Obstructive sleep apnea in children: Different approaches for screening, management, and patient engagement

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Medical Sciences - Dentistry
University of Alberta

Abstract

BACKGROUND: The disruption of normal respiratory and ventilation patterns during sleep, also called sleep-disordered-breathing (SDB), is a condition that may vary from simple snoring to obstructive sleep apnea (OSA). The heterogeneity of this disorder may result in difficulties in diagnosis and management, which may contribute to increased costs to the healthcare system and negative consequences for children and their families. The most common line of treatment for pediatric OSA is adenotonsillectomy (T&A), and the persistence of OSA after T&A is called residual OSA. Some orthodontic management options, such as rapid maxillary expansion and mandible repositioning, have displayed short-term improvement in pediatric OSA signs and symptoms; however, the association between craniofacial morphology and pediatric OSA is still mostly unclear. Beyond the craniofacial perspective, patients' experiences with OSA management alternatives may provide insights into their impact on sleep quality and their interaction with health services. The goals of this thesis are to *(i)* evaluate the role of craniofacial screening in identifying children at high-risk for OSA, (ii) understand parents' experiences with services for managing residual pediatric OSA and *(iii)* set up a prospective cohort study to assess the impact of orthodontic management alternatives in a group of children with residual OSA.

METHODS: To evaluate the role of craniofacial screening in identifying children at high-risk for OSA, a systematic review, three cross-sectional studies were completed. The systematic review explored the association between skeletal and soft craniofacial features in children with pediatric OSA. The first prospective study evaluated facial 3D stereophotogrammetry's effectiveness as a screening tool for pediatric OSA when used by dental specialists from a sample of children fully diagnosed with pediatric OSA through nocturnal polysomnography (PSG) or at high- or low-risk of pediatric OSA. In the second prospective study, we investigated the role of

craniofacial features as a means of identifying phenotypes of children with OSA symptoms, using a clustering analysis method to identify and characterize craniofacial phenotypes. The retrospective study evaluated differences in mandibular cortical width (MCW) among children diagnosed with OSA or at high- or low-risk for OSA. Parents' experiences with services for managing pediatric OSA were explored through a qualitative descriptive study. Finally, a protocol to develop a cohort study investigating the impact of orthodontic treatment among children with residual OSA was proposed.

RESULTS: Our systematic review suggested that neither an association nor a lack thereof between craniofacial features and pediatric OSA could be supported at this time. In both the prospective and the retrospective studies, even though a soft facial features analysis did not show reasonable results to be used alone as a pediatric OSA screening tool by dental specialists, some specific craniofacial features were associated to pediatric OSA. A reduced mandibular cortical width was observed among children diagnosed with or at high risk of OSA compared to healthy children. Children from 7-9 years with suspected OSA, without obesity, and moderate severity of obstructive sleep events, presented mildly arched palate, higher upper facial height, and higher mandible dimensions; however, children from the same age range and sleep features with obesity presented different craniofacial features suggestive of orthodontic treatment need, including excessive lower facial height and midface deficiency. Overall, parents reported that their actions and the services received from several care providers at primary, secondary, and tertiary levels of care were largely ineffective or suboptimal in addressing the sleep issue that negatively affected their children's sleep quality and life. Based on these findings and considering the need to better understand the role of orthodontic treatment among children with residual OSA, a cohort study evaluating the effectiveness of orthodontic interventions compared to a control group is proposed.

CONCLUSION: Soft craniofacial features, mandibular cortical width, and specific craniofacial features may help explain the heterogeneity and complexity of pediatric OSA and describe children with and without obesity presenting a high risk for the condition. However, soft-craniofacial-based tools alone cannot be used as a screening tool. Specific phenotyping may be the best way to identify a subgroup of pediatric OSA children that could be screened based on their craniofacial features or that would directly benefit from specific orthodontic interventions. There is also a suggested need for improving the effectiveness of services to deal with sleep issues.

Preface

This thesis is an original work by Nathalia Carolina Fernandes Fagundes. The three research projects, of which this thesis is a part of, received ethical research approval from the University of Alberta Research Ethics Board, Project names *Contribution of craniofacial form to the pathogenesis of pediatric obstructive sleep apnea*, Protocol No. Pro00057638, July 24,2015; *Obstructive sleep apnea and mandibular bone density*, Protocol No. Pro00057046, August 05, 2015; and *Residual pediatric obstructive sleep apnea: closing the treatment gap* Protocol No. Pro00084763, August 08, 2019. Two studies have been supported by American Association of Orthodontists Foundation research grants. Nathalia Fernandes Fagundes also received support from CAPES Foundation (Brazilian Federal Agency for Support and Evaluation of Graduate Education).

A version of Chapter 2 is published at the *Journal of Clinical Sleep Medicine* as Fagundes NCF, Gianoni-Capenakas S, Heo G, Flores-Mir C. Craniofacial features in children with obstructive sleep apnea: a systematic review and meta-analysis. *Journal of Clinical Sleep Medicine*, 2022;18(7):1865-1875. Available from: https://doi.org/10.5664/jcsm.9904. Nathalia Carolina Fernandes Fagundes prepared the protocol, screened abstracts and full-length articles and wrote the manuscript. Silvia Gianoni-Capenakas screened abstracts and full-length articles and revised the manuscript. Giseon Heo assisted in the conceptualization of the review, revised and edited the manuscript. Carlos Flores-Mir was the supervised all the steps of the review and edited the manuscript.

A version of Chapter 3 is published at the *Journal of Clinical Sleep Medicine* as Fagundes NCF, Carlyle T, Dalci O, Darendeliler MA, Kornerup I, Major PW, Montpetit A, Pliska BT, Quo S, Heo G, Flores-Mir C. Use of facial stereophotogrammetry as a screening tool for pediatric

obstructive sleep apnea by dental specialists. *Journal of Clinical Sleep Medicine*, 2022: 18(1):57-66. Available from: https://doi.org/10.5664/jcsm.9490. Nathalia Carolina Fernandes Fagundes collected, analyzed data, and wrote the manuscript. Terry Carlyle, Oyku Dalci, M. Ali Darendeliler, Ida Kornerup, Paul W. Major, Andree Montpetit, Benjamin T. Pliska, and Stacey Quo participated in data assessment and revised the manuscript. Giseon Heo and Carlos Flores-Mir were joint senior authors. They supervised all the steps of this study and edited the manuscript.

A version of Chapter 4 was submitted to *Journal of Clinical Sleep Medicine* as Fagundes NCF, Loliencar P, MacLean JE, Flores-Mir C, Heo G. Characterization of craniofacial-based clinical phenotypes in children with sleep-disordered breathing, 2022. Nathalia Carolina Fernandes Fagundes collected, analyzed part of the data, and wrote the manuscript. Prachi Loliencar performed all the statistical analysis, contributed to writing and revising the manuscript. Joanna E. MacLean assisted data collection, participated on data analysis conceptualizing, and revised the manuscript. Carlos Flores-Mir assisted on results interpretation and revised the manuscript. Giseon Heo was the senior authors. She supervised all the steps of this study and edited the manuscript.

A version of Chapter 5 was published at the *Journal of Clinical Sleep Medicine* as Fagundes NCF, D'Apuzzo F, Perillo L, Puigdollers A, Gozal D, Graf D, Heo G, Flores-Mir C. Potential impact of pediatric obstructive sleep apnea on mandibular cortical width dimensions. Journal of Clinical Sleep Medicine, 2021: 17(8):1627-34. Available from: https://doi.org/10.5664/jcsm.9262. Nathalia Carolina Fernandes Fagundes collected, analyzed data, and wrote the manuscript. Fabrizia D'Apuzzo, Letizia Perillo, Andreu Puigdollers assisted data collection and revised the manuscript. David Gozal and Daniel Graf assisted results interpretation and revised the manuscript. Giseon Heo assisted statistical analysis, results

interpretation and revised the manuscript. Carlos Flores-Mir supervised all the steps of this study and edited the manuscript.

A future version of Chapter 6 will be prepared for publication as Fagundes NCF, Young R, Heo G, Flores-Mir C, Perez A. Parents' perspectives of their journeys through health services for pediatric obstructive sleep apnea. An exploratory qualitative description study, 2022. Nathalia Carolina Fernandes Fagundes collected, analyzed data, and wrote the manuscript. Rochelle Young assisted the project conceptualization, data collection and revised the manuscript. Giseon Heo and Carlos Flores-Mir assisted project conceptualization, results interpretation and revised the manuscript. Arnaldo Perez supervised all steps of the study and edited the manuscript.

A version of Chapter 7 was published at the *BMJ Open* as Fagundes NCF, Perez-Garcia A, Graf D, Flores-Mir C, Heo G. Orthodontic interventions as a management option for children with residual obstructive sleep apnea: A cohort study protocol. BMJ Open, 2022 Jun 15: 12(6):e061651. Available from: http://dx.doi.org/10.1136/bmjopen-2022-061651. Nathalia Carolina Fernandes Fagundes prepared the protocol and wrote the manuscript. Arnaldo Perez-Garcia and Daniel Graf assisted manuscript writing. Carlos Flores-Mir and Giseon Heo supervised the conceptualization and design of the study and revised the manuscript.

Unless otherwise specified, the data presented in this thesis is Nathalia Carolina Fernandes Fagundes' original work.

Dedication

I dedicate this thesis to my daughter Julia. She presented me with new reasons to fight for my dreams while showing me the bittersweet taste of motherhood and teaching me the meaning of unconditional love.

Acknowledgements

To my supervisor, Dr. Carlos Flores-Mir. Thank you for the countless hours of reflecting, reading, editing, encouraging, and most of all patience throughout the years. I am very grateful for your unique mentorship, training and professional growth opportunities given throughout my PhD studies.

To my co-supervisor, Dr. Giseon Heo, for her thoughtful encouragement, support, and constant supervision to accomplish this work.

To my thesis committee member, Dr. Arnaldo Perez, for his unique mentorship and opportunities for professional growth.

To my committee member, Dr. Daniel Graf, for always providing with his unique collaboration, feedback and guidance during all steps of this work.

To my various collaborators, Dr. Terry Carlyle, Dr. Oyku Dalci, Dr. M. Ali Darendeliler, Dr. Ida Kornerup, Dr. Paul W. Major, Dr. Andree Montpetit, Dr. Benjamin T. Pliska, Dr. Stacey Quo, Dr. Prachi Loliencar, Dr. Joanna MacLean, Dr. Fabrizia D'Apuzzo, Dr. Letizia Perillo, Dr. Andreu Puigdollers, and Dr. David Gozal - thank you for supporting our work. It wouldn't have been what it is today without all your assistance.

To Nurse practitioner Rochelle Young and registered nurse Kellea Selmser, from the department of Pediatric Sleep Medicine, Stollery Children's Hospital; research coordinator Charlene Cars, and clinical research director Dr. Dory Sample from the Women & Children's Health Research Institute (University of Alberta, Canada). Their guidance and expertise were essential to develop my skills as clinical researcher. Many thanks also go to the Stollery Children's

Hospital Sleep clinic and Pediatric sleep lab staff; University of Alberta, Orthodontic Graduate Clinic personnel; and participants of this research.

To my former supervisors back home, in Brazil, Dr. David Normando and Dr. Rafael R. Lima. My inspiration to pursue an academic career came from both. My ability to think critically and understand science is primarily due to their mentorship since my undergraduate studies. Thank you for motivating me to always go the extra mile, even while living in a country with so many socioeconomic difficulties as Brazil. For this, I am very grateful.

To Julia, my beloved daughter, who arrived at the beginning of this PhD journey and gave me more reasons to fight for what I believe. To my parents, my sisters and my grandmother, who even from many miles away, gave me all the emotional support during this time and were always present physically when possible. To my friends, who gave me support and help me to have good laughs about life during this period.

To my funding sources, CAPES Foundation (Brazilian Federal Agency for Support and Evaluation of Graduate Education), Faculty of Medicine and Dentistry, Faculty of Graduate Studies and Research, Graduate Students Association – thank you for believing in my work and financially supporting me such that I focus on doing research as an international student.

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List of Common Symbols, Nomenclatures, and Abbreviations

Abbreviation	Definition
Akaike Information Criterion	AIC
Apnea-Hypopnea Index	AHI
Automatic Positive Airway Pressure	APAP
Bilevel Positive Airway Pressure	BiPAP
Bone-mass-index	BMI
Children's Sleep Habits Questionnaire	CSHQ
Cone-beam computed tomography	CBCT
Continuous Positive Airway Pressure	CPAP
Craniofacial Index	CFI
dual-energy X-ray absorptiometry	DXA
Ear-nose-throat physician	ENT
Electrocardiogram	ECG
Electroencephalogram	EEG
Electromyogram	EMG
Electrooculogram	EOG
Grading of recommendations, assessment, development, and evaluations	GRADE
Health Screening Questionnaire	HSQ
Home sleep apnea test	HSAT
Intraclass correlation coefficient	ICC
Mandibular advancement device	MAD
Mandibular cortical width	MCW
Most Frequent	MF
Negative Predictive Value	NPV
non-Rapid Eye Movement	n-REM
Obstructive Apnea-Hypopnea Index	OAHI
Obstructive sleep apnea	OSA
Obstructive–Mixed Apnea–Hypopnoea Index	OMAHI
Pediatric Daytime Sleepiness Scale	PDSS
Pediatric Quality of Life Inventory	PedsQL
Pediatric Sleep Questionnaire	PSQ
Periodic limb movement disorder	PLMD
Polysomnography	PSG
Positive airway pressure therapy	PAP
Positive Predictive Value	PPV
Preferred Reporting Items for a Systematic Review and Meta-analysis	PRISMA

Rapid Eye Movement	REM
Rapid maxillary expansion	RME
Restless legs syndrome	RLS
Reverse Pull Headgear	RPHG
Sensitivity	Se
Sleep-disordered breathing	SDB
Specificity	Sp
Statistical, Mathematical, Intelligence Learning E-algorithm	SmiLe
The Metabolomics Innovation Centre	TMIC
Three-dimensional	3D
Tonsillectomy and/or adenoidectomy	T&A
Unstructured to structured data	U2S
Variance inflation factor	VIF

Chapter 1 : Introduction

Obstructive sleep apnea (OSA) is a respiratory sleep disorder characterized by partial or complete upper airway obstruction that disrupts normal ventilation during sleep.[1] This condition affects 1 to 5% of children and adolescents worldwide.[2] Children with OSA may experience long-term social and health consequences. For example, their academic and professional performances may be lower than those of healthy children later in life.[3] This condition may increase healthcare utilization and hospital visits up to 40% before OSA is diagnosised.[4] In addition, pediatric OSA is also associated with multiple diseases and co-morbidities, such as asthma,[5] obesity,[6] and cardiac abnormalities.[7]

There are many challenges to screening and managing pediatric OSA. The standard diagnosis process includes overnight observed polysomnography (PSG) - evaluating multiple parameters during a whole night of sleep inside a hospital clinical setting.[8] This technique is expensive and difficult to access due to long wait times.[9] For example, in Canada, the wait for an PSG could be up to 24 months.[10] Improved screening processes are needed to streamline complete diagnosis among those at higher risk for OSA.

Usually, family physicians or pediatricians are the primary healthcare providers involved in identifying the early signs and symptoms of OSA.[11] If appropriate, these professionals may refer children with OSA to specialized sleep services for further diagnosis and management of this condition. Sleep specialists may also refer children with OSA to other professionals, such as dentists, ear-nose-throat physicians (ENT), and pediatric respirologists.[11, 12] Hypertrophic adenoids and tonsils in children might be an etiological factor for pediatric OSA via upper airway obstruction.[12] Tonsillectomy and/or adenoidectomy (T&A) is usually the first management option

for OSA among children with enlarged tonsils and adenoids, frequently observed in children between 2-7 years old.[13] However, this surgical option may not be suitable or improve OSA signs and symptoms in all cases. Research has shown that 20-30% of pediatric patients do not benefit from this treatment.[14]

Parents and caregivers play an important role in children's engagement in services for OSA due to the complexity and heterogeneity of OSA in this age group.[15] The uncertainty regarding best management options for pediatric OSA, especially in children without adenotonsillar hypertrophy, highlights the importance of parents' involvement in decision-making regarding management options.[16] Parents also play a key role in ensuring children's adherence to management options by providing the emotional and logistical support they need to comply with treatment regimens and recommendations.[17]

1.1. Pediatric OSA pathophysiology

OSA happens when there is an obstruction in the upper airways linked to hypoventilation during the sleep, however; the pathophysiology of this disorder is still not fully understood.[8, 18] The primary features that may explain this phenomenon are anatomical and functional factors resulting in upper airway narrowing and collapse during sleep breathing.[19, 20] More specifically, variations in the size and shape of both skeletal and soft craniofacial structures that may require orthodontic attention (e.g., arched palate, excessive lower facial height, open bite) and anomalies on the neuromuscular compensation of the upper airways may contribute to this health problem. [19, 20]

Among anatomical factors, both skeletal and soft tissue features may play a role in upper airway narrowing and collapse during sleep. Several skeletal abnormalities (i.e., growth

deficiencies, variations from craniofacial normal development pattern) have been suggested to contribute to this scenario, such as midfacial hypoplasia, nasal septum deviation, mandible retrognathia, an decreased posterior facial height.[12, 21, 22] The soft tissue features that may predispose children to airway narrowing and collapse might be an abnormal size of the upper airway soft tissues, such as tonsils, adenoids, fat pads and muscles, and increased size of adjacent structures (e.g., tongue and soft palate).[23, 24] Also, there are functional features, more specifically an abnormal neuromuscular tone, that may impair active dilation of the upper airway and lead to an obstruction.[20, 25]

Both anatomical and functional features may contribute to OSA via biomechanical changes. These features may lead to abnormal gas exchange in the upper airways, an increase in nasal airflow resistance and a drop in the pharyngeal pressure, resulting in a partial or complete airway obstruction during sleep.[26] However, the relative contribution of each feature and the mechanisms leading to OSA through biomechanical changes in children are not well documented in the available literature.[24]

In addition, the cause for these anatomical and functional features may have multiple sources, including genetic syndromes, obesity, altered bone development, respiratory infections, or inflammatory processes.[27-30] Often, these features are interpreted as risk or etiological factors for OSA in children, even though the precise pathways of how these factors may contribute to the development of OSA and their influence on the management outcomes of OSA interventions are not well understood.[24] For example, genetic factors may contribute to craniofacial skeletal disorders (e.g., Down syndrome, Treacher Collins) that may result in a narrow upper airway, while an infection or inflammatory process may result in the hypertrophy of adenoids and tonsils among children.[18-20] The hypertrophy of adenoids and tonsils and obesity, are considered primary risk

factors for pediatric OSA.[31] However, due to the heterogeneity of OSA among children, it is a challenge to understand the pathophysiology and etiological factors that contribute to this disorder.

1.1.Screening for pediatric OSA

The PSG is the gold standard for sleep parameters evaluation and OSA diagnosis in children. This exam records oxygen saturation, oronasal airflow, respiratory movement, electroencephalogram (EEG), body position, electromyogram (EMG), electrooculogram (EOG) and electrocardiogram (ECG) of a whole night of sleep.[32] The diagnosis of pediatric OSA is based on the presence of selected signs and symptoms (e.g.,snoring, obstructing breathing during sleep, sleepiness and behavioural problems) associated with PSG findings (e.g.,presence of one or more obstructive apneas, mixed apneas, or hypopneas - per hour of sleep, or a pattern of obstructive hypoventilation with concomitant snoring, flattening of the inspiratory nasal pressure waveform, or paradoxical thoracoabdominal motion).[8]

Using PSG as the standard method for pediatric OSA diagnosis is challenging due to accessibility barriers (e.g., cost, wait times) and an inherent limitations of this exam to assess the severity and monitor the management outcomes for OSA.[33, 34] Additionally, the sleep study setting is inherently different than the one a child faces at home. This questions if the measured parameters depict actual sleep performance or simply an uncomfortable night away from the home comfort.[35] Alternative evaluation methods are needed when PSG is unavailable and there is a need to investigate clinical parameters beyond the number of apneas episodes during sleep.

Alternative tools for screening pediatric OSA have focused on identifying children at high risk for this disorder. Some of these screening tools (e.g., Pediatric Sleep Questionnaire [PSQ] and the Children's Sleep Habits Questionnaire [CSHQ])[36] rely on self-reported signs and symptoms of

OSA, others focus the on the identification of anatomical factors (e.g., screening of adenotonsillar size or upper airway dimensions)[37, 38] and others evaluate sleep parameters, such as the monitoring of respiratory and cardiovascular features during sleep using overnight pulse oximetry, home sleep apnea tests (HSAT), and actigraphy.[39-41] Even though some of these tools might screen critical features of pediatric OSA, to date, there is no tool available with an acceptable level of accuracy, compared to PSG, to diagnose this disorder. The nocturnal oximetry and HSAT showed the best results compared to other alternative methods. Nocturnal oximetry had a reported sensitivity of 74% and specificity of 90%,[39] and HSAT with a reported sensitivity of 82% and specificity of 90%.[40, 42] The use of alternative screening tools, although not used as standard exams, may help offer personalized diagnosis and management options for this disorder.

1.1.1. Screening tools based on craniofacial analysis

An approach that might diminish the challenge in the screening and managing pediatric OSA is exploring phenotypes linked to OSA pathophysiology and their role in screening children for this condition. Previous cross-sectional studies have reported a higher prevalence of some skeletal craniofacial features in children with OSA compared to a group of children without OSA.[43, 44] These features include increased facial height, labial incompetency, mandible retrognathia, increased overjet, higher mandible angle, and a steeper mandibular plane. [43, 44] The association between craniofacial features and pediatric OSA has been previously hypothesized, but it is still not established. As mentioned earlier, it has been suggested that the position and size of craniofacial bones might be associated with upper airway narrowing.[19, 43]

During their craniofacial growth and development, different craniofacial configurations can be observed in children and adolescents. Most studies investigating the association between

craniofacial features and pediatric OSA are primarily based on skeletal features.[43, 45-47] Although somehow related, the most likely impact will come from alterations in the soft tissue surrounding the upper airways. In that sense, relying on a skeletal analysis might be limited to understanding this association. The evaluation of soft craniofacial features may explore additional characteristics contributing to the upper airway obstruction (e.g. nose width, nasofacial angle)[48], and it may add more details regarding the impact of bone-mass-index (BMI) of individuals, which may also help to understand the effect of obesity, a recognized risk factor for pediatric OSA.[44] Also, the assessment of soft tissue features may have some advantages compared to solely skeletal evaluation, considering that it may be used to screen some equivalent features from the skeletal assessment without exposing children to unnecessary radiation craniofacial features.[44, 49] In summary, the association between facial features and pediatric OSA remains to be understood. Therefore, it is still necessary to analyze the craniofacial changes, on a longitudinal basis, during childhood in this population. There may be a specific phenotype of interest with a robust craniofacial component.

In addition, the evaluation of specific craniofacial features may also be employed as a proxy to analyze other systemic changes that might be associated with pediatric OSA. Oral panoramic radiographs have been presented as an useful tool to evaluate mandibular cortical width (MCW) as a marker for bone density in adults and children.[50, 51] A possible association between low bone mass and pediatric OSA was highlighted in previous work from our group, showing that children at risk or diagnosed with OSA, with an average of 11.4 ± 2.9 years, presented an MCW 20% smaller than healthy children.[51] To our knowledge, this was the only study investigating this characteristic among children. Evaluating mandible morphology as a source to further explore the

relationship between pediatric OSA and low bone mass can be an accessible method due to the frequency of oral panoramic radiographs among dental and orthodontic records.[50]

There are also potential benefits for a craniofacial morphology evaluation in identifying patients at high-risk for pediatric OSA as their accessible and convenient techniques for routine clinical use. Facial analysis can be performed by a clinical examination in a dental office, oral panoramic radiographs, cephalometric analysis, and 2D or 3D photos. The involvement of dental professionals in the craniofacial assessment of children with OSA will also contribute to their integration in a transdisciplinary team led by the ENT and sleep medicine specialists. Dental professionals examine children more frequently than pediatricians after children are older than two years of age.[52] This opens the possibility for dental professionals to be at the front line to screen for patients at high risk of OSA.

1.2. Management of pediatric OSA

The current first line of action for pediatric OSA management is T&A, as hypertrophic adenoid and tonsillar tissues are the most likely obstructive cause.[53] Also, intranasal corticosteroids, nasal septum surgery, in addition to weight management and the monitoring of present comorbidities (e.g., asthma, cognitive disorders) may also represent appropriate management options.[54] In the cases which T&A may not be suitable or may not fully improve OSA, the persistence of the disorder is referred to as residual OSA.[55]

Pharmacological management, and positive airway pressure (PAP) therapy (e.g. Continuous Positive Airway Pressure (CPAP), Bilevel Positive Airway Pressure (BiPAP), Automatic Positive Airway Pressure (APAP) therapies) have been suggested as residual OSA management options in children.[56, 57] Other alternative options, such as oral appliances and myofunctional treatment that may also benefit children with residual pediatric OSA.[58-60] A

multidisciplinary team should facilitate the diagnosis and management of OSA. Such teams should consist of a sleep medicine physician and an ENT specialist, among other health professionals, as indicated by the individual case characteristics. Lately, there has been an interest in including dentists or orthodontists, when indicated, among these transdisciplinary management teams.[61] Figure 1 and Figure 2 provide a summary of the current management options for pediatric OSA.

CPAP therapy is the management of choice when T&A or if T&A is not effective or recommended.[62, 63] This device provides non-invasive ventilatory support and positive airway pressure to overpower upper airway obstruction during sleep. While this is a well-established therapy for adults, few prospective studies have evaluated this therapy in children. Changes in craniofacial growing are a possible undesirable effect of prolonged use of CPAP in children presenting sleep-disordered breathing.[62] The continuous pressure of the mask over the maxillo-mandibular complex can restrict the sagittal development of these structures.

Mandibular advancement devices (MADs) and rapid maxillary expansion (RME) have been proposed and evaluated as management options for mild and moderate pediatric OSA cases. An AHI (Apnea-Hypopnea Index) decrease of about 6 points after RMEs and MADs has been reported in systematic reviews.[59, 60] So far, these approaches have shown a capability to diminish some OSA symptoms, at least temporarily, in children with craniofacial problems or anomalies associated with an orthodontic indication.[59, 64] Another seldomly explored orthodontic approach uses a Reverse Pull Headgear (RPHG) to facilitate maxillary forward growth. This may also increase the nasopharyngeal dimension's sagittal dimension and potentially reduce the collapsibility of the nasopharynx.

Few clinical studies, with a significant risk of bias, have investigated orthodontic appliance-based management options for OSA children. Thus, further clinical studies evaluating

the effect of these appliances on OSA are needed to understand the role of orthodontic management and CPAP therapy in treating this disease, especially for patients from whom T&A was not an option or did not significantly improve airway obstruction.

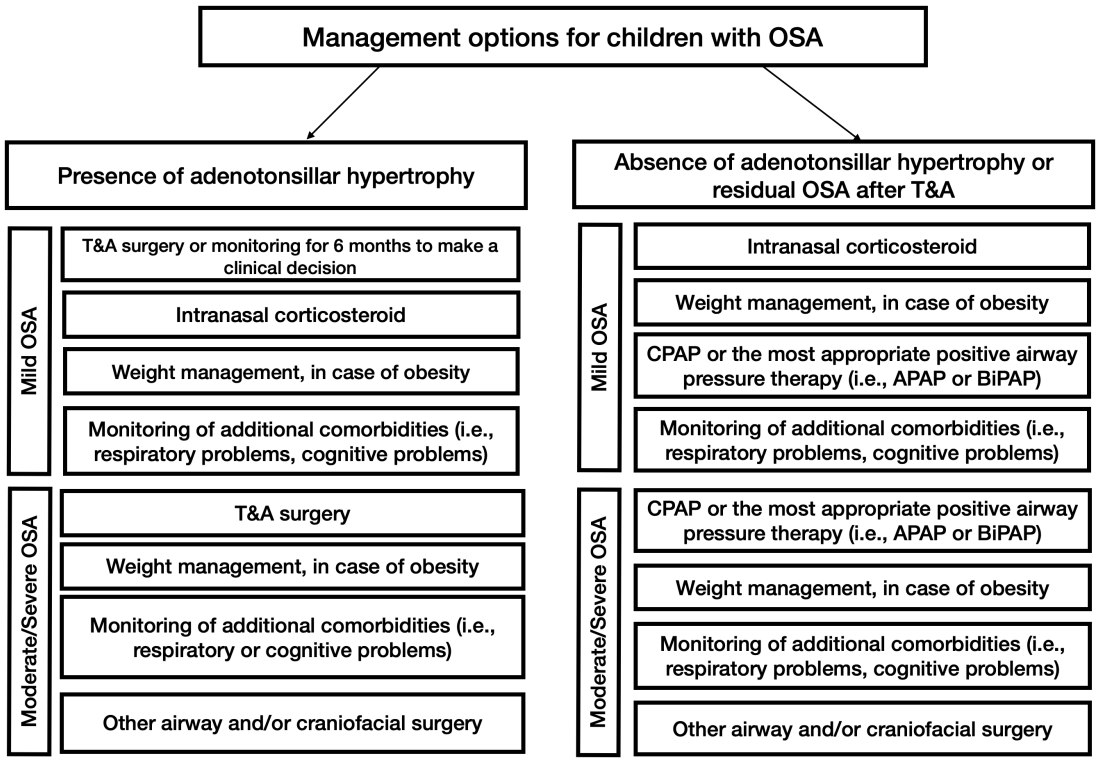

Figure 1.1 OSA management options among children.

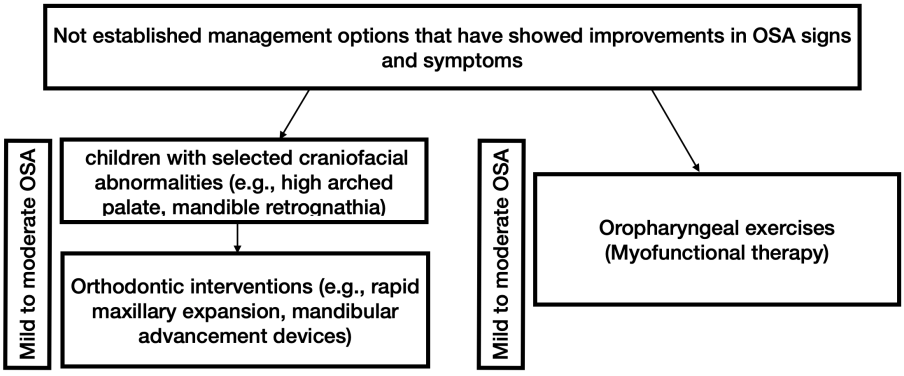

Figure 1.2 Not established management options that have showed improvements in OSA signs and symptoms in children with residual OSA.

1.3. Parents' perspectives of managing OSA in children

Physicians, more specifically ENT specialists, sleep specialists and pediatric respirologists are the frontline healthcare providers who manage pediatric OSA.[9] Nurse practitioners, dental professionals, psychologists, speech pathologists, nutritionists, physiotherapists may also be part of the care team.[12] As mentioned earlier, parents have an important role in facilitating their children's engagement in and compliance with services for managing OSA. They are also in a opposition to comment on the effectiveness of available management options for addressing OSA in terms of quality of life and symptom management based on their personal experiences.[65] Understanding parents' views and experiences with these management options may shed light on factors that facilitate or hinder the engagement of children in these services and their strengths and limitations.

Engagement in management options for chronic conditions has been found to be challenging for families and care providers. Dealing with these conditions over time requires preparation, support, and resources.[66] The lack of established protocols to manage pediatric OSA and the uncertainty surrounding the effectiveness of available management options may negatively affect families' decision to initiate, continue and adhere to treatment.[67] Parents play a key role engaging in services, communicating with healthcare providers, and facilitating their children's adjustments to the physical and emotional consequences of chronic conditions.[68] For example, among adolescents with OSA using CPAP, the high usage of this device was associated to a stable family structure and the active assistance and motivation of parents to use the device at home.[17, 69]

There is a lack of studies investigating parents' experience regarding managing OSA and other sleep disorders in children. In adults with sleep-breathing disorders, their management choices (e.g., CPAP, oral appliances) were linked to perceived effectiveness, cost, amount of noise,

and the device's impact on quality of life.[70, 71] A previous study on parent's decision to enroll their children in T&A surgery suggests that a clear description of management procedure to parents may reduce the level of decisional conflict and regret after engaging in this type of management.[72] However, their experiences with follow-up management options have not been explored.

1.4. Statement of the problem

One of the main challenges in screening and managing pediatric OSA is the complexity of its pathophysiology and the associated risk factors. The standard diagnosis tool, the PSG, is not easily accessible in several countries.[9, 54] In addition, the available consensus-based guidelines have not stated a clear management protocol when the first line of interventions, the T&A, does not improve this disorder.[14, 26] Craniofacial screening and specific management approaches (i.e., orthodontic treatment when properly indicated) have recently been considered as potential management options to address pediatric OSA.[10] Residual OSA further compromises the health and well-being of the affected children. Another step in addressing pediatric OSA management is to understand families' views of this process, including the effectiveness attributed to available management options.

The overarching goals of this thesis are to *(i)* evaluate the role of craniofacial screening in identifying children at high-risk for OSA, (ii) understand parents' experiences with services for managing residual pediatric OSA and *(iii)* set up a prospective cohort study to assess the impact of orthodontic management in a selective group of children with residual pediatric OSA.

From the screening perspective, we will focus on two components: first, the soft tissue facial feature's role in the screening of OSA, the dental specialist's screening performance and the role of soft facial features themselves when phenotyping this disease; and second, the association

of mandible cortical width, a possible marker of reduced bone density among pediatric OSA. From the management perspective, we will explore parents' experiences with services for managing children with OSA and set up a prospective cohort study to assess the impact of selective orthodontic interventions on residual OSA.

1.4.1. Specific objectives

1. Synthesize the available evidence on the portrayed link between craniofacial features and pediatric OSA.
2. Evaluate the role of facial soft tissue features in the screening for pediatric OSA when assessed by dental specialists with an interest in OSA in a sample of children diagnosed with OSA or without OSA.
3. Explore the role of craniofacial features, with emphasis on facial soft tissues, as a mean to identify phenotypes of children with suspected OSA.
4. Analyze differences in mandibular cortical width (MCW), as assessed through panoramic radiographs, among children with OSA compared to children at high- or low risk for OSA.
5. Explore parents' experiences and perceptions related to the engagement of their children in Albertan services for managing pediatric OSA.
6. Establish a prospective cohort protocol that aims to assess the effectiveness of orthodontic interventions for managing residual pediatric OSA in patients with craniofacial issues.

Chapter 2 : Craniofacial features in children with obstructive sleep apnea: a systematic review and meta-analysis

Chapter 1 presented the foundational concepts and states the problem guiding this thesis. There is uncertainty regarding the association between craniofacial features and obstructive sleep apnea in children. In this chapter, the current knowledge of this relationship was explored through a systematic review. Chapters 3-5 of this thesis showcase research addressing the knowledge gaps identified in this chapter.

Chapter 2 is based on this published article:

Fagundes NCF, Gianoni-Capenakas S, Heo G, Flores-Mir C. Craniofacial features in children with obstructive sleep apnea: a systematic review and meta-analysis. Journal of Clinical Sleep Medicine. 2022 Jul 1;18(7):1865-1875. Available from: https://doi.org/10.5664/jcsm.9904

2.1. Abstract

STUDY OBJECTIVES: This review aimed to evaluate the association between craniofacial features in children and adolescents with pediatric obstructive sleep apnea (OSA).

METHODS: Seven databases were searched to fulfill our research objectives. Clinical studies that included participants younger than 18 years with fully diagnosed OSA or without OSA and that evaluated skeletal, soft craniofacial features, or dental arch morphology, were considered for this review. The risk of bias and certainty of evidence were assessed. A meta-analysis was performed when low methodological and clinical heterogeneity were detected. This review followed all the protocols recommended by the Preferred Reported Items for Systematic reviews and Meta-analysis guideline.

RESULTS: Nine studies were identified at the end of the selection process, from which five did not report differences. Four studies reported differences between craniofacial features when comparing an OSA versus an asymptomatic control group. Mandibular retrognathia, reduced antero-posterior (AP) linear dimensions of the bony nasopharynx (decreased pharyngeal diameters at the levels of the adenoids), longer facial profile, and a narrower inter-canine width were described among children with OSA. A meta-analysis was performed considering the studies with a similar methodological approach, and no differences were observed in all the considered cephalometric angles (SNA, SNB, ANB, NSBa, U1-L1, U1-SN). Therefore, all the included studies were considered at low risk of bias even though some limitations were noted.

CONCLUSIONS: Due to the very low to moderate level of certainty, neither an association nor a lack thereof between craniofacial morphology and pediatric OSA can be supported at this time.

Key words: Obstructive sleep apnea; Child; Face; Diagnoses.

2.2. Introduction

Obstructive sleep apnea (OSA) is a respiratory sleep disorder resulting in partial or complete airflow obstruction.[1] Among children, OSA prevalence has been reported to vary from 1 to 5%.[2, 73] In the absence of proper management of OSA cases, a typical result of underdiagnoses, several health conditions may arise, including growth impairment,[74] behavioral and cognition problems,[75, 76] respiratory and cardiac comorbidities.[77] From a social perspective, pediatric OSA is related to an increased cost of healthcare services and unsatisfactory academic progress.[78, 79]

Previous cross-sectional studies suggested a subset of craniofacial features, such as increased facial height, labial incompetency, mandible retrognathia, increased overjet, higher mandible angle and steeper mandibular plane, presented a higher frequency in children with OSA when compared to a non-OSA control group.[43, 44] The presence of these craniofacial features has been hypothesized as a possible cause or consequence of airway obstruction and OSA development.

