissue face height ratio less than 1:1), an increased lower face height existed. Mandibular symmetry was assessed by determining the position of the chin point relative to the facial midline in the absence of a functional shift. Maxillary and mandibular dental midlines were assessed relative to the facial midline and if a deviation existed, the amount of deviation relative to the facial midline was recorded in millimeters. Incisor and gingival display in the anterior were assessed both at rest and during smile and recorded to the nearest 1 millimeter. Measurements were completed with a periodontal probe with markings at 1 mm intervals. Table 2.2 summarizes the frontal view examination.

Table 2.2 Frontal View Examination

Frontal View	
1. Facial Type (if borderline, choose mesocephalic)	☐ Mesocephalic ☐ Brachycephalic ☐ Dolichocephalic
2. Lower Face Height	☐ Normal ☐ Increased ☐ Decreased
3. Symmetry	☐ Symmetric ☐ Mandible shift to Right ☐ Mandible shift to Left
4. Dental Midlines (midline – use cusp of upper lip)	Upper: ☐ on with facial midline ☐ shift to Right ☐ shift to Left; Amount : ____mm Lower: ☐ on with facial midline ☐ shift to Right ☐ shift to Left; Amount : ____mm
5. Incisor Display at Rest	____ mm
6. Gingival Display on Smile	____ mm
7. Incisor Display on Smile	____ mm

Profile View

The profile view section of the clinical examination evaluated the participant's profile, the anteroposterior relationship of the maxilla, mandible, upper lip, and lower lip, the nasolabial angle and lip strain.[146] The facial profile was assessed by measuring the angle formed between a line extending from soft tissue nasion to soft tissue subnasale and a second line extending from soft tissue subnasale and soft tissue pogonion. A straight line indicated a straight profile, while an acute angle indicated a convex profile, and an obtuse angle indicated a concave profile. Lip position was determined relative to a straight line from the tip of the nose to the most anterior point on the curvature of the soft tissue chin. The nasolabial angle was measured as either normal (90°-100°), acute (<90°), or obtuse (>100°). Lip strain was assessed by the activity of

the mentalis muscle when the lips were brought into contact with each other. Table 2.3 summarizes the profile view examination.

Table 2.3 Profile View Examination

Profile View			
8. Facial Profile	☐ Straight	☐ Concave	☐ Convex
9. Skeletal Position - Maxilla	☐ Retrognathic	☐ Normal	☐ Prognathic
10. Skeletal Position - Mandible	☐ Retrognathic	☐ Normal	☐ Prognathic
11. Nasolabial Angle	☐ Normal 90º-100º	☐ Acute (<90º)	☐ Obtuse (>100º)
Lip Position 12. With respect to esthetic line: Upper lip	☐ Normal	☐ Retrusive	☐ Protrusive
13. With respect to esthetic line: Lower lip	☐ Normal	☐ Retrusive	☐ Protrusive
14. Lip strain to close	☐ Yes	☐ No	

Intra-Oral Examination

Table 2.4 summarizes the evaluation of tonsil size and history of mouth breathing. Tonsil size was evaluated and graded according to the Standardized Tonsillar Hypertrophy Grading Scale.[193] Surgically removed tonsils were graded as tonsil size 0. Tonsil size 1 denotes tonsils hidden within the tonsillar pillars. If the tonsils extended to the edge of the tonsillar pillars, a grading of tonsil size 2 was noted. Tonsil size 3 describes tonsils that extend beyond the pillars but not to the midline. When the tonsils are so enlarged that they extend to the midline, tonsil size 4 was recorded. Participants and parents were also asked about history of mouth breathing during the day and night.

Table 2.4 Tonsil Size and Mouth Breathing

Tonsil Size and Mouth Breathing	
15. Tonsils	☐ Removed ☐ 1+ ☐ 2+ ☐ 3+ ☐ 4+ (kissing tonsils)
16. History of Mouth Breathing	☐ Yes ☐ No If YES: ☐ During Day Time ☐ During Night Time

The intra-oral section of the clinical examination is summarized in Table 2.5. The intra-oral examination measured discrepancies in all 3 planes: horizontal, vertical, and anterior-posterior. Interarch relationships and maxillary and mandibular crowding and/or spacing were also assessed.

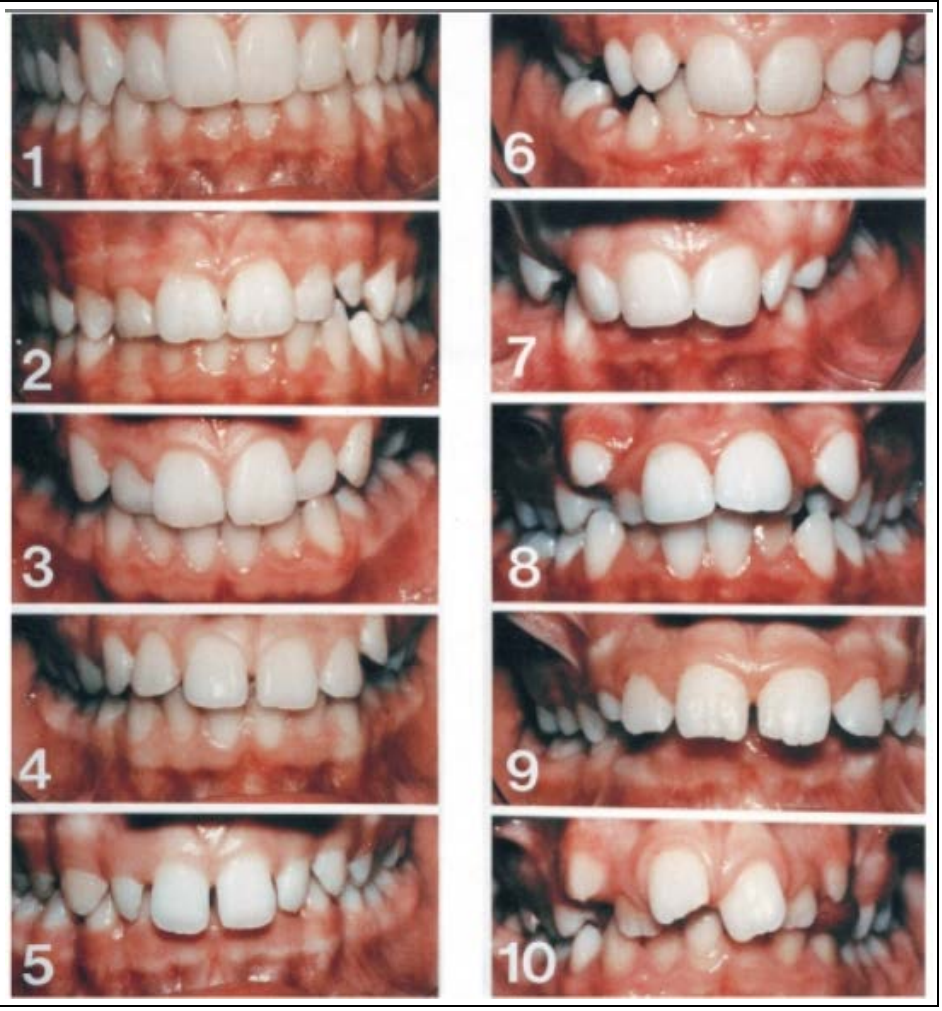
Participants were asked about oral habits and since when they started those habits as seen in Table 3.5. Overjet was measured by taking the average measurement from the labial of the mandibular central incisors to the incisal edge of the maxillary central incisors. Overbite was measured as the percentage of the total height of the mandibular central incisor that was overlapped by the opposing maxillary central incisor. If no overbite existed, 0% was recorded, and the amount of anterior open bite measured between the edges of the maxillary central incisor and mandibular central incisors was also recorded. Posterior open bite was measured to the nearest millimeter along the buccal segments. Measurements were completed with a periodontal probe to the nearest millimeter. The teeth that were present were charted on an odontogram. Anterior and posterior crossbites were recorded and the number of maxillary teeth in crossbite was specified. Posterior crossbites included maxillary posterior teeth that were in a cusp-to-cusp relationship or lingually positioned compared to the mandibular posterior teeth. CR/CO shifts were recorded with the direction of the shift. Intermolar width was measured from the lingual groove of the maxillary first molars at the gingival margin. Maxillary intercanine width was

measured from cusp tip to cusp tip. Intermolar and intercanine distances were measured with a Boley gauge with 0.1 mm accuracy. Tongue size was assessed and relative macroglossia was recorded if crenations were present on the lateral aspects of the tongue. Arch shape was noted as either U or V shaped and it was recorded if the palate was narrow. Palatal depth was measured from the occlusal plane of the maxilla at the level of the premolars or primary molars. Permanent molar relationships for both the left and right sides were classified according to Angle's classification (Class I, II, or III). Terminal plane relationships for mixed and primary dentition was noted and canine classifications were also recorded. Molar and canine relationships that deviated half a cusp or less from Class I were considered Class I. Crowding and/or spacing for both the maxillary and mandibular dental arches were recorded as either mild (< 3 mm), moderate (4-9 mm), or severe (> 10 mm). The Index of Orthodontic Treatment Need (IOTN) esthetic scale was used to match the participants' malocclusion.[194]

Table 2.5 Intra-Oral Examination

Intra-Oral Examination	
17. Oral Habits	☐ Yes ☐ No **If YES**, since when:_____ years
Which?	☐ Nail Biting ☐ Biting Lip/Cheek ☐ Bruxism ☐ Sucking Thumb/Finger ☐ Other: _____
18. Horizontal Excess	*Overjet*: ☐☐☐ mm
19. Vertical Excess	*Overbite*: ☐☐☐ %
20. Anterior Open Bite	*Open bite*: ☐☐☐ mm
21. Posterior Open Bite Right	☐☐☐ mm
22. Posterior Open Bite Left	☐☐☐ mm

