Efficacy of a Mandibular Advancement Appliance on Sleep Disordered Breathing in Children

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Dedicated to all children.
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This work is the product of my PhD journey, which would not have been possible without the support of many people whom I have had the pleasure to meet and work with over the past few years.

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**Individual roles of the research team:**

**-Ghassan Idris:** is the main researcher in the project. With guidance from the supervisors, he developed the protocol of the project, searched potential funding bodies and successfully applied for funding, sought ethical consent from the ethics committee, and coordinated participant recruitment, screening and clinical examination. He designed and implemented the pilot study to choose the best design of mandibular advancement appliance to use in the main study. The PhD candidate applied the oral splints and followed up the participants at the Dental school and at home visits (more than 68 visits) to apply the sleep monitor. He downloaded the generated data, analysed some of the sleep studies (20 sleep studies) before employing a sleep physiologist in the study who scored the sleep study blind to allocation group including those the researcher had already analysed. The candidate analysed and scored the questionnaire and diary data and coordinated blood test appointments for the participants. All collected data was arranged in data sheets and the descriptive statistics was performed by the main researcher and further statistical analysis was performed by a statistician.

**-Professor Mauro Farella:** The main supervisor in the study

**-Associate Professor Barbara Galland:** Co supervisor

**-Dr Christopher Robertson:** Co supervisor

**-Carmen Lobb:** Research assistant helped in preparing for sleep monitoring visits and home visits to set up the sleep monitor

**-Sue Filsell:** A sleep and respiratory physiologist, she analysed the sleep studies.

**-Andrew Gray:** Biostatistician who performed the statistical analyses
Abstract

**Background:** Sleep-Disordered Breathing (SDB) varies from habitual snoring to partial or complete obstruction of the upper airway, and can be found in up to 10% of children. SDB can significantly affect children’s wellbeing, as it can cause growth disorders, educational and behavioural problems, and even life-threatening conditions, such as cardiorespiratory failure. Adenotonsillectomy represents the primary treatment for paediatric SDB where adenotonsillar hypertrophy is indicated. For those with craniofacial anomalies, for whom adenotonsillectomy or other treatment modalities have failed, or surgery is contra-indicated, mandibular advancement splints (MAS) may represent a viable treatment option. Whilst the efficacy of these appliances has been consistently demonstrated in adults, there is little information about their effectiveness in children.

**Study objective:** The aims of this research are first, to define the most accepted appliance from different designs of MAS to be used in the main study and second, to determine the efficacy of mandibular advancement appliances (MAS) for the management of Sleep-Disordered Breathing (SDB) and related health conditions in children.

**Methods:** The first part of this research was a pilot study designed as a randomized controlled study with crossover application of four different MAS designs. Questionnaires filled out by the patient and parent were used to gauge effectiveness of the different MAS designs regarding: the effects on speech, the initial acceptance, and the acceptance after wearing the appliance for a full night. A clinical examination then followed to test the appliance retention. One volunteer (11 year old male with class II dental and skeletal jaw relationships) participated in this pilot study and he was suitable for functional appliance treatment. Appliances tested were: 1) traditional Twin-Block with vertical elastics added to ensure the anteroposterior and vertical predetermined position of the mandible when wearing the appliance during sleep; 2) Twin-Block with a metallic fastener in the anterior area to test the function of mandibular advancement; 3) Clear elastic Twin-block which has the same traditional Twin-Block design with vertical elastics but uses vacuum
formed retainers instead of the acrylic material; 4) a sham Twin-Block with upper and lower vacuum formed retainers without any mandibular repositioning. This pilot study showed that traditional Twin-Block was the best design to be used in the main study as it was highly accepted by the patient and showed the highest levels of retention in comparison to the other designs.

The main study was designed as a single-blind crossover randomised controlled trial with administration of both an ‘Active MAS’ (Twin-block) and a ‘Sham MAS’ (two Hawley retainers). Eligible participants were children aged 8 to 12 years, whose parents reported them snoring ≥ 3 nights per week. Exclusion criteria included class III incisor and/or skeletal relationship, confirmed by lateral cephalometric radiograph. 18 children participated in the study. Each child was randomly assigned to a treatment sequence, starting with either the Active or the Sham MAS. Participants wore the appliances for three weeks, separated by a two-week washout period. For each participant, home-based polysomnographic (PSG) data was collected four times, once before and once after each treatment period. The Apnoea Hypopnoea Index (AHI) represented the main outcome variable. Secondary outcomes, assessed at the same time with PSG recordings, included serum levels of Insulin-like Growth Factor 1 (IGF-1), obstructive sleep-related breathing symptoms, as assessed by the Paediatric Sleep Questionnaire (PSQ), quality of life, as assessed by the OSA-18 questionnaire, and childhood behaviour, as assessed by the Behavioural Assessment System for Children (BASC-2) Behavioural and Emotional Screening System (BESS), and nocturnal enuresis. In addition, blood samples were collected at the end of each treatment period to assess growth hormone changes by measuring blood levels of insulin-like growth factor-1 (IGF-1).

**Results:** Compared to a Sham MAS, wearing an Active MAS resulted in a significant reduction in AHI of 40% (p=0.002) with a decrease in AHI when using the Active MAS, and a tendency for an increase in AHI when using the Sham MAS. The separate assessment of AHI in supine and non-supine sleeping positions revealed that only the former was significantly influenced by treatment, with a reduction of 4.1 events per hour (95% CI=1.8-6.4; p<0.001). Snoring time was 46.3 minutes shorter with the Twin-Block than with the Sham appliance (95% CI=14.5-78.1;
p=0.004). The lowest oxygen saturation showed significant improvement of 3.4% (95% CI=0.9-5.9; p=0.007) with the Twin-block in comparison to the Sham MAS. Compared to a Sham MAS, the Active MAS also reduced SDB symptoms. Subjective assessment by parents showed significant improvement, as represented by PSQ, OSA-18, and BASC-2 scores (p≤0.028). IGF-1 levels, however, did not differ between the two treatment periods (p=0.172). There were no reports of nocturnal enuresis incidents during the study periods.

**Conclusion:** The short-term use of mandibular advancement splints significantly reduced AHI, supine AHI. The decrease in the overall AHI resulted from a combination of a decrease in AHI when using the Active MAS, and a tendency towards an increase in AHI when using the Sham MAS. Snoring time decreased significantly when using MAS in children with SDB, and participants showed improvement in subjectively assessed SDB symptoms and quality of life. In addition, significant improvement was detected in parent-reported child behaviour.
Overview

The present work is divided into five main chapters that are organised as follows:

Chapter 1 – Literature Review: This includes a general introduction and overview, describing the range of conditions of paediatric SDB, epidemiology, aetiology, and consequences of obstructive sleep apnoea. This introductory chapter also includes a review of the available diagnostic and treatment methods and focuses on the use of oral appliances in paediatric SDB treatment.

Chapter 2 – Feasibility study and study protocol: (This Chapter was published as an original article in Frontiers in Physiology. 2016; 7(353)) The second chapter discusses methodological details of the present work. Results of a pilot study to choose the best design of MAS to be used in the study are presented in this chapter. However, the chapter also covers aspects of study design, sample size estimation, participant recruitment, and data collection and analysis, and discusses the significance of this study. The study protocol has been published in Frontiers in Physiology journal.

Chapter 3 – Main study report: The main outcome of the overnight PSG results are presented, demonstrating changes in obstructive sleep apnoea with AHI and snoring as the measurements of interest. Secondary outcomes are discussed in this chapter, including Paediatric Sleep Questionnaire (PSQ), quality of life questionnaire (OSA-18), Parent reports of nocturnal enuresis and snoring frequency, insulin-like growth factor-1 (IGF-1) levels in the blood, and behavioural changes using the BASC-2 questionnaire. A more detailed account of the methods, analyses, and statistics used to investigate the study’s specific objectives is provided in this chapter.

Chapter 4 – Discussion: This chapter provides further discussion of the current study results, limitations, future perspective, and conclusion.

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List of Abbreviations

American Academy of Sleep Medicine (AASM)
American Sleep Disorders Association (ASDA)
Apnoea Hypopnoea Index (AHI)
Attention-Deficit/Hyperactivity Disorder (ADHD)
Behaviour Assessment System for Children, Second Edition (BASC-2)
Body Mass Index (BMI)
Continuous Positive Airway Pressure (CPAP)
Electrocardiography (ECG)
Electroencephalography (EEG)
Electromyography (EMG)
Electrooculography (EOG)
Epworth Sleepiness Scale (ESS)
Growth hormone (GH)
Insulin-like growth factor-1 (IGF-1)
Intelligence quotient (IQ)
Magnetic Resonance Imaging (MRI)
Mandibular advancement splints (MAS)
Obstructive Sleep Apnoea (OSA)
Parent Rating Scales (PRS)
Polysomnography (PSG)
Quality-of-life questionnaire (OSA-18)
Rapid maxillary expansion (RME)
Sleep-Disordered Breathing (SDB)
Sleep-Related Breathing Disorder scale of the Paediatric Sleep Questionnaire (PSQ)
The Behavioural and Emotional Screening System (BESS)
Tongue Stabilising Device (TSD)
Total symptom score of OSA-18 (TSS)
Upper Airway Resistance Syndrome (UARS)
(Oral presentation)

(Journal article)

(Oral presentation)

Idris G., Loke C., Farella M. The role of dentists in adult obstructive sleep apnoea, feature article. NZDA NEWS. 2016; Mar: 35-44.  
(Journal article)

Idris G., Galland B., Robertson C. J., Farella M. Efficacy of a mandibular advancement appliance on paediatric sleep disordered breathing: a preliminary report. 55th Annual Scientific Meeting of the IADR Australia & New Zealand Division, Dunedin, New Zealand, 24-26 August 2015.  
(Oral presentation)

(Manuscript in preparation)

(Manuscript in preparation)
CHAPTER ONE

SLEEP DISORDERED BREATHING IN CHILDREN

REVIEW OF THE LITERATURE
1. Sleep disordered breathing in children: review of the literature

4 Introduction
Sleep is defined as physiological and behavioural states characterized by partial isolation from the environment\(^1\), or as a state of decreased responsivity to environmental stimuli that occurs on a regular basis\(^2\). A sleeping brain maintains a sentinel function to awaken the organism for protection purposes\(^1\).

There is consensus today that sleep in terms of function is strictly linked to memory\(^3\), learning\(^4\) and, in general, to the mechanism of neural plasticity\(^5\).

There are many sleep disorders, such as insomnia, hypersomnia, circadian rhythm sleep disorders, sleep-related breathing disorders and sleep-related movement disorders. Sleep-related breathing disorders are the most common disorders involving dentists in terms of recognition and treatment\(^6\).

5 Sleep physiology
Normal sleep has an organised basic structure, it has two types: rapid eye-movement (REM) sleep, and non-rapid eye movement (NREM) sleep which consists of four stages identifying the sleep depth. Each of the sleep types has different characteristics including different brain wave patterns, muscle tone, and eye movement\(^7\). A sleep episode starts with stage 1 of NREM followed by the other stages (2, 3, and 4) and then progresses to REM sleep.
However, an individual does not stay in the REM for the rest of the night but will cycle between the stages of NREM and REM. The NREM takes 75-80% of the sleep with stage 2 composing 45-55% of a sleep episode and the REM takes 20-25% of the sleep. Table one summarises the physiological differences between NREM and REM sleep.

<table>
<thead>
<tr>
<th>Physiological Process</th>
<th>NREM</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain activity</strong></td>
<td>Decrease from wakefulness</td>
<td>Increases in motor and sensory areas, while other areas are similar to NREM</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td>Slows from wakefulness</td>
<td>Increases and varies compared to NREM</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td>Decreases from wakefulness</td>
<td>Increases (up to 30 percent) and varies from NREM</td>
</tr>
<tr>
<td><strong>Sympathetic nerve activity</strong></td>
<td>Decreases from wakefulness</td>
<td>Increases significantly from wakefulness</td>
</tr>
<tr>
<td><strong>Muscle tone</strong></td>
<td>Similar to wakefulness</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Blood flow to brain</strong></td>
<td>Decreases from wakefulness</td>
<td>Increases from NREM, depending on brain region</td>
</tr>
<tr>
<td><strong>Respiration</strong></td>
<td>Decrease from wakefulness</td>
<td>Increases and varies from NREM, but may show brief stoppages coughing suppressed</td>
</tr>
<tr>
<td><strong>Airway resistance</strong></td>
<td>Increases from wakefulness</td>
<td>Increases from wakefulness</td>
</tr>
<tr>
<td><strong>Body temperature</strong></td>
<td>Is regulated at lower set point than wakefulness; Shivering initiated at lower temperature than during wakefulness</td>
<td>Is not regulated; no shivering or sweating; temperature drifts toward that of the local environment</td>
</tr>
</tbody>
</table>
The circadian rhythm is a daily cycle of biological activity refers, collectively, to the daily rhythms in physiology and behaviour. This biological clock is based on a 24-hour period and influenced by regular variations in the environment, such as the alternation of night and day. The circadian rhythm controls the sleep-wake cycle, modulate physical activity and food consumption, and over the course of the day regulate body temperature, heart rate, muscle tone, and hormone secretion. The rhythms are generated by neural structures in the hypothalamus that function as a biological clock.

From Infancy to adulthood, there are significant and continuous changes in sleep architecture. This includes changes in how sleep is initiated and maintained, differences in the percentage of time spent in each stage during sleep and sleep efficiency (which means how successfully sleep is initiated and maintained). In general, sleep efficiency declines with age; New-borns sleep about 16 to 18 hours per day with short sleep episodes (2.5-4 hours). A new born has three types of sleep: quiet sleep (similar to NREM), active sleep (similar to REM), and indeterminate sleep. A baby in the second or third month starts to have a circadian rhythms which leads to sleep consolidation (longer times of wakefulness in the day and greater durations of sleep at night). By six months of age, a baby shows a slight reduction in the total sleep time with increase in the longest continuous sleep episode to nearly 6 hours. A twelve months old sleeps about 14-15 hours per day; one to two naps during the day time but the majority of sleep consolidated in the night time. Most children discontinue napping between 3-5 years.
Young children appears to sleep less as a child gets older (two hours decrease from age 2 to age 5) with estimated sleep time of 11 hours per day at age 5. By the time a child enter school, a child begins to manifest circadian sleep phase preferences “a tendency to be a “night owl” or “morning bird””

A complex and bidirectional relationship exists between pubertal development and sleep. Adolescents need 9-10 hours of sleep each night. Pubertal and hormonal changes in the onset of the puberty influences sleep causing several changes; for instance the time spent in stage 2 increased. Greater daytime sleepiness in the midpuberty and in the afternoon in more mature adolescents, besides decrease in total sleeping time and REM sleep with increasing age.

6 Sleep functions

Important processes occur during sleep to preserve a healthy function of the brain and the body physical health. In brain, during sleep, new pathways to process new information are formed. Adequate sleep improves memory and learning, plays a role in attention and creativity, besides aids in making decisions. Insufficient sleep leads to functional changes in the brain and peripheral tissues in the body which alter the brain activity and the body function.

Sleep has a significant role in memory consolidation and selecting of important revived information throughout the day. This process prioritises certain information and experiences due to an emotional or other connection. In addition to memory consolidation, sleep helps clear out toxins that accumulate in the brain by expanding
channels in the brain to allow the flow of cerebrospinal fluid to clear the debris\textsuperscript{26}. One example of these toxins is a protein associated with Alzheimer (Beta-amyloid protein)\textsuperscript{26}.

Sleep is important for maintenance of physical health, particularly healing and repairing of cells in body tissues\textsuperscript{23}. Sleep helps regulating the hormones and minting their balance in the body\textsuperscript{27}, such as Growth hormone, Insulin which regulates Glucose levels in blood, and Ghrelin and Leptin which regulate feeling of hunger and fullness, thus there is a relation between sleep and growth and development, diabetes, obesity, and other conditions.\textsuperscript{27} Furthermore, the immune system relies on sufficient sleep and the sleep quality; sleep deficiency is related to increased risk of sickness difficulty resisting infections\textsuperscript{28}.

7 **Sleep-disordered breathing**

Sleep-Disordered Breathing (SDB) is a term describing abnormal patterns of breathing present during sleep. SDB varies along a continuous spectrum according to the degree of obstruction from habitual snoring and Upper Airway Resistance Syndrome (UARS) to Obstructive Sleep Apnea (OSA)\textsuperscript{29}. Partial airway obstruction manifests as habitual snoring or UARS, whilst complete upper airway obstruction manifests as OSA\textsuperscript{29}. Obstructive sleep apnoea syndrome was first reported in children by Guilleminault in 1976. He described sleep apnoea symptoms in eight 5-14 years old children who showed similar polysomnographic characteristics as those seen in adults with sleep apnoea\textsuperscript{30}.

Habitual snoring is recognized by audible sonorous noises occurring more than three times per week without evidence of apnea, hypoventilation or significant sleep fragmentation.\textsuperscript{31} Snoring occurs when there is an imbalance between negative intrathoracic pressure and the oropharyngeal dilator muscles\textsuperscript{31, 32}. OSA is characterized by recurring episodes of complete
and/or partial obstruction of the upper airway during sleep, resulting in intermittent hypoxemia and hypercapnia, frequent arousals, and sleep fragmentation. A paediatric obstructive sleep apnea episode is defined as absence of airflow for two respiratory cycles (2 breaths) with continued chest wall and abdominal wall movement\textsuperscript{34}, whereas an obstructive hypopnoea episode is defined as a decrease in nasal flow $\geq30\%$ (the drop should last at least 2 breaths from baseline) with a corresponding decrease of $\geq3\%$ in oxygen saturation and/or arousal\textsuperscript{34}.

### 7.1 Epidemiology

In the past few decades, OSA has become widely recognized as a likely cause of considerable morbidity among children. Paediatric OSA differs from adult OSA in both clinical characteristics and determinants of its epidemiology\textsuperscript{35}. Subdiagnosis, lack of community awareness about the negative sleep-related consequences on the daily functioning of children, and parents’ tendency to downplay the problem and not report it to their physician, all contribute to an underestimation of its prevalence and make it difficult to accurately determine prevalence figures\textsuperscript{36, 37}. International studies report the prevalence of adult OSA to be within the range of 3 to 17\% \textsuperscript{38-41} with a higher prevalence reported recently in the “HypnoLaus” study\textsuperscript{42}. In children, it varies from 0.7 to 24\%, depending on the method used to diagnose OSA\textsuperscript{43-45}. However, most authors report a prevalence of 10\% for habitual snoring and 1.2 to 5.7\% for OSA in children\textsuperscript{35, 45-48}. In New Zealand, epidemiological studies show that OSA affects over 30\% of the adult male population and over 9\% of the adult female population, and that the prevalence of OSA in Māori ethnicity is approximately twice as high as that of non-Māori one\textsuperscript{49, 50}. In a community sample of New Zealand children aged 3 and 7 years, the prevalence of habitual snoring was found to be 9.2-11.3\% \textsuperscript{51, 52}. Habitual
snoring has been reported to be significantly higher among 3-year-old children of Māori ethnicity\textsuperscript{52-54}, but not in the smaller sample followed up at 7 years of age by Luo et al in 2015\textsuperscript{51}. However, it seems that no study clearly indicates the prevalence of OSA in New Zealand children.

\textbf{7.2 Aetiology and pathophysiology of sleep-disordered breathing}

During sleep, OSA events occur through a complex interaction between sleep states, the mechanics of pressure and flow within the airway, and respiratory drive. Therefore, the aetiology of paediatric SDB is multifactorial\textsuperscript{55}.

Enlarged adenoids and tonsils are the most common cause of OSA in children. Paediatric OSA peaks in the preschool years as the lymphoid tissue is largest in relation to other structures of the upper airway\textsuperscript{56}. Magnetic Resonance Imaging (MRI) studies have confirmed that the tonsils and adenoids of children with OSA are larger than in age-matched children who do not have OSA\textsuperscript{57, 58}. Furthermore, the retro-palatal region has been suggested as the site of maximal upper airway obstruction, specifically, the overlap between the lower pole of the adenoids and the upper pole of the tonsils\textsuperscript{59}.

Other anatomical factors which affect the airway structure, causing upper airway collapse, have been identified as possible causes of SDB, such as: retrognathia, narrow maxillary dental arch, and smaller nasopharyngeal airway spaces. These features are consistently found to be associated with an increased incidence of OSA\textsuperscript{60, 61}. It is not well known if the cephalometric features seen in OSA patients are the primary contributing cause of the obstruction, or the effect of airway obstruction due to another reason, such as chronic nasal
congestion. A study supporting the latter suggestion reported favourable cephalometric changes in OSA children after adenotonsillectomy. A study supporting the latter suggestion reported favourable cephalometric changes in OSA children after adenotonsillectomy.62.

Several genetic and congenital syndromes are associated with SDB. These include syndromes with micrognathia in their clinical picture and those producing midfacial hypoplasia. Syndromes in which craniofacial conditions affect the airways are summarised in (Table 2).

<table>
<thead>
<tr>
<th>Syndrome or condition</th>
<th>Features potentially affect airways and breathing (contributing to SDB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniofacial cleft</td>
<td>Short mandible, retrognathia, and nasal deformity</td>
</tr>
<tr>
<td>(Pierre Robin, Stickler, Treacher Collins, Goldenhar, and Nager syndromes)</td>
<td></td>
</tr>
<tr>
<td>Micrognathia syndromes</td>
<td>Micrognathia, glossoptosis, and midface hypoplasia</td>
</tr>
<tr>
<td>(Pierre Robin, Stickler syndromes)</td>
<td></td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>Midface hypoplasia</td>
</tr>
<tr>
<td>(Apert, Cruzon, Pfeiffer, Nuenke, and Saerthe-Chozen syndromes)</td>
<td></td>
</tr>
<tr>
<td>Down syndrome</td>
<td>Relative macroglossia, midface hypoplasia, reduced muscle tone</td>
</tr>
<tr>
<td>Achondroplasia</td>
<td>Midface hypoplasia, retrognathia</td>
</tr>
</tbody>
</table>
Literature Review

Approximately a quarter of all children are either overweight or obese\(^6^4\). It has been reported that childhood obesity increases the risk of developing OSA to the extent that, for every 1 kg/m\(^2\) increment in Body Mass Index (BMI) above the mean BMI for age and gender, there is a 12% increased risk of developing OSA\(^5^5\). Obesity contributes to OSA development by narrowing the upper airway due to fatty infiltration of upper airway structures, and because subcutaneous fat deposits in the anterior neck cervical region increase pharyngeal collapsibility\(^6^5\).

In addition, the extra fat in the abdominal wall and cavity and in the thoracic wall acts to reduce the resting lung volume, resulting in a loss of caudal traction on the upper airway and an increase in pharyngeal collapsibility\(^6^6\). Figure (1) illustrates the pathophysiology and the consequences of paediatric OSA.

![Figure 1 Pathophysiology and consequences of paediatric OSA](image)
7.3 Effects of body position and sleep state on OSA severity

It has long been known in adults that obstructive respiratory events are at their most severe and frequent in the supine sleeping position\(^67\). This represents a striking feature so that more than half of all obstructive sleep apnea patients can be classified as having supine-related OSA\(^67\). Typically, the Apnoea Hypopnoea Index (AHI) is reported to be higher in supine sleep and to a lesser extent during REM sleep\(^68\). More recently, the relation between body position and OSA severity has been reported in children. However, paediatric studies showed a significant effect of body position on OSA severity although those findings are inconsistent as a study showed an improvement in OSA severity in supine position\(^69\); some studies reported a worsening of OSA in supine position\(^70\)–\(^72\); and some others concluded no PSG positional difference in OSA children\(^73\)–\(^75\).

7.4 Consequences of obstructive sleep apnea

Excessive daytime sleepiness, the most prominent clinical symptom of OSA in adults, is not a common complaint in paediatric SDB\(^76\). However, it is seen in some children with severe OSA and is more common in adolescents, particularly if they are morbidly obese\(^77\). In contrast, younger children often become hyperactive rather than sleepy\(^29\).

