Paediatric Sleep-Disordered Breathing and Orthodontics

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A research thesis submitted to partially fulfil the requirements for the degree of Doctor of Clinical Dentistry

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Dedication

This thesis is dedicated

to my

Mother

Vijay Katyal

(3rd Sep 1953-31st Jul 1998)**.**

It was your love of children's welfare instilled in me that ignited the spark for this project.

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Overview

The format of this current thesis is represented by 3 papers that have been accepted for publication by peer-reviewed orthodontic journals. Following is an outline and a summary of the 3 presented papers:

Paper 1: **Paediatric sleep-disordered breathing due to upper airway obstruction in the orthodontic setting: a review**

This is a narrative literature review of the topic. Accepted for publication in the Australian Orthodontic Journal.

The essential feature of paediatric sleep-disordered breathing (SDB) is increased upper airway resistance during sleep presenting clinically as snoring. Paediatric SDB is a continuum ranging from primary snoring (PS), which is not associated with gas exchange abnormalities or significant sleep fragmentation, to obstructive sleep apnoea (OSA) with complete upper airway obstruction, hypoxaemia, and obstructive hypoventilation. Adenotonsillar hypertrophy, obesity and craniofacial disharmonies are important predisposing factors in the development and progression of paediatric SDB. Clinical symptoms are manifold and domains affected include behaviour, neurocognition, cardiovascular morbidity and quality of life. Overnight polysomnography is the current diagnostic gold standard method to assess SDB severity while adenotonsillectomy is the recommended first line of treatment. Other treatments for managing paediatric SDB include nasal continuous airway pressure, the administration of nasal steroids, dentofacial orthopaedic treatment and surgery. However, there are insufficient long-term efficacy data using dentofacial orthopaedics to treat paediatric SDB. Further studies are warranted to define the characteristics of patients who might benefit most from orthodontic treatment.

Paper 2: **Craniofacial and Upper Airway Morphology in Paediatric Sleep Disordered Breathing (SDB)- A Systematic Review and Meta-analysis**

Published in the American Journal of Orthodontics and Dentofacial Orthopaedics.

This study is a systematic review of the published literature with the results of the primary studies combined by meta-analyses in order to elucidate the nature of the association between craniofacial disharmony and paediatric SDB. Citations to potentially relevant published trials were located by searching Pubmed, Embase, Scopus and Cochrane Central

Register of Controlled Trials. Children with OSA and PS show an increased weighted mean difference (WMD) in ANB angle of 1.64° (95% CI 0.88 – 2.41, $p < 0.0001$) and 1.54° (95% CI 0.89 – 2.20, $p < 0.00001$), respectively in comparison to the controls. Increased ANB was primarily due to a decreased SNB angle in children with PS by 1.4° (95% CI -2.58 to -0.23, $p = 0.02$). Children with OSA had a PNS–AD1 distance reduced by 4.17 mm (WMD) (95% CI -5.85 to -2.50, $p < 0.00001$) and a PNS–AD2 distance reduced by 3.12 mm (WMD) (95% CI -4.56 to -1.67, $p < 0.0001$) in comparison to the controls. There is statistical support for an association between craniofacial disharmony and paediatric SDB. However, an increased ANB angle of <2° in children with OSA and PS, in comparison to the controls, could be regarded as of marginal significance. There is strong support of a reduced upper airway width in children in OSA as shown by reduced PNS–AD1 and PNS–AD2 distance.

Paper 3: **Craniofacial and Upper Airway Morphology in Paediatric Sleep-disordered Breathing and Changes in Quality of Life with Rapid Maxillary Expansion**

Accepted for publication in the American Journal of Orthodontics and Dentofacial Orthopaedics.

The aim of this study was to evaluate the prevalence of children at risk for SDB, as identified in an orthodontic setting by validated screening questionnaires, and to examine associations with presenting craniofacial and upper airway morphology. A further aim was to assess the change in the SDB-related quality of life (QoL) for affected children undergoing a rapid maxillary expansion (RME) to correct a palatal crossbite and/or widen a narrowed maxilla. 78 subjects were grouped as high risk (HR) or low risk (LR) for SDB based on the scores obtained by completing a validated 22-item Paediatric Sleep Questionnaire (PSQ) and the OSA-18 QoL questionnaire. Ten children who underwent RME were followed longitudinally until removal of the appliance (T2) approximately 9 months later with a repeat OSA-1 8 QoL questionnaire. All data were collected blinded to the questionnaire results. Children at high-risk for SDB are characterised by reduced SDB-related QoL, reduced nasopharyngeal and oropharyngeal sagittal dimensions, the presence of a palatal crossbite and reduced dentoalveolar transverse widths in the maxillary and mandibular arches. No sagittal or vertical craniofacial skeletal cephalometric predictors were identified for children at high-risk for SDB. In the short-term, RME might aid in improvement of SDB-related QoL for children with a narrow maxilla in the milder end of the SDB spectrum.

Statement of Purpose

The objectives of the thesis were to:

1. Conduct a systematic review of published literature and meta-analysis of the results of the primary studies to answer the nature of the association between craniofacial disharmonies, upper airway morphology and paediatric SDB.
2. Using screening questionnaires, estimate the prevalence of SDB in the paediatric orthodontic population and its association with SDB-related quality of life, facial, dental and airway characteristics as seen in a clinical screening examination or on lateral cephalograms and dental casts.
3. Report changes in health-related quality of life in children with suspected SDB diagnosed with dentoalveolar or skeletal crossbites and undergoing a rapid maxillary expansion procedure to widen a narrowed maxilla.

Significance to the Discipline

This thesis will aid in:

1. Providing a thorough understanding of the associations between paediatric SDB and craniofacial/upper airway morphology.
2. Establishing a screening standard for the general dental practitioner, orthodontist and paediatric specialists for early diagnosis of paediatric SDB. This in turn increases cost-effectiveness of health care utilisation.
3. Estimating efficacy of rapid maxillary expansion in the treatment of paediatric SDB. This might provide alternatives to primary treatments and/or enhance interdisciplinary treatment planning for the children suffering from SDB.
4. Establishing referral protocols and pathways between the Orthodontic Unit, Adelaide Dental Hospital, Adelaide and Sleep Disorders Unit, Women's & Children's Hospital, Adelaide to improve interdisciplinary communication for children suffering from SDB.
5. Establish limitations of current thesis for future research directions.

Statement of Authorship for Paper 1

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Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of principal author (candidate)	**Dr Vandana Katyal**		
Contribution to the paper	Conceptualisation of work, its realisation and its documentation. Literature review. Preparation and submission of manuscript.		
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Contribution to the paper	Supervised development of work, helped in literature and evidence interpretation and manuscript editions.		
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Paper 1: **Paediatric sleep-disordered breathing due to upper airway obstruction in the orthodontic setting: a review**

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ABSTRACT

The essential feature of paediatric sleep-disordered breathing (SDB) is increased upper airway resistance during sleep presenting clinically as snoring. Paediatric SDB is a continuum ranging from primary snoring (PS), which is not associated with gas exchange abnormalities or significant sleep fragmentation, to obstructive sleep apnoea (OSA) with complete upper airway obstruction, hypoxaemia, and obstructive hypoventilation. Adenotonsillar hypertrophy, obesity and craniofacial disharmonies are important predisposing factors in the development and progression of paediatric SDB. Clinical symptoms are manifold and domains affected include behaviour, neurocognition, cardiovascular morbidity and quality of life. Overnight polysomnography is the current diagnostic gold standard method to assess SDB severity while adenotonsillectomy is the recommended first line of treatment. Other treatments for managing paediatric SDB include nasal continuous airway pressure, the administration of nasal steroids, dentofacial orthopaedic treatment and surgery. However, there are insufficient long-term efficacy data on the use of dentofacial orthopaedics to treat paediatric SDB. Further studies are warranted to define the characteristics of patients who might benefit most from orthodontic treatment.

Introduction

The oral cavity, pharynx, and larynx constitute the components of the anatomic upper airway structures which underlie respiration, swallowing, and phonation in humans. In children, the upper airway is greatly influenced by the growth and development of the head and neck structures along a temporal continuum spanning from the neonatal period through to the end of adolescence.[1] Patency of the upper airway during sleep is controlled by complex interactions between upper airway resistance, pharyngeal collapsibility, the tone of the pharyngeal dilator muscles, and negative intra-lumenal pressure generated by the muscles of respiration.[2]

Sleep-disordered breathing (SDB) in children is clinically characterised by snoring and physiologically, by increased upper airway resistance, partial upper airway obstruction, or complete obstruction which disrupts ventilation, oxygenation, and sleep quality.[3] In this review, a focus has been placed on paediatric SDB due to upper airway obstruction. Paediatric SDB is a continuum which ranges from primary snoring (PS) which is not associated with gas exchange abnormalities or significant sleep fragmentation, through to upper airway resistance syndrome, characterised by repeated arousals and sleep fragmentation to obstructive sleep apnoea (OSA) with complete upper airway obstruction, hypoxaemia, and obstructive hypoventilation. PS is currently defined by the observation of audible sonorous noises occurring more than three times per week without evidence of apnoea, hypoventilation or significant sleep fragmentation.[4] The prevalence of snoring ranges from 3.2 - 35% with most authors reporting a prevalence of 10% for PS, while the prevalence of paediatric OSA ranges from 1% - 5%.[5-12] Paediatric SDB is most frequently encountered between 2 - 8 years of age which corresponds to the age range of greatest enlargement of upper airway lymphoid tissue relative to craniofacial size.[3,7,10,13-15] Paediatric OSA is more prevalent in some races as an increased incidence is found in African-American and Asian children, children with respiratory disease such as allergic rhinitis and asthma, obese children and children with a family history of OSA.[1,15]

The spectrum of SDB in children is gaining increased recognition as all levels of severity have been associated with deleterious health implications if not recognised and treated.[3,16,17] The domains affected include quality of life,[18] behaviour,[10] neurocognition[19] and cardiovascular changes.[20] Despite the significant morbidity associated with SDB in children it is often not recognised in clinical practice. A previous study reported that approximately 80% of symptomatic habitual snorers are not reported to their general

medical practitioners.[21] In addition, there is a 226% (2.3 fold) increase in health care utilisation among children with OSA when compared with unaffected individuals.[22] Hence, early diagnosis and intervention would be beneficial and cost-effective.

Predisposing factors for paediatric OSA

Similar to adults, there is no single cause of paediatric SDB and it is believed to be due to a complex interaction of neuromuscular, inflammatory and anatomic factors.[23-25]

Adenotonsillar hypertrophy

Paediatric SDB is most commonly associated with tonsillar and adenoidal hypertrophy.[26] While lymphatic tissue normally shrinks in volume after the age of ten,[27] the hypertrophic tonsillar and adenoid tissue might be so large that normal tissue reduction is insufficient to remove the obstruction.[25] The relative enlargement of lymphoid tissue can create a narrower airway which increases the likelihood of breathing resistance and the chance of airway collapse. The critical relationship is the size of the hypertrophied tonsils and adenoids relative to the size of the upper airway.[1] On careful inspection, two children with the same size tonsils may have different levels of obstruction depending on upper airway size during sleep.

Obesity

The prevalence of childhood obesity has tripled in the last 25 years and is presently estimated to be 18%.[28] Redline et al.[15] have found obesity to be a significant risk factor for OSA in children and adolescents (odds ratio = 4.59; 95%, confidence interval 1.58 to 13.33). This factor is important as it is now recognised that, even after SDB has been treated by adenotonsillectomy, there is a significant risk of ongoing obstruction.

Craniofacial anomalies

Craniofacial anomalies result from altered genetic expression, or from environmental insults or both.[29] Children and adolescents seeking orthodontic treatment might present with variable craniofacial disharmony. Children with long faces and retrognathic mandibles have been shown to have increased SDB and OSA symptoms.[17,30,31] In the transverse plane, maxillary constriction is a sign of reduced transverse dimension of the upper airways and an indirect measure of increased nasal resistance.[32]

A screening facial and dental examination in the general paediatric orthodontic population can reveal highly positive associations between parentally-reported paediatric SDB symptoms and long-face characteristics, a narrow palate and severe maxillary crowding.[31] However, antero-posterior deficiency, overjet and retrognathia as recorded by clinical examination is not highly associated with many reported SDB symptoms.[31]

Two recent meta-analyses suggest that sagittal and vertical craniofacial associations measured on a lateral cephalogram, might have low clinical significance in predicting childhood SDB, due to small differences between subjects and a control group.[33,34] Despite the limitations and inherent projection errors, the cephalometric radiograph remains a valid method for measuring dimensions of nasopharyngeal and retropalatal regions which correlates well with three-dimensional magnetic resonance imaging.[35] In addition, volumetric analyses of the lower facial skeleton measured by magnetic resonance imaging show no skeletal difference between non-syndromic children diagnosed with OSA and controls, although the soft palate is larger in children with OSA.[36,37]

A comprehensive analysis of the facial skeleton and occlusion requires an understanding of the upper airway. The three-dimensional airway has been shown to have a relationship with facial morphology and skeletal malocclusions. Grauer et al. have reported that skeletal Class II malocclusions show a smaller inferior compartment airway volume compared with Class I or Class III patients, but no correlation of airway volume with vertical facial types has been identified.[38] Additional studies have found no volume difference at various sites in the airway but found total airway volume in Class II malocclusion patients is smaller than in Class I patients.[39,40] Children with a Class III malocclusion show a larger and flatter oropharyngeal airway when compared with Class I children.[41] Whether these differences in airway shape and volume predispose an individual to SDB is not well understood.

Other factors

Any syndrome or disorder which affects upper airway structure, airway muscle tone, upper airway muscle control or sleep might predispose to OSA in children.[1]

Clinical symptoms

Daytime symptoms of SDB might be associated with a wide variety of symptoms.[19,42-48] Affected children can present with behavioural and discipline problems, neurocognitive deficits such as poor learning, impaired cognitive performance, memory and attention

deficits and are more likely to be diagnosed with attention deficit hyperactivity disorder (ADHD).[19,46,47,49] Other symptoms might manifest as morning headaches and mouth breathing.[50] Severe paediatric OSA has been associated with a failure to thrive, hypertension, insulin resistance and lipid dysregulation.[4]

Snoring is the most common night-time symptom of SDB in children.[3] Other night-time symptoms that might be noted are restless sleep, frequent arousals, snorting, gasping, unusual sleeping positions, sweating during sleep and nocturnal enuresis.[11,51]

Complications of paediatric SDB

Behavioural and neurocognitive deficits

Children with SDB show reduced attention capability, hyperactivity, increased aggression, irritability, emotional and peer problems and somatic complaints.[10,43,47,49,50] Neurocognitive deficits include a reduction in memory and intelligence.[46,50] A current challenge in this field is the determination of the severity of upper airway obstruction that results in neurocognitive sequelae. In addition, the recognition of more vulnerable periods in a young child's development when SDB may have a more injurious effect, would be beneficial. Gozal and Pope[52] have shown that 13-year-old children with low academic performance are more likely to snore during early childhood and have surgery for SDB compared with children with high academic performance, thereby suggesting that snoring in early childhood may have long term deleterious effects. Whether this restricts the affected children's future academic or occupational success is largely unknown.

Cardiovascular complications

Children with PS and OSA have been shown to have higher diastolic blood pressure compared with non-snoring children.[1,53] Increased blood pressure in childhood is predictive of hypertension in adulthood.[23] However, it is uncertain whether pressure changes are a precursor to cardiovascular disease. Potential mechanisms of OSA-mediated cardiovascular morbidity are similar in children and adults.[20] Factors such as hypoxia, oxidative stress, inflammation, endothelial dysfunction and sympathetic activation have been implicated in paediatric OSA.[20]

Growth

Severe OSA might result in failure to thrive although this is now not as common due to rising prevalence of obesity.[54] This is thought to reflect disruption of the normal growth hormone regulation during sleep and increased energy requirements of obstructed breathing. Not surprisingly, some children with SDB demonstrate increased growth velocity after adenotonsillectomy.[54,55] It is currently controversial whether craniofacial growth normalises post adenotonsillectomy.[56,57]

Quality of Life (QOL)

QOL is increasingly recognised as an important health outcome in medicine and dentistry. It reflects the World Health Organisation's definition of health as 'the state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity.' The impact of paediatric SDB extends beyond sleep parameters to affect children's behaviour, functioning and family life.[58] A complex relationship exists between paediatric OSA, behaviour and QOL, which highlights that children with OSA have poorer health status than unaffected children.[18]

Mortality

Death during sleep in children suffering from SDB is considered rare, and most deaths are believed to be peri-operative after adenotonsillectomy.[3] Children with unrecognised OSA and a compromised cardiovascular system might decompensate during general anaesthesia.[59,60]

Diagnosis of paediatric SDB

Since snoring is the cardinal symptom of paediatric SDB, screening for snoring has been recommended as part of routine health-care visits by the American Academy of Pediatrics (AAP).[61] However, history and clinical examination can be poor predictors of OSA with an overall predictive value of 55.8%.[62]

Role of polysomnography (PSG)

The 2012 AAP technical report for *Diagnosis and Management of Childhood Obstructive Sleep Apnoea* states that nocturnal, attended, laboratory PSG is considered the gold standard for diagnosis of OSA because it provides an objective, quantitative

evaluation of disturbances in respiratory and sleep patterns.[12] It allows an estimation of the severity of the disease and, therefore, provides a prediction for the risk of postoperative complications in children undergoing adenotonsillectomy.[1] Paradoxically, less than 10% of snoring children referred for adenotonsillectomy undergo an overnight PSG.[63] This could be due to its expense, the time required and reduced availability in some health care settings.