23. Odontogram	<table><tr><td>8</td><td>7</td><td>6</td><td>5</td><td>4</td><td>3</td><td>2</td><td>1</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td></tr><tr><td></td><td></td><td></td><td>E</td><td>D</td><td>C</td><td>B</td><td>A</td><td>A</td><td>B</td><td>C</td><td>D</td><td>E</td><td></td><td></td><td></td></tr><tr><td></td><td></td><td></td><td>E</td><td>D</td><td>C</td><td>B</td><td>A</td><td>A</td><td>B</td><td>C</td><td>D</td><td>E</td><td></td><td></td><td></td></tr><tr><td>8</td><td>7</td><td>6</td><td>5</td><td>4</td><td>3</td><td>2</td><td>1</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td></tr></table>
24. Dental Crossbite (including edge-to-edge bite)	Anterior crossbite: ☐ Yes; **If YES**, # of maxillary teeth involved: ____ ☐ No Posterior crossbite: ☐ Yes ☐ Unilateral; **If YES,** # of maxillary teeth involved: ____ ☐ Bilateral ☐ No
25. Narrow Palate	☐ Yes ☐ No
26. CR/CO Shift	☐ Yes, **specify**: ☐ Posterior-Anterior ☐ Vertically ☐ To the Right ☐ To the Left ☐ No
27. Intermolar Distance (from lingual groove at gingival margin)	☐☐☐ mm
28. Intercanine Distance (cusp tip to cusp tip)	☐☐☐ mm
29. Tongue Size	☐ Normal ☐ Microglossia ☐ Macroglossia (Relative)
30. Arch Shape	Upper: ☐ U shape ☐ V shape Lower: ☐ U shape ☐ V shape
31. Palatal Depth	☐☐☐ mm
32. Stage of Dentition	☐ Primary ☐ Mixed ☐ Permanent (No primary teeth present)

33. Molar Classification	Permanent: (<1/2 cusp = I) Right: ☐ I ☐ II ☐ III Left: ☐ I ☐ II ☐ III	Primary/Mixed: Right: ☐ Mesial Step ☐ Flush ☐ Distal Step Left: ☐ Mesial Step ☐ Flush ☐ Distal Step
34. Canine Classification (<1/2 cusp = I)	Right: ☐ I ☐ II ☐ III Left: ☐ I ☐ II ☐ III	
35. Space Analysis	☐ Crowding Upper: ☐ <3 mm ☐ 4-9 mm ☐ >10mm Lower: ☐ <3 mm ☐ 4-9 mm ☐ >10mm ☐ Spacing Upper: ☐ <3 mm ☐ 4-9 mm ☐ >10mm Lower: ☐ <3 mm ☐ 4-9 mm ☐ >10mm	
36. IOTN Esthetic Scale (match for overall occlusal attractiveness)		

2.3.4 Polysomnogram

Following the clinical examination, participants underwent a standard level one overnight PSG using XLTEK Sleep Diagnostics equipment with Natus SleepWorks Software (Natus Neurology Incorporated DBA XLTEK, Oakville, ON, Canada). The PSG recording used a 6-lead EEG (C3, C4, O1, O2, M1 and M2), two bilateral EOG leads, submental EMG leads and two tibial EMG leads. Respiratory measurements were accomplished with the use of a Braebon Q-RIP Respiratory Inductive Plethysmography kit, Braebon Ultima Nasal Pressure transducer, and Braebon Ultima Airflow Sensor (Braebon Medical Corporation, Kanata, ON, Canada). Oxygen saturation (SaO_2) was recorded with a pulse oximeter (Masimo Corpororation, Irvine, CA, USA). Sensors for transcutaneous carbon dioxide ($TcCO_2$) (SenTec AG, Therwil, Switzerland) were used and end-tidal carbon dioxide ($EtCO_2$) was monitored with a BCI Capnocheck Sleep CO_2 Detector (Smiths Medical, Dublin, OH, USA). Video and audio was also recorded during each PSG.

Sleep architecture, respiratory data, oxygen saturation, and carbon dioxide recordings from the PSG were analyzed and scored according to the American Academy of Sleep Medicine (AASM) scoring guidelines by a registered polysomnographic technologist.[10] Table 2.6 summarizes the variables that were collected from each PSG.

Table 2.6 PSG Recording Variables

PSG Recording Variable
Total Sleep Time (TST) (minutes)
Sleep Efficiency (%)
Wakefulness After Sleep Onset (WASO) (minutes)
Sleep Onset Latency (minutes)
REM Latency (minutes)
%TST in REM Sleep (%)
Arousal Index (# arousals/hour sleep)
Mean and Minimum Oxygen Saturation (%)
Oxygen Desaturation Index (#/hour)
Time spent < 90% Oxygen Saturation (minutes)
Mean Respiratory Rate (bpm)
Mean, Minimum, and Maximum Heart Rate (bpm)
Minimum and Maximum End-Tidal Carbon Dioxide ($EtCO_2$) (mmHg)
Minimum and Maximum Transcutaneous Carbon Dioxide ($TcCO_2$) (mmHg)
% Time > 50 mmHg $EtCO_2$ (%)
% Time > 50 mmHg $TcCO_2$ (%)
Central Apnea-Hypopnea Index (# events/hour)
Obstructive Apnea-Hypopnea Index (# events/hour)
Total Apnea-Hypopnea Index (# events/hour)

PSG reporting and the diagnosis of OSA was completed by clinical sleep physicians and respirologists at SickKids. OSA diagnosis and severity was based on measures from the PSG such as: obstructive apnea-hypopnea index (OAHI), mean and minimum oxygen saturations, and percentage of time the level of CO_2 was > 50 mmHg. OSA was diagnosed in children according to the following categories: normal (OAHI < 1), mild OSA ($1 \leq$ OAHI < 5), moderate OSA ($5 \leq$ OAHI < 10), and severe OSA (OAHI $\geq$ 10).[8]

2.3.5 Lateral Cephalogram

In the morning following their polysomnogram, participants presented to the Orthodontic Clinic at SickKids Hospital for a lateral cephalogram. Lateral cephalograms were taken with a PaX-i machine (VATECH America, Fort Lee, NJ, USA) with a setting of 85 kVp and a current of 9 mA. Participants wore a lead apron and thyroid collar during acquisition of the image. Lateral cephalograms were imported into Dolphin version 11.2 (Dolphin Imaging & Management Solutions, Chatsworth, CA, USA) and were traced by one investigator, C.N. The cephalometric measurements that were used for analysis are listed in Table 2.7.

Table 2.7 Cephalometric Measurements

Cephalometric Measurement
Sella-Nasion-A Point (SNA) (°)
Sella-Nasion-B Point (SNB) (°)
A point-Nasion-B point Angle (ANB) (°)
Upper Incisor to NA Distance (U1-NA) (mm)
Lower Incisor to NA Distance (L1-NA) (mm)
Pogonion to NB Distance (Pg-NB) (mm)
Interincisal Angle (°)
Mandibular Length (Co-Gn) (mm)
Maxillary Length (Co-A) (mm)
Unit Length Difference (Co-Gn – Co-A) (mm)
Lower Anterior Face Height (ANS-Me) (mm)
Frankfort Mandibular Plane Angle (MP-SN) (°)
Lower Incisor Protrusion (L1-APo) (mm)
Nasion-ANS (perpendicular to Horizontal Plane) (mm)
ANS-Gn (perpendicular to Horizontal Plane) (mm)
Nasolabial Angle (°)
Incisor Mandibular Plane Angle (L1-MP) (°)
Upper Incisor Palatal Plane Angle (U1-PP) (°)
Wits Appraisal (mm)
Overjet (mm)
Overbite (mm)
Upper Incisor Exposure (mm)

2.4 Statistical Analysis

The study results were summarized using descriptive statistics. Continuous data was presented as medians and interquartile ranges, while categorical variables were presented as counts and percentages. Due to a small sample size, non-parametric statistical tests were performed. Mann-Whitney U tests were used to compare continuous data between participants with OSA and without OSA within DS and Obesity groups. Spearman correlation coefficients

were used to determine the relationship between continuous variables from the clinical examination and lateral cephalograms with OAHI. The diagnostic abilities of the two questionnaires were summarized with receiver operating characteristics (ROC) curves, sensitivities, specificities, and odds ratios.

Intra-rater reliability testing was performed for the lateral cephalometric measurements. To calculate the intra-class correlation coefficient (ICC), ten randomly selected lateral cephalograms (5 from the DS group and 5 from the Obesity group) were re-traced 4 months after the initial tracing, producing two sets of 22 cephalometric measurements from 10 patients. ICC were calculated for each of the 22 cephalometric measurements using a 95% confidence interval. Multivariable regression analysis was not completed due to the overall small sample size. Data analysis and statistics were completed with SAS software version 9.4 (North Carolina, USA) and IBM SPSS software version 23 (Armonk, New York, USA).

2.5 Study Outcomes

The primary outcome was the prevalence of dentofacial abnormalities and malocclusions in two pediatric cohorts of DS or Obesity who were referred for a polysomnogram because of a history of query OSA. Our secondary outcome measure was the identification of clinical factors that can predict the obstructive apnea-hypopnea index (OAHI), a measure of the OSA severity, in these referred cohorts of children.

2.6 Hypothesis

Our study hypothesis was that there is an increased prevalence of dentofacial abnormalities and malocclusions in children in both the DS group and Obesity group with OSA as compared to those with these conditions without a PSG determined diagnosis of OSA.

Chapter 3: Results

3.1 Study Participants

Overall, sixty-eight children were approached to participate in this study over a recruitment period of 16 months (October 2016 – February 2018). Thirteen (19.1%) did not consent and the most common reason for declining participation was due to being unable to complete all study procedures, specifically the lateral cephalogram. Of the remaining fifty-five participants, thirteen (23.6%) did not have a lateral cephalogram taken. The final study sample consisted of forty two patients (DS = 20, Obesity = 22). The demographic information for the study sample is summarized in Table 3.1.

Table 3.1 Demographic Information for the Study Cohort

Characteristics	DS (n = 20)	Obesity (n = 22)	p
Age (Years)	11.5 (5.4)	12.9 (6.5)	0.33
Male	12 (60%)	14 (64%)	0.81
Height (cm)	136.3 (28)	161.3 (30.5)	< 0.01*
Weight (kg)	49.4 (36.3)	92.5 (71.4)	< 0.01*
BMI (kg/m^2)	22.7 (9.7)	37.5 (16.7)	< 0.01*
BMI Centile	75 (25.6)	99.0 (0.3)	< 0.01*
No OSA	3 (15%)	8 (36.4%)	0.12
OSA (OAHI > 1)	17 (85%)	14 (63.6%)	0.12
Adenotonsillectomy	15 (75%)	11 (50%)	0.10
Mouth Breather	17 (85%)	16 (73%)	0.33

Continuous variables are expressed as median (interquartile range)
Categorical variables are expressed as n (%)
*Statistically Significant as defined by $p < 0.05$

Compared to the DS group, the Obesity group was taller ($p < 0.01$), heavier ($p < 0.01$), and had and increased BMI ($p < 0.01$) and BMI centile ($p < 0.01$). OSA appeared to be more common in the DS group (85%) compared to the Obesity group (63.6%), although not statistically significant ($p = 0.12$). OSA was defined based on PSG findings of OAHI > 1 and the sample was further divided into 4 groups: 1) DS (n = 3); 2) DS with OSA (n = 17); 3) Obesity (n = 8); and 4) Obesity with OSA (n = 14).