Studies reported behavioural dysregulation as a common comorbidity of SDB in children\(^78\)–\(^82\), such as inattention, hyperactivity, aggressiveness, and social withdrawal\(^30\),\(^83\). There is good evidence that SDB leads to daytime disturbance, closely mimicking behavioural symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD)\(^78\),\(^84\). Furthermore, a four-year prospective cohort study showed that SDB symptoms are considered risk factors for the future emergence or exacerbation of hyperactive behaviour in children\(^85\).
### Table 3 Cognitive and behaviour consequences of SDB

<table>
<thead>
<tr>
<th>Hyperactivity</th>
<th>Hyperactivity is frequently reported in both children with habitual snoring as well as in SDB children formally diagnosed using polysomnography (PSG) (^{78, 79, 86-88}).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattention</td>
<td>Inattentive behaviours identified by parental report have been observed in children with habitual snoring(^{78, 80, 88, 89}) and PSG-defined SDB(^{90-93}).</td>
</tr>
<tr>
<td>ADHD</td>
<td>Attention-Deficit Hyperactivity Disorder (ADHD) is one of the most frequently reported comorbidities in SDB children. The major features of ADHD are inattention, hyperactivity, and impulsivity. Conversely, comorbid sleep problems are highly prevalent in ADHD(^94). Sleep problems have been parentally reported in ADHD with a frequency up to five times greater than that of healthy children(^95).</td>
</tr>
<tr>
<td>Aggressive and bullying</td>
<td>Large population-based studies reported that children with SDB symptoms were 20% to 100% as likely to have aggressive behaviours and other behavioural problems(^{79, 82}), which are similar to a study that also found that conduct problems were associated with symptoms of SDB(^96).</td>
</tr>
<tr>
<td>Intelligence Quotient (IQ)</td>
<td>Lower intelligence quotient (IQ) scores have been reported in children with SDB compared to controls, although these scores are typically still within the normal range(^{88, 93, 97-108}).</td>
</tr>
<tr>
<td>Academic performance</td>
<td>Several studies have reported that SDB children have deficits in academic performance. This includes lower grades in mathematics, spelling, reading and science(^{89, 109-111}).</td>
</tr>
<tr>
<td>Executive function</td>
<td>Executive function encompasses cognitive processes, such as planning, problem solving, and verbal reasoning. A recent study indicated that SDB children showed lower performance on executive function dimensions, such as inhibition, working memory, and planning compared to controls(^{112}).</td>
</tr>
</tbody>
</table>
In addition, learning problems and behavioural dysregulation can be commonly found in school-age children with SDB\textsuperscript{113}. Thus, mild SDB without true OSA has often been shown to carry the same morbidity as OSA in children, including daytime somnolence, behavioural problems, and poor school and cognitive performance\textsuperscript{114}. Table (3) summarises some of cognitive and behavioural consequences of SDB.

In addition to daytime behaviour and neuro-cognitive disturbance, there is compelling evidence that SDB affects the \textbf{quality of life} in children\textsuperscript{86, 115}. To evaluate quality of life in SDB children, survey instruments relying on proxy reports are used, such as the OSA-18\textsuperscript{116, 117}.

\textbf{Nocturnal enuresis}, in particular secondary enuresis, is associated with SDB in children\textsuperscript{118}. It is thought that fragmentation of sleep architecture caused by apneic events and arousals may affect normal secretion of anti-diuretic hormone, and contribute to enuresis development. Nocturnal enuresis can be the principal clinical manifestation in some children with SDB\textsuperscript{118, 119}.

\textbf{Obesity} is not only considered a risk factor for SDB development, but can also be aggravated by OSA, thus is potentially a consequence of SDB. This concept arose from recent studies where OSA was found to promote weight gain via sleep fragmentation and associated daytime sleepiness, resulting in reduced daily physical activity\textsuperscript{120, 121}. In addition, OSA exacerbates the magnitude of inflammatory responses, and is thus considered a risk factor for metabolic syndrome in children, which is a cluster of the most dangerous risk factors for type 2 diabetes and cardiovascular disease\textsuperscript{122-124}. 
Growth impairment is one of the main features in advanced paediatric OSA. SDB in children is accompanied by an abnormal secretion of growth hormone during sleep, and somatic growth impairment\textsuperscript{125}. This in turn may affect craniofacial morphology, particularly the vertical features of the mandibular ramus\textsuperscript{62}. Stunted growth in children with SDB could occur because of disturbance in growth hormone secretion from disruption in sleep architecture\textsuperscript{126}. Hypertrophy of the tonsils can lead to difficulty in swallowing and interfere with adequate caloric intake, causing growth impairment. In addition, increased respiratory effort during sleep can drain the child’s caloric resources, which otherwise would be used in somatic growth\textsuperscript{29}.

The relationship between SDB and cardiovascular dysfunction in children has been recognised in the last few decades\textsuperscript{127, 128}. This primarily manifests in elevated blood pressure and changes in cardiac structure and endothelial function\textsuperscript{129-131}. Left ventricular hypertrophy has been described in children with SDB, and flow-mediated dilatation of the brachial artery is an indirect measure of endothelial dysfunction that is altered in SDB\textsuperscript{132}.

8 Diagnosis of obstructive sleep apnea

Diagnosis of a child with suspected SDB requires clinical evaluation, by taking a thorough history of the child’s sleep patterns, parental observations of breathing during sleep, and daytime performance, in addition to a physical examination for the SDB risk factors, and finally, confirmation through objective assessment of sleep and breathing using polysomnography.
8.1 Symptoms of OSA in children

Symptoms of OSA can be classified into two categories: First, night time symptoms, which mainly include: habitual snoring, witnessed apneas and loud breathing, and frequent awakenings. Second, day time symptoms, which include: behavioural dysregulation (poor attention and hyperactivity), sleepiness, and mouth breathing\(^45, 133-135\). Table (4) demonstrates symptoms and signs of sleep disordered breathing in school age children (5-15 years).

Signs and symptoms of sleep-disordered breathing symptoms in children are different to those in adults. There are three main differences between adult and paediatric SDB patients. First, clinical presentation of SDB in children is more varied, and individual symptoms often lead to alternate diagnostic pathways, but consideration of a group of symptoms may help in defining SDB\(^136\). Second, unlike adults, excessive daytime sleepiness is not a major symptom of SDB in children, as only 7% present to a physician with excessive sleepiness during the day\(^120\). Rather, children tend to become hyperactive\(^84\). The third difference is that patients with paediatric SDB manifest different symptoms at different ages. However, some symptoms may present at any age, such as snoring and frequent arousals, while others are seen in certain age groups such as apparent life threatening events, poor day/night cycle, and breath holding spells in infants less than 12 months old; but in 1-5 year old children symptoms may include sleep terrors, daytime sleepiness, hyperactivity and inattention, and sleep in knee-chest position. In older age groups (between 5 to 18 years) we can see insomnia, learning difficulties, delayed puberty, depression, and hypertension\(^136\).
Table 4 School age (5-15 year) symptoms and signs of SDB\(^{6, 133, 136, 137}\)

<table>
<thead>
<tr>
<th>Night time symptoms</th>
<th>Day time symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Snoring</td>
<td>- Poor behaviour</td>
<td>- Adenotonsillar hypertrophy</td>
</tr>
<tr>
<td>- Witnessed apnoeas or labored breathing</td>
<td>- Inattention at school or preschool</td>
<td>- Micrognathia/retrognathia</td>
</tr>
<tr>
<td>- Gasping/choking/snorting</td>
<td>- Hyperactivity</td>
<td>- Nasal inflammation and obstruction</td>
</tr>
<tr>
<td>- Mouth breathing</td>
<td>- Mouth breathing</td>
<td>- Recurrent otitis media</td>
</tr>
<tr>
<td>- Sleeping with hyperextension of neck</td>
<td>- Learning difficulties</td>
<td>- Failure to thrive</td>
</tr>
<tr>
<td>- Restlessness/frequent awakenings</td>
<td>- Excessive sleepiness</td>
<td>- Obesity</td>
</tr>
<tr>
<td>- Sweating</td>
<td>- Morning headaches</td>
<td>- Hypertension</td>
</tr>
<tr>
<td>- Enuresis</td>
<td></td>
<td>- High-arched palate</td>
</tr>
<tr>
<td>- Nightmares</td>
<td></td>
<td>- Delayed puberty</td>
</tr>
<tr>
<td>- Sleepwalking</td>
<td></td>
<td>- Malocclusion (Class II or Class III), crossbite, crowded teeth</td>
</tr>
<tr>
<td>- Confusional arousal</td>
<td></td>
<td>- Mood disturbance, e.g.: depression, Delayed Sleep Phase Syndrome (DSPS)</td>
</tr>
<tr>
<td>- Sleep walking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Difficulty waking up in morning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Drooling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Insomnia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8.2 History and physical examination

The clinical evaluation of children with suspected OSA involves taking a thorough history of the child’s sleep patterns and parental observations of breathing during sleep\(^6\). The extent to which the disorder is impacting on the functioning of the child in domains such as daytime performance and quality of life may also be assessed clinically. Physical examination should include: factors associated with a risk of OSA, such as tonsil size\(^{138}\), nasal inflammation and retrognathia, and potential consequences of OSA, such as poor growth and hypertension\(^{139}\).
However, depending on clinical symptoms, identification and scoring of respiratory and arousal events to confirm OSA is not always reliable\textsuperscript{76,140}.

Oropharyngeal examination is a significant part of SDB patient assessment. This examination can be used to prioritize children who may need further investigations to confirm OSA diagnosis\textsuperscript{136}. Oropharyngeal examination includes Mallampati score and tonsillar size score. Mallampati score is a widely used subjective assessment of upper airway crowding, which involves visualization of the oropharynx with four classifications, shown in Figure (2)\textsuperscript{141}. Tonsil size grading classifies tonsils into five grades from 0-4\textsuperscript{142}. Those grades according to Friedman are illustrated in Figure (3)\textsuperscript{142}. Assessment of tonsil size to predict OSA severity is controversial and it has been reported that there is no clear evidence about the value of this assessment in predicting SDB\textsuperscript{143}.

![Figure 2 Mallampati classification of airway crowding\textsuperscript{141}](image)

**Figure 2 Mallampati classification of airway crowding\textsuperscript{141}**

Class I (Tonsils, pillars and soft palate are distinctly visible)
Class II (Tonsils, pillars and upper pole are visible)
Class III (Only part of the soft palate is visible and the tonsils, pillars and base of the uvula cannot be seen)
Class IV (Only the hard palate is visible)
Obstructive sleep-related breathing disorder questionnaires were introduced to find simple and non-invasive tools to diagnose and evaluate children suspected of having OSA\textsuperscript{144}. In 1999, Chervin developed the Sleep-Related Breathing Disorder scale of the Paediatric Sleep Questionnaire (PSQ)\textsuperscript{145}. This is a 22-question tool, which is filled in by parents and includes questions about history of breathing difficulties during sleep, snoring quality and frequency, daytime signs of sleepiness, inattention and hyperactivity, in addition to some other questions about morning headache, obesity, enuresis, and delayed growth\textsuperscript{145}.

Studies have consistently found that symptom scores are not reliable for OSA detection in snoring children\textsuperscript{76, 140}. However, the PSQ yields sensitivity and specificity values of 85\% and 87\% respectively\textsuperscript{145}, supporting the use of the questionnaire as an important screening tool, rather than a diagnostic one\textsuperscript{146}. In general, two systematic reviews have concluded that signs and symptoms of OSA, either alone or in combination, do not satisfactorily predict

\textbf{Figure 3 grading scale of tonsil size}\textsuperscript{142}

Grade 0: Tonsils absent
Grade 1: Hidden behind tonsillar pillars
Grade 2: Extend to pillars
Grade 3: Visible beyond pillars
Grade 4: Enlarged to midline
paediatric patients with OSA\textsuperscript{33, 147}. Polysomnography (PSG) continues to be the best diagnostic tool available for paediatric OSA, although it is time consuming, expensive, and often unavailable\textsuperscript{148}.

### 8.4 Video/Audio Recordings

Analysis of snoring sounds has been proposed as a method of assessing breathing during sleep\textsuperscript{149}. Use of audiotaping may be considered promising technique in establishing SDB diagnosis. Studies using these techniques have shown variability in their precision of predicting OSA, and therefore additional studies are required to confirm reliability\textsuperscript{150-152}.

Frequency domain analysis of snoring signals has also shown a promise in distinguishing OSA from Primary Snoring\textsuperscript{153}. Acoustic analysis of snoring is relatively accurate, but it is not considered a strong method for diagnosing OSA and rigorous studies are needed to confirm its diagnostic value\textsuperscript{154}.

Videotaping can also yield a noninvasive measure of movement and therefore arousal\textsuperscript{155-157}. Video recordings are also a useful adjunct to a comprehensive polysomnogram to evaluate body and head positioning, paradoxical movements, snoring, and mouth breathing. Studies correlating video scoring systems to standard polysomnography have been encouraging\textsuperscript{157}.\textsuperscript{158} Future research will be necessary to validate the utility of a particular domiciliary video/audio study in a population with a well characterized symptomatology.

### 8.5 Polysomnography (PSG)

Formal confirmation of SDB diagnosis requires overnight polysomnography (PSG) for a suspected SDB child. PSG is an objective method that measures multiple physiologic
parameters to assess disturbances in respiratory function and sleep architecture, and is thus considered the gold standard in diagnosis of SDB.\textsuperscript{45, 159}

The complete polysomnography is done in a specialized sleep laboratory and the following bioparameters are recorded: electroencephalography (EEG), chin electromyography (EMG), electrooculography (EOG), airflow, respiratory effort (measured by recording movements of the thorax and abdomen), pulse oximetry, and electrocardiography (ECG). Body position is also recorded and it is optional to record periodic leg movement.

According to the American Sleep Disorders Association (ASDA)\textsuperscript{160, 161}, the methods of investigating OSA can be classified by the type of sleep study employed. See Table (5).

Although in-lab polysomnography is considered the gold standard for the diagnosis of SDB, it is costly, involves a technically complex set-up, and scoring sleep stages is time-consuming\textsuperscript{162}. Some authors reported that SDB is underdiagnosed because of lack of awareness about this syndrome among physicians and patients. This may due to the fact that SDB consequences are not specific to this condition and the clinical history alone is insufficient to diagnose OSA amongst children in the general population\textsuperscript{163}. In addition to that, there are few sleep specialized laboratories around the world to confirm diagnosis in OSA suspected children\textsuperscript{164, 165}. Consequently, in recent decades, there has been an increased interest in exploring cost-effective methods of diagnosing SDB, and greater attention has therefore been focused on abbreviated polysomnography using portable monitoring devices\textsuperscript{166, 167}.

The apnoea hypopnoea index (AHI) is the main metric used to indicate SDB severity obtained from the PSG recording and a normal AHI value in children has been reported to
be < 1 event/hour\textsuperscript{168-170}. An AHI between 1-5 indicates mild OSA, an AHI <5 and ≤10 indicates moderate OSA, and an AHI >10/hour is considered to be severe OSA\textsuperscript{171}.

Level 3 home polysomnography has been used in the majority of the published studies on home testing of SDB children. These abbreviated studies, using Level 3 PSG, are even performed in sleep laboratories in several European countries, as they are much less time consuming to set up and score\textsuperscript{159}.

<table>
<thead>
<tr>
<th>Table 5 Polysomnography Levels\textsuperscript{160, 161, 167}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSG sleep studies Level</strong></td>
</tr>
<tr>
<td><strong>Level 1</strong></td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
</tr>
<tr>
<td><strong>Level 3</strong></td>
</tr>
<tr>
<td><strong>Level 4</strong></td>
</tr>
</tbody>
</table>

**Abbreviations:** electroencephalography (EEG), electromyography (EMG), electrooculography (EOG), electrocardiography (ECG), heart rate (HR)
8.6 Upper airway imaging modalities

Several studies evaluated the utility of radiographs in addition to clinical examination in establishing the diagnosis of SDB, relying on the detection the anatomical features associated with SDB\textsuperscript{172, 173}. Cephalometric and dental features in children with SDB are summarised in Table (6). A review of cephalometric studies form Marcus et al in 2012 concluded that the presence of airway narrowing indicates an increased probability of detecting OSA by PSG\textsuperscript{45}. Although related cephalometric studies did not assess sensitivity and specificity or positive and negative predictive values, measuring the ratio of tonsil width to the depth of the pharyngeal space on a lateral neck radiograph was reported to have good sensitivity and specificity (95.8\% and 81.8\% respectively) for distinguishing mild from moderate/severe OSA in a small number of patients\textsuperscript{138}. Cephalometric-measured adenoidal enlargement was present in over 80\% of SDB children and combining this measure with other SDB symptoms (mouth breathing or nocturnal enuresis) yielded more than 90\% sensitivity in SDB diagnosis\textsuperscript{174}.

Direct visualization of the adenoids using nasopharyngoscopy is the diagnostic standard to evaluate adenotonsillar hypertrophy\textsuperscript{175}, but neck radiographs may represent a valuable tool in a child who is difficult to examine, as adenoid hypertrophy evaluated by lateral radiograph correlates well with nasopharyngoscopy\textsuperscript{176}.

Rhinometry and pharyngometry may represent useful techniques in SDB diagnosis. Findings from a cohort study on children aged 8-11 years indicated that measuring the minimum pharyngeal cross-sectional area using acoustic pharyngometry is a useful screening
technique for paediatric OSA. Another (uncontrolled) study showed that nasal resistance measured using rhinometry had a high sensitivity and specificity for predicting polysomnographic OSA. This technique warrants further study and validation.

<table>
<thead>
<tr>
<th>Table 6 Cephalometric and dental features of children with SDB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skeletal class II features</strong></td>
</tr>
<tr>
<td>- Increased ANB angle (of less than 2° in comparison to control) in children with OSA and primary snoring 173, 179</td>
</tr>
<tr>
<td>- Retrognathic mandible 179, 180</td>
</tr>
<tr>
<td><strong>Mandible</strong></td>
</tr>
<tr>
<td>- Retrognathic mandible 180</td>
</tr>
<tr>
<td>- Short mandibular plane length 181</td>
</tr>
<tr>
<td>- Steeper mandibular plane 179</td>
</tr>
<tr>
<td><strong>Maxilla</strong></td>
</tr>
<tr>
<td>- A short maxilla (short nasal floor) 180</td>
</tr>
<tr>
<td><strong>Facial height</strong></td>
</tr>
<tr>
<td>- Increased posterior facial height 180</td>
</tr>
<tr>
<td>- Increased anterior lower facial height 180</td>
</tr>
<tr>
<td>- Lower ratio of posterior/anterior total face height 182</td>
</tr>
<tr>
<td><strong>A narrow pharyngeal airway space</strong></td>
</tr>
<tr>
<td>- There is strong support for reduced upper airway sagittal width in children with obstructive sleep apnea 173, 179, 180</td>
</tr>
<tr>
<td><strong>Soft tissues</strong></td>
</tr>
<tr>
<td>- An anterior tongue base position 180</td>
</tr>
<tr>
<td>- A long soft palate 180</td>
</tr>
<tr>
<td>- Increased tonsil size 138</td>
</tr>
<tr>
<td><strong>Dental features (Cephalometric &amp; dental models)</strong></td>
</tr>
<tr>
<td>- Increased overjet 183</td>
</tr>
<tr>
<td>- Reduced overbite 183</td>
</tr>
<tr>
<td>- Class II molar relationship 183</td>
</tr>
<tr>
<td>- A large interincisal angle 60</td>
</tr>
<tr>
<td>- Retroclined lower incisors 60</td>
</tr>
<tr>
<td>- Inclined occlusal plane 179</td>
</tr>
<tr>
<td>- Palatal cross bite 182, 184</td>
</tr>
<tr>
<td>- Deeper palatal height 182</td>
</tr>
<tr>
<td>- Reduced transverse widths of the maxillary and mandibular arches 182-184</td>
</tr>
</tbody>
</table>
Magnetic resonance imaging (MRI) of the upper airway in children with OSA compared to normal controls reveals a statistically smaller upper airway luminal volume and elongation of the soft palate, as well as enlarged tonsils and adenoids. MRI studies are inconsistent regarding the anatomical features of children. Although 3-dimensional studies of the upper airways and craniofacial morphology represents a valuable diagnostic tool, MRI is not indicated as a routine evaluation of SDB. However, MRI is reported to be a useful tool in identifying sites of obstruction, especially with persistent OSA in children.

### 8.7 Serum, urine and other breath-related biomarkers

Paediatric OSA is associated with both systemic and localized inflammation of the upper airways. The association between OSA and systemic inflammation has been reported by studies showing up-regulation of plasma CRP, increased neutrophils in the sputum, increased urinary levels of cysteinyl leukotrienes, and increased levels of leukotrienes in addition to condensation of prostaglandins in exhaled breath in children with OSA.

Markers of local upper airway inflammation have also been identified in children with OSA: increased pro-inflammatory cytokines TNF-α, IL-6, IL-1α and increased T cells and decreased B cells in tonsillar tissue, increased leukotriene receptor expression in tonsillar tissue, increased cysteinyl leukotriene receptor expression in T cells from tonsillar tissue and upregulation of glucocorticoid receptors in adenotonsillar tissue.

### 9 Treatment of obstructive sleep apnea

#### 9.1 Continuous positive airway pressure CPAP
Continuous Positive Airway Pressure (CPAP) is a ventilator therapy delivered through a face mask, nasal mask or nasal pillows. Nasal CPAP was first introduced in 1981 as a treatment for adult OSA, to maintain the open upper airway by acting as a pneumatic splint\textsuperscript{195}, with its first use in children with OSA was reported in 1986\textsuperscript{196}.

Nasal CPAP is effective in the treatment of both the symptoms and the polysomnographic evidence of OSA\textsuperscript{197}. CPAP is advocated for severely affected adolescent SDB patients, or for persistent OSA after adenotonsillectomy \textsuperscript{45}.

Not unlike adults, children’s adherence to CPAP treatment is a major obstacle to effective use. Studies report that the adherence to this type of treatment varies between 30-70% among treated children\textsuperscript{198, 199}. From a biomechanical perspective, there are anecdotal reports of potential growth disturbances from long-term use of CPAP because the elastic strap which maintains the mask may apply a restraining force on the maxilla\textsuperscript{200}.

\subsection*{9.2 Adenotonsillectomy}

The first line and most common treatment for paediatric OSA is adenotonsillectomy, particularly for moderate to severe cases with adenotonsillar hypertrophy and no contraindication to surgery\textsuperscript{45}. The incidence of adenotonsillectomy has increased in number in the past few decades and the indication for surgery has markedly shifted from recurrent infection to upper airway obstruction\textsuperscript{201, 202}.

Although significant improvements in AHI are observed following adenotonsillectomy, the cure rate of OSA after operation (defined as a post-adenotonsillectomy AHI <1 event/hour) ranges from 27\% to 60\%\textsuperscript{203, 204}. 
Current studies report that adenotonsillectomy for children with SDB is associated with improvements in quality of life, behaviour, and cognitive function\textsuperscript{205}. Moreover, the manifestation of enuresis can be reversed in 50\% to 75\% of the cases after adenotonsillectomy\textsuperscript{119, 206, 207}. Increased GH secretion after adenotonsillectomy improves facial morphology in addition to other factors of achieving balance between tongue and cheek forces, and retrieval of nasal breathing\textsuperscript{62, 208}.

Evidence supported by meta-analysis reviews showed that OSA children with comorbid conditions of obesity and dentofacial abnormalities are strong candidate cases for persistent OSA after adenotonsillectomy\textsuperscript{209-211}.

Although the American Academy of Paediatrics recommends that clinicians reassess all patients with OSA for persisting signs and symptoms after adenotonsillectomy\textsuperscript{45}, it is still uncommon (less than 5\% of cases) to utilise postoperative polysomnography for children after adenotonsillectomy, and therefore, cases of persistent OSA are highly likely to be missed\textsuperscript{212, 213}.

Repeated adenoidectomy is sometimes required because it is associated with an increased risk of persistent OSA in comparison to adenotonsillectomy\textsuperscript{214, 215}.

Adenotonsillectomy is associated with a risk of postoperative complications, particularly respiratory compromise (defined as intermittent or continuous oxygen saturation of 70\% or less, and/or hypercapnia, requiring intervention after surgery)\textsuperscript{216, 217}. Children with obesity, severe OSA, or craniofacial abnormality may require more protracted inpatient care and/or intensive care unit observation\textsuperscript{216, 218}. 
9.3 Medical treatment

Two types of medications, which offer a therapeutic alternative to adenotonsillectomy have been studied in paediatric OSA: corticosteroids and leukotriene modifiers.

Corticosteroids have been shown to reduce tonsillar proliferation in vitro, in tissue samples collected from children with OSA during adenotonsillectomy. A reduction in the size of lymphoid tissues is expected due to anti-inflammatory and lympholytic effects of corticosteroids, but short course systemic administration of corticosteroids was found not to have a significant effect on adenoidal size or the severity of OSA. However, topical corticosteroid, intranasal application, showed significant reduction in adenoidal size and snoring, as well as OSA severity.