PSG measures the Apnoea-Hypopnoea Index (AHI) as well as other sleep-breathing measures. AHI is the number of apnoeic events (obstructive, central and mixed) plus hypopnoeas per hour of sleep. This is also referred to as the Respiratory Distress Index (RDI). An AHI greater than 1 event per hour is considered to be abnormal in children while 5 events per hour is the current level for considering operative intervention with adenotonsillectomy.[64] The correlation of PSG indices with daytime sleepiness, hyperactivity, and neurocognitive function measured objectively, is generally poor,[65] however, it does give clear indications of the child's respiratory status.

Role of questionnaires

Questionnaires have been developed to aid in the identification of children with SDB.[66] The questionnaires help standardise history taking and are a valuable tool in epidemiologic research but they ultimately rely on parental recording. The commonly used and validated 22-item Paediatric Sleep Questionnaire (PSQ) used in screening children has reasonable sensitivity (0.85) and specificity (0.87)[67] to predict the risk of SDB when compared witha PSG.[66]

A health-related quality of life (QOL) survey focuses on the physical problems, functional limitations and emotional consequences of a disease. Several disease-specific QOL instruments such as the validated OSA-18[68] have been developed for children with OSA. The OSA-18 is the most widely used QOL questionnaire for paediatric OSA and has been validated as a discriminative and worthy evaluative instrument. The correlation between OSA-18 scores and RDI is fair (r = 0.43).[68,69] The fair correlation may be explained by the reliance of PSG on physiological sleep parameters whereas the OSA-18 relies on caregiver concerns.

Role of lateral cephalometric radiographs

The lateral cephalogram is recommended as a screening radiograph and is a valid method for measuring dimensions of the nasopharyngeal and retropalatal region. The cephalogram correlates well with three-dimensional magnetic resonance imaging.[35] It has the added advantage of providing a means of evaluating craniofacial morphology in the sagittal and vertical plane.

Treatment modalities for paediatric SDB

Adenotonsillectomy

As adenotonsillar hypertrophy is commonly associated with SDB in children, adenotonsillectomy is the recommended first line of treatment.[61] The correlation between the severity of apnoea and adenotonsillar size is variable but not surprising given the size of the upper airway is the other determinant.[37,70] However, the use of this surgical treatment option for those with PS, remains controversial.[71] A meta-analysis of published research[72] suggests that the procedure is effective in curing 75% of paediatric OSA cases. However, several large and more recent meta-analyses have reported that complete normalisation of PSG results might occur in only 25 - 60% of treated children.[73-76] Cephalometric abnormalities and obesity account for persistent snoring and upper airway obstruction in adolescents who have undergone adenotonsillectomy for upper airway obstruction.[75,77]

It should be noted that the prevalence of paediatric SDB may change with time. Marcus et al.[78] (CHAT study) reported the normalisation of PSG scores in nearly 47% of OSA-affected children randomised to watchful waiting for 7 months, in comparison with an adenotonsillectomy-surgery group. This might have been due to growth enlargement of the airway, regression of lymphoid tissue or routine medical care, and highlights the change in the disease symptoms over time. However, there is a lack of long-term studies. Even though complete resolution is not always achieved, adenotonsillectomy has been found to improve several other sequelae of SDB such as quality of life,[18] behaviour[19] and neurocognition.[19] However, adenotonsillectomy as a surgical procedure carries risks such as haemorrhage, respiratory decompensation, anaesthetic complications and in rare cases, death.[71]

Nasal Continuous Positive Airway Pressure (CPAP)

Nasal CPAP is second-line therapy for paediatric OSA if adenotonsillectomy cannot be performed or if there is residual OSA post-surgery.[61] The distinct advantage of CPAP is its non-surgical nature. The disadvantages of CPAP treatment relate to the patient's inability to acclimatise and accept the device. Additionally, there is emerging evidence of mid-face hypoplasia and other craniofacial side effects in children using CPAP.[79,80]

Supplemental medical treatment

Additional treatments include the use of oral leukotriene-receptor antagonists, anti-inflammatory drugs and the application of nasal corticosteroids.[3] These treatments can be effective in mild or residual cases.

Surgery

Surgical treatment options in complicated OSA can include uvulopaltopharygoplasty (UPPP), distraction osteogenesis, and mandibular or maxillary advancement procedures.[25,45] These are utilised in specific circumstances, particularly in syndromal children.

Dentofacial orthopaedics and orthodontic treatment

A variety of oral appliances provide potential additional treatment alternatives for paediatric SDB. Oral appliances might help improve upper airway patency during sleep by enlarging the upper airway and/or decreasing upper airway collapsibility, thereby enhancing upper airway muscle tone.[81] Rapid maxillary expansion (RME), mandibular advancement to attempt growth modification in patients with a Class II dentofacial relationship and maxillary advancement in Class III SDB patients, could be effective.[82,83]

Several publications provide direct evidence of the positive effects of RME in children diagnosed with OSA.[84-87] Palmisano et al.[87] have reported on 10 'young' patients (range 14–37 years old) in which 9 patients improved with 7 brought into the normal range. One patient showed no improvement. Obvious weaknesses of the study include a small sample size (N = 10), a variation in the expansion techniques applied (six surgical expansions, four non-surgical), affected patients had only mild to moderate sleep apnoea and the study included adolescent and adult patients. Pirelli et al.[84] have addressed several of the limitations by investigating expansion in 31 children with a mean age of 8.7 years and a

mean pretreatment AHI of 12.2. The experimental group was stratified into three categories; AHI of 5–10, 10–15 and 15+ with the largest group in the 10–15 range. Immediately following expansion (mean expansion was 4.32 mm), 29 of the 31 patients had an AHI of less than 5. At review (6–12 months post-expansion), all patients had an AHI less than 1 and were therefore considered within the normal range. The final improvement might have been a result of expansion appliance removal, which allowed the tongue additional space. Villa et al.[86] have conducted a prospective examination of 16 patients (mean age 6.9 years; range 4.5–10.5) a year following the RME. The study aimed to examine the effect of expansion and also correlate the size of the tonsils. While 2 patients were lost to follow-up, AHI improved from a mean of 5.8 at the start to a mean of 2.7 at 6-month follow-up. The final AHI was 1.5 at 12-month follow-up, even with the presence of enlarged tonsils in 11 of the 14 patients. The result has demonstrated that expansion can produce significant improvement in OSA. For the small group of patients who did not reach an acceptable AHI level, the residual OSA may have been better treated by adenotonsillectomy following expansion. It remains to be determined whether children with PS benefit as well as children with OSA with the RME treatment.

Biobloc therapy, to enhance maxilla-mandibular horizontal projection and posterior airway space, has been reported to produce a 31% increase in the nasopharyngeal area, a 23% increase in the oropharyngeal area and a 9% increase in the hypopharyngeal area.[88] However, the participants were not assessed for SDB and the study failed to recruit control subjects. To date, only one randomised trial assessing sagittal growth modification in a paediatric OSA population has been published.[89] The treated adolescent patients wore the mandibular advancement appliance full time (except when eating) in an attempt to treat the OSA and the deficient mandibular growth. All patients improved and the mean AHI reduced from a pre-treatment value of 7.1 to a post-treatment level of 2.6. Using the low threshold for success of a 50% decrease in AHI, the majority of patients (64%) were successfully treated. Using the more stringent level of success of normalising the AHI, only 50% of patients were successfully treated. However, the effect of relapse was not explored.

Evidence for Class III growth modification by maxillary advancement is indirect, weak and some benefits may be due to the RME phase of the treatment.[24] Encouraging reports of enhanced protraction with skeletal anchorage have been published, which may see benefits greater than those previously reported.[90] A recent randomised clinical trial, with 3

years follow-up, has shown that 70% of children treated with a protraction face mask retain favourable changes to their maxillary and mandibular bases, which suggests that changes may be retained in the longer-term.[91] Further studies are required to evaluate the effects of maxillary advancement upon the upper airway.

A Cochrane database systematic review of data in the literature until 2005 has found that evidence is not sufficient to state that oral appliances or functional orthopaedic appliances are effective in the treatment of OSA in children.[92] However, the authors have concluded that oral appliances or functional orthopaedic appliances may be helpful in the treatment of children with craniofacial anomalies that represent risk factors for apnoea.

Oropharyngeal exercises (Myofunctional therapy)

Derived from speech therapy, the role of myofunctional training in treating paediatric SDB is unclear. It may be an effective treatment option in promoting correct oral breathing patterns,[82] however, its efficacy and cost-effectiveness is yet to be proven in controlled studies.

Multi-therapies in paediatric SDB

Multi-therapies might act synergistically in treating paediatric SDB. In snoring and mild OSA cases without obesity (AHI > 1 < 5), Villa et al.[82] have proposed orthodontic treatment in conjunction with medical and myofunctional therapy. In non-obese OSA cases with AHI > 5, adenotonsillectomy, along with orthodontic treatment with or without myofunctional therapy, should be considered.[82] Kaditis et al.[93] have proposed a stepwise treatment approach which starts with weight control and is followed by nasal corticosteroids, adenotonsillectomy surgery, orthodontic devices, CPAP and, finally, craniofacial surgery or tracheostomy in severe cases.

Conclusions

1. All children should be screened for snoring and signs of upper airway obstruction at a first consultation.
2. Craniofacial disharmony might be an important predisposing factor in the development and progression of paediatric SDB but remains poorly understood and controversial.
3. Adenotonsillectomy is the recommended first line treatment of OSA in children.

4. Although dentofacial orthopaedics is one therapeutic option in the management of paediatric SDB, there are insufficient long-term data on its efficacy. Further studies are indicated to define the patients who may benefit most from orthodontic intervention.
5. A greater degree of collaboration between sleep medicine, ear, nose and throat specialists and orthodontists is required to establish individualised approaches for successful treatment.
6. There is currently no consensus on the best method of multi-therapy management for paediatric SDB. Therefore, there is an urgent need to research and establish effective protocols and delineate the relative contributions of each therapy.

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Paper 2: Craniofacial and Upper Airway Morphology in Paediatric Sleep Disordered Breathing (SDB)- A Systematic Review and Meta-analysis

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ABSTRACT

Objectives: Paediatric sleep–disordered breathing (SDB) is a continuum, with primary snoring (PS) at one end and complete upper airway obstruction, hypoxemia and obstructive hypoventilation on the other. The latter end gives rise to obstructive sleep apnoea (OSA). An important predisposing factor in the development and progression of paediatric SDB may be craniofacial disharmony. This study is a systematic review of the published literature with the results of the primary studies combined by meta-analyses in order to elucidate the nature of the association between craniofacial disharmony and paediatric SDB. ***Methods:*** Citations to potentially relevant published trials were located by searching Pubmed, Embase, Scopus and Cochrane Central Register of Controlled Trials. An effort to identify potentially relevant unpublished trials was made by searching the metaRegister of controlled trials database. Additionally, hand searching, Google Scholar searches and contact with experts in the area were undertaken to identify potentially relevant published and unpublished studies. Inclusion criteria were 1) randomised controlled trials (RCT), case–control trials or cohort studies with controls; 2) studies in non–syndromic children 0 – 18 years of age with a diagnosis of SDB or OSA by either a sleep disorders unit, screening questionnaires or polysomnography (PSG); and 3) with principal outcome measures of craniofacial and/or upper airway dimensions or proportions with various modalities of imaging for the craniofacial and neck region. The quality of the studies selected was evaluated by assessing their methodology. Treatment effects were combined by meta–analyses using the random effects method. ***Results:*** Children with OSA and PS show an increased weighted mean difference (WMD) in ANB angle of 1.64° (95% CI 0.88 – 2.41, $p < 0.0001$) and 1.54° (95% CI 0.89 – 2.20, $p < 0.00001$), respectively in comparison to the controls. Increased ANB was primarily due to a decreased SNB angle in children with PS by 1.4° (95% CI -2.58 to -0.23, $p = 0.02$). Children with OSA had a PNS–AD1 distance reduced by 4.17 mm (WMD) (95% CI -5.85 to -2.50, $p < 0.00001$) and a PNS–AD2 distance reduced by 3.12 mm (WMD) (95% CI -4.56 to -1.67, $p < 0.0001$) in comparison to the controls. ***Conclusion:*** There is statistical support for an association between craniofacial disharmony and paediatric SDB. However, an increased ANB angle of <2° in children with OSA and PS, in comparison to the controls, could be regarded as of marginal significance. Therefore evidence for a direct causal relationship between craniofacial structure and paediatric SDB is unsupported by this meta–analysis. There is strong support of a reduced upper airway width in children in OSA as shown by reduced PNS–AD1 and PNS–AD2 distance. Where there is a clinical diagnosis of craniofacial

jaw discrepancy in children suffering from paediatric SDB there is sufficient published literature to suggest dentofacial orthopaedic and orthodontic treatment may serve as an adjunctive treatment to primary treatment of OSA and PS in children. A multidisciplinary approach to management of paediatric SDB is recommended.

INTRODUCTION

Sleep–disordered breathing (SDB) is a disorder of breathing during sleep characterised by prolonged increased upper airway resistance, partial upper airway obstruction, or complete obstruction that disrupts pulmonary ventilation, oxygenation or sleep quality.[1] Paediatric SDB is a continuum, with primary snoring (PS) at one end and complete upper airway obstruction, hypoxemia and obstructive hypoventilation at the other giving rise to obstructive sleep apnoea (OSA).[1]

Sleep–disordered breathing is associated with a wide variety of symptoms in children.[2-8] Snoring is the most common night–time symptom of SDB in children.[1] Chronic snoring, although common in adults, is considered abnormal in a paediatric population.[7] Other symptoms associated with SDB may include restless sleep, frequent arousals, snorting, gasping, unusual sleeping positions (e.g. sitting), sweating during sleep and nocturnal enuresis.[2-8] The most prominent day–time symptom of SDB in adults is excessive daytime sleepiness[9] which is absent in most children with polysomnography–proven OSA.[10] Sleep–disordered breathing in children is also associated with behavioural and impaired cognitive or school performance.[6,11,12]

The current view is that adenotonsillar hypertrophy is the major cause of SDB in otherwise normally healthy children.[13] Adenotonsillar hypertrophy results in upper airway narrowing and when superimposed with other factors (e.g. reduced muscle tone) can lead to a clinically significant dynamic airway obstruction during sleep.[13] Adenotonsillectomy (T&A) is therefore often the first line of treatment for paediatric SDB and is deemed curative in approximately 25-75% of cases.[14-18] Nasal continuous positive airway pressure (CPAP) is often the next course of treatment but there is emerging evidence of mid-face hypoplasia and other craniofacial side effects in children with the use of this approach.[19,20] There is currently no consensus on the best method of managing of OSA in childhood.[21] Kaditis et al. propose a stepwise approach to treatment which starts with weight control and is followed by nasal corticosteroids, T&A surgery, orthodontic devices, CPAP and finally craniofacial surgery or tracheostomy in severe cases.[21]

Craniofacial disharmony may also be an important predisposing factor in the development and progression of paediatric sleep–disordered breathing (SDB). Studies in non–syndromic children have shown a positive association between craniofacial disharmony and paediatric SDB.[22-25] Other contradictory studies however do not report such associations.[26,27] There is also a lack of a systematic review in the literature of the

association between craniofacial and upper airway morphology in paediatric sleep–disordered breathing (SDB).

This aim of this study is to conduct a systematic review of the published and unpublished literature. A further aim is that the results of the primary studies will be combined by meta–analyses in order to statistically elucidate the nature of the association between craniofacial disharmony and paediatric SDB. This will aid clinicians by increasing the diagnostic sensitivity of SDB and may provide suggestions for alternative treatments for the children suffering from SDB.

METHODS

Literature Searching

Citations to potentially relevant trials published in journals and dissertations were located by searching the appropriate databases (Pubmed, Embase, Scopus and Cochrane Central Register of Controlled Trials). An effort to identify potentially relevant unpublished or ongoing trials was made by searching the metaRegister of controlled trials database. Additionally, hand searching, Google Scholar searches and contact with experts in the area were undertaken to identify potentially relevant published and unpublished studies. The references cited in relevant review articles were also checked. The search date was 27th December 2011 across all databases and the search was updated monthly for Pubmed and Scopus until April 2012. Appendix Table I shows the search strategy for this systematic review with a list of keywords used in the search.