A potential benefit of a craniofacial morphology evaluation to identify pediatric OSA is that it is accessible and convenient for routine clinical use in dental practices. The facial analysis can be performed by a clinical examination in the dental office and a craniofacial skeletal screening done by x-rays (i.e., cephalometric analysis).

A systematic review and meta-analysis published eight years ago summarized the differences of skeletal craniofacial features in children with OSA.[43] However, there was a paucity of controlled studies with a definitive non-OSA control group (assessed through the overnight observed polysomnography (PSG). The PSG is the standard exam to diagnose OSA in children and adults. Standardizing methodological approaches to analyze OSA patients and associated factors is important for fair comparison among groups. In addition, new studies have been

published over the last five years, and other craniofacial techniques have been explored among children, such as the assessment of soft facial features, measurements of dental arches and the evaluation of tooth position.[44, 80] There is a need to update this literature synthesis.

This systematic review aims to evaluate the association between craniofacial features in children and adolescents with pediatric OSA. The further investigation of pediatric OSA pathophysiology, specifically the craniofacial morphology role, may improve OSA screening methods and reduce the backlog on PSG assessment by improving the referral algorithms.

2.3. Material and methods

2.3.1. Protocol and registration

This systematic review has followed PRISMA Statement (Preferred Reporting Items for a Systematic Review and Meta-analysis) and was registered at PROSPERO database (University of York, York, UK) under the code CRD42020203051.[81]

2.3.2. Search strategy and eligibility criteria

The definition of eligibility criteria was guided by a PECO (Population, Exposure, Comparison and Outcome) question: "In children and adolescents, are specific craniofacial features linked to fully diagnosed pediatric OSA?". The studies focused on Children or adolescents (P) in which the craniofacial features were assessed with a positive OSA diagnosis through PSG (E) compared to those with a negative diagnosis for OSA through PSG (C), evaluating the differences in mean values of craniofacial variables (O).

Observational studies were included if they evaluated OSA by a whole night PSG monitored by a sleep technician. To be considered as a non-OSA group, the participants should have a negative diagnosis after an PSG. As exclusion criteria in this review, we have not considered studies with adults (≥18 years) without an PSG non-OSA control group. We also excluded studies

that evaluated only patients with obesity, children presenting with known craniofacial syndromes or those who had received orthodontic or orthognathic treatment before craniofacial evaluation. No restrictions were made regarding the type of craniofacial assessment or craniofacial area that was considered. Studies using lateral cephalometrics, photographic analysis, *in vivo* clinical evaluation were deemed eligible for this review. Reviews, letters, conference abstracts and personal opinions were also excluded. No restriction of sex or ethnicity was considered.

Searches were conducted in seven electronic databases until May 2021: PubMed, MEDLINE via Ovid sp, Embase, Web of Science, The Cochrane Library and LILACS. A narrow grey literature search was also performed in OpenGrey. According to the rules of each database and with the guidance of a health sciences librarian, all searches were conducted using a combination of controlled pre-defined MeSH and free terms related to the topic. (Supplemental Table 2.1) The results were imported to a reference manager software (Rayyan software, Qatar Computing Research Institute, Doha, Qatar), and the duplicate citations were excluded.[82]

2.3.3. Study selection

The selection process was conducted in two phases by two reviewers (NCFF and SGC) and checked by a third examiner (CFM) in cases of disagreement. First, the citations were evaluated according to their title and abstract. Second, the selected articles were assessed through their full text. After these two steps, additional citations were sought from analyzing the reference lists of all previously selected articles. Finally, the eligibility criteria, including the specified PECO strategy and study types, were considered to analyze the articles in both phases.

2.3.4. Data extraction

A table was used to report the country, year of publication, demographic features (age, body mass index (BMI) and ethnicity), criteria adopted to define OSA, methods used to assess the

craniofacial area, main results, and statistical analysis. This extraction was performed by two examiners (NCFF and SGC). If necessary, in the case of lack of information, attempts to contact the authors were made by e-mail. The contact attempts consisted of sending weekly emails for up to three consecutive weeks.

2.3.5. Outcomes

The main considered outcome was the differences in the craniofacial features of children and adolescents with and without OSA. Secondary outcomes were the association of these results with demographic features and OSA severity.

2.3.6. Risk of Bias among included studies

The risk of bias evaluation was performed using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-sectional Studies.[83] The included articles were judged as high risk (yes score ≥ 49%), moderate risk (yes score= 50%-69%) and low risk (yes score ≥ 70%).[84] The evaluation was performed by two reviewers (NCFF and SGC), and the disagreements were resolved by a third reviewer (CFM).

2.3.7. Synthesis of results

The difference between craniofacial features of children with and without OSA was assessed using Review Manager software v.5.3 when a low methodological and clinical heterogeneity was detected. The statistical heterogeneity significance was evaluated using the I^2 index. Thresholds for the interpretation of the I^2 statistic were considered as suggested by Cochrane handbook (www.training.cochrane.org/handbook): 0–40%: might not be significant, 30–60%: may represent moderate heterogeneity, 50–90%: may represent substantial heterogeneity, 75–100%: considerable heterogeneity.

2.3.8. Risk of bias across studies

The overall strength of evidence was evaluated using the 'Grading of recommendations, assessment, development, and evaluations' (GRADE) tool. Included studies were evaluated according to their study design, risk of bias, inconsistent results, indirect evidence, imprecision, and publication bias.[85]

2.4. Results

2.4.1. Study selection

From electronic searches, 8,288 citations were identified. After removing duplicate results, 3475 records were assessed by title and abstract, and out of these, 87 were considered for full-text reading. Among these, 76 studies did not meet our eligibility criteria and were excluded. (Supplemental Table 2.2) in addition to the electronic searches, the nine studies included in the previous version of this systematic review were also screened in the full-text phase.[43] However, none of these articles met the updated inclusion criteria proposed by the present review. After the selection process, nine studies fit our criteria and were included.[44-47, 80, 86-89] (Figure 2.1).

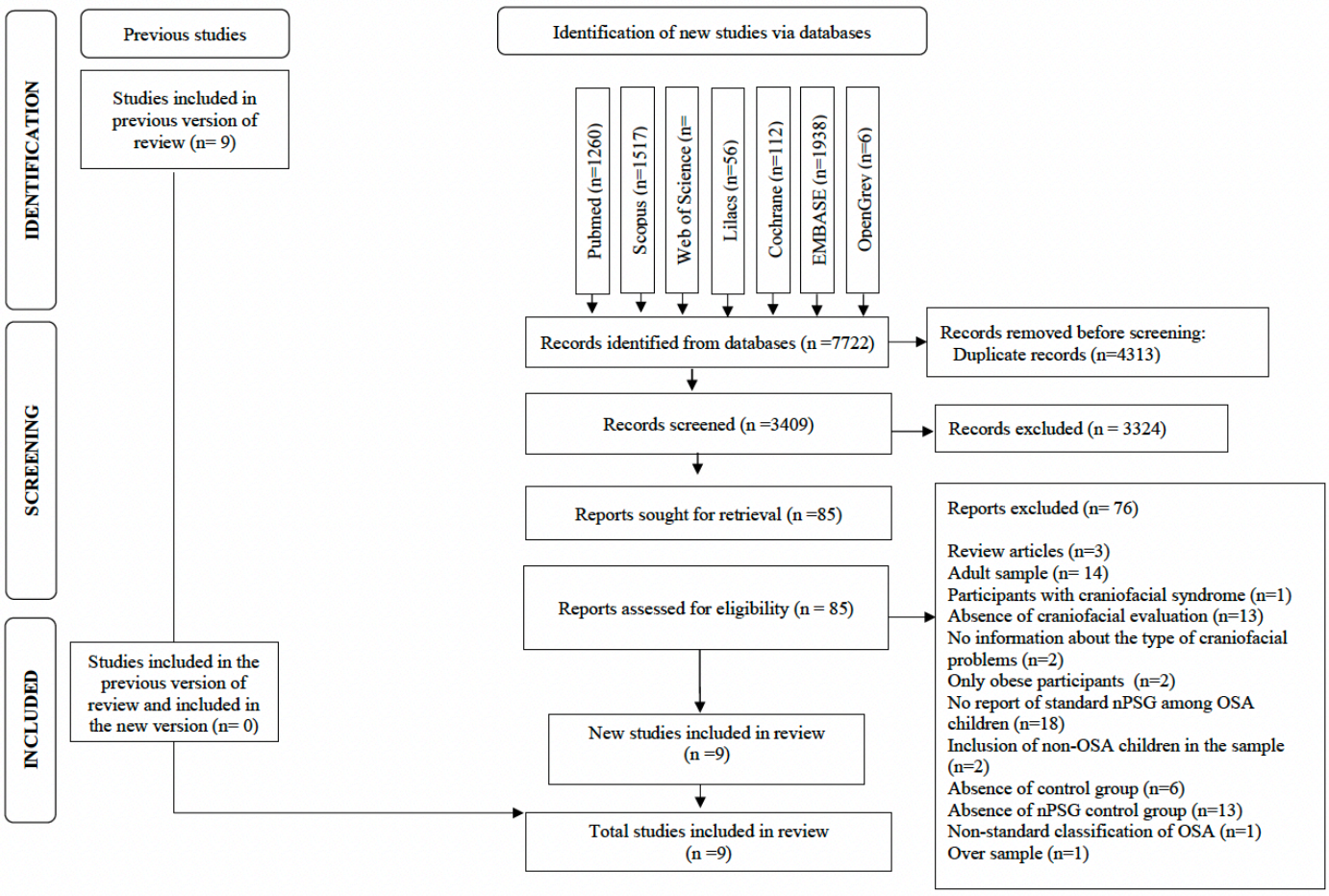

Figure 2.1 Flowchart diagram according to Preferred Reporting Items for Systematic Review and Meta Analyses (PRISMA) guidelines outlining the review process and numerical results.

2.4.2. Study characteristics

Among the nine included studies, four presented a cross-sectional design,[44, 45, 47] four were case-control studies,[46, 80, 87, 88] and one was a prospective cohort.[89] For the studies that were not cross-sectional, only the relevant information at the initial data gathering point was considered (at that data point cross-sectional in nature). Six studies evaluated craniofacial skeletal features assessed through lateral cephalometrics.[45-47, 86-88] Two studies analyzed dental arch dimensions and tooth position through dental models,[80, 89] and one study performed a facial soft tissue features evaluation through two-dimensional photo analysis.[44] (Table 2.1)

In the six studies that evaluated skeletal craniofacial features, 182 children with OSA and 133 control children were screened. Three studies found differences between children with OSA and the non-OSA control group.[46, 86, 87] For example, children with OSA presented with a retrusive mandible (reduced SNB angle, OSA group=75.8±4.3º vs. Control=78.71±2.6),[46] deficient chin (increased PG-NB line, OSA group=1.3±0.8 mm vs. Control= 0.62±0.60 mm),[46] and long lower face (increased ANS-ME, OSA group= 67.4±6.4 mm vs. Control= 62.2±3.1 mm).[46] In addition, among boys, some craniofacial features, including dolichocephaly facial pattern (r=-0.33), mandibular plane (r=0.48), and facial depth (r=-0.33), were correlated to OSA in one study.[86] The other three studies did not report statistical differences in craniofacial skeletal features. A reduced antero-posterior (AP) linear dimensions of the bony nasopharynx (decreased pharyngeal diameters at the levels of the adenoids) was observed when children with OSA were compared to a PSG group (reduced pns-ad1, OSA group= 17.3±6.2 mm vs. Non-PSG control= 20.9±3.9 mm; reduced ve1-ve2, OSA group= 4.0±3.0 mm vs. Non-PSG control= 7.4±2. 9 mm; reduced u1-u2, OSA group= 5.6±3.3 mm vs. Non-PSG control= 9.6±3.4 mm; reduced rl1-rl2, OSA group= 12.7±3.8 mm vs. Non-PSG control= 10.1±3.0 mm).[86]

Two studies analyzed dental arch dimensions and tooth position, in which 35 children with OSA and 41 non-OSA snoring children were evaluated.[80, 89] Patients from different age groups were included in both studies. Compared to a negative PSG control group, both studies did not show differences in the variables being assessed. In a group of 2.5-year-old children, a narrower upper inter-canine width in the OSA group (median=27mm) when compared to a non-snoring group (median=28.2mm) was identified (p=0.03).[89]

One study evaluated soft facial features of 59 children with OSA and 9 non-OSA, non-snoring, control children by analyzing two-dimensional facial photos. An increase in the

Obstructive Apnea-Hypopnea Index (OAHI) was associated with an increase in the cervicomental angle (β= 0.18, 95%CI= 0.07, 0.29) and an increase in the ratio of upper to lower face height (β= -37.16, 95%CI= -65.71, -8.62).[44]

Eight of the nine studies included the evaluation of co-morbidities associated with pediatric OSA (ethnicity, BMI/obesity status and adenotonsillar hypertrophy).

Three studies assessed the size of adenoids and tonsils in their sample without analyzing the interaction between OSA and craniofacial morphology.[80, 87, 89]

Regarding the characteristics of the non-OSA control groups, all studies included children with a negative PSG result (AHI<1 or OAHI<2). In addition, three studies included snoring patients,[80, 87, 88] three studies included children with respiratory or OSA symptoms,[45, 47, 86] and three studies had only non-snoring children in the control group.[44, 46, 89]

Table 2.1 Characteristics of the included studies

Author/Year/	Source of sample	n	Age	Control group	OSA index in OSA group	Main results
Deng 2012	Beijing Children's Hospital and Department of Orthodontics, Peking University, China	Total: 30 OSA: 15 Control: 15	9.5 ±1.0	Non-snoring	AHI: 6.29±6.48	SNB (78.71±2.61 vs.75.82±4.30), PG-NB (0.62±0.60 mm vs. 1.32±0.84), Na-Me (108.50±6.93 mm vs. 13.62±10.0 mm), and ANS-Me (61.51±3.22 mm vs. 65.12±5.91 mm), showed differences between groups. A more inferior and retrusive hyoid was described in OSA group.
DiFrancesco 2012	Otolaryngology Department, University of São Paulo Medical School, Brazil.	Total: 77 OSA: 36 Control: 41	3.0-12.0	OSA symptoms	NI	Facial depth (r= -0.336), vertical growth tendency (r= -0.337) and mandibular plane (r= 0.486) correlated with AHI in boys, but no correlations were found in girls.
Markkanen 2019	Tampere University Hospital, Finland	Total: 27 OSA: 9 Control: 18	1.9-2.8	Non-snoring	OAHI: 1.2-6.3	Children with OSAS (median: 27.0mm) had narrower inter canine width than non-snoring children (median: 28.2 mm).
Rennella 2017	Pontificia Universidad Javeriana, Colombia	Total: 43 OSA: 19 Control: 24	6.0-13.0	Indication to PSG	NI	Children with OSAS had same features than controls.
Soares 2022	Centro do Respirador Bucal Clinics,	Total: 76 OSA: 62 Control: 14	7.0-10.0	Respiratory and OSA	OAHI: 13.0 ± 8.4	There were no differences between the two groups for any craniofacial measure. Children with OSA showed a more inferior hyoid position in relation to the

	University de São Paulo, Brazil			sympto ms		mandibular plane (HyMP: control: 10.9 ± 0.9 and OSA: 13.1 ± 0.5; 95% CI: 0.08; 4.32).
Sutherland 2020	Melbourne Children's Sleep Centre for PSG, Australia.	Total: 59 OSA: 50 Control: 9	7.2 ± 3.4	Non-snoring	Mild OSA: OAHI: 2.8 ± 1.3; moderate-severe OSA: OAHI: 14.5 ± 11.1.	No association was observed between OSA and facial features. A direct association was observed between OSA severity and the inferior and posterior position of the hyoid bone.
Pirilä-Parkkinen 2009	Children referred from primary health care to the Oulu University Hospital, Finland	Total: 123 OSA: 41 Snoring: 41	3.8-11.4	Snoring	OSA: AHI: 3.5± 3.60.	Children with OSAS had same features than snoring children.
Pirilä-Parkkinen 2010	Children referred from primary health care to the Oulu University Hospital, Finland	Total: 140 OSA: 26 Snoring: 27 UARS: 17 Control: 70	4.7±2.1	Snoring children	AHI: 2.5±1.2	Children with OSAS had same features than snoring children.
Wang 2012	Qilu Hospital, Shandong University, Jinan, China	Total: 70 OSA: 24 Snoring:12 Control:34	9.6±1.9	Snoring children	AHI: 8.5±3.6	Children with OSAS had same features than snoring children. A reduced antero-posterior (AP) linear dimensions of the bony nasopharynx (decreased pharyngeal diameters at the levels of the adenoids) was observed when children with OSA were compared to a non-PSG group.

OSA: Obstructive sleep apnea, AHI: Apnea-Hypopnea Index, OAHI: Obstructive Apnea-Hypopnea Index, PSG: polysomnography.

2.4.3. Risk of bias among included studies

The risk of bias was classified as low in all included studies. Nevertheless, specific problems were identified in some domains. None of the studies considered confounding factors. Rennella et al. 2017 presented unclear information regarding how the PSG diagnosed the OSA.[45] Soares et al. 2022 did not report the period of data collection.[47] (Supplemental Table 2.3)

2.4.4. Synthesis of results

Among the six studies which evaluated cephalometric parameters, three studies reported a few consistent cephalometric variables and have presented methodological and clinical comparable data to justify a quantitative synthesis.[46, 87, 88] Six independent meta-analyses were performed to evaluate the mean differences of SNA (1), SNB (2), ANB (3), NSBA (4), U1-L1 (5) AND U1-SN (6). For the SNA, ANB and NSBA, all three studies were included.[46, 87, 88] For the

U1-L1 and U1-SN features, only two studies were compared.[46, 88] The meta-analyses results did not show differences in any of the six evaluated features. (Figure 2.2)

A quantitative evaluation was impossible among the studies that analyzed dental arches and tooth position because the age range in the two studies was not comparable. Markkanen et al. (2019) included children at 2.5 years old, while Pirilä-parkkinen (2009) evaluated children from 3-10 years old.[80, 89]

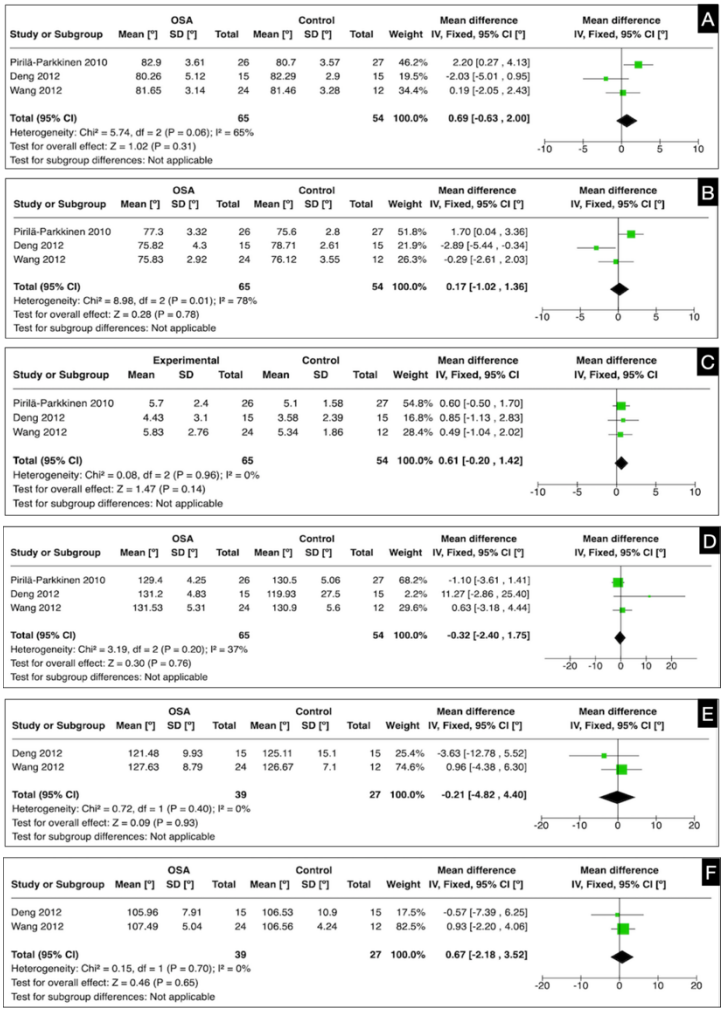

Figure 2.2 Forest plot of meta-analysis. Mean difference among OSA and control groups for the following skeletal angles: A- SNA; B- SNB; C- ANB; D- NSBa; E- U1-L1; F-U1-SN.

2.4.5. Risk of bias across studies

Two certainty analyses were performed after data collection. Due to the small number of studies included on each outcome (n<10), publication bias was not considered. In the first analysis, three main outcomes were considered: skeletal features, soft facial features, and dental arch morphology. A low to moderate certainty level was observed in which only the skeletal features reported some differences between OSA and non-OSA groups. (Table 2.2)

A very low to moderate certainty level was detected among the six cephalometric assessed outcomes following the meta-analyses results: SNA (1), SNB (2), ANB (3), NSBA (4), U1-L1 (5) and U1-SN (6). A serious and very serious inconsistency was observed in sna and snb outcomes due to moderate to high statistical heterogeneity. Another pitfall that downgraded the overall certainty was the presence of a serious imprecision in the ANB outcome and a very serious imprecision in the SNA, SNB, NSBA, U1-L1 and U1-SN outcomes. (Supplemental Table 2.4)

Table 2.2 Certainty assessment (GRADE tool) for the evaluation of skeletal, soft facial features and dental arched morphology outcomes.

Outcome № of participants (studies)	Relative effect (95% CI)	Certainty	What happens
Skeletal features № of participants: 315 (6 observational studies)	not estimable	⊕⊕◯◯ LOW [a]	Three studies found differences in the cephalometric features in the OSA group. Two studies reported a class II skeletal pattern and vertical craniofacial growth tendency in the OSA group. One study reported an inferiorly positioned hyoid in the OSA group.
Soft facial features № of participants: 59 (1 observational study)	not estimable	⊕⊕⊕◯ MODERATE [b]	OSA probably results in little to no difference in soft facial features.
Dental arches morphology № of participants: 109 (2 observational studies)	not estimable	⊕⊕◯◯ LOW [a]	Children with OSA may present little to no difference in dental arches morphology.

[a]Overlap among confidence intervals was observed accross studies; bOnly one study was included, presenting a wide variation among Confidence Intervals.

2.5. Discussion

Previously, craniofacial morphology has been suggested as one of the potential causes of airway collapsibility during sleep. This systematic review screened over 8,000 citations and identified nine studies investigating this relationship. Among those, five articles reported no differences in the craniofacial features of OSA and control groups. The other four articles suggested that a specific group of children with OSA might present with a set of skeletal and craniofacial features suggestive of a Class II tendency and a long facial profile. However, these results were not supported by meta-analyses. In sum, these results indicate that we should not suggest the existence of an association between specific craniofacial features and pediatric OSA. Even though a particular subgroup of pediatric OSA might present with an increased mandibular retrognathia, maxillary transverse deficiency, or a long facial profile, the investigation of associated clinical factors is needed to confirm or refute these features as possibly being causatively or consequentially associated with OSA in children. An important consideration is that this lack of strong association may reflect the methodological approaches. Lately, stronger arguments have arisen that imply that specific clinical phenotypes may have a stronger association with craniofacial features while other phenotypes do not.

The evaluation of the main features of craniofacial morphology included skeletal, soft features and dental analysis. Regarding dental assessment, a narrower inter canine width was described among children with OSA.[89] The reported skeletal differences suggest a Class II malocclusion tendency (retruded mandible) and a vertical craniofacial growth tendency (long lower face, dolichocephaly facial pattern).[46, 87] In concordance with skeletal results, the analysis of the soft features also suggested an increase in lower face height (relative to upper face height) among children with OSA.[44] However, when data of this review was quantitatively evaluated, none

of the six skeletal variables (SNA, SNB, ANB, NSBa, U1-L1 and U1-SN) compared through a meta-analysis showed a difference between OSA and non-OSA groups. These findings indicate the need to further investigate craniofacial morphology as a clinical phenotyping factor in pediatric OSA. Even though some of the included studies reported differences, there is no consensus in the literature.

Our group conducted a previous systematic review on the same topic and only considered skeletal features and no exclusion criteria were defined for non-PSG control groups.[43] Similarly to the results reported in the present review, a vertical direction of growth and a tendency to Class II malocclusion were described.

We raise some hypotheses to justify a possible or lack of an association between some craniofacial features and pediatric OSA. One of them is the influence of craniofacial bones and position on airway size and contribution to airway obstruction. On the other hand, reduced mandibular growth might be a consequence of airway obstruction and sleep-disordered breathing (SDB). Children presenting with a mandible retrognathia, resulting in a Class II, were associated with a narrower pharyngeal airway.[86] However, the association between a Class II skeletal pattern and a reduced airway size among healthy children is still controversial.[90] Also, other craniofacial features, including the cranial base length, have not presented an association (or the lack of it) to OSA in children.[91] In summary, the differences in the craniofacial pattern observed in children with OSA might be linked to other factors not exclusively dependent on these anatomical features.

A vertical craniofacial direction of growth, and an increased lower anterior face height, could also represent a consequence of airway obstruction, as suggested by animal studies.[92] This feature was associated with multiple OSA signs and symptoms, including mouth breathing and adenotonsillar hypertrophy. To better understand a possible interaction between the vertical

direction of growth and OSA, the causal relationship of this association should be explored in a prospective cohort.

The reported differences between craniofacial features of children with OSA and an PSG negative control group in only part of the studies included in this review could also be explained by the heterogeneity and multifactorial nature of OSA. Despite the variations on size and shape of craniofacial bones, other anatomical factors (i.e., muscle tone), including obesity, adenotonsillar size, pharyngeal size, and genetic or biomechanical factors (i.e., fluid dynamics), as airflow resistance, could be a risk factor for pediatric OSA.[93]

Overall, there is limited knowledge of clinical and physiological phenotypes of OSA, and the majority of evidence is focused on PSG sleep variables.[94] Available evidence suggests that lateral pharyngeal wall thickness and blood pressure are potential OSA phenotypes in children and adolescents.[24] There is a need to explore further the clinical phenotypes linked to pediatric OSA to improve the understanding regarding the role of craniofacial morphology on this disease.

Regarding the influence of other pediatric OSA risk factors on the craniofacial assessment, the adenotonsillar size and mouth breathing have been evaluated by the studies included in this systematic review. The adenotonsillar size was assessed in two studies. One of them reported no association between this variable and AHI values in a group of 4- to 11-year-old children.[80] The other study observed a larger adenoid size and increased mouth breathing among the OSA group in a group of 2.5 year-old children.[89] However, the interaction between those factors and craniofacial features was not explored in any of the included articles. In all selected studies, only non-obese or participants with matched BMI values were included.

The influence of age has not been investigated in the papers included in this review. However, a wide age range has been considered in the studies. Three studies included participants

from preschoolers' case until adolescence,[80, 86, 87] while one study only included minors younger than three years,[89] and the other five articles included children older than six years.[44-47, 88] None of the included studies investigated the relationship between anatomical craniofacial changes and pediatric OSA over time. Understanding the effect of normal growth among children with and without OSA might explain the role of craniofacial growth in this population.

This systematic review aimed to evaluate the differences in craniofacial features among OSA and non-OSA groups of children. The criteria defined as control was the presence of a negative result in an PSG evaluation. First, it is important to highlight the controversies associated with identifying a negative PSG control group. During the selection process of the articles, twelve studies reported healthy children without OSA symptoms and without an PSG exam, as a control group.[51, 95-105] Among those, different results were also observed. While five studies reported no differences between OSA and the control group, the other seven described differences in craniofacial morphology. Differences in craniofacial features were observed in the mandible, maxilla, facial height, naso-pharyngeal airway at the adenoids and position of the hyoid bone, and narrower intertooth distances for the first and second deciduous molars and the first permanent molars in children with OSA. (Supplemental Table 2.5)

Adopting the PSG based diagnosis might also have limitations due to the reliance on a single sleep index, the AHI or the OAHI. In the review, all the selected studies used these indices to define an OSA case. The sole use of these indices for diagnostic and management approaches has been questioned.[106] Both AHI and OAHI are based only on the number of obstructive events, without further consideration to comorbidities, OSA symptoms and quality of life. Other studies should explore the pediatric OSA in its multiple clinical nature, including associated factors, for a more reliable diagnosis and understanding of the clinical and physiological phenotypes associated.

Collectively, despite myriad published studies over the previous one hundred years within medical and dental journals indicating a secular trend towards a co-morbid association between specific malocclusion phenotypes and SDB/OSA symptoms, the results of this systematic review indicate that neither an association nor a lack thereof between craniofacial morphology pediatric OSA can be supported or refuted. Some specific sets of craniofacial features, including mandible retrognathia, smaller cranial base angle, deficient inter-canine width, and a long facial profile, were more frequent among a specific subgroup of pediatric OSA. However, there is limited evidence of clinical phenotypes that would help understand the nature of this association. In the future, if this link is confirmed to be a reliable indicator of increased SDB/OSA risk, dental professionals may become even more helpful with collaborative efforts aimed at identifying children at high risk of OSA when SDB signs and symptoms are also identified in this group of children.[12] Children presenting these characteristics and other SDB signs and symptoms should be monitored by a sleep medicine or ENT specialist when justified.

2.5.1. Limitations

As a limitation of this systematic review, we may highlight the small sample size and the absence of a sample size justification in the included studies. These characteristics likely represent a bias in the interpretation of the results outside the study. One reason that might explain the difficulty of achieving larger sample sizes among children with pediatric OSA is the accessibility barriers to the PSG exam, including the high cost and long wait lines for public health services.[107, 108]

The eligibility criteria for the control group in this review was a negative PSG result. However, only three of the selected papers reported that the participants from the control group did not present with any signs or symptoms of SDB.[44, 46, 89] The presence of these signs and

symptoms may represent a confounding factor for the craniofacial assessment. Some of these features, such as mouth breathing, are associated with increased clockwise rotation of the mandible and increased lower facial height.[109]

Even though a low risk of bias was identified, some problems were found in defining and controlling confounding factors when analyzing the individual studies. That explains why the certainty level for the conclusions was downgraded.

OSA has been associated with multiple comorbidities and disorders in children, including respiratory problems, obesity, adenotonsillar hypertrophy, craniofacial and behavioral syndromes. Most of the included studies reported excluding or matching participants regarding obesity, craniofacial syndromes and adenotonsillar size.[4] However, none of the studies evaluated the influence of these features in their results. The consideration of other associated OSA risk factors, such as respiratory problems and behavioral conditions, could be included in future investigations to narrow the possible confounding factor for pediatric OSA.

2.6. Conclusion

Due to the very low to moderate certainty level, neither an association nor a lack thereof between craniofacial morphology in pediatric OSA cases can be supported at this time.

2.7. Supplemental Files

Supplemental Table 2.1 Terms used on database search.

Database	Search format
PubMed	((((((((((((((((((((((((((((((((((("pediatric*"[All Fields] OR "paediatric*"[All Fields]) OR "child*"[All Fields]) OR "newborn*"[All Fields]) OR "congenital*"[All Fields]) OR "infan*"[All Fields]) OR (((((("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields])) OR "newborn infant"[All Fields]) OR "baby"[All Fields]) OR "infant"[MeSH Terms]) OR "infant"[All Fields])) OR ((((("baby s"[All Fields] OR "babys"[All Fields]) OR "infant"[MeSH Terms]) OR "infant"[All Fields]) OR "babies"[All Fields])) OR ("neonat*"[All Fields] AND (("parturition"[MeSH Terms] OR "parturition"[All Fields]) OR "born"[All Fields]) AND ((((("premature birth"[MeSH Terms] OR ("premature"[All Fields] AND "birth"[All Fields])) OR

	"premature birth"[All Fields]) OR ("pre"[All Fields] AND "term"[All Fields])) OR "pre term"[All Fields]))) OR "preterm*"[All Fields]) OR "premature birth*"[All Fields]) AND ((((("intensive care units"[MeSH Terms] OR (("intensive"[All Fields] AND "care"[All Fields]) AND "units"[All Fields])) OR "intensive care units"[All Fields]) OR "icu"[All Fields]) AND "preschool*"[All Fields])) OR "pre school*"[All Fields]) OR "kindergarten*"[All Fields]) OR "kindergarden*"[All Fields]) OR "elementary school*"[All Fields]) OR "nursery school*"[All Fields]) OR ("day care*"[All Fields] NOT "adult*"[All Fields])) OR "schoolchild*"[All Fields]) OR "toddler*"[All Fields]) OR (("men"[MeSH Terms] OR "men"[All Fields]) OR "boys"[All Fields])) OR "girl*"[All Fields]) OR "middle school*"[All Fields]) OR "pubescen*"[All Fields]) OR "juvenile*"[All Fields]) OR "teen*"[All Fields]) OR "youth*"[All Fields]) OR "high school*"[All Fields]) OR "adolesc*"[All Fields]) OR "pre pubesc*"[All Fields]) OR "prepubesc*"[All Fields]) OR "child"[MeSH Terms]) OR "infant"[MeSH Terms]) OR "child, exceptional"[MeSH Terms]) OR "adolescent"[MeSH Terms]) OR "pediatrics"[MeSH Terms]) OR "child, abandoned"[MeSH Terms]) OR "child, orphaned"[MeSH Terms]) OR "child, unwanted"[MeSH Terms]) OR "minors"[MeSH Terms]) AND (((((((((("sleep apnea syndrom*"[All Fields] OR "sleep apnoea syndrom*"[All Fields]) OR "sleep apnea*"[All Fields]) OR "sleep apnoea*"[All Fields]) OR "obstructive sleep apnea*"[All Fields]) OR "obstructive sleep apnoea*"[All Fields]) OR "Upper Airway Resistance Sleep Apnea Syndrome"[All Fields]) OR "Sleep-Disordered Breathing"[All Fields]) OR "nocturnal upper airway obstruction*"[All Fields]) OR "sleep apnea syndromes"[MeSH Terms])) AND ("face"[MeSH Terms] OR ((((("skeletal*"[All Fields] OR "dental*"[All Fields]) OR "craniofacial*"[All Fields] OR “Facial phenotyping*"[All Fields]) OR "face*"[All Fields]) OR ((((("face"[MeSH Terms] OR "face"[All Fields]) OR "facial"[All Fields]) OR "facials"[All Fields]) AND "bone*"[All Fields]))))
Medline via Ovid	1 adolescent development/ or childhood development/ or pediatrics/ or exp Congenital Disorders/ or child characteristics/ or child abuse/ or exp child welfare/ or chronically ill children/ or child neglect/ or child psychiatry/ or child psychopathology/ or exp child care/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre term or preterm* or premature birth or NICU or preschool* or pre school* or kindergarten* or elementary school* or nursery school* or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or prepubesc* or pre pubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn. (5096895) 2 Sleep Apnea, Obstructive/ (20245) 3 (Sleep Apnea Syndrom* or Sleep Apnoea Syndrom* or Sleep Apnea* or Sleep Apnoea* or Obstructive Sleep Apnea* or Obstructive Sleep Apnoea* or Upper Airway Resistance Sleep Apnea Syndrome or Sleep-Disordered Breathing or Nocturnal upper airway obstruction*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (47360) 4 exp Face/ (158522) 5 (Skeletal* or Dental* or Craniofacial* or Face* or Facial bone* or Facial phenotyping).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1096857) 6 2 or 3 (47360) 7 4 or 5 (1201941) 8 1 and 6 and 7 (1224)
Embase via Ovid	1 juvenile/ or exp adolescent/ or exp child/ or exp postnatal development/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre term or preterm* or premature birth or NICU or preschool* or pre school* or kindergarten* or elementary school* or nursery school* or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or prepubesc* or pre pubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn. (4725179) 2 exp sleep disordered breathing/ or upper airway resistance syndrome/ (51517)

	3 (Sleep Apnea Syndrom* or Sleep Apnoea Syndrom* or Sleep Apnea* or Sleep Apnoea* or Obstructive Sleep Apnea* or Obstructive Sleep Apnoea* or Upper Airway Resistance Sleep Apnea Syndrome or Sleep-Disordered Breathing or Nocturnal upper airway obstruction*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (85685) 4 2 or 3 (86458) 5 exp face/ (103616) 6 (Skeletal* or Dental* or Craniofacial* or Face* or Facial bone* or Facial phenotyping).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1117155) 7 5 or 6 (1164734) 8 1 and 4 and 7 (2052)
Web of Science	#1: TOPIC: (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or "pre term" or preterm* or "premature birth" or NICU or preschool* or "pre school*" or kindergarten* or "elementary school*" or "nursery school*" or schoolchild* or toddler* or boy or boys or girl* or "middle school*" or pubescen* or juvenile* or teen* or youth* or "high school*" or adolesc* or prepubesc* or pre pubesc*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years #2: TOPIC: ("Sleep Apnea Syndrom*" or "Sleep Apnoea Syndrom*" or "Sleep Apnea*" or "Sleep Apnoea*" or "Obstructive Sleep Apnea*" or "Obstructive Sleep Apnoea*" or "Upper Airway Resistance Sleep Apnea Syndrome" or "Sleep-Disordered Breathing" or "Nocturnal upper airway obstruction*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years #3: TOPIC: (Skeletal* or Dental* or Craniofacial* or Face* or "Facial phenotyping" or “Facial bone*”) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years Final search: #3 AND #2 AND #1
Scopus	((TITLE-ABS-KEY (pediatric* OR paediatric* OR child* OR newborn* OR congenital* OR infan* OR baby OR babies OR neonat* OR "pre term" OR preterm* OR "premature birth" OR nicu OR preschool* OR "pre school*" OR kindergarten* OR "elementary school*" OR "nursery school*") OR TITLE-ABS-KEY (schoolchild* OR toddler* OR boy OR boys OR girl* OR "middle school*" OR pubescen* OR juvenile* OR teen* OR youth* OR "high school*" OR adolesc* OR prepubesc* OR pre AND pubesc*))) AND ((TITLE-ABS-KEY ("Sleep Apnea Syndrom*" OR "Sleep Apnoea Syndrom*" OR "Sleep Apnea*" OR "Sleep Apnoea*" OR "Obstructive Sleep Apnea*" OR "Obstructive Sleep Apnoea*" OR "Upper Airway Resistance Sleep Apnea Syndrome" OR "Sleep-Disordered Breathing") OR TITLE-ABS-KEY ("Nocturnal upper airway obstruction*"))) AND (TITLE-ABS-KEY (skeletal* OR dental* OR craniofacial* OR face* OR "Facial phenotyping" OR "Facial bone*"))
LILACS	(tw:((child$) OR (pediatric$) OR (paediatric) OR or (newborn$) OR (infan$) OR (baby) OR (babies) OR (neonat$) OR (pre term) OR (preterm$) OR (premature birth) OR (NICU) or (kindergarten$) OR (nursery school$) OR (elementary school$) OR (schoolchild$) OR (toddler$) OR (boy) OR (boys) OR (girl$) OR (preschool$) OR (pre-school$) OR (middle school$) OR (pubescen$) OR (juvenile$) OR (teen$) OR (youth$) OR (adolesc$) OR (pre-pubesc$) OR (prepubesc$))) AND (tw:((Sleep Apnea Syndrom$) or (Sleep Apnoea Syndrom$) or (Sleep Apnea$) or (Sleep Apnoea$) or (Obstructive Sleep Apnea$) or (Obstructive Sleep Apnoea$) or (Upper Airway Resistance Sleep Apnea Syndrom$) or

	(Sleep-Disordered Breathing) or (Nocturnal upper airway obstruction$))) AND (tw:((Skeletal$) or (Dental$) or (Craniofacial$) or (Face$) or (Facial phenotyping$) or (Facial bone$)))
Cochrane Library	#1: pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or "pre term" or preterm* or "premature birth" or NICU or preschool* or "pre school*" or kindergarten* or "elementary school*" or "nursery school*" or schoolchild* or toddler* or boy or boys or girl* or "middle school*" or pubescen* or juvenile* or teen* or youth* or "high school*" or adolesc* or prepubesc* or pre pubesc* in Title Abstract Keyword - (Word variations have been searched) #2: "Sleep Apnea Syndrom*" or "Sleep Apnoea Syndrom*" or "Sleep Apnea*" or "Sleep Apnoea*" or "Obstructive Sleep Apnea*" or "Obstructive Sleep Apnoea*" or "Upper Airway Resistance Sleep Apnea Syndrome" or "Sleep-Disordered Breathing" or "Nocturnal upper airway obstruction*"in Title Abstract Keyword - (Word variations have been searched) #3: Skeletal* or Dental* or Craniofacial* or Face* or "Facial bone*" or "Facial phenotyping" in Title Abstract Keyword - (Word variations have been searched) Final search: #1 AND #2 AND #3
Open Grey	Sleep apnea AND face

Supplemental Table 2.2 Articles excluded after full-text evaluation, with reasons (n=76).