Leukotriene modifiers such as montelukast have been considered as a therapy option for children with mild OSA due to its anti-inflammatory properties. According to an RCT study, oral montelukast appears to be effective in improving respiratory disturbances in children with mild to moderate OSA, as demonstrated by improvements in AHI.

A combination of intranasal corticosteroid and oral montelukast is considered a promising treatment and may provide an alternative to adenotonsillectomy in cases of mild paediatric OSA. A recent study comparing anti-inflammatory drugs to adenotonsillectomy recommended surgical treatment as the first choice for children with moderate and severe OSA and confirmed the role of anti-inflammatory drugs in mild OSA cases.

10 Oral appliances in the treatment of obstructive sleep apnea

A mutual interaction has been reported between the nasopharyngeal airway and the craniofacial complex. Jaw malposition and anomalies are correlated to changes in airway
morphology and respiratory problems\textsuperscript{228, 229}. Reciprocally, obstruction of the airways has an influence on the development of the stomatognathic system\textsuperscript{230, 231}.

A narrow upper airway, maxillary constriction and mandibular retrusion are thought to be common phenotypes of paediatric SDB\textsuperscript{180, 211, 232-234}. After adenotonsillectomy, enhancement and acceleration of ramus and mandibular growth have been indicated further to normalisation of GH in paediatric OSA patients\textsuperscript{208, 235}, but in many cases, growth acceleration was not sufficient to solve the already formed malocclusion. In turn, this requires further orthodontic treatment to solve the problem\textsuperscript{236}.

\textbf{10.1 Oral appliances therapy mechanism of action and types}

Oral appliances have been widely used for the treatment of OSA, mainly in adults\textsuperscript{237-242}. These appliances aim to increase the posterior oropharyngeal airway by reducing upper airway collapsibility during sleep\textsuperscript{137}, and by triggering the stretch receptors, which in turn activate the airway supporting muscles\textsuperscript{28}. Because of improved comfort, quietness, and portability, oral appliance treatment could potentially result in better patient adherence and acceptance than CPAP treatment\textsuperscript{239, 243, 244}.

The orthodontic interventions that have been introduced for treatment of paediatric SDB are: mandibular advancement splints (MAS), rapid maxillary expansion (RME), and facial mask\textsuperscript{245, 246}.

MAS is the most common type of oral appliance used in the treatment of SDB. Evidence supporting their use and efficacy in adults is increasing\textsuperscript{239, 247}, but their use in children for SDB treatment is less common and they are usually designed as a functional appliance for growth modification in children\textsuperscript{248}. It is generally accepted that advancing the mandible in
growing patients may improve jaw skeletal and dentoalveolar relationships\textsuperscript{249-251}, as well as increase nasopharyngeal airway dimensions\textsuperscript{252, 253}. Therefore, it may improve SDB symptoms\textsuperscript{237, 242, 243} on the basis of the significant relationship between paediatric OSA and craniofacial morphology\textsuperscript{172, 180, 254-256}.

RME is used when the patient has been diagnosed with a narrow upper jaw. RME decreases nasal resistance and allows tongue repositioning. As a result, it may reduce the risk of the obstruction that contributes to sleep apnoea\textsuperscript{257}. The idea of using RME in SDB treatment arose when it was shown to decrease nocturnal enuresis in children\textsuperscript{258}, which can be an associated symptom of SDB. RME caused a significant reduction in nocturnal enuresis in all treated cases\textsuperscript{259}. RME is currently performed most often using a fixed intra-oral orthodontic appliance, which can be adjusted and worn at all times during the treatment. An expansion of 5 to 8 mm can be obtained over 30 days, with the expansion screw activated daily by parents (active phase); following this active phase, the expansion screw is locked into place for a retention phase of 2-6 months to allow re-calcification of the palatine suture (retention phase)\textsuperscript{260}.

Maxillary protraction devices may be considered as a treatment option, as the sagittal growth of the maxilla causes increases in the size of the upper airway\textsuperscript{245}.

\section*{10.2 Efficacy of Oral appliances therapy in paediatric OSA}

Both MAS and RME have the potential to become valuable alternative treatments for patients with known craniofacial risk factors for SDB, who are not candidates for adenotonsillectomy or who are unable to tolerate or are unaffected by first-line treatments; adenotonsillectomy or CPAP\textsuperscript{246}. 
MAS might be an effective treatment for children with SDB\textsuperscript{244}. They are relatively well tolerated by patients\textsuperscript{261}, so they can easily be used for incremental advancement of the lower jaw\textsuperscript{262}. MAS can also expand the upper arch\textsuperscript{263}. They are suitable for both mixed and permanent dentitions\textsuperscript{263}, and these appliances have low failure treatment rates\textsuperscript{261}. The therapeutic rationale is that all orthodontic anomalies (except class III) benefit from mandibular advancement capable of enlarging the retro-lingual space and at the same time promoting lingual advancement\textsuperscript{237}.

Although there is increasing evidence regarding the efficacy of MAS in adults with SDB, there is a paucity of information about their efficacy in children\textsuperscript{246, 264-266}. The few studies carried out to date suffer from methodological flaws, including: heterogeneous samples, lack of randomization, limited power to detect a clinically relevant effect, and lack of an adequate control conditions, such as the use of a placebo-like appliance. A Cochrane review by Carvalho et al. (2007) showed that there is not enough evidence to affirm that oral appliances and functional orthopedic appliances are effective in the treatment of OSA in children\textsuperscript{266}. This conclusion was supported by two recent systematic reviews and meta-analyses\textsuperscript{246}, which confirmed that the current evidence is limited and suggested possible short-term effectiveness in paediatric OSA treatment\textsuperscript{265}. Therefore, it is currently difficult to draw a conclusion regarding the possible efficacy of mandibular advancement appliances in children affected by SDB\textsuperscript{237, 242, 244, 267}.

To determine the cutoff point of successful treatment of OSA with an oral appliance, a decrease of 50\% in AHI is considered appropriate in adults and was adopted in paediatric OSA research\textsuperscript{265}. Table (7) summarises the four main studies on using mandibular advancement splints in paediatric SDB treatment.
### Table 7 Summary of the published studies about mandibular advancement devices in children with SDB

<table>
<thead>
<tr>
<th>Study</th>
<th>Villa et al., 2002&lt;sup&gt;237&lt;/sup&gt;</th>
<th>Cozza et al., 2004&lt;sup&gt;242&lt;/sup&gt;</th>
<th>Schutz et al., 2011&lt;sup&gt;268&lt;/sup&gt;</th>
<th>Zhang et al., 2013&lt;sup&gt;269&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>RCT</td>
<td>CCT</td>
<td>CT</td>
<td>CT</td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
<td>7.1±2.6 years</td>
<td>5.91 years</td>
<td>12.9 years ± 11.5 months</td>
<td>9.7±1.5 years</td>
</tr>
<tr>
<td><strong>Participant number</strong></td>
<td>32 (20 males)</td>
<td>20 OSA (10 males)</td>
<td>- 16 (treatment group)</td>
<td>- 46 (31 males)</td>
</tr>
<tr>
<td></td>
<td>-19</td>
<td>-13 control</td>
<td>- No control</td>
<td>- No control</td>
</tr>
<tr>
<td><strong>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</strong></td>
<td>17.9±5.2</td>
<td>16.2±3.4</td>
<td>18.7±1.8</td>
<td>18.1±1.04</td>
</tr>
<tr>
<td><strong>Follow up</strong></td>
<td>6 months</td>
<td>6 months</td>
<td>12 months</td>
<td>10.8 months</td>
</tr>
<tr>
<td><strong>Attrition rate</strong></td>
<td>28%</td>
<td>0.0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Appliance &amp; procedures</strong></td>
<td>Acrylic oral bite plate (positioning the mandible in its correct position in every patient as needed (advance receding mandible, raising deep bite, or recentering cross-bite))</td>
<td>Upper mandibular advancement splint with slow maxillary expansion to follow the maxillary transversal growth. A Tucat’s pearl was added to the splint, with a sliding wire for reference of the tip of the tongue and lower lingual arch soldered to bands on the primary molars</td>
<td>Herbst appliance and maxillary expander</td>
<td>Twin-Block, without maxillary expansion</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>- AHI reduction from 7.1±4.6 to 2.6±2.2</td>
<td>- AHI reduction from 7.8±1.8 to 3.6±1.7</td>
<td>- significant reduction in respiratory disturbance index from 7.3±5.6 to 1.3±1.8 (P&lt;0.05)</td>
<td>- Significant reduction in AHI from 14.08±4.25 to 3.39±1.86 (P&lt;0.01)</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

RCT: randomised controlled trial, CCT: Clinical controlled Trial, CT: Clinical trial, AHI: Apnoea Hypopnoea Index,
10.3 Adherence to oral appliance treatment

Studies using oral appliances for children with OSA reported that these appliances were well tolerated. A landmark study by Villa et al. (2002) reported a high dropout of 28% because of lack of tolerability and simple inconvenience at school\textsuperscript{237}.

Some available studies used new modifications of MAS appliances\textsuperscript{237, 242}. On the other hand, some others used well known and commonly used mandibular advancement appliances such as Twin-Block and Herbst\textsuperscript{244, 268}. Using new different designs may pose a challenge concerning children compliance and acceptance of those modified appliances, which are not tested in this regard. This was represented in high withdrawal rates in the Villa et al. (2002) study\textsuperscript{237}. Adversely, when using Twin-Block as an example of commonly used and well accepted design, the attrition rate was 0% in one of the studies\textsuperscript{244}.

11 Adult SDB versus Paediatric SDB

Paediatric OSA differs from adult OSA in both clinical characteristics and determinants of its epidemiology\textsuperscript{35}. Consequently, diagnostic criteria and treatment protocols and methods differ from those in adults. Table (8) summarises the major differences between adult and paediatric OSA. More information about SDB in adults was reported in the New Zealand Dental Association News journal\textsuperscript{270}.(Appendices, publications)
<table>
<thead>
<tr>
<th><strong>Table 8 Summary of the differences between adult and paediatric OSA</strong></th>
<th><strong>Children</strong></th>
<th><strong>Adults</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex distribution</strong></td>
<td>Male: Female= 1:1</td>
<td>Male: Female= 8:1</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>- Normal or underweight - Obesity increases the risk of developing OSA</td>
<td>Commonly obese</td>
</tr>
<tr>
<td><strong>Snoring</strong></td>
<td>Continuous</td>
<td>Intermittent with pause</td>
</tr>
<tr>
<td><strong>Mouth breathing</strong></td>
<td>Common</td>
<td>Less common</td>
</tr>
<tr>
<td><strong>Chief complaint</strong></td>
<td>Snoring, difficult breathing</td>
<td>Daytime sleepiness</td>
</tr>
<tr>
<td><strong>Enlarged tonsils/adenoids</strong></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Obstructive pattern</strong></td>
<td>Mostly apneas</td>
<td>Mostly hypopneas</td>
</tr>
<tr>
<td><strong>State with most obstruction</strong></td>
<td>REM</td>
<td>REM or non-REM</td>
</tr>
<tr>
<td><strong>Clinical arousal</strong></td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Sleep architecture</strong></td>
<td>Preserved</td>
<td>Fragmented</td>
</tr>
<tr>
<td><strong>Apnoea definition</strong></td>
<td>absence of airflow for two respiratory cycles (2 breaths) with continued chest wall and abdominal wall movement(^\text{34})</td>
<td>absence of airflow for at least 10 seconds with continued chest wall and abdominal wall movement(^\text{34})</td>
</tr>
<tr>
<td><strong>Hypopnoea definition</strong></td>
<td>decrease in nasal flow ≥30% (the drop should last at least 2 breaths from baseline) with a corresponding decrease of ≥3% in oxygen saturation and/or arousal(^\text{34})</td>
<td>decrease in nasal flow ≥30% (the drop should last at least 10 seconds) with a corresponding decrease of ≥3% in oxygen saturation and/or arousal(^\text{34})</td>
</tr>
<tr>
<td><strong>OSA severity (AHI)</strong></td>
<td>- mild(AHI &lt;1) - moderate (AHI =1-9) - severe(AHI ≥10)</td>
<td>- mild(AHI =5-15) - moderate(AHI =16-30) - severe (AHI &gt;30)</td>
</tr>
<tr>
<td><strong>Cephalometric features</strong></td>
<td>- small nasopharyngeal airway space(^\text{45, 172}) - Class II skeletal tendency(^\text{172, 271})</td>
<td>- Low position of the hyoid relative to the mandibular plane(^\text{272}) - Class II skeletal tendency(^\text{273})</td>
</tr>
<tr>
<td><strong>Differential diagnosis</strong></td>
<td>Other causes of snoring or breathing difficulty during sleep</td>
<td>Other causes of excessive sleepiness or sleep disruption</td>
</tr>
<tr>
<td><strong>Main sequelae</strong></td>
<td>Behavioural changes Neurocognitive deficits</td>
<td>Daytime sleepiness Cardiovascular disease</td>
</tr>
<tr>
<td><strong>Primary treatment</strong></td>
<td>Adenotonsillectomy</td>
<td>CPAP therapy</td>
</tr>
<tr>
<td><strong>Surgical treatment</strong></td>
<td>The most frequent surgical procedure is adenotonsillectomy</td>
<td>The most frequent surgical procedures are Uvulopalatopharyngoplasty and other soft palate surgical techniques, maxillomandibular advancement, hyoid suspension, tracheostomy, and linguoplasty(^\text{274}).</td>
</tr>
<tr>
<td><strong>Oral appliance treatment</strong></td>
<td>RME- MAS(^\text{266})</td>
<td>MAS- Tongue Stabilising Device(TSD)(^\text{275, 276}).</td>
</tr>
</tbody>
</table>
12 Statement of the problem

SDB can significantly affect children’s wellbeing, as it can cause growth disorders, educational and behavioural problems, and even life-threatening conditions, such as cardiorespiratory failure.

Adenotonsillectomy represents the primary treatment for paediatric SDB where adeno-tonsillar hypertrophy is indicated. However, the invasive nature of this treatment with the risk of postoperative complications and reports of persistent OSA after the surgery encouraged researchers to look for alternatives especially for those with craniofacial anomalies, or for whom adenotonsillectomy or other treatment modalities have failed, or surgery is contra-indicated.

Mandibular advancement splints (MAS) may represent a viable treatment option. Whilst the efficacy of these appliances has been consistently demonstrated in adults, there is little information about their effectiveness in children. This raises the significance and importance of embarking on research to explore this field further and test the efficacy of MAS as an option or a supportive treatment to other modalities.
13 References


91. Beebe DW, Ris MD, Kramer ME, Long E, Amin R. The association between sleep disordered breathing, academic grades, and cognitive and behavioral functioning among overweight subjects during middle to late childhood. Sleep. 2010;33(11):1447-56.


Copyright (c) 2014 Canadian Agency for Drugs and Technologies in Health.; 2014.


270. Idris G LC, Farella M . The role of dentists in adult obstructive sleep apnoea, feature article. . NZDA NEWS 2016;Mar:: 35-44.


CHAPTER TWO

EFFICACY OF A MANDIBULAR ADVANCEMENT APPLIANCE ON SLEEP DISORDERED BREATHING IN CHILDREN

A STUDY PROTOCOL OF A CROSSOVER RANDOMISED CONTROLLED TRIAL
2. Efficacy of a mandibular advancement appliance on sleep disordered breathing in children: a study protocol of a crossover randomised controlled trial

Summary

Background: Sleep-Disordered Breathing (SDB) varies from habitual snoring to partial or complete obstruction of the upper airway and can be found in up to 10% of children. SDB can significantly affect children’s wellbeing, as it can cause growth disorders, educational and behavioural problems, and even life-threatening conditions, such as cardiorespiratory failure. Adenotonsillectomy represents the primary treatment for paediatric SDB where adeno-tonsillar hypertrophy is indicated. For those with craniofacial anomalies, or for whom adenotonsillectomy or other treatment modalities have failed, or surgery is contra-indicated, mandibular advancement splints (MAS) may represent a viable treatment option. Whilst the efficacy of these appliances has been consistently demonstrated in adults, there is little information about their effectiveness in children.

Aims: To determine the efficacy of mandibular advancement appliances for the management of SDB and related health problems in children.

Methods/design: The study will be designed as a single-blind crossover randomized controlled trial with administration of both an ‘Active MAS’ (Twin-Block) and a ‘Sham MAS’. Eligible participants will be children aged 8 to 12 years whose parents report they snore ≥ 3 nights per week. Sixteen children will enter the full study after confirming other inclusion criteria, particularly Skeletal class I or class II confirmed by lateral cephalometric radiograph. Each
child will be randomly assigned to either a treatment sequence starting with the Active or the Sham MAS. Participants will wear the appliances for three weeks separated by a two-week washout period. For each participant, home-based polysomnographic data will be collected four times; once before and once after each treatment period. The Apnoea Hypopnoea Index (AHI) will represent the main outcome variable. Secondary outcomes will include, snoring frequency, masseter muscle activity, sleep symptoms, quality of life, children behaviour, and nocturnal enuresis. In addition, blood samples will be collected to assess growth hormone changes.

**Trial registration:** This study was registered in the Australian New Zealand Clinical Trials Registry (ANZCTR): [ACTRN12614001013651]
1 Introduction

The health impact of sleep-disordered breathing (SDB), particularly, obstructive sleep apnoea (OSA) has been increasingly recognized in both adults and children. The prevalence of OSA in children varies from 1 to 4% \(^2^\text{4}\), while most authors report a 10% prevalence of habitual snoring in children. SDB has been associated with growth disorders, daytime sleepiness, educational and behavioural problems, and nocturnal enuresis. In the most severe cases, OSA may have life-threatening consequences like cardiorespiratory failure, which can lead to death.

Enlarged adenoids and tonsils are the most common aetiology of OSA in children. Obesity during childhood represents another important risk factor for OSA. Craniofacial anomalies are also associated with changes in airway morphology and respiratory problems. These anomalies, basically, include maxillary and mandibular retrognathia, increased facial height, decreased facial width, increased overjet, and palatal crossbite.

Polysomnography (PSG) is considered the gold standard for SDB diagnosis, and the apnoea hypopnoea index (AHI) is the main outcome to aid diagnosis. AHI is defined as the number of apnoea and hypopnoea events recorded per hour of sleep. A paediatric obstructive sleep apnoea event, relying on PSG, is defined as absence of airflow for two respiratory cycles (2 breaths) with continued chest wall and abdominal wall movement. Whereas obstructive hypopnea is defined as a decrease in nasal flow ≥ 30% (lasting at least 2 breaths) with a corresponding decrease in oxygen saturation ≥ 3% and/or arousal.

Full PSG is costly to perform in sleep laboratory, and scoring sleep stages is time consuming. Consequently, over the last decades, there has been increased interest in cost-effective methods.
of diagnosing SDB within the home setting using portable monitoring devices. Type 3 home PSG, also referred to as abbreviated PSG without electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (EMG), has been used in the majority of the published studies on home testing of SDB in children; this abbreviated PSG, is more suitable for use in children, it is less time-consuming, and it is easier to set up and score.

The first line and the most common treatment for paediatric OSA is adenotonsillectomy. Although significant improvements in the Apnea Hypopnea Index (AHI) are observed following adenotonsillectomy, full resolution of OSA (AHI≤ 1) occurs only in 27% to 60% of cases. Adenotonsillectomy is also associated with risk of postoperative complications beyond the anaesthetic and surgical procedures. For example, OSA children show a significantly higher risk of respiratory compromise, defined as intermittent or continuous oxygen saturation of 70% or less, and/or hypercapnia, requiring intervention after surgery. Children with obesity, severe OSA, or craniofacial abnormalities may require more protracted inpatient care and/or intensive care unit observation. Studies have reported an accelerated mandibular ramus growth and improved facial morphology after adenotonsillectomy in paediatric OSA patients. This improvement may be due to normalization in growth hormone (GH) serum levels, also to a change of tongue and cheek posture. However, this growth acceleration is not sufficient to correct the malocclusion and the underlying skeletal discrepancy often requires subsequent dentofacial growth modification treatment.

Continuous positive air pressure (CPAP) is the primary treatment option for adult OSA. CPAP is also advocated for severe paediatric SDB, or for persistent OSA after adenotonsillectomy, but it is generally not well tolerated by children. Adherence to CPAP treatment in children is a major problem, with rates of only 30-70%. From a biomechanical stand-point, there are...
anecdotal reports of potential facial growth disturbances from long-term use of CPAP due to
the elastic strap which maintains the mask, as it may apply a restraining force on the growing
maxilla\textsuperscript{41}.

Oral appliances have also been widely used for the treatment of OSA, particularly in adults\textsuperscript{1, 42, 43}. These appliances increase the posterior oropharyngeal airway and reduce upper airway
collapsibility by holding the mandible in a protruded position during sleep; furthermore, the
device may trigger stretch receptors, which in turn activate the airway supporting muscles\textsuperscript{1}.

Previous studies have shown that oral appliances are better tolerated than CPAP treatment\textsuperscript{43}
because of improved comfort, quietness, and portability. Mandibular advancement appliances
are the most common type of oral appliances used in the treatment of SDB in adults, but their
use in children is less common, with little information about their efficacy\textsuperscript{43}. The few studies
on the subject suffer from important methodological flaws, making it difficult to reach a
definitive conclusion about the efficacy of MAS appliances in children with SDB\textsuperscript{42, 44-47}.

\section{Objectives}

Aims of the study are: (1) to test the short-term efficacy of MAS in the treatment of children
with SDB; and (2) to assess the effect of MAS treatment on quality of life, behaviour, growth
hormone levels, and nocturnal enuresis in SDB children.

\section{Materials and methods}

\subsection{Study design}

This study will be carried out as a single-blind crossover randomized controlled trial. Each
participant will wear two appliances consisting of an active MAS and non-active MAS (Sham
MAS). Each appliance will be worn for a three-week treatment period, which will be separated by a two-week washout period. A similar study design and treatment time have been used in previous studies comparing the efficacy of MAS to nasal CPAP treatment in adults \(^{48,49}\).

This study will be conducted in the Discipline of Orthodontics, School of Dentistry University of Otago, New Zealand. Ethical approval has been granted by the Human Ethics Committee at University of Otago [H14/054], and New Zealand Health Research South Ethics Committee-Southern District Health Board [01050]. The research has also been approved by Ngāi Tahu Research Consultation Committee (Research consultation with Māori).

3.2 Participants

3.2.1 Sample size estimation

A reduction of 50% in AHI is generally considered clinically relevant \(^{43}\). This change corresponds to a large effect size (Cohen’s \(d\) = 1.5). To detect this effect size, and setting \(\alpha\) error to 0.05 and \(\beta\) error to 0.20 using a repeated-measurement design, we have estimated that at least 13 participants are needed. We will recruit 16 children to account for possible dropouts.

3.2.2 Recruitment

We will advertise in local newspapers to invite children who live in Dunedin city/New Zealand, to participate in the study according to the following eligibility criteria: age 8-12 years; parental report of snoring three nights or more per week; A score for the Paediatric Sleep Questionnaire (PSQ) ≥ 0.33\(^{50}\).

Exclusion criteria include severe OSA defined as an AHI >10 \(^{51}\); craniofacial syndromes and genetic syndromes; neuromuscular diseases; skeletal maxillomandibular class III confirmed
by lateral cephalometric radiograph (ANB angle)\textsuperscript{52, 53}, or class III incisor relationships, or previous orthodontic treatment.

Patients diagnosed with severe OSA will be referred to a Medical Specialist.

### 3.3 Oral appliances

An n-of-1 pilot study was undertaken to compare the acceptance, and the mechanical retention of different splint designs to choose the best design to be used in the main study. Four appliances were identified and tested in an eleven-year old boy with class II dental and skeletal jaw relationships, the appliances were: Traditional Twin-Block\textsuperscript{54}, Twin-Block with metallic fastener (TAP\textregistered-splint, SCHEU Dental Technology, Brussels, Belgium); Clear elastic Twin-Block; Sham Twin-Block Figure (1).