Selection of Studies

Inclusion criteria were limited to: 1) randomised controlled trials (RCT), case–control trials or cohort studies; 2) studies in non–syndromic children 0 – 18 years of age with a diagnosis of SDB or OSA by either a sleep disorders unit, screening questionnaires or polysomnography (PSG); and 3) studies with principal outcome measures of craniofacial and/or upper airway dimensions or proportions with various modalities of imaging for the craniofacial and neck region. Study selection criteria are given in Table I.

Table I. Study selection criteria

Criteria	Definition
Study characteristics	The studies should be prospective or retrospective in design. Included study design will be: RCT, case–control trials or cohort studies with controls.
Patient characteristics	Non-syndromic children of 0 – 18 years of age with a diagnosis of SDB, PS or OSA by either a Sleep Disorders Unit, screening questionnaires or a PSG. Studies in medically compromised patients and those studying craniofacial syndromes will be excluded.
Study method characteristics	Studies with various modalities of imaging for the craniofacial and neck region in children will be included.
Outcome characteristics	Trials reporting outcome measures as below: • Craniofacial dimensions and/or morphology • Upper airway dimensions and/or morphology

Data Abstraction and Study Characteristics

The primary author (VK) independently reviewed titles and the abstracts of all identified citations. Any studies not fulfilling the inclusion criteria were excluded from further evaluation, and the full articles were retrieved for those meeting the criteria. Primary author (VK) and a co–author (CD) independently reviewed the retrieved full text articles.

Data abstraction was performed independently by the two authors (VK and CD) in Microsoft Excel which included year of publication, demographic details of patients, details of study design, participant's characteristics, method of SDB diagnosis, measurement tool, study quality assessment, and statistical details. Any disagreements were resolved by discussion and mutual agreement between the two authors. Angular variables were recorded in degrees (± standard deviations) and linear variables were recorded in mm (± standard deviations).

Statistical Analyses

Revman v5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) was used for statistical analyses. The data categories common amongst studies were used for the

pooled analysis. Due to the anticipated variability in included trials, a random effects model was chosen. To identify heterogeneity, the overlap of the 95% CI for the results of individual studies was inspected graphically, and the Cochran test for homogeneity and the I^2 test were calculated to check for heterogeneity and inconsistency, respectively.

Forest plots to calculate the weighted mean difference (WMD) were generated for the following cephalometric variables (Figure 1) in children with OSA: 1) SNA angle (angle between Sella, Nasion & A–point), 2) SNB angle (angle between Sella, Nasion & B–point), 3) ANB angle (difference of SNA & SNB angles), 4) SN–MP angle (angle made by Sella–Nasion plane to mandibular plane), 5) PP–MP angle (angle made by palatal plane extending from ANS–PNS to mandibular plane), 6) IMPA (angulation of lower incisor to mandibular plane), 7) BaSN angle (angle formed between Basion, Nasion & Sella), 8) PNS–AD1 (distance from Posterior Nasal Spine to nearest adenoid tissue measured along the line PNS–Basion) and 9) PNS–AD2 (distance from Posterior Nasal Spine to nearest adenoid tissue measured along the line perpendicular to Sella–Basion). For children with primary snoring the analysis was pooled for SNA, SNB, ANB and BaSN angles due to limited data availability from the included primary studies.

Planned subgroup analyses were based on age, gender, body mass index (BMI) and apnoea–hypopnoea index (AHI).

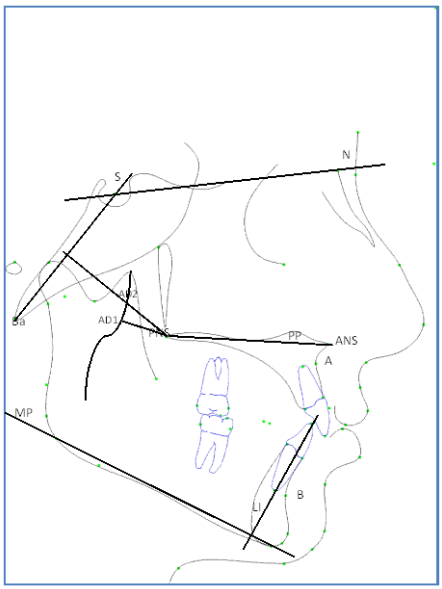


Figure 1. Cephalometric references and landmarks used in the meta–analysis

Key: S=Sella, N=Nasion, Ba=Basion, ANS=Anterior Nasal Spine, PNS=Posterior Nasal Spine, PP=Palatal Plane, A=A Point, B=B Point, MP=Mandibular Plane (Gonion─Menton), PNS─AD1=Distance from Posterior Nasal Spine to nearest adenoid tissue measured along the line PNS─Ba, PNS─AD2 =Distance from Posterior Nasal Spine to nearest adenoid tissue measured along the line perpendicular to S─Ba and LI=Long Axis of Lower Incisor.

Validity Assessment

The quality of the studies selected was evaluated by assessing their methodology. The assessment criteria were those from the Centre for Reviews and Disseminations in York, United Kingdom.[28] These are presented in Table II.

Table II. Criteria for Study Appraisal

Strong Evidence (S)	Moderately Strong Evidence (M)	Limited Evidence (L)
• Randomised controlled trial, prospective studies/ large study samples • Well–defined and adequate control group • Clearly defined and clinically relevant variables • Low dropout rate • Relevant statistical analysis	• Prospective study, cohort, controlled clinical trial, or well–defined retrospective study with large study group • Clearly defined and clinically relevant variables • Low dropout rate • Relevant statistical analysis	• Cross–sectional study • Clinically inadequate result variables • High dropout rate • No control group of its own in the study • Limited/no statistical analysis • Addressing the issue in question only in part

RESULTS

No restrictions were placed on year of publication. Restrictions were placed on the age of participants and language. The initial search revealed 875 citations across the four databases. Fourteen citations were in a foreign language and were excluded from this review. The search process is presented in Figure 2. The characteristics of the 9 included trials[27,29-36] including their methodological quality are summarised in Table III. Only 2 included trials reported blinding of observers to the diagnosis of children during data collection.[32,33]

Children with OSA and PS show an increased WMD in ANB angle of 1.64° ($p < 0.0001$) and 1.54° ($p < 0.00001$), respectively, in comparison to the controls (Figure 3 and Figure 4). Increased ANB was primarily due to a decreased SNB angle in children with PS by WMD of 1.4° ($p = 0.02$) (Figure 5). Children with OSA had a PNS–AD1 distance reduced by 4.17 mm (WMD) ($p < 0.00001$) and a PNS–AD2 distance reduced by 3.12 mm (WMD) ($p < 0.0001$) in comparison to the controls (Figure 6 and Figure 7).

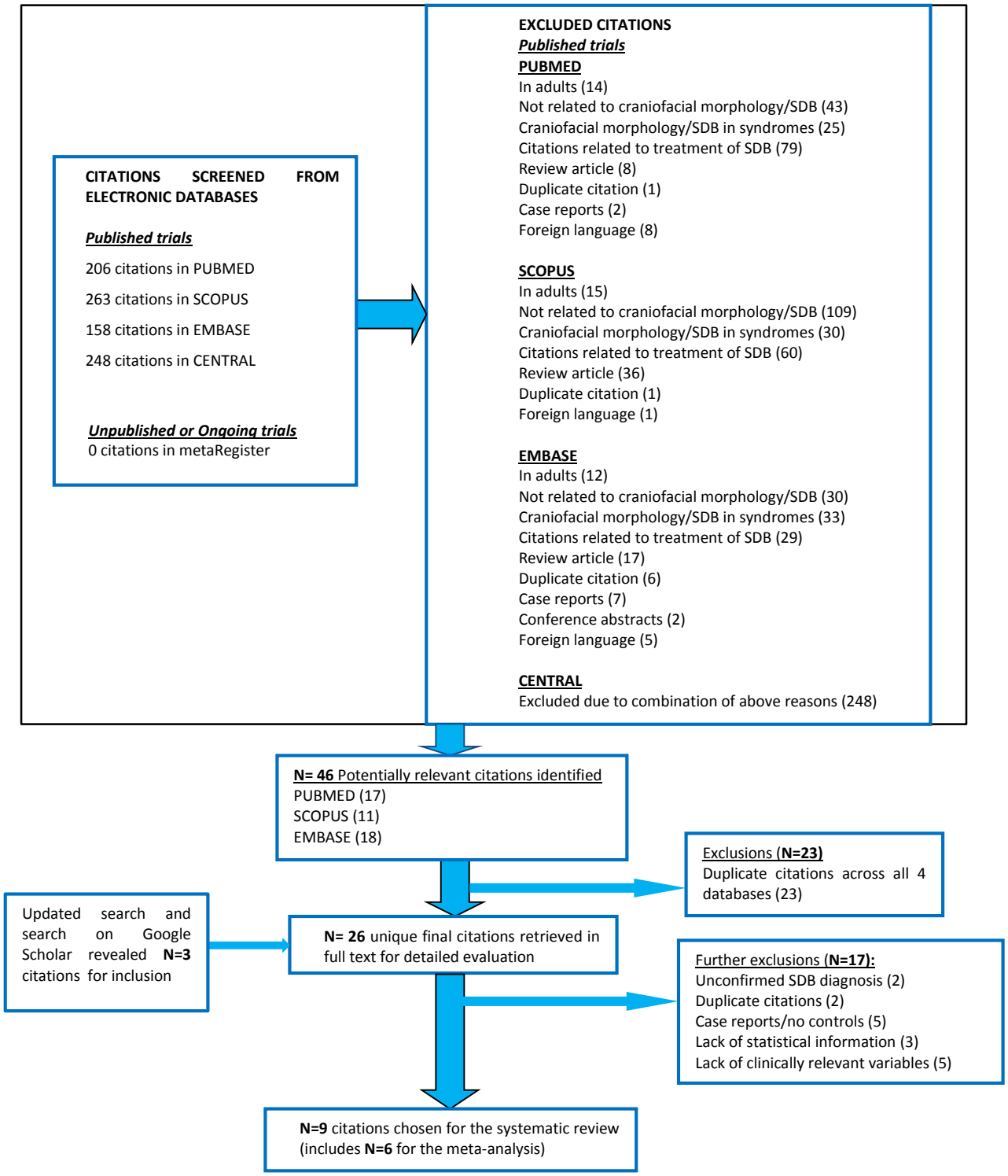


Figure 1. Flowchart of the search process

Table III. Characteristics of included studies

Study		Banabilh et al. 2008	Cozza et al. 2004	Deng et al. 2012	Lofstrand-Tidestrom et al. 1999	Pirila-Parkkinen et al. 2009	Pirila-Parkkinen et al. 2010	Schiffman et al. 2004	Zettergren-Wijk et al. 2006	Zucconi et al. 1999
Design & Participant Characteristics										
Design		Prospective case-control	Prospective case-control	Prospective case-control	Prospective cohort	Prospective case-control	Prospective case-control	Prospective case-control	Prospective case-control	Prospective case-control
Total number of subjects		60 (30 snorers & 30 controls)	40 (20 OSA & 20 controls)	30 (15 OSA & 15 controls)	21 obstructed cases & 40 controls for cephalometric exam. 22 obstructed cases & 48 controls for study model exam.	123 (41 OSA, 41 snorers & 41 controls)	140 (70 cases & 70 controls). Cases- 26 OSA, 27 snorers	48 (24 OSA & 24 controls)	34 (17 OSA & 17 controls)	52 (26 OSA & 26 controls)
Mean Age (yrs) ± SD or range (yrs) P=Participants, C=Controls, O=OSA, S=Snorer	P	9.5 ± 2.47	5.91 ± 1.14	9.5 ± 1.0	4.52 ± 0.37	(O) 7.2 ± 1.93 (S) 7.2 ± 1.79	(O) 7.7 ± 1.91 (S) 7.3 ± 1.61	4.9 ± 1.7	5.6 ± 1.34	4.6 ± 1.5
	C	10.47 ± 2.28	6.00 ± 0.71	9.6 ± 1.8	4.58 ± 0.25	7.2 ± 1.90	7.3 ± 1.78	4.9 ± 1.8	5.8 ± 1.40	5.1 ± 0.5
Gender distribution of subjects (Males / Females)	P	16 M / 14F	10 M / 10 F	11 M/ 4 F	–	(O) 22 M / 19 F (S) 22 M / 19 F	(O) 14 M / 12 F (S) 9 M / 18 F	14 M / 10 F	10 M / 7 F	–
	C	21 M / 9 F	10 M / 10 F	11 M/ 4 F	20 M / 20 F	22 M / 19 F	34 M / 36 F	14 M / 10 F	10 M / 7 F	
BMI distribution of participants	P	21.22 ± 3.12	16.02 ± 3.40	–	–	–	(O) 16.6 ± 3.46 (S) 16.8 ± 2.52	Ht: 109 ± 13 Wt: 19.8 ± 5.7	–	–
	C	21.42 ± 2.98	20.98 ± 0.48				16.6 ± 2.23	Ht: 108 ± 13 Wt: 20.1 ± 5.5		
Controls matched for age & gender		No	Yes	Yes	Age-matched	Yes	Yes	Yes	Yes	Age-matched
Methods Used										
Method of SDB Diagnosis		Berlin questionnaire for cases & controls	Overnight PSG and Epsworth sleepiness scale in cases only	PSG for cases and controls.	PSG for cases. Historical controls (cephalometrics). Controls from cohort study (study models).	Overnight PSG for OSA cases and snorers only. Controls selected by exam & parental reported history.	Overnight PSG for cases only. Controls selected by exam & parental reported history.	Overnight PSG in cases and 12 controls. Brouillette sleep questionnaire for control selection.	Overnight PSG in cases. 11 controls had ENT exam. 6 controls from growth study.	Validated sleep questionnaire for all cases & controls. Diurnal PSG for cases.
Measurement Tool NHP=Natural head position		Cephalogram	Cepahlogram & dental models (width between centroids-Moyers method)	Cephalogram in NHP. Magnification corrected for.	Cephalogram in NHP & dental models.	Dental models (width between ML cusps-Moorrees method)	Cephalogram in NHP Magnification =5%	MRI under IV sedation	Cephalogram	Cephalogram in NHP. Magnification corrected for.
Error of the Method N.S.=Not significant		N.S.	N.S.	0.5° / 0.5 mm	<1.1° / 0 .6 mm	N.S.	N.S.	N.S.	N.S.	N.S.
Study Quality Appraisal										
Evidence Level		L	M	M	M	M	M	M	M	L
Comment		Diagnosis by parental report	Apnoea=10 secs OSA: AHI >1	OSA: AHI>1. Bonferroni corection for statistics.	Cases were not subdivided as snorers & OSA. Results discluded from meta-analyses.	Apnoea=10 secs OSA: AHI >1	Apnoea=10 secs OSA: AHI >1	Apnoea=Absence of oro-nasal thermistor signal for 2 respiratory cycles.	OSA:AHI>1. Bonferroni corection for statistics.	Apnoea=10 secs OSA: AHI >1

The WMD in SNA angle, SNB angle, SN–MP angle, PP–MP angle, IMPA and BaSN angle for children with OSA in comparison to the controls, are presented in Appendix Figure 1-6, respectively. The WMD in SNA angle and BaSN angle for children with PS in comparison to controls are presented in Appendix Figure 7 and Appendix Figure 8, respectively.

The pooled cephalometric variables in children with OSA and PS are summarised in Table IV and Table V, respectively. There was significant heterogeneity for the variables SN–MP ($p = 0.04$) and PP–MP ($p < 0.00001$) in children with OSA. The increased WMD in SN–MP angle of 2.74° ($p = 0.006$) may indicate a trend toward increased lower anterior face height

in paediatric OSA. However this result must be interpreted with caution due to the borderline heterogeneity.

Subgroup analyses that were planned were not completed due to limited data availability from the included studies.