Article excluded	Reasons for exclusion
(Cobo Plana and de Carlos Villafranca 2010)	1
(Müller-Hagedorn et al. 2015)	1
(Rangel Chávez, Espinosa Martínez, and Medina Serpa 2016)	1
(Aktas et al. 2016)	2
(Albajalan, Samsudin, and Hassan 2011)	2
(Brasil et al. 2016)	2
(Chang and Shiao 2008)	2
(Chi et al. 2011)	2
(Endo, Mataki, and Kurosaki 2003)	2
(Faria et al. 2012)	2
(Ito et al. 2001)	2
(Lee, Chan, et al. 2009)	2
(Lee, Petocz, et al. 2009)	2
(Sawanyawisuth et al. 2016)	2
(Frohberg, Naples, and Jones 1995)	2
(Tangugsorn et al. 1999)	2
(Vezina et al. 2012)	2
(Llombart et al. 2007)	3
(Guilleminault et al. 2016)	4
(Huang et al. 2019)	4
(Shigeto Kawashima et al. 1999)	4
(Lai et al. 2018)	4
(Leach et al. 1992)	4
(Ni et al. 2007)	4

(Nanaware, Gothi, and Joshi 2006)	4
(Pirelli et al. 2010)	4
(J. Wang et al. 2019)	4
(Wu et al. 2019)	4
(Xu et al. 2020)	4
(Yan et al. 2020)	4
(Hotwani, Sharma, and Jaiswal 2018)	4
(Martinelli et al. 2017)	5
(Shen et al. 2018)	5
(Arens et al. 2011)	6
(Tong et al. 2016)	6
(Al Ali et al. 2015)	7
(Ardehali et al. 2016)	7
(Carvalho et al. 2014)	7
(Cuccia, Lotti, and Caradonna 2008)	7
(Angela Galeotti et al. 2018)	7
(A Galeotti et al. 2019)	7
(Hultcrantz and Löfstrand Tideström 2009)	7
(Ikävalko et al. 2018)	7
(Juliano et al. 2013)	7
(S Kawashima 2002)	7
(Shigeto Kawashima et al. 2003)	7
(Lopatienė et al. 2016)	7
(Nikakhlagh et al. 2010)	7
(Sato et al. 2012)	7
(Watanabe and Miyamoto 2002)	7
(Kushida 1997)	7
(Shigeto Kawashima et al. 2012)	7
(Pirilá et al. 1995)	7
(Zucconi et al. 1999)	8
(Yap et al. 2019)	8
(Lian et al. 2017)	9
(Marino et al. 2009)	9
(Vilovic et al. 2019)	9
(Matsumoto et al. 2007)	9
(Ozdemir et al. 2004)	9
(K. Ågren, B. Nordlander 1998)	9
(AlHammad, Hakeem, and Salama 2015)	10
(Bergamo et al. 2014)	10
(Cappabianca et al. 2013)	10
(Hotwani, Sharma, and Jaiswal 2018)	10
(Shigeto Kawashima et al. 2012)	10
(S Kawashima et al. 2000)	10
(Perillo et al. 2013)	10
(Pirila-Parkkinen et al. 2009)	10

(Pirila-Parkkinen et al. 2010)	10
(Vieira et al. 2011)	10
(Zettergren-Wijk 2006)	10
(W. Wang, Wang, and Wang 2012)	10
(Vieira et al. 2014)	10
(Löfstrand-Tideström et al. 1999)	11
(Deng, Gao, and Zeng 2010)	12

ł Reasons for exclusion: 1- Review articles ; 2- Adult sample ; 3- Participants with craniofacial syndrome ; 4- Absence of craniofacial analysis ; 5- No information about the type of craniofacial problems ; 6- The study included only obese participants ; 7- No report of standard PSG among OSA children; 8- Inclusion of non-OSA children in the sample ; 9- Absence of control group; 10- Absence of PSG control group; 11- Non-standard classification of OSA; 12- Over sample.

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Supplemental Table 2.3 Risk of Bias assessment.

	Deng et al. 2012	**Di Francesco et al. 2012**	**Markkanen et al. 2019**	**Rennella et al. 2017**	**Soares et al. 2020**	**Sutherland et al. 2019**	**Piriläe-Parkkinen et al. 2009**	**Piriläe-Parkkinen et al. 2010**	**Wang et al. 2012**
Were the criteria for inclusion in the sample clearly defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the study subjects and the setting described in detail?	Y	Y	Y	Y	N	Y	Y	Y	Y
Was the exposure measured in a valid and reliable way?	Y	Y	Y	U	Y	Y	Y	Y	Y
Were objective, standard criteria used for measurement of the condition?	Y	Y	Y	Y	Y	Y	Y	Y	Y

Were confounding factors identified?	N	N	N	N	N	N	N	N	N
Were strategies to deal with confounding factors stated?	NA	NA	NA	NA	NA	NA	NA	NA	NA
Were the outcomes measured in a valid and reliable way?	Y	Y	N	Y	Y	Y	Y	Y	Y
Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Final RoB	Low	Low	Low	Low	Low	Low	Low	Low	Low

Y: Yes, N: No, NA: Not Applicable.

Supplemental Table 2.4 Certainty assessment (GRADE tool) for the quantitative cephalometric variables evaluated.

Certainty assessment							**Summary of findings**				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With OSA**		**Risk with control**	**Risk difference with OSA**
SNA											
119 (3 observational studies)	not serious	serious [a]	not serious	very serious [b]	none	⨁◯◯◯ VERY LOW	54	65	-	The mean SNA was **81.5 º**	MD **0.69 º higher** (0.63 lower to 2 higher)
SNB											
119 (3 observational studies)	not serious	very serious [c]	not serious	very serious [b]	none	⨁◯◯◯ VERY LOW	54	65	-	The mean SNB was **76.81 º**	MD **0.17 º higher** (1.02 lower to 1.36 higher)
ANB											

119 (3 observational studies)	not serious	not serious	not serious	serious	none	⊕⊕⊕◯ MODERATE	54	65	-	The mean ANB was **4.7** º	MD **0.61** º **higher** (0.2 lower to 1.42 higher)
NSBa											
119 (3 observational studies)	not serious	not serious	not serious	very serious	none	⊕⊕◯◯ LOW	54	65	-	The mean NSBa was **127.11** º	MD **0.32** º **lower** (2.4 lower to 1.75 higher)
U1-L1											
66 (2 observational studies)	not serious	not serious	not serious	very serious	none	⊕⊕◯◯ LOW	27	39	-	The mean U1-L1 was **125.89** º	MD **0.21** º **lower** (4.82 lower to 4.4 higher)
U1-SN											
66 (2 observational studies)	not serious	not serious	not serious	very serious [b]	none	⊕⊕◯◯ LOW	27	39	-	The mean U1-SN was **106.54** º	MD **0.67** º **higher** (2.18 lower to 3.52 higher)

CI: Confidence interval; **MD:** Mean difference a. I^2=65%; b. A large variation in 95% CI was detected.; c. I^2=78%

Supplemental Table 2.5 Characteristics of the controlled studies without a negative PSG control group.

Author/ Year/	Source of sample	n	Age	Control group	OSA index	Craniofacial evaluation	Main results
AlHammad 2015	OSA: Ear-Throat and Nose Clinic of King Abdul-Aziz Hospital and Al Habeeb Medical Center, Saudi Arabia. Control group: College of	Total: 60 OSA: 30 Control:30	4.3 ±1.57	Healthy subjects	NI	Soft facial and oclusal features evaluated by clinical analysis.	There was no difference between OSA and control groups in facial morphology or facial profile.

	Dentistry, Saudi Arabia.						
Bergamo 2014	OSA: Mouth Breathing Center, the School of Medicine of Ribeirao Preto, Brazil Control: Periodontic Clinic, University of Sao Paulo, Brazil.	Total: 43 OSA: 21 Control (nasal breathers): 22	5.0-10.0	Nasal breathers	AHI= 7.5 ± 7.6	Cephalometric analysis (14 skeletal craniofacial variables)	The length of the mandibular ramus (ArGo) was smaller in the control group when compared to the OSA group (43.23 for OSA vs. 40.47 for controls, p ¼ 0.030). The lower anterior facial height (AFAi) was increased in the OSA group (64.39 cm) when compared to the controls (61.61cm, p< 0.041).
Cappabianca 2013	Department of Diagnostic Imaging, Second University of Naples, Italy.	Total: 80 OSA: 40 Control group: 40	OSA: 8.9 Control: 9.4	Not affected by OSA or any other type of sleep-related breathing disorder	OAHI = 8.1± 3.5	MRI evaluation (soft tissues and craniofacial skeleton)	The mandibular volume of the OSA group was lower when compared to controls (22.2±2.2 cm3 versus 25.4±2.4 cm3, p < 0.05). The vertical position of the hyoid bone in the view of the indices hy–n, hy–B and particularly hy–s (9.8 cm±1.3 in the OSA group versus 8.9±1.2 in the control group, p value < 0.01) was lower in the OSA group compared with controls.
Eimar 2019	University of Alberta–Orthodontics Clinics, Canada	Total: 96 OSA: 72 Control: 24	11.4± 2.9	Healthy subjects without SDB symptoms	AHI= 2.9 ± 0.6	Mandibular cortical width (MCW) from panoramic radiographs and cephalometric analysis (FMA, SNA and SNB), nasopharynx airway volume.	MCW values were significantly lower in OSA children (MCW = 2.9 ± 0.6 mm) compared to control children (MCW =3.5 ± 0.6 mm; P = 0.002). Children with OSA had a more vertical direction of mandibular growth (28.4 ±8.2 degrees) than controls (24.1± 5.4, p= 0.004). OSA children had a significantly smaller nasopharynx airway volume (3,325 ±1,233 mm3) in comparison to controls (4,658 ± 1,676 mm3; P = 0.004).
Kawashima 2002	Saitama Prefecture Children's Medical Center in Japan, Japan	Total: 69 OSA: 38 Control: 32	4.7	Healthy subjects without SDB symptoms	NI	Cephalometric analysis (34 variables: skeletal craniofacial features, postural features and hyoid bone position)	There were no differences in the cranial base angulation or hyoid bone position between groups. Compared with the control group children with OSA had a retrognathic mandible (facial axis and location of pogonion), a large posterior facial height, a large interincisal angle with retroclined lower incisors (L1 to ML), a narrow pharyngeal airway space (d–ad1, d–ptv and upper pharynx), an anterior tongue base position (lower pharynx) and a long soft palate.

Schiffman 2004	Children's Hospital of Philadelphia, USA.	Total: 36 OSA: 24 Control: 12	OSA: 4.9 ± 1.7; controls: 4.9 ± 1.8.	Healthy subjects without SDB symptoms	AHI= 9.8 ± 11.1	Three-dimensional segmentation of the mandible, using MRI	Individual measurement comparisons revealed no significant differences between groups
Perillo 2013	Sleep Centre of the Infantile Neuropsychiatry, Seconda Università di Napoli, Italy.	Total: 80 OSA: 40 Control group: 40	8.9	Healthy subjects	NI	27 angular and linear variables related to both craniofacial skeletal and dental morphology were measured by cephalometric evaluation.	Anterior facial height, height of the lower half of the anterior face, mandible inclination, were greater in the OSA group than in controls. The hyoid bone was displaced inferiorly and anteriorly in children with OSA.
Smith 2016	NI	Total: 61 OSA: 42 Control:19	7.3±1.8	Healthy subjects	4.1 ± 4.8	Dimensions of dental arches measured by dental casts and dental clinical measurements.	Among children with OSA, the intertooth distances for the first and second deciduous molars and the first permanent molars were narrower than in controls.
Vieira 2011	OSA: Mouth Breathing Center, School of Medicine, University of São Paulo, Brazil. Nasal breathers (control): Pediatric Clinic, Dental School, University of Sao Paulo, Brazil.	Total: 49 OSA: 20 Control:20	7.0-10.0	Healthy subjects	NI	11 linear variables related to craniofacial skeletal were measured by cephalometric evaluation.	A significant increase in the total and lower anterior heights of the face was observed among children with OSA. The hyoid bone was found to be in a more anterior and inferior position in children with OSA.
Vieira 2014	OSA: Mouth Breathing Center, School of Medicine, University of São Paulo, Brazil. Nasal breathers (control): Pediatric Clinic, Dental School, University of Sao Paulo, Brazil.	Total: 29 OSA: 14 Control:15	3.0-6.0	Healthy subjects (nasal breathers)	NI	10 linear variables related to craniofacial skeletal were measured by cephalometric evaluation.	The hyoid bone was inferiorly positioned to the palatal (44.5 ± 4.9 for nasal breathing vs. 48.7 ± 4.7 for OSA). The mandibular plane presented an increased inclination (8.1 ± 3.7 for nasal breathing vs. 11.8 ± 4.4 for OSA) in the OSA group.
Zettergren-Wijk 2006	NI	Total: 34 OSA: 17 Control:17	OSA: 5.6±1.3 Control: 5.8±1.4	Healthy subjects	NI	14 linear variables related to craniofacial skeletal were measured by cephalometric evaluation.	In subjects with OSA, the mandible was more posteriorly inclined, the maxilla was more anteriorly inclined compared with the controls. The anterior face height, the anterior facial ratio and the anetrior craniofacial base were greater and posterior face height was smaller in the patients with OSA. The upper and lower incisors were more retroclined in the OSA patients than controls. The position of the

							tip of the nose (APEX – FHP) was slightly more advanced in OSA group than control subjects. The width of nasopharyngeal airways (ad1 – pm and ad2 – pm) were reduced in OSA group.

OSA: Obstructive sleep apnea, AHI: Apnea-Hypopnea Index, OAHI: Obstructive Apnea-Hypopnea Index, PSG: polysomnography.

Chapter 3 : Use of facial stereophotogrammetry as a screening tool for pediatric obstructive sleep apnea by dental specialists

Chapter 2 presented the current knowledge regarding the association between craniofacial features and pediatric OSA, suggesting that neither an association nor a lack thereof between craniofacial morphology and pediatric OSA can be supported at this time. Also, there was a lack of evidence evaluating soft tissue craniofacial features and a difficult access to the standard method to diagnosis pediatric OSA, the PSG, as highlighted in Chapter 1. Thus, chapter 3 evaluates the effectiveness of an analysis of facial soft tissue features through stereophotogrammetry as a screening tool for pediatric obstructive sleep apnea by dental specialists.

Chapter 3 is based on this published article:

Fagundes NCF, Carlyle T, Dalci O, Darendeliler MA, Kornerup I, Major PW, Montpetit A, Pliska BT, Quo S, Heo G, Flores-Mir C. Use of facial stereophotogrammetry as a screening tool for pediatric obstructive sleep apnea by dental specialists. Journal of Clinical Sleep Medicine, 2022: 18(1):57-66. Available from: https://doi.org/10.5664/jcsm.9490

3.1. Abstract

STUDY OBJECTIVES: To evaluate facial 3D stereophotogrammetry's effectiveness as a screening tool for pediatric obstructive sleep apnea (OSA) when used by dental specialists.

METHODS: One hundred forty-four subjects aged 2-17 years, including children fully diagnosed with pediatric OSA through overnight observed polysomnography (PSG) or at high- or low-risk of pediatric OSA, participated in this study. 3D stereophotogrammetry, Craniofacial Index (CFI) and Pediatric Sleep Questionnaire (PSQ) were obtained from all participants. Ten dental specialists with interest in pediatric sleep breathing disorders classified OSA severity twice. Once, based only on 3D stereophotogrammetry, and then based on 3D stereophotogrammetry, CFI and PSQ. Intra-rater and inter-rater reliability, and diagnostic accuracy of pediatric OSA classification, were calculated. A cluster analysis was performed to identify potential homogeneous pediatric OSA groups based on their craniofacial features classified through the CFI.

RESULTS: Intra-rater and inter-rater agreement suggested a poor reproducibility when only 3D facial stereophotogrammetry was used and when all tools were assessed simultaneously. Sensitivity and specificity varied among clinicians, indicating a low screening ability for both 3D facial stereophotogrammetry, ranging 0.36-0.90, and 0.10-0.70, and all tools ranging 0.53-1.0 and 0.01-0.49, respectively. A high arched palate and reversed or increased overjet contributed to explaining how participating dental clinicians classified pediatric OSA.

CONCLUSIONS: 3D stereophotogrammetry-based facial analysis does not seem predictive for pediatric OSA screening, alone or combined with PSQ and CFI, when used by dental specialists interested in SDB. Some craniofacial traits, more specifically significant sagittal overjet discrepancies and an arched palate, seem to influence participating dental specialist's classification.

Key-words: Sleep apnea, obstructive; Child; Screening; Cluster Analysis.

3.2. Introduction

Obstructive sleep apnea (OSA) is a respiratory sleep disorder resulting in partial or complete airway obstruction.[1] Among children, OSA prevalence has been reported to vary from 1 to 5%.[2, 73] In the absence of proper management of OSA cases, commonly a result of underdiagnoses, several health conditions can arise. These include cognitive problems,[76] respiratory and cardiac comorbidities.[77] OSA is related to an increased cost of health services and poor academic progress from a social perspective.[78, 79]

Different factors can contribute to pediatric OSA development, such as craniofacial features,[43] tonsils and/or adenoid tissue hypertrophy,[110] reduced upper airway space,[111, 112] and obesity.[6] Enlarged tonsils and adenoids are the leading cause of OSA in children.[53] Craniofacial features, more specifically, a high arched palate, convex facial profile and an anterior open bite, have been linked to OSA in some children.[43]

A key component of pediatric OSA diagnosis is the PSG, an exam that monitors oxygen saturation, oronasal airflow, respiratory movement, electroencephalogram, body position, electro-myogram, electrooculogram and electrocardiogram of a full night of sleep.[9] This exam faces some barriers in many countries, including the high cost and long wait lines for public health services.[33] Alternatively, several screening tools have been used to evaluate pediatric OSA's sleep signs and symptoms,[113] consider adenoid and tonsil sizes and monitor sleep parameters at home.[114, 115] However, relatively little attention is given to the potential screening of craniofacial features linked to pediatric OSA.

A facial soft tissue analysis as part of a pediatric OSA screening may represent a safe and accessible method for dental professionals' routine clinical use. Dentists and dental specialists are trained to perform facial analysis and are typically incorporated into dental patients' clinical exams. Using craniofacial anthropometry and photogrammetry to evaluate facial features has been proposed as an alternative technique to suggest OSA in adults.[116, 117] There is a need to determine if this method would help pediatric OSA screening and how craniofacial features may influence this diagnosis.

Considering some degree of contribution of craniofacial features to the upper airway collapse during sleep, identifying homogenous categories of craniofacial patterns potentially linked to this collapse may help. One of the approaches used to identify these patterns is clinical phenotyping based on clustering methods.[118, 119] There is a scarcity of studies exploring the identification of specific craniofacial patterns in pediatric OSA. Among adults, this method has been used to characterize clinical phenotypes in OSA subjects. Adults presenting skeletal Class II hyperdivergent pattern, posteriorly displaced hyoid, and retroclined soft palate were features identified to group moderate to severe OSA subjects.[118]

This study aims to evaluate the effectiveness of an analysis of facial soft tissue features through stereophotogrammetry as a screening tool for pediatric obstructive sleep apnea by dental specialists.

Understanding the craniofacial feature's role and its evaluation by dental professionals may help identify patients at higher risk for pediatric OSA. This could improve early diagnosis and proper management of OSA in children.

3.3. Material and methods

This study was approved by the Health Research Ethics Board of the University of Alberta (Pro00057638). Children and adolescents aged 2-17 years, fully diagnosed with pediatric OSA through PSG or at high- or at low-risk for pediatric OSA (normative subjects), participated in this study based on PSQ score study. The presence of craniofacial syndromes was considered an exclusion criterion.

Children and adolescents under the care of two different facilities: a Children's hospital sleep center (Pediatric sleep laboratory, Stollery Children's Hospital, Edmonton, AB, Canada) and a university's dental clinic (Dental Clinic at the University of Alberta, Edmonton, AB, Canada) were invited to participate in this study. The participants from the hospital site presented SDB clinical signs and symptoms and had an PSG exam. The dental clinic participants were at high- or at low-risk for pediatric OSA, assessed by a PSQ questionnaire.

The sample size was calculated based on a type I error rate of 5%, the statistical power of 80%, a null hypothesized value of 0.6 and an alternative hypothesized value of 0.7 for sensitivity and specificity.[113, 120] We also set the prevalence rate at 5 %. Therefore, the OSA group's minimum required sample sizes are 181 (sensitivity) and 10 (specificity). At the same time, the total sample sizes (both OSA and control group) are 3620 (sensitivity) and 191 (specificity). However, achieving a total sample size of 3620 is not realistic, so we set our goal in terms of minimum sample size as an average of sensitivity and specificity for the OSA group, which is approximately 96 and implies that we need to set a total of both OSA group and control group as 192. Consequently, we set the sample size 100 per group and a total of 200.

Nine orthodontists and one pediatric dentist, with a special interest in pediatric sleep disorders, were invited to suggest the potential for pediatric OSA severity on a 4-point ordinal

scale (not-likely, or mild, moderate, severe OSA) among these children based on 3D stereophotogrammetry, Craniofacial Index (CFI),[121] and Pediatric Sleep Questionnaire (PSQ).[122] The CFI is a tool developed to identify the orthodontic treatment need in pediatric patients with obstructive sleep apnea. This index evaluates the frequency of the eight most frequent orthodontic problems observed in children with OSA.[121]

The dental specialists have clinical experience in providing dental care to children with sleep-breathing disorders and research interests in pediatric sleep disorders. However, their actual OSA-related knowledge was not directly assessed. This group of clinicians were from Canada, the United States and Australia.

The pediatric sleep questionnaires and craniofacial parameters were collected from all children included in this study. The sex, age and body mass index (BMI) were collected when available from a subsample of the included children. The BMI z-scores were calculated, following the growth standards of the Centers for Disease Control and Prevention. A BMI z-score between 1-1.9 indicates overweight, and BMI z-score ≥ 2 indicates obesity.[123]

After PSG, the Obstructive–Mixed Apnea–Hypopnoea Index (OMAHI) was calculated. This index was calculated based on the number of apneas and hypopneas during sleep divided by the total sleep time, excluding the central respiratory events. Children presenting an OMAHI index ≥ 2 events/h were classified as presenting pediatric OSA.[124] (MacLean, Fitzsimons, Fitzgerald, & MBBS, 2017) The OSA severity was categorized as mild (OMAHI= 2-4.9), moderate (OMAHI= 5-9.9) and severe (OMAHI≥10).[124]

The PSQ was collected in all 200 subjects and PSG only among 103 participants. 3D stereophotogrammetry was collected in 152 children. Children presenting a PSQ score of ≥ 8 were considered at high-risk for OSA, whereas a PSQ score of < 8 indicated at low-risk for OSA.[122] The

three-dimensional facial stereophotogrammetry (3dMD, Atlanta, GA) and the CFI were adopted to evaluate the craniofacial parameters. Facial stereophotogrammetry comprises the estimation of 3D coordinates of facial features utilization of images taken by multiple cameras simultaneously. The cameras are set in different positions around the face. Besides rendering a 3D image, this data can be utilized to perform anthropometric analyses of facial soft tissue landmarks.[125] (Figures 3.1A & 3.1B)

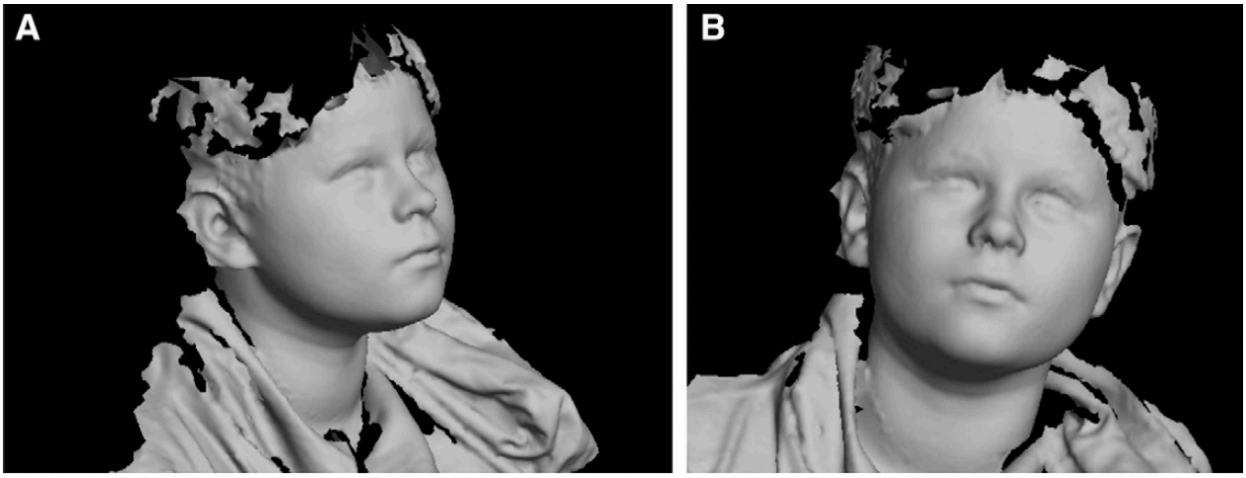


Figure 3.1 Three-dimensional stereophotogrammetry used in the clinician's evaluation. Lateral (A) and frontal (B) views.

The involved clinicians categorized all children according to each participant's perceived OSA severity as not likely, mild, moderate, or severe in two ways. First, only based on the 3D facial stereophotogrammetry records. After that, based on the stereophotogrammetry and additional information obtained from the CFI and the PSQ. Only the total score of PSQ was provided to the clinicians. Only the CFI scores from the intra-oral evaluation were available to the evaluators. The clinicians had virtual access to the 3D facial stereophotogrammetry file and rotated and zoomed the images. All clinicians received the same level of instruction regarding the assessment of 3D stereophotogrammetry images. There was no access to the initial severity ranking as determined using the stereophotogrammetry records for this second assessment round.

The intra-rater and inter-rater reliability were calculated among clinicians. The intra-rater reliability was evaluated in a subsample of five clinicians from the University of Alberta, four orthodontists and one pediatric dentist, in which Delta was calculated. Only this group was able to evaluate the data twice. The inter-rater reliability was checked among all ten clinicians, in which both Delta and Fleiss' Kappa were calculated. Delta was chosen as an alternative to Cohen's kappa due to the presence of unbalanced marginal totals.[126] The Delta measurement considers the total proportion of answers in agreement and is valid in all circumstances in which Cohen's kappa is valid.[126] We reported Fleiss' kappa because it measures the agreement among multiple raters.

The agreement level was considered excellent if above 0.9; good if between 0.75 and 0.9; moderate if in the range of 0.5-0.75; and poor if below 0.5.[127] This agreement level was used for both Delta and Fleiss' Kappa analysis.

The diagnostic value of the classification was evaluated through sensitivity (Se), specificity (Sp), Positive Predictive Value (PPV) and Negative Predictive Value (NPV). In addition, the prevalence of pediatric OSA was considered 5% to the PPV and NPV calculation.[2, 73] The classification suggested by the participating clinicians was compared to pediatric OSA diagnosis in the group of patients submitted to PSG.

A cluster analysis was performed to identify and characterize the children's craniofacial features included in this study. This analysis also aimed to understand the relationship between sleep status variables and pediatric OSA classification on children's specific craniofacial features in this sample. A two-step cluster analysis was performed. First, the eight craniofacial feature scores evaluated through the Craniofacial Index were entered as unique variables to identify clusters. These scores are representative of the most common craniofacial features suggestive of orthodontic treatment need (e.g., arched palate, excessive lower facial height, open bite) observed

in children with OSA.[121] The best cluster solution was chosen based on the Akaike Information Criterion (AIC) and the log-likelihood distance. The number of groups was defined according to the large ratio of AIC changes and the large ratio of distance measures.

After clustering analysis, a post-hoc analysis was performed as follows. The distribution of demographic (sex, age and BMI z-score) and sleep status variables (PSQ score, diagnosis of pediatric OSA, when available) between clusters were evaluated by descriptive analysis (frequency or mean and standard deviation). We compared the distribution of pediatric OSA classification by all clinicians with clusters. To compare the distribution of OSA classification performed by clinicians across clusters, we combined the classes determined by all ten clinicians into one category by choosing the Most Frequent (MF) classification by all ten clinicians for each patient. For example, if ten clinicians' classification for a patient was 1, 1, 2, 2, 3, 4, 2, 2, 3, 4, then MF is 2. If the most frequent classes were tied, the lower class was chosen.

We combined 4-category pediatric OSA classification into two not likely (previously categorized as not likely) or likely (previously classified as mild, moderate, or severe) for statistical analysis. The SPSS statistical package for the social sciences (version 23; IBM, Armonk, NY) was used for data analysis. A p-value <0.05 was set as statistical significance.

3.4. Results

Among the 200 patients enrolled in the study, 103 participants were recruited from a sleep laboratory and 97 participants from the dental clinic. The 3D stereophotogrammetry was collected in 152 children registered in a sleep laboratory at a pediatric hospital (PSG sample, n = 78) and at a university dental clinic (non-PSG sample, n= 74). The subsample without an PSG (n=74) was not considered in the diagnostic evaluation of the 3D stereophotogrammetry screening tool. Even though a complete list of 152 patients was sent to all ten dental specialists, some missing data was

detected during data analysis. In the first categorization performed by all ten clinicians (only 3D stereophotogrammetry available), one patient's evaluation was missing (n=151). In the second categorization (3D stereophotogrammetry, CFI and PSQ available), eight evaluations were missing (n=144). A detailed diagram of participant's flow in the study is presented in Figure 3.2.

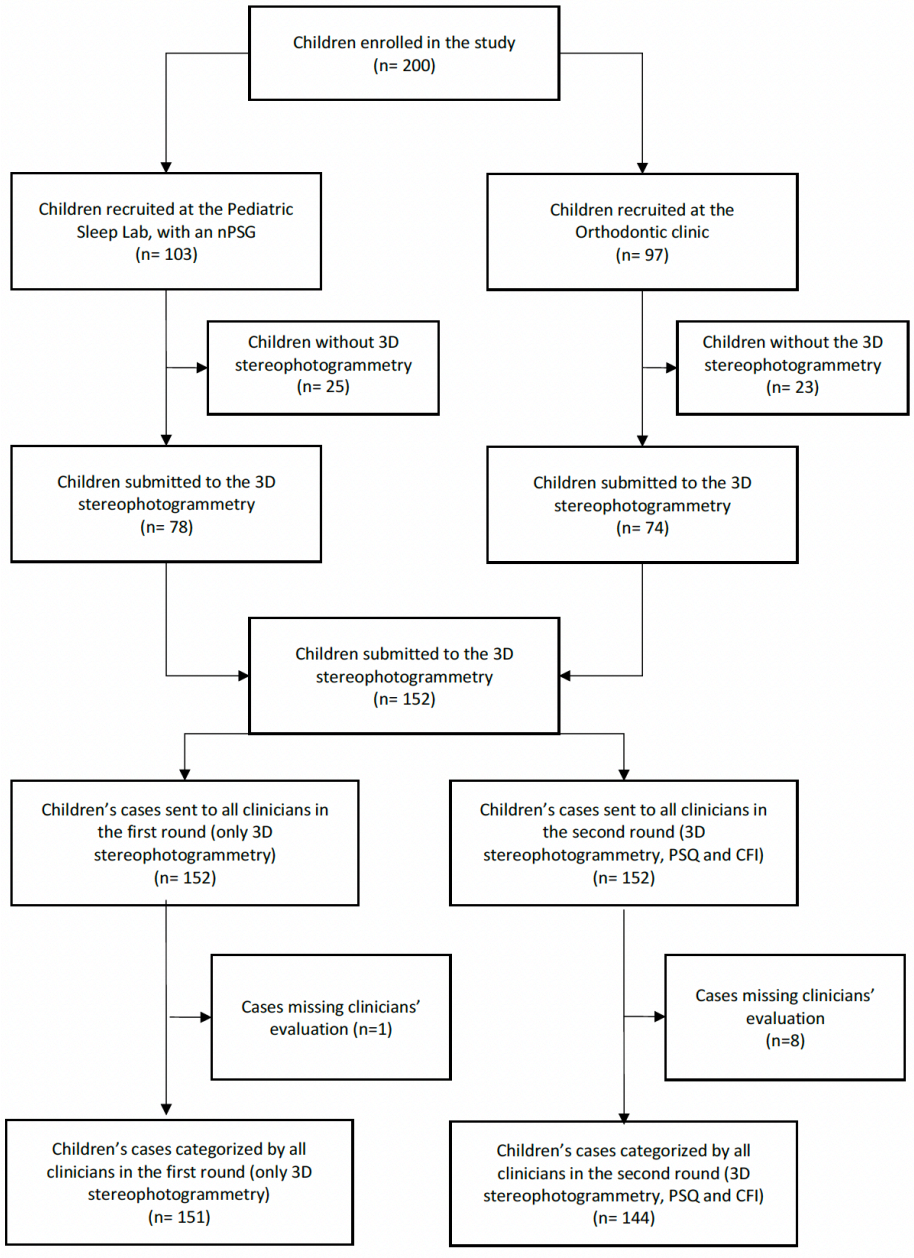


Figure 3.2 Flow chart for participants and missing data in the study.

In the PSG sample of participants submitted to the 3D photogrammetry (n=78), 53% (n=41) had a positive diagnosis of OSA, including mild to severe cases (Table 3.1). The OSA risk defined by PSQ was high in 76% (n=59) of the subjects, with a mean age of 8.5±4.1 years and a BMI z-score= 0.6±1.6 (n=65). No strong correlation (r=0.07, p=0.57) was observed between PSQ and OMAHI scores (Supplemental Material, Table S1). In the group of participants without an PSG, 13% (n=20) were at high risk for OSA, with a mean age of 8.9±2.5 years. (Table 3.1).

The consistency between two trials among five University of Alberta clinicians was poor when only 3D stereophotogrammetry was available (Δ= 0.39-0.45) and improved from poor to good (Δ= 0.44-0.75) when 3D stereophotogrammetry, CFI and PSQ were available. (Supplemental Table 3.1).

Table 3.1Characteristics of participants submitted to 3D stereophotogrammetry.