As discomfort affects adaptation and acceptance\textsuperscript{55, 56}, this was evaluated in a pilot study using two assessment methods: the participant was firstly asked to report how comfortable each appliance was immediately after insertion into the oral cavity in compare to the other appliances. The four appliances were presented in pairs to compare each appliance to the remaining three (a total of 12 pairs were generated to avoid confounding caused by sequence of appliances application); the participant was instructed to insert an appliance into the mouth and he was asked to move the mandible to the right and left, front and back, and then to swallow, then to repeat the same to another appliance; after that the participant was asked to indicate which of the two appliances was more comfortable to wear. The effect on speech was evaluated by asking the participant to count from 60 to 70 with each appliance inside the mouth, and comparing this with counting without the appliance in the mouth; the counting was audio recorded and assessed later by the researcher. The second method for evaluating discomfort
aimed to assess acceptance after wearing the appliance for two hours while awake and during one night sleep. One night appliance-free was allowed as washout period between two sequentially-tested appliances. Discomfort was assessed by using a 100-mm visual analogue scale (VAS) with words (worse than I can imagine; better than I can imagine) anchored at the left and right end of the scale, corresponding to worse discomfort and best comfort, respectively. The participant rated the discomfort intensity by putting a vertical slash on the line that best represented the intensity of discomfort. The higher the VAS score the better the appliance acceptance. Two separate VAS scores were collected after both the awake and asleep wearing periods.
Retention was tested using both a subjective and an objective assessment. Subjective assessment was made by asking the participant 1) if the appliance was held in the mouth the

**Figure 1 Appliances tested in a pilot study to identify the most suitable appliance design to be used in the main study**

A- Traditional Twin-Block: Removable upper and lower acrylic plates, each plate has matching pieces to encourage the lower jaw to slide forward, bilateral hooks were added to insert vertical elastics.

B- Metallic fastener Twin-Block: Removable upper and lower vacuum formed plates and a metallic fastener (TAP) is used to hook the upper and the lower plates enabling the mandible to be advanced forward.

C- Clear elastic Twin-Block: Removable upper and lower vacuum formed plates with matching pieces to encourage the lower jaw to slide forward, bilateral plastic hooks were added to accommodate vertical elastics.

D- Sham Twin-Block: Removable upper and lower vacuum formed plates, without any lower jaw advancing device.
whole night, 2) if the upper and lower splints were fitting well to the teeth, and 3) if the upper and lower splints stay attached to each other. Response options were yes/no.

Passive and active retention were also objectively tested by two independent examiners (GI, MF) by checking whether the appliance was stable in-mouth upon, 1) maximum jaw opening and, 2) direct pulling of the examiner.

**Results of the pilot study:**

**Initial acceptance**

Initial acceptance was based on the most accepted appliance. The following were used:

(Sham appliance, traditional Twin-Block, Metallic Fastener Twin-Block, Clear elastic Twin-Block)

The traditional Twin-Block was the easiest appliance to remove as reported by the patient. This was because it was easy for the patient to find the clasps and take the splints out of the mouth. On the other hand, the Clear Elastic TB was the hardest one to remove out of the mouth because the patient had to take the appliance out by pushing the flange edges which extended high in the vestibule, taking care not to scratch the soft tissue.

To observe retention of the appliances inside the mouth, the patient was asked to open their mouth to the maximum. The Traditional Twin-Block displayed the best retention followed by the metallic fastener Twin-Block. The Clear elastic Twin-Block was the worst for resisting the vertical elastic force and the appliance easily came off the upper and the lower arches.

The sound recording assessment whereby the patient counted from 60 to 70 when wearing the appliance was compared to the recording when not wearing the appliance (reference). This
showed that the clearest pronunciation was found with the Sham Twin-Block, followed by the traditional Twin-Block, then the clear elastics Twin-Block, and finally use of the metallic fastener Twin-Block resulted in the worst speech pronunciation.

Acceptance after use

The patients rated the comfort of each appliance twice: during the day, and after waking up in the morning. These ratings showed that the Sham Twin-Block was the most comfortable MAS appliance followed by the traditional Twin-Block and then metallic fastener Twin-Block. The least acceptable was the clear elastic Twin-Block. Results are presented in the graph in Figure 2.

![Bar graph showing comfort levels](image)

**Figure 2** Self-reported level of discomfort after using the appliances in the pilot study: Self-reported comfort level during the day and night time using different appliance designs tested in the pilot study to identify the most suitable appliance design to be used in the main study.

TB: Twin-Block

Retention and stability inside the mouth
This was reported by the parents after their child going to deep sleep by answering the following questions: does the two splints stay link to each other; both splints stay stick to the upper and the lower arches; the appliance does not fall out the mouth during sleep.

<table>
<thead>
<tr>
<th>Table 1 Retention and stability of the different appliances in the pilot study as reported by parents</th>
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<tbody>
<tr>
<td>Traditional TB</td>
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<tr>
<td>Splints stay fitting together</td>
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<tr>
<td>Splints stay attached to the top and the lower teeth</td>
</tr>
<tr>
<td>Splints fall out the mouth during sleep</td>
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</table>

TB: Twin-Block

The upper and the lower arches; the appliance does not fall out the mouth during sleep. Table (1)

The retention of the Twin-block VE and the Metallic Fastener TB was good.

The vertical 1/8 Heavy elastic bands was good in keeping the upper and the lower splints together with the traditional design of the Twin-block. But they (the elastic bands) failed to do the same with the Clear Elastic TB (suck-down appliance). The metallic fastener was good in keeping the two splints together.

There were significant differences among the appliances tested in the pilot study in the level of discomfort reported by the patient considering the day and night scores when using each appliance for one night p= 0.001, Analysis of variance)
Since the traditional Twin-Block appliance showed the best retention and acceptance this was chosen as the study protocol intervention. Additional arguments in support of this decision were:

- It is easy to titrate and can also be used to expand the upper arch\(^{57}\).
- It includes metal clasps to increase retention as required\(^{57}\).
- It is very popular amongst orthodontists and has been extensively tested in previous research\(^{58}\).
- It has a low failure rate and is well tolerated by children\(^{59}\).
- It can be used for facial growth modification in patients with skeletal class II jaw relationship\(^{58}\).

### 3.3.1 Twin-Block design (active MAS):

This consists of two removable upper and lower plates; each plate has matching pieces which encourage the lower jaw to posture or slide forward as the teeth come together Figure (2)\(^{54}\). Hooks will be added to the Twin-Block bilaterally to insert vertical elastics. These elastics will hold the mouth closed during sleep and the mandible postured in a forward position\(^{60}\). The construction bite of the appliance will be determined using the George Gauge\(^{TM}\)\(^{61}\), which allows an accurate determination and registration of the mandibular advancement. The bite registration will be taken for all participants by advancing the mandible 75% of the maximum protruded position of the jaw with minimum bite opening.

### 3.3.2 Sham MAS design (non-active MAS):

This consists of two non-active upper and lower acrylic plates resembling the design of the active MAS, but without any component to protrude the mandible Figure (3).
3.4 Randomisation

Participants will be randomly assigned to either a sequence starting with the Twin-Block or the Sham MAS. Thereafter, participants will wear the appliances for three weeks separated by a two-week washout period. Participants will not be told whether they wear the active or the non-active appliance. Each night of wear time will be recorded by parents using diaries.

Patients will be allocated to active or sham treatment using four randomised n-of-4 blocks that are balanced for treatment sequence (Sequence 1: Twin-Block MAS first followed by Sham MAS; sequence 2: Sham MAS first followed by Twin-Block MAS) Figure (3). Allocation will be concealed in opaque envelopes, and disclosed by a member of the research team (MF) immediately after enrolment. Participant flow is illustrated in Figure (4)
Figure 4 Participants’ flow in the study
4 Outcome measurements and stepwise procedure

4.1 Sleep data

Home-based abbreviated polysomnography, (cardio-respiratory Level 3) 27, will be performed using a portable monitoring unit (Embletta MRP PG-XS-ENU, Natus Neurology Incorporated, Ontario, Canada).

PSG recording channels in the Embletta unit will be comprised of one electromyographic (EMG) channel, a finger pulse oximetry, nasal airflow (using a nasal pressure catheter), nasal and mouth thermistry, thoracic and abdominal respiratory effort bands (two piezoelectric belts will be placed around the rib cage and abdomen and monitor respiratory movement), body position sensors, and a microphone attached to the nasal cannula extension. The following variables will be measured: pulse oximetry, airflow, respiratory effort, snoring sound, body position, and EMG of the masseter muscle. This equipment has previously been validated for the diagnosis and management of SDB 62-65.

The portable device is set up through the use of a separate application software, RemLogic-E version 3.4 (Embla system, Natus Europe, Planegg, Germany). Channels are configured and identified, sampling rates set, filtering options defined, recording timing (on/off times), etc. through the same software.

Home-based PSG data will be collected four times for each participant at baseline and after treatment with Twin-Block or Sham MAS, with the support of a research assistant Figure (5).

The AHI will be calculated according to the American Academy of Sleep Medicine (AASM) criteria for scoring paediatric respiratory sleep studies 24. AHI is the main outcome of interest.
and sleep position will be considered in AHI scoring because sleep related obstructive respiratory events in children occur more commonly in the supine sleep position.  

**Figure 5** The study design is a crossover randomized controlled trial. Sixteen patients will be randomly assigned to two sequences; both sequences include a three-week treatment period with active and non-active (sham) mandibular advancement splints but in a different order (Active followed by Non-active and Non-active followed by Active). Treatment periods will be separated by a two-week washout period. Assessments will be taken at baseline (T0) and four times throughout the study. Abbreviations: Abbreviated polysomnography (PSG), Cephalograms (Ceph), Pediatric Sleep Questionnaire (PSQ), Behaviour Assessment System for Children, second edition (BASC-2), and Quality of Life questionnaire (OSA-18).

### 4.2 Snoring frequency

Snoring sounds will be assessed by analyzing audio recordings recorded using the portable PSG equipment. Snoring will be scored manually by listening to the audio recording using RemLogic-E software and the result will be reported as: total snoring time, relative snoring time, number of snoring episodes, average snoring episodes, and longest snoring episode.
The use of audio recordings is one of the recommended methods to aid visualise snoring oscillations. Embletta MPR microphone (an analogue omnidirectional condenser microphone) attached to nasal cannula will record the snoring sounds. All signals will be fed into analogue/digital (A/D) converter with a 200 Hz sampling rate (each channel has 200 points or samples per second). For optimal visualisation of snoring, a high-pass filter to remove very low frequencies (20Hz) and a low-pass filter to remove high frequencies (3 kHz) will be used, this will permit acquiring relevant information of snoring sounds.

Subjective reports of snoring frequency will also be collected by parents using daily diaries throughout each treatment period Figure (5).

### 4.3 Growth hormone levels

Blood samples will be taken from all participants by a certified phlebotomist in a medical laboratory (Southern Community Laboratories). Growth hormone will be indirectly assessed by determination of insulin-like growth factor-1 (IGF-1) levels.

Two samples will be collected at the end of each treatment period and collected in a nonfasting state in the morning to early afternoon. IGF-1 concentrations will be assayed using a human IGF-I quantikine ELISA Kit (PDG100, R&D Systems, Minneapolis, USA). The human IGF-1 immunoassay employs the quantitative sandwich enzyme technique. Samples will be stored in a –80 °C freezer until batch assayed by a technician who will be blinded to the treatment period. Disposal of medical wastes will follow the World Health Organization guidelines, and disposal with appropriate karakia (Māori prayer) will be offered to participant if needed.
4.4 SDB Questionnaire

SDB associated symptoms will be assessed using the Pediatric Sleep Questionnaire and the Sleep Related Breathing Disorder (SRBD) subscale of the Paediatric Sleep Questionnaire (PSQ) \(^{50}\). This 22-question tool will be filled in by parents and includes questions about history of breathing difficulties during sleep, snoring quality and frequency, daytime signs of sleepiness, Inattention and hyperactivity, in addition to a few other questions about morning headache, obesity, enuresis, and delayed growth. The optimal PSQ scale cut-off to indicate presence of SDB would be 0.33 (i.e. \(\geq 33\%\) of the 22 question-items answered positively) \(^{50}\).

PSQ questionnaire will be administered four times during the study Figure (5).

4.5 Quality of life

The OSA-18 instrument is a quality-of-life questionnaire focusing on paediatric sleep disordered breathing. It has been used as a screening tool for paediatric OSA \(^{75}\). This questionnaire consists of 18 questions grouped into five subscales: sleep disturbance, physical symptoms, emotional distress, daytime function, and caregiver concerns. The 18 survey items are scored using a 7-point scale, where the parent/caregiver is asked to report how often during the previous 2-3 weeks their child has had specific symptoms using the following response scale: (1) none of the time, (2) hardly any of the time, (3) a little of the time, (4) some of the time, (5) a good bit of the time, (6) most of the time and (7) all of the time. The total symptom score (TSS) may vary from 18 to 126 points. A TSS at or above 60 is considered abnormal and is associated with SDB. Scores of 60–80 suggest a moderate impact on the disease-specific quality of life and a score above 80 suggests a large impact \(^{75}\).
OSA-18 questionnaire will be administered four times and parents/caregivers will rate the
total number of symptoms before and at the end of each treatment period Figure (5).

4.6 Neurobehavioural assessment

Behaviour will be assessed using the Behaviour Assessment System for Children: second
edition (BASC-2). The BASC-2 tool has been widely used in studying behavioural differences
in paediatric SDB patients. Parent Rating Scales (PRS) are used to measure both adaptive and maladaptive behaviours in
the community and home setting. Parents or caregivers can complete forms at three age levels—
preschool (ages 2 to 5), child (ages 6 to 11), and adolescent (ages 12 to 21). The PRS contains
134-160 items and uses a four-choice response format. Clinical and adaptive scales include the
following domains: activities of daily living, adaptability, aggression, anxiety, attention
problems, atypicality, conduct problems, depression, functional communication, hyperactivity, leadership, social skills, somatization, and withdrawal.

It takes a parent approximately 10-20 minutes to complete this form and requires approximately
a fourth-grade reading level for completion. Questionnaire for ages 6 to 11 will contains 160
items; but the brief questionnaire of this scale consists of 30 items and will be used in our study.
This questionnaire will be administered before and at the end of each treatment period Figure
(5).

4.7 Parent-report of nocturnal enuresis

As about 24% of children with sleep apnea have nocturnal enuresis, urine incontinence will
be assessed during the study by parents/caregivers using diaries in both treatment periods to
report frequency of enuresis.
4.8 Sleep study scoring

A certified sleep technologist will manually score all PSG data to determine the AHI according to the AASM criteria \(^{24}\). PSG scoring will be performed using a special software RemLogic-E version 3.4 (Embla system, Natus Europe, Planegg, Germany). The scorer will be blinded to the patients’ information and to any indication of the treatment period and appliance used, moreover the technologist will have no contact with the participants through the study progress. To test reliability of scoring PSG data, ten PSG recordings will be chosen randomly and re-scored by the same sleep technician to detect intra-rater reliability.

4.9 Statistics

Data will be analysed by SPSS (SPSS, IBM Corp. Version 22.0. Armonk, NY, USA) to perform descriptive statistics, and a mixed model analysis, and Bonferroni corrected post-hoc tests as appropriate. The significance level will be set at \(P = 0.05\).

5 Anticipated results

Early treatment of SDB in children is vital to prevent significant health issues that may develop later. Therefore, SDB may have a significant impact on the wellbeing of many children. With a significant number of cases having persistent OSA after adenotonsillectomy or failure to tolerate CPAP treatment, it is worth exploring alternative options to the current advocated treatment modalities. The MAS intervention may be a valuable and effective alternative for patients who have known craniofacial risk factors of SDB, are on long waiting lists for adenotonsillectomy, are not suitable candidates for adenotonsillectomy, or are not able to tolerate or failed either first-line treatments, such as adenotonsillectomy or CPAP \(^{47}\).
MAS may be particularly suitable for children with SDB, because it is relatively well tolerated and can be easily titrated to obtain an incremental advancement of the lower jaw. MAS can also expand the upper arch, is suitable for both mixed and permanent dentitions, and has a low failure rate. The therapeutic rationale is that the majority of orthodontic anomalies (except class III-protruded mandible), benefit from mandibular advancement capable of enlarging the retrolingual space and at the same time promotes lingual advancement.

Although there is increasing evidence regarding the efficacy of MAS in adults with SDB, there is a paucity of information about their efficacy in children. The few studies carried out to date suffer from methodological flaws including: heterogeneous samples; lack of randomization; limited power to detect a clinically relevant effect; and lack of an adequate control conditions such as the use of a placebo-like appliance. A Cochrane review has concluded that there is not enough evidence to support the efficacy of oral appliances and functional orthopedic appliances for the treatment of OSA in children. This conclusion was also reached by two recent systematic reviews and a meta-analysis which confirmed that the current evidence is limited, but suggests possible short-term effectiveness for treating paediatric OSA. Therefore it is currently difficult to draw a conclusion regarding the possible efficacy of mandibular advancement appliances in children affected with SDB, and there is a strong need to carry out well-designed RCTs.

Cross over RCT design has been widely used in studying efficacy of oral appliances with obstructive sleep apnea patients. Potential advantages of the crossover design that will be used in current study are its robustness and simplicity of application. Despite these advantages, the current study protocol will have some limitations as it depends on short-term evaluation.
weeks for each treatment period), and the study will rely on subjective assessment of several secondary outcomes by using questionnaires in evaluating these measures by parents/caregivers. In addition to the possibility of having limited power regarding the secondary outcomes because the sample size estimation was assessed only relying on the main outcome (AHI). However the study will serve to provide descriptors of these, useful for planning further research in the field.

Randomised clinical trials represent the gold standard for the evaluation of therapeutic effectiveness \(^2\) therefore, unlike the previous studies, it is expected the current study protocol will provide new robust and reliable information about the possible efficacy of MAS for the management of SDB in children. The crossover design will allow each participant to act as his/her own control, thus increasing the power of the study. This study will also systematically address efficacy of MAS on other important health outcomes related to SDB, such as quality of life, neurobehavioural functioning and growth hormone changes; outcomes that have not been widely addressed in previous intervention studies investigating pediatric snoring or OSA \(^4\).

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6 References


CHAPTER THREE

EFFICACY OF A MANDIBULAR ADVANCEMENT APPLIANCE ON SLEEP DISORDERED BREATHING IN CHILDREN: A CROSSOVER RANDOMISED CONTROLLED TRIAL
3. Efficacy of a mandibular advancement appliance on sleep disordered breathing in children: a crossover randomised controlled trial

Abstract

Study objective: The objective of this study was to test the efficacy of a mandibular advancement appliance (MAS) for the management of Sleep-Disordered Breathing (SDB) and associated symptoms in children.

Methods: The study was carried out as a single-blind crossover randomised controlled trial (RCT) with administration of both an Active and a Sham MAS. Eighteen children were recruited in the trial and randomly assigned to a treatment sequence, starting with either the Active or the Sham MAS. Participants wore the appliances for three weeks, separated by a two-week washout period. For each participant, home-based abbreviated polysomnographic data (cardio-respiratory Level 3) were collected four times before and at the last night of each treatment period. The apnoea hypopnea index (AHI) and snoring frequency (snoring time and number of snoring episodes) were assessed as the main outcome variables. Secondary outcomes included serum levels of Insulin-like Growth Factor 1 (IGF-1), obstructive sleep-related breathing symptoms, as assessed by the Paediatric Sleep Questionnaire (PSQ), quality of life, as assessed by the OSA-18 questionnaire, and childhood behaviour, as assessed by the Behavioural Assessment System for Children (BASC-2) Behavioural and Emotional Screening System (BESS).

Results: Compared to a Sham MAS, wearing an Active MAS resulted in a significant reduction in AHI of 40% (p=0.002). The separate assessment of AHI in supine and non-supine sleeping positions revealed that only the former was significantly influenced by treatment, with a reduction of 4.1 events per hour (95% CI=1.8-6.4; p<0.001). Snoring
time per night was 46.3 minutes shorter with the Twin-Block than with the Sham appliance (95% CI=14.5-78.1; p=0.004).

Compared to a Sham MAS, the Active MAS also reduced SDB symptoms, as represented by PSQ, OSA-18, and BASC-2 scores (P≤0.028). IGF-1 levels, however, did not differ between the two treatment periods (P=0.172).

**Conclusion:** Within the limitations of this study, it can be concluded that wearing a mandibular advancement splint over a short period can be beneficial for children affected by SDB.
1 Introduction

Sleep disordered breathing (SDB) encompasses a continuous spectrum of disorders, ranging from habitual snoring to obstructive sleep apnoea (OSA), which are depending on the degree of upper airway obstruction. The health impact of SDB has become increasingly recognised in children\(^1,2,3\). The prevalence of OSA in children ranges from 1 to 4\(^%\)\(^2,4,5\), while most authors report a 10\(^%\) prevalence of habitual snoring in children\(^6\).

SDB has been associated with growth disorders, daytime sleepiness\(^7\), educational and behavioural problems\(^8\), and nocturnal enuresis\(^9\). In the most severe cases, OSA may have life-threatening consequences, such as cardiorespiratory failure\(^1,7\).

Oral appliances have also been widely used for the treatment of OSA in selected patients\(^1,10,11\). These appliances increase posterior oropharyngeal airway and reduce upper airway collapsibility by holding the mandible in a protruded position during sleep. Furthermore, the appliance may trigger stretch receptors, which in turn activate the airway supporting muscles\(^1\) increasing airway patency.

Previous studies have shown that oral appliances are better tolerated than continuous positive air pressure (CPAP), which is currently considered the first-line treatment option for adult OSA, due to improved comfort, quietness, and portability\(^1,11\). Mandibular advancement splints (MAS) are the most widely used oral appliance for treating SDB in adults, but their use in children is less common, and there is little information about their efficacy\(^11-15\). To date, there are only a few studies testing the efficacy of MAS in children, which suffer from methodological flaws, including: heterogeneous samples, lack of randomisation, limited power to detect a clinically relevant effect, and lack of adequate control conditions, such as the use of a placebo-like or sham appliance. One Cochrane review\(^14\) concluded that there is not enough evidence to support the efficacy of oral
appliances and functional orthopaedic appliances for the treatment of OSA in children. This conclusion was also reached by two recent systematic reviews and a meta-analysis, which confirmed that the current evidence is limited, but suggests possible effectiveness of MAS for treating paediatric OSA\textsuperscript{12, 13}. Therefore, it is currently difficult to draw a conclusion regarding the efficacy of mandibular advancement appliances in children affected with SDB\textsuperscript{10, 16-18}, and there is a strong need to carry out well-designed RCTs.

2 Objectives

The aims of this study were: (1) to test the short-term efficacy of MAS in the treatment of children with SDB, and (2) to assess the effect of MAS treatment on quality of life, behaviour, and growth hormone levels.

3 Methods

3.1 Study design

This study was carried out as a single-blind crossover randomised control trial. Each participant wore two appliances, consisting of an Active and a Sham MAS. Each appliance was worn for a three-week treatment period. The first and second treatment periods were separated by a two-week washout period Figure (1).
Figure 1 Study design

The study was designed as a crossover randomised control trial, with participants serving as their own controls. Participants were randomly assigned to one of two sequences. Both sequences included two three-week treatment periods, where the participant had to wear either an active or a sham mandibular advancement splint. The order of splint delivery differed between sequences (active splint followed by sham splint, and vice-versa). The first and second treatment periods were separated by a two-week washout period.

3.2 Participants and setting

This study took place between May 2014 and December 2015, and was conducted at the Discipline of Orthodontics, School of Dentistry, University of Otago, Dunedin, New Zealand. Ethical approval was granted by the University of Otago Human Ethics Committee [H14/054], and Health Research South Ethics Committee - Southern District Health Board [01050]. The research protocol was submitted to the Ngāi Tahu (Māori) Research Consultation Committee, and was considered of importance to Māori health. The trial was registered in the Australian New Zealand Clinical Trials Registry (ACTRN12614001013651). The full protocol has been published\(^\text{19}\).
3.2.1 Sample size estimation

A reduction of 50% in AHI is generally considered clinically relevant in previous study which used oral appliances in paediatric OSA. Sample size was determined using previous estimates of AHI variability in children by setting α error to 0.05 and β error to 0.20 using a repeated-measurement design. We estimated that at least 13 participants would be needed. We aimed to recruit additional children to account for any possible dropouts.

3.2.2 Recruitment

Advertisements were placed in local newspapers and on community noticeboards to invite children who snore regularly and loudly, were 8-12 years old, and lived in Dunedin, New Zealand to participate in the study.