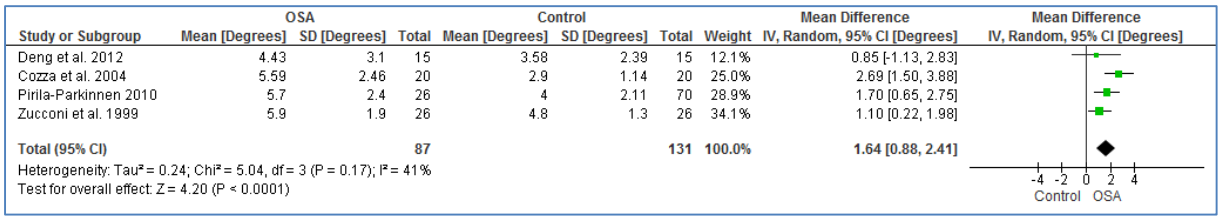


Figure 3. Pooled weighted mean difference in ANB angle between children with obstructive sleep apnoea (OSA) and controls

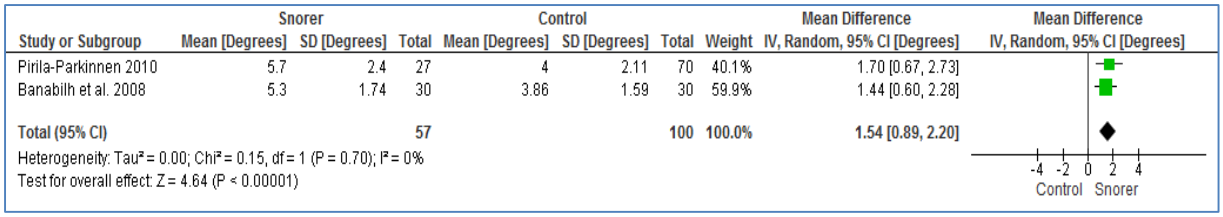


Figure 4. Pooled weighted mean difference in ANB angle between children with primary snoring (PS) and controls

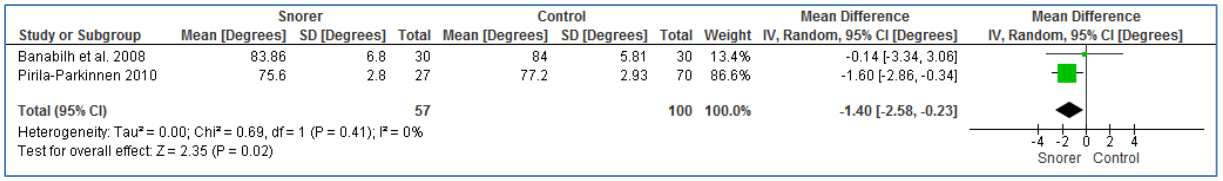


Figure 5. Pooled weighted mean difference SNB angle in children with primary snoring (PS) and controls

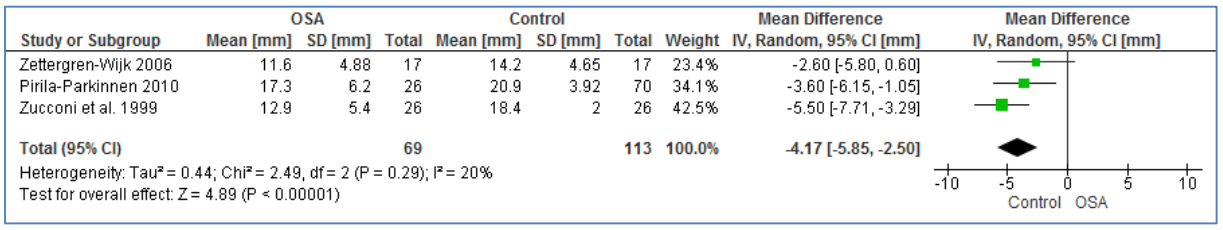


Figure 6. Pooled weighted mean difference in PNS-AD1 distance between children with obstructive sleep apnoea (OSA) and controls

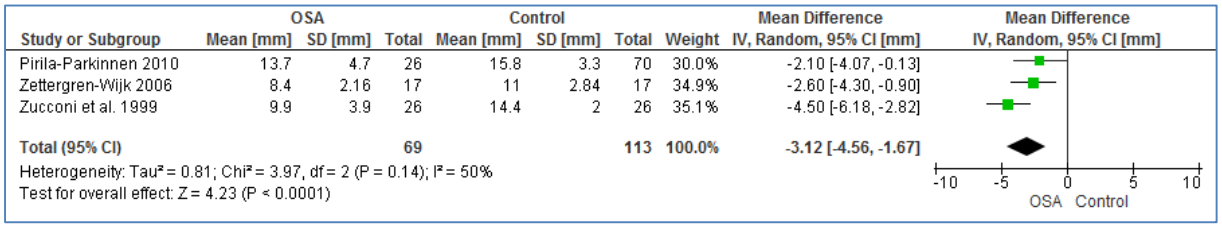


Figure 7. Pooled weighted mean difference in PNS-AD2 distance between children with obstructive sleep apnoea (OSA) and controls

Table IV. Pooled results for cephalometric variables seen in children with obstructive sleep apnoea (OSA) in comparison to the controls

Cephalometric Measurements in children with OSA versus controls	Weighted Mean Difference (OSA - Control)	95% Confidence Intervals	Heterogeneity (Significance P<0.05) †-Significant	Statistical significance for overall effect *-Significant
SNA (°)	0.61	-0.67, 1.89	P=0.16	P=0.35
SNB (°)	-0.95	-2.09, 0.20	P=0.25	P=0.11
ANB (°)	1.64	0.88, 2.41	P=0.17	P<0.0001*
SN–MP (°)	2.74	0.80, 4.68	P=0.04†	P=0.006*
PP–MP (°)	6.88	-2.34, 6.09	P<0.00001†	P=0.14
IMPA (°)	-2.43	-7.26, 2.41	P=0.08	P=0.32
BaSN (°)	3.02	-8.41, 4.45	P=0.09	P=0.60
PNS-AD1 (mm)	-4.17	-5.85,-2.50	P=0.29	P<0.00001*
PNS-AD2 (mm)	-3.12	-4.56,-1.67	P=0.14	P<0.0001*

Table V. Pooled results for cephalometric variables seen in children with Primary Snoring (PS) in comparison to the controls

Cephalometric Measurements in children with Snoring versus controls	Weighted Mean Difference (PS - Control)	95% Confidence Intervals	Heterogeneity (Significance P<0.05) †-Significant	Statistical significance for overall effect *-Significant
SNA (°)	-1.49	-3.69, 0.70	P=0.14	P=0.18
SNB (°)	-1.40	-2.58,-0.23	P=0.41	P=0.02*
ANB (°)	1.54	0.89, 2.20	P=0.70	P<0.00001*
BaSN (°)	-1.27	-4.29, 1.75	P=0.13	P=0.41

DISCUSSION

Summary of Key Findings

This meta-analysis supports the argument that children with PS and OSA show an increased ANB angle on a lateral cephalogram in comparison to the controls. This increase is due to a decreased SNB angle in children with PS. In addition, children with OSA show reduced antero–posterior width of the upper airway at the level of posterior nasal spine and superiorly at the level of adenoidal mass.

The mandibular plane angle to the cranial base shows a trend towards hyperdivergence, but with significant heterogeneity across the primary studies. Hence, it is inconclusive from this meta–analysis whether these children show excessive vertical facial patterns.

Biological and Clinical Interpretation

Most cephalometric measurements have inherent problems with landmark identification, measurement errors and representation of 3–dimensional anatomical patterns by 2–dimensional analyses. Two included primary studies[29,35] did not control for the error of the method and reported this to be significant.

ANB angle is a measure of apical base sagittal discrepancy as measured on a lateral cephalogram. ANB angle is affected by angulation of upper and lower incisors, vertical and horizontal position of nasion and rotation of jaws during growth.[37,38] Therefore, ANB angle is not a true measure of sagittal jaw discrepancy. This meta–analysis shows a highly significant

increase in ANB angle in paediatric SDB in comparison to the control; however, the increase of 1.64° may not be clinically significant.

Interestingly, increased ANB angle was attributed to mandibular retrusion in children with PS but not in children with OSA, as measured by a reduced SNB angle. Schifmman et al.[27] show no difference in the volumetric size of the mandible in non-syndromic children with OSA when compared with controls. Thus the position of the mandible in reference to cranial base might be at fault rather than the mandible size and shape.

In children diagnosed with OSA the upper airway shows narrowing. Upper airway narrowing in children with PS has also been reported in the literature but it is to a lesser extent in comparison to children with OSA.[11,32] This is not surprising as the current view suggests that adeno–tonsillar hypertrophy causes upper airway narrowing. Adeno–tonsillar hypertrophy superimposed with other factors such as craniofacial anomalies, reduced upper airway muscle tone and neural reflexes, obesity and/or genetics leads to a clinically significant dynamic airway obstruction during sleep.[1]

Comparison with Previous Work

A relevant meta–analysis in the area is lacking for the purpose of comparison. Evidence from case series and some excluded trials suggests that children with mouth breathing, adeno–tonsillar hypertrophy and/or SDB show an increased lower anterior face height, increased mandibular plane angle, retropositioned mandible, narrow maxillae and a smaller airway space.[23,24,29,39,40] This meta–analysis did not show an association between paediatric SDB and mandibular plane hyperdivergence due to significant heterogeneity across primary studies.

Narrow maxilla cannot be diagnosed on a lateral cephalogram as it is a view of the sagittal plane. None of the pooled variables reported in this meta–analysis indicate the transverse width of the maxilla. Two of the nine included studies[29,33] show a statistically significant narrow maxillary inter-molar width, as measured on dental casts in children with SDB when compared with controls. Children with snoring show a similar trend but to a lesser extent.[33] In contrast, Cozza et al.[31] show statistically significant reduced mandibular inter–molar width in children with OSA when compared with controls. The above three included studies could not be pooled due to significant heterogeneity in measurement techniques[31,33] and unclear diagnosis of selected cases[29].

From the existing literature it is not possible to determine whether transverse jaw discrepancies are strongly associated with paediatric SDB. However there is recent evidence, from a randomised clinical trial with up to 36–month follow–up, of improvement in AHI scores by use of a rapid maxillary expansion (RME) device in children with narrow maxilla and a diagnosis of OSA.[41,42] This supports use of the RME device in reducing nasal airway resistance[43] and reducing associated symptoms seen in paediatric SDB, such as nocturnal enuresis, as proposed by Timms.[44,45] Similarly, in a study conducted on a small group of adult and one adolescent patient, Guilleminault et al., showed that surgical maxilla–mandibular expansion improves sleep–disordered breathing in patients with maxillary and mandibular constriction.[46] In the sagittal dimension, advancement of the mandible in children with OSA and a diagnosis of mandibular retrognathia, by a modified functional appliance (FA) shows a significant reduction in AHI scores from an average of 7.88 to 3.66 and improved sleep quality at a 6-month follow up.[31] This suggests that RME and mandibular advancement by a functional appliance might serve as therapeutic adjuncts or alternatives in managing paediatric SDB.

Increased lower anterior face height and mandibular plane hyperdivergence is common in adults diagnosed with OSA.[47] A meta–analysis in adults has shown the strongest correlation between mandibular plane hyperdivergence and the severity of OSA.[48] However, the correlation is not strong enough to show evidence that craniofacial morphology has a direct causal effect in the development of OSA in adults.[48] A treatment strategy for severe OSA in adults is orthognathic surgery. A systematic review and meta–analysis shows pooled surgical success and cure (AHI <5) rates of 86.0% and 43.2%, respectively with maxilla–mandibular advancement surgery in adults with OSA.[49] Younger age, lower preoperative weight, AHI, and a greater degree of maxillary advancement were predictive of increased surgical success.[49] This suggests that craniofacial morphology might have a role in adult OSA but most probably not a major one.

Limitations

The exhaustive literature search, explicit selection criteria used and validity assessment of the included trials contributed to a thorough and systematic approach in reaching the conclusions. When information was doubtful in a study, the authors were contacted to clarify.

A limitation of this review is possible language bias, as indicated by the exclusion of trials in foreign languages. However, the effect of this exclusion is probably minor as judged from their English abstracts. Having two reviewers perform the data abstraction decreases the likelihood of inaccuracy and bias. Additionally, data abstraction was checked several times by co–authors to avoid errors in data collection. Seven out of nine studies included in this meta–analysis were rated as moderately strong on the level of evidence and two[35,36] were rated as limited on methodological validity assessment which could bias the results. None of the included studies were assessed as providing strong evidence. Lack of blinding in seven out of nine primary studies might have introduced observer bias and hence the results of this meta-analysis should be interpreted with caution (Table III).

One of the potential confounding problems in assessing craniofacial morphology is that the lateral cephalogram is taken in upright position and with teeth in occlusion while the patient is conscious. Paediatric SDB is determined under supine conditions where loss of muscle tone might occur while sleeping. It has been shown that measurements made from awake supine position lateral cephalograms reveal no additional differences between adult OSA and snoring subjects in comparison to radiographs taken in the upright position.[50] It is unclear if the orientation difference has negligible effect in children with SDB and whether the state of consciousness would affect upper airway measurements.

Future Research Direction

Further standardisation of research methods is recommended. The need for standardisation includes the establishment, and acceptance, of valid definitions for normal respiration, SDB and overt OSA. There was considerable variation in the cephalometric measurements used in the included studies and standardisation of appropriate cephalometric measurements is warranted for conclusive evidence. Further studies addressing the 3–dimensional volumetric characteristics of airway and position of the maxilla and mandible to the cranial base are required to understand not only the sagittal but also the transverse discrepancies in paediatric SDB.

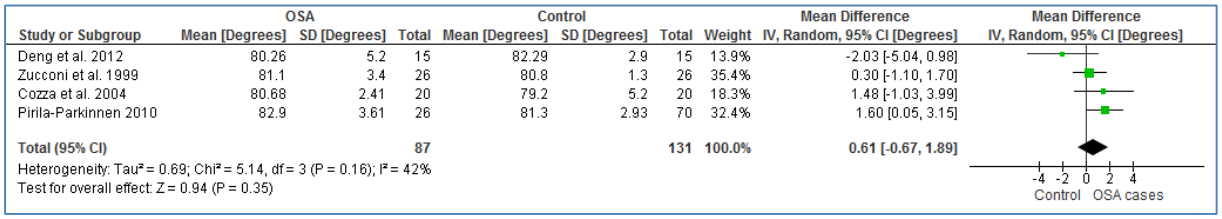
CONCLUSION

There is statistical support for an association between craniofacial disharmony and paediatric SDB. However, an increased ANB angle of <2° in children with OSA and PS, in comparison to the controls, could be regarded as of marginal clinical significance. Evidence for a direct causal relationship between craniofacial structure and paediatric SDB is

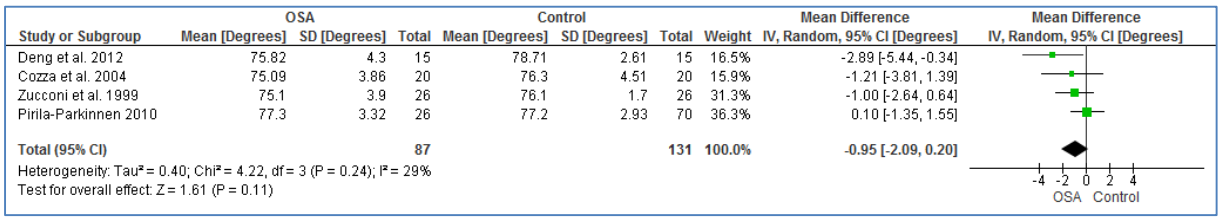
unsupported by this meta–analysis. There is strong support of a reduced upper airway sagittal width in children in OSA as shown by reduced PNS–AD1 and PNS–AD2 distance. Larger well controlled trials are required to address the relationship of craniofacial morphology to paediatric SDB in all three dimensions.