	PSG sample (n=78)[a]	**non-PSG sample (n=74)[a]**
OSA diagnosis		
negative	37 (47%)	NA
mild	17 (22%)	NA
moderate	20 (26%)	NA
severe	4 (5%)	NA
OSA risk evaluated by PSQ		
At low risk	19 (24%)	64 (87%)
At high risk	59 (76%)	10 (13%)
Age	8.5±4.1	8.9±2.5
Sex		
Male	41 (52%)	39 (53%)
Female	37 (48%)	35 (47%)
BMI z-score	0.6±1.6 (n=65)	*

[a]The frequency, n(%), or mean±Standard deviation were reported when applicable. NA: Not Applicable; *BMI z-score not available for this subgroup.

Fleiss' Kappa evaluated the agreement among all ten clinicians. (Supplemental Material, Table S1). The Fleiss' Kappa was poor in both situations. It was 0.12 when only 3D photos were considered for classification and slightly improved to 0.37 when 3D photos, CFI and PSQ were assessed. Each clinician's agreement contributed to understanding each clinician's role in the reliability. According to Delta, the agreement was poor to moderate when only the 3D stereophotogrammetry was available (Δ= 0.24-0.53). These results improved when the 3D stereophotogrammetry, PSQ and CFI were available before pediatric OSA classification in 9 of 10 clinicians, which showed a poor to good reliability (Δ= 0.14-0.86). (Supplemental Material, Table S1) Compared to the other nine dental specialists, clinician 2 showed a weak performance when all tools were considered together compared to only 3D stereophotogrammetry.

In the first classification of OSA performed by clinicians, only 3D stereophotogrammetry was available. In this scenario, the sensitivity (0.36-0.90) and specificity (0.10-0.56) values presented a large variability among ten participating clinicians. PPV values varied from 0.05 to 0.07, and NPV varying from 0.95 to 0.98 among ten clinicians. Among the clinicians, the average values for these measurements were Se= 0.51, Sp=0.35, PPV=0.04, NPV=0.93. (Table 3.2; Supplemental Table 3.2)

The second classification of OSA performed by clinicians was based on all tools (3D stereophotogrammetry, PSQ and CFI). The sensitivity values (0.55-1.0) and specificity (0.01-0.49) increased for nine of the ten clinicians than the first classification, but a large variability among the clinicians was still present. The PPV (0.04-0.06) remained very low and NPV (0.87-0.96) very high across the clinicians. Among the clinicians, the average values for these measurements were Se= 0.78, Sp=0.13, PPV=0.04, NPV=0.92. (Table 3.2; Supplemental Table 3.2)

Table 3.2 Sensitivity, specificity, PPV and NPV of pediatric OSA classification. Most frequent values among all 10 clinicians.

Diagnostic values	**Only 3D stereophotogrammetry**	**3D stereophotogrammetry, CFI and PSQ**
	Total (n=78)	**Total (n=75)**
Sensitivity (95%CI)	0.51 (0.35, 0.67)	0.78 (0.62, 0.89)
Specificity (95%CI)	0.35 (0.20, 0.52)	0.13(0.01 ,0.28)
PPV (95%CI)	0.04 (0.03, 0.06)	0.04(0.03, 0.05)
NPV (95%CI)	0.93 (0.89, 0.96)	0.92(0.80, 0.98)

PPV= Positive Predictive Value; NPV= Negative Predictive Value.

The two-step clustering analysis identified two different clusters based on the frequency of eight craniofacial features observed in the sample, identified by the CFI assessment. The clusters presented an acceptable quality (Silhouette's index= 0.5). The cluster's size ratio was 1.5 (Cluster A, n= 120 and Cluster B, n= 80 children). The most important variables to distinguish clusters were Overjet, Soft Tissue Lateral Profile and Palate Depth. Cluster B presented more children with craniofacial disharmonies linked to pediatric OSA than cluster A. More specifically, cluster B children presented a high arched palate and a significantly increased or reversed overjet, while children in cluster A presented a more normal craniofacial pattern. (Table 3.3)

Table 3.3 Variables used to determine clusters— distribution of craniofacial features across groups. The variables are presented in order of predictor importance to clustering.

	Craniofacial features	**Cluster A (n= 120)**	**Cluster B (n= 80)**	**Total (n= 200)**
Overjet	Normal	**120 (100%)**	24 (30%)	144 (72%)
	Increased or reverse	0 (0%)	**56 (70%)**	56 (28%)
Profile	Normal	**120 (100%)**	46 (58%)	166 (83%)
	Severely Convex or concave	0 (0%)	**34 (42%)**	34 (17%)
Palate	Normal	**89 (74%)**	31 (39%)	120 (60%)
	Mildly high arched	30 (25%)	**39 (49%)**	69 (35%)

	Severely high arched	1 (1%)	10 (12%)	11 (5%)
Midface deficiency	Normal	**89 (74%)**	49 (62%)	138 (69%)
	Mild Loss of Fullness	31 (26%)	**25 (31%)**	56 (28%)
	Substantial Loss of Fullness	0 (0%)	6 (7%)	6 (3%)
Over bite	Normal or deep bite	**120 (100%)**	65 (81%)	185 (92%)
	Open bite	0 (0%)	**15 (19%)**	15 (8%)
Posterior bite	Normal	**118 (98%)**	62 (78%)	180 (90%)
	Unilateral crossbite	2 (2%)	8 (10%)	10 (5%)
	Bilateral crossbite	0 (0%)	10 (12%)	10 (5%)
Lip Strain	Normal	**99 (82%)**	43 (54%)	142 (71%)
	Mildly Strained Closing lips	21 (18%)	**24 (30%)**	45 (23%)
	Very Strained Closing lips	0 (0%)	13 (16%)	13 (6%)
Lower face height	Normal	**91 (76%)**	45 (56%)	136 (68%)
	Mildly Excessive	28 (23%)	26 (32%)	54 (27%)
	Severely Excessive	1 (1%)	9 (12%)	10 (5%)

Approximately the same percentage of patients diagnosed with pediatric OSA by PSG was observed in Cluster A (47%) and B (50%). The frequency of children categorized as high risk for OSA, defined after PSQ screening, was slightly higher in Cluster B (60%) than Cluster A (42%). Cluster B presented more patients categorized as likely to have OSA than Cluster A in both clinicians' evaluations. This frequency was higher when the CFI and PSQ were added to the assessment, in which only 37% were classified as likely in Cluster A, and 76% of patients were classified as likely in Cluster B. (Table 3.4)

Table 3.4 Variables used in the post-hoc analysis. Distribution of demographic features and sleep status across groups.

		Cluster A	**Cluster B**	**Total**
	Male	61 (57%)	35 (48%)	96 (53%)
	Female	46 (43%)	38 (52%)	84 (47%)
	Age (n=196)	8.2±3.5	9.8±3.6	8.8±3.6

	BMI z-score (n=65)	0.1±1.9	1.1±1.1	0.6±1.6
OSA risk evaluated by PSQ (n=200)	At low risk	70 (58%)	32 (40%)	102 (51%)
	At high risk	50 (42%)	48 (60%)	98 (49%)
OSA status evaluated by an PSG (n=103)	OSA negative	26 (53%)	27 (50%)	53 (52%)
	OSA positive	23 (47%)	27 (50%)	50 (48%)
OSA classification based only on 3D stereophotogrammetry (n=150)[a]	Not Likely	69 (75%)	28 (49%)	97 (64%)
	Likely	23 (25%)	30 (51%)	53 (36%)
OSA classification based on 3D stereophotogrammetry, CFI and PSQ (n=144)[a]	Not Likely	57 (63%)	13 (24%)	70 (49%)
	Likely	33 (37%)	41 (76%)	74 (51%)

[a]Most frequent pediatric OSA classification among all ten clinicians. BMI: Body Mass Index

Regarding the distribution of craniofacial features among PSG children, OSA negative and OSA positive patients presented the same magnitude of craniofacial features suggestive of orthodontic treatment need (e.g., arched palate, excessive lower facial height, open bite). (Supplemental Table 3.4).

Regarding demographic aspects, only part of the sample reported sex (n=180), age (n=196) and BMI z-score (n=65) due to miscommunication between recruitment sites. In clusters A and B, a balanced ratio of male and female patients was observed. The mean age was higher in cluster B (9.8±3.6 years) than the mean age in cluster A (8.2±3.5 years). The BMI z-score was higher in cluster B (1.1±1.1) than cluster A (0.1±1.9). However, firm conclusions cannot be drawn due to the lack of information for the entire sample.

3.5. Discussion

The evaluation of soft facial features by dental specialists based on 3D stereophotogrammetry analysis showed poor intra-rater and inter-rater reliability and low values of sensitivity, specificity, PPV, and a high NPV value among all dental specialists. The availability of additional information about craniofacial features and PSQ scores in addition to the images

improved both intra-rater and inter-rater reliability among clinicians but remained questionable for screening purposes. Also, to 9 of 10 clinicians, the sensitivity increased when all tools were assessed, but a negligible specificity was still observed. The presence of significantly reversed or increased overjet, along with a high arched palate, seems to affect how these dental specialists classified patients regarding perceived OSA risk. However, these features appear not to be associated with the final pediatric OSA status evaluated through an PSG. What this seems to imply is that dental specialists are likely biased by their perception that specific clinical malocclusion traits are highly likely associated with OSA when in reality, their presence is not expected to imply pediatric OSA automatically. This is an important finding as dental clinicians may target a specific subgroup of pediatric OSA patients while potentially ignoring those with OSA but without evident known malocclusion traits.

The evaluation of craniofacial features among children with obstructive sleep apnea has been previously explored through cephalometric,[43, 128] and photographic methods.[44] To our knowledge, this is the first study to evaluate the diagnostic value of 3D facial stereophotogrammetric analysis for pediatric OSA screening. Among OSA adults, the diagnostic value of craniofacial evaluation by 2D photographs has been explored by assessing anesthesiologists, otolaryngologists, and internists. Their photo diagnosis has observed a 61.8% accuracy in comparison to PSG.[129]

In the present study, the facial evaluation using 3D facial stereophotogrammetry by dental specialists with a known interest in sleep-disordered breathing showed considerable variability in the sensitivity and specificity among all ten clinicians, regardless of the access to PSQ score and CFI index information. The PPV was very low (0.05-0.07), and NPV was high (0.87-0.98) in both classifications.

Overall, when assessing these diagnostic values, it can be concluded that 3D facial stereophotogrammetry without or with the addition of specific craniofacial morphological data was not a valid screening tool for pediatric OSA among this selected group of dental specialists. A moderate number of false positives and a high number of false negatives is suggested in either approach. Significant negative implications could ensue. The false positives will further burden the health system unnecessarily, while the false negatives will deny children the option of being assessed for potential pediatric OSA.

The performance of these screening approaches were lower in comparison to other alternative tools adopted for pediatric OSA screening such as the PSQ (sensitivity= 0.71 to 0.84 and specificity= 0.13 to 0.72, among five studies),[130] overnight oximetry (sensitivity-specificity= 0.80-0.65, 0.85-0.79 and 0.82-0.90 for models classifying children with AHI≥1, AHI≥5, and AHI≥10, respectively),[131] and Mallampati score (sensitivity= 0.88, 95% CI: 0.80, 0.96; specificity: 0.77, 95%CI: 0.77, 0.68).[114] PSQ is useful due to its simplicity and minimal cost. The problem is that it may generate over-testing when compared to overnight oximetry or the Mallampati score.

In our analysis, we collected the evaluation of ten independent dental specialists and then assessed their reliability. Our results showed poor to good intra-rater reliability. The depicted diagnostic values were not necessarily better when additional craniofacial information and PSQ sleep questionnaire results were made available. This may indicate that relying on 3D stereophotogrammetry evaluation alone is questionable for screening OSA status among children. Additional tools that present an actual quantification of SDB clinical signs and symptoms were necessary to attempt a more reliable screening approach. Even then, the performance could not be considered clinically reasonable. Indeed, it has been previously demonstrated that clinical

parameters, including patient demographic information, palate position and tonsillar size, provide limited information on the severity of OSA in children.[132]

In addition to those results, a cluster analysis was performed to understand better the role of craniofacial features in implying OSA status and probable OSA classification performance by this selected group of dental specialists. Eight craniofacial features previously associated with an increased risk of pediatric OSA were used to investigate if there was a specific craniofacial pattern in the group of children included in this study. Two clusters were identified. Cluster B presented more children with craniofacial features previously linked to pediatric OSA, specifically high arched palate and significantly increased or reversed overjet. However, the frequency of pediatric OSA patients diagnosed by PSG or at high-risk for OSA, as suggested through the PSQ score, did not differ between clusters. Therefore, clinical judgement of risk for pediatric OSA was not improved when the craniofacial form was considered.

Specific craniofacial features defined by these clusters may have impacted how dental specialists categorized potential pediatric OSA patients. For example, an increased overjet and a constricted palate may be linked to a compromised airway space and an increased probability of muscle collapsibility during sleep facilitating OSA.[128] The current evidence links Class II malocclusions (usually showcasing increased overjet) and constricted maxilla to pediatric OSA,[43, 44, 128] which may have biased the dental specialists' classification decisions. Perhaps dental clinicians overestimate the real impact of craniofacial features in pediatric OSA's complex and multifactorial entity as craniofacial morphology does not directly correlate with upper airway function.

Our findings do not support a clear categorical link between craniofacial features and OSA in children. Children with normal oropharyngeal anatomy may suffer from OSA. This work

contrasts the many studies that describe craniofacial alterations in pediatric OSA cases. Dental clinicians should not oversimplify the diagnosis and screening for pediatric OSA.

The evaluation of craniofacial features evaluation as a possible source of clinical phenotyping in OSA children needs further probing. Many factors leading to pediatric OSA impart secondary morphologic changes in a growing patient, suggesting that some craniofacial features develop as both a cause and consequence of OSA. There is a lack of studies investigating the role of specific clinical traits in pediatric OSA, in which the available evidence is mainly focused on the PSG sleep variables.[133-135] The dependence on the AHI for diagnosis or even a communication tool to evaluate OSA severity of pediatric OSA might be challenging because this index relies only on the number of obstructive events. The reliance on this single index has been questioned due to its limited information about other OSA-relevant characteristics.[106] Information about associated comorbidities, OSA symptoms and quality of life are still needed to establish a treatment plan or monitor treatment outcomes.[136] Nevertheless, the evaluation of facial features could help identify specific traits associated with OSA, as suggested among adult patients.[118, 119]

A higher prevalence of children at high-risk for OSA has been recently reported in an orthodontic population.[137] The involvement of orthodontists and pediatric dentists in identifying OSA risk factors may improve the screening process for this disease and reduce the long-wait line for an PSG by enhancing patients' identification at high-risk for OSA and subsequent earlier OSA diagnosis and treatment. Dental clinicians have the training and knowledge to evaluate facial features, and their involvement in the screening process, as part of a transdisciplinary group led by a sleep medicine physician, may help diagnose and treat pediatric OSA on time.

This study's overall impact would be that only patients with a clear higher risk should be referred (reduced number of false positives) to avoid further saturating the medical environment

with unnecessary referrals. Over-reliance on craniofacial features as a standalone criterion should be discouraged. Much emphasis is placed on the palatal morphology of a high arched, narrow palate in children. This data suggests that these often-cited features do not consistently correlate with OSA status. Treatment is usually initiated from daytime or nighttime symptoms, and the dental practitioner has a key role in the early query of symptoms. Whether these symptoms translate to morphologic changes as the pediatric OSA patient matures is the subject of future studies.

3.5.1. Limitations

Not the entire sample of children had an PSG exam that is considered a key component for a precise pediatric OSA diagnosis.

This study may have been subjected to selection bias. A convenience sample of two independent centers (a university orthodontic clinic and a sleep center) was included and may not reflect the general pediatric population.

In addition, the OMAHI index and the cut-off of 2 events per hour may have some limitations in the identification of some OSA cases. The OMAHI index reports the average number of apneas and hypopneas during sleep, excluding the central respiratory events per hour in sleep.[124] However, it has been suggested that additional features, including event duration, arousal intensity, flow limitations and obstructive hypoventilation, may also be helpful to understand pediatric OSA characteristics.[106] In future studies, these additional features should also be considered in OSA evaluation.

The definition of clusters was based on eight features evaluated by CFI. The clinicians had access to CFI and 3D stereophotogrammetry and PSQ scores in one of the OSA classifications

performed in this sample of children. The access to CFI information may have influenced the distribution of clinicians' judgement in clusters A and B.

The effect of the obesity and the BMI z-score was not evaluated due to the amount of missing data for a sample of the included patients. However, an increased BMI may increase the risk of children to sleep breathing disorders.[138]

The adenotonsillar size and adenotonsillectomy history were not collected in this study. Adenotonsillar hypertrophy is a risk factor for pediatric OSA and might be associated with craniofacial features suggestive of orthodontic treatment need (e.g., arched palate, excessive lower facial height, open bite).[139] Also, the presence of craniofacial anomalies, such as a smaller mandible size, were associated with residual OSA after adenotonsillectomy.[140] 3D stereophotogrammetry is a reliable method to evaluate craniofacial features among children.[141] However, the impact of different craniofacial developmental stages in assessing images obtained by 3D stereophotogrammetry has not been explored previously or in the present study.

As a time-series study, the number of children with and without craniofacial features suggestive of orthodontic treatment need (e.g., arched palate, excessive lower facial height, open bite) observed in children with OSA was not matched regarding the pediatric OSA status.

Different sleep medicine physicians interpret PSG values differently in combination with clinical exams and relevant medical history. There is no worldwide agreement on how to interpret a given set of data. Hence, the final diagnosis decision may be different when other health providers would have been involved.

No specific verbal information was provided on how to interpret the provided PSQ values. Some of the involved dental specialists may have an idea of using 8 as a cut-off. Still, others may have simply used PSQ as a continuous variable and not as a dichotomous variable.

The ethnicity of patients not evaluated in this study. The sample of this study assessed Canadian children from multiple cultures. The prevalence of bony and soft-tissue craniofacial features suggestive of orthodontic treatment need (e.g., arched palate, excessive lower facial height, open bite) may vary according to ethnic groups and fat distribution. This might result in differences in OSA prevalence and severity among children.[142, 143]

Pre-term birth history was also not considered, and it is an important risk factor.[144]

3.6. Conclusions

3D stereophotogrammetry-based facial analysis does not seem predictive for pediatric OSA screening when used alone or combined with PSQ and CFI when assessed by dental specialists interested in SDB in this sample. Some craniofacial traits, more specifically significant sagittal overjet discrepancies and a high-arched palate, seem to influence participating dental specialist's classification, but these were not accurate markers of OSA.

3.7. Supplemental Files

Supplemental Table 3.1 Intra-rater and inter-rater agreement of pediatric OSA classification among clinicians at the University of Alberta.

Clinician	**Intra-rater reliability**				**Inter-rater reliability**					
	Only 3D stereophotogrammetry		**3D stereophotogrammetry, CFI and PSQ**		**Only 3D stereophotogrammetry**			**3D stereophotogrammetry, CFI and PSQ**		
	n	**Δ**	**n**	**Δ**	**n**	**Δ**	**Fleiss' Kappa**	**n**	**Δ**	**Fleiss' Kappa**
1					151	0.49	0.12(± 0.01)*	144	0.66	0.37 (±0.01)*
2					151	0.44		144	0.14	
3					151	0.5		144	0.82	

4	150	0.42	148	0.69	151	0.34		144	0.36	
5	150	0.36	148	0.49	151	0.53		144	0.86	
6	150	0.45	148	0.75	151	0.39		144	0.78	
7					151	0.44		144	0.85	
8	150	0.36	148	0.49	151	0.35		144	0.83	
9					151	0.32		144	0.65	
10	150	0.45	148	0.75	151	0.24		144	0.65	

CFI= Craniofacial Index, PSQ= Pediatric Sleep Questionnaire. *p<0.0001.

Supplemental Table 3.2 Sensitivity, specificity, PPV and NPV of pediatric OSA classification.

	3D stereophotogrammetry only (n=78)				**3D stereophotogrammetry, PSQ and CFI (n=75)**			
Clinician	**Sv (95%CI)**	**Sp (95%CI)**	**PPV (95%CI)**	**NPV (95%CI)**	**Se (95%CI)**	**Sp (95%CI)**	**PPV (95%CI)**	**NPV (95%CI)**
1	0.48 (0.3,0.64)	0.56 (0.39,0.72)	0.06 (0.03,0.09)	0.95 (0.93, 0.97)	0.88 (0.74, 0.96)	0.13 (0.04,0.28)	0.05 (0.04,0.06)	0.95 (0.87,0.98)
2	0.75 (0.59,0.87)	0.27 (0.13,0.44)	0.05 (0.04,0.07)	0.95 (0.91, 0.97)	0.53 (0.46,0.78)	0.38 (0.22,0.55)	0.05 (0.04,0.07)	0.95 (0.91,0.97)
3	0.48 (0.32,0.64)	0.67 (0.50,0.82)	0.07 (0.04,0.12)	0.96 (0.94, 0.97)	0.71 (0.54,0.84)	0.22 (0.09,0.38)	0.04 (0.03,0.06)	0.93 (0.86,0.97)
4	0.48 (0.32,0.64)	0.62 (0.44,0.77)	0.06 (0.04,0.10)	0.96 (0.94,0.97)	0.55 (0.38,0.71)	0.49 (0.32, 0.66)	0.06 (0.04, 0.10)	0.96 (0.94,0.97)
5	0.36 (0.22,0.53)	0.70 (0.53,0.84)	0.06 (0.03,0.11)	0.95 (0.94,0.96)	0.90 (0.76,0.97)	0.08 (0.01,0.22)	0.05 (0.04,0.06)	0.94 (0.79,0.98)
6	0.56 (0.39,0.71)	0.54 (0.36,0.70)	0.06 (0.04,0.09)	0.96 (0.94,0.97)	0.80 (0.65,0.91)	0.06 (0.01, 0.20)	0.05 (0.04,0.06)	0.94 (0.86,0.98)
7	0.61 (0.44,0.75)	0.51 (0.34,0.68)	0.06 (0.04,0.09)	0.96 (0.94,0.98)	0.71 (0.54,0.84)	0.11 (0.03,0.26)	0.04 (0.03,0.05)	0.87 (0.72,0.95)
8	0.56 (0.39,0.71)	0.43 (0.27,0.60)	0.05 (0.03,0.07)	0.95 (0.92,0.97)	0.93 (0.80,0.98)	0.05 (0.01,0.18)	0.05 (0.04,0.05)	0.93 (0.71,0.98)

9	0.90 (0.76,0.97)	0.21 (0.09,0.38)	0.06 (0.05,0.07)	0.98 (0.93,0.99)	1 (0.91,1)	0.01 (0.01,0.09)	0.05 (0.05,0.05)	*
10	0.90 (0.76,0.97)	0.10 (0.03,0.25)	0.05 (0.04,0.06)	0.95 (0.85,0.98)	0.80 (0.65,0.91)	0.16 (0.06,0.32)	0.04 (0.04,0.05)	0.92 (0.81,0.97)

Sv: Sensitivity, Sp: Specificity, PPV: Positive Predictive Value, NPV: Negative Predictive Value.

Supplemental Table 3.3 Correlation of OMAHI and PSQ scores in the sample of children submitted to PSG.

	OMAHI score		
	n	**r***	**p-value**
PSQ score	78	0.07	0.57

*Pearson correlation; OMAHI: Obstructive-Mixed Apnea-Hypopnea Index.

Supplemental Table 3.4 Distribution of Craniofacial Features evaluated by CFI in the children submitted to PSG.

	Craniofacial features	**OSA negative (n=53)**	**OSA positive (n=50)**	**Total (n= 103)**
Overjet	Normal	37 (70%)	31 (62%)	68 (66%)
	Increased or reverse	16 (30%)	19 (38%)	35 (34%)
Profile	Normal	44 (83%)	36 (72%)	80 (78%)
	Severely Convex or concave	9 (17%)	14 (28%)	23 (22%)
Palate	Normal	20 (38%)	24 (48%)	44 (43%)
	Mildly high arched	31 (58%)	22 (44%)	53 (51%)
	Severely high arched	2 (4%)	4 (8%)	6 (6%)
Midface deficiency	Normal	32 (61%)	31 (62%)	63 (61%)
	Mild Loss of Fullness	20 (38%)	19 (38%)	39 (38%)
	Substantial Loss of Fullness	1 (1%)	0 (0%)	1 (1%)
Overbite	Normal or deep bite	47 (89%)	47 (94%)	94 (91%)
	Open bite	6 (11%)	3 (6%)	9 (9%)
P o s	Normal	46 (87%)	42 (84%)	88 (85%)

	Unilateral crossbite	5 (9%)	3 (6%)	8 (8%)
	Bilateral crossbite	2 (4%)	5 (10%)	7 (7%)
Lip Strain	Normal	37 (70%)	33 (66%)	70 (68%)
	Mildly Strained Closing lips	14 (26%)	15 (30%)	29 (28%)
	Very Strained Closing lips	2 (4%)	2 (4%)	4 (4%)
Lower face height	Normal	30 (56%)	34 (68%)	64 (62%)
	Mildly Excessive	21 (40%)	15 (30%)	36 (35%)
	Severely Excessive	2 (4%)	1 (2%)	3 (3%)

OSA: Obstructive Sleep Apnea.

Chapter 4 : Characterization of craniofacial-based clinical phenotypes in children with suspected OSA

Chapter 3 explored the use of 3D stereophotogrammetry by dental specialists to screen for pediatric OSA. This research, along with previous findings from the systematic review present in Chapter 2, highlighted to need to comprehensively understand the role of soft craniofacial features as a phenotype for children with suspected pediatric OSA. Thus, this chapter explores the role of craniofacial features as a means of identifying phenotypes of children with suspected OSA.

Chapter 4 is based on the article to be submitted to Journal of Clinical Sleep Medicine:

Fagundes NCF, Loliencar P, MacLean JE, Flores-Mir C, Heo G. Characterization of craniofacial-based clinical phenotypes in children with sleep-disordered breathing, 2022.

4.1Abstract

Objectives: To explore the role of soft facial features and specific craniofacial features suggestive of orthodontic treatment need to identify phenotypes of children with suspected obstructive sleep apnea (OSA).

Methods: Seventy-three children aged 2-17 years who underwent overnight observed polysomnography (PSG) participated in this study. Soft facial features were assessed using a 3D stereophotogrammetric imaging system to evaluate twelve linear and two angular facial measurements. Craniofacial features suggestive of orthodontic treatment need were assessed through the Craniofacial Index (CFI), which describes common facial features associated with pediatric OSA. Data regarding lifestyle, sleep habits, sleep quality, age, body mass index, and sex were collected from medical records. Fuzzy clustering with medoids was adopted to identify and characterize craniofacial phenotypes.

Results: The cluster analysis identified three clusters. Cluster 1 showed a group of young children (5.9±3.8 years) without obesity, representing children without craniofacial features suggestive of orthodontic treatment need and smaller soft facial features dimensions. Cluster 2 showed older children (9.6±3.9 years) without obesity, larger mandibular dimensions and a higher upper facial height, and a mildly arched palate. Cluster 3 showed a group of older children (9.2±3.9 years) with obesity, a history of health issues (68.4%), sleep habits compatible with a high risk of SBD, excessive lower facial height (63.2%) and midface deficiency (73.7%). The soft facial features dimensions in Cluster 3 were similar to Cluster 2 but larger than Cluster 1 for nose width (30.7±3.4 mm) and mandibular dimensions. No differences were observed across clusters regarding sleep features. In all three clusters, a moderate severity of obstructive and mixed respiratory events was observed.

Conclusions: Age, obesity and a specific set of soft facial features and craniofacial most common craniofacial features suggestive of orthodontic treatment need might be used to characterize children with sleep-breathing disorders and moderate severity of obstructive respiratory sleep events.

Keywords: Child; Face; Photogrammetry; Cluster Analysis.

4.2. Introduction

Obstructive sleep apnea (OSA) has a prevalence between 1% and 4% in pre-school and school-aged children, respectively,[2, 73] and includes multiple symptoms, etiological factors and associated comorbidities.[145, 146] The complexity and heterogeneity of this disorder may result in difficulties in its diagnosis and management, which may contribute to increased costs to the healthcare system and negative consequences to children with OSA and their families.[3]

One of the strategies that may improve the knowledge of OSA pathophysiology and potential management options is the investigation of different groups of children with similar features or phenotypes within this heterogeneous disorder. A phenotype can be represented by one or multiple features that describe similarities in a subgroup of persons with the condition.[20] This type of stratification may help identify the clinical characteristics of different groups of children with OSA who are more likely to respond to particular management options, increasing the chances of getting more children to the proper management approach.[147] This would lead to targeted strategies based on specific clinical phenotypes instead of a standard, algorithmic approach where options are considered in sequence.

Regarding pediatric OSA, adenotonsillar hypertrophy is the leading risk factor,[53] and other primary comorbidities such as obesity are linked to behavioural and cognitive problems.[74]

Available evidence suggests that the upper airway dimensions (i.e., pharyngeal wall thickness) and blood pressure are potential OSA discerning phenotypes among children.[20, 24]

Even though some craniofacial anatomical and upper airway muscle features have been linked to OSA pathophysiology, more specifically to OSA, clear consistency in whose presence has not been demonstrated.[12] This implies limited knowledge of craniofacial clinical factors contributing to pediatric SBD's development and management outcomes.[20] Some skeletal craniofacial features, such as mandibular retrognathia, reduced anteroposterior linear dimensions of the bony nasopharynx, smaller cranial base angle, and a long facial profile, have been shown to be more frequent among 6-9 years old children diagnosed with OSA. These features have been hypothesized as anatomical factors associated with airway narrowing and pediatric OSA.[148] Soft facial features might also be related to this sleep disorder, reflecting, to a degree, underlying skeletal features. The role of a 3D soft facial features assessment has been explored on a subjective facial analysis performed by dental specialists, showing a poor potential to screen children with OSA.[149] However, studies investigating soft facial features rarely use an objective methodology, such as measurements of landmarks and angles from 3D facial photometry.

Building on what is already known about skeletal craniofacial features frequently associated with children with OSA, this study aims to explore the role of a set of soft facial features and craniofacial features suggestive of orthodontic treatment need (e.g., arched palate, excessive lower facial height, open bite) as a means of identifying phenotypes among children with sleep-breathing disorders, including children fully diagnosed obstructive sleep apnea.

4.3. Material and Methods

4.3.1. Ethics and sample definition

This cross-sectional study was approved by the Health Research Ethics Board of the University of Alberta (Pro00057638). Children aged 2-17 years who underwent overnight observed PSG and presented symptoms of obstructive sleep apnea (e.g., snoring, loud breathing during sleep, sleepiness during the day) were included. Those children who presented with diagnosed craniofacial syndromes and those unable to tolerate the PSG exam were excluded. Consecutive children and their guardians were approached in the Pediatric Sleep clinic at the Stollery Children's Hospital (Edmonton, AB, Canada) for the study.

4.3.2. Data collection and parameters evaluated

Data regarding age, sex, body mass index (BMI), history of health issues and allergies, parent smoking, and frequency of physical activity was collected through a survey completed by parents on the day of their child's craniofacial assessment and their medical history was collected from medical chart. The body mass index (BMI) was calculated for each patient when weight and height information were available and compared using BMI z-scores as derived from the growth standards of the US Centers for Disease Control and Prevention.[123]

Sleep habits and their impact on quality of life were assessed using the following validated questionnaires: Children's sleep habits questionnaire (CSHQ),[150] Pediatric Sleep Questionnaire (PSQ),[122] Obstructive Sleep Apnea Questionnaire (OSA-18).[151] Sleep efficiency, sleep respiratory parameters (central AHI index and Obstructive–Mixed Apnea–Hypopnoea Index (OMAHI), oxygen desaturation (Oxygen Desaturation Index (ODI), percentage of sleep time with end-tidal Carbone dioxide ($ETC0_2$) above 50%, and the percentage of sleep time with an Oxygen saturation (Spo2) below 90% were collected from the PSG. Each participant underwent an overnight in-

laboratory diagnostic PSG. This exam was conducted and scored by sleep technologists in the Pediatric Sleep Laboratory at the Stollery Children's Hospital (Edmonton, AB, Canada), following the American Academy of Sleep Medicine recommendations.[32]

Soft facial features were assessed using a 3D stereophotogrammetric imaging system (3dMD face system, Atlanta, GA). Craniofacial features suggestive of orthodontic treatment need were considered using the craniofacial index (CFI), which focused on the eight most common facial and intra-oral features suggestive of orthodontic treatment need observed among children with OSA.[121]

Soft facial features were evaluated using twelve linear variables and two angles measuring multiple facial dimensions previously associated with pediatric obstructive sleep apnea.[148] The measurements were taken from all participants from 3D stereophotogrammetric imaging (3dMD face system, Atlanta, GA). After the face image collection, each file was exported to the 3dMD patient software (version 4.0), and 14 soft tissue facial landmarks were identified while rotating the 3D facial depiction. Total facial width, mandible width, intercanthal width, and nose width were measured in the frontal view. In the lateral view, total facial height, upper facial height, lower facial height, mandibular length, posterior mandibular height, anterior mandibular height, mandibular length, facial angle and nasofacial angle were measured (Figure 4.1). Each feature was measured by the surface distance between landmarks (Supplemental Table 4.1).The CFI score can range between 0-16 and investigates the presence of eight facial and intra-oral features, previously described as common among children with OSA: profile convexity, midface deficiency, strained lips, high arched palate, excessive lower face height, posterior crossbite, increased/reverse overjet, and open bite.[121] (Supplemental Figure 4.1) In addition to these, a history of orthodontic management was also collected.

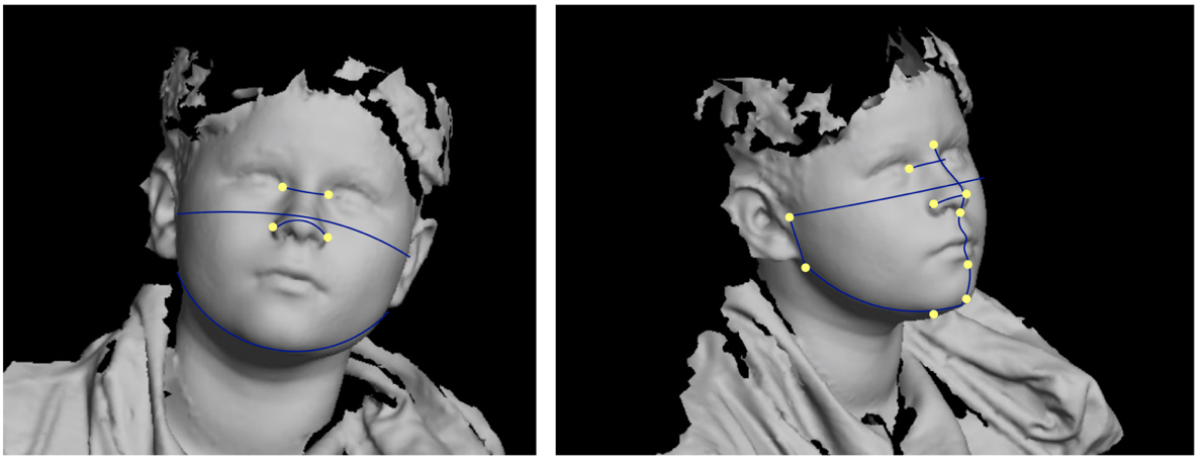


Figure 4.1 Representation of landmarks and features evaluated through 3D stereophotogrammetry.

4.3.3. Reliability analysis

To assess measurement reproducibility, a trained orthodontist (NF) quantified the intra-rater reliability among the soft facial features in 20 subjects, chosen randomly and measured three times, with an interval of one week between each measurement. The intraclass correlation coefficient (ICC) was calculated in a two-way mixed-effects model, where the level of agreement can be characterized as being excellent (≥0.9), good (0.75-0.89), moderate (0.5-0.74) or poor (<0.5).[10] Good to excellent agreement level among all soft facial features measurements was achieved (ICC between 0.84-0.91/ 0.84-0.95 - Supplemental Table 4.2).

4.3.4. Data analysis

From the collected data, all 37 features were identified and considered for the data analysis. To facilitate analysis, features were divided into four categories based on their clinical relevance: soft facial features (12), craniofacial features suggestive of orthodontic treatment need (8), survey results (8), and polysomnography features (6). Patients' age, sex and BMI z-scores were then added

to each category before clustering. Missing values within each category were imputed using the *mice* (Multiple Imputations by Chained Equations)[152] package in R using predictive mean matching (PMM). Two strategies were used for data analysis. First, only soft facial features were considered in the fuzzy cluster analysis (Analysis 0). After this, a different approach, using four sequential combinations of feature categories, was considered, following this order: 1- only craniofacial (CFI) features (Analysis 1), 2- CFI features and soft facial features (Analysis 2), 3- CFI features, soft facial features, and survey results (Analysis 3), and 4- CFI features, soft facial features, survey results and sleep features (PSG values) (Analysis 4). Sequential analysis was considered to assess how the patients clustered based on the different clinical categories of variables and to observe changes in clustering patterns as more variables are added.

Fuzzy clustering with medoids is a generalization of the more popularly used k-means clustering.[153] These methods group observations into clusters that are determined using a notion of "center" or representative of the cluster. This is performed using two steps that are iterated until convergence: 1) assign each observation to the cluster whose center is closest to it, 2) recalculate the centers of all clusters. K-means uses the notion of a centroid or geometric mean for the center of a cluster.[153, 154] This method suffers from the center usually not being a real observation, thereby taking values that may not manifest in the real world or make clinical sense. A medoid of a cluster, on the other hand, is a real observation that already belongs to the cluster, namely, the observation with the shortest average distance to all cluster members. Clustering using medoids as cluster representatives is therefore superior for interpretability and for ensuring that the algorithm only uses clinically relevant points in the feature space. In addition to this, fuzzy clustering generalizes K-means by giving the degree of membership (or probability) of a patient belonging to different clusters, instead of the usual single cluster output (most likely cluster). From a diagnosis

perspective, this allows the clinician to weigh the likelihood of a patient belonging to two phenotypes and assign treatments based on their risks. For example, if a patient has a 48% chance of belonging to a cluster with severe symptoms and a 52% chance of belonging to one with more manageable symptoms, this information may be important for the clinician in watching out for worsening symptoms or using more aggressive treatment options.