Thirty-one parents contacted the research team with expressions of interest, and were sent information sheets by mail. Twenty-two respondents presented to the Dental School for a clinical screening, and their parents were asked to complete the Paediatric Sleep Questionnaire (PSQ). Individual height and weight measurements were taken at the first appointment to calculate the body mass index (BMI), and an oral examination was performed. Tonsil size and oropharyngeal patency were visually inspected and scored according to Mallampati. Dental impressions were taken using alginate impression material (Orthotrace, Cavex Holland BV, Haarlem, The Netherlands), and poured with stone (Ortho Stone & Ortho Plaster, Nobilium Company, New York, USA) to obtain study and work models. Additional records that were collected included intra-oral and extra-oral photographs and lateral cephalograms in the maximum intercuspal position (Carnex Tome Ceph, SOREDEX, Tuusula, Finland). The cephalometric landmarks and measurements assessed are illustrated in Figure (2).
Figure 2 Cephalometric landmarks and measurements used to describe the dentofacial features of participants enrolled in the trial.

1- **SNA (deg)** the angle formed by the planes sella-nasion and nasion-point A
2- **SNB (deg)** the angle formed by the planes sella-nasion and nasion-point B
3- **ANB (deg)** the angle formed by the planes nasion-point A and nasion-point B
4- **Wits appraisal** (mm) distance between the projection of points A and B on the occlusal plane
5- **SN-MP (deg)** the angle between the mandibular plane and sella-nasion
6- **MMPA (deg)** the angle formed between the palatal (ANS-PNS) and mandibular planes
7- **Lower face height (LFH)** (ANS-Me) (mm) measured by the distance from ANS to menton
8- **Total face height (TFH)** (N-Me) (mm) measured by the distance from N to menton
9- **UIA** the angle formed by the long axis of the upper incisor and the maxillary plane
10- **LIA** the angle formed by the long axis of the lower incisor and the mandibular plane
11- **Li-APog** (mm) distance between the tip of the lower incisor (Li) and (A-Pog)
12- **Interincisal angle** (deg) the angle formed by the long axis of the upper and lower incisor
13- **Upper lip relation to Ricketts E line** (mm) measured by the distance between labrale superius (Ls) to Ricketts E line
14- **Lower lip relation to E line** (mm) measured by the distance between labrale inferius (lower lip) to Ricketts E line
Eligible patients had to meet the following inclusion criteria: an age range from 8 to 12 years, and a parental report of heavy snoring for three or more nights per week.

Exclusion criteria were: previous orthodontic treatment, craniofacial and genetic syndromes (e.g. cleft lip and/or palate), neuromuscular disorders, and Class III incisor and/or skeletal relationship, as confirmed by lateral cephalometric radiograph (ANB angle ≤ 0 degrees).\(^{21}\)

Eighteen participants met these criteria, and were enrolled in the study after signing a written informed consent.

### 3.3 Oral appliances

The performance of different MAS designs in terms of retention and comfort was tested in a pilot study (see Chapter 2 for details). Since Clark’s Twin-Block\(^{22}\) was ranked as the most retentive and best tolerated appliance, it was chosen as the active intervention for this RCT. Treatment was provided by a member of the research team (GI).

#### 3.3.1 Twin-Block design

This consisted of two removable upper and lower acrylic plates, each with matching surfaces, which encourage the lower jaw to posture forward as the upper and lower teeth come together Figure (3A).\(^{23}\) Bilateral hooks were added to the appliance in order to insert vertical elastics. The purpose of these elastics was to hold the mouth closed during sleep, and to keep the mandible in a forward position.\(^{24}\) A construction bite was taken of the appliance, using a commercial device\(^{25}\) (George Gauge\(^\text{TM}\), Scheu Dental Technology, Brussels, Belgium). For all participants, the bite registration was taken by advancing the mandible to 75% of the maximum jaw protrusion, with minimum bite opening\(^{26-28}\).
3.3.2 Sham MAS design

This consisted of two upper and lower acrylic plates, resembling the design of the active MAS, but without any component to protrude the mandible Figure (3B).

Figure 3 Appliances used in the study: the Twin-Block appliance (A) consisted of removable upper and lower acrylic plates, which hold the mandible in the forward position with interlocking blocks. The bite registration was taken by advancing the mandible to 75% of the maximum jaw protrusion, with minimum bite opening. To keep the mandible in this position during sleep, bilateral hooks were added to the appliance in order to insert vertical elastics. The Sham appliance (B) consisted of a removable upper and lower acrylic plates without any component to protrude the mandible forward.
3.4 Outcome measurements and procedure

Primary Outcomes

3.4.1 Apnoea-hypopnoea index and snoring frequency

Level 3 home-based abbreviated polysomnography (cardio-respiratory) \textsuperscript{29} data were collected using two portable sleep monitoring units (Embletta MRP PG-XS-ENU, Natus Neurology Incorporated, Ontario, Canada). The monitoring unit allows the recording of the following data: finger pulse oximetry, nasal flow (nasal cannula connected to a pressure transducer in the recording unit), nasal and mouth thermistry, thoracic and abdominal respiratory effort (using two piezoelectric belts that were placed around the rib cage and abdomen to monitor respiratory movement), electromyography (EMG), gravity, activity, and sound amplitude recorded by a microphone attached to the nasal cannula extension. For the purpose of the present study, the following variables were assessed: pulse oximetry, nasal and oral pressure/airflow, respiratory effort, and snoring sounds. This equipment has previously been validated for the diagnosis of SDB\textsuperscript{30-33}. EMG activity from the masseter muscles was also collected however EMG data are not presented in this report. The superficial head of the masseter muscle (right side) was located by palpation after asking the child to clench his/her teeth. The bipolar EMG electrodes were placed on the masseter muscle position spaced approximately 6 cm apart, and a monopolar ground electrode was placed on the mastoid on the same side,

The portable unit and the recording time (on/off times) were set by software (RemLogic-E version 3.4, Embla system, Natus Europe, Planegg, Germany). PSG signals were acquired at 24-bit resolution and sampled up to 8000 Hz (snoring sounds). Nasal pressure was sampled at 250 Hz, whereas the effort signals recorded by inductance bands were sampled at 100Hz.
For each participant, home-based PSG data were collected four times before and after each treatment period with the Twin-Block or the Sham. The sleep studies were carried out with the support of a research assistant, who was experienced in sleep research.

The AHI scoring also included sleep position, because sleep related obstructive respiratory events in children are more common in the supine sleep position\(^\text{34}\). The AHI was calculated according to the American Academy of Sleep Medicine (AASM) criteria for scoring paediatric respiratory sleep studies\(^\text{35}\).

Snoring was assessed by audio recordings, which is one of the recommended methods to aid visualising snoring oscillations\(^\text{35}\). The Embletta MPR microphone used to record snoring is an analogue omnidirectional condenser microphone, which was attached to the nasal cannula. For optimal visualisation of snoring, a high-pass filter was used to remove very low frequencies (20Hz), and a low-pass filter to remove high frequencies (3 kHz). This allowed researchers to acquire relevant information on the sound of snoring\(^\text{36}\).

Subjective reports of snoring frequency and wearing of appliances (i.e. treatment adherence) were recorded in diaries, to be filled in by parents every night throughout each treatment period. Snoring was scored as a polychotomous variable (yes, no, don’t know), while wearing of appliances was scored as a dichotomous variable (full-night, less than full-night).

### 3.4.2 Sleep study scoring

Recorded data from the Level 3 Sleep Studies was analysed automatically using custom RemLogic-E software (version 3.4, Embla system, Natus Europe, Planegg, Germany). Respiratory events and snoring periods were then manually edited over generally 2 minute epochs by a registered respiratory/sleep physiologist. The sleep physiologist was blind to patient information, including appliance worn and treatment sequence. An
obstructive apnoea was defined as a decrease ≥ 90% of the pre event baseline measured by thermistor or a valid alternative sensor (nasal pressure sensor) for at least 2 breaths and associated with continued respiratory effort. An hypopnoea was defined as a decrease ≥ 30% from pre event baseline measured by nasal pressure sensor, lasting at least 2 breaths with a corresponding decrease in oxygen saturation ≥ 3% or arousal indicated by surrogate measures including movement measured by actigraphy, changes in snoring sounds, >10% increase in heart rate or abrupt changes in thoracoabdominal effort. A central apnoea was defined as a decrease ≥ 90% of the pre event baseline measured by thermistor or a valid alternative sensor, lasting 20 seconds or at least the duration of 2 breaths and associated with a ≥ 3% oxygen desaturation or arousal indicated by surrogate measures as above, or lasts at least the duration of 2 breaths and is associated with a decrease in heart rate to <50 BPM for 5 seconds. The apnoeas are associated with absence of inspiratory effort. A mixed apnoea was defined if it met the 2 breath apnoea criteria and was associated with absence of effort during one portion of the event and the presence of inspiratory effort in another portion. Snoring was scored manually by listening to the recordings in synchrony with the respiratory variables. Snoring events were tagged on the recorded audio graph. The occurrence of snoring was assessed as total snoring time per night and the number of snoring episodes over the entire duration of the recorded sleep period.

To test intra-examiner reliability of AHI scoring, ten PSG recordings were chosen randomly, and AHI was re-scored by the same sleep physiologist one month after the initial scoring period.

**Secondary outcomes**
3.4.3 Growth hormone levels

Blood samples were taken from all participants by a certified phlebotomist in a specialised laboratory (Southern Community Laboratories, Dunedin, New Zealand). Growth hormone levels were indirectly assessed by determining the levels of insulin-like growth factor-1 (IGF-1)\textsuperscript{39}. 

Two samples were collected from each participant in a non-fasting state at the end of each treatment period in the morning to early afternoon. IGF-1 concentrations were assayed using a human IGF-1 Quantikine ELISA Kit (PDG100, R&D Systems, Minneapolis, USA). The human IGF-1 immunoassay employs the quantitative sandwich enzyme technique\textsuperscript{40}. Samples were stored in a freezer at -80°C until batch assayed by a technician who will be blinded to the treatment period. Disposal of medical wastes followed the World Health Organisation guidelines\textsuperscript{41, 42}, and disposal with appropriate Karakia (Māori prayers) were offered to participants on request.

3.4.4 SDB questionnaire

SDB associated symptoms were assessed using the sleep related breathing disorder Paediatric Sleep Questionnaire (PSQ)\textsuperscript{43}. The PSQ cut-off to indicate the presence of SDB is 0.33 (\textit{i.e.} positive answers on \geq 33\% of the 22 question items)\textsuperscript{43}.

The questionnaire was completed by parents/caregivers. PSQ and ESS questionnaires were administered four times during the study, before and after each treatment period. Further information about this questionnaire is available in Chapter 2, and a copy of the questionnaire can be found in the Appendix.
3.4.5 Quality of life

The OSA-18 instrument is a quality-of-life questionnaire with a focus on paediatric sleep disordered breathing. It has been used as a screening tool for paediatric OSA. This questionnaire consists of 18 questions about sleep and respiratory disturbance, as well as other symptoms caused by OSA. The total symptom score (TSS) resulting from this questionnaire may vary from 18 to 126 points. A TSS at or above 60 is considered abnormal, and is associated with SDB. Scores of 60–80 suggest a moderate impact on the disease-specific quality of life, and a score above 80 suggests a large impact.

The OSA-18 questionnaire was administered four times, and parents/caregivers rated the frequency of symptoms before and at the end of each treatment period.

3.4.6 Neurobehavioural assessment

The Behavioural and Emotional Screening System (BESS) is a recently developed set of measures consisting of brief (30 items) derived from the Behaviour Assessment System for Children, Second Edition (BASC-2). This BASC-2 tool has been widely used in studying behavioural differences in paediatric SDB patients. The shorter BESS questionnaire is designed to quickly screen children and adolescents from preschool to high school for current or future emotional or behavioural problems. Parent rating scales from questionnaires validated for use in 6-11 year old children were used to measure both adaptive and maladaptive behaviours in the community and home setting. The BASC-2 BESS was administered before and at the end of each treatment period. A T Score was calculated for BASC-BESS. The T score is a score derived from the total raw score of the questionnaire (30 questions) to adjust for the gender (male, female) and age group differences (preschool 2-5 years, child 6-11 years, adolescent 12-21 years).
3.4.7 Parent report of nocturnal enuresis

Since around 24\% of children with sleep apnoea report nocturnal enuresis\textsuperscript{54}, the frequency of bed-wetting was recorded by parents/caregivers using written diaries (yes/no question), and completed throughout the study period.

3.5 Randomisation

Participants enrolled in the trial were randomly assigned to one of two different sequences. During sequence #1, the Twin-Block MAS treatment was delivered first, and was followed by the Sham MAS. In sequence #2, the Sham MAS was delivered first, and was followed by treatment with the Twin-Block MAS.

Randomisation was performed using computer-generated n-of-4 blocks, which were balanced for treatment sequence, so that an equal number of participants were allocated to the two different sequences. Allocation was concealed using opaque envelopes, which were only disclosed immediately after enrolment by a member of the research team (MF). Participant flow is illustrated in Figure (4).

Participants were not made aware of whether the appliance they received was the active (\textit{i.e.} Twin-Block) or Sham appliance.

3.6 Statistics

Data were analysed using Stata Statistical Software (\textit{Stata 14}, StataCorp LP, Texas, USA). PSG and questionnaire data were analysed through a linear mixed-effect model, with baseline data entered as a covariate. The fixed effects entered in the model were ‘treatment’, ‘sequence’, and ‘period’. A term to test for a possible carry-over effect was also entered. The term ‘participant’ was entered as a random factor. The model residuals were checked for normality and homoscedasticity, and where necessary, data were log-
transformed. The results were presented as mean ± standard deviation of the mean, unless otherwise stated in the tables. IGF-1 and diary data were analysed using a paired t-test. Intraclass correlation coefficients (ICC) were calculated to estimate intra-examiner reliability of AHI. The significance level was set at P = 0.05 (two-tailed).

4 Results

Three participants dropped out of the study, all from sequence 1. One of these withdrew during the early stages of the first treatment period (Twin-Block). This participant was a 10.2 years old girl, with a skeletal Class II intermaxillary relationship, an overjet=8mm, and a BMI=16.0 kg/m² (BMI%=5-85). The reason offered for this withdrawal was “living in a remote suburb, and difficulty in regularly coming to the clinic”. The second participant was a 10.0 years old boy, with a skeletal Class I intermaxillary relationship, an overjet=6mm, and BMI=28.1 kg/m² (BMI% ≥ 95th). This boy was identified as a very severe case of OSA (AHI > 80 event/h), and therefore immediately referred to the paediatric clinic in Dunedin Hospital for sleep specialist support. A third participant was a 10.1 years old boy, with skeletal Class I intermaxillary relationship, an overjet=3mm, and a BMI% ≥ 95th). This participant withdrew from the study during the second treatment period (Sham MAS), because of a lack of cooperation and subsequently failure to show for appointments. Data collected from this patient, however, could be used for the analyses.

Demographic data of the 16 participants enrolled in the study are listed in Table (1). The frequency of snoring reported by the parents was 6.1 ± 1.4 nights per week.

The sample consisted of seven normal weight (BMI < 85th percentile), four overweight (85th < BMI < 95th percentile), and five obese children (BMI ≥ 95th percentile). Eight participants were New Zealand European, three were Māori, three Asian, one Pacific,
and one of Middle Eastern ethnicity. Thirteen participants (81.2%) had an overjet $\geq$ 4 mm. The most common medical condition reported by parents was eczema (n=6 participants), followed by asthma (n=4), and hay fever (n=3). Most patients (n=9) did not report any regular use of medications throughout the study period, the time of administering the questionnaires, when asking parents about any medication that their child use. Four children used antihistamine medication as reported by parents (25%).
Figure 4 Participants’ flow in the study
Oropharyngeal patency varied across participants, and was classified as Class II in one participant, Class III in six participants, and Class IV in nine participants\(^\text{20}\) (for details about the classification criteria see Chapter 1). Enlarged tonsils \((\geq \text{Class II}^\text{51})\) were observed in twelve participants and normal in one participant. Three participants had tonsils removed.

The cephalometric data of the sample are presented in Table (2). The cephalometric features indicated that twelve participants had skeletal Class I jaw relationships (ANB angle=2.9±2.5 degrees)\(^\text{21}\), and four participants had Class II, as revealed by an ANB angle \(\geq 5\) degrees\(^\text{21}\).

A total of 16 participants (13 males, 3 females; average age 9.8±1.4 years) were finally available for the analysis Figure (4).
<table>
<thead>
<tr>
<th>Measurement</th>
<th>Mean</th>
<th>SD</th>
<th>Min-Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SNA (deg)</td>
<td>80.2</td>
<td>3.5</td>
<td>72.0-86.0</td>
</tr>
<tr>
<td>2 SNB (deg)</td>
<td>75.9</td>
<td>3.5</td>
<td>70.0-82.0</td>
</tr>
<tr>
<td>3 ANB (deg)</td>
<td>4.2</td>
<td>1.8</td>
<td>0.5-7.0</td>
</tr>
<tr>
<td>4 Wits (mm)</td>
<td>-0.7</td>
<td>4.7</td>
<td>-11.0-5.5</td>
</tr>
<tr>
<td>5 SN-MP(deg)</td>
<td>35.0</td>
<td>6.4</td>
<td>26.0-46.5</td>
</tr>
<tr>
<td>6 MMPA(deg)</td>
<td>27.5</td>
<td>5.6</td>
<td>19.0-39.0</td>
</tr>
<tr>
<td>7 LAFH (%)</td>
<td>55.2</td>
<td>2.1</td>
<td>52.0-59.0</td>
</tr>
<tr>
<td>8 UIA(mm)</td>
<td>111.9</td>
<td>4.8</td>
<td>99.0-122.0</td>
</tr>
<tr>
<td>9 LIA(mm)</td>
<td>92.1</td>
<td>8.7</td>
<td>80.0-108.0</td>
</tr>
<tr>
<td>10 Li-APog(mm)</td>
<td>2.4</td>
<td>2.4</td>
<td>-2.0-8.0</td>
</tr>
<tr>
<td>11 Interincisal angle(deg)</td>
<td>128.4</td>
<td>7.9</td>
<td>116.0-141.0</td>
</tr>
<tr>
<td>12 Upper lip/E-Line(mm)</td>
<td>-0.1</td>
<td>2.8</td>
<td>-6.0-5.0</td>
</tr>
<tr>
<td>13 Lower lip/E-Line(mm)</td>
<td>-0.1</td>
<td>3.7</td>
<td>-7.0-5.0</td>
</tr>
</tbody>
</table>

4.1 PSG results

The intraclass correlation coefficients for duplicate measurements of overall, supine and non-supine AHI were 0.97 (95% CI=0.88-0.99; p<0.001), 0.99 (95% CI=0.95-0.99; p<0.001), and 0.93 (95% CI=0.76-0.98; p<0.001), respectively.

PSG results are summarised in Table (3) and illustrated in Figures (5-9).

![Box plot showing overall AHI score before and after the Sham and Active appliances (blue boxes). Red boxes show the changes of AHI after each treatment intervention. Comparison between the two treatment modalities showed a significant treatment effect (effect ratio = 0.6; 95% CI=0.5-0.8; p=0.002). Treatment effect represents the ratio of geometric means.](image)

Compared to a Sham MAS, wearing an Active MAS resulted in 40% reduction in AHI (95% CI=0.5-0.8; p=0.002). The separate assessment of AHI in supine and non-supine.
sleeping positions revealed that only the former was significantly influenced from treatment, with a reduction of 4.1 events per hour (95% CI=1.8-6.4; p<0.001). Snoring time when wearing the Twin-Block was 46.3 minutes shorter than wearing the Sham appliance (95% CI=14.5-78.1; p=0.004).

A significant increase in oxygen saturation (+0.5%; 95% CI= 0.1-1.0; p=0.017) resulted from the Active MAS treatment, when compared to the Sham MAS. The lowest recorded oxygen saturation showed a significant increase with the Active MAS, compared to the Sham MAS (+3.4%; 95% CI= 0.9-5.9; p=0.007). On the other hand, oxygen desaturation variables did not show significant differences between Active and Sham MAS treatment, particularly oxygen desaturation index (ODI) (p>0.05).

There was no evidence of carry-over effect for any of the PSG variables (p>0.05). This indicates that two weeks’ wash-out period was sufficiently long to allow the wash-out of any possible effect from the intervention.
Table 3 PSG results using Twin-Block versus Sham MAS. The results are presented as mean ± standard deviation, unless differently indicated.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Twin-Block baseline</th>
<th>Twin-Block follow-up</th>
<th>Sham MAS baseline</th>
<th>Sham MAS follow-up</th>
<th>Treatment effect (TB Vs. Sham)</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI (event/h)</td>
<td>2.8 (3.0)</td>
<td>1.9 (2.1)</td>
<td>2.4 (3.0)</td>
<td>3.7 (4.7)</td>
<td>0.6(^b)</td>
<td>0.5, 0.8</td>
<td>0.002**</td>
</tr>
<tr>
<td>AHI_supine (event/h)</td>
<td>4.7 (6.7)</td>
<td>2.2 (3.2)</td>
<td>3.8 (7.4)</td>
<td>5.7 (7.3)</td>
<td>-4.1</td>
<td>-6.4, -1.8</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>AHI_non-supine (event/h)</td>
<td>2.2 (2.2)</td>
<td>1.5 (1.7)</td>
<td>1.8 (2.1)</td>
<td>2.3 (2.8)</td>
<td>-0.8(^b)</td>
<td>-2.0, 0.4</td>
<td>0.176</td>
</tr>
<tr>
<td>Average oxygen saturation (%)</td>
<td>96.8 (1.0)</td>
<td>97.2 (0.7)</td>
<td>95.7 (4.6)</td>
<td>96.6 (0.9)</td>
<td>0.5</td>
<td>0.1, 1.0</td>
<td>0.017*</td>
</tr>
<tr>
<td>Lowest oxygen saturation (%)</td>
<td>85.4 (11.3)</td>
<td>90.6 (5.2)</td>
<td>87.9 (10.6)</td>
<td>89.1 (5.3)</td>
<td>3.4</td>
<td>0.9, 5.9</td>
<td>0.007**</td>
</tr>
<tr>
<td>Average oxygen desaturation (%)</td>
<td>3.8 (0.4)</td>
<td>8.7 (20.9)</td>
<td>3.7 (0.6)</td>
<td>3.6 (0.4)</td>
<td>-0.3</td>
<td>-0.8, 0.2</td>
<td>0.287</td>
</tr>
<tr>
<td>Number of desaturation events (event/h)</td>
<td>22.1 (23.0)</td>
<td>15.6 (12.7)</td>
<td>28.3 (32.7)</td>
<td>32.5 (32.9)</td>
<td>0.6(^b)</td>
<td>0.3, 1.2</td>
<td>0.146</td>
</tr>
<tr>
<td>ODI (event/h)</td>
<td>2.3 (2.2)</td>
<td>1.7 (1.4)</td>
<td>2.8 (3.0)</td>
<td>3.4 (3.1)</td>
<td>0.7(^b)</td>
<td>0.5, 1.1</td>
<td>0.105</td>
</tr>
<tr>
<td>Snoring time per night (min)</td>
<td>52.9 (61.8)</td>
<td>39.0 (51.5)</td>
<td>46.0 (61.8)</td>
<td>73.7 (108.4)</td>
<td>-46.3</td>
<td>-78.1, -14.5</td>
<td>0.004**</td>
</tr>
<tr>
<td>Number of snoring episodes per night(^c)</td>
<td>82.0 (190.0)</td>
<td>42.0 (85.0)</td>
<td>61.5 (95.5)</td>
<td>51.0 (111.5)</td>
<td>0.5*</td>
<td>0.2, 1.5</td>
<td>0.250</td>
</tr>
<tr>
<td>Snoring time / total sleeping time (%)</td>
<td>9.9 (11.7)</td>
<td>7.5 (10.1)</td>
<td>8.5 (11.7)</td>
<td>13.5 (20.2)</td>
<td>0.6(^b)</td>
<td>0.3, 1.1</td>
<td>0.080</td>
</tr>
<tr>
<td>Longest Snoring Episodes (min)</td>
<td>8.6 (11.2)</td>
<td>8.4 (10.7)</td>
<td>7.1 (7.0)</td>
<td>11.0 (13.6)</td>
<td>0.8(^b)</td>
<td>0.5, 1.4</td>
<td>0.455</td>
</tr>
<tr>
<td>HR (Bpm)</td>
<td>75.3 (12.6)</td>
<td>74.4 (8.2)</td>
<td>72.4 (8.7)</td>
<td>75.1 (9.5)</td>
<td>1.0*</td>
<td>0.9, 1.0</td>
<td>0.099</td>
</tr>
</tbody>
</table>

Polysomnographic data were analysed through a linear mixed-effect model, and log-transformed. Zero data were corrected by adding one.