Appendix Table 1. Literature search and keywords

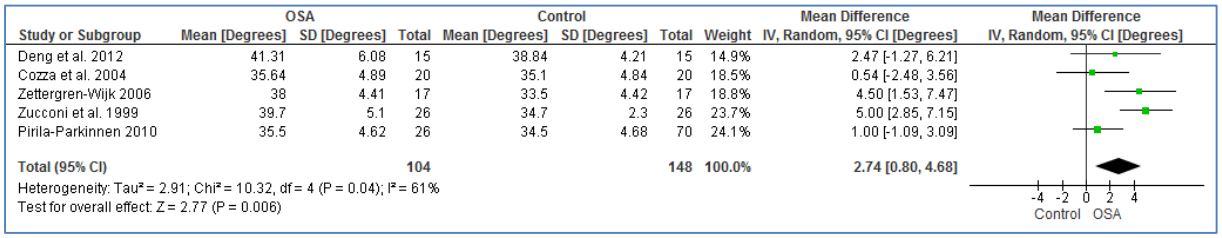
Databases	Keywords
Databases of published studies	
PUBMED Searched via The University of Adelaide customised version (27th Dec 2011). Updated monthly until April 2012.	(cephalometry[mh] OR cephalometr*[tw] OR cephalogram*[tw] OR lateral neck radiograph*[tw] OR MRI[tw] OR Tomography, X-Ray[mh] OR x-ray tomography[tw] OR computed tomography[tw] OR Cone-Beam CT[tw] OR Volumetric CT[tw] OR Spiral Cone Beam[tw] OR Spiral Volume[tw]) AND (child[mh] OR child*[tw] OR juvenile*[tw] OR infant*[tw] OR preschool*[tw] OR Adolescen*[tw] OR teen*[tw] OR pubert*[tw] OR youth*[tw] OR paediatric[tw] OR pediatric[tw] OR neonat*[tw] OR newborn*[tw]) AND (sleep apnea, obstructive[mh] OR obstructive sleep apnea*[tw] OR obstructive sleep apnoea*[tw] OR disordered sleep breathing[tw] OR sleep disordered breathing[tw] OR sleep breathing disorder*[tw]) AND ((structural[tw] OR airway [tw] OR craniofacial [tw] OR dentoskeletal[tw]) AND (trait*[tw] OR dimension*[tw] OR morpholog*[tw] OR feature*[tw] OR character*[tw] OR structur*[tw] OR shape*[tw]) OR (facial bones[mh] OR pharyn*[tw] OR skull[mh:noexp] OR maxillofacial[tw] OR cranial suture*[tw] OR jaw*[tw] OR mandib*[tw] OR maxilla*[tw] OR dental arch*[tw] OR palat*[tw] OR Nasopharyn*[tw]))
EMBASE Searched via The University of Adelaide (27th Dec 2011).	(cephalomet*:de,ti,ab OR 'computer assisted tomography'/exp OR cephalogram*:ti,ab OR 'lateral neck radiography':ti,ab OR 'lateral neck radiograph':ti,ab OR 'MRI':ti,ab OR 'x-ray tomography':ti,ab OR 'computed tomography':ti,ab OR 'Cone-Beam CT':ti,ab OR 'Volumetric CT':ti,ab OR 'Spiral Cone Beam':ti,ab OR 'Spiral Volume':ti,ab) AND (child/exp OR child*:ti,ab OR infant:de,ab,ti OR preschool*:ab,ti OR juvenile*:ab,ti OR adolescent/exp OR adolescen*:ti,ab OR teen*:ti,ab OR youth*:ti,ab OR paediatric:ti,ab OR pediatric:ti,ab OR newborn:ti,ab OR neonat*:ti,ab) AND ("sleep apnea syndrome":de OR "obstructive sleep apnea":ab,ti OR "obstructive sleep apnoea":ab,ti OR 'obstructive sleep apnoeas':ab,ti OR 'obstructive sleep apneas':ti,ab OR "disordered sleep breathing":ab,ti OR "sleep disordered breathing":ab,ti OR "sleep breathing disorder":ab,ti OR "sleep breathing disordered":ab,ti) AND ((structural:ti,ab OR airway:ti,ab OR craniofacial:ti,ab OR dentoskeletal:ti,ab) AND (trait*:ti,ab OR dimension*:ti,ab OR morpholog*:ti,ab OR feature*:ti,ab OR character*:ti,ab OR structur*:ti,ab OR shape*:ti,ab) OR (pharyn*:de,ab,ti OR 'facial bone':de,ab,ti OR 'facial bones':ab,ti OR palat*:ab,ti))
SCOPUS Searched via The University of Adelaide (27th Dec 2011). Updated monthly until Apr 2012.	(child* OR infant* OR preschool* OR juvenile*) AND ("sleep apnea" OR "sleep apnoea" OR "disordered sleep breathing" OR "sleep disordered breathing" OR "sleep breathing disorder" OR "sleep breathing disordered") AND (mouth OR teeth OR pharyngeal OR pharynx OR 'structural abnormality' OR 'airway abnormality' OR 'airway morphology' OR 'craniofacial malformation' OR 'craniofacial abnormality' OR 'craniofacial anomaly' OR 'craniofacial deformity' OR 'craniofacial structure' OR 'craniofacial structural' OR 'craniofacial morphology' OR 'facial bone' OR 'mouth malformation' OR tongue* OR palate OR 'maxillofacial development' OR (airway* AND (shape* OR structur*)))
Cochrane Central Register of Controlled Trials (CENTRAL) (1991-December 2011)	((sleep disordered breathing OR obstructive sleep apnoea) AND children AND craniofacial morphology)
Databases of research registers	
metaRegister of Controlled Trials searched via www.controlled-trials.com (27th Dec 2011 & Apr 2012)	(sleep disordered breathing in children and craniofacial morphology)



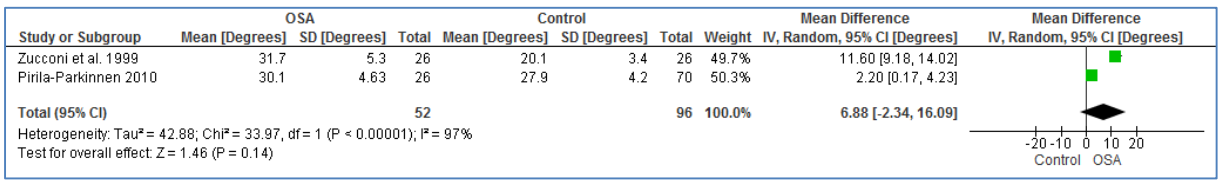
Appendix Figure 1. Pooled weighted mean difference in SNA angle between children with obstructive sleep apnoea (OSA) and controls



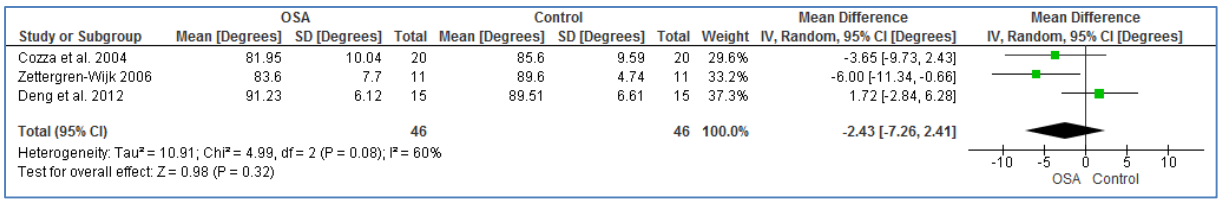
Appendix Figure 2. Pooled weighted mean difference in SNB angle in children with obstructive sleep apnoea (OSA) and controls



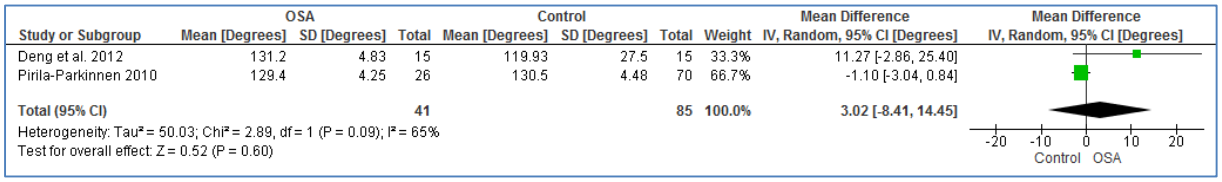
Appendix Figure 3. Pooled weighted mean difference in SN-MP angle in children with obstructive sleep apnoea (OSA) and controls



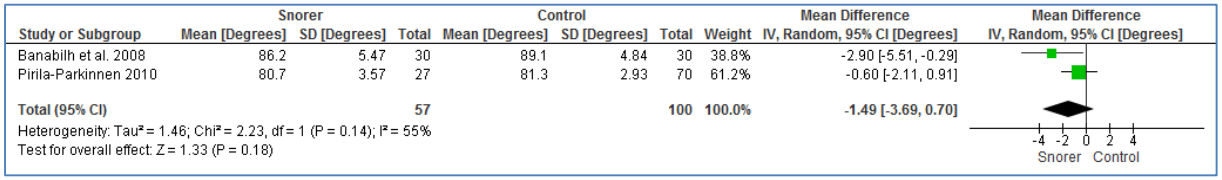
Appendix Figure 4. Pooled weighted mean difference in PP-MP angle in children with obstructive sleep apnoea (OSA) and controls



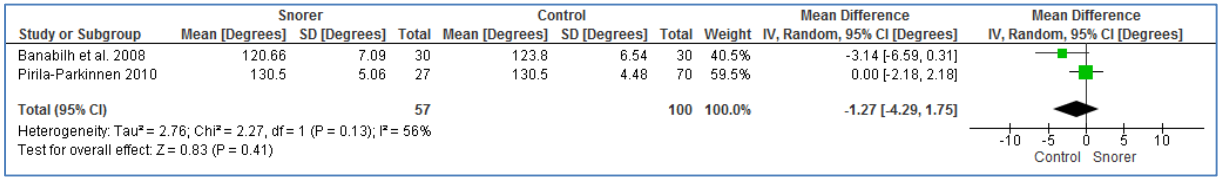
Appendix Figure 5. Pooled weighted mean difference in Lower incisor to MP angle in children with obstructive sleep apnoea (OSA) and controls



Appendix Figure 6. Pooled weighted mean difference in BaSN angle in children with obstructive sleep apnoea (OSA) and controls



Appendix Figure 7. Pooled weighted mean difference in SNA angle in children with primary snoring (PS) and controls



Appendix Figure 8. Pooled weighted mean difference in BaSN angle in children with primary snoring (PS) and controls

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By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of principal author (candidate)	**Dr Vandana Katyal**		
Contribution to the paper	Conceptualisation of work, its realisation and its documentation. Developed protocol and submitted for ethical permission. Performed data collection, analysis and its interpretation. Preparation and submission of manuscript.		
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Name of author	**Dr Yvonne Pamula**		
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Signature		Date	13/09/2013

Name of author	**Dr A. James Martin**		
Contribution to the paper	Supervised development of work, helped in data interpretation and manuscript evaluation		
Signature		Date	(8/9/13

Name of author	**Dr Cathal N. Daynes**		
Contribution to the paper	Editing the manuscript and performed all statistical analyses		
Signature		Date	8/10/2013

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Contribution to the paper	Supervised development of work, helped in error of the method, data interpretation and manuscript evaluation		
Signature		Date	8/10/13

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Signature		Date	3/10/13

Paper 3: Craniofacial and Upper Airway Morphology in Paediatric Sleep-disordered Breathing and Changes in Quality of Life with Rapid Maxillary Expansion

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ABSTRACT

Introduction – The association between paediatric sleep-disordered breathing (SDB) due to upper airway obstruction and craniofacial morphology is poorly understood and contradictory. The aim of this study was to evaluate the prevalence of children at risk for SDB, as identified in an orthodontic setting by validated screening questionnaires, and to examine associations with presenting craniofacial and upper airway morphology. A further aim was to assess the change in the SDB-related quality of life (QoL) for affected children undergoing rapid maxillary expansion (RME) to correct a palatal crossbite and/or widen a narrowed maxilla. **Methods** –A prospective case-control study with children between 8 – 17 years of age (n=81) presenting to an orthodontic clinic was undertaken. Subjects were grouped as high risk (HR) or low risk (LR) for SDB based on the scores obtained by completing a validated 22-item Paediatric Sleep Questionnaire (PSQ) and the OSA-18 QoL questionnaire. Variables pertaining to a screening clinical examination, cephalometric assessment and dental cast analysis were tested for differences between the two study groups at baseline (T1). Ten children who underwent RME were followed longitudinally until removal of the appliance (T2) approximately 9 months later with a repeat OSA-18 QoL questionnaire. All data were collected blinded to the questionnaire results. **Results** – The prevalence of children at high risk of SDB in the sample was 28.2%. The prevalence of palatal crossbite involving at least 3 teeth (PXB3) was significantly higher in the HR group at 68.2% when compared with the LR group at 23.2% (p<0.0001). Average QoL scores in the HR group indicated a reduction in SDB-related QoL by 16% when compared with children in the LR group at T1 (p<0.0001). Cephalometrically, the mean inferior airway space (IAS), posterior nasal spine to adenoidal mass distance (PNS-AD1) and adenoidal mass to soft palate distance (AD1-SP) were reduced in the HR group compared with the LR group by 1.87 mm (p<0.03), 2.82 mm (p<0.04) and 2.13 mm (p<0.03), respectively. The mean maxillary intercanine (MxIC), maxillary inter-1st premolar (MxIPM), maxillary inter-1st molar (MxIM), mandibular intercanine (MdIC) and mandibular inter-1st premolar (MdIPM) widths were reduced in the HR group compared with the LR group by 4.22 mm (p<0.0001), 3.92 mm (p<0.0001), 4.24 mm (p<0.0001), 1.50 mm (p<0.01) and 1.84 mm (p<0.01), respectively. RME-treated children showed an average improvement of 14% in QoL scores in the HR group, when compared with the LR group who showed a very slight worsening in SDB-related QoL by an average of 1% (p<0.04), normalising QoL scores in HR group children to baseline scores comparable with the LR group. **Conclusion** – Children at high-risk for SDB are characterised by reduced

SDB-related QoL, reduced nasopharyngeal and oropharyngeal sagittal dimensions, the presence of a palatal crossbite and reduced dentoalveolar transverse widths in the maxillary and mandibular arches. No sagittal or vertical craniofacial skeletal cephalometric predictors were identified for children at high-risk for SDB. In the short-term, RME might aid in improvement of SDB-related QoL for children with a narrow maxilla in the milder end of the SDB spectrum.

INTRODUCTION

Paediatric Sleep-disordered Breathing (SDB) due to upper airway obstruction is associated with the cardinal symptom of snoring.[1] In children, SDB exhibits a spectrum of severity ranging from primary snoring (PS) as the mildest form to obstructive sleep apnoea (OSA) as the most severe. PS is not associated with any gas exchange abnormalities or sleep fragmentation whereas OSA is characterised by repetitive and prolonged partial or complete upper airway obstruction which disrupts normal ventilation during sleep.[2] The spectrum of SDB (Figure 1) in children has gained increasing attention due to the deleterious health implications if left undiagnosed or untreated.[1,3-5]

The reported prevalence of PS ranges from 3.2 – 35% and OSA ranges from 0.7 – 10.3% in children, depending on the diagnostic instrument used to measure SDB, with most authors reporting a prevalence of 10% for PS and <3% for OSA.[6-8] Although once believed to be ''benign,'' it is now recognised that snoring might be associated with significant sleep disruption and daytime symptoms.[1] Both PS and OSA are known to impact the quality of life (QoL)[9], behaviour and neurocognition[10], the cardiovascular system and lipid regulation in children.[2,11] SDB affected children are more likely to be diagnosed with attention deficit hyperactivity disorder (ADHD).[12] There is relatively poor recognition of paediatric SDB in clinical practice as approximately 80% of symptomatic habitual snorers are not reported to their general medical practitioners.[13] In addition, there is a 226% (2.3 fold) increase in health care utilisation among children with OSA when compared with the unaffected population.[14] Hence early diagnosis and intervention should be beneficial and cost-effective.

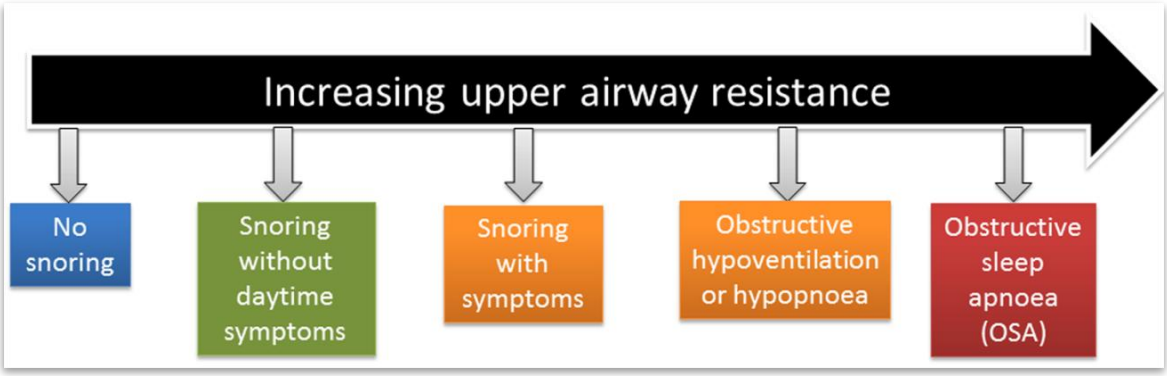

Figure 1. Spectrum of symptoms of paediatric sleep-disordered breathing (SDB). Adapted from Carroll 2003

Many studies report a positive relationship between craniofacial characteristics such as high palatal vault, narrow maxilla, mandibular retrognathia, increased facial height and

SDB in non-syndromic children.[15-20] However, evidence from two meta-analyses[21,22] suggests that the sagittal and vertical craniofacial associations, as measured on a lateral cephalogram, might have low clinical significance in predicting childhood SDB. In contrast, evidence from clinical trials indicates rapid maxillary expansion (RME) might be an effective treatment for children with narrow maxilla and OSA.[23,24] Little attention has been paid to children in the snoring end and the middle of the SDB spectrum. A recent questionnaire-based screening study by Huynh et al.[25] assessed patients in an orthodontic setting, with the majority of the children in the milder end of the SDB spectrum, and found that SDB was primarily associated with adenotonsillar hypertrophy and morphologic features such as narrow palate, dolichofacial pattern, high mandibular plane angle and severe maxillary and mandibular crowding. Interestingly, Huynh et al.[25] did not assess radiographic or dental cast measurements and relied solely on a visual clinical screening examination. Hence, the association between craniofacial and upper airway morphology and paediatric SDB in the orthodontic setting can be regarded as poorly understood and somewhat contradictory.