3.2 Clinical Orthodontic Examination Results

Features of the study participants identified during the clinical orthodontic examination for the DS and Obesity groups are summarized in Table 3.2 and Table 3.3, respectively.

Table 3.2 The Frequency of Clinical Examination Features of the DS Group

Frequency of Clinical Features	DS (n = 3)	DS with OSA (n = 17)	p
Normal LFH	2	7	
Increased LFH	-	-	0.41
Decreased LFH	1	10	
Straight Profile	1	6	
Convex Profile	1	1	0.33
Concave Profile	1	10	
Orthognathic Mx	2	6	
Retrognathic Mx	1	11	0.31
Prognathic Mx	-	-	
Orthognathic Md	2	14	
Retrognathic Md	1	1	0.31
Prognathic Md	-	2	
Normal Tongue Size	2	4	
Microglossia	-	1	0.32
Macroglossia (Relative)	1	12	
Class I	3	8	
Class II	-	2	0.27
Class III	-	7	

Table 3.3 The Frequency of Clinical Examination Features of the Obesity Group

Frequency of Clinical Features	Obesity (n = 8)	Obesity with OSA (n = 14)	p
Normal LFH	4	10	
Increased LFH	2	3	0.45
Decreased LFH	2	1	
Straight Profile	5	5	
Convex Profile	3	9	0.23
Concave Profile	-	-	
Orthognathic Mx	8	14	
Retrognathic Mx	-	-	-
Prognathic Mx	-	-	
Orthognathic Md	5	5	
Retrognathic Md	3	9	0.23
Prognathic Md	-	-	
Normal Tongue Size	7	13	
Microglossia	-	-	0.67
Macroglossia (Relative)	1	1	
Class I	7	9	
Class II	0	3	0.35
Class III	1	2	

Upon clinical orthodontic examination, DS with OSA appeared to frequently present with a decreased lower face height (LFH), concave profile, retrognathic maxilla, relative macroglossia, and Class III malocclusion compared to DS without OSA. However, these findings were not statistically significant between DS with OSA and without OSA. Obesity with OSA appeared to present with a convex profile and retrognathic mandible compared to Obesity without OSA. However, these frequencies were also not statistically significant between Obesity with OSA and without OSA.

Measurements made during the clinical orthodontic examination for the DS and Obesity groups are summarized in Table 3.4 and Table 3.5, respectively.

Table 3.4 Clinical Examination Measurements for the DS Group

Measured Variables	DS (n = 3)	DS with OSA (n = 17)	p
Incisor Display at Rest (mm)	0	0 (1.5)	0.62
Gingival Display on Smile (mm)	0	0	0.49
Incisor Display on Smile (mm)	3.0	3.0 (3.8)	0.88
Overjet (mm)	2.0	-0.25 (2.3)	0.21
Overbite (%)	0	2.5 (20)	0.21
Intermolar Distance (mm)	30.5	32.5 (4.3)	0.36
Intercanine Distance (mm)	28.0	29.0 (4.8)	0.62
Palatal Depth (mm)	15.0	20.5 (5.1)	<0.01*
Median (Interquartile Range); *Statistically Significant as defined by $p < 0.05$			

Table 3.5 Clinical Examination Measurements for the Obesity Group

Measured Variables	Obesity (n = 8)	Obesity with OSA (n = 14)	p
Incisor Display at Rest (mm)	2.0 (2.8)	1.5 (2.0)	0.57
Gingival Display on Smile (mm)	0 (1.0)	0 (0.3)	0.71
Incisor Display on Smile (mm)	6.0 (4.5)	9.5 (4.0)	0.15
Overjet (mm)	3.0 (2.4)	2.0 (3.3)	0.87
Overbite (%)	40.0 (43.8)	30.0 (42.5)	0.71
Intermolar Distance (mm)	36.5 (7.6)	38.8 (6.9)	0.30
Intercanine Distance (mm)	33.8 (7.4)	32.7 (4.1)	0.66
Palatal Depth (mm)	22.3 (3.4)	23.0 (7.8)	0.92
Median (Interquartile Range); *Statistically Significant as defined by $p < 0.05$			

DS with OSA had a significantly deeper palatal vault compared to DS without OSA ($p < 0.01$). None of the clinical measurements were significantly different between Obesity with OSA and without OSA.

Table 3.6 and Table 3.7 shows the correlation between the clinical examination measurement and OAHI for the DS and Obesity groups, respectively.

Table 3.6 The Correlation Between Clinical Examination Measurements and OAHI for the DS Group

Measured Variables	Spearman's Correlation Coefficient	p
Incisor Display at Rest (mm)	0.15	0.54
Gingival Display on Smile (mm)	0.03	0.90
Incisor Display on Smile (mm)	0.17	0.48
Overjet (mm)	0.03	0.92
Overbite (%)	0.14	0.58
Intermolar Distance (mm)	0.42	0.07
Intercanine Distance (mm)	0.48	0.03*
Palatal Depth (mm)	0.42	0.08
*Statistically Significant as defined by $p < 0.05$		

Table 3.7 The Correlation Between Clinical Examination Measurements and OAHI for the Obesity Group

Measured Variables	Spearman's Correlation Coefficient	p
Incisor Display at Rest (mm)	-0.18	0.42
Gingival Display on Smile (mm)	0.15	0.52
Incisor Display on Smile (mm)	0.17	0.44
Overjet (mm)	0.01	0.98
Overbite (%)	0.002	0.99
Intermolar Distance (mm)	0.09	0.70
Intercanine Distance (mm)	-0.16	0.49
Palatal Depth (mm)	-0.04	0.85
*Statistically Significant as defined by $p < 0.05$		

Intercanine distance (Spearman's correlation coefficient = 0.48, p = 0.03) for the DS group was significantly correlated to OAHI. Figure 3.1 shows a positive relationship between DS intercanine distance and OAHI.

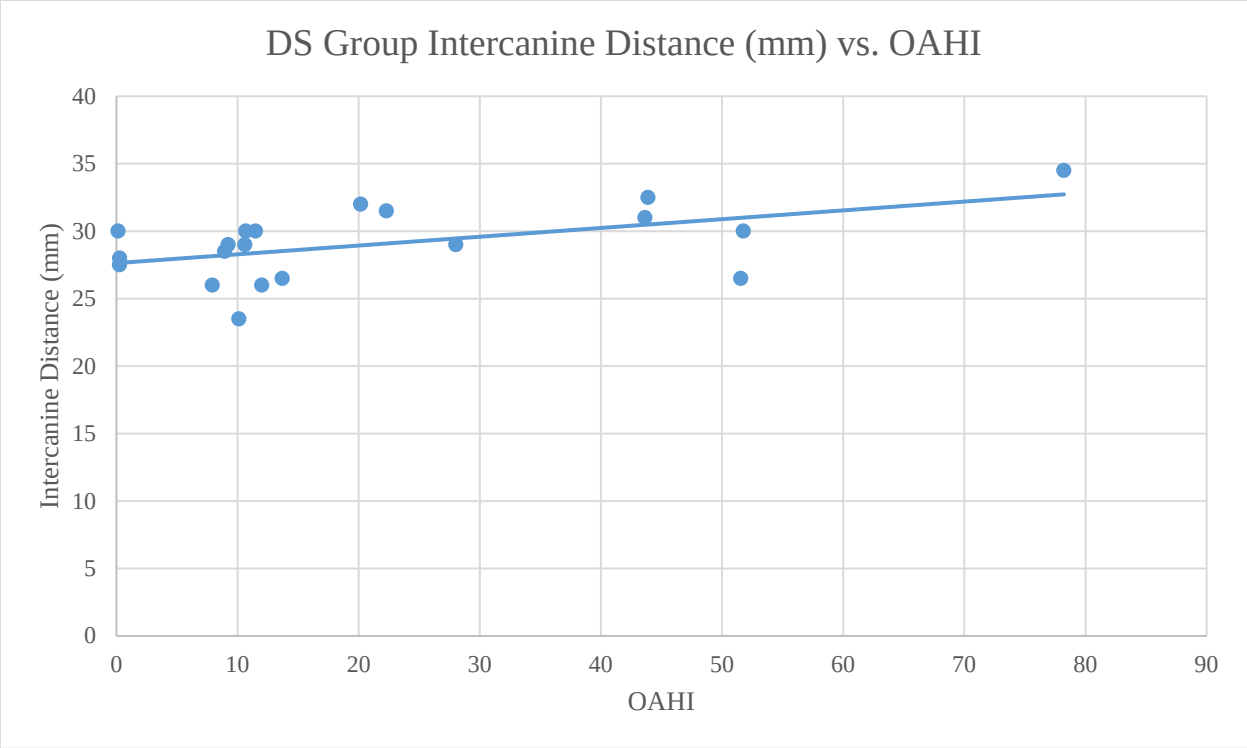


Figure 3.1 The Correlation Between Intercanine Distance (mm) and OAHI for the DS Group (r = 0.48, p = 0.03)

3.3 Polysomnography Results

Table 3.8 and Table 3.9 below summarize the findings from the overnight PSG recordings for DS and Obesity groups, respectively.