**Abbreviations**: Apnoea hypopnoea index (AHI); oxygen desaturation index (ODI); heart rate (HR).

\(^a\) Log-transformed for linear mixed model analysis; treatment effect is the ratio of geometric means

\(^b\) Log-transformed after adding one (due to zero values) for linear mixed model analysis; treatment effect represents the ratio of geometric means

\(^c\) Median (IQR), * significant changes \(P \leq 0.05\), ** significant changes \(P \leq 0.01\)
Figure 6 Box plot showing supine AHI score before and after the Sham and Active appliances (blue boxes). Red boxes show the changes of AHI after each treatment intervention. There was a significant treatment effect of -4.1 events per hour (p<0.001).

Figure 7 Box plot showing non-supine AHI score before and after the Sham and Active appliances (blue boxes). Red boxes show the changes of AHI after each treatment intervention. The treatment effect was not significant (p=0.172).
Figure 8 Box plot showing **snoring time** before and after the Sham and Active appliances (blue boxes). Red boxes show the changes of snoring time after each treatment intervention. There was a significant treatment effect (p=0.004)

Figure 9 Box plot showing **snoring episodes** before and after the Sham and Active appliances (blue boxes). Red boxes show the changes of snoring episodes after each treatment intervention. Treatment effect was not statistically significant (p=0.250)
4.2 Secondary outcomes results

IGF-1 levels after wearing the Active MAS were 221 ± 129.3 ng/mL, and 204 ± 116.9 ng/mL after wearing the Sham MAS. The difference between the Sham and Active intervention was not statistically significant (p=0.172).

The data collected using the diaries, summarised in Table (4), were used to estimate the percentage of snoring nights over each three-week treatment period. The percentage of nights with snoring was lower with the Twin-Block MAS (23%) than with the Sham MAS (43%; p=0.017).

Reports of the appliance wearing time indicated that both appliances were regularly worn for over 90% of the prescribed time. A few problems were reported in the first few days of treatment, so some of the patients experienced initial discomfort when wearing the appliances, such as salivation, feeling pressure, and experiencing dental pain for a short period in the morning after wearing the Active MAS. All of these problems were alleviated in the first week of wearing the appliances. One problem reported by some parents was lack of retention of the appliance, particularly the maxillary plate of the Active MAS, due to using vertical elastics to maintain the mandible in the right forward and vertical position. This problem was solved by adjusting the appliance to increase retention and resistance to the action of vertical elastics.

No episode of nocturnal enuresis was reported throughout the entire study period.
Most of the children in the study (n=14; 88%) had a baseline PSQ score > 0.33, which is considered the critical threshold suggestive of high risk for sleep-disordered breathing. PSQ scores were significantly influenced by the treatment, and decreased with the Active MAS treatment, compared to the Sham MAS (p=0.012). Similarly significant changes were detected in the quality of life questionnaire OSA-18, as shown by the significant improvement in TSS scores with the Active MAS, compared to the Sham MAS (p=0.028). Table (5)
Improvement was observed in behaviour (BASC-2 BESS questionnaire) after wearing the Active MAS, compared to the Sham MAS, as T score changes were significantly different between the two appliances (p<0.01) Table (5).
Table 5 Questionnaire results using Twin-Block versus Sham MAS. The results are presented as mean ± standard deviation, unless differently indicated.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Twin-Block baseline</th>
<th>Twin-Block follow-up</th>
<th>Sham MAS baseline</th>
<th>Sham MAS follow-up</th>
<th>Treatment effect (TB vs Sham)</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQ</td>
<td>0.44 (0.2)</td>
<td>0.32 (0.2)</td>
<td>0.39 (0.1)</td>
<td>0.42 (0.2)</td>
<td>1.08*</td>
<td>1.02, 1.14</td>
<td>0.012*</td>
</tr>
<tr>
<td>OSA_18 (TSS score)</td>
<td>45.6 (14.8)</td>
<td>35.7 (15.2)</td>
<td>40.8 (8.8)</td>
<td>41.8 (14.4)</td>
<td>8.9</td>
<td>1.0, 16.8</td>
<td>0.028*</td>
</tr>
<tr>
<td>BASC-2 BESS (T score)</td>
<td>51.1 (11.3)</td>
<td>48.4 (12.1)</td>
<td>48.8 (14.0)</td>
<td>50.1 (9.7)</td>
<td>5.0</td>
<td>1.3, 8.7</td>
<td>0.008**</td>
</tr>
</tbody>
</table>

Questionnaire data were analysed through a linear mixed-effect model, and log-transformed. Zero data were corrected by adding one.

**Abbreviations:** PSQ = Paediatric Sleep Questionnaire; OSA-18 = Obstructive Sleep Apnoea Quality of Life Questionnaire; TSS = Total Symptom Score; BASC-2 = Behaviour Assessment System for Children, Second Edition; BESS = Behavioural and Emotional Screening System.

* Log-transformed after adding one (due to zero values) for linear mixed model analysis; treatment effect represents the ratios of geometric means after adding one.

* significant changes $P \leq 0.05$, ** significant changes $P \leq 0.01$
5 References


CHAPTER FOUR

DISCUSSION
4 Discussion

1 Discussion of the results

1.1 PSG results

The findings of this randomised controlled trial suggest that the Twin-Block appliance may be an effective short-term treatment for SDB in selected children with a Class II or Class I malocclusion. Compared to the Sham appliance, the use of the Twin-Block resulted in significantly lower AHI scores, an increase in the minimum and average oxygen saturation, and a reduction in snoring time.

The overall AHI represents a combined measure of supine and non-supine AHI, and was used as the primary outcome measure of this RCT. Interestingly, the AHI score at baseline was more severe in the supine position than the overall AHI, thus indicating that participants exhibited more position-related OSA prior to treatment. A relationship between body position and OSA severity in SDB children has been reported in previous studies\(^1\)-\(^3\), and consistently higher AHI values have been reported in the supine position in adults with OSA\(^4\). Supine-related OSA is possibly due to unfavourable airway geometry, reduced lung volume, and an inability of airway dilator muscles to adequately compensate as the airway collapses, particularly during REM sleep\(^5\). It is therefore not surprising that the effect of the Twin-Block was more pronounced when children were sleeping in the supine position, as revealed by changes in supine AHI.

The main criterion for recruiting study participants was heavy snoring, as reported by parents. Nonetheless, the vast majority of the participants included in the final sample were confirmed to have OSA. When considering the results of the two baseline abbreviated PSG studies, the vast majority of participants (i.e. 87%) presenting with
parentally reported habitual snoring scored an AHI \( \geq 1 \), and only two participants scored an AHI < 1. Average OSA severity in the sample was mild (12 cases with an AHI=1-5 event/h). One participant had moderate OSA (AHI=7.7 event/h), and another had severe OSA (AHI=11.7 event/h). Hence, our findings can be generalised not only to children with heavy snoring, but also to children with different degrees of OSA.

AHI values in the current study were assessed using the Level 3 home-based abbreviated polysomnography (cardio-respiratory) and estimates of arousals depended on actigraphy movement artefact and listening to audio recordings. Portable home-based monitors show good diagnostic accuracy compared to Level 1 sleep tests in adults with a high pre-test probability of moderate to severe OSA and no unstable comorbidities. Thus they provide a useful additional diagnostic tool for the management of patients with uncomplicated OSA. In contrast, Level 3 PSG in children has been shown to underestimate AHI compared to Level 1 in-lab full PSG, which remains the gold standard for the evaluation of OSA. This underestimation can be due to missed hypopneas causing arousals without desaturation. The abbreviated PSG, however, represents a more accessible and less expensive alternative to in-lab PSG and recording several channels of data (e.g., oximetry, airflow, respiratory effort), thus allowing the assessment of the AHI. Unlike Level 1 studies, Level 3 sleep studies cannot detect sleep stages, accurately measure sleep duration, or identify arousals. This limitation should be taken into consideration when comparing the results of the current study with previous studies using Level 1 PSG.

PSG results of the current study are in agreement with previous studies in children, which found significant reduction in AHI following mandibular advancement treatments, ranging from 53% to 75\%\textsuperscript{10-12}. The reported decrease in the previous studies is greater
than that seen in the current study (31% reduction in overall AHI). Beyond the methodological flaws in the previous studies, this may be due to fact that previous studies have a longer follow-up (6-12 months) and recruited participants through sleep clinics, who were already confirmed to have moderate to severe OSA on average. In the present research, we recruited habitual snorers, and ended up with a group with mild OSA on average. Indeed, there appears to be a relationship between OSA severity and the magnitude of patients’ PSG response to a specific treatment. This applies both to children\textsuperscript{13} and adults\textsuperscript{14}, with a larger reduction of AHI in patients with more severe OSA.

In the present study, active MAS treatment showed an average decrease in the overall AHI and AHI in the supine position of 31% and 53% respectively. The reduction of supine AHI cannot be compared to previous studies using MAS in children, as they did not assess position-related AHI. This amount of reduction would be considered clinically significant according to one of the common definitions of successful OSA treatment, which is a reduction of $\geq 50\%$ in AHI\textsuperscript{15,16}. According to this definition, seven participants (44\% of the sample) were successfully treated with the Active MAS, showing $\geq 50\%$ reduction in overall AHI, and eight participants (50\% of the sample) showed $\geq 50\%$ reduction in AHI in supine position. A reduction in the AHI to less than one event/hour is another criterion for successful treatment of OSA, and means a complete resolution of OSA symptoms. When adopting this stringent definition, five participants (31\% of the sample) were successfully treated with the Active MAS, showing overall AHI and supine AHI $< 1$ event/h after treatment.

Variations in response to the Twin-Block treatment may be due to the multifactorial nature of SDB, considering the different aetiologies that cause narrowing of the oropharyngeal airway, such as obesity, adenotonsillar hypertrophy, or retrognathia,
which can lead to airway obstruction. Another possible reason for this variation in response is the wide range of SDB severity included in the study, from primary snoring (2 participants) to severe OSA (1 participant). Such variation in response to MAS treatment has also been reported in adults, when the use of MAS resulted in complete resolution of OSA in 35-40% of patients. When adopting more liberal criteria in assessing successful treatment of AHI reduction < 50%, more than 70% of adult patients experience a successful response to MAS treatment. On the other hand, four participants (25% of the sample) in the present study showed an increase in AHI following MAS. The average increase in the AHI of this group of non-responders was 0.6 ± 0.4 events/hour. Such a failure in treatment was reported in a study on MAS in OSA adults, and it was estimated to have occurred in 37.5% of patients.

The positive effect of the Twin-Block versus the Sham Appliance on both overall and supine AHI may be slightly inflated by an unfavourable response to the Sham MAS. Indeed, with the use of the Sham MAS, the AHI showed a tendency to increase after treatment. This may due to the inevitable bite opening of 0.5–1 mm with the Sham MAS (upper and lower Hawley retainers), because of the retention clasps on posterior teeth. Such an increase in the relationship between bite opening and AHI score has been reported in adults. Another possible cause is the acrylic base plates, which cover the palate and the lingual side of the mandibular dental arch, and may occupy some of the tongue space and push the tongue to a slightly backward position. Moreover, several participants were suffering from the flu or common cold during a sleep study at the end of one treatment period, which caused an increase in abbreviated PSG evaluated AHI compared to baseline recordings, and this may have played a role in AHI changes observed during the study. We were able to control this problem at the time of baseline
recording by postponing the PSG study until complete resolution of cold symptoms, but this problem was not well controlled in the PSG studies at the end of the treatment period. This was a possible reason for the recorded variation in response in both treatment periods, Sham and Active MAS. However, uncertainty still remains as to why the AHI increased in four patients in response to the Sham appliance, and this factor needs to be considered in future treatment studies in children.

Slight but significant improvements were observed in the average and lowest levels of oxygen saturation with the Active MAS in comparison to Sham MAS. In contrast, the few available previous studies using MAS in paediatric OSA patients showed insignificant changes in oxygen saturation\textsuperscript{10, 12, 21}. Unlike in adults, oxygen saturation shows variations in paediatric OSA. Changes in oxygen saturation are not well correlated with AHI changes, and children do not show significant changes in oxygen saturation unless they have severe OSA. This may due to the fact that OSA in children results in arousals and sleep fragmentation without significant desaturation. In addition, lots of movement artefact may be recorded because children tend to move a lot during sleep\textsuperscript{22}.

1.2 Snoring

Snoring is the most commonly manifested symptom in children with SDB, and its detection is a key element in diagnosis. This is important, because studies showed that a significant number of habitual snoring cases, more than a third in one study, progress to OSA\textsuperscript{23}, and habitual snoring has a significant negative health impact on children, with neurobehavioural consequences\textsuperscript{23-27}. In the current study, subjective ratings of snoring frequency improvement by parents differed significantly between the Twin-Block and the Sham treatment. Subjective ratings were consistent with the analysis of audio recordings of snoring, which showed a significant reduction in the total time, but not in
the number of snoring episodes, assessed during the Active and Sham MAS treatment. Previous studies on the use of oral appliances in OSA children have not assessed snoring, and therefore our findings cannot be compared to previous ones. Our preliminary findings indicate that the analysis of snoring with audio recordings may represent a promising tool for monitoring SDB. Further research, however, is required to confirm its validity and reliability\textsuperscript{28-30}. During the study, it was found that the microphone plug of one of the recording units was faulty. This resulted in some low quality audio recordings, which made 14 of these (22\% of the recordings) difficult to analyse. Low quality sound records were discarded and treated as missing data.

1.3 Growth hormones

Growth hormones was indirectly evaluated by measuring serum levels of IGF-1 after using the Twin-Block, and compared to levels after using the Sham MAS. No significant differences were detected in IGF-1 levels between the two treatments, although they tended to be higher after use of the Twin-Block. Failure to detect significance may be due to the limited power of this statistical test, to the wide range of IGF-1 norms in a specific age group, and to large differences in norms among different age groups, which vary widely over one year intervals\textsuperscript{31}. Previous studies showed that reduction in AHI is associated with improvement in growth hormone levels after adenotonsillectomy\textsuperscript{32}. The trend toward increased levels of IGF-1 in blood when using the Twin-Block warrants further investigation to confirm its significance. Previous reports on the efficacy of mandibular advancement splints for growth modification treatment showed that jumping the bite resulted in an increase of the mandibular length by enhancing mandibular growth\textsuperscript{33, 34}, due to the direct effect of MAS on temporomandibular joint growth\textsuperscript{35}. It is
Discussion

possible that increased serum levels of growth hormone during MAS treatment can enhance mandibular growth. This hypothesis should be tested in future research.

1.4 Pediatric Sleep Questionnaire

Parentally reported SDB symptoms are commonly used for screening children suspected to have SDB, and the validated 22-item Paediatric Sleep Questionnaire (PSQ) has a sensitivity of 0.85 and a specificity of 0.87\textsuperscript{36}, which can be considered as reasonable. Our PSQ findings showed that SDB symptoms improved with Twin-Block treatment, and this improvement may be the consequence of a reduction in AHI. This observation supports the validity of parents’ observations in detecting changes in SDB symptoms, which were consistent with the objective assessment with PSG in this study. The participants showed a trend towards a “normal range” of PSQ scores (\textit{i.e.} PSQ < 0.33) after Twin-Block treatment. The results of the current study are in agreement with previous findings by Villa et al.\textsuperscript{11}, which showed significant improvement in SDB symptoms after MAS treatment. In Villa’s study, however, SDB symptoms were assessed using the Brouillette questionnaire\textsuperscript{37}, which was filled in by parents before and after treatment with oral appliances\textsuperscript{11}.

1.5 Quality of life OSA-18

OSA-18 has been suggested as a useful tool in predicting OSA severity, but no significant correlation between the severity of paediatric OSA and OSA-18 has been found\textsuperscript{45, 46}. Positive changes have been reported in quality of life in children with OSA after adenotonsillectomy and rapid maxillary expansion\textsuperscript{47, 48}. In the present study, a significant reduction in OSA-18 TSS score was detected with the Twin-Block treatment in comparison to the Sham treatment, but an average TSS score of OSA-18 prior to treatment was within the normal range (TSS < 60), suggesting that the OSA cut-off may
Discussion

not have been appropriate. A recent study (Kobayashi et al., 2014) showed that using a lower TSS cut-off, set at 40, resulted in 100% sensitivity when screening OSA patients. This was just 51.1% at the original cut-off point of 60, when Franco et al. proposed the OSA-18 in 2000\(^9\). This may enhance the clinical significance of the results of the current study, and suggest an association between use of the Twin-Block and clinically significant improvement in SDB-related quality of life in children.

1.6 Behavioural assessment (BASC-2 BESS)

A brief BESS questionnaire level two (ages 6-11), containing 30 items, was used in our study. BESS is designed to quickly screen children’s behavioural and emotional changes. In the current study, the calculated T score showed significant positive changes in participants’ behaviour in the Twin-Block period, compared to the Sham MAS period. Seven participants showed an above normal T score (T > 50), but the average calculated T score was close to normal on the four occasions when the BESS questionnaire was administered (baseline T scores= 51.1 ± 11.4; 48.8 ± 8.7 in Twin-Block and Sham-MAS periods respectively). The positive behavioural changes when using MAS in the current study are in agreement with reported positive behavioural changes after adenotonsillectomy, due to the resolution of obstruction in the upper airway\(^50\).

1.7 Nocturnal Enuresis

Nocturnal enuresis is an important sign of OSA\(^51\), and previous findings suggest that oral appliances, particularly rapid maxillary expansion, can reduce enuresis in paediatric OSA\(^52\). Adenotonsillectomy can also reduce enuresis in children with adenotonsillar hypertrophy\(^53\). Therefore, in the current study, we collected parental reports of bedwetting to explore the possible effect of MAS on enuresis. Enuresis in children with suspected SDB is highly prevalent in those under seven years of age\(^54, 55\). This may
explain why the current study, which recruited snorers in the age range from 8 to 12 years, failed to include patients who experienced bedwetting, especially when considering that the incidence of enuresis in 10-year-old children is estimated at approximately 5%, and this rate decreases every year, until only 1% continue to experience nocturnal enuresis into adulthood\textsuperscript{56}.

2 Problems reported by parents, treatment adherence and attrition rate

Although the Twin-Block appliance was well tolerated by children, some parents (of four children) reported that it was sticking off the maxillary arch. Consequently, this demanded adjustments to increase the appliance retention. Some initial discomfort was also reported, which was gradually alleviated in the next few days. Acceptance of the appliance was evident through parents’ diary reports. Both appliances were regularly worn for over 90% of the prescribed treatment time of three weeks. In addition, the few withdrawals from the study were not for reasons related to the treatment. One participant lived in a remote area, one parent failed to cooperate, and a third participant was diagnosed with a very severe sleep apnoea (AHI > 80 event/h) from the abbreviated-PSG study, and was thus referred urgently to a sleep specialist for full assessment and treatment. The fact that none of the patients abandoned the therapy because of problems tolerating the active treatment indicates that MAS, particularly Twin-Block, may be suitable for treating SDB children. In the current study, joining the upper and the lower pieces of Clark’s Twin-Block together with vertical elastics allowed a degree of lateral and vertical lower jaw movements, and consequently enhanced compliance. Generally, the Twin-Block holds significant features to make it relatively well tolerated and easily titratable to obtain an incremental advancement of the lower jaw\textsuperscript{57}. The Twin-Block can also expand the upper arch\textsuperscript{58}, is suitable for both mixed and permanent dentitions\textsuperscript{58}, and
Discussion

has a low failure rate\textsuperscript{59}. The therapeutic rationale of using a Twin-Block in SDB cases is that the majority of orthodontic anomalies (except Class III-protruded mandible) benefit from mandibular advancement capable of enlarging the retrolingual space, and at the same time, this promotes lingual advancement\textsuperscript{10,11}.

3 Strengths of the Study

This study has several strengths. Firstly it was designed as randomised control trial, which represents the gold standard for the evaluation of therapeutic effectiveness\textsuperscript{60}. Therefore, unlike previous studies, the current study provided new robust and reliable information about the possible efficacy of MAS for the management of SDB in children. Another strength is the crossover design of the current study, which has previously been used to examine the efficacy of oral appliances in adult patients with obstructive sleep apnoea\textsuperscript{61-63}. The study design allowed each participant to act as his/her own control, thus increasing the power of the statistical tests and precision of estimates. This study also systematically addressed the efficacy of MAS on other important health outcomes related to SDB, such as quality of life and neurobehavioural functioning, using validated questionnaires. These outcomes have not been widely addressed in previous intervention studies investigating paediatric snoring or OSA\textsuperscript{64}.

The adequate power for the main outcome variable, the multivariate approach to data analysis, and the low attrition rates represent further strengths of this research.

Although this could not be considered a double-blind RCT, our study participants were not told which appliance was expected to be active. Furthermore, the sleep physiologist who scored the PSG data was blinded to all participants’ information and treatment type. This sleep physiologist was a registered Respiratory and Sleep Physiologist, with
extensive experience in the technology of sleep laboratories in Australia and New Zealand. The statistician analysing the study results was also blinded to the treatment intervention.

The use of validated devices for home based PSG is another strength of the current study. Indeed, the Embletta monitors used in our research have been previously validated for the diagnosis of SDB\textsuperscript{65-68}.

4 Study limitations

This study had some limitations, the main one being the short duration of treatment intervention (\textit{i.e.} 3 weeks for each treatment period). Further research with a longer duration of treatment is required to confirm the medium- to long-term effect of MAS. Although this study had adequate power for statistical testing of AHI, the sample size should still be regarded as small, with limited power in testing some of the secondary outcomes, such as IGF-1. However, this study provided preliminary findings that can be used for planning further research in the field.

This small study sample may not be representative of SDB in the broader population of children. Furthermore, the SDB manifestations of study participants were rather broad, ranging from primary snoring to severe OSA. A larger sample size would also be needed to explore the efficacy of MAS in relation to SDB severity, site of upper airway obstruction, obesity, and other factors that may play a role in response to MAS treatment.

Although the majority of patients presented with Class II incisor relationship the sample included a skeletal Class II and Class I inter-maxillary relationship. In patients with a normal inter-maxillary skeletal relationship (\textit{i.e.} Class I) the use of a Twin-Block for
prolonged periods of time may be contraindicated, as it may result in unfavourable facial growth modification and unwanted dentoalveolar changes.

The Sham appliance still influenced mandibular and tongue posture, and therefore it could not be considered as a non-active placebo control condition. Interestingly, an effect on SDB and related symptoms in association with the use of control or sham appliances has previously been reported in adults \(^{19,69-71}\), but not in children. The construction of an intraoral placebo appliance can be very challenging or even impossible in orthodontic research because when intervention studies involve procedures rather than pills, sham procedures take place to match the experience of the treatment as close as possible \(^72\). In SDB trials, however, it is very important to have a control condition, because even the use of a placebo tablet for the management of SDB may have a significant influence on SDB symptoms \(^73\).

Finally, an additional limitation of this study is the use of subjective assessments for several secondary outcomes, such as parental reports with diaries, which may not be accurate or valid.

5 Future directions

In future research, the effectiveness of MAS should be compared with the primary treatment, ‘adenotonsillectomy’. This may confirm the indication of MAS as an alternative treatment option for paediatric OSA. More research is also needed to investigate possible sources of variations in response to MAS treatment. These sources may include OSA severity, obesity, tonsil size, and the site of upper airway obstruction.

Some parents reported that the main issue with the Twin-Block was their child’s inability to retain the splint on the maxillary arch. Therefore, adding modifications to the Twin-
Block design may be necessary to enhance the retention of this appliance to the teeth and, consequently, to ensure that the lower jaw remains in the forward and vertical position, which is known to be favourable to the expansion of the oropharyngeal airway during sleep.

Increasing evidence has emerged about the efficacy of rapid maxillary expansion (RME) in paediatric OSA. It is worth comparing RME with MAS in a future randomised controlled trial, considering the significant effect of MAS use in OSA children in the current study. Furthermore, combining these two orthodontic modalities (MAS & RME) may have a favourable effect on paediatric OSA, and should be investigated in a study using adequate controls. Combined MAS and RME treatment may be more effective than using just one modality, as the mode of action differs between the MAS treatment and the RME appliances. MAS targets the mandible by forward repositioning along the sagittal and vertical planes, and RME targets the upper jaw by transverse expansion.

In addition to combining orthodontic appliances, other appliances should also be considered and tested. For example, mandibular arch expansion in selected cases may play a role in alleviating paediatric SDB by providing more space for the tongue. Appliances used for the treatment of Class III intermaxillary skeletal cases (maxillary retrusion and/or mandibular protrusion) may expand the upper airway and the space of the tongue. All of these appliances are worth exploring in future studies, and this may enhance the role of orthodontic appliances in the field.