The primary cause of SDB in children is reported to be adenotonsillar hypertrophy which results in upper airway obstruction particularly when accompanied by other factors affecting airway patency or muscle tone.[26] Adeno-tonsillectomy (T&A) is, therefore, recommended as the first line of treatment for paediatric SDB and is curative in 25 – 80% of the cases.[27-31] Normalisation post-T&A surgery is less frequently seen in black children, obese children and children with severe baseline OSA.[31] Nasal continuous positive airway pressure (CPAP) is a non-surgical alternative treatment but there is emerging evidence of developmental mid-face hypoplasia and other craniofacial side effects in children with the use of this approach.[32,33] Dentofacial orthopaedics, particularly RME, is an emerging treatment modality in the management of paediatric OSA.[23,24]

Overnight polysomnography (PSG) is considered the “gold standard” for diagnosis of OSA in children; however, PSG is expensive, time-consuming and frequently inaccessible.[34] Various validated screening questionnaires have been developed to aid in the screening of children with SDB by standardising history-taking and evaluating QoL, behaviour, neurocognition and caregiver concerns.[35] The quality of sleep is related to the QoL[9] and the measurement of health-related QoL provides an assessment of the health status of a clinical sample and the effects of intervention, as perceived by the parent or the patient.[36] To date, there are no identified data on changes in SDB-related QoL after RME treatment for children in the snoring end of the SDB spectrum. Therefore, the main aim of this study was to

evaluate the prevalence of children at risk for SDB, as identified in an orthodontic setting by validated screening questionnaires, and to examine associations with presenting craniofacial and upper airway morphology. A further aim was to assess the change in the SDB-related QoL for affected children undergoing RME to correct a palatal crossbite and/or widen a narrowed maxilla.

METHODS

Ethical permission was granted by the Royal Adelaide Hospital (Adelaide, Australia) Human Research Ethics Committee. Informed consent was obtained from all parents or guardians and verbal assent from the children prior to study data collection.

The study design was a prospective case-control type. The subjects were children aged <18 years who presented to the orthodontic clinic for diagnosis and treatment between February 2012 and April 2013. Good general health, normal weight, the availability of study models or lateral cephalometric radiographs within 6 months of baseline orthodontic examination (T1) and no previous orthodontic treatment were required for inclusion. The initial sample comprised 81 children. Individual weight and height were measured at the time of the orthodontic examination in order to calculate the body mass index (BMI, weight in kilograms divided by height in metres squared) for each child. Since obesity might be a confounding factor,[31] 3 children with BMI above the 95th percentile (>31.9 kg/m^2) of the group were removed from primarily statistical analyses leaving a final study cohort of 78 children (33 males and 45 females). Lateral cephalograms for 6 and dental casts for 11 children were not taken at T1 for patient management reasons.

The parents or guardians present at the clinical examination were asked to complete a medical history and two questionnaires on behalf of their children to assess sleep, daytime behaviour, sleep duration and quality at T1. The sleep and daytime behaviour questionnaire was a modified and validated 22-item paediatric sleep questionnaire (PSQ).[37] All positive response categories were grouped under the response “Yes” and all negatives under “No”. Each “Yes” response for the PSQ was given a score of 1. The second questionnaire was the validated and modified version of OSA-18 to assess the QoL of the referred children in four domains which included sleep disturbance, physical discomfort, emotional distress and caregiver concerns.[38] At the end of the OSA-18 QoL questionnaire, parents were asked to mark the perceived QoL (PQoL) of their child due to sleep and breathing related issues on a 0 – 10 visual analog scale (VAS) with higher scores indicating a better SDB-related QoL. The scoring for PSQ varies from 0 – 22 points with higher scores indicating greater severity and

the scoring for OSA-18 varies from 15 – 126 points with higher scores indicating a worse QoL.[37,38] Studies have validated that if a child's PSQ scored greater than 7 "Yes" responses or the OSA-18 scored greater than 60, a high probability of SDB could be expected.[35,37,38] The PSQ has a sensitivity of 0.85 and specificity of 0.87 in predicting paediatric SDB in comparison with the PSG.[37] Children were grouped as "High Risk" (HR) or "Low Risk" (LR) according to the two questionnaire results, with the HR group showing >7 "Yes" responses to the PSQ and/or score ≥60 with the OSA-18 questionnaire.

Fifteen participants (68.2%) in the HR group and 13 (23.2%) in the LR group were diagnosed with a palatal crossbite or a narrow maxilla and were recommended an RME treatment. Five children in the HR group and 5 in the LR group (n=10) who underwent RME (mean age 10.3 ± 1.3 years) were followed longitudinally until removal of the appliance (T2) approximately 7 – 9 months after (mean age at T2 was 10.9 ± 1.3 years). The RME appliance was a 4-banded hyrax-type with a rate of activation of 0.5 mm daily. The expansion was stopped between 14 – 21 days or once the palatal cusps of the maxillary molars were in line with the buccal cusps of the mandibular molars, to allow for some relapse. Following expansion, the RME device served as a passive retainer to allow sutural and bony adaptation. Since the OSA-18 QoL questionnaire has been validated to measure changes in SDB-related QoL in a paediatric sample,[35] it was repeated at T2 to assess QoL changes in the RME-treated children.

Orthodontic Examination

All subjects were clinically evaluated at T1 under supervision by orthodontists, blinded to the questionnaire results, using a standardised orthodontic evaluation form covering dental, skeletal, functional and aesthetic factors. Sagittal craniofacial form was recorded as skeletal Class I, II or III. Vertical evaluation included the visual categorisation of face height as mesofacial, brachyfacial and dolichofacial. The presence or absence of a palatal crossbite involving at least 3 teeth (PXB3) was recorded.

Cephalometric Assessment

Fifty-five children in the LR and 17 in the HR group (n=72) had lateral cephalograms taken at T1. All cephalograms were taken at T1 on the same machine (Kodak Carestream CS 9000, Eastman Kodak Company, Rochester NY), with the patient erect in natural head position, the teeth in maximum intercuspation and the lips relaxed. The enlargement factor (8%) was

adjusted to provide true size measurements. The cephalograms were digitised and analysed using Dolphin Imaging software (version 11.5, Dolphin Imaging & Management solution, Patterson Dental Supply, Inc.). The description of cephalometric landmarks and analysed planes are depicted in Figure 2. Cephalometric measurements included 17 morphological, 3 airway and 1 hyoid position variables. Cephalometric variables tested are as follows:

(1) Cranial base assessment – cranial base length (SN length in mm) and cranial base flexion (N-S-Ba angle),

(2) Maxillary and mandibular skeletal assessment – maxillary position in relation to cranial base (S-N-A angle), mandibular position in relation to cranial base (S-N-B angle), maxillary-mandibular sagittal differential (A-N-B angle and WITS in mm), maxillary length (Co-A point in mm), mandibular length (Co-Gn in mm) and maxillary-mandibular length differential (Mx-Md, difference between maxillary and mandibular length in mm),

(3) Vertical skeletal assessment – palatal plane to cranial base reference (SN-PP angle), mandibular plane to cranial base (FH-MP angle), maxillary-mandibular divergence (PP-MP angle), posterior face height (Co-Go in mm) and lower anterior face height (ANS-Me in mm),

(4) Dental measurements – angulation of upper incisor to cranial base (U1-SN angle), angulation of lower incisor to mandibular plane (L1-MP angle), occlusal plane in relation to cranial base (OP-FH angle),

(5) Airway dimensions – oropharyngeal airway dimension (IAS in mm), nasopharyngeal airway dimension (PNS-AD1 in mm) and patency of nasopharyngeal airway (AD1-SP in mm) and

(6) Hyoid position – perpendicular distance from antero-superior point on hyoid body to mandibular plane (Hy-MP in mm).

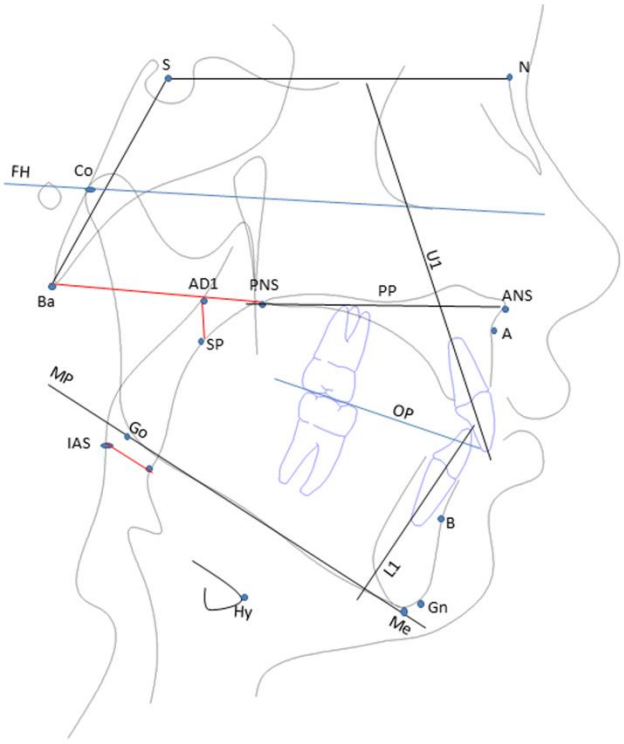

Figure 2. Cephalometric points and planes used in analysis of children in the study

Key: Points- A=A Point, ANS=Anterior Nasal Spine, B=B Point, Ba=Basion, Co=Condylion, Gn=Gnathion, Go=Gonion, Hy=Antero-superior point on Hyoid body, Me=Menton, N=Nasion, PNS=Posterior Nasal Spine and S=Sella. **Planes and distances-** AD1–SP =Distance from nearest adenoid tissue to most convex point on soft palate (SP), AFH=Anterior face height measured as distance between ANS and Me, FH=Frankfort horizontal plane, IAS=Inferior Airway Space measured from posterior pharyngeal wall to anterior pharyngeal wall around gonial angle, L1=Long Axis of Lower Incisor, Mandibular length=Distance from Co-B point, Maxillary length=Distance from Co-A point, MP=Mandibular Plane (Go–Me), OP=occlusal plane along maximum intercuspation of posteriors, PFH=Posterior face height measured as distance between Co and Go, PNS–AD1=Distance from Posterior Nasal Spine to nearest adenoid tissue measured along the line PNS–Ba line, PP=Palatal Plane (ANS-PNS), WITS= Distance measured along OP between perpendiculars projected from A-point & B-points and U1=Long axis of upper incisor.

Dental Cast Measurements

Forty-six children in the LR and 21 children in the HR group had dental casts available (n=67) at T1. Photocopies of dental models were taken for measurements and analysed to true size (photocopier Aficio MP C5502a, Ricoh Company Limited, Tokyo). The dental casts were not used for direct data collection to prevent their damage during repeated measures. Centroids of the crowns of canines, 1st premolars and 1st molars were located in the occlusal plane according to the method devised by Moyers.[39] The centroid of a dental crown in the occlusal plane is defined as the point halfway between two points which have been calculated by joining the two approximal midpoints and the buccal and lingual midpoints. The corresponding centroids were used for intra-arch linear measurements recorded in millimetres. Calibrated digital sliding calipers were used for all measurements which included maxillary inter-canine width (MxIC), maxillary inter-1st premolar width (MxIPM),

maxillary inter-1st molar width (MxIM), mandibular inter-canine width (MdIC), mandibular inter-1st premolar width (MdIPM) and mandibular inter-1st molar width (MdIM). When the permanent teeth were absent or unerupted, their deciduous counterparts were used as substitutes.

Blinding & Method Errors

All cephalometric and dental cast measurements were made by the same investigator (VK) who was blinded to the two questionnaire results. Ten radiographs and study models were chosen at random and analysed at least 2 weeks apart to calculate the error of the method. Intraclass correlation coefficients (ICC) were calculated using a two-way mixed model and absolute agreement type for all angular and linear cephalometric variables. ICC varied from 0.973 to 0.997 for angular cephalometric measurements and from 0.912 to 0.981 for linear cephalometric measurements. ICC varied from 0.992 to 0.998 for dental cast measurements. This indicates a satisfactory level of intra-observer reliability.

Statistical Analyses

Sample size calculations were done *a-priori* using cephalometric variables (ANB angle, FH-MP angle and PNS-AD1) from previous meta-analyses.[21,22] The calculated power of the study exceeded 0.90 at an alpha = 0.05 with sample sizes of the examined groups ranging from 55 to 70 subjects.

All data were analysed using IBM SPSS Statistics for Windows software (version 21; IBM Corp; Armonk, NY). The assumptions behind each of the statistical tests performed were assessed and validated. Data are presented as the mean and the standard deviation (SD) for continuous variables and as frequency or percentages for categorical variables. Pearson's correlations (*r*) were performed to check the association between different questionnaire scores and patient data. The differences between the two groups for continuous variables at T1 were tested for statistical significance with a *t*-test for independent samples and for matched pairs with a paired sample *t*-test. HR and LR group participants were further subdivided by age at T1 into young children (YC) aged 8 – 12.9 years and teenage children (TC) aged 13 – 18 years for subgroup analysis. Where an independent *t*-test indicated significant difference, subgroup analysis was performed to enable greater resolution of the results using a univariate ANOVA by pairwise comparison with a Bonferroni correction applied. Odds ratios (OR) were calculated for exposure and outcome categorical variables

and significance was tested with a 2x2 *chi*-squared test. Statistical significance was assessed at P<0.05 (2-tailed). The data at T1 from the 3 excluded children were analysed separately in a sensitivity analysis.

RESULTS

The mean age of the final cohort of 78 children at T1 was 12.3 ± 2.5 years and the age range 8.3 – 17.6 years. Sixty-eight children (87.1%) were of Caucasian descent. Sixty (76.9%) of the questionnaires were completed by mothers, 10 (12.8%) by fathers and 8 (10.3%) by guardians or grandparents of the children. The LR group (control group) comprised 23 males and 33 females and the HR group comprised 10 males and 12 females. No child in the LR group was reported as an habitual snorer based on the two questionnaires.

Demographic data at T1 for the HR and LR groups are presented in Table I. At T1, QoL scores in the HR group were 39.9 ± 15.6 when compared with children in the LR group at 22.6 ± 6.9 indicating a worsening in SDB-related QoL by 16% in the HR group when compared with the LR group (p<0.0001). The prevalence of PXB3 was significantly higher in the HR group at 68.2% when compared with the LR group at 23.2% (p<0.0001). At T1, OSA-18 Qol scores and PSQ scores correlated highly with each other (r=0.81, p<0.0001) but PQoL correlated moderately with OSA-18 QoL scores (r = -0.61, p<0.0001) and PSQ scores (r = -0.53, p<0.0001). Frequency of positive responses to the 22-item PSQ survey are shown in Table II. OR and their 95% confidence intervals (CI) with statistical significance are also presented in Table II for the presence of a PXB3 and its association with each of the 22 PSQ questions.

Table III summarises the statistically significant differences in cephalometric and dental cast variables found between the 2 study groups. The mean IAS, PNS-AD1 and AD1-SP were lower in the HR group compared with the LR group by 1.87 mm (p<0.03), 2.82 mm (p<0.04) and 2.13 mm (p<0.03), respectively. There were highly statistically significant differences between the groups in all width measurements except for MdIM width (p=0.20). The mean MxIC, MxIPM, MxIM, MdIC, MdIPM widths were reduced in the HR group compared with the LR group by an average of 4.22 mm (p<0.0001), 3.92 mm (p<0.0001), 4.24 mm (p<0.0001), 1.50 mm (p<0.01) and 1.84 mm (p<0.01), respectively.

Table IV provides a summary of QoL changes after maxillary expansion at T2.There was a statistically significant difference pre- and post-RME in OSA-18 Qol scores between the two groups indicating an average improvement by 14% (mean score -15.2 ± 13.8 score) for children in the HR group when compared with the LR group who showed a very slight

worsening in QoL by an average of 1% (mean score 1.2 ± 3.9) (p<0.04). At T2, PQoL change did not correlate with the calculated OSA-18 score change (r = -0.62, p=0.06).

Subgroup analyses by age (YC and TC) and risk category (HR and LR) enabled greater resolution of association between SDB risk and dental cast variables (Figure 3). Narrower MxIC, MxIPM and MxIM widths indicated an increased risk of SDB across all age groups whereas the association of MdIC, MdIPM and MdIM widths were not significant in all age groups. Mean MxIC width <27 mm was highly associated with increased risk for SDB in YC (p<0.01) and TC subgroups (p<0.0001) whereas MdIC width <24 mm, on average, was associated with increased risk for SDB only in the YC subgroup (p<0.05). Mean MxIPM and mean MxIM widths were of high predictive value in the YC subgroup (p<0.01) and the TC subgroups (p<0.0001). Mean MdIPM width was associated with increased risk for SDB only in the TC subgroups (p<0.02).The results of the sensitivity analyses showed no statistically significant differences in any of the analysed variables tested at T1 by the inclusion of the previously excluded 3 children except for an increase in prevalence of children at high-risk for SDB which changed from 22 children (28.2%) to 24 children (29.6%).