Table 3.8 PSG Recording Measurements for the DS Group

PSG Recording		DS (n = 3)	DS with OSA (n = 17)	p
Total Sleep Time (TST) (Minutes)		436.5	391 (63.3)	0.01*
Sleep Efficiency (%)		93.6	82.9 (17)	0.31
Wakefulness After Sleep Onset (WASO; Minutes)		20.0	41.0 (59.3)	0.55
Sleep Onset Latency (Minutes)		13.6	20.8 (42.3)	0.55
REM Latency (Minutes)		218.5	201.5 (119.0)	0.92
% TST in REM Sleep		18.0	12.0 (9.0)	0.48
Arousal Index (# arousals/hour sleep)		10.6	14.8 (13.0)	0.09
Oxygen Saturation	**Mean (%)**	96	96 (3)	> 0.99
	Minimum (%)	92	85 (9.5)	0.01*
Oxygen Desaturation Index (#/hour sleep)		1.7	16.6 (30.6)	< 0.01*
Time Spent < 90% Oxygen Saturation (Minutes)		0	1.3 (16.9)	0.02*
Mean Respiratory Rate (bpm)		20.8	18.4 (10.6)	0.45
Heart Rate (bpm)	**Mean**	78.9	74.4 (15)	0.82
	Minimum	56.5	53 (14.7)	0.22
	Maximum	119.0	127.1 (21.8)	0.69
CO_2 (mmHg)	**$EtCO_2$ Min**	36	38 (5)	0.77
	$EtCO_2$ Max	46	53 (6.8)	0.14
	$TcCO_2$ Min	38	40 (5.5)	0.36
	$TcCO_2$ Max	50	50 (4)	0.77
% Time > 50 mmHg $EtCO_2$ (%)		0.10	2.3 (10)	0.12
% Time > 50 mmHg $TcCO_2$ (%)		0	0.8 (7.2)	0.18
CAI (# events/hour)		0.5	0.8 (4.6)	0.62
OAHI (# events/hour)		0.26	13.7 (33.4)	< 0.01*
AHI (# events/hour)		1.0	14.7 (26.6)	< 0.01*
Median (Interquartile Range); *Statistically Significant as defined by $p < 0.05$				

Table 3.9 PSG Recording Measurements for the Obesity Group

PSG Recording		Obesity (n = 8)	Obesity with OSA (n = 14)	p
Total Sleep Time (TST) (Minutes)		391.3 (102.0)	375.5 (96.1)	0.44
Sleep Efficiency (%)		87.8 (20)	86.8 (23)	0.82
Wake After Sleep Onset (WASO; Minutes)		22.3 (30.1)	23.3 (78.5)	0.48
Sleep Onset Latency (Minutes)		16.8 (21.7)	18.2 (30.2)	0.87
REM Latency (Minutes)		151.0 (61.5)	118.8 (146.6)	0.86
% TST in REM Sleep		14.8 (8.8)	17.7 (8.7)	0.57
Arousal Index (# arousals/hour sleep)		10.0 (5.3)	12.7 (5.0)	0.21
Oxygen Saturation	**Mean (%)**	97 (2)	97 (1)	0.48
	Minimum (%)	91.5 (3)	88.5 (7)	0.03*
Oxygen Desaturation Index (#/hour sleep)		1.6 (3.9)	5.0 (11.5)	0.02*
Time Spent < 90% Oxygen Saturation (Minutes)		0 (0.1)	0.1 (1.4)	0.10
Mean Respiratory Rate (bpm)		19.3 (14.9)	18.5 (12.0)	0.44
Heart Rate (bpm)	**Mean**	76.8 (17.4)	83.3 (18.0)	0.66
	Minimum	58.5 (22.8)	61.6 (21.7)	0.92
	Maximum	116.8 (21.4)	122.7 (14.4)	0.48
CO_2 (mmHg)	**$EtCO_2$ Min**	35.0 (7.0)	33.0 (10.0)	0.58
	$EtCO_2$ Max	47.0 (8.5)	49.0 (7.0)	0.74
	$TcCO_2$ Min	38.0 (5.3)	37.5 (8.5)	0.40
	$TcCO_2$ Max	46.5 (3.8)	46.0 (5.5)	0.92
% Time > 50 mmHg $EtCO_2$ (%)		0.05 (3.4)	0.05 (0.3)	0.71
% Time > 50 mmHg $TcCO_2$ (%)		0 (0)	0 (0)	0.92
CAI (# events/hour)		0.4 (1.4)	0.6 (2.0)	0.97
OAHI (# events/hour)		0.6 (0.8)	3.9 (11.9)	< 0.01*
AHI (# events/hour)		1.5 (2.2)	5.9 (12.7)	0.01*
Median (Interquartile Range); *Statistically Significant as defined by $p < 0.05$				

DS with OSA had a statistically significant decreased total sleep time ($p = 0.01$) and minimum percent oxygen saturation ($p = 0.01$) than DS without OSA. DS with OSA also had a statistically significant greater oxygen desaturation index ($p < 0.01$), time spent < 90% oxygen saturation ($p = 0.02$), OAHI ($p < 0.01$), and AHI ($p < 0.01$) score than DS without OSA.

Obesity with OSA had a lower minimum percent oxygen saturation ($p = 0.03$) than obesity without OSA. Obesity with OSA also had a greater time spent with < 90% oxygen saturation ($p = 0.02$), OAHI ($p < 0.01$), and AHI ($p = 0.01$) score than obesity without OSA.

3.4 Lateral Cephalometric Results

Lateral cephalograms were traced and measurements were calculated by Dolphin version 11.2 (Dolphin Imaging & Management Solutions, Chatsworth, CA, USA). The measurements for the DS and Obesity groups are listed in Table 3.10 and Table 3.11, respectively.

Table 3.10 Cephalometric Measurements for the DS Group

Cephalometric Measurement	DS (n = 3)	DS with OSA (n = 17)	p
SNA (°)	77.8	78.8 (8.3)	0.62
SNB (°)	73.8	80.4 (7.4)	0.26
ANB (°)	2.9	0.4 (6.8)	0.22
U1-NA (mm)	1.5	4.6 (4.3)	0.31
L1-NB (mm)	3.5	5.9 (3.3)	0.42
Pog-NB (mm)	-0.1	-0.4 (2.2)	0.62
Interincisal Angle (U1-L1) (°)	127.9	120 (18.1)	0.69
Mandibular Length (Co-Gn) (mm)	94.1	97.2 (14.2)	0.77
Midface Length (Co-A) (mm)	74.5	71.3 (8)	0.36
Mx/Md Diff (Co-Gn - Co-A) (mm)	19.7	26.4 (9.1)	0.12
FMA (Md Plane-SN) (°)	41.0	34.6 (10.8)	0.36
LAFH (ANS-Me) (mm)	55.2	56.7 (10.0)	0.62
L1 Protrusion (L1-APo)	1.3	5.3 (4.5)	0.18
N-ANS (perp HP) (mm)	42.1	42.1 (5.6)	0.77
ANS-Gn (perp HP)	48.6	54.7 (11.4)	0.12
Nasolabial angle (Col-Sn-UL) (°)	100.6	106.2 (15.2)	0.48
IMPA (L1-MP) (°)	91.6	100.5 (7.8)	0.48
U1-PP (°)	119.3	117.2 (15.6)	> 0.99
Wits appraisal (mm)	-1.1	-1.9 (5.7)	0.42
Overjet (mm)	1.4	0.2 (4.9)	0.26
Overbite (mm)	-1.6	-1.7 (8)	0.62
Upper 1 Exposure (mm)	0.9	-0.6 (4.4)	0.36
Median (Interquartile Range)			

Table 3.11 Cephalometric Measurements for the Obesity Group

Cephalometric Measurement	Obesity (n = 8)	Obesity with OSA (n = 14)	p
SNA (°)	84.6 (9.8)	85.2 (10.0)	0.62
SNB (°)	82.6 (10.8)	81.5 (4.9)	0.53
ANB (°)	1.5 (1.9)	4.3 (4.1)	0.03*
U1-NA (mm)	4.7 (4.1)	3.7 (3.9)	0.30
L1-NB (mm)	2.6 (4.7)	4.3 (4.6)	0.19
Pog-NB (mm)	2.6 (6.4)	-0.15 (3.7)	0.11
Interincisal Angle (U1-L1) (°)	130.2 (24.9)	126.8 (22.8)	0.66
Mandibular Length (Co-Gn) (mm)	116.9 (18.9)	107.9 (13.9)	0.40
Midface Length (Co-A) (mm)	83.2 (11.2)	80.6 (8.0)	0.57
Mx/Md Diff (Co-Gn - Co-A) (mm)	31.1 (10.5)	27.7 (8.6)	0.30
FMA (Md Plane-SN) (°)	26.8 (19.0)	36.4 (8.1)	0.21
LAFH (ANS-Me) (mm)	61.5 (14.6)	64.7 (9.0)	0.66
L1 Protrusion (L1-APo)	0.7 (6.9)	2.1 (5.3)	0.66
N-ANS (perp HP) (mm)	48.1 (11.3)	48.4 (5.1)	0.87
ANS-Gn (perp HP)	60.5 (16.3)	62.8 (9.6)	0.82
Nasolabial angle (Col-Sn-UL) (°)	108.3 (19.4)	110.6 (21.2)	0.33
IMPA (L1-MP) (°)	91.6 (7.8)	89.2 (8.6)	0.48
U1-PP (°)	114.4 (20.5)	110.9 (13.2)	0.62
Wits appraisal (mm)	-1.8 (2.4)	-1.9 (5.4)	0.97
Overjet (mm)	2.7 (2.0)	3.3 (3.5)	0.82
Overbite (mm)	0.3 (3.4)	0.6 (3.6)	0.57
Upper 1 Exposure (mm)	4.1 (3.6)	3.9 (5.4)	0.76
Median (Interquartile Range); *Statistically Significant as defined by $p < 0.05$			

For the DS group, there were no statistically significant differences between those with OSA and those without OSA. ANB angle was significantly greater in Obesity with OSA compared to those without OSA ($p = 0.03$). Table 3.12 and Table 3.13 show the correlation

between cephalometric measurements and OAHI for both the DS and Obesity groups, respectively.