In our analysis, fuzzy clustering with medoids was used to determine clusters of patients for each combination of feature categories. This was done using the usual Euclidean distance and the R package *fclust*. In order to address the high dimensionality problem, i.e. a high feature to sample ratio, principal component analysis (PCA) was used. Features were first scaled to have a mean of 0 and a standard deviation of 1. PCA was then performed to obtain the top 15 principal components accounting for a majority of the variance in the data. Fuzzy clustering was then performed on a scaled version of these components. In each case, the number of clusters was selected by optimizing the Xie-Beni index.[155]

Clustering results for all the four analyzes are presented in Results section. The tables display distributions of variables for each clustering analysis, with frequency for categorical variables and mean ± standard deviation for continuous variables presented for each cluster. MANOVA analysis showed statistical significance for 37 variables jointly. Follow-up analyses, either ANOVA or chi-square test, was carried out to compare the differences between each variable across clusters groups. The SPSS (Statistical Package for the Social Sciences, version 23; IBM, Armonk, NY) software was used for this analysis.

4.4. Results

Seventy-three children were enrolled in this study. Considering the potential and the scarce evidence assessing soft facial features in children with symptoms of OSA, first, only soft facial

features were considered to define clusters (Analysis 0). Two clusters were identified from the analysis. Even though eight of twelve soft facial features yielded statistical significance, the clinical relevance was limited, and the differences observed were likely biased by the age difference between cluster 1 and cluster 2 (cluster 1=10.8±6.0 years, cluster 2=3.8±3.1 years) (Supplemental Table 4.3 and Supplemental Figure 4.2).

A sequential analysis was performed (Analysis 1-4). Overall, differences in craniofacial features and z-BMI were observed across the four analyses, while PSG features remained not statistically significant in any of the analyses performed. Only Analysis 2 that used CFI and soft facial features to define clusters yielded consistent clinical and statistical significance between variables.

Overall, among the four analyses, only two variables remained significant in all scenarios: only one soft facial variable, nose width, and the z-BMI. The tables containing a summary of Analysis 2 in Table 2, Analysis 1, 3-4 are presented in the Supplemental files section (Supplemental Tables 4.3-4.5). A multidimensional scaling plot showing the distribution of patients across clusters for Analysis 2 is illustrated in Figure 4.2, and analyses 1, 3-4 are in the Supplemental Figure 4.2.

Regarding the clinical significance and the presence of distinguishable patterns across clusters, Analysis 2, which used CFI and soft facial features to define clusters, presented the best results. After analyzing all data presented in the four sequential cluster analyses performed within this sample, we considered Analysis 2 the most representative of the data. In Analysis 2 analysis, three clusters (1-3) were identified (Figure 4.2), with different soft facial tissue craniofacial features, z-BMI, distinct age groups and no differences regarding sleep features when assessed by a PSG. A detailed description of these clusters is presented in the following paragraphs.

Cluster 1 showed a group of young children (5.9±3.8 years) without obesity, worse sleeping habits than the other two clusters, and no history of orthodontic treatment. Regarding CFI and soft facial features, cluster 1 represents children without craniofacial features suggestive of orthodontic treatment need requiring orthodontic treatment and smaller soft facial features dimensions compared to the other clusters.

Cluster 2 represented a group of older children (9.6±3.9 years) without obesity, allergies, no history of health issues or orthodontic treatment, and sleep habits compatible with a high risk of SBD. Regarding craniofacial features that may require orthodontic treatment (CFI index), these children showed a mildly arched palate compared to clusters 1 and 3. The soft facial features dimensions describe a higher upper (43.4±5.9 mm) facial height, a higher nose width (30.6±3.5 mm), higher posterior mandibular height (35.1±5.6 mm), and higher anterior mandibular height (42.8±5.7 mm) when compared to cluster 1.

Cluster 3 showed a group of older children (9.2±3.9 years) with a similar age range observed in cluster 2. Cluster 3 was representative of children with obesity, without allergies, a history of health issues (68.4%), and sleep habits compatible with a high risk of SBD. There was a small frequency of orthodontic treatment (21.1%) and some features suggestive of orthodontic treatment need, including excessive lower facial height (63.2%) and midface deficiency (73.7%). The soft facial features dimensions were similar to cluster 2 and higher than cluster 1 for nose width (30.7±3.4 mm), posterior mandibular height (35.8±5.6 mm), and anterior mandibular height (42.7±5.2 mm).

No differences were observed across clusters regarding sleep efficiency, central and obstructive sleep events (central AHI and OMAHI indices), or gas exchange during sleep (ODI,

ETC02> 50 and SpO2<90). In all three clusters, a moderate severity of obstructive and mixed respiratory events was observed.

Summaries of frequency and mean values of all variables evaluated in this cluster analysis are described in Tables 4.1-4.3, and the distribution of patients in the three clusters are presented in Figure 4.2. A summary of clinical findings observed in the four clusters is illustrated in Figure 4.3.

Table 4.1 Distributions of demographics, health, lifestyle and sleep habits variables across clusters. Craniofacial features suggestive of orthodontic treatment need s and soft facial features were used to define clusters (Analysis 2).

		Cluster 1 (n=26)	**Cluster 2 (n=28)**	**Cluster 3 (n=19)**	**p-value**
Demographics					
Age[a]		5.9±3.8	9.6±3.9	9.2±3.9	0.002
Sex[b]	Male	16 (61.5%)	15 (53.6%)	8 (42.1%)	0.439[#]
	Female	10 (38.5%)	13 (46.4%)	11 (57.9%)	
BMI z-score[a]		0.4±1.3	0.7±1.1	2.1±0.9	<0.001
Health and lifestyle habits					
Has your child ever been diagnosed with any health issues?[b]	No	11 (42.3%)	16 (57.1%)	6 (31.6%)	0.240[#]
	Yes	15 (57.7%)	12 (42.9%)	13 (68.4%)	
Does the child have any known allergies? [b]	No	15 (57.7%)	18 (64.3%)	11 (57.9%)	0.868[#]
	Yes	11 (42.3%)	10 (35.7%)	8 (42.1%)	
Does anyone in the household smoke cigarettes or other inhaled substances? [b]	No	17 (65.4%)	19 (67.9%)	15 (78.9%)	0.653[#]
	Yes	9 (34.6%)	9 (32.1%)	4 (21.1%)	
How many hours per week does your child exercise? [a]		4.2±1.2	4±1.3	3.8±1.5	0.597
Sleep habits and quality of life questionnaires					
CSHQ[a]		60.1±7.7	53.5±13.6	53.6±8.2	0.040
OSA-18[a]		74.8±27.9	57.8±24.6	56.8±24.6	0.015
PSQ[a]		12.5±3.5	10.8±4.4	10±3.8	0.095

[a]mean±Standard deviation, [b]n (%). CSHQ: Children's sleep health questionnaire, OSA-18: Obstructive Sleep Apnea Questionnaire, PSQ: Pediatric Sleep Questionnaire. The statistical result from Analysis 2, ANOVA and Chi-square test. Chi-square test is indicated by the symbol #.

Table 4.2. Distribution of orthodontic assessment frequency, craniofacial features suggestive of orthodontic treatment need , and soft facial features variables across clusters. Craniofacial features suggestive of orthodontic treatment need and soft facial features were used to define clusters (Analysis 2).

		Cluster 1 (n=26)	**Cluster 2 (n=28)**	**Cluster 3 (n=19)**	**p-value**
Orthodontic assessment					
Has the child had orthodontic treatment?[b]	No	26 (100%)	22 (78.6%)	15 (78.9%)	0.019[#]
	Yes	0 (0%)	6 (21.4%)	4 (21.1%)	
Craniofacial features suggestive of orthodontic treatment need					
Profile[b]	Normal	21 (80.8%)	21 (75%)	16 (84.2%)	0.738[#]
	Severely Convex or concave	5 (19.2%)	7 (25%)	3 (15.8%)	
Midface deficiency[b]	Normal	23(88.5%)	15(53.6%)	5(53.6%)	<0.001[#]
	Mild Loss of Fullness	3(11.5%)	13 (46.4%)	14 (73.7%)	
	Substantial Loss of Fullness	0 (0%)	0 (0%)	0 (0%)	
Lower face height[b]	Normal	20(76.9%)	20 (71.4%)	8 (36.8%)	0.006[#]
	Mildly Excessive	6(23.1%)	8 (28.6%)	11 (57.9%)	
	Severely Excessive	0 (0%)	0 (0%)	1 (5.3%)	
Lip Strain[b]	Normal	20(76.9%)	19(67.9%)	10 (52.6%)	0.457[#]
	Mildly Strained Closing lips	5(19.2%)	8 (28.6%)	9 (47.4%)	
	Very Strained Closing lips	1 (3.8%)	1 (3.6%)	0 (0%)	
Palate[b]	Normal	22(84.6%)	4 (14.3%)	11 (57.9%)	<0.001[#]
	Mildly high arched	4(15.4%)	20 (71.4%)	8 (42.1%)	
	Severely high arched	0 (0%)	4 (14.3%)	0 (0%)	
Overjet[b]	Normal	19(73.1%)	17 (60.7%)	13 (68.4%)	0.631[#]
	Increased or reverse	7 (26.9%)	11 (39.3%)	6 (31.6%)	
Overbite[b]	Normal or deep bite	24(92.3%)	27 (96.4%)	15 (78.9%)	0.128[#]
	Open bite	2 (7.7%)	1 (3.6%)	4 (21.1%)	
Posterior bite[b]	Normal	21(80.8%)	25 (89.3%)	15 (78.5%)	0.683[#]
	Unilateral crossbite	2 (7.7%)	1 (3.6%)	2 (10.5%)	
	Bilateral crossbite	3 (11.5%)	2 (7.1%)	2 (10.6%)	
Soft facial features					

Facial width (mm)[a]	124.8±8.2	129.1±10	129.9±9.4	0.124
Mandible width (mm)[a]	100±8.8	101±6.8	106±7.5	0.052
Intercanthal width (mm)a	28.5±3.3	29.9±3.1	29.4±2.9	0.25
Nose width (mm)a	27.3±2.5	30.6±3.5	30.7±3.4	<0.001
Upper facial height (mm)a	38.7±4.9	43.4±5.9	40.4±4.9	0.006
Lower facial height (mm)a	45.8±4.4	50.1±6.2	48.3±3.4	0.011
Upper height/Lower height (ratio)a	0.84±0.1	0.87±0.1	0.83±0.1	0.513
Mandibular sagittal length (mm)a	80.7±10.4	85.8±11.0	86.6±11.2	0.125
Posterior mandibular height (mm)a	32.1±5	35.1±5.6	35.8±5.6	0.046
Anterior mandibular height (mm)a	38.1±4.1	42.8±5.7	42.7±5.2	0.002
Facial angle (degrees)a	128.6±4.6	130.8±5	129.0±4.2	0.19
Nasofacial angle (degrees)a	148.1±7.5	149.5±9.5	147.1±8.2	0.606

[a]mean±Standard deviation, [b]n (%). The statistical result from Analysis 2, ANOVA and Chi-square test. Chi-square test is indicated by the symbol #.

Table 4.3. Distribution of PSG sleep features variables across clusters. Craniofacial features suggestive of orthodontic treatment need and soft facial features were used to define clusters (Analysis 2).

	Cluster 1 (n=26)	**Cluster 2 (n=28)**	**Cluster 3 (n=19)**	**p-value**
Sleep features				
Sleep Efficiency (%)a	86.8±5.8	82.3±13	81.3±8.3	0.119
Central AHI (events/h)a	1.8±1.3	2.8±3.7	1.9±2.2	0.363
OMAHI (events/h)a	7.1±21.7	4.8±6.6	3.6±3.3	0.69
ODI (events/h)a	10.5±24.8	11.2±11.8	10.1±7.2	0.973
ETC02> 50a	2.9±12.7	1.8±5.2	0.9±3.0	0.721
SpO2<90a	0.6±1.5	0.5±1.9	0.6±1.6	0.971

[a]mean±Standard deviation, [b]n (%). AHI: Apnea-Hypopnea Index, OMAHI: Obstructive-Mixed Apnea-Hypopnea Index, ODI: Oxygen Desaturation Index, $ETC0_2$> 50: percentage of sleep time with end-tidal Carbone dioxide ($ETC0_2$) above 50%, SpO_2<90: percentage of sleep time with an Oxygen saturation below 90%. The statistical result from Analysis 2, ANOVA and Chi-square test. Chi-square test is indicated by the symbol #.

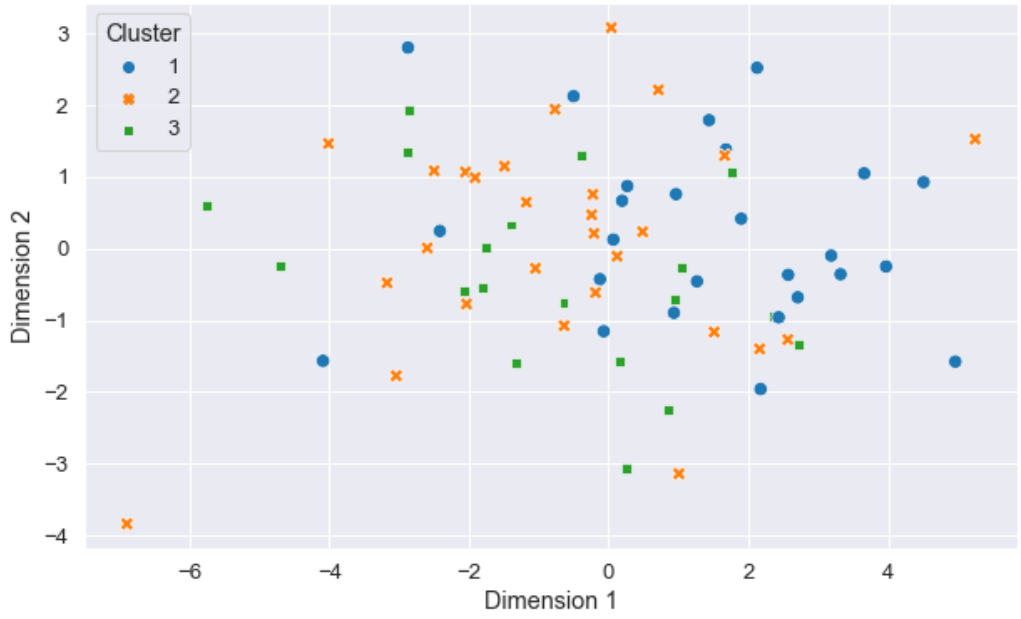


Figure 4.2 Multidimensional scaling plot showing the distribution of patients in the three clusters identified on Analysis 2. This method projects the original 10-dimensional data into two dimensions for visualization. Each cluster is represented by a unique color.

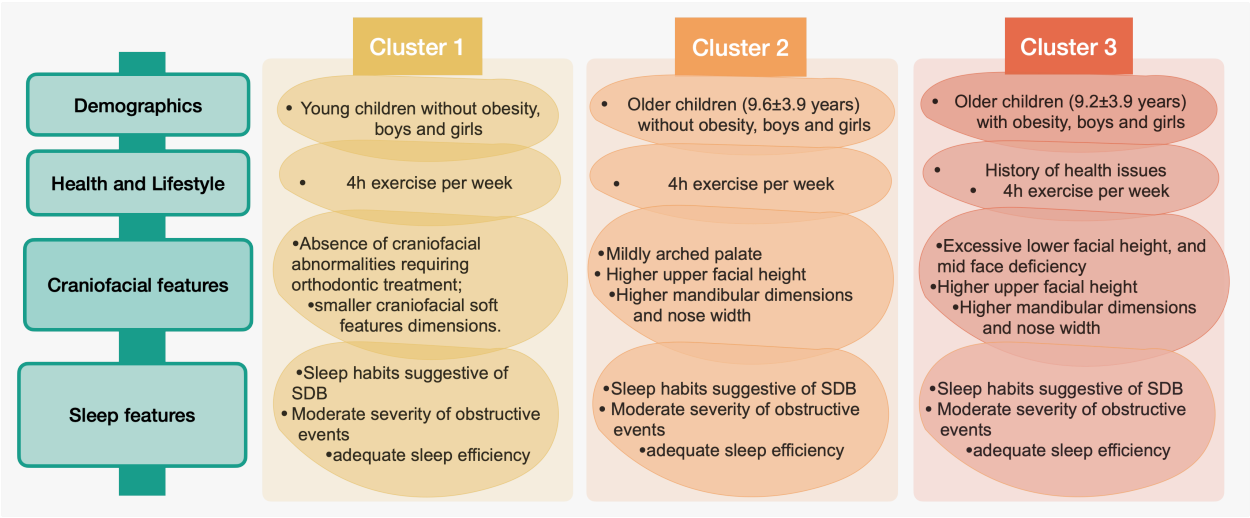


Figure 4.3 Chart displaying clinical features observed among phenotypic clusters. Features were obtained using survey questionnaires as well as PSG summaries.

4.5. Discussion

This study aimed to investigate the possible presence of phenotypes among children with OSA symptomatology based on soft facial features and craniofacial features indicating orthodontic treatment need. After performing four sequential cluster analyses, we found that CFI and soft facial variables may represent a reasonable alternative to distinguish independent subgroups. We identified three subgroups in the sample with similar sleep features but different age ranges, z-BMI, and craniofacial features. Older children with OSA symptomatology, without obesity, and with a moderate severity of obstructive sleep events showed distinct craniofacial features and soft facial features dimensions, including mildly arched palate, higher upper facial height, and higher mandible dimensions. Different craniofacial features suggestive of orthodontic treatment need were observed among children from the same age range and sleep features that presented obesity, including excessive lower facial height and midface deficiency. These results suggest that age, specific craniofacialfeatures suggestive of orthodontic treatment need, and obesity may represent phenotypes that characterize children with OSA symptomatology.

In the present study, the distinct craniofacial features identified varied according to age and obesity status. While children around six years old did not show any distinct craniofacial features associated with OSA symptomatology, children around nine years old showed a higher rate of features suggestive of orthodontic treatment need in maxillary width (i.e., arched palate) that may require orthodontic treatment, as well as in mid and lower facial dimensions, varying according to the presence or absence of high BMI z-scores suggestive of obesity. In children without obesity, an arched palate was described, and among children with obesity, an excessive lower facial height and midface deficiency was observed. The mentioned craniofacial features have been associated

with increased upper airway resistance and OSA, which may help to explain their role in children with SBD and moderate severity of obstructive respiratory events during sleep.[44, 148, 156]

An excessive lower facial height is associated with multiple craniofacial alterations in dentoalveolar morphology, including high arched palate and retrognathia.[157] This alone might indicate a vertical facial disharmony, which may be associated with increased upper airway resistance and OSA. In addition, these features may also be linked to mouth breathing, which is a risk factor for OSA.[12] It is hypothesized that mouth breathing due to nasal obstruction may increase airway resistance and impair oxygen desaturation levels.[109, 158] An increased upper facial height and arched palate were also observed among children from this sample, which may also trigger vertical facial unbalance and upper airway resistance.

The increased presence of craniofacial features suggestive of orthodontic treatment need in children around nine years old, when compared to a group of children around six years old, may be explained by craniofacial growth development and the increased prevalence of craniofacial features suggestive of orthodontic treatment need in this age group. Considering that in this study, we have excluded children presenting craniofacial syndromes. It is expected that younger healthy children may present fewer craniofacial features suggestive of orthodontic treatment need when compared to older children.[145]

A relationship between obesity, craniofacial features and the moderate severity of obstructive respiratory events during sleep was identified. Children with obesity shown an increased prevalence of OSA compared to those without obesity.[159] Pediatric obesity has been associated with excessive adipose tissue deposition on muscles and soft tissues surrounding airways, which may increase the risk of upper airway obstruction and OSA .[159] There is a lack of studies exploring the role of specific craniofacial features in this scenario. A systematic review

from our group could not find an association between differences in craniofacial features and an increased BMI.[148] Among adults with OSA and obesity, midface deficiency was associated with a higher AHI index and BMI, suggesting a possible interaction between these factors.[160]

It has been suggested that mandible dimensions (i.e., ramus height and mandibular corpus length) in children with obesity were larger than in children without these problems. Children with a higher BMI may present an acceleration in craniofacial growth.[161] This evidence may support our findings of an excessive lower facial height present in cluster 3. We might hypothesize that children with obesity may present a different craniofacial growth and larger craniofacial dimensions, which might negatively impact pediatric OSA if these features could constrict airway dimensions. The confirmation of these results suggests a possible role of craniofacial features and obesity as a possible clinical phenotype in pediatric OSA that must be further investigated.

This is the first study investigating soft facial features using 3D stereophotogrammetry among children with full OSA diagnosis and lifestyle features. Previous studies have focused on evaluating soft facial features based on two-dimensional photos or linear measurements between soft facial features landmarks.[44, 141] The assessment of external soft facial features using 3D stereophotogrammetry appears reliable and easy to perform among children.[141] It represents a safe and fast assessment compared to other methods that generate ionizing radiation (e.g., cephalometrics and cone-beam computed tomography).[162]

The evaluation of soft facial features and their association to OSA has been explored among adults in two studies, in which mandibular length, facial width and lower facial width angle were associated with this disorder when assessed by 3D stereophotogrammetry.[48, 156] In children with OSA, increased cervicomental angle and lower-to-upper face height ratio have been associated with a higher AHI.[44] Considering the potential of soft facial feature evaluation as a

screening tool among children with sleep-breathing disorders, and studying craniofacial-based phenotypes could help identify children at risk for SBD.

Collectively, the findings of this study may suggest a relationship between obesity and specific craniofacial features suggestive of orthodontic treatment need in children without craniofacial syndromes. Identifying a particular set of features among this group of children may help narrow a phenotype for OSA in the future and help understand the management options and their outcomes. Further investigations are needed to understand the impact of these features on pediatric OSA's diagnosis and management outcomes.

4.5.1. Limitations

Some limitations were identified as part of this study. Some recognized risk factors for sleep-breathing disorders in children, such as adenoid hypertrophy, have not been evaluated in this study.[139] Data regarding adenotonsillar size was not available for this sample.

The ethnicity of participants was not assessed in this study; ethnicity has previously been linked to sleep-breathing disorders in children and may impact OSA severity and prevalence.[142] This characteristic may also affect the soft facial features evaluation.[163] Our sample included Canadian residents from multiple cultures. In future studies, ethnicity should be evaluated as part of the demographic features of the sample.

3D stereophotogrammetry appears to be a reliable method for evaluating facial features. However, there is still an absence of clear cut-off values to identify craniofacial abnormalities for soft facial measurements in children.[163]

It must be noted that the noted soft facial features differences are of relatively small amounts, hence not necessarily noticeable in a direct clinical assessment without using 3D stereophotogrammetry.

4.6. Conclusion

Age, obesity, and specific craniofacial features might characterize a subgroup of children with sleep-breathing disorders and moderate severity of obstructive respiratory sleep events. An excessive facial height, arched palate and midface deficiency might be associated with pediatric SDB in such subgroup. At the same time, this study does not support the hypothesis that a specific set of craniofacial features is consistently associated with children suspected of OSA.

4.7. Supplemental Files

Supplemental Table 4.1 Craniofacial features obtained from the 3D stereophotogrammetry analysis.

Craniofacial features	Description
Facial width (mm)	Transverse surface distance from tragion right Tr(R) to tragion left Tr(L)
Mandible width (mm)	Transverse surface distance from menton right Me(R) to menton left Me(L)
Intercanthal width (mm)	Surface distance from endocanthion right en(R) to endocanthion left en(L).
Nose width (mm)	Transverse surface distance from alar right Al(R) to alar left Al(L).
Total facial height (mm)	Vertical surface distance from nasion (N) to pogonion (Pg)
Upper facial height (mm)	Vertical surface distance from nasion (N) to subnasale (Sn)
Lower facial height (mm)	Vertical surface measurement of lower facial dimension as measured from subnasale (Sn) to pogonion (Pg)
Upper/lower facial ratio	The ratio between upper and lower facial height
Mandibular length (mm)	Vertical surface distance from gonion (Go) to menton (Me).
Posterior mandibular height (mm)	Vertical surface distance from tragion right Tr(R) to gonion (Go).
Anterior mandibular height (mm)	Vertical surface distance from stomion (Sto) to gnathion (Gn).
Facial angle (degrees)	The angular measurement from nasion (N) to pronasale (Pn) to pogonion (Pg)
Nasofacial angle (degrees)	The angular measurement from pronasale (Pn) to subnasale (Sn) to pogonion (Pg)

Supplemental Table 4.2 Intra-rater reliability of the craniofacial features measured.

Variables	Intraclass correlation	95% Confidence Intervals
Total facial width	0.91	0.83, 0.96
Intercanthal width	0.90	0.81, 0.95
Nose width	0.85	0.71, 0.93
Mandibular width	0.89	0.80, 0.95
Total facial height	0.91	0.82, 0.96
Upper facial height	0.90	0.81, 0.95
Lower facial height	0.96	0.92, 0.98
Mandibular length (right)	0.92	0.85, 0.96
Mandibular length (left)	0.89	0.81, 0.93
Posterior mandibular height (right)	0.85	0.73, 0.93
Posterior mandibular height (left)	0.91	0.83, 0.91
Anterior mandibular height	0.84	0.70, 0.92
Nasofacial angle	0.95	0.90, 0.98
Facial angle	0.84	0.71, 0.93

Supplemental Table 4.3 Distributions of variables across clusters, while using only soft facial features to define clusters (Analysis 0). Variables used to define clusters are presented in bold.

		Cluster 1 (n=33)	*Cluster 2 (n=40)*	*p-value*
Demographics				
Age[a]		10.8±6.0	3.8±3.1	<0.001
Sex[b]	Male	16 (48.5%)	23 (57.5%)	0.486[#]
	Female	17 (51.5%)	17 (42.5%)	
BMI z-score[a]		1.1±0.8	1.3±1.4	0.478
Health and lifestyle habits				
Has your child ever been diagnosed with any health issues?[b]	No	14 (42.4%)	19 (47.5%)	0.814[#]
	Yes	19 (57.6%)	21 (51.5%)	
Does the child have any known allergies? [b]	No	17 (51.5%)	27 (67.5%)	0.230[#]
	Yes	16 (48.5%)	13 (32.5%)	
Does anyone in the household smoke cigarettes or other inhaled substances? [b]	No	27 (81.8%)	24 (60.0%)	0.072[#]
	Yes	6 (18.2%)	16 (40.0%)	
How many hours per week does your child exercise? [a]		3.7±4.2	1.3±1.3	0.108
Sleep habits and quality of life questionnaires				
CSHQ[a]		54.6±8.3	57.1±12.6	0.372

OSA-18[a]		60.7±20.9	73.4±19.4	0.012
PSQ[a]		10.3±3.8	12±4.1	0.100
Orthodontic assessment				
Has the child had orthodontic treatment?[b]	No	27 (75.8%)	38 (95%)	0.036
	Yes	8 (24.2%)	2 (5%)	
Craniofacial features suggestive of orthodontic treatment need				
Profile[b]	Normal	27 (81.8%)	31 (77.5%)	0.774[#]
	Severely Convex or concave	6 (18.2%)	9 (22.5%)	
Midface deficiency[b]	Normal	17 (51.5%)	26 (65.0%)	0.339[#]
	Mild Loss of Fullness	16 (48.5%)	14 (35.0%)	
	Substantial Loss of Fullness	0 (0%)	0 (0%)	
Lower face height[b]	Normal	18 (54.5%)	29 (72.5%)	0.139[#]
	Mildly Excessive	15 (45.5%)	10 (25.0%)	
	Severely Excessive	0 (0.0%)	1 (2.5%)	
Lip Strain[b]	Normal	23 (69.7%)	26 (65%)	0.425[#]
	Mildly Strained Closing lips	10 (30.3%)	12 (30.0%)	
	Very Strained Closing lips	0 (0.0%)	2 (5%)	
Palate[b]	Normal	9 (27.3%)	28 (70.0%)	<0.001[#]
	Mildly high arched	23 (69.7%)	9 (22.5%)	
	Severely high arched	1 (3.0%)	3 (7.5%)	
Overjet[b]	Normal	22 (66.7%)	27 (67.5%)	0.568[#]
	Increased or reverse	11 (33.3%)	13 (32.5%)	
Overbite[b]	Normal or deep bite	31 (93.9%)	35 (87.5%)	0.446[#]
	Open bite	2 (6.1%)	5 (12.5%)	
Posterior bite[b]	Normal	28 (84.8%)	33 (82.5%)	0.539[#]
	Unilateral crossbite	3 (9.1%)	2 (5.0%)	
	Bilateral crossbite	2 (6.1%)	5 (12.5%)	
Soft facial features				
Facial width (mm)[a]		132.5±9.6	123.8±7.1	<0.001
Mandible width (mm)[a]		104.7±7.9	100.8±7.7	0.036
Intercanthal width (mm)[a]		30.7±3.2	28.1±2.6	<0.001
Nose width (mm)[a]		31.7±3.1	27.6±2.7	<0.001
Upper facial height (mm)[a]		45.2±4.2	37.5±4.2	<0.001

Lower facial height (mm)[a]	51.0±5.2	45.7±4.0	<0.001
Upper height/Lower height (ratio)[a]	0.9±0.1	0.8±0.1	0.007
Mandibular sagittal length (mm)[a]	89.7±11.3	79.7±8.6	<0.001
Posterior mandibular height (mm)[a]	37.1±5.8	79.7±8.6	<0.001
Anterior mandibular height (mm)[a]	44.2±5.1	38.5±4.3	<0.001
Facial angle (degrees)[a]	128.9±4.4	130.9±5.2	0.080
Nasofacial angle (degrees)[a]	147.1±9.4	149.5±7.6	0.232
Sleep features			
Sleep Efficiency (%)[a]	81.8±12.2	85.2±7.2	0.145
Central AHI (events/h)[a]	1.9±3.3	2.5±2.1	0.361
OMAHI (events/h)[a]	6.5±19.5	4.3±5.1	0.497
ODI (events/h)[a]	12.4±23.1	9.2±8.7	0.410
$ETC0_2$> 50[a]	1.4±4.0	2.4±10.7	0.625
SpO_2<90[a]	0.5±1.4	0.6±1.9	0.800

[a]mean±Standard deviation, [b]n (%). CSHQ: Children's sleep health questionnaire, OSA-18: Obstructive Sleep Apnea Questionnaire, PSQ: Pediatric Sleep Questionnaire, AHI: Apnea-Hypopnea Index, OMAHI: Obstructive-Mixed Apnea-Hypopnea Index, ODI: Oxygen Desaturation Index, $ETC0_2$> 50: percentage of sleep time with end-tidal Carbone dioxide ($ETC0_2$) above 50%, SpO_2<90: percentage of sleep time with an Oxygen saturation below 90%.
The statistical result from Analysis 2, ANOVA and Chi-square test. Chi-square test is indicated by the symbol #.

Supplemental Table 4.4 Distributions of variables across clusters, while using only CFI features to define clusters (Analysis 1). Variables used to define clusters are presented in bold.

		Cluster 1 (n=42)	***Cluster 2 (n=31)***	***p-value***
Demographics				
Age[a]		9.6±4.1	6.2±3.6	<0.001
Sex[b]	Male	11 (26.2%)	28 (90.3%)	0.430[#]
	Female	31 (73.8%)	3 (9.7%)	
BMI z-score[a]		1.2±1.1	0.5±1.5	0.010
Health and lifestyle habits				
Has your child ever been diagnosed with any health issues?[b]	No	21 (50%)	12 (38.7%)	0.230[#]
	Yes	21 (50%)	19 (61.3%)	
	No	27 (64.3%)	17 (54.8%)	0.470[#]

Does the child have any known allergies? [b]	Yes	15 (35.7%)	14 (45.2%)	
Does anyone in the household smoke cigarettes or other inhaled substances? [b]	No	32 (76.2%)	19 (61.3%)	0.201[#]
	Yes	10 (23.8%)	12 (38.7%)	
How many hours per week does your child exercise? [a]		3.7±1.2	4.4±1.3	0.010
Sleep habits and quality of life questionnaires				
CSHQ[a]		54.4±12.7	57.9±7.5	0.170
OSA-18[a]		62.1±22.1	74.7±17.1	0.010
PSQ[a]		10.8±4.1	11.8±3.9	0.260
Orthodontic assessment				
Has the child had orthodontic treatment?[b]	No	36 (85.7%)	25 (80.6%)	1.000[#]
	Yes	6 (14.3%)	6 (19.4%)	
Craniofacial features suggestive of orthodontic treatment need				
Profile[b]	Normal	33 (78.6%)	25 (80.6%)	0.830[#]
	Severely Convex or concave	9 (21.4%)	6 (19.4%)	
Midface deficiency[b]	Normal	24 (57.1%)	19 (61.3%)	0.720[#]
	Mild Loss of Fullness	18 (42.9%)	12 (38.7%)	
	Substantial Loss of Fullness	0 (0%)	0 (0%)	
Lower face height[b]	Normal	26 (61.9%)	21 (67.7%)	0.500[#]
	Mildly Excessive	15 (35.7%)	10 (32.3%)	
	Severely Excessive	1 (2.4%)	0 (0%)	
Lip Strain[b]	Normal	22 (52.4%)	27 (87.1%)	0.001[#]
	Mildly Strained Closing lips	18 (42.9%)	4 (12.9%)	
	Very Strained Closing lips	2 (4.8%)	0 (0%)	
Palate[b]	Normal	11 (26.2%)	26 (83.9%)	<0.001[#]
	Mildly high arched	27 (64.3%)	5 (16.1%)	
	Severely high arched	4 (9.5%)	0 (0%)	
Overjet[b]	Normal	26 (61.9%)	23 (74.2%)	0.276[#]
	Increased or reverse	16 (38.1%)	8 (25.8%)	
Overbite[b]	Normal or deep bite	37 (88.1%)	29 (93.5%)	

	Open bite	5 (11.9%)	2 (6.5%)	0.441[#]
Posterior bite[b]	Normal	32 (76.2%)	29 (93.5%)	0.054[#]
	Unilateral crossbite	4 (9.5%)	1 (3.2%)	
	Bilateral crossbite	6 (14.3%)	1 (3.2%)	
Soft facial features				
Facial width (mm)[a]		129.3±10.3	125.7±7.6	0.100
Mandible width (mm)[a]		104.6±7.3	99.7±8.1	0.008
Intercanthal width (mm)[a]		30.1±3.5	28.3±2.3	0.016
Nose width (mm)[a]		30.3±3.7	28.3±2.8	0.016
Upper facial height (mm)[a]		42.7±5.6	38.6±4.7	0.002
Lower facial height (mm)[a]		48.2±5.8	47.9±4.5	0.810
Upper height/Lower height (ratio)[a]		0.88±0.1	0.80±0.1	0.001
Mandibular sagittal length (mm)[a]		87.0±10.2	80.4±11.2	0.012
Posterior mandibular height (mm)[a]		35.7±6.2	32.1±3.8	0.006
Anterior mandibular height (mm)[a]		42.7±5.7	38.8±4.2	0.002
Facial angle (degrees)[a]		130.8±5.1	129.0±4.2	0.144
Nasofacial angle (degrees)[a]		146.3±7.4	151.2±9.1	0.014
Sleep features				
Sleep Efficiency (%)[a]		82.3±10.7	85.5±8.5	0.167
Central AHI (events/h)[a]		2.7±3.3	1.6±1.3	0.105
OMAHI (events/h)[a]		4.4±5.8	6.4±19.9	0.546
ODI (events/h)[a]		11.2±10.5	9.9±22.7	0.105
$ETC0_2$> 50[a]		4.4±5.8	6.4±19.9	0.546
SpO_2<90[a]		0.6±1.8	0.5±1.5	0.819

Sleep Apnea Questionnaire, PSQ: Pediatric Sleep Questionnaire, AHI: Apnea-Hypopnea Index, OMAHI: Obstructive-Mixed Apnea-Hypopnea Index, ODI: Oxygen Desaturation Index, $ETC0_2$> 50: percentage of sleep time with end-tidal Carbone dioxide ($ETC0_2$) above 50%, SpO_2<90: percentage of sleep time with an Oxygen saturation below 90%.
The statistical result from Analysis 2, ANOVA and Chi-square test. Chi-square test is indicated by the symbol #.

Supplemental Table 4.5 Distributions of variables across clusters, while using CFI, soft facial features, and sleep questionnaires scores (Analysis 3) to define clusters. Variables used to define clusters are presented in bold.