Developing a robust method for snoring diagnosis is important, as our preliminary findings showed that the analysis of audio recordings of snoring may represent a promising method for detecting and monitoring SDB. Snoring is considered the main manifestation of paediatric SDB. Further research is required to develop an objective
analysis method to determine snoring frequency and intensity in children, and relate this to aetiological factors such as upper airway obstruction (severity and site of obstruction). Employing this method in SDB diagnosis and monitoring will be valuable after confirming its validity and reliability.

The findings of this study, which demonstrated a trend of IGF-1 changes after the Twin-Block treatment, are worth further investigation to confirm the possible effect of MAS treatment on the serum levels of growth hormone. If the relationship between MAS use and increased growth hormone serum levels can be proven to be significant, then this will enhance the role of MAS as a tool for mandibular growth modification. These appliances have already been used for decades to encourage mandibular growth in Class II intermaxillary cases, but on the basis of the direct effect of MAS on temporomandibular joint growth. An additional potential outcome of these appliances is worth considering *i.e.* enhancing growth hormone secretion.

6 Conclusion

1 Short term use of the Twin-Block appliance seems to help in the treatment of OSA in children

   The short-term use of the Twin-Block appliance was found to significantly reduce overall AHI and supine AHI in children with SDB. Wearing the Twin-Block appliance also resulted in decreased snoring time and a statistically significant increase in the average and lowest levels of oxygen saturation. Symptoms related to SDB, such as quality of life, behaviour, and paediatric sleep questionnaire scores, showed improvement when the Twin-Block was used.

2- Long term/growth modification of mandibular deficiency in children with OSA should be evaluated

3- Potential complementary effects of the use of Twin-Block appliance with adenotonsillectomy and/or orthopaedic expansion of the maxilla should be evaluated.
2 References


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CHAPTER FIVE

APPENDICES
3 Appendices

1 Study Participants

Study Participants (n=18)
2 Ethical approvals

Professor M Farella
Sir John Walsh Research Institute
Department of Oral Diagnostic and Surgical Sciences
Faculty of Dentistry

19 May 2014

Dear Professor Farella,

I am again writing to you concerning your proposal entitled “Efficacy of a Mandibular Advancement Appliance on Sleep Disordered Breathing in Children”, Ethics Committee reference number H14/054.

Thank you for your detailed comments in relation to the issues raised by the Committee.

The Committee appreciates the further clarification given in respect of whether participants will be treated with high priority, the further consideration given in respect of side-effects and the undertaking of x-rays. The Committee further notes that you have increased the wash-out period to 2 weeks.

On the basis of this response, I am pleased to confirm that the proposal now has full ethical approval to proceed.

Approval is for up to three years from the date of this letter. If this project has not been completed within three years from the date of this letter, re-approval must be requested. If the nature, consent, location, procedures or personnel of your approved application change, please advise me in writing.

Yours sincerely,

Mr Gary Witte
Manager, Academic Committees
Tel: 479 8256
Email: gary.witte@otago.ac.nz

cc. Sir John Walsh Research Institute

Ethical Approval
25/09/2011

Dr. Barbara Galland
Women's & Children's Health, DSM

Dear Barbara

REF: Efficacy of a mandibular advancement appliance on sleep disordered breathing in children

I am writing on behalf of Health Research South to confirm that the project mentioned above has been granted approval to proceed.

According to our records:

This project is due to commence on: 25/09/2014
It is due to be completed by: 31/12/2015

If you have any questions with regards to this process, please contact me quoting the project ID shown above.

Yours sincerely,

Ruth Sharpe
Clinical Research Advisor

CC: Elaine Chisnall, Southern DHB
    Ghasan Idris, UO School of Dentistry

Health Research South
University of Otago, Dunedin School of Medicine and Southern District Health Board
PO Box 50, Dunedin 9054
Ruth Sharpe, Clinical Research Advisor, Pte 03 470 9302 (Hosp 9092); Ruth.Sharpe@otago.ac.nz

Health Research South Approval
Tuesday, 15 April 2014.

Professor Mauro Farella,
Faculty of Dentistry - Department of Oral Science,
DUNEDIN.

Tēnā koe Professor Mauro Farella,

Efficacy of a mandibular advancement appliance on sleep disordered breathing in children

The Ngāi Tahu Research Consultation Committee (The Committee) met on Tuesday, 15 April 2014 to discuss your research proposition.

By way of introduction, this response from The Committee is provided as part of the Memorandum of Understanding between Te Rūnanga o Ngāi Tahu and the University. In the statement of principles of the memorandum it states "Ngāi Tahu acknowledges that the consultation process outline in this policy provides no power of veto by Ngāi Tahu to research undertaken at the University of Otago". As such, this response is not "approval" or "mandate" for the research, rather it is a mandated response from a Ngāi Tahu appointed committee. This process is part of a number of requirements for researchers to undertake and does not cover other issues relating to ethics, including methodology they are separate requirements with other committees, for example the Human Ethics Committee, etc.

Within the context of the Policy for Research Consultation with Māori, the Committee base consultation on that defined by Justice McGregor:

"Consultation does not mean negotiation or agreement. It means: setting out a proposal not fully decided upon; adequately informing a party about relevant information upon which the proposal is based; listening to what the others have to say with an open mind (in that there is room to be persuaded against the proposal); undertaking that task in a genuine and not cosmetic manner. Reaching a decision that may or may not alter the original proposal."

The Committee considers the research to be of importance to Māori health.

As this study involves human participants, the Committee strongly encourage that ethnicity data be collected as part of the research project. That is the questions on self-identified ethnicity and descent, these questions are contained in the latest census.

The Committee suggests dissemination of the findings to relevant Māori health organisations, for example the National Māori Organisation for Dental Health, Oranga Nīhau and to Professor John Broughton, who is involved in Māori Dental Health, University of Otago.

We wish you every success in your research and The Committee also requests a copy of the research findings.

This letter of suggestion, recommendation and advice is current for an 18 month period from Tuesday, 15 April 2014 to 2 October 2015.

The Ngāi Tahu Research Consultation Committee for membership;

Te Rūnanga o Ōhakune Incorporated
Kaiti Harunga Rūnanga ki Ōtepoti
Te Rūnanga o Waitaki

Māori Consultation (page 1)
NGÄI TAHU RESEARCH CONSULTATION COMMITTEE
TE KOMITI RAKAHAU KI KAI TAHU

Nähāhu roa, nā

Mark Brunton
Kaiwhakahaere Rangahau Mäori
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Mäori Consultation (page 2)
Appendices

3 Recruitment notices

Severe snoring in children can be a sign of a sleep or breathing problem, with consequences on general health.

Does your child snore regularly and loudly while sleeping?

If so, he/she is invited to take part in our research study.

This study is going to test the efficacy of an in-mouth plate which may be effective to stop/reduce snoring without any surgery.

We are looking for children who:

- Are 8-12 years of age.
- Snore regularly and loudly while they sleep.
- Live in Dunedin.
- Are willing to wear a simple orthodontic removable appliance (this means that the child will be able to take the appliance out of the mouth by him/herself).

If you and your child are interested, or you would like further information, please contact Ghassan Idris on:

Tel: (03) 479 7084 or Email : kids.snoring@otago.ac.nz

Discipline of Orthodontics / Department of Oral Sciences, School of Dentistry

[This project has been reviewed and approved by the University of Otago Human Ethics Committee, (Health). Reference: H14054]
Notice of recruitment in Otago Daily Times
Snoring children needed to help with study

SAMANTHA MCPHERSON
@thestar.co.nz

Snoring is often a sign of sleep-disordered breathing — which could be causing serious harm to your child’s wellbeing.

A research project, being carried out by University of Otago PhD candidate Ghassan Idris, is looking into alternative treatments to the removal of tonsils for children suffering from sleep-disordered breathing.

An alternative treatment is wearing a mouth appliance while sleeping, which has proved effective in adults. The study aims to look at its efficacy in children.

Mr Idris said 16 participants aged between 8 to 12 years were needed. So far, there were seven.

“We are asking for children who snore. It is something that is essential to worry about. It affects the wellbeing of the children, their education, their growth is affected and it can lead to behaviour issues. Taking part in this study will be beneficial,” he said.

The mandibular advancement splints, which were chosen out of four appliances, bring the lower jaw forward and expand the upper airways.

“If we are able to expand the upper airways, that will have the same target of removing the tonsils. It is something that is simple, especially in mild to moderate cases. It could also be used to help relieve the child prior to tonsil removal if they are on a waiting list for six months,” he said.

Mr Idris said up to 10% of children in New Zealand were affected by sleep-disordered breathing syndrome.

“It is something that is often undiagnosed. The idea [using the device] is widely used and accepted in growth modification and is common around the world,” he said.

As part of the research project, Mr Idris hoped to increase awareness about the issue, as it was "hard to discover and/or diagnose". He may spread the word using dental clinics and as a follow-up for children in hospital.

For more information about the research project contact Ghassan Idris on 470-7084 or kids.snoring@otago.ac.nz.

Story about this research published in The Star, for the purpose of recruiting participants
# Parents/ Caregivers Information Sheet

<table>
<thead>
<tr>
<th>Study title</th>
<th>Efficacy of A Mandibular Advancement Appliance on Sleep Disordered Breathing in Children</th>
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<tbody>
<tr>
<td><strong>Principal investigators</strong></td>
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<tr>
<td><strong>Name</strong></td>
<td>Prof. Mauro Farella</td>
</tr>
<tr>
<td><strong>Department</strong></td>
<td>Discipline of Orthodontics, Department of Oral Sciences.</td>
</tr>
<tr>
<td><strong>Position</strong></td>
<td>Professor of Orthodontics, Head of Discipline of Orthodontics</td>
</tr>
<tr>
<td><strong>Name</strong></td>
<td>Dr. Ghassan Idris</td>
</tr>
<tr>
<td><strong>Department</strong></td>
<td>Discipline of Orthodontics, Department of Oral Sciences, School of Dentistry.</td>
</tr>
<tr>
<td><strong>Position</strong></td>
<td>PhD candidate.</td>
</tr>
</tbody>
</table>

**Contact**
Tel: 0 3 479 7084
Email: kids.snoring@otago.ac.nz

Thank you for showing interest in this project. Please read this information sheet carefully. Take time to consider, and if you wish, talk with relatives or friends before deciding whether or not to participate.
If you decide to participate we thank you. If you decide not to take part there will be no disadvantage to you and we thank you for considering our request.

Introduction

Children who snore may suffer from a problem called Sleep Disordered Breathing (SDB). SDB varies in intensity from just snoring to no breathing at all for a few seconds, which disturbs sleep. Although this disease has many negative effects on health but SDB is not recognised in most children with mild to moderate symptoms. The primary cause of SDB in children is the enlarged adenoids or tonsils which block the airways during sleep. On the other hand, the primary treatment for SDB is doing a surgery to expand the airways by removing these tissues.

It is generally accepted that gradually moving the lower jaw forward in growing children may improve jaws and teeth relationships, and also increase the airway space thus improving the symptoms of SDB. This may offer an alternative treatment modality for children with mild to moderate symptoms of SDB.

Why are we doing this study?

The aim of our research is to test the efficacy of mandibular advancement appliances in treating children with sleep disordered breathing (SDB).

Mandibular Advancement Splints (MAS) are devices place the lower jaw in advance position. MAS are one of the most acceptable orthodontic functional appliances; MAS are mainly used in treatment of underdeveloped lower jaw, and this study will test the efficacy of MAS in improvement of the main symptoms of SDB such as snoring and stopping breathing during the night, and other secondary symptoms such as quality of life, daytime sleepiness, and bed wetting. This study will also check potential changes that may happen to growth hormone levels as a result of the treatment.

Who is funding this project?

This project is funded by the University of Otago and New Zealand Association of Orthodontists and other funding bodies may also participate with the progress of this research.

Who are we seeking to participate in the project?
We are mainly looking for children between 8-12 years old who snore regularly and loudly (about 3 times per week), without previous orthodontic treatment.

**If you participate, what will you be asked to do?**

At the first stage you will receive an information sheet about this study and a consent will be obtained from you and your child if you decide to participate.

We will check if your child is suitable to receive the orthodontic treatment offered in this study; checking eligibility will be confirmed by evaluating and examining the following:

- Face appearance, teeth and jaw relations.
- Impressions of the teeth to get models.
- X-rays of the teeth and the head.
- Parents/caregivers will answer a questionnaire about SDB symptoms and severity.
- An electronic monitor may be provided for a full night monitoring of SDB at home.

Based on the results of the above investigations, suitable children will be invited to participate. We are expecting to have about 16 patients in the study.
Participants will be randomly divided into two groups, with 8 children in each group. All the children participating in the study will receive the same treatment with two MAS appliances (figure 2), but in different order as the following:

- The first group will receive a treatment consisting of two periods: the first period of 3 weeks with an active MAS and the second treatment period of 3 weeks with a reference MAS. Participants will have a 2 weeks break without treatment between the two treatment periods to avoid interlocking effect between the two appliances.
- The second group will receive the same two MAS appliances but in different order (The reference MAS first then the active MAS and a break of 2 weeks in between).

The MAS appliance which is considered as a reference will serve as a control appliance to assess the efficacy of the effective MAS. The patients will not be informed about which of the two appliances they are wearing in a specific period of the treatment. Children will be asked to wear MAS appliances during sleep at night.
Parents/caregivers will be asked to answer questionnaires before and after each period of wearing the appliances and they will be provided with a diary to record bed wetting and snoring every week.

Children will be provided with a monitor to observe the SDB symptoms including snoring, blood oxygen levels, and heartbeat, airflow in the nose, and many other measurements. This will be applied before and after each period (figure 1).

A specialist in venipuncture will take blood samples by inserting a needle into a vein in the arm, as it is done routinely to take blood samples. This will not require any specific test preparation (such as fasting). Blood samples will be taken only twice throughout the study to check for possible positive changes in growth hormone levels in the blood after using MAS appliances.

**Treatment cost**

The treatment during the study is free of charge, but you will be charged after finishing the study if you want to continue your child’s orthodontic treatment at the School of Dentistry. One of the benefits of participating in this study is that your child may use the same MAS appliance to continue the orthodontic treatment...
for correcting the bite and a child can continue the remaining orthodontic treatment at the School of Dentistry with a high priority.

**What specimens, data or information will be collected, and how will they be used?**

Blood sample collection, storage, tests, and disposal of medical wastes will be done according to World Health Organization guidelines. Blood samples will not be stored but will be disposed off after getting the result of the tests.

Other data collected in the study through clinical examination, X-rays, breathing and snoring monitors or questionnaires will be reviewed and analyzed by the research group. The collected data will be saved for 10 years at the Discipline of Orthodontics at School of Dentistry/University of Otago.

**Is there any risk of discomfort or harm from participation?**

MAS appliances are well-accepted among children with a low failure rate. It is non-invasive (does not require any surgery) but these appliances do need a period of adaptation. There might be mild levels of discomfort and/or tenderness of the facial muscles in the first few days your child wears the appliance, but this will disappear soon. Your child may also experience initial speech difficulties and excessive salivation for the first few days, but these problems will diminish over time. The appliance used in the study may slightly change your bite. This is very unlikely to happen over a few weeks of the MAS appliance use, but if this will be the case, the changes will be transitory and favourable to correct your bite.

Collecting blood samples from the arm veins using a syringe with a needle is sometimes accompanied by anxiety, but we will collect blood only twice throughout the study. This procedure will be done by a specialist in venipuncture to guarantee a high quality procedure and to ensure the child’s comfort and minimizing any potential complication.

**What about anonymity and confidentiality?**

Personal information and the collected data from you and your child during the study which identify you will only be used by the researchers and people involved in evaluation and reviewing this study. The results of the study will be written up for the University work, and they may be written up in journals and talked about at conferences, but. Your identity will not be disclosed to anyone.

**If you agree to participate, can you withdraw later?**

You may withdraw from participation in the project at any time and without any disadvantage to yourself or your child.
Any questions?

If you have any questions now or in the future, please feel free to contact either:

<table>
<thead>
<tr>
<th>Name</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof. Mauro Farella</td>
<td>Name: Prof. Mauro Farella</td>
</tr>
<tr>
<td>Position</td>
<td>Position Professor of Orthodontics</td>
</tr>
<tr>
<td></td>
<td>Head of Discipline of Orthodontics</td>
</tr>
<tr>
<td>Department</td>
<td>Department Oral Science/ School of Dentistry</td>
</tr>
<tr>
<td></td>
<td>Phone number: 03 479 7084</td>
</tr>
<tr>
<td></td>
<td>Email: <a href="mailto:kids.snoring@otago.ac.nz">kids.snoring@otago.ac.nz</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Ghassan Idris</td>
<td>Name: Dr. Ghassan Idris</td>
</tr>
<tr>
<td>Position</td>
<td>Position PhD candidate</td>
</tr>
<tr>
<td>Department</td>
<td>Department Discipline of Orthodontics/ Oral</td>
</tr>
<tr>
<td>Science, School of</td>
<td>Science, School of Dentistry.</td>
</tr>
<tr>
<td>Dentistry.</td>
<td></td>
</tr>
</tbody>
</table>

This study has been approved by the University of Otago Human Ethics Committee (Health). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (phone +64 3 479 8256 or email gary.witte@otago.ac.nz). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.
Efficacy of a mandibular advancement appliance on sleep disordered breathing in children

Principal Investigator: Professor Mauro Farella

(Kids.sonoring@otago.ac.nz Tel: 03 479 7084)

CONSENT FORM FOR PARTICIPANTS

Following signature and return to the research team this form will be stored in a secure place for ten years.

Name of participant:…………………………………………..

1. I have read the Information Sheet concerning this study and understand the aims of this research project.
2. I have had sufficient time to talk with other people of my choice about participating in the study.
3. I confirm that I meet the criteria for participation which are explained in the Information Sheet.
4. All my questions about the project have been answered to my satisfaction, and I understand that I am free to request further information at any stage.
5. I know that my participation in the project is entirely voluntary, and that I am free to withdraw from the project at any time without disadvantage.
6. As a participant, I know that the results of the project may be published and will be available in the University of Otago Library (Dunedin, New Zealand) but every attempt will be made to preserve my anonymity and my child’s anonymity.
7. I know that the questionnaires provided in the study will explore the things related to check for the sleep disordered breathing symptoms and changes in their severity, changes in our child behaviour also will be detected as well as quality of life.
8. I understand the nature and size of discomfort or harm which are explained in the Information Sheet.
9. I know that when the project is completed all personal identifying information will be removed from the paper records and electronic files which represent the data from the project, and that these will be placed in secure storage and kept for at least ten years.
10. I understand that the results of the project may be published and be available in the University of Otago Library, I agree that any personal identifying information will
remain confidential between myself and the researchers during the study, and will not appear in any spoken or written report of the study.

11. I know that there is no remuneration offered for this study, and that no commercial use will be made of the data.

12. At the end of the study, I consent to any remaining blood samples being disposed of using:
   - [ ] Standard disposal methods, OR;
   - [ ] Disposed with appropriate karakia

I agree to take part in this project.

Signature of participant: ___________________________ Date: ___________________________

Signature and name of witness: ______________________ Date: ________________________
Children's Information Sheet

A study about children who snore while they sleep. Would you like to help us in a research project using a device to stop snoring?

We would like you to help us in a project that is trying to stop snoring in children.

What I will be asked to do?

First of all, come in to visit some people in the dental school where they will ask you a few questions about yourself and look at your teeth, face and the way you breathe. They will also take x-rays of your teeth and head so they can look at your jaw bones, teeth and throat.

On another day you will be given a small machine to be used at bed time. We will attach some sticky things on you which will be joined up to the machine so we can record:

- The way you breathe, by putting stretchy bands around your chest and tummy
- The air coming in and out of your nose, by sticking a piece of tubing on (like a moustache)
- Your heart beat, by putting two sticky circles on your chest and one on your tummy.
- How much noise you make while you sleep
- A special light that glows red in the dark placed on to your finger
- A special strip will attach to your leg

We will give you a device to put in your mouth. This device is mainly made of plastic and small metallic parts and it is made to fit your teeth and mouth. It consists of two pieces; one to hold with your upper teeth and the other to be held with your lower teeth. You are able to take the two pieces out of your mouth by yourself without any help. We will ask you to have the device for 3 weeks, after that you will stop using it for 2 weeks, then we will give you a new device to use for another 3 weeks. We will provide you with full information about how to use this device and how to overcome any problems when using it.

During the treatment we will take some blood from your arm using a syringe; this procedure is to check if the device is useful in making you grow better.

Your Mum or Dad will complete some information about you before and during the research and they will answer specific questions about the changes they notice about you and your snoring after wearing the devices.

You can come to meet us and ask more questions before you decide to say 'Yes' or 'No'. You don't have to say 'yes' and you can decide to stop at any time. If you would like to help us in
this project, just ask your Mum or Dad or the person who looks after you. This is a chance to learn a lot of exciting things about how your body works, and you might find it very interesting to have this and to stop snoring. Remember you can ask us any questions whenever you like.

The people involved in the project are:

Dr. Ghassna Idris, Prof. Dr. Mauro Farella, Dr. Christopher Robertson, Prof. Dr Babara Galland

Consent

I have read this sheet, and it has also been explained to me by my Mum or Dad or the person who looks after me. I understand it all and would like to be a part of this project.

Signed: ___________________________ Date: ___________________________
Thank you for taking part in the Study. This is a questionnaire about your child’s sleep and daytime activities and your family.

Please try and answer all the questions. If you feel uncomfortable about answering any question, or you do not know the answer, you can leave it blank, ask us for more information, or add a written comment.

There are no right or wrong answers, and all information given to us will be treated as confidential.

Thank you,

Ghassan Idris
PhD Student
Discipline of Orthodontics
Department of Oral Sciences
University of Otago
Tel 64 3 479 7084

Please complete this section below.

Name of person who completed this survey: ____________________________________________________________

Date survey was completed: _________________________________________________________________________
Information regarding your child

These questions are about your child. For most questions, please circle the best answer. For Yes/No questions, please answer ‘yes’ if this is something you have ever noticed in your child, even if it is rare or not currently a problem. For questions that require you to judge on a scale, please try to think about what your child is like most of the time. Do not judge your answer based on a particularly good or bad day.

1 What is your child’s ethnicity (please tick as many boxes as apply)?
   ☐ New Zealand European
   ☐ Maori (please specify iwi) _____________________
   ☐ Samoan
   ☐ Cook Island Maori
   ☐ Tongan
   ☐ Niuean
   ☐ Chinese
   ☐ Other (please specify) _____________________

2 Would you describe your child’s health as (please select one answer):
   ☐ Poor
   ☐ Fair
   ☐ Good
   ☐ Very good
   ☐ Excellent

3 Is your child currently on medication? If yes please provide the name of medication

   ☐ Yes ☐ No

4 Has your child had their tonsils removed?

   ☐ Yes ☐ No
- Has your child had their adenoids removed?
- Has your child ever had grommets?

- Does your child suffer from any of the following?
  - Down Syndrome
  - Asthma
  - Hay fever
  - Eczema
  - Epilepsy
  - Frequent sore throat. If yes, how often?
  - Glue ear
  - Hearing problems
  - None of the above

- Has your child ever had any other serious medical conditions apart from those already mentioned?
  - Yes. If yes, what?____________________________________________________
  - No

- Has your child ever been assessed and/or treated for developmental or behavioural problems?
  - Yes. If yes, what was the problem?
    _________________________________________________________________
  - No

- What time does your child normally go to bed on weekdays?  
  Time ______________________ : __________ AM/PM

- What time does your child normally wake up on weekdays?  
  Time ______________________ : __________ AM/PM

- What time does your child normally go to bed on weekends?  
  Time ______________________ : __________ AM/PM

- What time does your child normally wake up on weekends?  
  Time ______________________ : __________ AM/PM

- How many minutes does it normally take for your child to fall asleep? _________________ minutes
### While sleeping does your child...