Table 3.12 The Correlation Between Cephalometric Measurements and OAHI for the DS Group

Cephalometric Measurement	Spearman's Correlation Coefficient	p
SNA (°)	0.17	0.47
SNB (°)	0.29	0.21
ANB (°)	-0.35	0.13
U1-NA (mm)	0.22	0.34
L1-NB (mm)	0.09	0.72
Pog-NB (mm)	-0.17	0.48
Interincisal Angle (U1-L1) (°)	0.05	0.85
Mandibular Length (Co-Gn) (mm)	0.14	0.55
Midface Length (Co-A) (mm)	-0.13	0.59
Mx/Md Diff (Co-Gn - Co-A) (mm)	0.30	0.20
FMA (Md Plane-SN) (°)	-0.15	0.52
LAFH (ANS-Me) (mm)	0.11	0.66
L1 Protrusion (L1-APo)	0.31	0.19
N-ANS (perp HP) (mm)	-0.24	0.31
ANS-Gn (perp HP)	0.27	0.26
Nasolabial angle (Col-Sn-UL) (°)	0.17	0.47
IMPA (L1-MP) (°)	0.03	0.91
U1-PP (°)	-0.16	0.50
Wits appraisal (mm)	-0.14	0.57
Overjet (mm)	-0.10	0.68
Overbite (mm)	0.18	0.45
Upper 1 Exposure (mm)	0.08	0.75

Table 3.13 The Correlation Between Cephalometric Measurements and OAHI for the Obesity Group

Cephalometric Measurement	Spearman's Correlation Coefficient	p
SNA (°)	0.16	0.48
SNB (°)	-0.25	0.27
ANB (°)	0.58	< 0.01*
U1-NA (mm)	-0.53	0.01*
L1-NB (mm)	0.17	0.44
Pog-NB (mm)	-0.33	0.14
Interincisal Angle (U1-L1) (°)	0.14	0.53
Mandibular Length (Co-Gn) (mm)	-0.32	0.15
Midface Length (Co-A) (mm)	-0.28	0.21
Mx/Md Diff (Co-Gn - Co-A) (mm)	-0.35	0.11
FMA (Md Plane-SN) (°)	0.33	0.14
LAFH (ANS-Me) (mm)	-0.01	0.95
L1 Protrusion (L1-APo)	-0.05	0.82
N-ANS (perp HP) (mm)	-0.03	0.90
ANS-Gn (perp HP)	-0.07	0.77
Nasolabial angle (Col-Sn-UL) (°)	0.19	0.40
IMPA (L1-MP) (°)	-0.02	0.39
U1-PP (°)	-0.41	0.06
Wits appraisal (mm)	0.02	0.94
Overjet (mm)	0.04	0.86
Overbite (mm)	0.18	0.42
Upper 1 Exposure (mm)	-0.08	0.72
*Statistically Significant as defined by $p < 0.05$		

None of the cephalometric measurements for the DS group were significantly correlated with OAHI. For the Obesity group, ANB angle (Spearman correlation coefficient = 0.58, p <

0.01) and Upper Incisor to Nasion-A point distance (Spearman correlation coefficient = -0.53, p = 0.01) were significantly correlated with OAHI. Figure 3.2 shows a positive relationship between ANB angle and OAHI in the Obesity group, while Figure 3.3 shows a negative relationship between upper incisor distance to nasion-A point line and OAHI in the Obesity group.

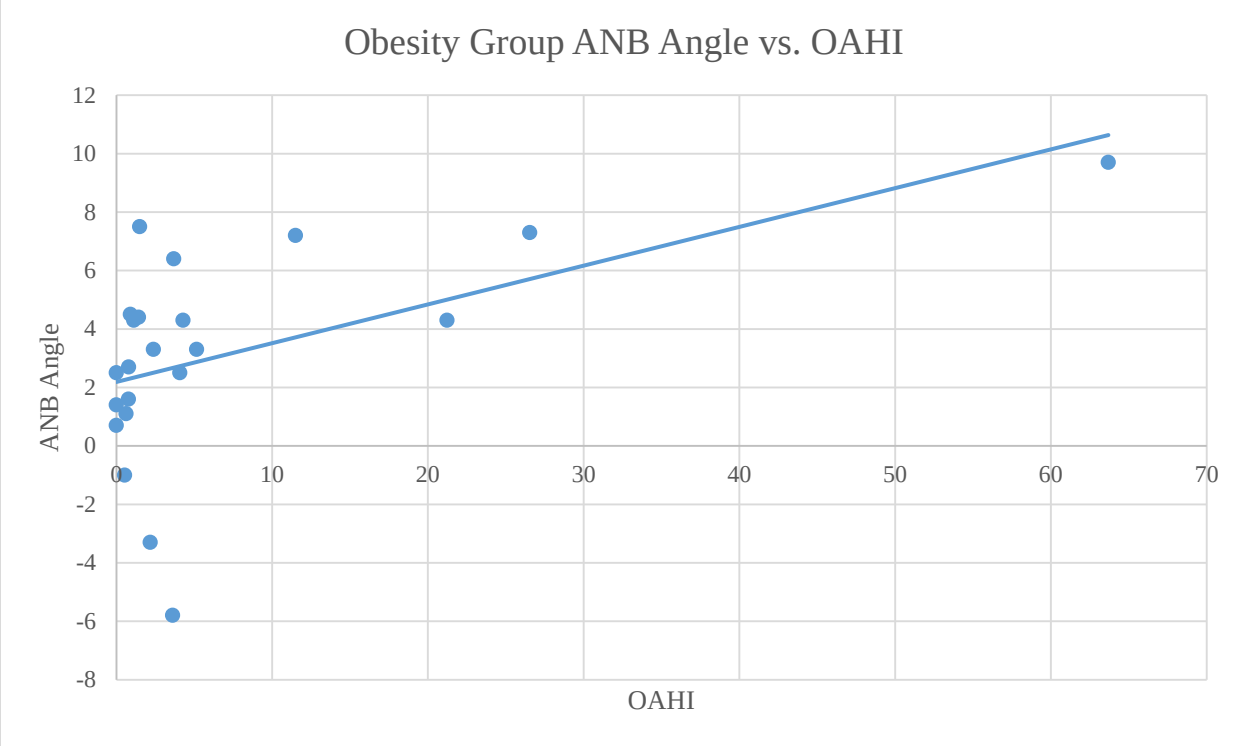


Figure 3.2 The Correlation Between ANB Angle and OAHI in the Obesity Group (r = 0.58, p < 0.01)

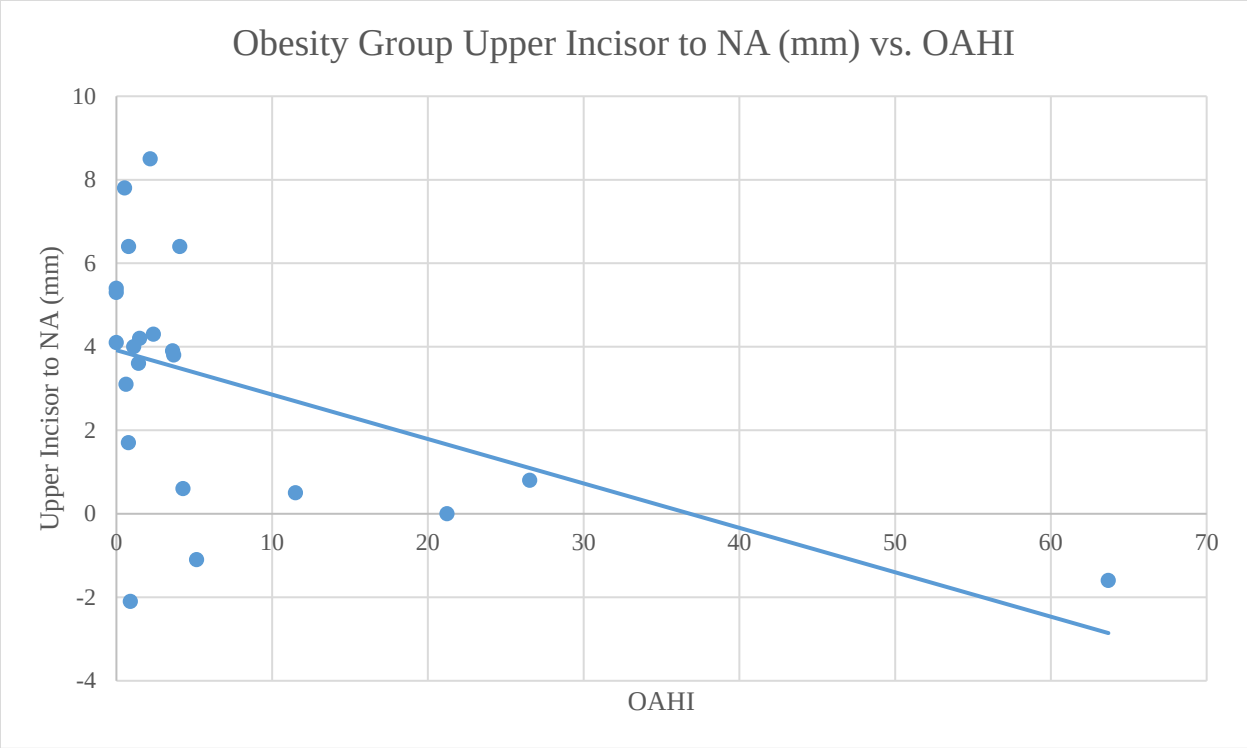


Figure 3.3 The Correlation between Upper Incisor to NA Plane (mm) and OAHI in the Obesity Group (r = -0.53, p = 0.01)

3.5 Intra-Class Correlation Coefficient

To test intra-examiner reliability, after 4 months of the first cephalometric tracing and measurements, cephalograms for 10 randomly selected subjects (5 subjects from the DS group and 5 subjects in the Obesity group) were retraced and cephalometric analysis was performed again, using the same method and cephalometric software as used in the first tracing and analysis. These two sets of measurements in 10 subjects were used to determine the intra-class correlation coefficients (Table 3.14). Each of the 22 cephalometric measurements had an ICC > 0.9, demonstrating excellent agreement between each of the measurements at the two time points.

Table 3.14 Intra-Class Correlation Coefficient for all 22 Cephalometric Measurements Recorded 4 months Apart

Cephalometric Measurement	Intra-Class Correlation Coefficient	95% Confidence Interval	p
SNA (°)	0.993	0.971 to 0.998	< 0.01
SNB (°)	0.996	0.985 to 0.999	< 0.01
ANB (°)	0.979	0.917 to 0.995	< 0.01
U1-NA (mm)	0.991	0.963 to 0.998	< 0.01
L1-NB (mm)	0.987	0.949 to 0.997	< 0.01
Pog-NB (mm)	0.957	0.826 to 0.989	< 0.01
Interincisal Angle (U1-L1) (°)	0.991	0.965 to 0.998	< 0.01
Mandibular Length (Co-Gn) (mm)	0.993	0.974 to 0.998	< 0.01
Midface Length (Co-A) (mm)	0.977	0.906 to 0.994	< 0.01
Mx/Md Diff (Co-Gn - Co-A) (mm)	0.993	0.973 to 0.998	< 0.01
FMA (Md Plane-SN) (°)	0.993	0.971 to 0.998	< 0.01
LAFH (ANS-Me) (mm)	0.994	0.974 to 0.998	< 0.01
L1 Protrusion (L1-APo)	0.994	0.977 to 0.999	< 0.01
N-ANS (perp HP) (mm)	0.992	0.968 to 0.998	< 0.01
ANS-Gn (perp HP)	0.993	0.971 to 0.998	< 0.01
Nasolabial angle (Col-Sn-UL) (°)	0.966	0.863 to 0.992	< 0.01
IMPA (L1-MP) (°)	0.983	0.933 to 0.996	< 0.01
U1-PP (°)	0.972	0.889 to 0.993	< 0.01
Wits appraisal (mm)	0.965	0.861 to 0.991	< 0.01
Overjet (mm)	0.995	0.979 to 0.999	< 0.01
Overbite (mm)	0.972	0.885 to 0.993	< 0.01
Upper 1 Exposure (mm)	0.989	0.954 to 0.997	< 0.01

3.6 Sleep Questionnaire Results

The 2 x 2 contingency tables for the Spruyt and Gozal Sleep Questionnaire for the diagnosis of OSA are shown in Table 3.15 and Table 3.16 for the DS and Obesity groups, respectively.