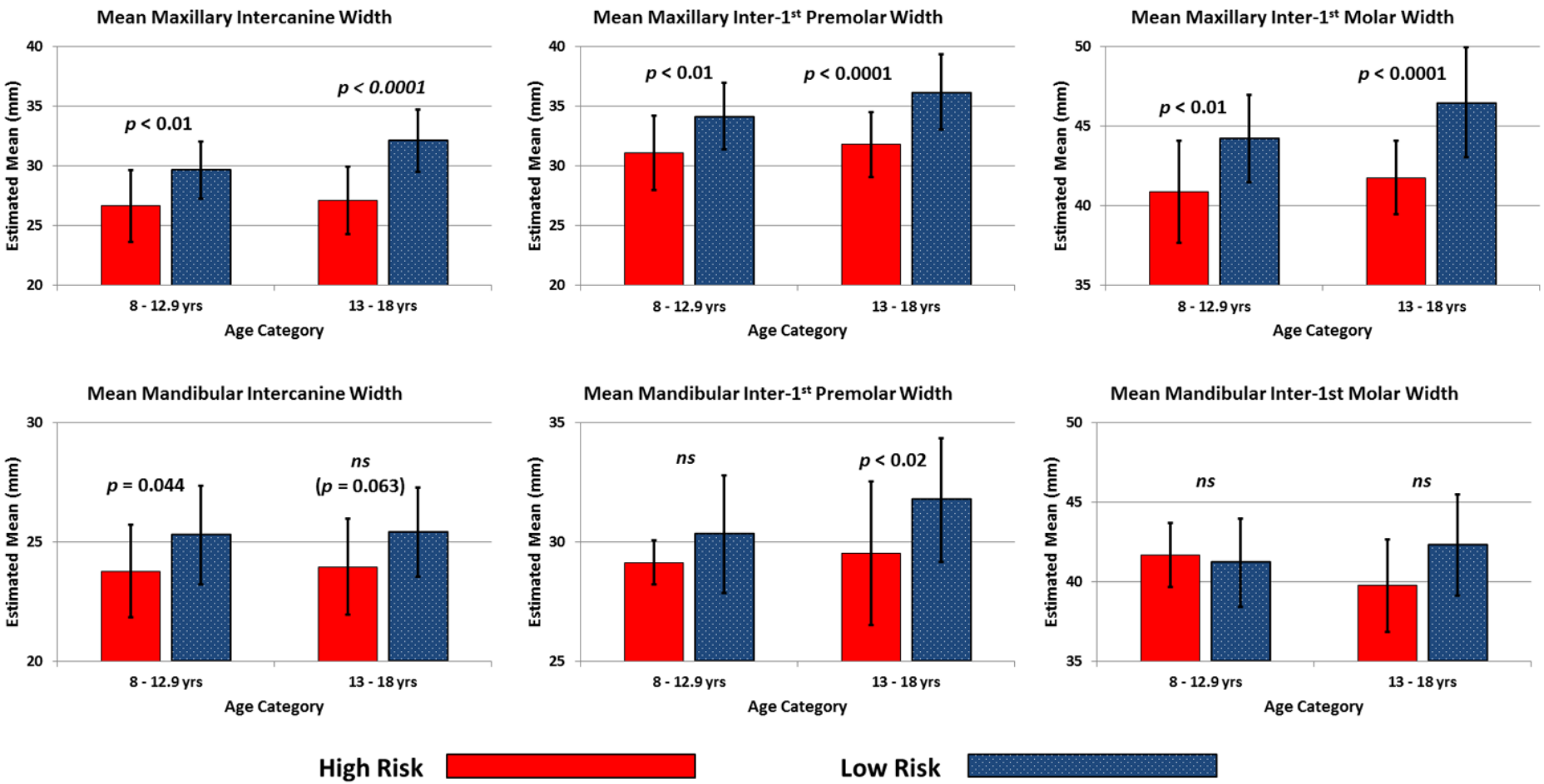

Figure 3. Analyses of transverse dental cast measurements (mm) by pairwise comparison of high and low risk patients within the 8 – 12.9 and 13 – 18 years subgroups. A Bonferroni correction was applied to control type I errors. Error bars indicate one standard deviation. (Key: NS-not significant)

Table I. Descriptive data of demographic and clinical variables at T1 for children at high risk (HR) and children at low risk (LR or control group) of paediatric SDB.

Demographics at Baseline (T1)	*High Risk group (HR) n=22* Mean ± SD	*Low Risk group (LR) n=56* Mean ± SD	*Significance p-value*
Age at T1 (years)	12.10 ± 2.26	12.49 ± 2.64	$p = 0.54$ (NS)
Young children : Teen children (n)	13 : 9	28 : 28	$p = 0.80$ (NS)
Male : Female ratio (T1)	10 : 12	23 : 33	$p = 0.72$ (NS)
BMI (kg/m^2) (T1)	21.04 ± 4.76	21.26 ± 3.67	$p = 0.84$ (NS)
Previous adenotonsillectomy (n at T1)	4	4	$p = 0.15$ (NS)
Clinical examination sagittal type (Class I : II : III) (T1)	9 : 9 : 4	15 : 33 : 8	$p = 0.34$ (NS)
Clinical examination vertical type (Brachyfacial:Mesofacial:Dolichofacial) (T1)	8 : 6 : 7	23 : 16 : 17	$p = 0.96$ (NS)
Presence of palatal crossbite ≥3 teeth (PXB3) at T1 (n(%))	15 (68.2%)	13 (23.2%)	$p < 0.0001^{***}$
PSQ scores (T1)	9.73 ± 3.43	2.88 ± 2.01	$p < 0.0001^{***}$
OSA-18 QoL score (T1)	39.91 ± 15.64	22.63 ± 6.91	$p < 0.0001^{***}$
OSA-18 QoL parental score (T1)	7.30 ± 1.65	8.72 ± 1.28	$p < 0.0001^{***}$
Total Sleep Time (hr) (T1)	10.06 ± 0.79	9.71 ± 0.98	$p = 0.14$ (NS)
Key: NS-Not significant, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$			

Table II. Positive responses to the 22-item Paediatric Sleep Questionnaire (PSQ) in the study population at T1 and Odds Ratio (OR) for presence of a maxillary palatal crossbite involving >3 teeth (PXB3) with the 22 questions

PSQ 22-item survey to evaluate risk for paediatric SDB (T1)	Frequency of response - Yes (%)	OR (95% CI) for presence of PXB3	*Significance p*-value
Q1. Child usually snores at night?	34	4.32 (1.57 – 11.90)	$p<0.01^{**}$
Q2. Child always snores at night?	14	4.03 (1.01 – 16.17)	$p<0.04^{*}$
Q3. Child snores loudly at night?	25	7.17 (2.27 – 22.62)	$p<0.0001^{***}$
Q4. Child breathes loudly or heavily at night?	34	6.60 (2.18 – 20.25)	$p<0.0001^{***}$
Q5. Child has trouble breathing at night?	8	11.50 (1.26 – 104.86)	$p<0.01^{**}$
Q6. Child ever stops breathing at night?	7	8.73 (0.92 – 82.69)	$p<0.03^{*}$
Q7. Child breathes through the mouth during the day?	58	2.08 (0.71 – 6.09)	NS
Q8. Child has dry mouth on waking?	44	4.00 (1.38 – 11.58)	$p<0.01^{**}$
Q9. Child occasionally wets the bed at night?	3	1.82 (0.11 – 30.18)	NS
Q10. Child appears unrefreshed after sleep?	37	2.46 (0.90 – 6.71)	*NS*
Q11. Child has daytime sleepiness?	12	0.91 (0.21 – 3.99)	NS
Q12. Teacher has commented that child has daytime sleepiness?	6	1.25 (0.20 – 8.00)	NS
Q13. Hard to wake up child in the morning?	31	0.83 (0.30 – 2.28)	NS
Q14. Child wakes up with morning headaches?	7	8.36 (0.88 – 79.31)	$p<0.03^{*}$
Q15. Child had abnormal growth rate at any time?	4	4.27 (0.37 – 49.68)	NS
Q16. Is child overweight?	14	0.49 (0.10 – 2.51)	NS
Q17. Child does not listen when spoken too?	31	3.21 (1.16 – 8.89)	$p<0.02^{*}$
Q18. Child has difficulty organising tasks / activities?	27	1.55 (0.55 – 4.39)	NS
Q19. Child easily distracted?	43	1.58 (0.61 – 4.12)	NS
Q20. Child hand fidgets or squirms in their seat?	33	1.72 (0.64 – 4.61)	NS
Q21. Child acts as “constantly on the go”?	25	3.66 (1.21 – 11.11)	$p<0.02^{*}$
Q22. Child interrupts / intrudes on others?	21	1.37 (0.43 – 4.41)	NS

Key: NS-Not significant, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$

Table III. Summary of differences between high-risk (HR) & low risk (LR) study groups for cephalometric and dental cast variables at T1

Cephalometric & Dental Cast Variables	Mean difference between study groups (LR minus HR)	95% Confidence Intervals	Significance *p*-value
Cephalometric Analysis (n=72)			
Cranial Base analysis			
S-N (mm)	1.22	-0.68 to 3.13	*p*=0.20 (NS)
N-S-Ba (°)	-0.10	-3.06 to 2.86	*p*=0.95 (NS)
Maxillary & mandibular skeletal analysis			
SNA (°)	-0.19	-2.07 to 1.68	*p*=0.84 (NS)
SNB (°)	0.71	-1.40 to 2.81	*p*=0.51 (NS)
ANB (°)	-0.66	-2.44 to 1.11	*p*=0.46 (NS)
WITS (mm)	-0.87	-3.26 to 1.53	*p*=0.47 (NS)
Co-A (mm)	1.18	-1.73 to 4.10	*p*=0.42 (NS)
Co-Gn (mm)	-0.12	-4.29 to 4.04	*p*=0.95 (NS)
Mx-Md (mm)	-1.30	-4.50 to 1.90	*p*=0.42 (NS)
Vertical skeletal analysis			
SN-PP (°)	0.35	-1.31 to 1.99	*p*=0.68 (NS)
FH-MP (°)	-0.51	-3.45 to 2.43	*p*=0.73 (NS)
PP-MP (°)	-1.34	-4.57 to 1.90	*p*=0.41 (NS)
Co-Go (mm)	0.28	-2.42 to 2.97	*p*=0.84 (NS)
ANS-Me (mm)	-0.77	-3.67 to 2.12	*p*=0.59 (NS)
Dental analysis			
U1-SN (°)	-0.68	-5.18 to 3.81	*p*=0.76 (NS)
L1-MP (°)	2.26	-2.33 to 6.85	*p*=0.33 (NS)
OP-FH (°)	0.75	-1.67 to 3.16	*p*=0.54 (NS)
Airway analysis			
IAS (mm)	1.87	0.24 to 3.49	*p*<0.03*
PNS-AD1 (mm)	2.82	0.26 to 5.39	*p*<0.04*
AD1-SP (mm)	2.13	0.34 to 3.92	*p*<0.02*
Hyoid position			
Hy-MP (mm)	-0.61	-3.68 to 2.47	*p*=0.69(NS)
Dental Cast Analysis (n=67)			
Maxillary Arch Widths			
Maxillary inter-canine MxIC (mm)	4.22	2.73 to 5.70	*p*<0.0001***
Maxillary inter-1st premolar MxIPM (mm)	3.92	2.31 to 5.53	*p*<0.0001***
Maxillary inter-1st molar MxIM (mm)	4.24	2.57 to 5.91	*p*<0.0001***
Mandibular Arch Widths			
Mandibular inter-canine MdIC (mm)	1.50	0.46 to 2.53	*p*<0.01**
Mandibular inter-1st premolar MdIPM (mm)	1.84	0.55 to 3.13	*p*<0.01**
Mandibular inter-1st molar MdIM (mm)	0.98	-0.54 to 2.50	*p*=0.20 (NS)

Key: NS-Not significant, *$p<0.05$, **$p<0.01$, ***$p<0.001$

Table IV. Statistical analyses post maxillary expansion (T2) for children at high risk for paediatric SDB (HR) and children at low risk (LR or control group)

At RME removal (T2)	*High Risk group (HR) n= 5* Mean ± SD	*Low Risk group (LR) n=5* Mean ± SD	*Significance p-value*
Age in years (T2)	11.37 ± 1.64	10.45 ± 0.83	$p = 0.30$ (NS)
OSA-18 QoL score (T2)	28.40 ± 13.35	22.00 ± 2.45	$p = 0.32$ (NS)
OSA-18 QoL parental score (T2)	9.00 ± 1.00	8.80 ± 1.10	$p = 0.77$ (NS)
Post-RME QoL score change (T2-T1). $^{\alpha}$	-15.20 ± 13.83	1.20 ± 3.96	$p < 0.04^{*}$
Post-RME QoL parental score change (T2-T1). ^{ß}	1.80 ± 1.64	-1.10 ± 1.75	$p < 0.03^{*}$

Key: NS-Not significant, *$p<0.05$, **$p<0.01$, ***$p<0.001$. $^{\alpha}$Negative value implies improvement. ^{ß} Negative value implies worsening.

DISCUSSION

The prevalence of children at high risk for SDB in the orthodontic sample was 28.2% which was higher than the estimate of 10% from a recent questionnaire-based study by Huynh et al.[25] with a large sample size of 604 children. This might have been due to the different sample sizes, study methodologies, questionnaires, evaluation and scoring methods employed in the two studies. At baseline, children in the HR groups showed a worse SDB-related QoL score by approximately 16% when compared with children in the LR group. The prevalence of PXB3 was significantly higher in the HR group at 68.2% when compared with the LR group at 23.2%. A PXB3 most likely suggests a transversely narrow maxilla.[40] Children with PXB3 were 4 times more likely to be frequent and loud snorers, 6 – 12 times more likely to have heavy breathing or troubled breathing at night. They were also more likely to wake up with a dry mouth, have morning headaches and have parentally-reported behavioural concerns such as “not listening when spoken to directly” and “acting constantly on the go”.

Our inclusion criteria had a wide age range to reflect routine orthodontic practice and hence makes this study clinically applicable. Although overall *a-priori* sample size calculations for cephalometric variables were met, the 2 study groups were unequal in number of subjects. This could be a reason for study being underpowered in the HR group and hence the finding of no significant differences in cephalometric measurements between the HR and LR groups. However, the sample determination was based on previous studies of children with OSA due to lack of available standardised cephalometric data for children at

the snoring end of the SDB spectrum. The absence of statistically significant vertical and sagittal skeletal differences as measured on a cephalometric film in the present sample is in contrast to two meta-analyses which reported that children with SDB showed increased ANB angle due to mandibular retrognathia by a marginally clinically significant value of 1.6° and an increased mandibular plane angle of approximately 4° when compared with the controls.[21,22] The primary studies chosen in the above-mentioned meta-analyses included PSG-proven OSA whereas children in the present sample were more likely to be in the snoring end of the SDB spectrum. In addition, most primary studies in the reported meta-analyses were considered to be of low to moderate quality primarily due to lack of blinding. Our results support those of Schiffman et al.[41] who did not find any differences in mandibular length, width, area or volume as measured by magnetic resonance imaging between children with OSA and controls. At baseline, the two sample groups differed in airway dimensions (PNS-AD1, AD1-SP and IAS) which were reduced by approximately 2 – 3 mm in the HR group when compared with the LR group. The reduction of the nasopharyngeal dimension (PNS-AD1) seen in the HR group was on average 2.8 mm which is in accordance with the meta-analysis by Katyal and co-workers.[21] In the absence of any clinically significant sagittal and vertical craniofacial skeletal disharmony, this finding might be either due to adenotonsillar hypertrophy or a thicker than usual soft palate.

Dental cast analyses confirmed the HR group had a reduced transverse maxillary dimension by an average of 4 mm in all measured widths and approximately 1.5 mm in the MdIC and MdIPM areas. Studies by Lofstrand-Tidestrom et al.[16] and Pirila-Parkkinen and colleagues[18] reported reduced maxillary widths by 2 mm between OSA-affected children and controls, which were slightly lower than the present study, but found no differences in inter-mandibular transverse widths. However, the highly statistically significant reduction of mandibular inter-canine and inter-1st premolar width by approximately 1.5 mm seen in the present study might be regarded as having a low clinical significance. The present study did not find any significant reduction in MdIM width, whereas Cozza et al.[42] reported reduced MdIM width by an average of 2 mm in OSA-affected children. This may have been due to different study populations and facial skeletal patterns. Subgroup analysis showed a highly significant predictive value of MxIC, MxIPM, and MxIM in assessing SDB risk in all age categories whereas MdIC was significantly predictive only in the YC subgroup and MdIPM in the TC subgroup. MdIM measurements were not associated with increased risk for SDB in any age category. Since the inter-canine widths stabilise much earlier than other

dentoalveolar transverse dimensions,[43] it might be a useful clinical predictor across different age groups. Our data suggests that children between 8 – 17 years of age with MxIC width <27 mm, on average, are at high risk for SDB and this could be employed clinically as an efficient screening tool.