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Don't Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
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<td>2.</td>
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<td>4.</td>
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<tr>
<td>5.</td>
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</tr>
</tbody>
</table>

### Have you ever...

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Don't Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.</td>
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</tr>
</tbody>
</table>

### Does your child...

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Don't Know</th>
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</thead>
<tbody>
<tr>
<td>7.</td>
<td></td>
<td></td>
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<tr>
<td>8.</td>
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<tr>
<td>11.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Don't Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.</td>
<td></td>
<td></td>
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<tr>
<td>13.</td>
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<td>14.</td>
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<td>15.</td>
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<tr>
<td>16.</td>
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<td></td>
</tr>
</tbody>
</table>

### Your child often...

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Don't Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.</td>
<td></td>
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<tr>
<td>18.</td>
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<td>21.</td>
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</tr>
<tr>
<td>22.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
During the past 3 weeks, how often has your child had…

<table>
<thead>
<tr>
<th></th>
<th>None of the time</th>
<th>Hardly any of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>A good bit of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.</td>
<td>Loud snoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31.</td>
<td>Breath holding or pauses in breathing at night</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32.</td>
<td>Choking or made gasping sounds while asleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33.</td>
<td>Restless sleep or awakenings from sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34.</td>
<td>Mouth breathing because of nasal obstruction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>35.</td>
<td>A cold or upper respiratory infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>36.</td>
<td>Nasal discharge or a runny nose</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>None of the time</td>
<td>Hardly any of the time</td>
<td>A little of the time</td>
<td>Some of the time</td>
<td>A good bit of the time</td>
<td>Most of the time</td>
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</tr>
<tr>
<td>37</td>
<td>Difficulty swallowing food</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>Mood swings or temper tantrums</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>Aggressive or hyperactive behaviour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Discipline problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>Excessive daytime sleepiness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>A poor attention span or concentration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>Difficulty getting up in the morning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>Caused you to worry about your child’s general health</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>Created concern that your child is not getting enough air</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>Interfered with your ability to perform daily activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Made you frustrated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Never</td>
<td>Occasionally</td>
<td>1-2 days a week</td>
<td>3-4 days a week</td>
<td>5-6 days a week</td>
<td>Every day</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>48. How often does your child behave irritably during the day?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>49. How often does your child behave hyperactively during the day?</td>
<td></td>
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</tr>
</tbody>
</table>
**BASC-2**

**Behavioral and Emotional Screening System**

**Child/Age-related Form**

**Grades K-12**

**Parent Form**

**Appendices**

---

**Directions**
- Use a No. 2 pencil only.
- Make solid marks that fill the circle completely.
- Make no stray marks on this form.
- Erase cleanly any marks you wish to change.

**Child's Birth Date**

<table>
<thead>
<tr>
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<th>Day</th>
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</thead>
<tbody>
<tr>
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**Today's Date**

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</thead>
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<td>Dec</td>
<td>23</td>
<td>1982</td>
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</tbody>
</table>

**Parent Form**

**Child's Name**

- **First Name**: [Blank]
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**Child's Grade**

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- **1**: 8
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**Child's Sex**

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- **Male**: [Blank]

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164
Instructions:
Listed below are phrases that describe how children may act. Please read each phrase, and mark the response that describes how this child has behaved recently (in the last several months).

Mark □ if the behavior never occurs.
Mark □ if the behavior sometimes occurs.
Mark □ if the behavior often occurs.
Mark □ if the behavior almost always occurs.

Please mark every item. If you don’t know or are unsure of your response to an item, give your best estimate.

Before starting, please fill in the information in the boxes on the first two pages of this form.

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8 Publications


Idris G., Galland B., Robertson C. J., Farella M. Efficacy of a mandibular advancement appliance on paediatric sleep disordered breathing. The 92nd European Orthodontic Society Congress, Stockholm, Sweden, 11-16 June 2016. *(Oral presentation)*

Idris G., Loke C., Farella M. The role of dentists in adult obstructive sleep apnoea, feature article. NZDA NEWS. 2016; Mar: 35-44. *(Journal article)*

Idris G., Galland B., Robertson C. J., Farella M. Efficacy of a mandibular advancement appliance on paediatric sleep disordered breathing: a preliminary report. 55th Annual Scientific Meeting of the IADR Australia & New Zealand Division, Dunedin, New Zealand, 24-26 August 2015. *(Oral presentation)*
The role of dentists in adult obstructive sleep apnoea


discipline_of_orthodontics, university_of_otago

DR GHASSAN IDRIS DENT, FGDP Orthodontics, MBCh, Orthodontics, Diplomate of Jordanian Board of Orthodontics, PhD, DR COREEN LOKE BDS, DCDental and

PROF MAURO FARELLA BDS, FDS, FDS ortho, FDS ortho (Hons), Spec Cert ortho, Spec Cert sleep.


Introduction

SDB refers to a wide spectrum of sleep-related breathing abnormalities. The mildest form of SDB is primary snoring, while gradually increasing in severity include upper airway resistance syndrome (UARS), OSA and obesity hypoventilation syndrome (OHS). OSA is characterised by the presence of repeated complete or partial blockages of the upper airway during sleep. Despite an effort to breathe, these blockages are respectively referred to as apnoeas and hypopnoeas (Table 1). The severity of OSA is typically measured by the apnoea-hypopnoea index (AHI) (Table 2). OSA is also often accompanied by daytime symptoms such as excessive daytime sleepiness, as well as impaired memory and cognitive function. The pathophysiology of OSA is complex with multiple risk factors involved.

TABLE 1

<table>
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<tr>
<th>Condition</th>
<th>Clinical Definition</th>
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<tr>
<td>Apnoea</td>
<td>Absence of breathing for &gt; 10 seconds¹</td>
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<tr>
<td>Hypopnoea</td>
<td>&gt; 30% airflow reduction, with &gt;3% oxygen desaturation for &gt; 15 seconds or an arousal in sleep²</td>
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TABLE 2

<table>
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<tr>
<th>Apnoea-Hypopnoea Index (AHI) scores</th>
<th>Severity of OSA</th>
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<td>5-15 episodes per hour</td>
<td>Mild</td>
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<td>&gt;16 episodes per hour</td>
<td>Moderate</td>
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<tr>
<td>&gt;30 episodes per hour</td>
<td>Severe</td>
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¹Apnoea-Hypopnoea Index (AHI) measures the total number of apnoeas and hypopnoeas per hour of sleep

²Apnoea-Hypopnoea Index (AHI) measures the total number of apnoeas and hypopnoeas per hour of sleep

This article will review the role of dentists in the management of OSA patients with oral appliances.
Prevalence

The prevalence of OSA in adults ranges from 3 to 7%, and middle-aged men were the most affected. Epidemiological studies carried out in New Zealand reported that over 15% of the adult male population had OSA, and that males of Maori descent were affected approximately twice more than that of other descents. It was estimated that about 20-30% of OSA cases were asymptomatic and undiagnosed in the middle-aged population. Therefore, it was recommended that primary health care workers should increase suspicion for OSA in patients.

Risk factors

Obesity is a well-known risk factor for OSA. Excessive fat accumulation around the neck and waist, also known as central obesity, is a strong predictor for OSA. In a non-obese individual, the most likely risk factor for OSA include craniofacial anatomical features such as retro-positioned maxilla and/or mandible.

Males are more prone to be affected by OSA as the testosterone hormone was found to increase upper airway collapsibility. On the contrary, the progesterone hormone was found to act as respiratory stimulant. However, post-menopausal women have lower progesterone levels, and were reported to have a higher prevalence of OSA.

OSA has a strong heritable component, where 35-40% of its variance can be attributed to genetic factors. Other less common risk factors of OSA in adults include hypertrophy of lymphoid tissues, such as adenoids and tonsils. However, these are considered the most common etiology of OSA in children.

Other well-established risk factors include smoking, excessive alcohol consumption, some ethnicities (Pacific Islanders, Maori, Asian, African-American), and craniofacial abnormalities associated with certain conditions (Table 3).

**Table 3: Risk Factors of OSA**

- Obesity
- Male gender
- Menopause
- Genetics
- Ethnicity (Maori)
- Smoking and alcohol consumption
- Enlarged adenoids, tonsils, tongue, soft palate
- Craniofacial abnormalities (retro-positioned maxilla and/or mandible)
- Down’s, Marfan, and Pierre Robin syndromes
- Hypothyroidism
- Acromegaly

Dentists may identify undiagnosed OSA patients by recognizing risk factors and checking for important symptoms such as snoring and daytime sleepiness.
Diagnosis

Dentists may play a significant role in identifying OSA patients by recognising the symptoms and risk factors of OSA. A referral to the sleep physician should be made in patients reporting of persistent snoring, occurrences of cessation of breathing at night, and excessive daytime sleepiness. The sleep physician will then arrange for an overnight polysomnography (PSG) sleep study to confirm the presence and severity of OSA. PSG identifies the origin of apnoea via recordings of sleep and breathing-related measurements. This test can be undertaken in sleep laboratories or at patients’ homes using portable devices.17

The dentist should take accurate and comprehensive records of the patient’s clinical history (medical and dental). A major symptom of OSA is snoring, and it occurs in up to 95% of patients with OSA. Excessive daytime sleepiness is also a common occurrence leading to daytime fatigue and higher risk of traffic accidents.14 The Epworth Sleepiness Scale (ESS) is a widely used questionnaire to measure subjective excessive daytime sleepiness.15

Physical examination includes the measurement of height and weight, in order to determine the body mass index (BMI). Facial profile and craniofacial anatomy such as the chin-neck angle, nasolabial angle, presence of mandibular retrusion and maxillary deficiency should be recorded. These features can be useful in the prediction of the severity of OSA and treatment options. Table 4 summarises the features and symptoms of a potential OSA patient.

<table>
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<th>TABLE 4</th>
<th>OSA DIAGNOSIS</th>
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| Clinical history<sup>12,13</sup> | - Presence of loud snoring, witnessed apnoea and daytime sleepiness.  
- Frequent arousals and choking at night, increased irritability, absence of dreams and morning headaches.  
- Epworth Sleepiness Scale (ESS) questionnaire measures subjective excessive daytime sleepiness (Scores >10 out of 24 warrant further investigation of OSA) |
| Medical history | Presence of diabetes, hypothyroidism, sinusitis, hypertension, use of antidepressants, and familial history of OSA |
| Physical examination<sup>14</sup> | - Facial profile and craniofacial anatomy  
- Height and weight to determine body mass index (BMI)  
| The following cut-offs may represent predictors for OSA patients:  
- BMI>30 Kg/m²  
- Neck circumference >42 cm for men and >37 cm for women  
- Waist circumference of >102 cm for men and >90 cm for women  
- Waist to hip ratio >1 for men and >0.85 for women |
| Cephalometric examination<sup>15,16</sup> | - Low position of the hyoid relative to the mandibular plane.  
- A distance >15.4 mm indicates a person at OSA risk.  
- Greater class II skeletal tendency. |

Oropharyngeal anatomy such as the size of tonsils and tongue, soft palate tissue redundancy, uvula length and thickness, and the presence of tongue indentations must also be assessed and be graded using the modified Malmquist classification (Figure 3). Class III and Class IV indicates more severe cases of OSA.16

Several techniques have been used to study the upper airway anatomical structures and estimate the size of upper airway. These include lateral cephalometry, acoustic reflection, fluoroscopy, nasopharyngoscopy, computed tomography (CT) and magnetic resonance imaging (MRI).
Lateral cephalometry has become one of the standard diagnostic tools in patients with SDB, especially in the evaluation of the skeletal craniofacial morphology. It can also be helpful in orthodontic treatment planning, evaluation of the airway with the oral appliances, orthognathic surgery, and the assessment of the long-term dento-facial changes associated with oral appliance therapy. However, some disadvantages include issues with image reproducibility, measurement errors, a limited two-dimensional picture, a less accurate image of the airway taken with the patient standing instead of a supine position, and that it provides limited information on the soft tissues. However, it has the merit of being simpler, inexpensive and more readily available than CT scanning and MRI techniques.20,21

A recent study using lateral cephalograms has shown that patients with bimaxillary retrusion and a greater class II skeletal tendency were good responders to MAD. However, more research in a larger sample size is required before clinical recommendations can be substantiated.22

Intra-oral and extra-oral examination, including palpation of the jaw muscles are important to determine the suitability and eligibility of the patient for oral appliances. This assessment is summarised in Table 5.

Oral appliances are currently considered a viable treatment among the available modalities, particularly in mild to moderate OSA cases.
### TABLE 5: JAW FUNCTIONAL AND DENTAL EXAMINATION

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<th>EXAMINATION</th>
<th>SPECIFIC CONSIDERATIONS</th>
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| Masticatory muscles, temporomandibular joints, and jaw excursions | - Presence of temporomandibular disorders (TMD) with pain is considered as a contraindication for MAD.  
- Adequate mouth opening and promotive jaw movements (> 65 mm) is required. |
| Periodontal health | - There is association between periodontitis and OSA.  
- Healthy periodontal tissues and alveolar ridge are required to support MAD and teeth to retain the device.  
- Compromised periodontal status may require periodontal care or may be considered a contraindication for MAD. |
| Presence of malocclusion | - Useful in identifying suitable patients for oral appliances treatment (favourable in class II with increased overjet and overbite) and to be cautious of possible dental side effects of long-term MAD wear (in class I or II with minimal overjet and overbite). |
| Sleep bruxism | - There is a weak association between OSA and sleep bruxism. Consider co-morbidity. |
| The condition and number of teeth present | - A sufficient number of teeth is required to retain the device (more than 6 to 10 teeth per arch in good periodontal health).  
- Dental restorations may be required before use of MAD. |

**Management options**

CPAP is the first treatment option offered to patients with symptomatic, moderate to severe OSA. CPAP maintains the upper airway patency during sleep and the pressure is delivered by a nasal or facemask. It is considered as the gold standard treatment, due to its efficacy in reducing AHI scores and daytime symptoms, which in turn significantly improves the quality of life of OSA patients. Although CPAP devices are constantly being improved for patient comfort, long-term compliance remains an issue. CPAP usage has a low patient adherence with 46 to 83% of patients being non-compliant. Poor compliance is mainly due to the adverse effects accompanying mask wear. These include skin irritation, pain, dryness of the nasal and oral mucosal membranes, as well as dislodgement of the mask during sleep. Moreover, the machine can be noisy and may be difficult to transport.

Surgery should be considered in severe OSA patients with unsuccessful CPAP treatment, which is mainly due to compliance. Successful surgical outcomes depend on proper patient selection as well as the choice of surgical procedure.

Surgical options include tracheotomy, uvulopalatopharyngoplasty (UPPP), isolated hard (nasal turbinates) or soft tissues (tonsils and adenoids) surgery, and maxillo-mandibular advancement (MMA). MMA is the most successful OSA treatment option for severe OSA after tracheotomy. It improves the dimension and stability of the airway by addressing the anatomic abnormalities.

**Oral appliances**

The American Academy of Sleep Medicine (AASM) guidelines recommend use of oral appliances for mild to moderate OSA patients, who are not responding (or not adhering) to CPAP and behavioural measures such as weight loss. It is not recommended as a first treatment choice in severe OSA as the severity of OSA poses a high risk of mortality, so those patients need more efficient treatment rather than oral appliances. In comparison to CPAP oral appliances are simpler to use, cheaper, more portable, quiet, and do not require a power source.
**Tongue Stabilising Devices (TSD)**

The TSD keeps the tongue forward by suction, thus widening the upper airway dimensions during sleep. Patients self-adjust the appliance by increasing the amount of suction and the forward positioning of the tongue into the appliance, until snoring and symptoms are improved. Some discomfort associated with the use of TSD includes irritation of the lingual frenum. The efficacy of TSD in the reduction of AHI score is comparable to MAD. However, a more recent MRI study reported significantly greater volumetrically upper airway changes with the TSD compared to the MAD. TSD is a good treatment option in patients who are edentulous or are lacking dentition to support other types of oral appliances.

![Tongue Stabilising Devices](Image)

**Mandibular Advancement Devices (MAD)**

The mechanism of action of the MAD consists of holding the mandible in a forward position. This results in anatomical changes that facilitate the patency of the upper airway, such as the increase of the lateral and anterior posterior upper airway dimensions. The activation of neuromuscular reflexes has also been reported to increase muscle tone and prevent airway collapsibility during sleep. However, the anatomical changes of the upper airway were not consistently seen in all patients.

MAD can be constructed as a single piece appliance (monobloc) or in two pieces (biloblock). The biloblock permits more flexibility in mandibular movements, such as lateral excursive movements, bite opening and mandible protrusion. Newer MAD appliances allow titration of the amount of mandible protrusion by the use of jackscrew or elastics. The ability to adjust the amount of mandibular protrusion is an advantage as it allows for gradual advancement of mandibular protrusion until OSA symptoms are relieved. The ability to titrate the amount of mandibular advancement also allows for better patient adaptation and acceptance to the appliance, hence increasing the success rate of the treatment.

![Mandibular Advancement Devices](Image)
Treatment outcome with oral appliances

A complete resolution of OSA is defined as a reduction of AHI to below 5, while it is deemed to be a clinically significant result with a 50% reduction of the baseline AHI.18

Although MADs are not recommended in severe OSA cases, a study reported that 30% of severe OSA patients showed resolution of OSA, i.e., AHI was < 5 events/hour.19 Overall, oral appliances therapy with the MAD produced clinically significant results or complete resolution in more than half of patients (52%) with varying severities of OSA.20 MAD constructed at 75% of maximum mandibular protrusion was found to be most efficient in reducing AHI to below 10.21

Managing the OSA patient with MAD

First, a thorough dental history and examination must be taken to assess the suitability of the patient for a MAD. At least 8 to 10 teeth in each arch are required to provide support and retention of the appliance. A contraindication to the use of MAD include orofacial pain due to temporomandibular disorders (TMD), and limited jaw opening and mandible protrusion of less than 3mm.22 Potential good responders include patients with mild OSA, younger age, lower BMI, females, and with class II skeletal tendency malocclusion have been reported to benefit from the MAD.23,24

The construction of a MAD requires an impression of the maxillary and mandibular arches, as well as an occlusal registration taken at the desired amount of protrusion (50-75% maximum protrusion is recommended). It is generally accepted that the more the mandibular advancement, the more effective the MAD in opening the airway. In mild to moderate cases, there was no difference in the effect with 50% or 75% of maximum advancement.25 However, in severe OSA, 75% of maximum advancement will provide the best treatment outcome.26

Bite opening is inevitable with the use of MAD, and has been shown to have adverse effects on the upper airway patency in the majority of OSA patients.27 However, there was no significant differences in MAD treatment outcome when 4 to 14 mm of interincisal bite opening were compared.28

The customised MAD must be delivered and fitted accordingly, ensuring the presence of even occlusal contacts without interferences on lateral movements. In titratable MADs, the amount of mandibular protrusion can start at centric occlusion and gradually increased every few weeks or months, until OSA symptoms disappear or when the patient begins to experience discomfort of the temporomandibular joint (TMJ).

During the initial stages of treatment, the patient should be followed up regularly (every 1-2 weeks) to evaluate compliance, possible side effects, and the efficacy of the appliance with the chosen degree of mandibular protrusion. Regular follow-up appointments are crucial to manage and eliminate the patient’s potential discomfort, hence increasing adherence and acceptance of the oral appliance. When PSG is not available, reports from the patient’s partner can be useful to evaluate improvement of OSA symptoms.

Once the patient has adapted to regular use of the MAD, it is important to review the efficacy of the appliance with another polysomnography (PSG). The AASM guidelines published in 2005, recommend follow up appointments to be 6 months in the first year and at least annually thereafter. These follow up appointments would focus on managing potential adverse effects of the appliance and evaluating the deterioration and condition of the appliance, the integrity and health of the oral structures and occlusion, and to monitor for signs and symptoms of worsening OSA.29
Side effects

Consistent with Newton’s third law of motion, MADs generate reciprocal forces on both the teeth and jaws (maxilla and mandible). These forces are usually mild and transient, and they include drooling (excessive saliva), mucosal dryness, dental pain, gingival tissues irritation, headaches, myofacial pain and stiffness of the jaw. The frequency of these adverse effects was reported to vary from 6 to 86%, and was higher with the use of mono-block, in MADs, with increased amount of mandibular protrusion and in patients who were irregular with their follow up visits.46

**Table 7**

**LONG-TERM DENTAL AND SKELETAL CHANGES**

- Increase in facial height
- Increase in mandibular plane angle
- Changes in molar relationship towards mesio-occlusion
- Retroclination of maxillary incisors
- Proclination of mandibular incisors

Some authors have reported that greater mandibular advancement may lead to greater side effects.47 However, in 14% of the treated cases there was no occlusal significant changes in addition to favourable changes in more than 40% of the cases.48 Most of the occlusal changes occur in the first two years and remained relatively constant thereafter.49 Other studies have shown no significant changes in the occlusion with the short-term use of MADs within a year.5051

A long-term study of MAD use (mean period of 7.3 years) reported significant changes in 85% of patients on the occlusal and dental structures, which mainly consisted of the dental movement of the incisors.48 Favourable changes were associated with Class II corrections while unfavourable changes were found in patients with Class I occlusion with minimal overbite and overjet.

Treatment of OSA with oral appliances is likely to be life-long, hence it is important that all patients have informed consent. It is also important to monitor the use of the appliance and for any dento-skeletal changes. Records such as study models, radiographs, as well as intra-oral and extra-oral photographs should be encouraged in all clinical OSA protocols to facilitate the monitoring of the progressive changes. Although the long-term use of MAD may cause undesirable changes in certain patients, it is still an effective treatment for a life-threatening disease, thus outweighing the cons.

**Conclusion**

Oral appliances represent a promising treatment modality for OSA. Dental professionals are playing an increasingly important role in the diagnosis and the management of patients with OSA. Hence, it is necessary that dentists are updated with information related to the diagnosis, treatment options, and management of patients with OSA. It is also important that dentists are aware of the variation of oral appliances designs available, and the possible side-effects resulting from their long-term use. Furthermore, it is also of utmost importance that the dentist liaises with a multi-disciplinary team of specialists to achieve a proper diagnosis and treatment plan, as well as an adequate follow up.

**REFERENCES**
### Sleep study data

#### Table 5-1 Twin block results (apnoea hypopnoea index (AHI))

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**Abbreviations**: 
P: participant number; Seq: sequence in the study sequence 1 started with Twin-block followed by Sham MAS and sequence 2 started with Sham MAS followed by Twin-block; T1: sleep monitoring before using Twin-block; T2: sleep monitoring last night of using Twin-block (3 weeks); AHI: apnoea hypopnoea index, AHI_Sup: AHI in supine position; AHI_Nsup: AHI in non-supine position
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**Abbreviations**

- **P**: participant number;
- **Seq**: sequence in the study sequence 1 started with Twin-block followed by Sham MAS and sequence 2 started with Sham MAS followed by Twin-block;
- **T1**: sleep monitoring before using Twin-block;
- **T2**: sleep monitoring last night of using Twin-block (3 weeks);
- **O2 Sat**: Average Oxygen saturation;
- **LoO2Sat**: Lowest Oxygen saturation;
- **DesEvent**: number of desaturation events during sleep;
- **ODIndex**: number of desaturation events per hour of sleep.
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**Abbreviations**
P: participant number; Seq: sequence in the study sequence 1 started with Twin-block followed by Sham MAS and sequence 2 started with Sham MAS followed by Twin-block; T1: sleep monitoring before using Twin-block; T2: sleep monitoring last night of using Twin-block (3 weeks); SnorTime: snoring time during sleep time (minutes); SnoT% : Relative snoring time to whole sleep duration; SnorEpis: number of snoring episodes during sleep; EpisDura: Average snoring episode duration; LongstEpis: Longest snoring episode. Highlighted blank cells represent missing data.
### Table 5-4 Sham MAS results (apnoea hypopnoea index (AHI))

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**Abbreviations**
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**Abbreviations**
P: participant number; Seq: sequence in the study sequence 1 started with Twin-block followed by Sham MAS and sequence 2 started with Sham MAS followed by Twin-block; S1: sleep monitoring before using Sham MAS; S2: sleep monitoring last night of using Sham MAS (3 weeks); O2 Sat: Average Oxygen saturation; Lo02Sat: Lowest Oxygen saturation; DesEvent: number of desaturation events during sleep; ODIndex: number of desaturation events per hour of sleep.

**Highlighted blank cells represent missing data**
### Table 5-6 Sham MAS (snoring measurement results)

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**Abbreviations**
- **P**: participant number; **Seq**: sequence in the study sequence 1 started with Twin-block followed by Sham MAS and sequence 2 started with Sham MAS followed by Twin-block; **S1**: sleep monitoring before using Sham MAS; **S2**: sleep monitoring last night of using Sham MAS (3 weeks); **SnorTime**: snoring time during sleep time (minutes); **SnoT%**: Relative snoring time to whole sleep duration; **SnorEpis**: number of snoring episodes during sleep; **EpisDura**: Average snoring episode duration; **LongstEpis**: Longest snoring episode

**Highlighted blank cells represent missing data**