Table 3.15 Contingency Table for the Spruyt and Gozal Sleep Questionnaire and the Diagnosis of OSA for the DS Group

DS		OSA (OAHI > 1.0)	
		Yes	No
Spruyt and Gozal Score > 2.72	Yes	3	1
	No	14	2

Table 3.16 Contingency Table for the Spruyt and Gozal Sleep Questionnaire and the Diagnosis of OSA for the Obesity Group

Obesity		OSA (OAHI > 1.0)	
		Yes	No
Spruyt and Gozal Score > 2.72	Yes	3	0
	No	11	8

The Spruyt and Gozal Questionnaire was able to correctly identify children who have OSA (OAHI > 1.0) with a sensitivity of 17.7% and specificity of 66.7% for the DS group. A sensitivity of 21.4% and specificity of 100% were calculated for the Obesity group. The odds ratio for DS having OSA with a Spruyt and Gozal score that was greater than 2.72 was 0.4 (95% confidence interval (0.03-6.4), p = 0.54). The odds ratio for Obesity having OSA with a Spruyt and Gozal score that was greater than 2.72 was 5.2 (95% confidence interval (0.2-114.1), p =

0.30). Neither of these odds ratios were significant. Receiver operating characteristics (ROC) curves for the Spruyt and Gozal questionnaire to screen for OSA in the DS and Obesity groups are shown in Figure 3.4 and Figure 3.5, respectively. Both curves closely approximate the straight diagonal reference line, suggesting that the Spruyt and Gozal questionnaire is a poor screening tool for OSA diagnosis in both the DS and Obesity groups.

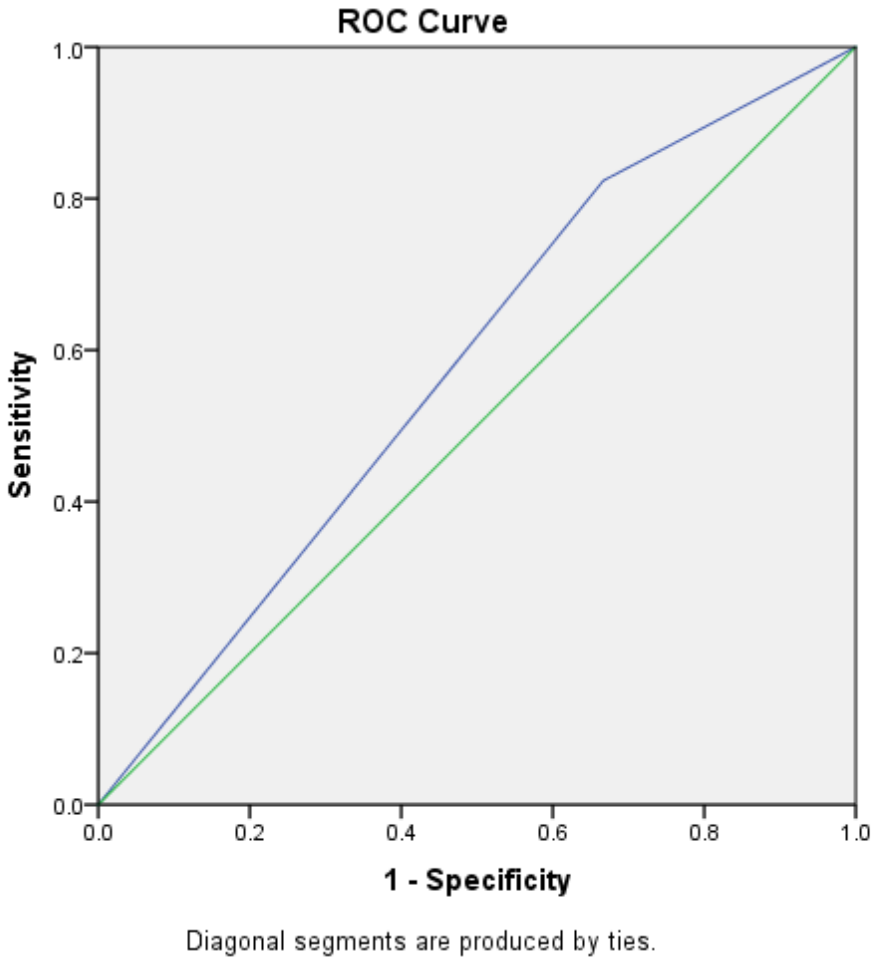


Figure 3.4 ROC Curve for Spruyt & Gozal Questionnaire for screening OSA in the DS Group (Blue = ROC Curve; Green = Diagonal reference line; Area under the curve = 0.58; Standard error = 0.19)

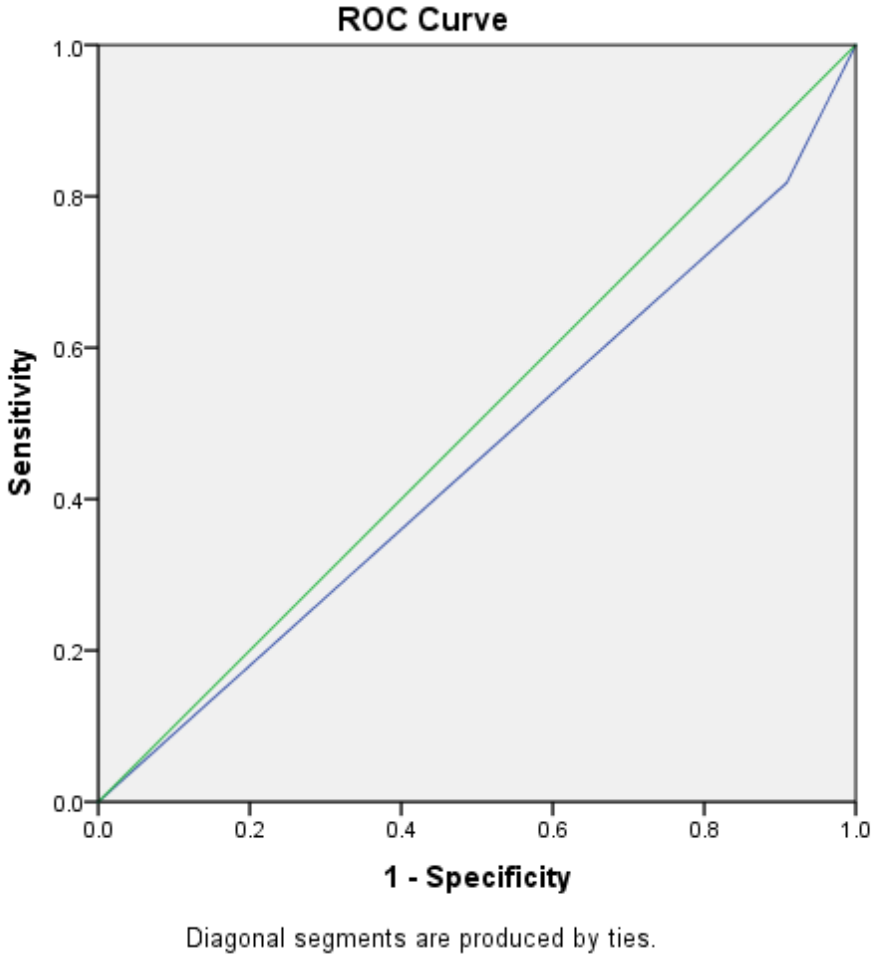


Figure 3.5 ROC Curve for Spruyt & Gozal Questionnaire for screening OSA in the Obesity Group (Blue = ROC Curve; Green = Diagonal reference line; Area under the curve = 0.46; Standard error = 0.13)

Likewise, the 2 x 2 contingency tables for the SRBD scale of the PSQ for the diagnosis of OSA are shown in Table 3.17 and Table 3.18 for the DS and Obesity groups, respectively.

Table 3.17 Contingency Table for the SRBD Scale of the PSQ and the Diagnosis of OSA for the DS Group

DS		OSA (OAHI > 1.0)	
		Yes	**No**
SRBD Score > 0.33	**Yes**	12	2
	No	5	1

Table 3.18 Contingency Table for the SRBD Scale of the PSQ and the Diagnosis of OSA for the Obesity Group

Obesity		OSA (OAHI > 1.0)	
		Yes	**No**
SRBD Score > 0.33	**Yes**	9	6
	No	5	2

The SRBD scale of the PSQ was able to identify DS with OSA (OAHI > 1) with a sensitivity of 70.6% and specificity of 33.3%. For the Obesity group, a sensitivity of 64.3% and specificity of 25.0% were calculated. The odds ratio for the children with OSA having a SRBD score that was greater than 0.33 was 1.2 for the DS group (95% confidence interval = 0.09-16.4, p = 0.89) and 0.6 for the Obesity group (95% confidence interval = 0.08-4.1, p = 0.61). ROC curves for the SRBD scale of the PSQ to screen for OSA in the DS and Obesity groups are shown in Figure 3.6 and Figure 3.7, respectively. Both curves closely approximate the straight diagonal reference line, suggesting that the SRBD scale of the PSQ is a poor screening tool for OSA diagnosis in DS and Obesity groups.