To our knowledge, a change in SDB-related QoL scores for RME-treated children in the milder end of SDB spectrum has not been reported previously. Although the sample size at RME removal was small and caution is recommended in interpretation of such data, the present study shows an improvement in SDB-related QoL scores by an average of 14% with the use of a RME device in the HR group when compared with the LR group which showed a very slight worsening by 1%. The worsening in the LR group might have been due to the appliance which reduces intra-oral volume and affects oral hygiene maintenance as well as speech. The improvement in OSA-18 QoI scores after RME in the HR group might be regarded as having some clinical significance as these children were "normalised" in SDB-related QoL scores which were comparable to the LR group QoL scores at baseline. However, long-term follow-up and a larger sample size are required to assess the stability of such changes in SDB-related QoL after RME treatment. It should be noted that the prevalence of paediatric SDB might change with time. Marcus et al.[31] reported normalisation of PSG scores in nearly 47% of OSA-affected children randomised to watchful waiting for 7 months in comparison with the T&A surgery group. This might have been due to growth of the airway, regression of the lymphoid tissue, routine medical care or regression to the mean. Interestingly, at T2, change in PQoL did not correlate well with the calculated OSA-18 QoL score change. This might have been due to parental attitudes towards overall health of their children rather than the SDB-related effects on QoL.

The floor of the nose and maxillary vault are anatomically related. When the midpalatal suture is opened by RME, the nasal cavity's lateral walls are also displaced laterally which increases nasal volume and decreases upper airway resistance.[44,45] This increase in nasal cavity width after RME might be a reason for the increase seen in total pharyngeal and retropalatal airway volume in RME-treated children.[46-48] The changes after RME, as measured by objective tests of nasal airway patency such as rhinomanometry and acoustic rhinometry show improved conditions for nasal breathing up to 11 months after RME.[49] Maxillary constriction might also lead to a decreased oral volume due to a lower tongue position which might decrease further in a supine sleeping position. This lowered tongue posture has been shown to improve after maxillary expansion.[47] Since maxillary

width changes very little after T&A,[15] orthodontic maxillary widening of a narrow maxilla in cases in which snoring persists or relapses after T&A is gaining support.[23,24]

Multi-therapies might act synergistically in treating paediatric SDB which is a complex multi-factorial problem. Management of the child with suspected diagnosis of PS or OSA should take under consideration severity of upper airway obstruction during sleep and presence of morbidity or other coexisting conditions. There is no consensus presently, however, Kaditis et al.[50] have proposed an integrated and hierarchical stepwise evidence-based algorithm for the diagnosis and multi-therapeutic management of childhood SDB. This approach starts with weight control followed heirarchical by use of nasal corticosteriods, adenotonsillectomy, dentofacial orthopaedics such as mandibular advancement or maxillary expansion, CPAP and maxillofacial surgery.

One of the drawbacks of the present study is the reliance on the 2-dimensional lateral cephalogram to assess 3-dimensional structures. The intra-observer reliability in the present study for landmark identification and measurements was high, however there might have been errors in projection and anatomic interpretation that were overlooked as these are inherent problems of the technique.[51] Although Major et al.[52] found that there was at best a moderate correlation (r=0.68) between linear measurements of the upper airway in a cephalometric film and the diagnosis of upper airway blockage, Pirila-Parkkinen et al.[53] showed that the cephalometric film is a reliable tool to measure nasopharyngeal and retropalatal dimensions but not oropharyngeal width in children with adenotonsillar hypertrophy. Nevertheless, it is a valid screening tool with higher accessibility, lower costs and lower radiation dose than the 3-dimensional volumetric cone-bean computed tomography (CBCT) scan in an orthodontic setting. It also remains controversial whether a lateral cephalogram should be taken in an upright or a supine position to screen for paediatric SDB; however, it has been shown that the state of consciousness may be the more important factor affecting upper airway muscle tone rather than the head position.[54] An issue in the present study stems from parental reporting of their children's SDB-related symptoms and QoL. Although no identified study has compared parental reporting of SDB symptoms with self-reported child's perception, relatively high agreement between parental and self-reported childhood ADHD-related sleep symptoms have been reported in the literature.[55] Since the majority of our sample was of Caucasian descent, the results may not be applicable to other ethnicities. Other limitations of the present study include failure to record adenotonsillar size clinically, inaccessibility to a PSG for diagnosis of paediatric SDB, a

small sample size at T2 undergoing RME treatment and a short-term follow up of the RME-treated children.

Future research should be directed towards studies utilising 3-dimensional assessment of craniofacial morphology, nasopharyngeal and oropharyngeal airway that may help in the further understanding of such anatomic factors related to paediatric SDB, particularly in refractory cases. In addition, future studies should compare SDB-related QoL changes for different treatment modalities in the management of paediatric SDB. There is an urgent need to research and establish protocols for multi-therapies to account for the relative contributions of each therapy in the management of paediatric SDB. A greater degree of collaboration between sleep medicine physicians, ear, nose and throat surgeons and orthodontists is required to establish individualised approaches for a successful treatment and/or cure.

CONCLUSION

Children at high-risk for SDB are characterised by reduced SDB-related QoL, reduced nasopharyngeal and oropharyngeal sagittal dimensions, the presence of a palatal crossbite and reduced dentoalveolar transverse widths in the maxillary and mandibular arches. No sagittal or vertical craniofacial skeletal cephalometric predictors were identified for children at high-risk for SDB. In the short-term, RME might aid in improvement of SDB-related QoL for children with a narrow maxilla in the milder end of the SDB spectrum. Long-term follow up and larger sample size of RME-treated children at risk for SDB is required to confirm and assess the stability of changes seen.

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CONCLUSION

The main aim of this thesis was to establish the association between craniofacial and upper airway morphology and paediatric SDB. Secondary aims were to report on prevalence and SDB-related quality of life in children at-risk for SDB in an orthodontic treatment need population; and evaluate changes in SDB-related quality of life with rapid maxillary expansion.

It was established that children with OSA show evidence of mild craniofacial skeletal disharmony in the sagittal and vertical dimensions and moderately reduced nasopharyngeal sagittal widths. In contrast, children with PS showed little evidence skeletal craniofacial disharmony in the sagittal and vertical dimensions. However, children with PS showed reduced nasopharyngeal sagittal width similar to that seen in children with OSA.

In the transverse dimension, snoring children at-risk for SDB were characterised by a narrow maxilla, a moderately reduced transverse inter-maxillary width and mildly reduced transverse inter-mandibular widths. It was a secondary aim to establish a screening standard for the general dental practitioner, orthodontist and paediatric specialists for early diagnosis of paediatric SDB. Our results suggest that for children 8 years and above, a maxillary inter-canine width <27 mm could be employed as a screening tool to alert clinicians to further explore risk of SDB.

Snoring children showed some reduction in SDB-related quality of life. Rapid maxillary expansion was shown to be beneficial in improving the lowered SDB-related quality of life, in snoring children deemed at-risk of SDB, in the short-term.

Future research should endeavour to establish the association between craniofacial and upper airway morphology and paediatric SDB in all three dimensions. Airway fluid-flow dynamics are also an area that needs to be defined and researched to establish individualised treatments for SDB-suffering children. Further studies are warranted to define the characteristics of patients who may benefit most from orthodontic treatment. Larger sample sizes and longer follow up periods are recommended to show the relative

contributions of each therapy when managing these children with a multi-disciplinary approach.

A greater degree of collaboration between sleep medicine, ear, nose and throat specialists and orthodontists is required to establish individualised approaches for a successful treatment and/or cure when managing paediatric SDB. It is imperative to set-up referral pathways between relevant departments for efficient access to multi-disciplinary treatments. Such an attempt is currently underway between the Orthodontic Unit at the Adelaide Dental Hospital, Adelaide, Australia and the Sleep Disorders Unit at the Womens and Childrens Hospital, Adelaide, Australia to improve access towards a multidisciplinary treatment plan for children suffering from SDB. This will also facilitate future research projects in evaluating the efficacy of multi-therapeutic treatments for the management of paediatric SDB.

The woods are lovely, dark and deep.
But [we] have promises to keep,
And miles to go before [we] sleep,
And miles to go before [we] sleep.

Robert Frost

APPENDIX A: Ethical Approval

Government of South Australia
SA Health

Central Adelaide Local Health Network

SA Dental Service

Evaluation and Research Unit

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SADS

16 February 2012

Prof Wayne Sampson
Dental School
The University of Adelaide
Adelaide 5005

Dear Wayne,

RE: Prevalence of paediatric Sleep Disordered Breathing (SDB) and effects of dentofacial orthopedic treatment on quality of life in paediatric SDB)

RAH HREC approved: 120102 (dated 09/01/2012)

Following the project submission by Dr Vandana Katyal to SA Dental Service, the above proposal involving a request to contact suitable Orthodontic Unit clients for participation in repeated completion of two questionnaires, was approved by the CALHN Statewide Services, SA Dental Service, Strategic Executive meeting on 15 February 2012.

This letter confirms the endorsement of SA Dental Service to support this research project proposal and the approval for the project to proceed with suitable study cases recruited from clients attending the Orthodontic Unit, ADH, as outlined in the submitted project methodology.

Should you or Vandana require any assistance or should any further logistical issues arise, to support your research project within the day to day running of the operational aspects of the project, in the first instance please discuss this with Dr Bronwyn Scopacasa, A/Director, Orthodontic Unit, Adelaide Dental Hospital.

Yours sincerely

Andrew Chartier
Director Evaluation & Research Unit
SA Dental Service

cc: Dr. Bronwyn Scopacasa, A/Director Orthodontic Unit, ADH
Ms Anne Pak-Poy, General Manager ADH
Dr Vandana Katyal (postgraduate student)

Sleepdisorderedbreathing_Katyal_Feb12- General_RESEARCH APPROVAL.Docx

APPENDIX B: Paediatric Sleep Questionnaire

CHILD SLEEP BREATHING STUDY QUESTIONNAIRE NO. 1

STUDY ID: _____ DATE: _____

Please circle questions as Yes, No or Unsure. Thank you.

1. **While sleeping, does your child…**
   a. …ever snore? Yes/No/Unsure
   b. …snore usually? Yes/No/Unsure
   c. …always snore? Yes/No/Unsure
   d. …snore loudly? Yes/No/Unsure
   e. …have "heavy" or loud breathing? Yes/No/Unsure
   f. …have trouble breathing, or struggle to breathe? Yes/No/Unsure

2. **Have you ever…**
   a. …seen your child stop breathing during the night? Yes/No/Unsure
   b. …been concerned about your child's breathing during sleep? Yes/No/Unsure
   c. …had to shake your sleeping child to get him or her to breathe, or wake up and breathe?
      Yes/No/Unsure

3. **Does your child…**
   a. …tend to breathe through the mouth during the day? Yes/No/Unsure
   b. …have a dry mouth on waking up in the morning? Yes/No/Unsure
   c. …occasionally wet the bed? Yes/No/Unsure
   d. …have restless sleep? Yes/No/Unsure
   e. …sweat overnight? Yes/No/Unsure

4. **Does your child…**
   a. …wake up feeling unrefreshed in the morning? Yes/No/Unsure
   b. …have a problem with sleepiness during the day? Yes/No/Unsure

5. **On a normal week day….**
   a. …what time does your child normally go to sleep? _____AM/PM
   b. …what time does your child normally wake up? _____AM/PM

6. **Has a teacher or other supervisor commented that your child appears sleepy during the day?** Yes/No/Unsure

7. **Is it hard to wake your child up in the morning?** Yes/No/Unsure

8. **Does your child wake up with headaches in the morning?** Yes/No/Unsure

9. Did your child stop growing at a normal rate at any time since birth?

Yes/No/Unsure

10. Is your child overweight? Yes/No/Unsure

11. Does your child often…

a. …not listen when spoken to directly Yes/No/Unsure

b. …have difficulty organising task & activities Yes/No/Unsure

c. …becomes easily distracted Yes/No/Unsure

d. …fidget with hands or feet or squirm in their seat Yes/No/Unsure

e. …often acts as if they are "driven by a motor", that is "constantly on the go"

Yes/No/Unsure

f. …interrupt or intrude on others Yes/No/Unsure

12. Has your child had tonsils or adenoids removed? Yes/No/Unsure

a. Adenoids only? Yes/No Date:_____

b. Tonsils only? Yes/No Date:_____

c. Tonsils and adenoids? Yes/No Date:_____

13. Has your child had any surgery or procedures performed on their nose or mouth?

Yes/No/Unsure

Details if answer is **YES** above:_____

14. Does the child's father…

a. …snore? Yes/No/Unsure

b. …have any breathing problems? Yes/No/Unsure

c. Details of problem _____

15. Does the child's mother…

a. …snore? Yes/No/Unsure

b. …have any breathing problems? Yes/No/Unsure

c. Details of problem _____

16. Your relationship to the child? (Tick one)

a. Mother

b. Father

c. Grandparent

d. Guardian / Carer

e. Other (Please specify) _____

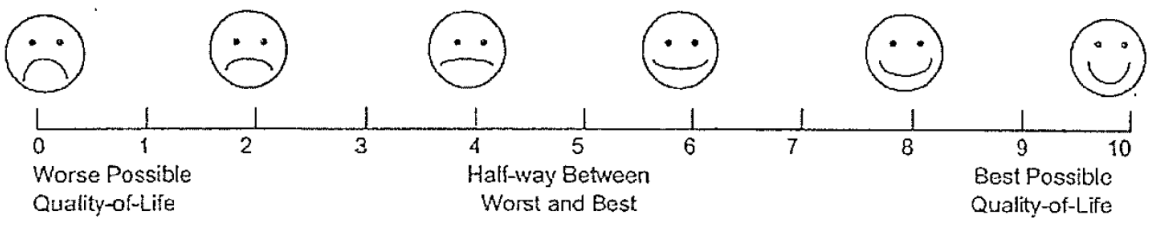
APPENDIX C: OSA-18 QoL Questionnaire

CHILD SLEEP BREATHING STUDY QUESTIONNAIRE NO. 2
STUDY ID: _____ DATE: _____

For each question below, please circle the number that best describes how often each symptom has occurred during the past 4 weeks. Thank you.

	None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
SLEEP DISTURBANCE							
During the past 4 weeks, how often has your child had..							
..loud snoring?	1	2	3	4	5	6	7
..breath holding spells or pauses in breathing at night?	1	2	3	4	5	6	7
..choking & gasping sounds while asleep?	1	2	3	4	5	6	7
..restless sleep or frequent awakenings from sleep?	1	2	3	4	5	6	7
PHYSICAL DISCOMFORT							
During the past 4 weeks, how often has your child had..							
..mouth breathing because of nasal obstruction?	1	2	3	4	5	6	7
..frequent colds or upper respiratory infections?	1	2	3	4	5	6	7
..nasal discharge or runny nose?	1	2	3	4	5	6	7
..difficulty in swallowing food?	1	2	3	4	5	6	7
EMOTIONAL DISTRESS							
During the past 4 weeks, how often has your child had..							
..mood swings or temper tantrums?	1	2	3	4	5	6	7
..poor attention span or concentration?	1	2	3	4	5	6	7
..difficulty getting out of bed in the morning?	1	2	3	4	5	6	7
CAREGIVEN CONCERNS							
During the past 4 weeks, how often have the above problems..							
..caused you to worry about your child's general heath?	1	2	3	4	5	6	7
..created concern that your child is not getting enough air?	1	2	3	4	5	6	7
..interfered with your ability to perform daily activities?	1	2	3	4	5	6	7
..made you frustrated?	1	2	3	4	5	6	7

OVERALL, HOW WOULD YOU RATE YOUR CHILD'S QUALITY OF LIFE AS A RESULT OF THE ABOVE PROBLEMS?
(Circle one number)



APPENDIX D: Recommendations to the Sleep Disorders Unit, Womens and Childrens Hospital.

Following findings and recommendations were reported to the Sleep Disorders Unit, WCH during the period of this thesis following an audit of patient records:

1. Lateral Neck xrays (unstandardised) were taken in a different head positions. Although this may be appropriate for younger children, it may not be so for older children. This may change the airway dimensions. A standardised lateral cephalogram is recommended as the radiograph most suited to the diagnosis of nasopharyngeal dimensions as well as craniofacial morphology. It is also preferred for future research as the magnification factor can be determined with accuracy.

2. Most lateral neck radiographs audited were taken in an open mouth posture that increases lower anterior facial height erroneously and does not allow correct comparisons across the sample.

3. A cross-referral pathway should be instated for children suffering from sleep-disordered breathing to seek orthodontic diagnosis and treatment.

4. A multi-disciplinary clinic involving paediatricians, sleep physicians, ENT surgeons, orthodontists, etc. should be planned to discuss diagnosis, treatment alternatives and progress for children suffering from sleep-disordered breathing.

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