	Cluster 1 (n=23)	***Cluster 2 (n=20)***	***Cluster 3 (n=17)***	***Cluster 4 (n=13)***	***p-value***
Demographics					
Age[a]	7.1±4.4	9±3.9	6.4±3.9	11.3±2.8	0.01

Sex[b]	Male	13(56.5%)	11(55%)	12(70.6%)	3 (23.1%)	0.070[#]
	Female	10 (43.5%)	9(45%)	5(29.4%)	10(76.9%)	0.040[#]
BMI z-score[a]		0.6±1.5	0.6±1.1	1.2±1.4	1.7±0.8	
Health and lifestyle habits						
Has your child ever been diagnosed with any health issues?[b]	No	10 (43.5%)	11 (55%)	7 (41.2%)	5 (38.5%)	0.673[#]
	Yes	13 (56.5%)	9 (45%)	10 (58.8%)	8 (61.5%)	
Does the child have any known allergies? [b]	No	11 (47.8%)	14 (70%)	9 (52.9%)	10 (76.9%)	0.260[#]
	Yes	12 (52.2%)	6 (30%)	8 (47.1%)	3 (23.1%)	
Does anyone in the household smoke cigarettes or other inhaled substances? [b]	No	15 (65.2%)	14 (70%)	13 (76.5%)	9 (69.2%)	0.890[#]
	Yes	8 (34.8%)	6 (30%)	4 (23.5%)	4 (30.8%)	
How many hours per week does your child exercise? [a]		4.2±1	4±1.4	4.3±1.5	3.6±1.4	0.563
Sleep habits and quality of life questionnaires						
CSHQ[a]		59.6±7.8	53.3±15.3	54.6±8.0	55±9.5	0.245
OSA-18[a]		74.6±18.7	64.2±25.3	67.1±19.9	60.9±16.8	0.213
PSQ[a]		12.2±3.9	10.7±4.4	11.1±3.7	10.5±4	0.549
Orthodontic assessment						
Has the child had orthodontic treatment?[b]	No	21 (91.3%)	17 (85%)	14 (82.4%)	11 (84.6%)	0.850[#]
	Yes	2 (8.7%)	3 (15%)	3 (17.6%)	2 (15.4%)	
Craniofacial features suggestive of orthodontic treatment need						
Profile[b]	Normal	16 (69.6%)	14 (70%)	16 (94.1%)	12 (92.3%)	0.112[#]
	Severely Convex or concave	7 (30.4%)	6 (30%)	1 (5.9%)	1 (7.7%)	
Midface deficiency[b]	Normal	21(91.3%)	9(45%)	7(41.2%)	6(46.2%)	0.001[#]
	Mild Loss of Fullness	2(8.7%)	11(55%)	10(58.8%)	7(53.8%)	

	Substantial Loss of Fullness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Lower face height[b]	Normal	14(60.9%)	12 (60%)	13 (76.5%)	8 (61.5%)	0.925[#]
	Mildly Excessive	9 (39.1%)	8 (40%)	3 (17.6%)	5 (38.5%)	
	Severely Excessive	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	
Lip Strain[b]	Normal	17(73.9%)	13(65%)	10 (58.8%)	9 (69.2%)	0.682[#]
	Mildly Strained Closing lips	6 (26.1%)	7 (35%)	6 (35.3%)	3 (23.1%)	
	Very Strained Closing lips	0 (0%)	0 (0%)	1 (5.9%)	1 (7.7%)	
Palate[b]	Normal	18(78.3%)	2 (10%)	14 (82.4%)	3 (23.1%)	<0.001[#]
	Mildly high arched	5 (21.7%)	15 (75%)	3 (17.6%)	9 (69.2%)	
	Severely high arched	0 (0%)	3 (15%)	0 (0%)	1 (7.7%)	
Overjet[b]	Normal	16(69.6%)	12 (60%)	12 (70.6%)	9 (69.2%)	0.894[#]
	Increased or reverse	7 (30.4%)	8 (40%)	5 (29.4%)	4 (30.8%)	
Overbite[b]	Normal or deep bite	20(87%)	19 (95%)	15 (88.2%)	12 (92.3%)	0.823[#]
	Open bite	3 (13%)	1 (5%)	2 (11.8%)	1 (7.7%)	
Posterior bite[b]	Normal	21 (91.3%)	18 (90%)	16 (94.1%)	6 (46.2%)	<0.001[#]
	Unilateral crossbite	1 (4.3%)	1 (5%)	1 (5.9%)	2 (15.4%)	
	Bilateral crossbite	1 (4.3%)	1 (5%)	0 (0%)	5 (38.5%)	
Soft facial features						
Facial width (mm)[a]		125.6±8.4	132±9.8	125.6±6.3	128±12.1	0.098
Mandible width (mm)[a]		99.5±8.4	102.1±6.7	103.2±7.7	107.7±7.4	0.026
Intercanthal width (mm)[a]		27.9±3.4	31±2.9	28.3±1.9	30.5±2.9	0.002
Nose width (mm)[a]		27.9±2.6	30.86±3.5	28.2±2.9	31.8±3.8	0.001
Upper facial height (mm)[a]		39.8±4.6	43.7±6.4	37.3±4.6	43.4±4.3	0.001
Lower facial height (mm)[a]		47.1±5	50.8±6.9	46.7±3.6	47.7±3.1	0.059

Upper height/Lower height (ratio)[a]	0.85±0.1	0.86±0.1	0.8±0.1	0.91±0.1	0.043
Mandibular sagittal length (mm)[a]	80.4±11.2	85.9±9.8	81.7±9.8	91.7±10.8	0.001
Posterior mandibular height (mm)[a]	33.7±5.2	34.9±6.1	30.6±3.6	38.4±4.8	0.001
Anterior mandibular height (mm)[a]	39.1±4.4	43.8±6.4	38.8±4.3	43.2±4.7	0.004
Facial angle (degrees)[a]	126.8±4.1	130.2±5.2	132.7±4.6	131.8±3.6	0.001
Nasofacial angle (degrees)[a]	147.8±7.5	130.2±5.2	132.7±4.6	142.3±6.3	0.014
Sleep features					
Sleep Efficiency (%)[a]	85.4±6.6	81.4±13.8	83.1±13.8	84.8±6.6	0.594
Central AHI (events/h)[a]	1.9±1.4	3.2±4.1	2.1±1.9	4.0±3.3	0.312
OMAHI (events/h)[a]	7.4±23	4.9±7.8	3.9±3.2	4.0±3.3	0.846
ODI (events/h)[a]	11.9±26.3	11.3±13.5	8.8±5.2	10.0±8.6	0.944
$ETC0_2$> 50[a]	0.6±1.5	2.5±6.1	3.9±15.8	4.0±3.3	0.655
SpO_2<90[a]	0.6±1.7	0.9±2.6	0.2±0.2	0.3±0.3	0.554

Sleep Apnea Questionnaire, PSQ: Pediatric Sleep Questionnaire, AHI: Apnea-Hypopnea Index, OMAHI: Obstructive-Mixed Apnea-Hypopnea Index, ODI: Oxygen Desaturation Index, $ETC0_2$> 50: percentage of sleep time with end-tidal Carbone dioxide ($ETC0_2$) above 50%, SpO_2<90: percentage of sleep time with an Oxygen saturation below 90%.
The statistical result from Analysis 2, ANOVA and Chi-square test. Chi-square test is indicated by the symbol #.

Supplemental Table 4.6 Distributions of variables across clusters, while using CFI, soft facial features, sleep questionnaires scores, and PSG features (Analysis 4) to define clusters. Variables used to define clusters are presented in bold.

		Cluster 1 (n=18)	***Cluster 2 (n=20)***	***Cluster 3 (n=18)***	***Cluster 4 (n=17)***	***p-value***
Demographics						
Age[a]		8.3±4.3	7.4±4.4	9.5±4.7	7.8±3.4	0.459
Sex[b]	Male	13(72.7%)	11(55%)	8(44.4%)	7 (41.2%)	0.247[#]
	Female	5 (27.8%)	9(45%)	10(55.6%)	10(58.8%)	
BMI z-score[a]		0.9±0.9	0.1±0.9	1.0±1.6	2.1±1.2	<0.001
Health and lifestyle habits						
Has your child ever	No	11 (61.1%)	12 (60%)	2 (11.1%)	8 (47.1%)	0.010[#]

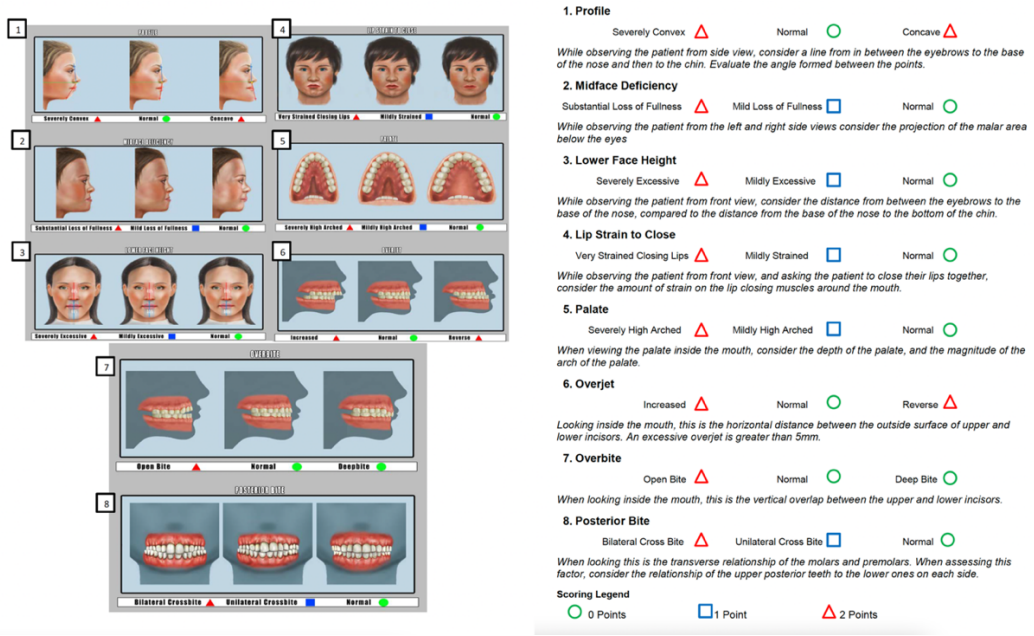
been diagnosed with any health issues?[b]	Yes	7 (38.9%)	8 (40%)	16 (88.9%)	9 (52.9%)	
Does the child have any known allergies? [b]	No	15 (83.3%)	15 (75%)	3 (16.7%)	11 (64.7%)	<0.001 [#]
	Yes	3 (16.7%)	5 (25%)	15 (83.3%)	6 (35.3%)	
Does anyone in the household smoke cigarettes or other inhaled substances ? [b]	No	10 (55.6%)	15 (75%)	11 (61.1%)	15 (88.2%)	0.107[#]
	Yes	8 (44.4%)	5 (25%)	7 (38.9%)	2 (11.8%)	
How many hours per week does your child exercise? [a]		4±1.3	3.8±1.1	3.6±1.4	4.9±1.1	0.044[#]
Sleep habits and quality of life questionnaires						
CSHQ[a]		53.4±8.8	61.2±7.8	55.9±7.8	52.3±16.4	0.049
OSA-18[a]		66.6±20.2	76.9±18.1	69.2±21.2	55.4±20.6	0.016
PSQ[a]		9.8±14	12.2±3.5	12.3±4.2	10.6±4.3	0.171
Orthodontic assessment						
Has the child had orthodontic treatment? [b]	No	15 (83.3%)	18 (90%)	16 (88.9%)	14 (82.4%)	0.880[#]
	Yes	3 (16.7%)	2 (10%)	2 (11.1%)	3 (17.6%)	
Craniofacial features suggestive of orthodontic need						
Profile[b]	Normal	13 (72.2%)	16 (80%)	16 (88.9%)	13 (76.5%)	0.661[#]
	Severely Convex or concave	5 (27.8%)	4 (20%)	2 (11.1%)	4 (23.5%)	
Midface deficiency [b]	Normal	5(27.8%)	19(95%)	10(55.6%)	9(52.9%)	<0.001 [#]
	Mild Loss of Fullness	13(72.2%)	1(5%)	8 (44.4%)	8 (47.1%)	

	Substantial Loss of Fullness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Lower face height[b]	Normal	13(72.2%)	16 (80%)	9 (50%)	9 (52.9%)	0.134[#]
	Mildly Excessive	5 (27.8%)	5 (20%)	9 (50%)	7 (41.2%)	
	Severely Excessive	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)	
Lip Strain[b]	Normal	17(94.4%)	16(80%)	13 (72.2%)	3 (17.6%)	<0.001[#]
	Mildly Strained Closing lips	1 (5.6%)	4 (20%)	5 (27.8%)	12 (70.6%)	
	Very Strained Closing lips	0 (0%)	0 (0%)	0 (0%)	2 (11.8%)	
Palate[b]	Normal	4(22.2%)	12 (60%)	11 (61.1%)	10 (50.7%)	0.117[#]
	Mildly high arched	13 (72.2%)	7 (35%)	7 (38.9%)	5 (29.4%)	
	Severely high arched	1 (5.6%)	1 (5%)	0 (0%)	2 (11.8%)	
Overjet[b]	Normal	13(72.2%)	13 (65%)	14 (77.8%)	9 (52.9%)	0.449[#]
	Increased or reverse	5 (27.8%)	7 (35%)	4 (22.2%)	8 (47.1%)	
Overbite[b]	Normal or deep bite	18 (100%)	17 (85%)	16 (88.9%)	15 (88.2%)	0.450[#]
	Open bite	0 (0%)	3 (15%)	2 (11.1%)	3 (11.8%)	
Posterior bite[b]	Normal	12 (66.7%)	17 (85%)	17 (94.4%)	15 (88.2%)	0.173[#]
	Unilateral crossbite	3 (16.7%)	0 (0%)	1 (5.6%)	1 (5.9%)	
	Bilateral crossbite	3 (16.7%)	3 (15%)	0 (0%)	1 (5.9%)	
Soft facial features						
Facial width (mm)[a]		131.4±9.5	126.1±7.8	129.9±10.5	123.7±8.5	0.054
Mandible width (mm)[a]		103.4±8.1	99.1±6.8	105.4±8.3	102.8±8.1	0.101

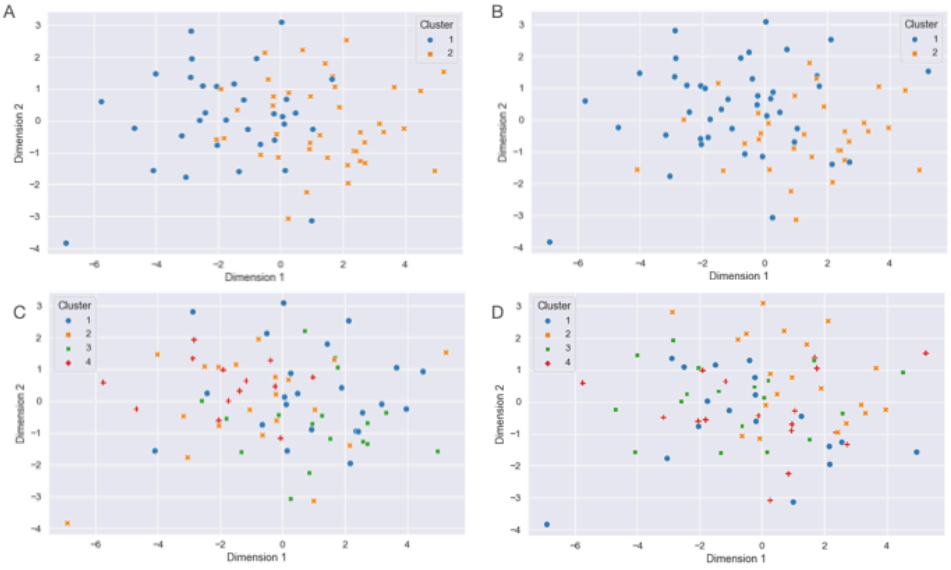
Intercanthal width (mm)[a]	31.0±2.9	27.4±2.7	30.6±2.8	28.6±3.1	0.001
Nose width (mm)[a]	30.6±3.9	27.5±2.8	30.9±2.8	29.3±3.8	0.009
Upper facial height (mm)[a]	41.3±6.8	40.1±4.6	43.0±5.3	39.7±5.7	0.296
Lower facial height (mm)[a]	50.3±7.2	45.3±4.3	49.3±3.6	48.1±4.4	0.019
Upper height/Lower height (ratio)[a]	0.8±0.1	0.9±0.1	0.9±0.1	0.8±0.1	0.201
Mandibular sagittal length (mm)[a]	85.1±9.9	78.9±6.2	89.0±12.6	84.6±13	0.038
Posterior mandibular height (mm)[a]	34.2±4.1	33.1±5.8	35.7±6	33.9±6.3	0.560
Anterior mandibular height (mm)[a]	42.3±6.0	38.7±4.2	42.3±5.6	41.3±5.7	0.137
Facial angle (degrees)[a]	130.4±5	130.4±3.6	128.0±5.6	131.4±5.5	0.205
Nasofacial angle (degrees)[a]	148.1±8	147.3±4.9	151.0±11	147.4±9.5	0.528
Sleep features					
Sleep Efficiency (%)[a]	86.7±7.5	86.1±4.6	79.9±15.3	81.6±8.5	0.096
Central AHI (events/h)[a]	3.3±4.2	2.2±2	1.3±1.6	2.2±2.1	0.185
OMAHI (events/h)[a]	6.4±8.1	2.9±2.4	8.7±26.1	3.5±3.2	0.552
ODI (events/h)[a]	12.7±14.5	7.7±5.1	13.7±29.7	8.9±6.1	0.652
$ETC0_2$> 50[a]	5.2±15.6	1.3±4.8	1.2±3.4	0.3±0.8	0.310
SpO_2<90[a]	0.9±2.3	0.1±0.2	0.8±1.9	0.6±1.8	0.538

Sleep Apnea Questionnaire, PSQ: Pediatric Sleep Questionnaire, AHI: Apnea-Hypopnea Index, OMAHI: Obstructive-Mixed Apnea-Hypopnea Index, ODI: Oxygen Desaturation Index, $ETC0_2$> 50: percentage of sleep time with end-tidal Carbone dioxide ($ETC0_2$) above 50%, SpO_2<90: percentage of sleep time with an Oxygen saturation below 90%.

The statistical result from Analysis 2, ANOVA and Chi-square test. Chi-square test is indicated by the symbol #.



Supplemental Figure 4.1 Craniofacial Index (CFI). On left, the eight parameters evaluated were graphically presented. On right, the index form completed by dental clinicians. Reproduced from: Altalibi M, 2015. Patients with Obstructive Sleep Apnea: A Communication Tool between Physicians and Orthodontist [Master's thesis, University of Alberta] https://doi.org/10.7939/R3JS9HK00



Supplemental Figure 4.2 Multidimensional scaling plot showing the distribution of patients among the clusters identified on Analysis 0, 1, 3, and 4 (A-D, from left to right). This method projects the original 10-dimensional data into two dimensions for visualization. Each cluster is represented by a unique color and symbol in the scatterplot.

Chapter 5 : Potential impact of pediatric obstructive sleep apnea on mandibular cortical width dimensions

Chapter 2-4 investigated the association between craniofacial features and OSA diagnosis and the screening potential of craniofacial features as a phenotyping component for OSA. As presented in Chapter 1, some specific craniofacial features might be used as a proxy to analyze other systemic changes (e.g., bone density) that might be associated with pediatric OSA. In this chapter, we explore the differences in mandibular cortical width (MCW) among children diagnosed with Obstructive sleep apnea (OSA) or at high- or low-risk for OSA.

Chapter 5 is based on this published article:

Fagundes NCF, D'Apuzzo F, Perillo L, Puigdollers A, Gozal D, Graf D, Heo G, Flores-Mir C. Potential impact of pediatric obstructive sleep apnea on mandibular cortical width dimensions. Journal of Clinical Sleep Medicine, 2021: 17(8):1627-34. Available from: https://doi.org/10.5664/jcsm.9262

5.1. Abstract

STUDY OBJECTIVES: To analyze differences in mandibular cortical width (MCW) among children diagnosed with Obstructive sleep apnea (OSA) or at high- or low-risk for OSA.

METHODS: 161 children were assessed: 60 children with polysomnographically (nPSG) diagnosed OSA, 56 children presenting symptoms suggestive of high-risk for OSA, and 45 children at low-risk for OSA. Children at high- and low-risk for OSA were evaluated through the Pediatric Sleep Questionnaire (PSQ). MCW was calculated from panoramic radiograph images available from all subjects using ImageJ software. Differences between MCW measurements in the three groups were evaluated using ANCOVA and Bonferroni post-hoc tests, with age as a covariate. The association between MCW and specific cephalometric variables was assessed through regression analysis.

RESULTS: The participants' mean age was 9.6±3.1 years (59% male and 41% female). The mean BMI z-score was 0.62±1.3. The nPSG-OSA group presented smaller MCW than at low-risk for OSA group (mean difference= -0.385 mm, p=0.001), but no difference with the at high-risk for OSA group (nPSG-OSA vs. high-risk OSA: p=0.085). In addition, the MCW in the at high-risk for the OSA group was significantly smaller than the at low-risk for the OSA group (mean difference= -0.301 mm, p=0.014). The cephalometric variables (SNA and FMA) explained only 8% of the variance in MCW.

CONCLUSIONS: Reductions in MCW appear to be present among children with OSA or those at high risk for OSA, suggesting potential interactions between mandibular bone development and/or homeostasis and pediatric OSA.

Keywords: Sleep apnea syndromes, Mandible, Cortical Bone, Child.

5.2. Introduction

Obstructive Sleep Apnea (OSA) is a sleep disorder characterized by either partial or complete upper airway obstruction.[1] Among children, a prevalence of 1 to 5% has been reported,[2, 73] and the disorder has been linked to increased risk for the development of cognitive and behavioral problems,[76] as well as cardiovascular and metabolic comorbidities.[164]

OSA has been implicated in altered bone metabolism in adults,[165] as evidenced by increases in bone resorption markers, reduced bone density, and a higher risk of osteoporosis. The potential association of bone morphological changes and OSA has only been preliminarily explored in children, whereby reduced mandibular cortical width (MCW) was detected in children at a mean age of 11.4 ± 2 years and at high risk of presenting sleep breathing disorders in a retrospective study.[51]

Measurements of MCW using specific landmarks as location reference points (i.e., mental foramen) have been proposed as a proxy to assessments of regional alterations in bone metabolism.[50] The standard method to assess bone density in children is the dual-energy X-ray absorptiometry (DXA). This technique has some limitations, including the reduced reliability among children under 4 years, or who are small for their age, as well as presenting delayed sexual maturation and chronic disorders, which may justify the search and implementation of alternative morphometric methods.[166] DXA. Panoramic radiographs are readily available for most children that regularly attend dental appointments. Suppose reduced MCW does indeed suggest a higher risk for OSA. In that case, this measurement could be used as a complementary initial screening approach in dental offices where such x-rays are routinely obtained before more definitive diagnostic options are contemplated.

This study aims to analyze differences in MCW among children either diagnosed with OSA by overnight observed polysomnography,[8] or identified as at high-risk for OSA or at low-risk for OSA based on the Pediatric Sleep Questionnaire (PSQ).[122] This study presents a new assessment with a different sample coming from different centers with a broader age range compared to a previous related study,[51] and reflects an attempt to explore further the previously reported association in a larger and more diverse cohort.

5.3. Material and methods

This study was submitted and approved by the Health Research Ethics Board of the University of Alberta (Health Research Ethics Board - Health Panel, University of Alberta, Edmonton, Canada) under Pro00057046.

A total of 161 children were evaluated: 36 children with OSA diagnosed by PSG, 56 children presenting symptoms suggestive of at high-risk for OSA and 45 children at low-risk for OSA evaluated through the PSQ.[122] Available records of patients aged <18 years, with demographic data (sex, age and gender) and panoramic radiographs, were included in the sample. Patients with diagnosed medical conditions known to substantially affect bone metabolism and patients who used medications known to affect bone metabolism were excluded. The Body Mass Index (BMI) was calculated for each patient, when weight and height information were available, and compared using BMI z-scores as derived from the growth standards of the Centers for Disease Control and Prevention.[123] Mouth breathing status (present or absent) was also collected when available.

In the OSA group, children had a polysomnographic-supported OSA diagnosis through a standard overnight sleep study in the sleep laboratory, considering the medical history and an Apnea-Hypopnea Index (AHI) ≥ 1/hr total sleep time. The AHI index summarizes the number of

obstructive events per hour of sleep during the sleep test. According to the International Classification of Sleep Disorders, released by the American Academy of Sleep Medicine, the criteria to diagnoses pediatric OSA requires one or more obstructive events per hour of sleep or obstructive hypoventilation for 25% of sleep time. Along with these findings, the presence of snoring, paradoxical thoracoabdominal movements, or flattening of the nasal airway pressure waveform is also required.[8] In the other two groups, only PSQ scores were considered. Children presenting a PSQ score of ≥ 8 (33% or more of completed answers) were considered at high-risk for OSA, whereas a PSQ score of < 8 (less than 33% of complete answers) indicated at low-risk for OSA.[122]

A convenience sample of children from three orthodontic centers was included in this study. The records of the patients involved were retrieved before June 2020 from three sources: the Orthodontic and Sleep Clinic at the University of Alberta, Edmonton (Canada); the Orthodontic Program at the University of Campania *Luigi Vanvitelli* in Naples (Italy); and the Department of Orthodontics of the International University of Catalonia in Barcelona (Spain). Patient records retrieved from the Canadian institution comprised patients at low- and at high-risk for OSA (n= 101). The patient records from the Universities in Italy (n= 21) and Spain (n=39) comprised patients diagnosed with OSA based on nPSG recordings.

The inclusion of three different sample sources was needed due to the scarce number of readily available patients fully diagnosed with OSA through nPSG who also have a panoramic radiograph taken within the same month. In addition, the inclusion of three centers allowed for a greater diversity of patients, thereby potentially adding further external validity to the findings.

The MCW was calculated from panoramic images from all individuals using ImageJ software v1.47 (National Institutes of Health) by two trained orthodontists. (Figure 5.1). In the

panoramic image, the following protocol was used to perform the measurements: first, the side that allowed better visualization of the area of interest was determined; a line was then traced from the center of the mental foramen and perpendicular to the tangent to the lower border of the mandible; the distance between the lower border of the mandible to the superior margin of the mandible cortex was measured, in mm with the software measuring tool. The MCW was measured in one location in each patient.

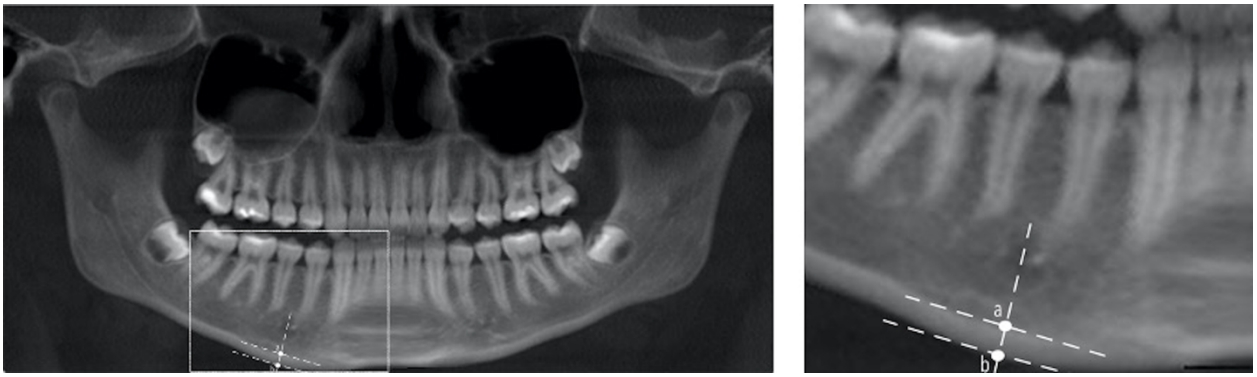


Figure 5.1 Measurement of mandibular cortical width on panoramic radiographs. On left, a panoramic image presenting the measurements. On right, a higher magnification. The mandibular cortical width is calculated by measuring the distance between points.

In addition to MCW, specific craniofacial features previously associated with pediatric OSA were assessed from cephalometric radiographs and frontal and lateral facial photos by a trained orthodontist when available. The sagittal skeletal malocclusion (SNA, SNB and ANB angles) and mandibular growth direction (FMA angle) were measured from the lateral cephalograms.[167, 168] From the photos, the facial convexity and vertical proportion were evaluated.[169] (Supplemental Table 5.1)

Panoramic radiographs and lateral cephalograms were directly obtained or reconstructed from Cone-beam computed tomography (CBCT) scans using Dolphin 3D software (Dolphin Imaging & Management Solutions) from one location (Canada). CBCT scans (ICAT, Imaging

Science International) were obtained following a standardized protocol consisting of 0.3-mm voxel, 120 kVp, 18.54 m. An exposure time of 8.5s, and a field of view of 16 cm in diameter and 6 cm in height, allowing for a low effective radiation dose (approximately 35 microsieverts).[170] In the other two locations, the panoramic radiographs and lateral cephalograms were obtained from two different machines and using different protocols in Spain (Planmeca ProMax 3D Classic, at 5'6mA, 60-66KVp) and Italy (Orthophos XG 5 dental x-ray/Ceph 1.4, 8-12 mA, 60-85 KVp) centers.

The process of generating panoramic radiographs from CBCT reconstructions followed by MCW calculation has been previously validated, showing no significant differences in MCW measurements performed on standard panoramic images and reconstructed from CBCT.[51, 171]

The Dolphin Imaging software (Patterson Technology, Chatsworth, CA, USA) was used to trace and digitize cephalograms.

5.3.1. Statistical analysis

Reliability, systematic and random errors of the MCW measurements were evaluated in 10 subjects from each sub-group (n=30) by two trained orthodontists. The random error evaluation was measured using the Dahlberg formula, while overall reliability and systematic error evaluation were assessed through the Intraclass correlation coefficient (ICC). The intra-examiner reliability of lateral cephalometric measurements and photo evaluation was verified among 20 subjects randomly selected from the entire sample by one trained orthodontist. The ICC was adopted for the cephalometric variables and Cohen's kappa for the photo evaluation. For ICC, a two-way mixed-effects model was considered. The agreement in both ICC or Cohen's Kappa was classified

according to the following values: excellent (> .0.9), good (0.75-0.9), moderate (0.5-0.75), or poor (< 0.50).

The homogeneity of the demographic (gender, age and BMI) and craniofacial features (SNA, SNB, ANB, FMA, vertical proportion and facial profile) was assessed according to the at-risk for/diagnosis of OSA and to the source of the sample. A chi-square test, Fisher's exact test and ANOVA followed by Bonferroni post-hoc tests were applied when appropriate.

Differences in MCW across the three groups were evaluated using ANCOVA followed by Bonferroni post-hoc tests, with age as a covariate.

The association between MCW and skeletal craniofacial features (SNA, SNB and FMA) was evaluated using multiple regression analyses. The collinearity was assessed using the variance inflation factor (VIF) and Pearson correlation. Variables that showed multicollinearity issues were excluded from the final model.

A two-way ANOVA was performed to evaluate the differences in MCW according to mouth breathing and OSA status.

The SPSS statistical package for the social sciences (version 26; IBM, Armonk, NY) was used for data analysis. A p-value < 0.05 was considered as achieving statistical significance.

5.4. Results

Among all participants of this study, 59% were male and 41% female. The mean BMI z-score was 0.62±1.3. Children between 2-17 years old have participated in this study, with a mean age of 9.6±3.1 years. The frequency of mouth breathing was 62% (n= 30) in the OSA group, 75% in the at high-risk group (n= 42) and 58% in the at low-risk group (n= 26). (Table 1) No differences based on BMI z-score, mouth breathing, or gender were observed among the three groups and the grouping of the patients based on country of origin. (Table 5.1 and 5.2)

Regarding craniofacial features, lateral cephalograms were unavailable for four patients in the sample, and the FMA angle was not measurable in ten patients. Lateral and frontal photos were not available for thirty-seven patients. Overall, no differences were observed between cephalometric variables or facial profile and the different OSA statuses. The diagnosed OSA group presented more brachyfacial children than the other two groups; the at low-risk group presented fewer dolichofacial participants than the other groups. (Table 5.1) The children from the Italian sample showed a lower FMA angle (22.5±4.8 degrees) when compared to Spain (29.1±3.0 degrees) and Canada (27.5±6.2 degrees) centers. (Table 5.2)

Reliability assessments indicated that excellent reliability was achieved for MCW measurements, and the detected random error was 0.153 mm when all samples were analyzed concurrently. When the three samples were separately analyzed, an excellent ICC and a random error between 0.108 to 0.204 mm were observed. (Table 5.3) Regarding the craniofacial features, excellent intra-examiner reliability was attained to all variables. (Supplemental Table 5.2)

The patients from the diagnosed OSA group (7.4±2.3 years) were younger than patients at high- (11±2.4 years) and at low-risk (10.8±2.9 years) for OSA groups. (Table 5.2)

Table 5.1 Characteristics of patients with different OSA status.

Variables	**Diagnosed OSA**	**At high-risk for OSA**	**At low-risk for OSA**	**Total**	**p-value**
Sex					
Male n (%)	38 (63%)	34 (61%)	24 (53%)	96 (59%)	0.574[a]
Female n (%)	22 (37%)	22 (39%)	21 (47%)	65 (41%)	
Age Mean±SD (n)	7.4±2.3 (60)	11.0±2.4 (56)	10.8±2.9 (45)	9.6±3.1 (161)	<0.001[b]
BMI z-score Mean±SD (n)	0.51±1.2 (38)	0.88±1.3 (42)	0.41±1.4 (33)	0.62±1.3 (113)	0.249[c]
Mouth breathing n (%)	30 (62%)[d]	42 (75%)	26 (58%)	98 (66%)[e]	0.165[a]
Cephalometric variables					

SNA Mean±SD (n)	80.2±3.9 (58)	81.3±4.5 (54)	79.7±4.8 (45)	80.4±4.4 (157)	0.180[c]
SNB Mean±SD (n)	76.2±3.8 (58)	76.9±4.0 (54)	77.7±4.6 (45)	76.9±4.1 (157)	0.176[c]
ANB Mean±SD (n)	3.9±2.6 (58)	3.5±2.9 (54)	2.7±3.0 (45)	3.4±2.9 (157)	0.124[c]
FMA Mean±SD (n)	26.2±5.1 (48)	28.9±6.1 (54)	28.1±6.3 (45)	27.1±5.9 (147)	0.291[c]
Facial profile					
Straight n (%)	8 (38%)	33 (61%)	30 (68%)	71 (60%)	0.220[a]
Convex n (%)	7 (33%)	10 (18%)	8 (18%)	25 (21%)	
Concave n (%)	6 (29%)	11 (21%)	6 (14%)	23 (19%)	
Vertical proportion					
Brachyfacial n (%)	5 (24%)	2 (2%)	1 (4%)	8 (7%)	0.01[f]
Mesofacial n (%)	11 (52%)	44 (75%)	33 (81%)	88 (74%)	
Dolichofacial n (%)	5 (24%)	8 (23%)	10 (15%)	23 (19%)	

[a]Chi-square test; [b]ANOVA. Bonferroni post-test showed p<0.001 for *Diagnosed OSA* group compared to both *At high OSA risk* and *At low OSA risk* groups; [c]ANOVA; SD= Standard Deviation; ; [d]n=48; [e]n=149; [f]Fisher's exact test; α=0.05 to all tests

Table 5.2 Characteristics of patients from different centers.

Variables	Italy	Spain	Canada	Total	p-value
Sex					
Male n (%)	12 (57%)	26 (67%)	58 (56%)	96 (59%)	0.475[a]
Female n (%)	9 (43%)	13 (33%)	43 (44%)	57 (41%)	
Age Mean±SD (n)	8.9±1.9 (21)	6.6±2.2 (39)	10.9±2.6 (101)	9.6±3.1 (161)	<0.001[b]
BMI Mean±SD (n)	0.89±0.9 (21)	0.1±1.1 (17)	0.67±1.7 (75)	0.62±1.3 (113)	0.108[c]
Mouth breathing n (%)	12 (57%)	18 (67%)[d]	68 (67%)	98 (66%)[e]	0.702[a]
Cephalometric variables					
SNA Mean±SD (n)	79.8±3.7 (21)	80.4±4.1 (37)	80.7±4.7 (99)	80.4±4.4 (157)	0.787[c]
SNB Mean±SD (n)	76.2±3.8 (21)	76.2±3.9 (37)	77.4±4.3 (99)	76.9±4.1 (157)	0.270[c]
ANB Mean±SD (n)	3.4±3.2 (21)	4.1±2.1 (37)	3.1±3.0 (99)	3.4±2.9 (157)	0.241[c]
FMA Mean±SD (n)	22.5±4.8 (21)	29.1±3.0 (27)	27.5±6.2 (99)	27.1±5.9 (147)	0.001[f]
Facial profile					
Straight n (%)	8 (38%)	NA	63 (64%)	71 (60%)	0.08[a]
Convex n (%)	7 (33%)	NA	18 (19%)	25 (21%)	

Concave n (%)	6 (29%)	NA	17 (17%)	23 (19%)	
Vertical proportion					
Brachyfacial n (%)	5 (24%)	NA	3 (3%)	8 (7%)	0.07[g]
Mesofacial n (%)	11 (52%)	NA	77 (79%)	88 (74%)	
Dolichofacial n (%)	5 (24%)	NA	18 (18%)	23 (19%)	

[a]Chi-square test; [b]ANOVA. Bonferroni post-test showed p<0.001 for *Spain* group compared to both *Italy* and *Canada* groups; [c]ANOVA; [d]n=27; [e]n=148; [f]ANOVA. Bonferroni post-test showed p<0.001 for *Italy* group compared to both *Spain* and *Canada* groups; [g]Fisher's exact tes;t SD= Standard Deviation; NA= data not available; α=0.05 to all tests

Table 5.3 Inter-examiner reliability, systematic and random error among examiners.

Center	n	Systematic error		Random error (mm)[a]
		Intraclass correlation	95% Confidence Intervals	
Spain	10	0.961	(0.851, 0.990)	0.126
Italy	10	0.953	(0.824, 0.988)	0.108
Canada	10	0.930	(0.746, 0.982)	0.204
Total	30	0.955	(0.906, 0.979)	0.153

[a] Dahlberg formula.