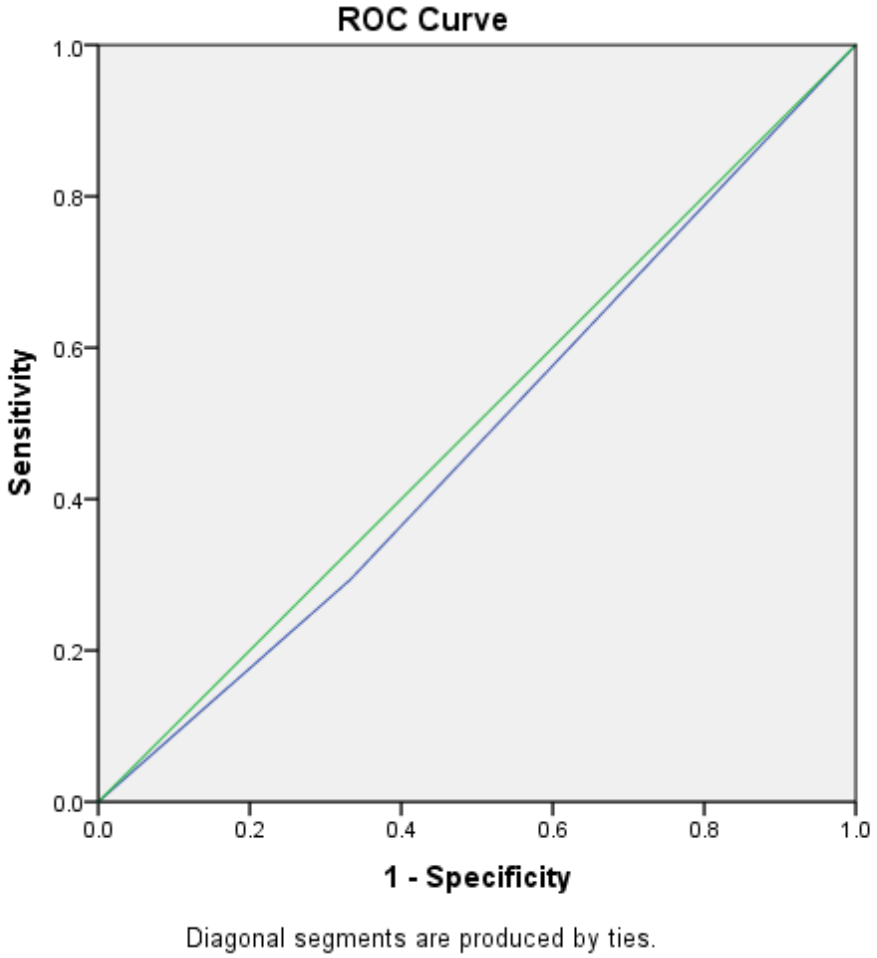


Figure 3.6 ROC Curve for SRBD scale of the PSQ for screening OSA in the DS Group (Blue = ROC Curve; Green = Diagonal reference line; Area under the curve = 0.48; Standard error = 0.19)

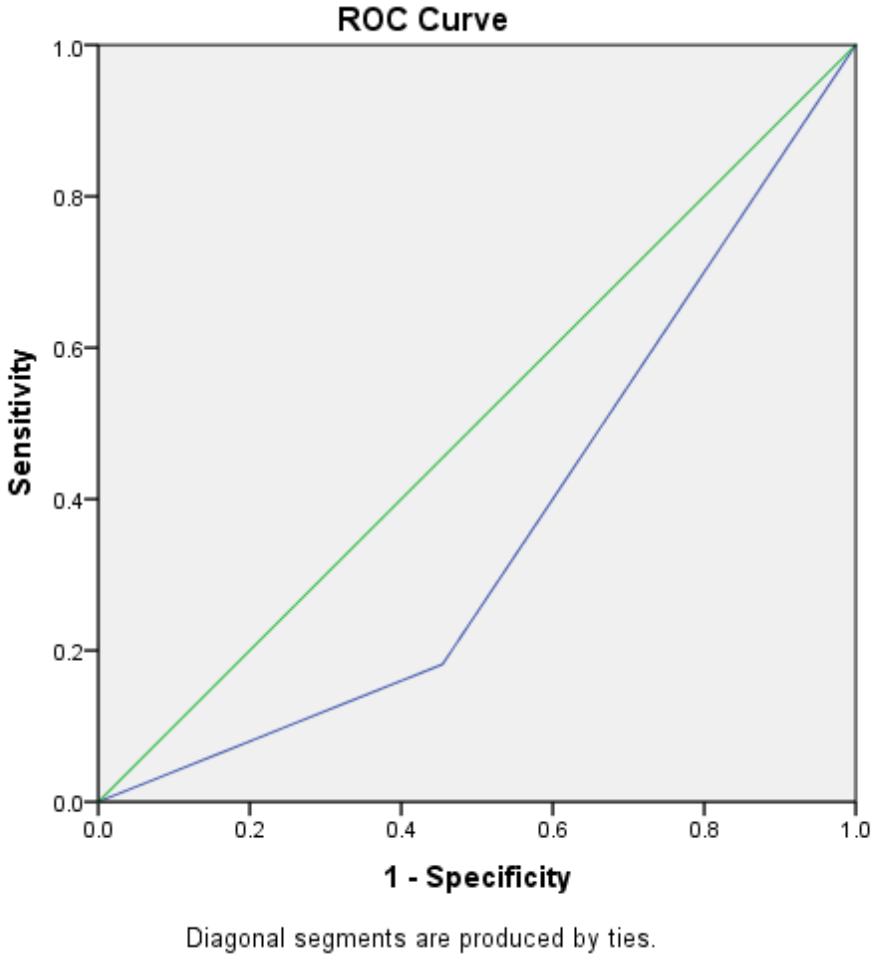


Figure 3.7 ROC Curve for SRBD scale of the PSQ for screening OSA in the Obesity Group (Blue = ROC Curve; Green = Diagonal reference line; Area under the curve = 0.36; Standard error = 0.12)

Table 3.19 summarizes the correlation with OAHI for the Spruyt and Gozal scores and SRBD scores for both the DS and Obesity groups. None of the relationships were statistically significant.

Table 3.19 The Correlation Between Questionnaire Scores and OAHI for Each of the DS and Obesity Cohorts

Group	Questionnaire	Spearman's Correlation Coefficient	p
DS	Spruyt & Gozal Score vs. OAHI	0.23	0.33
	SRBD Score vs. OAHI	0.33	0.16
Obesity	Spruyt & Gozal Score vs. OAHI	0.26	0.24
	SRBD Score vs. OAHI	-0.06	0.79

Chapter 4: Discussion

We are reporting for the first time on dentofacial and craniofacial predictors of PSG confirmed pediatric OSA in DS and Obesity populations. We have identified simple clinical and radiographic measurements that can be collected at minimal cost and effort in these two populations. OSA predictors identified in the DS group include palatal depth ($p < 0.01$) and maxillary intercanine distance ($p = 0.03$), while those in the Obesity group include ANB angle ($p = 0.03$) and upper incisor position ($p = 0.01$).

PSG findings identified DS and Obesity individuals with OSA as defined by an OAHI > 1. OSA was diagnosed in 85% of the DS group and in 63.6% of the Obesity group ($p = 0.12$). The children were examined clinically and were evaluated in all three planes of space: vertical, transverse, and anterior-posterior. It was found that none of the dentofacial features were more frequently identified in children with OSA and without OSA in either the DS or Obesity groups. Clinical measurements showed no statistically significant differences between Obesity with and without OSA. For the DS group, it was found that those with OSA had a deeper palatal vault compared to those without OSA ($p < 0.01$). However, the median age for the DS group without OSA was 8.9 years compared to 12.6 years for children with OSA. One potential explanation for this finding is that the greater palatal depth found in the DS group with OSA was due to regular growth. The maxilla grows vertically and remodels with deposition on the nasal floor side and resorption on the palatal side, according to Enlow's "V" principle.[195,196] However, it has been shown that children with obstructed breathing present with higher palatal vaults than those without breathing disorders, and the effects of OSA on these children may have contributed to the higher palatal vaults.[56,183,197]

We found a positive correlation of maxillary intercanine width with OAHI ($r = 0.48$, $p = 0.03$) in the DS group. This transverse measurement can be performed clinically or on dental models but cannot be measured on a lateral cephalogram due to the projection of the x-ray beam, which only allows for anterior-posterior and vertical measurements. This result does not agree with the findings from a similar study on predictors of OSA reported by Skotko *et al*, who were unable to identify any clinical measurements that positively predicted the presence of OSA in DS patients between the ages of 3 and 24 years.[111] These differences may be due to the parameters used to define OSA as this study used an AASM scored OAHI > 1 per hour while theirs used an AASM scored AHI > 1 per hour. AHI scoring includes both central and obstructive events while OAHI only includes obstructive events.[10] Therefore, our definition and methods of determining OSA was more appropriate in identifying predictors of OSA that are related to dentofacial and craniofacial features. We also found that as the intercanine width increases in the DS group, the severity of OAHI also increases. It would be expected that a narrower maxilla and therefore a decreased intercanine width would be present in most patients with airway obstruction.[197] However, in the DS population, the most common dentofacial abnormality is a fissured tongue and relative macroglossia.[40] Individuals with DS also have tongue protrusion, maxillary hypoplasia, and peri-oral muscular hypotonia, which may result in buccally directed forces on the maxillary canines, resulting in an increased intercanine distance.[198] To further illustrate that increased tongue volume or posture seen in DS individuals may be related to increased intercanine distance, the opposite scenario can be considered, in which patients with ankyloglossia were shown to have decreased maxillary intercanine width and patients who underwent partial glossectomy had decreased resting tongue pressures on the maxillary teeth.[199,200] Therefore, the relationship between OAHI and intercanine width identified in the DS

group may be a result of a combination of the underlying dentofacial and craniofacial anomalies of DS.

There were no differences between lateral cephalometric measurements in DS with OSA and without OSA. As well, for the DS group, none of the cephalometric measurements were correlated to OAHI. These findings are similar to those reported by Skotko *et al.* who also didn't find any cephalometric predictors of OSA in children with DS.[111]

The present study found that ANB angle was significantly increased in Obesity with OSA compared to those without OSA ($p = 0.03$). ANB angle was also positively correlated to OAHI in the Obesity group ($r = 0.58$, $p < 0.01$). A greater ANB angle suggests that the mandible is more posteriorly positioned relative to the maxilla, resulting in an anteroposterior discrepancy. A retrognathic or posteriorly positioned mandible is associated with a smaller upper airway and after mandibular advancement, oropharyngeal diameter was increased and collapsibility was decreased.[201,202] Lowe *et al.* reported that a higher apnea index was seen in association with greater anteroposterior discrepancy between the maxilla and mandible as measured on lateral cephalograms in 80 non-obese participants (29.9 ± 7.6 years) with PSG confirmed OSA (AHI > 5 per hour).[201] Laxmi *et al.* reported that in a sample of 25-45 year old adults, ANB angle was significantly increased in questionnaire determined OSA patients.[151] Both of these studies described similar findings to ours but in adult populations, highlighting the importance of early detection as these craniofacial features can persist into adulthood.[151]

Another cephalometric measurement that was correlated with OAHI in the Obesity group was upper incisor distance to nasion-A point line (U1-NA) ($r = -0.53$, $p = 0.01$). This relationship was negative, suggesting that the greater the OAHI, the more posteriorly positioned

or retruded the upper incisors were. This finding is consistent with those presented by Subtelny and Solow who identified that the upper incisors are retroclined and retruded relative to the anterior cranial base in children who were mouth breathers.[203,204] However, Gungor *et al.* reported that the upper incisor was significantly protrusive in non-obese OSA adult patients as determined by an AHI > 10.[205] This difference between childhood and adulthood may be due to the development of a lower lip trap between the upper and lower incisors when trying to achieve lip competency, causing proclination and protrusion of the upper incisors as the individual ages.[206]

As expected, both the DS and Obesity groups with OSA had significantly increased OAHI ($p < 0.01$ for both DS and obese) and AHI ($p < 0.01$ for DS, $p = 0.01$ for obese) compared to those without OSA. DS with OSA had significantly decreased total sleep time ($p = 0.01$) and minimum percent oxygen saturation ($p = 0.01$) than DS children without OSA. DS with OSA also had a statistically significant greater oxygen desaturation index ($p < 0.01$) and time spent < 90% oxygen saturation ($p = 0.02$) than DS without OSA. Obesity with OSA had a statistically significant lower minimum percent oxygen saturation ($p = 0.03$) than Obesity without OSA. Obesity with OSA also had a greater time spent with < 90% oxygen saturation ($p = 0.02$) than Obesity without OSA. These findings are expected as obstructive events are associated with oxygen desaturations (increased time with oxygen saturations less than 90% and increased desaturation index) and/or cortical arousals leading to sleep fragmentation and shorter total sleep time.

The Spruyt and Gozal sleep questionnaire had poor predictive ability for OSA. Compared to the sensitivity of 59.03% that was originally reported by Spruyt and Gozal, the sensitivity found in our study population was greatly reduced for both the DS and Obesity groups

(DS = 17.7%, Obesity = 18.2%).[136] The specificities that we calculated for the DS (66.7%) and Obesity (90.9%) groups were not similar to that reported by Spruyt and Gozal (82.85%).[136] These differences may be because the original questionnaire was validated on healthy non-syndromic children without comorbidities.[136] Furthermore, there was no significant correlation found between Spruyt and Gozal scores and OAHI scores, suggesting that the Spruyt and Gozal sleep questionnaire is an unreliable diagnostic tool for pediatric OSA in DS and obese pediatric populations.

Chervin *et al.* reported that a SRBD score cutoff of 0.33 had a sensitivity of 85% and specificity of 87%.[127] The sensitivities that were calculated for the DS (70.6%) and Obesity (81.8%) groups were fairly similar to the 85% sensitivity value reported in the original validation study. However, the specificities were greatly reduced for both the DS (33.3%) and Obesity (45.5%) groups. As well, the SRBD score was not correlated to the severity of OAHI. The SRBD of the PSQ had a better predictive ability to identify those of the DS and Obesity group at risk of OSA compared to the Spruyt and Gozal sleep questionnaire. However, the SRBD was less successful than the Spruyt and Gozal sleep questionnaire at identifying individuals that did not have OSA. Overall, the two sleep questionnaires used in this study have limited accuracy as screening tools for diagnosing OSA in DS and obese pediatric populations. Likewise, Schechter *et al.* and Lin *et al.* would not recommend the use of sleep questionnaires for the diagnosis of pediatric OSA.[135,207] Therefore, based on the extensive documentation in the literature and the results of our study, sleep questionnaires should not be used clinically as screening or diagnostic tools for pediatric OSA in DS and obese populations.

This study has presented many important and novel findings, however, while considering the significance of these results, it is also important to discuss the limitations of our

investigation. Firstly, our study included a small sample size, which limited the extent of testing that could be applied to the data. A larger sample would have allowed for stronger parametric statistical testing and multiple logistic regression modelling to be performed. Because the participants were recruited from the Hospital for Sick Children, a tertiary referral hospital, the effect of referral bias limits the generalizability of these results to large population groups. However, the referral population is that which may be greatly affected by their comorbidities, allowing for clear distinction and detection of predictors for OSA. Long term follow up which could include multiple time points would be helpful to see the changes in growth in these children over time and their relationship with changes in OSA severity. However, a longitudinal study would potentially suffer from loss to follow up and drop outs. On the lateral cephalogram radiographs, there was partial obstruction of the airway and hyoid bone from the lead apron and thyroid collar, making it impossible to apply certain cephalometric analyses, such as McNamara's upper and lower pharyngeal airway analysis.[208] However, departmental guidelines and the principles of ALARA were followed for the benefit of these patients. It may be beneficial to analyze the craniofacial skeleton in 3 dimensions with CT or CBCT scans, which could also provide insight on airway and soft tissue volumes. Soft tissue measurements on traditional two-dimensional lateral cephalograms are unreliable as there are many magnification errors and superimposition makes measurements inaccurate.[209] However, there may be additional concerns with the increased radiation that is inherent to CT and CBCT scans. Lateral cephalograms and CBCT scans are taken in a sitting or standing posture, which may not precisely reflect the skeletal relations that are in effect during sleep in the supine position. Lastly, all of the orthodontic examinations and cephalometric measurements were performed by a single clinician, which may result in the introduction of observer bias into our study results.

Having at least two clinicians performing a standardized systematic orthodontic examination would help mitigate this effect. Nonetheless, the ICC for each of the cephalometric measurements between both time points, showed excellent agreement, indicating that these cephalometric measurements are both reproducible and accurate. Additionally, we incorporated objective cephalometric measurements in addition to our clinical examination to confirm the dentofacial and craniofacial features identified during the clinical examinations.

Chapter 5: Conclusion

Based on our results, OSA in children with DS is associated with maxillary dimensions. Upper incisor position and maxillo-mandibular relationships are associated with OSA in children with Obesity. Our study provides a good foundation for future studies that may utilize craniofacial analysis as it is the first to describe reproducible clinical and cephalometric measures that can be used to predict PSG verified OSA in DS and obese pediatric populations. Future studies could include a longitudinal study design that measures the presence and/or severity of OSA over time as a child grows, with lateral cephalograms taken at regular intervals. This would strengthen our understanding of the pathophysiology of OSA as it relates to craniofacial growth and development, which is currently lacking in the pediatric literature. Furthermore, the effects of treatment modalities such as adenotonsillectomy and PAP therapy on craniofacial morphology and development in the pediatric population may influence clinical decisions. Due to the multi-factorial nature of OSA, collaboration between sleep medicine physicians, orthodontists, and other health professionals may facilitate the diagnosis and management of OSA in children.

Appendix A

Pediatric Sleep Questionnaire: Sleep-Disordered Breathing Subscale[127]

Child's Name: _____ **Study ID #:** _____
Person completing form: _____ **Date:** ____/____/____

Please answer these questions regarding the behavior of your child during sleep and wakefulness. The questions apply to how your child acts in general during the past month, not necessarily during the past few days since these may not have been typical if your child has not been well. You should circle the correct response or *print* your answers neatly in the space provided. A "Y" means "yes," "N" means "no," and "DK" means "don't know."

1.	WHILE SLEEPING, DOES YOUR CHILD:			
	Snore more than half the time?.....	Y	N	DK	A2
	Always snore?	Y	N	DK	A3
	Snore loudly?	Y	N	DK	A4
	Have "heavy" or loud breathing?	Y	N	DK	A5
	Have trouble breathing, or struggle to breathe?	Y	N	DK	A6
2.	HAVE YOU EVER SEEN YOUR CHILD STOP BREATHING DURING THE NIGHT?	Y	N	DK	A7
3.	DOES YOUR CHILD:			
	Tend to breathe through the mouth during the day?.....	Y	N	DK	A24
	Have a dry mouth on waking up in the morning?	Y	N	DK	A25
	Occasionally wet the bed?	Y	N	DK	A32
4.	DOES YOUR CHILD:			
	Wake up feeling unrefreshed in the morning?	Y	N	DK	B1
	Have a problem with sleepiness during the day?	Y	N	DK	B2
5.	HAS A TEACHER OR OTHER SUPERVISOR COMMENTED THAT YOUR CHILD APPEARS SLEEPY DURING THE DAY?	Y	N	DK	B4
6.	IS IT HARD TO WAKE YOUR CHILD UP IN THE MORNING?	Y	N	DK	B6
7.	DOES YOUR CHILD WAKE UP WITH HEADACHES IN THE MORNING?.....	Y	N	DK	B7
8.	DID YOUR CHILD STOP GROWING AT A NORMAL RATE AT ANY TIME SINCE BIRTH?	Y	N	DK	B9
9.	IS YOUR CHILD OVERWEIGHT?	Y	N	DK	B22
10.	THIS CHILD **OFTEN**:			
	Does not seem to listen when spoken to directly.	Y	N	DK	C3
	Has difficulty organizing tasks and activities.	Y	N	DK	C5
	Is easily distracted by extraneous stimuli.	Y	N	DK	C8
	Fidgets with hands or feet or squirms in seat.	Y	N	DK	C10
	Is "on the go" or often acts as if "driven by a motor".	Y	N	DK	C14
	Interrupts or intrudes on others (eg., butts into conversations or games).	Y	N	DK	C18

Appendix B

Spruyt and Gozal Sleep Questionnaire[136]

Last Name: _____ First Name: _____

Gender: F M Date of birth: Month ____ Day ____ Year ____ Age: _____

Over the last 6 months: *Please mark each of the following items.*

	Never	**Rare** (1 night/week)	**Occasional** (2 nights/week)	**Frequent** (3-4 nights/week)	**Almost Always** (>4 nights/week)
1) Do you ever shake your child to make him/her breathe again when asleep?					
2) Does your child stop breathing during sleep?					
3) Does your child struggle to breathe while asleep?					
4) Are you ever concerned about your child's breathing?					
	Hardly Noticeable	**Moderately Strong**	**Strong**	**Very Strong**	**Extremely Strong**
5) How loud is your child snore?					
	Never	**Rare** (1 night/week)	**Occasional** (2 nights/week)	**Frequent** (3-4 nights/week)	**Almost Always** (>4 nights/week)
6) How often does your child snore?					

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