Overall, children at low-risk for the OSA group showed higher MCW values than PSG-diagnosed OSA and at high-risk for OSA groups. (Figure 5.2) Children with PSG-diagnosed OSA presented significantly smaller MCW values than those at low-risk for the OSA group (mean difference= -0.385 mm, p= 0.001). The at high-risk for the OSA group also exhibited smaller MCW values than at low-risk for the OSA group (mean difference= -0.301 mm, p= 0.014). No differences emerged when diagnosed OSA patients were compared to the at high-risk for the OSA group. (Tables 5.4 and 5.5)

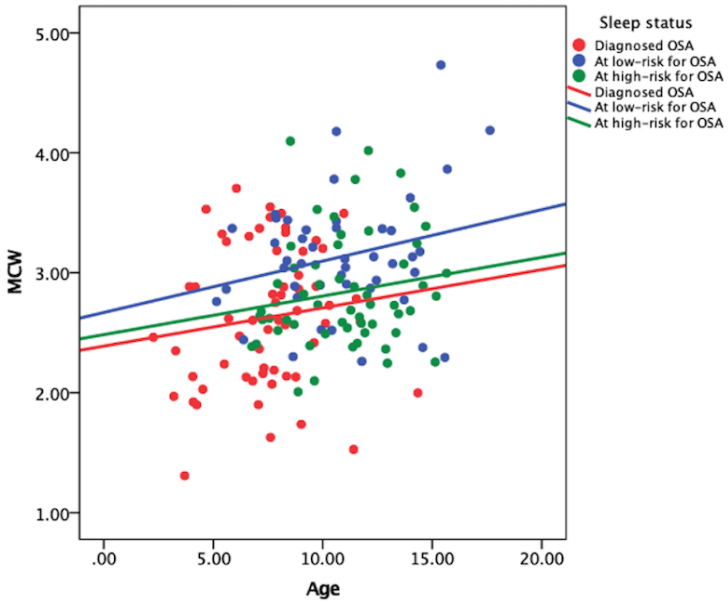


Figure 5.2 Scatterplot of the MCW value vs age according to sleep status.
MCW: mandibular cortical width, OSA: obstructive sleep apnea.

Table 5.4 Descriptive measurements of mandibular cortical width (in mm) across groups.

Group	Mean[a]	SE	95% CI
Diagnosed OSA	2.70	0.08	(2.50, 2.82)
At high-risk for OSA	2.78	0.452	(2.72, 2.96)
At low-risk for OSA	3.09	0.467	(2.97, 3.28)

SE: Standard Error, 95% CI 95%: Confidence Interval 95%. [a]Age was evaluated as co-variate at the value 9.64.

Table 5.5 Multiple comparisons of MCW measurements in patients with different OSA status.

Group of Comparison	MD	SE	95% CI	p-value*
Diagnosed OSA/at high-risk for OSA	-0.085	0.112	(-0.14, 0.30)	0.085
Diagnosed OSA/at low-risk for OSA	-0.385	0.116	(0.16, 0.61)	0.001
At high-risk for OSA/at low-risk for OSA	-0.301	0.104	(0.01, 0.51)	0.014

MD= Mean Difference, SE= Standard Error, 95% CI= 95% Confidence Interval. *p-value for ANCOVA with Bonferroni correction for pairwise analysis and age as a covariate.

The presence of mouth breathing did not present differences in MCW across groups. (Supplemental Table 5.3).

The cephalometric variables were able to explain only 8% of the variance in MCW. A weak positive association was observed between SNB and MCW, as well as between FMA and MCW. No association was identified between SNA and MCW. (Table 5.6)

Table 5.6 Association of MCW and cephalometric variables: Multiple Linear Regression model (n= 147).

Variables	Coefficients		
	β	CI 95%	p-value
SNA	-0.03	-0.06, 0.01	0.070
SNB	0.05	0.02, 0.08	0.002
FMA	0.01	0.01, 0.03	0.033

R^2=0.08, p=0.008. R^2: percentage of the variance in the MCW variable explained by the predictors; β: regression coefficient.

5.5. Discussion

In this pediatric sample originating from three different centers, MCW values were reduced in polysomnographically-diagnosed OSA patients as well as among those at high risk for OSA.

Measurements of MCW were previously evaluated as a screening approach to assess whether children and adults with sleep-disordered breathing are more likely to present altered bone density. Among adults, a systematic review reported relatively high specificity of MCW as a radiological correlate of reduced bone mineral density, with values varying from 0.71 for an MCW cut-off of <3 mm to 0.93 for a cut-off value of <4 mm compared to DXA, the gold standard exam.[50] In children, very few studies have used this technique and did not compare with DXA; however, an association between bone metabolism and MCW values was also suggested.[51, 172]

The findings of lower values of MCW in children with OSA as well as in those at high-risk for OSA were previously reported in a retrospective study.[51] The present study included a different and larger cohort of younger children and originated from one North American and two different European centers. A similar magnitude of mean difference emerged in the present study, whereby

a reduced bone mandibular density was observed in children diagnosed with OSA or at high-risk of OSA compared to children at low-risk of OSA. Similar differences were reported in the previous study, with a difference of -0.6mm in MCW between patients diagnosed with OSA compared to those at low-risk, and a difference of -0.4mm when children at high-risk of OSA were compared to low-risk.[51] The results reported by the present study suggest that the same magnitude of differences in MCW reported by the previous study is observed in a group of children with OSA or at high-risk of OSA between 2-12 years old.

The consistency of these results in a new sample of younger patients provides additional support to the previous suggestion that MCW may be used as a screening tool for OSA while also suggesting altered mandibular bone metabolism/homeostasis in children with or at high risk of OSA. Further reference standard assessments would be needed to confirm these assumptions.

Approaching a sample of younger children showed important results, in which we may hypothesize a possible relationship between age and MCW in children with OSA. In our study, children bellow six years showed a lower MCW when compared to children above six years. This may indicate that changes in bone homeostasis may directly impact OSA disorder at a younger age but may not be the main associated factor to this sleep disorder in a later stage of childhood and adolescence. As considered by previous studies, upper airway obstruction may be a result from changes in bone homeostasis may trigger osteoclasts and osteoblasts.[21] Future studies must explore the role of a reduced MCW, as well as the role of other interplaying factors (e.g., obesity, adenotonsillar size, respiratory disorders) in a sample of children under six years, to understand their association to MCW and contribution to OSA development.

In our sample, a weak association was observed between certain cephalometric variables and MCW. Those variables imply vertical craniofacial growth direction and skeletal Class II

malocclusion, previously linked to pediatric OSA.[43] It is not likely that the mandible and maxillary bones' skeletal position and the mandible growth direction can by themselves explain the variance in MCW values.

In addition, children with mouth breathing did not present different MCW values alone or when three OSA statuses were compared. This may suggest that mouth breathing pattern was not associated with mandibular cortical changes in the cross-sectional evaluation presented by this study. Longitudinal studies are needed to evaluate the long-term impact of mouth breathing on mandibular cortical width of children, considering the association of mouth breathing with worsening on oxygen desaturation levels as well as to craniofacial development as suggested by previous studies.[109, 173]

As mentioned, the association between bone metabolism and OSA has not been extensively explored in children. The scarce information may be accounted for the operational challenges to establish a sample of patients with OSA, including the cost and waiting times required for performing PSG in a pediatric laboratory; in addition, the lack of reliable screening methods to evaluate bone density in children without exposing them to unnecessary radiation may have contributed to the scarcity of information on this issue. Cross-sectional and longitudinal studies conducted in adults linked OSA to increased bone resorption markers, reduced bone mineral density and a higher risk of osteoporosis.[50] Despite the presence of OSA, the severity of the disease presented a discrepant association to bone mineral density in previous studies.[165, 174]

The presence of a high risk for OSA, as suggested by PSQ scores, was associated with reduced MCW values and may indicate that alterations in sleep patterns can interfere with bone homeostasis. The PSQ score was associated with the predictive ability of MCW values in

retrospective studies.[51] Among adults, poor sleep quality, measured by the Pittsburgh Sleep Quality Index (PSQI), was associated with a reduced bone stiffness index of the calcaneus bone.[175]

Several hypotheses have been put forth to explain a link between bone metabolism and sleep disorders, including OSA. The inflammatory nature of OSA can inhibit bone deposition by inducing osteoclast activation.[176] Another hypothesis has suggested that either a genetic predisposition or the presence of metabolic diseases, such as obesity and glucose intolerance,[177, 178] may cause changes in bone metabolism among OSA patients. In children with OSA, however, it has been suggested that weight, height and/or BMI index might not influence MCW values, opposite to the findings in adults.[165]

One of the main contributing factors could be the Intermittent Hypoxia (IH) consequences of sleep apnea.[179] These episodes can promote changes in melatonin hormone levels, cause oxidative stress or even trigger an imbalance in osteoblast and osteoclast activities, all of which can result in altered bone metabolism with the reduced bone formation or bone mass.

The reduction in bone mass as a consequence of IH has been reported in both humans and animals.[179] In the craniofacial area, it has been suggested that IH may induce growth retardation in the mandible of growing rats.[180] In addition, chronic IH can contribute to the development of cardiovascular morbidities by activating intracellular signalling cascades and resulting in increased cell death,[181] and fostering the development of metabolic dysfunctions in obese and non-obese rodents, which would enhance the reduction in bone mass in children.[182, 183] Although an association between IH and bone changes is reported in animal models, IH's role in the bone development of children with OSA has not been clarified for humans.

Alternatively, as a different hypothesis, the presence of intrinsic conditions affecting bone development among children, such as bone genetic syndromes and bone development defects,

could lead to growth deficiency in craniofacial area,[179] including a reduced midfacial and craniofacial base growth that may contribute to airway obstruction and OSA.

Despite these intrinsic conditions, the presence of nasal obstruction or chronic mouth breathing in children, not necessarily linked to significant bone defects, was associated with craniofacial growth changes and sleep-disordered breathing diseases. In rodents, the presence of nasal obstruction was linked to craniofacial growth deficiency,[92] such as alveolar bone density reduction,[184] reduction in cartilage differentiation of mandibular condyle,[185] and a shorter skull base and nasomaxillary complex.[186] Studies in humans reported a narrow naso-maxillary complex.[187] Nasal obstruction might result in local bone changes that may affect OSA children.

In addition, the presence of chronic mouth breathing, which may result from airway obstruction caused by a nasal obstruction or enlarged adenoid and tonsils, could contribute to craniofacial bone changes among children. The presence of mouth breathing during childhood is associated with craniofacial dimension changes, including an increased overjet and the development of a long face and a narrowing of dental arches.[109]

It is challenging to state a specific direction in the relationship between OSA and mandible cortical width differences, i.e., risk factor or consequence, since multiple factors have been individually linked to OSA and can promote an imbalance in bone metabolism.

The clinical relevance of the present study resides in the wide availability of panoramic radiographs in children. Panoramic radiographs are commonly used as part of regular dental checkups among children, and this exam is extensively adopted in the screening for dental infection, trauma, developmental disorders, and dental anomalies.[188] The mandible bone assessment would represent a complementary tool to investigate existent signs and symptoms of

sleep-disordered breathing suggested by PSQ and anamnesis. If the additional obtained information supplements validated tools, such as PSQ alone, it remains unclear at this time.

Contrasting to a possible role in the screening of OSA children, the assessment of MCW may also be adopted as a tool for bone health evaluation. Among dental specialists seeing OSA children, identifying a reduced mandible cortical width, when adequately reported to the physician, may help identify other systemic bone alterations. In addition, identifying a reduced MCW may help dentists in the assessment and predictability of oral health surgeries and develop a rational treatment plan to deal with a possible mandible growth deficiency in OSA patients.

5.5.1. Limitations

As limitations of this study, we should mention the absence of PSG supported diagnosis among the at-risk groups to confirm OSA presence or not. Patients at high risk for the OSA group would need nPSG testing to confirm OSA. However, the cost and waiting time in public services precluded the use of the reference standard.

The absence of non-snoring children is also considered a limitation of this sample. The participants included in all three groups of this study presented at least one sign or symptom of SDB. In addition, there was no negative nPSG group, working as a proven control group due to the lack of children with a negative nPSG result and panoramic radiographs taken around the same time available.

The retrospective nature of this study is also a limitation. The follow-up of pediatric OSA patients and the impact of any dental treatment or underlying OSA co-morbidities over mandibular bone morphology needs to be clarified. Changes in mandibular bone density after some forms of dental treatment have been suggested in animal models.[189]

The inclusion of children from multiple centers with different climate conditions and sunlight availability may contribute to different vitamin D uptake levels. Vitamin D stimulates the absorption of calcium and phosphate from the gut and contributes to changes in bone metabolism.[190]

Mandibular cortical bone alterations may or not reflect the status of other craniofacial or body bones.

A measurement error of 0.3 mm was detected when assessing MCW in panoramic radiographs. This value may also limit the clinical applicability of the reported results.

Intrinsic errors, such as machine motion, mandible asymmetries, and patient's head positioning, might influence vertical measurements' accuracy, causing distortion and magnification in the radiographs.[191] Changes in rotation and inclination of the head from 10-20° degrees may promote an enlargement in the image,[192] but slight skull rotations (2-4° degrees) would not result in a significant negative effect in vertical measurements.[193] In the present study, the positioning was checked during radiography, and any head misalignment would likely have little influence on the cortical measurement.

In addition, there is still a strong need for further validation on larger samples before considering MCW as a reliable screening tool for mandibular bone mineral density evaluation. Ideally, a sample of children with available DXA examination, full OSA diagnosis and panoramic radiographs would be ideal for this purpose, along with longitudinal assessments following therapeutic interventions.

Additional mandible measurements in panoramic radiographs have not been considered in this study due to the absence of proper guidelines for alternative linear measurements in children and low accuracy in performing measurements in trabecular bone.[50, 172]

In this study, the mean age differences were considered during the statistical analysis. The ANCOVA was adjusted for age differences. This diminished the possibility that the age differences between groups would impact the MCW values and alter the differences observed between groups. However, there was a clear age difference between the nPSG diagnosed group and the PSQ-based at risk for OSA groups. Morphological craniofacial bone changes due to age differences should not be discarded. Ideally, the three samples should have had a similar mean age.

5.6. Conclusions

MCW appears to be slightly reduced among pediatric patients diagnosed with OSA or among those at high-risk for OSA. These findings are not clinically meaningful to justify screening of this feature among a high-risk for OSA population. However, these results may imply potential interactions between mandibular bone homeostasis and pediatric OSA through analysis of panoramic radiographs.

5.7. Supplemental Files

Supplemental Table 5.1 Description of craniofacial features evaluated among the sample.

Measurement	Description
Cephalometric measurements	
SNA angle	The angle between the sella-nasion (SN) and nasion-subspinal (NA) lines. This measurement assesses the degree of maxillary protrusion in relation to the cranial base.
SNB angle	The angle between the sella-nasion (SN) and nasion-subramental (NB) lines. This measurement assesses the degree of mandible protrusion in relation to the cranial base.
ANB angle	The angle represented by the intersection between the nasion-subspinal (NA) and nasion-supramental lines and corresponding to the difference between the SNA and SNB angles. This measurement assesses the anteroposterior relationship between the maxilla and mandible.
FMA angle	Angular measurement between the Frankfort plane (from porion to orbitale) and the mandibular plane (from menton to gonion). This measurement assesses the mandibular growth direction.
Photo evaluation	

Facial profile	Visually categorized as straight, concave or convex.
Vertical proportion	Visually categorized as brachyfacial, mesofacial or dolichofacial.

Supplemental Table 5.2 Intra-examiner reliability for the craniofacial measurements.

Variables	Agreement
SNA	0.98 (0.96, 0.99)[a]
SNB	0.99 (0.93, 0.99)[a]
ANB	0.97 (0.96, 0.99)[a]
FMA	0.98 (0.97, 0.99)[a]
Facial profile	0.83 (0.11)[b]
Vertical proportion	0.86 (0.15)[b]

[a]Intra-class correlation and 95% CI; [b]Cohen's Kappa coefficient and standard error.

Supplemental Table 5.3 Intra-examiner reliability for the craniofacial measurements.

OSA status	Mouth breathing	n	MCW Mean±SD	p-value
Diagnosed OSA	Absent	18	2.73±0.51	
	Present	30	2.69±0.60	
At high-risk for OSA	Absent	14	2.70±0.34	0.221[a]
	Present	42	3.04±0.34	
At low-risk for OSA	Absent	19	3.25±0.66	
	Present	26	3.04±0.34	
Total	Absent	51	2.92±0.59	0.592[b]
	Present	98	2.86±0.51	

SD= Standard deviation; [a]interaction between OSA status and Mouth breathing, two-way ANOVA; [b]one-way ANOVA.

Chapter 6 : Parents' perspectives of their journeys through health services for pediatric obstructive sleep apnea. An exploratory qualitative description study

Chapter 2-5 investigated the association between craniofacial features and SBD, and how some features might have or not a potential to be used in the screening of pediatric OSA. As presented in Chapter 1, parents have an important role in facilitating their children's engagement in and compliance with services for managing OSA. Chapter six explores the clinical experiences of parents through the management of pediatric OSA.

Chapter 6 is derived from this manuscript being prepared for publication:

Fagundes NCF, Young R, Heo G, Flores-Mir C, Perez A. Parents' perspectives of their journeys through health services for pediatric obstructive sleep apnea. An exploratory qualitative description study, 2022.

6.1. Abstract

BACKGROUND: Limited evidence has been generated on families' experiences with health services to manage obstructive sleep apnea (OSA) in children across levels of care. This study explored the experiences and perceptions of parents regarding their engagement in health services to manage pediatric OSA.

METHODS: Qualitative description informed the study design. Data were collected through semi-structured interviews with parents of children who had diagnosed residual OSA and received care in a specialized sleep clinic participated. Inductive, manifest content analysis was used to analyze data. Several strategies were employed to ensure rigour through this study, including congruence between the research question and the method and systematic verification of the representativeness of the categories and sub-categories developed to account for the study data.

RESULTS: Five interviews were conducted. Parents' views were organized into five main categories: becoming aware of the issue, interacting with non-sleep specialists, interacting with sleep specialists, interacting with dental professionals, and further actions and support. Parents reported their actions and services received from several care providers at primary, secondary, and tertiary levels of care were suboptimal to address sleep issues. They also perceived several engagement problems such as identifying and raising the sleep problem on their own, feeling the issue was not taken seriously by care providers, waiting a long time to be referred for sleep services, being offered conflicting or insufficient treatment recommendations.

CONCLUSION: Our data suggest that equal attention should be given to the effectiveness of health services to manage pediatric OSA and the engagement of patients and care providers in those services at different levels of care. The development of clinical guidelines for pediatric OSA

screening and management tailored to different levels of care combined with opportunities for continuous education to non-sleep specialists regarding the screening and management of this condition are promising strategies to improve health outcomes in children living with OSA, including residual OSA.

Key-words: Sleep apnea, obstructive; Child Health Services; Therapy.

6.2. Introduction

Obstructive sleep apnea (OSA) is a respiratory sleep disorder that results in partial or complete airway obstruction,[1] and affects 1 to 5% of children and adolescents.[2, 73] This disorder is often underdiagnosed and the management protocol is not well established, leading to several health problems, such as growth impairment,[74] behavioral and cognition disorders,[75, 76] and respiratory and cardiac comorbidities.[77] If untreated, OSA can increase health care utilization by up to 215%.[74] From a social perspective, pediatric OSA is related to a poor academic progress and negative professional performance in adulthood.[78, 79]

The first line of management for pediatric OSA is tonsillectomy and/or adenoidectomy (T&A), as hypertrophic adenoid and tonsillar tissues are the most likely cause for airway obstruction among children.[53] T&A may not be suitable or fully improve OSA signs and symptoms in some cases.[14] The persistence of OSA after an intervention is called residual OSA.[55] The prevalence of residual OSA is 38% and can be higher in children with severe OSA and obesity.[194] The provision of care among children with residual OSA is not well established and remain challenging.[54]

Due to the complexity and chronic nature of residual OSA in children, the interactions of parents with healthcare services to manage this condition is expected to be challenging. Indeed,

access to specialized sleep services has been to be found to be challenging is several countries, with a long wait time and limited availability of specialists.[10, 107, 195] In addition, the presence of other comorbities and the lack of standard diagnosis for residual OSA make it difficult to diagnose and timely and optimally treat children with this condition across levels of care.

Exploring the experiences of parents with pediatric health services for sleep apnea, including residual OSA, may provide important insights on the effectiveness of the services received and the engagement of families and care providers in those services. To date, little has been documented about the experiences of children and their parents with health services for managing pediatric OSA.

The objective of this study was to explore the clinical experiences and perceptions of parents regarding health services for managing pediatric OSA. Specifically, we sought to answer the following questions:

1. What were the experiences and perceptions of parents regarding conventional and/or alternative management options for pediatric OSA?
2. What were the experiences of parents with dental and medical services in relation to managing pediatric OSA?

6.3. Methods

6.3.1. Design

A qualitative description was adopted as the study design. This method is adequate to provide a straightforward description of individuals' experiences and perceptions using categories and sub-categories.[196] The Health Research Ethics board at University of Alberta (Edmonton, Canada) approved this study (Pro00084763).

6.3.2. Participants and Recruitment

Parents or main caregivers of children with residual OSA who were screened at the Stollery's Children Hospital sleep clinic (Edmonton, Canada) for managing this disorder were invited to participate in the study. A nurse practitioner and a research assistant from the sleep clinic informed the parents about the study. The eligible parents were contacted by the research team and formally invited to participate in the study. The potential participants received all information regarding the study's objective, risks, and benefits, as well as their rights as participants (e. g., confidentiality, voluntary participation).

6.3.3. Data collection

All participants were invited to a semi-structured, individual interview. The interviews were conducted online (Zoom Video Communications, version 5.11.6 [Computer software]). An interview protocol was developed to elicit parents' experiences with pediatrics OSA and conventional and alternative approaches to manage this condition, including their experience with services (Supplemental File 6.1). A research methodologist and an orthodontist with research experience in sleep-breathing disorders developed the interview protocol based on the relevant literature on the study topic. Each interview lasted approximately 45 minutes. Participants gave consent to be interviewed and recorded prior to data collection.

6.3.4. Data analysis

The interviews were recorded and transcribed verbatim by a professional transcription company. The data was checked for accuracy imported into NVivo 12 (QSR International) software and analyzed through inductive content analysis. In this approach, the identification of categories and sub-categories was guided by the data collected itself, without following a specific framework.[196] Two research team members systematically coded the data focusing on the manifest

content. Developed codes were subsequently sorted into potential categories. Conceptual maps and tables showing the code groupings were used to facilitate discussion between team members. The data sorted into potential categories and sub-categories were checked to ensure that the categories accounted for the entire data set. Lastly, the essence and structure of each category were defined, names of categories and sub-categories were refined, and representative quotes were selected to support the study's findings.

Several verification strategies were adopted to ensure methodological rigor, such as congruency between the research question and the method (including data collection and analysis strategies), systematic checking of categories against the data, debriefing of each interview to informed further data collection, and selection of information-rich participants.[197]

6.4. Results

Five interviews were conducted with parents of children with diagnosed OSA. One parent was interviewed twice because her two children engaged in services for OSA at different points in time. The age of children ranged between 6-13 years. They all were active patients in a children's hospital sleep clinic (Stollery's Children Hospital, Edmonton, Alberta, Cananda) to which they were referred by a primary care provider (e.g., a family physician) or a non-sleep specialist (e.g., pediatrician, neurologist). Parents' views of the journey they went through when their children received care for sleep issues were organized into five main categories: Becoming aware of the issue, interacting with non-sleep specialists, interacting with sleep specialists, interacting with dental professionals, and further actions and support.

6.4.1. Becoming aware of the issue

Most parents became aware of a sleep issue on their own through direct observation of their child's sleep pattern. Others used additional means (e.g., video capture) to monitor sleep: "I've just noticed, like I said (…). He does the little snort thing like he can't catch his breath. He'll 'snort, snort.' But he'll go straight back to sleep so it doesn't wake him up completely to do that. We hear that at least once a night." P02. Having another child with diagnosed OSA facilitated parent awareness: "So my child was a snorer from really young. He woke up frequently. (…) And I had some troubles with my older son's sleep already. So I was kind of aware that this was a possibility" P01. Signs and symptoms that made parents aware of the sleep issue included waking up through the night, snoring, bed wetting, parasomnias (e.g., sleep talking and sleepwalking), and increased movements while sleeping: "I discovered that he was stirring a lot, especially in the second half of the night, where he was, you know, very restless, all over the place, falling out of bed, all that kind of stuff. Also that he was getting up for drinks of water – he was waking up with a very dry throat" P01. Parents reported that their children were not always aware of the severity of the sleep symptoms: "He is a little bit but I think I'm a little bit more concerned about it than he is, like when I see him because maybe he – he doesn't realize that that's not normal, but the parent – I realize that that's not normal" P03. Parents were not only worried about the sleep issue per se but also about the physical and emotional consequences they observed. Perceived consequences included difficulties concentrating in classroom, excessive tiredness, and negative mood throughout the day: "He's very tired throughout the day. He lacks on his focus. Yeah, he's very fatigued during the day now" P03, "The social just went kind of downhill […] Getting along with the kids and mood wise. He's very emotional, extremely emotional and I do have, I think that has a lot to do with the sleep" P05. After becoming aware of the issue, some parents actively sought

information on the Internet to know more about the sleep problems and potential solutions: “I did a little bit of research with the sleep apnea and all this stuff and I was, the first thing that comes up is basically a mouth guard to try that first to open up the airways” P05. Others attempted to deal with the sleep issue on their own by improving sleep hygiene (e.g., limiting screens before bedtime) and waking up the child to avoid nightmares and prevent bedwetting: “We’ve tried doing things before, like the routine – before his sleep, his bedtime to help him sleep better. [...] It’s just something that we thought about as a family, like try to – maybe a warm glass of milk. Try to avoid technology before bedtime, things like that” P03, “I try to wake him up in the middle of the night, try to get him out of bed, (…) he would get up and he would go to the bathroom” P05. At some point, some parents sought professional support to deal with the observed sleep issue. This support was sought from different healthcare providers, including their primary healthcare provider, dentists, and other non-sleep specialists: “We’ve been trying to find and figure out what’s going on with him. I’ve taken him to the dentist, I wanted a mouth guard, I wanted to buy a mouth guard and he said no, we’re going to send you to the orthodontist” P05.

6.4.2. Interacting with non-sleep specialists

When raising the sleep issue to non-sleep specialists, some parents felt heard and supported: “What I liked is the fact that my family physician, I felt heard with her and she’s kind of helped me push through everything. She’s kind of been like my backbone, like if I’m not getting the help I needed, I’m going to her” P05. However, some reported that care providers did not take the issue seriously, so they had to discuss it with multiple care providers at different points in time to have the sleep issue considered: “I would mention it to the nurses (…), I would mention it to the pediatrician. (…) we were starting to get other help, like the psychiatrist. And they were saying he should have support for this years ago” P04. According to parents, once the sleep issue was

taken seriously, non-sleep specialists offered interventions to address the problem and/or referred the child to a sleep specialist. Parents reported that these care providers often relied on medications to address the sleep issue, including nasal sprays and melatonin pills. In some cases, parents perceived that the intervention offered brought some improvements but did not effectively address the sleep issue: “I would say although it [the melatonin] helps him to go to sleep faster, I'm not convinced it makes a big difference to how much he moves in the night (…) And I expect the melatonin’s not still really doing anything at this point” P01. Parents mentioned that some interventions were discontinued due to adverse reactions to medications: “We tried a nasal spray, and unfortunately it landed him in emergency because he got nosebleeds that were really severe and we couldn’t get them stopped. So we had to take him off the nasal spray” P01. Parents shared that they asked to be referred to a sleep specialist, especially when the intervention offered by the non-sleep specialist failed to manage the sleep issue: “I didn’t feel like we were going in the right direction (…) I could not put the nasal spray up his nose for the life of me and I believe there was one other one that was a pill that he couldn’t take. (…) I had to beg for the sleep study through my original doctor and then I had to go back again and say OK, I need the [sleep] specialist.” P05. Although parents valued the referral to a sleep specialist, they voiced that it took a long time for their child to be referred: “Raising the issue was not a problem. But getting the sleep test was difficult. I think I had asked for about five years before he was actually referred” P03. They also felt that they needed to “push” healthcare providers to timely refer their children to a sleep specialist: “So within, I would say, four months between seeing my doctor and seeing [the Sleep clinic] (…). I pushed for it and I kept calling the hospital asking and I called back to my doctor saying I need this done and I need this done now” P05. Some parents felt conflicted in relation to the interventions and recommendations suggested by non-sleep specialists. In such circumstances,

parents shared that they generally trusted the opinion of their primary care provider and followed their advice: “I was going to try it, but then I saw our family doctor just coincidentally before I started treating him. (…) So I did not go through with trialing that because both the family doctor and the pediatrician were like, ‘No, don’t do it’” P01.

6.4.3. Interacting with sleep specialists

Parents reported that sleep specialists offered different types of interventions (e.g., medications, changes in the sleep routine) to their children and also referred them to otolaryngologists and dentists for additional treatments if necessary. A parent shared that some interventions (e.g., oral appliances, melatonin) improved their children's sleep quality: “What I had been giving him is Melatonin at night to calm his brain. That has helped me (…) he’s getting his sleep now, I know he is. It might be restless but he is still getting enough sleep” P05. Hoverer, some stated that the intervention received was not beneficial: “I don’t really know if it does anything [the melatonin pills]. He’s taking it, but I don’t know if it does anything. He woke up again last night, like waking up for him is nightly thing” P03.

Parents reported a range of experiences regarding their interactions with sleep specialists. Some described sleep specialists as supportive: “I would’ve felt nowhere if it wasn’t for talking to family doctor and you, actually you guys [Sleep clinic] trying to figure out where the disconnect is” P05. Others shared that their communication with these specialists was challenging. A mom who was a biomedical engineering commented that having background in health sciences facilitated her communicate with the sleep specialists, especially in relation to management options: “So we can’t press, because let’s say you have a background, medical background, you may have a discussion – you can have a discussion with some clinicians, you’re well informed and those things help kind of to motivate them or to press them to do something” P04. Concerns

regarding management options were also reported. Some parents felt that some available options to improve obstructive sleep apnea were offered to them (e.g., adenotonsillectomy, Continuous Positive Airway pressure- CPAP): “He’s actually never been to an ENT. […] And equally, nobody has suggested trying a CPAP with him. And I’m not sure, you know, why those options really haven’t been on the table?” P04. They also felt that, sometimes, the management received failed to improve their child’s sleep: “It feels like this whole time I’ve been like trying to get him better sleep and we fixed various other things and the sleep still kind of stays the same” P04.

6.4.4. Interacting with dental professionals

Parents shared that they interacted with dental professionals (i.e., general dentists and orthodontists) as a primary source of care when they were seeking treatment to address their child's sleep problem and as a further source of care when their children were referred by a sleep specialist.

As a primary source of care, parents commented that dentists, including orthodontists, did not address the sleep issue and referred the child directly to a physician: “The dentist said that he would probably grow out of it (…) and then the orthodontist was like no, I’m going to send you directly to the U of A [university hospital]. There were no treatments, there was no nothing, there was no help, there was nothing.” P05.

As a further source of care, when referred by the sleep specialist, parents shared that orthodontists were able to provide interventions, and that these interventions resulted in limited improvements on their child’s sleep issues. According to parents, the referral from a sleep specialist to an orthodontist happened after the specialist dealt with other health issues: “we kind of worked through the whole allergies and asthma and that kind of stuff with, and again, with it still not helping. Then she said, ‘Well what if I sent you to A. Dental?’” P04. Parents stated that

interventions offered by the orthodontist were mainly rapid maxillary expansion and myofunctional therapy, which they found difficulty to comply with, especially at the beginning of the treatment process: “He was kind of gagging on the device because of where he was holding tongue and that kind of thing. But once we got that sorted out he’s handled the device really well and is fine with wearing it and is very cooperative.” P04. Parent observed some improvements on sleep and other health issues after a few months using appliances: “I think there’s been improvements from what we’ve seen from the sleep studies, but he certainly isn’t free of sleep apnea at this point. (…) He has a diagnosis of OCD and generalized anxiety disorder, and I would say both of those are better. I would say there’s some things that have improved and some that are about the same.” P04.

6.4.5. Further actions and support

Some parents undertook some management actions (e.g., trying a compression sheet, changing home sleep routine) during or after their interactions with the sleep specialists to address the sleep issue their children were still experiencing: “We actually ended up getting him a compression sheet that goes around the bed because he would fall out so much” P04. These options included alternative sources of care such as seeing a chiropractor: “I could see potentially a chiropractor. (...) When he was born, his neck was turned to one side and I had to do physio with him for – until he could hold his head up. I wouldn’t be surprised if he still has some neck issues.” P01. Parents reported that schools also supported their children in dealing with the medical and psychosocial consequences resulting from the sleep issue: “I got the school involved and I had to beg for that as well because I wasn’t, I didn’t know where to go or what to do (…) one day I just came to school, I was just bawling my eyes out and the teacher was like, OK, I notice you need the help.” P05. Most parents felt lost and discouraged after receiving care from different care

providers and tried to address the sleep issue on their own: “I'm not sure what else needs to change to get him to have better sleep. Or if, at some point, you just go like, ‘This is what my kid is and this is – you know, this is how much he's going to sleep and what he's going to sleep like and there's nothing you can do about it’”. P04. However, they expected further support to address their children’s sleep issue, even though they did not know the specific support their children needed: “I’m not sure. I did not know what kind of support there would be, I guess. Yeah I guess it just depends on what kind of support there would be available.” P02.

6.5. Discussion

To our knowledge, this is the first study exploring parents’ experiences and perceptions regarding the engagement of their children in services for managing pediatric OSA. Overall, parents reported that their own actions and the services received from several care providers at primary, secondary, and tertiary levels of care were largely ineffective or suboptimal to address the sleep issue that negatively affected their children’s quality of sleep and life. They also commented on several engagement issues such as identifying and raising the sleep problem on their own, feeling that this problem was not taken seriously by some care providers, waiting a long time to be referred for specialized sleep services, being offered conflicting or insufficient treatment recommendations, experiencing difficulties to comply with some treatment recommendations due to challenges faced and the side effects of the therapies offered, and having difficulties to follow and understand the information provided by care providers. As a result of these experiences, parents felt discouraged and lost, but still optimistic.

Interventions received and recommended to manage the sleep issues experienced by the children of the parents involved in the study ranged from over-the-counter sleep medications (e.g., melatonin) to specific interventions (e.g., nasal sprays, orthodontic devices) aiming to address

determinants of pediatric OSA such as snoring, nasal obstruction, and a reduced upper pharyngeal airway space. However, none of these interventions included CPAP, which is a common treatment option to manage residual OSA in children.[9, 54] Children of interviewed parents engaged in services for pediatric OSA at different levels of care. According to our data, family physicians and non-sleep specialists mainly relied on medications and advice on changing sleep routines to address the sleep problem, while sleep specialists performed compressive assessments of the sleep issue, investigated causes of and comorbidities linked to this disorder, and worked in partnership with other healthcare providers (e.g., orthodontists). Medications used to address sleep problems (e.g., melatonin) largely focus symptom management and may have some side effects, including morning drowsiness, increased enuresis, and headache.[198] Similarly, advice on behavioral change may have limited impact on patients' behaviors unless clinicians are properly trained to facilitate changes of this nature and use effective behavioral change techniques. Research is warranted to evaluate the effectiveness of services offer at primary and secondary levels of care to address pediatric OSA.

Although the interventions recommended and offered differed across levels of care, their perceived lack of efficacy to improve children's quality of sleep and life was consistently reported by parents across these levels. Perceiving that interventions do not yield the expected outcomes is common among parents of children experiencing chronic conditions.[199] This finding highlights the need for enhancing parents' knowledge of pediatric OSA and managing their treatment expectations whenever possible. Managing pediatric OSA, and specifically residual OSA, is very challenging due to its multifactorial and chronic nature.[54] Thus, current recommendations to effectively manage residual OSA include multidisciplinary care and the adoption of individualized strategies to identify and manage underlying pediatric OSA risk factors, including obesity.[54]

In our study, parents were actively looking for online information regarding pediatric OSA characteristics and management before, during, and after their engagement in health services, which has been found to be a common practice among parents whose children experience chronic conditions at different stages of development.[200] Self-management practices among parents before seeking professional care have been reported, especially when they believe their children are experiencing non-serious health issues.[201] Parents may also seek alternative care when they perceive that health services are not sufficiently effective.[202] Currently, there is no established clinical guidelines and evidence-based interventions for OSA,[54] which may increase parents' attempts to find and implement treatments options on their own.

Most parents reported that they were the ones who raised the sleep issue with primary and secondary care providers. They also mentioned that these care providers did not always take the sleep issue seriously, so they had to somehow "push" them to provide some level of care. Parents of children with pediatric OSA and adenotonsillar hypertrophy that underwent adenotonsillectomy have also reported difficulties to have the sleep problem acknowledged by general practitioners.[203, 204] These findings confirm the need for clinical guidelines covering not only pediatric OSA management but also screening to help primary and secondary care providers identify children at high risk for this conditions and provide a level of care according to their training and resources.

Many reasons may explain the reported delays in referring children for specialized sleep services, including limited information among primary and secondary care providers about these services and their efficacy, a mismatch between demand and supply of these services, and the lack of training and resources of the care providers to identify and assess the severity of pediatric OSA. For example, the diagnosis of pediatric sleep apnea is solely based on the overnight PSG exam

performed by a sleep technician in a sleep clinic. In some countries (e.g., Canada), the waiting time may take up to 24 months, and children may receive treatment without a proper diagnosis.[107]

Reasons for referral delays to specialized sleep services need to be further explored. Among adults with OSA, some barriers among primary care providers to refer patients to sleep specialized services included the difficulties to find suitable referral options for sleep services for patients living in rural or outside metropolitan areas, and the lack of clarity about the perceived non-sleep specialists' role regarding when and to whom refer patients with possible sleep disorders.[195, 205, 206] Whether these reasons are similar to those preventing primary care providers from referring children to specialized sleep services remains to be elucidated.

The finding that parents trusted their primary care providers, especially family physicians, when other non-sleep specialists suggested different treatment recommendations, highlights the important role that the former care providers play in family's healthcare decisions. Primary care providers seen as a important source of clinical and emotional support to families when dealing with pediatric chronic illness and severe disorders has been attributed to their long-term relationships with families, which increases their chance to build trust and mutual respect.[207] Our data suggest that primary care providers can play an important role in identifying and managing pediatric OSA, including the referral of children with this condition for specialized sleep services.

Parents reported difficulties to comply with treatment recommendations, including the side effects of the therapies offered. Children with OSA often present other comorbidities and health issues that may affect their eligibility and compliance to specific interventions.[16, 208] For example, children with cognitive disorders may not tolerate the PSG exam or the use of orthodontic

appliances.[54] These findings suggest the need for developing new OSA interventions that are both effective and easy to follow.

A great deal of the engagement issues that parents perceived were directly or indirectly related to communication with non-sleep specialists. This may be linked to potential training gaps among these care providers regarding screening and managing pediatric sleep disorders. The American Pediatric Academy has suggested some recommendations regarding pediatric sleep-disordered breathing screening that may fall within the attributions of the primary care provider: screening all children for habitual snoring, performing focused evaluation of children who snore, referring children to specialized services when snoring and presenting one or more additional signs or symptoms of OSA.[9] However, survey research in several jurisdictions has suggested primary care providers and other non-sleep specialists may not routinely perform screening and referrals of children with suspected OSA.[209-212] Reasons attributed to insufficient screenings and referrals include limited training of physicians during their medical school years, limited opportunities to receive additional training, and lack of confidence to screen children with sleep issues.[211, 213, 214]

In their journey to find and receive care, parents interacted with both general dentists and orthodontists, and engaged in interventions offered by orthodontists. However, parents perceived the care received as limited to improve OSA and associated health issues of their children.[12] As presented by previous studies, there is scarce evidence regarding the effectiveness of orthodontic interventions (e.g., rapid maxillary expansion, mandibular advancement) among children with OSA.[12, 60] It has been suggested that rapid maxillary expansion may improve sleep signs and symptoms and reduce the Apnea-Hypopnea Index (AHI) in a short-term analysis. Future clinical studies are needed to investigate the effectiveness of these interventions and parent's experiences in long-term.

This study presents some limitations that need to be acknowledged. First, this is an exploratory study with a small sample size that may not account for all the experiences of parents seeking and receiving care for their children's sleep issues, including residual OSA; however, our study uncovered several perceived issues related to treatment effectiveness and engagement that need to be further described and understood. Second, all interviewed parents were recruited from the same sleep center. Thus, the applicability of the study findings will depend on the similarities between the context of the study and those in which the study results may be implemented. Lastly, parents may experience difficulties to recall events that happened before and during their interactions with care providers, which might compromise the accuracy of the information provided.[215]

6.6. Conclusion

Our data suggest that equal attention should be given to the effectiveness of interventions to address pediatric OSA and families' engagement in health services to manage this condition. The development of specific policies and continuous education opportunities to non-sleep specialists, focused on screening and management of children with suspected OSA are needed. to improve the perceived problems.

6.7. Supplemental Files

Supplemental file 6.1: Interview guide.

Preamble

This interview is part of a research project that aims to understand the experiences of parents with treatments for obstructive sleep apnea (OSA) in children, including access to services.

Today, you will be asked several questions; however, there are no correct or incorrect answers. The information you share will remain confidential. We will record our conversation to facilitate data analysis afterward. Our interview will last ~45 minutes.

Questions:

1. How has your week been so far?

2. My understanding is that you child has experienced some sleep issues. Please tell me about those issues.
   - How long has your child experienced those issues?
   - How have those issues affected your child's sleep?
   - How have those issues affected your child's quality of life in general?

3. Tell me about the treatments your child has received so far. How did you engage in those treatments?
   - How would you describe your experiences with those treatments?
   - How did you feel?
   - What did you like?
   - What did not you like? What worked?
   - What did not work?
   - Overall, how would you describe the effectiveness of those treatments?

4. Aside from those treatments, what else have you tried to help your child?
   - How would you describe the effectiveness of the things you have tried?

5. What other treatment options are you aware of?
   - How did you know about those options?
   - What do you think about those options?
   - Tell me about your intention to engage on those treatments option.
   - What are the things that may facilitate or hinder your engagement in those treatment options?

6. Recommendations to improve services

7. What kind of support does your child need at this point for addressing his/her sleep issue?

8. Is there anything else you wish to tell us about your experiences?

On behalf of our research team, we would like to thank you for sharing with us your thoughts about engaging in treatments for residual Obstructive sleep apnea.

Chapter 7 : Orthodontic interventions as a management option for children with residual obstructive sleep apnea: A cohort study protocol

In the previous chapters we explored the role of craniofacial screening in identifying children at high-risk for OSA and the parents' experiences with related services for managing residual pediatric OSA. Chapter seven covers the third overarching thesis goal, which is to set up a prospective cohort study to assess the impact of orthodontic management in a selective group of children with residual pediatric OSA.

Chapter 7 is based on this published article:

Fagundes NCF, Perez-Garcia A, Graf D, Flores-Mir C, Heo G. Orthodontic interventions as a management option for children with residual obstructive sleep apnea: A cohort study protocol. BMJ Open, 2022 Jun 15: 12(6):e061651. Available from: http://dx.doi.org/10.1136/bmjopen-2022-061651

7.1. Abstract

INTRODUCTION: Obstructive sleep apnea (OSA) is a sleep-breathing disorder that seems likely to have long-term negative social and health consequences in children and adolescents. There are no established standard management approaches when the first line of therapy, the tonsillectomy and/or adenoidectomy (T&A), is not indicated or fails to address pediatric OSA (residual pediatric OSA). This protocol describes a prospective cohort study that aims to assess the effectiveness of orthodontic interventions for managing residual pediatric OSA in patients with concomitant craniofacial issues.

METHODS AND ANALYSIS: Children aged 6-16 years who with an OSA diagnosis and did not benefit from previous T&A or qualified for adenotonsillectomy will be recruited. Orthodontic intervention(s), when adequately indicated (maxillary expansion, mandibular advancement, or maxillary complex advancement with skeletal anchored headgear), and a control (orthodontic intervention declined) cohorts will be involved. A sample size of 56 participants (n=28 per cohort) is planned. Effectiveness data will be assessed through overnight observed polysomnography (PSG), a craniofacial index, sleep questionnaires, and medical records. Additionally, the association of residual OSA and two comorbidities, obesity and asthma, will be investigated through assessing blood, urine and saliva metabolites. The association between residual pediatric OSA and periodic limbs movement, restless leg syndrome and insomnia will also be considered. All participants will be followed up for 12 months after treatment allocation.

ETHICS AND DISSEMINATION: This study was approved by the Health Research Ethics Board – Health Panel, University of Alberta, Edmonton, Canada (Pro00084763). The findings will be shared with scientific and patient content-specific social network communities to

maximize their impact on clinical practice and future research in the study topic. Trial Registration Number: NCT03821831.

Keywords: Obstructive, sleep apnea; Children; Orthodontic treatment.

7.2. Introduction

Pediatric obstructive sleep apnea (OSA) is a sleep-related breathing disorder that results in partial or complete airway airflow obstruction, with a prevalence varying from 1 to 5%.[1, 2, 73] This condition is associated with multiple diseases and comorbidities such as asthma, obesity, and cardiac abnormalities.[5-7] Pediatric OSA also increases healthcare utilization by up to 40% when compared to children without OSA.[4] Children with OSA are more likely to experience poor school performance and long-lasting adverse consequences later in life, such as difficulties to find employment and a reduced monthly income.[3]

Diagnosing and managing pediatric OSA is challenging. Overnight observed polysomnography (PSG) exam is required to properly diagnose this disorder, which is costly and difficult to obtain in many countries.[9] Similarly, adenotonsillectomy (T&A), the most performed management option for OSA due to the increased frequency of hypertrophic adenoids and tonsils among these cases, may not be indicated or effective in improving OSA signs and symptoms. Between 19% to 49% of children with OSA may not benefit from T&A.[9, 14, 216] OSA persistence after T&A is referred to as residual OSA. This condition is more common among children with obesity and severe OSA than children with normal weight and mild to moderate OSA.[14] Additional management options have been suggested for residual OSA in children, such as pharmacologic drugs, Continuous Positive Airway Pressure (CPAP), and selected orthodontic interventions (e.g., maxillary expansion, mandibular advancement).[56, 59, 217]

Altered craniofacial anatomical features have been linked to pediatric OSA. The mandibular advancement devices (MADs), rapid maxillary expansion (RME) and maxillary complex advancement approaches are promising orthodontic interventions to address residual OSA in children.[12] These interventions have been found to reduce some OSA symptoms in children with craniofacial problems or anomalies associated with an orthodontic indication, at least temporarily.[59, 64] It is hypothesized these interventions may increase upper airway space (naso- and oropharynx) and reduce airflow resistance, improving sleep breathing.[12] However, few clinical studies with a significant risk of bias have investigated orthodontic-based management options for children with OSA and their consequences to quality of life and associated comorbidities.[12, 218] Based on them, these orthodontic interventions may represent a potential option to manage residual OSA in children, but its effectiveness remains to be elucidated.

In addition, the impact of OSA-related comorbidities on the management of this disorder is not well understood. Among those, obesity and asthma have been linked to pediatric OSA with a negative consequence on sleep quality and quality of life.[30, 219] Additionally, other sleep breathing disorders, including insomnia, periodic limb movement disorder (PLMD), and restless legs syndrome (RLS), can share symptoms and comorbidities with OSA and may contribute to an increased OSA severity.[220-223] OSA management's impact on these comorbidities needs to be further investigated, considering the multifactorial nature of OSA disorder and its long-term health consequences.

Difficulties accessing PSG also affect the OSA management in children.[107] Adjunctive tools have been proposed to screen for risk factors and symptoms of OSA as a possible option to identify children at high-risk for OSA and better support a referral for PSG.[40, 41, 156] Sleep monitoring through biometric shirts was found beneficial for screening purposes in adults but has

not been evaluated in children yet.[224, 225] Identifying new validated screening methods will likely reduce healthcare costs, decrease diagnosis time, and improve the follow-up of children with OSA.[118]

In summary, pediatric OSA is a complex disorder associated with multiple risk factors and the available consensus-based guidelines have not provided a clear management protocol for residual OSA, including the role that alternative management options can play in managing this condition.[9, 54] This highlights the need to understand residual OSA screening and management better, so that provided alternatives are more effective and feasible. For a residual OSA subgroup with a specific craniofacial phenotype, orthodontic treatment alternatives may be a helpful management alternative.[64, 226] Hence, the primary aim of this prospective cohort study is to assess the effectiveness of orthodontic management, when adequately justified, in residual OSA symptoms and quality of sleep and life in children with this condition. In addition, we will also investigate the changes in severity and symptoms of PLMD, insomnia, obesity, and asthma across the management and control arms; and the use of a biometric shirt as an alternative to PSG for sleep monitoring in children with residual OSA.

7.3. Methods and Analysis

7.3.1. Study design

A prospective cohort study is planned to evaluate the effectiveness of selective orthodontic interventions on sleep parameters and quality of life in children with residual OSA or children with OSA and without an indication for T&A who have craniofacial disturbances. Each participant will choose between properly indicated orthodontic intervention or no intervention. An observational design was chosen as randomization was not possible due to the lack of clearly established clinical management indications and the fact that selective orthodontic interventions have a high cost for

families in our setting. This study is part of a major project investigating the effectiveness of Continuous Positive Airway Pressure (CPAP) in children with residual OSA in an independent cohort from the present study.

7.3.2. Sample definition and eligibility criteria

The participants must be 6-16 years of age. Children with an established OSA diagnosis who present persistent OSA after surgical removal of the tonsils and adenoid tissue will be considered for inclusion, and those who did not qualify for this first management option. Children of any sex will be eligible. For simplicity, we adopted the term residual OSA to refer to both groups of participants. To be eligible for orthodontic management, the child must have craniofacial anatomical disturbances, such as a high arched palate, retrusive mandible or dental crowding, which will justify the need for the orthodontic interventions part of this study (RME, MAD, or class III midface advancement with skeletal anchored headgear).

Children presenting the following diagnosed syndromes will be excluded: autism spectrum, due to sensory concerns and inability to tolerate PSG or dental exam; Down syndrome, because of problems (e.g., difficulties to sleep outside home, fear and anxiety related to multiple sensors used in these exams, sensory sensitivities.) affecting the ability to tolerate PSG.[8]

7.1.1. Recruitment and Sample size rationale

Sleep specialists and nurse practitioners will recruit participants in the Pulmonary and Sleep Medicine Division at the Stollery Children's Hospital (Edmonton, AB, Canada). Potential participants will be identified during virtual or in-person clinical appointments depending on Covid-19 restrictions. The nurse practitioners of the Pulmonary and Sleep Medicine Division will ask patients who meet the inclusion criteria and are interested in participating in the study whether they consent to be contacted by the research team. The research team will then contact the child's

family to provide additional information about the study. Full consent/assent to participate would follow.

Our sample size justification is based on expert observation. According to the clinical team of the Pulmonary and Sleep Medicine Division, 2-3 potential participants, on average, can be identified per week. Considering the cost and commitment to an orthodontic intervention option for young children and a typical trial dropout rate, we anticipate 50% of participants would be eligible for orthodontic intervention. Thus, approximately two participants per month will be included in our study, either in the intervention or no intervention cohort arm. We plan to recruit 7 participants per cohort each year over five years (70 participants in total). Once a management arm has 35 participants, it will be closed to additional participants. Each participant will be followed for one year after enrollment. Considering a 20% dropout rate, which is common in similar studies, we expect to follow up 17 patients per year for a total of 56 participants over five years (n=28 per cohort). This sample size is assumed to be statistically relevant to determine the effectiveness of the target treatments.

7.3.3. Management and control cohorts

The two options (orthodontic intervention or no intervention) will be presented to the child and their guardians. They will choose to engage in one of the two cohorts based on their inclusion criteria.

In both cohorts, the participants will be followed-up for 12 months. Parameters related to sleep quality, quality of life, craniofacial features, medical history and sleep monitoring will be collected to assess both primary and secondary outcomes. Among participants who choose to engage in an orthodontic management option, three possibilities might be available: RME, mandibular advancement or maxillary complex advancement with skeletal anchored headgear.

These three options were included in this study due to previous literature associating these approaches to an improvement in paediatric OSA signs and symptoms among children in selected cases.[12] An orthodontist will assess the eligibility for these management options at the beginning of the study and will provide with the intervention, if applicable.

Table 7.1 describes the protocol for intervention and follow-up in each cohort from this study.

Table 7.1 Description of cohorts and interventions.

Intervention	Description
Orthodontic management	According to each case, the RME, MAD, or maxillary complex advancement with skeletal anchored headgear will be presented as options. In all three situations, the patient should have an indication for treatment despite their sleep problem. The MAD and RME devices will be made in the orthodontic dental lab (Orthodontic Clinic in Kaye Edmonton Clinic, University of Alberta, Canada). The Class III mid-face advancement device is manufactured by Ormco (Protraction Face Mask, Part # 716-0001). The rest of the device will be made in the orthodontic dental lab (Orthodontic Clinic in Kaye Edmonton Clinic). A trained orthodontist will perform the clinical steps in each group.
Control	No intervention will be performed. This cohort will be followed up for 12 months.

7.3.4. Primary Outcome

The primary outcome of this study is the effectiveness of orthodontic management on OSA symptom reduction and quality of sleep and life. To evaluate these outcomes, data will be collected through PSG, a craniofacial index,[121] multiple sleep questionnaires,[122, 150, 227-230] and medical records at baseline and 12 months after enrollment. (Table 7.2)

Table 7.2 Parameters assessed in the primary outcome.

Parameters	Methods of assessment
Sleep parameters and quality of life	*PSG exam* The PSG will be conducted at baseline and after 12 months in each cohort. The following information will be collected: date, AHI (obstructive and central) index, low and mean oxygen saturations, CO_2 (transcutaneous and end-tidal).
	Questionnaires Five questionnaires will be evaluated during baseline and after 12 months: Pediatric Sleep Questionnaire (PSQ); Pediatric Daytime Sleepiness Scale (PDSS); The validated Nasal Obstruction Symptom Evaluation scale (NOSE); Children's Sleep Habits Questionnaire (CSHQ); Pediatric Quality of Life Inventory (PedsQL 4.0) (child-self report and parent proxy responses); Health Screening Questionnaire (HSQ).
Anthropometric measurements	Blood pressure, growth percentiles for height and weight (baseline and 12 months, Mallampati score, and tonsil size will be collected from the medical records of each participant
Craniofacial parameters	A craniofacial index focused on the most common orthodontic problems observed among children with OSA will be assessed at baseline and after 12 months.
Demographic and clinical variables	*Medical charts* Data from the first sleep consult (reason for appointment, date of sleep referral and PSG), anthropometric data (blood pressure, growth percentiles for height and weight (pre- and post-intervention), Mallampati score and tonsil size), additional diagnosis and past surgeries, family history, age at the time of sleep consult and Postal code.

7.3.5. Secondary Outcomes

Secondary outcomes include the effectiveness of a biometric shirt as a tool for sleep monitoring and the relationships between residual OSA and specific sleep-related disorders, asthma, and obesity.

7.3.5.1. Sleep monitoring

To evaluate an alternative sleep monitoring method, all the participants in this study will wear a biometric shirt (Hexoskin, model HX1, Carre Technologies, Montreal, Canada) during both the baseline and 12-month follow-up PSG exams. Additionally, participants enrolled in orthodontic management and control cohorts will be offered the shirt to take home for additional measures during the 12 months (2 nights in a row, every month). Sleep parameters measured by the biometric shirt will be compared to those obtained by the PSG (e.g., total sleep time, sleep efficiency, wake after sleep onset, sleep latency and time in NREM sleep) to determine if the body movements and breathing rates obtained through the biometric shirt correlate with the same parameters obtained from the PSG.[231]

7.3.5.2. Sleep-related disorders and residual OSA

The changes in severity and symptoms of RLS, PLMD and pediatric insomnia across the three cohorts will be examined. The Pediatric Restless Legs Syndrome Severity Scale (P-RLS-SS) and the PSG exam will be used to assess RLS and PLMD, respectively. The assessment of pediatric insomnia will be performed using history and physical examinations and the Children's Sleep Habits Questionnaire (CSHQ). All three conditions will be assessed at baseline and after 12 months.

7.3.5.3. Existing comorbidities and residual OSA

To examine possible asthma and obesity metabolomic markers (e.g., alanine, glucose, uric acid) associated with intervention's effectiveness, blood, urine, and saliva samples will be collected and assessed at baseline and after 12 months.[232, 233] The information regarding existing comorbidities and/or previous health conditions related to OSA will be collected from medical records. A panel of 140 metabolites will be screened at The Metabolomics Innovation Centre (TMIC, University of Alberta), including amino acids, organic acids, monosaccharides,

Glycerophospholipids, and Carboxylic acid previously associated with obesity and asthma in children.[42,43] The blood and urine collection procedure will follow the TMIC requirements.[233-235] Metabolite concentrations from the control cohort will be used to establish normal metabolite concentrations that will be used to determine any differences between cohorts. A seven-fold cross-validation will be adopted to evaluate the differences between metabolite concentrations across cohorts.[236, 237]

7.3.6. Secondary Outcomes

The effectiveness of the intervention will be determined through sleep parameters, medical history (from medical chart reviews), questionnaire responses, craniofacial characteristics, and metabolomic markers at baseline and 12 months after enrollment. Results will be compared to changes or lack thereof in the control cohort.

For the data analysis, we will develop an algorithm called SmiLe (Statistical, Mathematical, Intelligence Learning E-algorithm), which is based on a combination of three scientific branches — statistics, mathematics and deep learning in artificial intelligence. The SmiLe algorithm will determine the evidence for each aim of this study. Furthermore, as subroutines of the algorithm, OSA severity by PSG will be validated by the severity determined by (1) questionnaires and craniofacial index, (2) data obtained from the biometric device, (3) combined both (1) & (2) data sets.

Types of data, in general, can be differentiated into structured or unstructured data. For example, upper-airway shape and PSG time series are considered unstructured, while the rest of the data sets described in our study are considered structured. There are two different approaches to analyzing unstructured data. The first approach is to explore it alone using advanced techniques, such as persistent homology from computational topology and/or convolutional and recurrent

networks from deep learning.[238, 239] This approach is advantageous because it will likely discern signals from noise in the data. However, a disadvantage is that it is not easy to incorporate its analysis with structured data. The second approach is to transform unstructured to structured (U2S) data; classical analytical methods in statistics and machine learning make a joint analysis of the combined structured and U2S data possible. However, a disadvantage of U2S might be that it is less likely to detect essential features from unstructured data than the first approach. In this project, we will utilize both techniques.

Analysis 1: Questionnaires, metabolic concentrates, and medical data will be analyzed using Bayesian networks.[49] Bayesian models of all questionnaire responses will determine whether the OSA symptoms and quality of life have improved after the intervention. Analysis of metabolite concentrations modelled by Bayesian networks might detect an association between OSA and other diseases. We will also compare the apnea-hypopnea index (AHI) before and after the intervention to quantify OSA improvement.

Analysis 2: We will concentrate on predicting sleep states. The five sleep states that will be considered are wake, 1-3 non-Rapid Eye Movement (n-REM), and Rapid Eye Movement (REM), as recommended by the American Academy of Sleep Medicine. Time series is an example of unstructured data. We will analyze the PSG time series using advanced methods in computational topology and deep learning.[240, 241] We will apply Hidden Markov models to obtain the most plausible sleep states using EEG, EOG, ECG, and EMG for children with OSA. We use a probabilistic graphical structure in the Hidden Markov model where sleep states are unknown and observed time-series signals. The optimal sleep states will be calculated using the EM and Baum-Welch algorithms.[241, 242] The same analysis will be repeated using heart rate, breathing rate, and one-channel ECG. The reason for this is to compare sleep states between PSG and biometric

shirt data. Biometric shirts can measure heart rate, one-channel ECG, breathing rate and movements (acceleration, activity level 1Hz, step counting, cadence and energy expenditure estimate). Still, none of the measures are on other functional parts of the body. To make accurate comparisons between PSG tests and the biometric shirt, the participants will wear biometric shirts during their PSG tests. Biometric devices can only determine sleep states of wake, n-REM and REM.[231] The main objective of Analysis 2 is to determine any relationship between sleep stages and severity of pediatric OSA. The second objective of analysis 2 is to see whether sleep stages determined by PSG and biometric devices are well matched.

Analysis 3: We will analyze all the PSG time series to estimate AHI by utilizing recurrent neural networks in deep learning. The estimated AHI will be compared to AHI scored by sleep specialists. We will also calculate AHI for biometric device outputs, including heart rate, breathing rate, and ECG channel. Finally, AHI from PSG will be compared to the estimated AHI from the Biometric shirt.

7.4. Ethics and Dissemination

This project was approved by the Health Research Ethics Board (Pro00084763, Health Research Ethics Board – Health Panel, University of Alberta, Edmonton, Canada).

Study findings will be disseminated in both Sleep Medicine and Orthodontics disciplines through peer-reviewed journals and conference presentations. These findings will be shared with the Sleep division of the Stollery Children's hospital to inform clinical practice. Summaries of our findings will be made accessible to laypeople, such as parents and caregivers of children with obstructive sleep apnea, in formats (e.g., Hospital's magazine, handouts shared to parents during visits to sleep clinic) that facilitate their understanding. These summaries will be posted on our website and shared in social media venues targeted to our participants' population.

7.5. Discussion

The management protocol for residual obstructive sleep apnea in children, when T&A is not an option or is unsuccessful, is not clearly defined. Considering the chronic nature of OSA and the long-term health consequences of this condition, investigating the effectiveness of alternative management options is urgent. This study will evaluate the effectiveness of orthodontic interventions compared to a control cohort. Outcome data will be collected at baseline and 12 months after enrollment.

Some orthodontic interventions (e.g., rapid maxillary expansion and mandibular advancement) have been shown to improve the AHI index and OSA signs and symptoms in children.[64, 226, 243] The difference between this proposed cohort study and previous related attempts lies in focusing on a sample of residual OSA children. These children were unresponsive to T&A, or T&A was not indicated. This follows the currently known management pathway for pediatric OSA. This study will provide a detailed assessment of several physiological responses when orthodontic management is indicated and followed up, lacking in the existing literature. Most previous related studies relied only on the AHI index as an outcome measurement.[244] It has been suggested that the adoption of this metric only, without considering other sleep evaluation features (e.g., event duration, arousal intensity, flow limitations, and obstructive hypoventilation) may limit the understanding of pediatric OSA management results.[106]

Nevertheless, evidence on the effectiveness of orthodontic management in children with OSA is limited and inconclusive. A reduction in the AHI index and daytime sleepiness have been reported. However, these findings are based on either short-term or uncontrolled studies.[226, 243] A broader analysis of the effectiveness of orthodontic management for residual OSA in comparison to other options is required to establish whether orthodontic interventions may be able to address residual OSA in children with selected craniofacial features suggestive of orthodontic need (e.g.,

arched palate, excessive lower facial height, open bite) . The primary outcome of the present study is to evaluate the effectiveness of orthodontic interventions as a management option for residual OSA. Assessment includes the analysis of sleep parameters, craniofacial parameters, quality of life and lifestyle changes.

In addition to assessing treatment effectiveness, we aim to analyze how other sleep-related disorders, including insomnia, PLMD, and RLS, relate to residual OSA and the adopted management options.[216, 231] Along with OSA, insomnia, PLMD, and RLS figure as primary sleep disorders.[11,41] In adults, it has been suggested that sleep-related movement disorders and insomnia were more frequent in individuals with OSA compared to healthy subjects.[220, 221] However, there is a lack of evidence exploring the association of both conditions in children with OSA.

A secondary outcome in our project will be the association of two comorbidities, obesity, and asthma, with residual OSA. Obesity is recognized as a risk factor for pediatric OSA, and it was associated with poor outcomes for some OSA management options.[145, 244] Also, children with asthma are more likely to develop chronic snoring and OSA.[5] A relationship between both comorbidities and pediatric OSA has been suggested.[219] The present study will evaluate this association from the metabolomics perspective, showing higher accuracy in diagnosis, prediction, and therapeutic targets for diseases.[245] Among the multiple medical conditions associated with OSA, the investigation of obesity and asthma metabolites may represent a source to improve pediatric OSA understanding and future screening approaches. This technique may clarify the influence of both asthma and obesity in managing residual OSA in children.

We will assess the suitability of a biometric shirt as an adjunct screening option for identifying children with OSA. Biometric shirts have been used and previously validated in adults for sleep screening purposes.[231, 246] However, no studies have investigated these wearable devices

in children to date. These devices monitor movements, heart and breathing rates, and sleep parameters with more accurate sensors than actigraphy and nocturnal oximetry.[231]

Collectively, we aim to understand the effectiveness of orthodontic approaches for residual OSA management and screening from a comprehensive perspective. Along with the effectiveness of the target interventions on disorder management and quality of sleep and life, we will examine associations between residual OSA and obesity comorbidities and other sleep disorders. In addition, other potential screening options for pediatric OSA will be assessed to enhance monitoring and identification of this condition.

As an exploratory study, this project presents some limitations. First, the absence of randomization when assigning participants to each cohort can result in a selection bias that cannot be avoided. For example, uneven proportions of children with different OSA severity or BMI across cohorts. However, adequate statistical techniques will be used to control these covariates if needed. In addition, the reduced number of in-person interactions due to the COVID-19 restrictions might prolong the recruitment of participants for the study.

After the orthodontic intervention, we expect children to improve their OSA symptoms and quality of life. This project will determine if metabolite changes in management cohorts will differ from those in the untreated control cohort. Metabolomics biomarkers may represent an effective tool in finding (and possibly predicting) comorbidities associated with pediatric OSA. To date, no research has been conducted on residual pediatric OSA and its association with other diseases based on metabolomics.

The target population for our study is children for whom T&A was not successful in managing OSA. Our study will provide evidence on whether orthodontic management improves, at least temporarily, OSA symptoms and the quality of life of these individuals. This evidence is

important for the practice of orthodontics. Unfortunately, research on this potential benefit for children that responded unsuccessfully to T&A is limited.

Chapter 8 : Discussion, Conclusions and Future Directions

8.1. Discussion

In this thesis, and assessment of the evidence on a portrayed association between craniofacial features and pediatric OSA, as well as new screening approaches were explored. Parents' engagement in and experiences with health services for addressing this condition were also investigated. A protocol for a prospective cohort study assessing the impact of orthodontic management approaches on residual pediatric OSA is proposed. Our main findings focused on the lack of a clear association of specific craniofacial features to pediatric OSA, the limited accuracy of craniofacial-based screening methods to identify children at high risk of OSA, the need for prospective studies to understand the effectiveness of orthodontic-based approaches to manage residual pediatric OSA, and the issues that parents experience when engaging in services for managing residual pediatric OSA.

Chapters 2-5 aimed to understand how craniofacial features might be associated with pediatric OSA and their screening value. Based on previous literature published on the topic, our main hypothesis was that these features were potentially associated with the condition and might be a helpful approach available to dental professionals when screening for OSA. However, our main findings could not support this hypothesis (Chapter 2). After systematically assessing the literature, we could not confirm or refute an association between soft/skeletal craniofacial features and pediatric OSA.[148] Based on these results, mostly based on retrospective studies with small sample sizes, our next step was to explore what contribution craniofacial features, assessed clinically, may improve our understanding of alternative screening approaches that included craniofacial features.

Collectively, in Chapters 3-5, we suggested a set of independent features that may be linked to OSA or high risk for pediatric OSA: reduced mandibular cortical width, mild arched palate and higher upper facial height in children without obesity, and excessive lower facial height and an increased mandibular dimensions in children with obesity.[149, 247] We also pointed out the low predictive value of a facial features-based screening tool and the risks of an oversimplification of OSA screening solely based on the facial evaluation done by dental specialists.[149] Overall, some specific craniofacial clinical features may be associated with pediatric OSA and SDB. Still, these portrayed features should be interpreted considering simultaneously other OSA risk factors and health history, due to the complexity of this disorder. Previous position papers directed to orthodontists also suggested the importance of integrating craniofacial features analysis with other health and sociodemographic features.[248]

Our findings highlight the need to continuously explore the role and applicability of craniofacial features in the screening of pediatric OSA towards a more personalized medicine approach. Pediatric OSA is a multifactorial disorder with multiple pathophysiology components; some are not well elucidated yet.[20] The current paradigm to screen and manage the disease is based on a one-size-fits-all strategy, based on single PSG indices to screen (e.g., AHI, OMAHI) and limited management options that may contribute to sub-optimal results.[249] Our results suggested a possible link between specific craniofacial features and other children's characteristics, including OSA severity and obesity, which may help to tailor sub-groups of children with pediatric OSA based on their facial features. In addition, future research is needed to understand the effect of growth on the identified association and the role of other clinical aspects that may impact pediatric OSA (e.g., the presence of other disorders and respiratory problems) in this scenario.

The multifactorial etiology of OSA (anatomical upper airway characteristics, anatomical lower airway characteristics, surrounding muscle tone, obesity, tongue position, systemic inflammation degree, etc.) challenges the idea of a simplified unique management option for OSA. Only some of these factors may affect or be reflected in craniofacial changes. The definitive diagnosis via PSG does not seem to be controversial, but such test does not inform on the actual problem etiology.

Also, this thesis described the poor discrimination results of a facial features-based tool to suggest high-risk of pediatric OSA, although some facial features individually might be associated to the disorder. These contrasting findings seem to indicate that a specific set of craniofacial features may not be enough to strongly suggest the disorder presence, but they may represent important etiological features for pediatric OSA. As the level of evidence is very low, the inclusion of a craniofacial screening analysis to children with pediatric OSA to define treatment plan and monitor management outcomes, or the use of this analysis as a tool to better characterize sub-groups of children with OSA, might still be an important approach to be explored in future research.

Another key finding from this thesis was the engagement issues that parents reported regarding their use of health services for managing pediatric OSA. Considering the insufficient evidence on proper screening and management of pediatric OSA, we may hypothesize these knowledge gaps may also affect the engagement in services of both patients and care providers. Previous studies have found that non-sleep specialists care providers may not feel confident and prepared to assess early pediatric OSA signs and symptoms.[211, 212] This findings suggest that there is a need for training care providers at different levels of care in screening and management of OSA. The reported engagement issues also suggest the need for better approaches to improve

families' engagement in sleep health services for pediatric OSA, regardless of advances in the disorder's pathophysiology or management approaches. As found in other areas (e.g., pediatric obesity, adult OSA) patients and their families may experience some barriers to engaging in recommended services such as the efficacy attributed to the service offered and perceived logistical challenges (e.g., distance, costs) .[70, 250] All these possible factors may represent barriers to parent's engagement in health services and must be given attention, concomitantly while exploring pathophysiology and management alternatives for the disorder.

In addition, the possible association between craniofacial features and OSA, as well as the views of parents regarding the sub-optimal perceived effectiveness of orthodontic approaches in sleep signs and symptoms of their children, may also highlight the need for exploring further the effectiveness of these management options among children with pediatric OSA. The 19-49% prevalence of residual OSA post-A&T might also suggest that targeting one single management option is not an effective approach to manage all children with OSA.[10, 11] Previous literature has already showcased the benefits of some orthodontic treatment options to improve signs and symptoms of pediatric OSA,[218] but findings from this thesis suggested uncertainty regarding parent's perceived effectiveness of orthodontic interventions. As presented in Chapter 7, investigating the efficacy of orthodontic approaches among children with residual pediatric OSA could leverage the knowledge of this therapy applicability and individualize management for children who do not benefit from A&T.

Ultimately, this thesis also suggests that dental professionals, more specifically orthodontists and pediatric dentists, might be important care providers in a multidisciplinary team led by a sleep specialist to manage pediatric OSA. Although dental professionals might not be ready to screen pediatric OSA on their own efficiently, our findings highlighted their willingness

to contribute to the field and their actual participation in providing interventions among children with pediatric OSA, as reported by parents in Chapter 6. Further studies are needed to assess their knowledge and training regarding pediatric OSA.

Another factor to be considered in the role of dental professionals as part of a multidisciplinary management team for pediatric OSA is the different regulations adopted by each country. While some countries may allow dentists to independently manage OSA, other may fully rely on sleep specialists' management.[248, 251] This may represent a barrier to formulate a unified multidisciplinary protocol for pediatric OSA. Along with the emerging evidence, collaboration of researchers and policy makers is needed to understand the specificities of different nations and inform their practice.

8.2 . Conclusions and Future Directions

- The work presented in this thesis addressed some knowledge gaps regarding the role of soft facial features and craniofacial features suggestive of orthodontic treatment need needed for pediatric OSA. Also, it suggests issues are still present in both the effectiveness of interventions to address pediatric OSA and families' and care providers' engagement in health services for pediatric OSA. Together, these findings inform several research directions:
- Further exploring the suggested craniofacial phenotypes in a larger sample of children with pediatric OSA, at high-risk of the disorder, and without the disorder. As indicated in Chapter 4, larger mandible dimensions, mid-face deficiency, higher upper facial height, and arched palate, as well as age and obesity, might be features that characterize children with SDB. To better understand the role of these features in paediatric OSA, we must

develop well-deigned prospective cohort studies, to enhance our understanding of the existence of a subgroup with specific clinical craniofacial phenotypes among children with pediatric OSA that may benefit from an orthodontic-focused intervention. This study should include a larger sample of diverse ethnicity.

- Investigating the association between skeletal, soft facial features and pediatric OSA in a prospective cohort study to understand the impact of growth on craniofacial changes and SDB. This observational study must include children with without OSA, diagnosed with residual OSA and at high-risk for the disease. Also, sub-groups of children with and without craniofacial features suggestive of orthodontic treatment need must also be considered.
- Assessing the impact of craniofacial features on management outcomes of children with OSA in a prospective cohort study. As presented in this thesis, another possible field of study that needs further exploration is the relationship of craniofacial features to OSA management outcomes: whether clinical craniofacial traits may impact management outcomes. As an initial approach to comprehensively explore the topic, we suggest developing a prospective study of children initiating treatment for residual pediatric OSA in a sleep clinic in which their soft and skeletal craniofacial features are investigated at baseline and interpreted to the outcomes observed of the intervention received for residual OSA management.
- Exploring the association between pediatric OSA, MCW assessment and standard bone density assessment (i.e., Dual-energy X-ray absorptiometry- DXA) in a cohort study. Assessing the association of MCW findings in a sample of children with OSA compared

to non-snoring healthy children may help to understand the role of MCW in characterizing children with OSA and further validate this method.

- Evaluating the effectiveness of orthodontic treatment as an alternative management option for children with residual pediatric OSA. As proposed in chapter 7, a prospective cohort study would be important to understand the role of orthodontic intervention in this specific sample of children.
- Expanding the qualitative exploration of parents' and care providers' engagement in health services for pediatric OSA by using larger sample sizes and involving families from different countries and sleep centres.
- Understanding the pathways followed by primary care providers to refer or not children to sleep specialized services, using a qualitative descriptive design. As suggested in Chapter 6, primary care providers might not take a paediatric sleep issue seriously when first raised by the parents and may take a long period until referral of the child to sleep specialized services. Exploring primary care providers' views regarding pediatric sleep assessment and referral practices may shed some light on this topic.

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