UNIVERSITÀ DEGLI STUDI DI MILANO

FACULTY OF MEDICINE AND SURGERY

DEPARTMENT OF BIOMEDICAL, SURGICAL AND DENTAL SCIENCES

PhD Programme in CLINICAL RESEARCH

Cycle XXXIV

PhD Thesis:

"Effectiveness of orthodontic treatment with Prefabricated Myofunctional Appliances in children with Sleep-Related Breathing Disorders and Obstructive Sleep Apnea: an 18-month follow-up".

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A.Y. 2020-2021

To my husband Boštjan,
for his unconditional love
and support.

Nothing in life is to be feared,
it is only to be understood.
Now is the time to understand more,
so that we may fear less.

Marie Curie

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Abstract

Sleep-Related Breathing Disorders (SRBD) include various clinical entities, from primary snoring to Obstructive Sleep Apnea Syndrome (OSAS). They are characterized by intermittent partial or complete (hypopnea/apnea) upper airway obstruction during sleep which lead to sleep disturbance, cardio-respiratory, and neuro-behavioral impairments. Malocclusion and oral-facial dysfunctions such as having a retrusive bite, narrow maxilla, mandibular hypoplasia, oral breathing, or visceral swallowing are considered risk factors for SRBD and OSAS in pre-schoolers.

The present study aims to assess the effectiveness of orthodontic treatment in childhood SRBD and the changes which occur in oral functions and cranio-facial structures.

Participants were recruited if they were less than 6 years of age, presented signs and symptoms of SRBD together with malocclusion and/or oral dysfunctions, and had a baseline apnea index < 5 event/h. Children were assigned to a 12-month treatment with a preformed myofunctional appliance (EFline®, Orthoplus), then to an additional 6-month retention period. At baseline, all children underwent physical examination, orthodontic assessment, nocturnal polygraphy, lateral cephalograms and dental casts. A 6-month nocturnal polygraphy was performed only in OSAS patients. Validated tools for assessing risk of SRBD and OSAS (Sleep Clinical Score, SCS), frequency of sleep disturbances (Sleep Disturbances Scale for Children, SDSC) and neuro-behavioral impairment (Child Behavior Checklist, CBCL) were performed at baseline (T0) and after 12 months (T1). Custom cephalometric analyses and dental arch width measurements were digitally performed at baseline and after 18 months (T2).

Of the 12 patients initially recruited (4 females, 8 males; mean age 5.0±0.47 years), one child dropped-out. Overall, children tolerated the treatment well and recovered from oral dysfunctions ($p<0.001$). The OSAS subgroup completely recovered from apnea (AHI<1). Significant improvements were seen in respiratory, sleep and dento-skeletal variables: mean SCS ($p<0.001$), SDSC and CBCL ($p<0.01$) scores decreased after 12 months; a mean increase of 2-3 mm occurred in pharyngeal airway widths ($p<0.01$) and 6 mm in mandibular length ($p<0.001$), a less hyperdivergent facial

growth pattern and favourable advancement of the hyoid bone occurred; mean inter-canine widths increased by 2.3-3 mm in the mandible ($p<0.001$) and in the maxilla ($p<0.05$). No significant differences were detected between OSAS and SRBD non-OSAS subgroups with the exception of the SCS and CBCL scores at baseline which were resolved after treatment.

Orthodontic treatment with PMAs may produce significant improvements in respiratory and sleep patterns together with significant cranio-facial and dental changes. PMAs might be an effective tool in the multidisciplinary treatment of SRBD and mild-to-moderate OSAS in pre-schooled children.

Chapter 1
Pediatric Sleep-Related Breathing Disorders

Sleep-Related Breathing Disorders (SRBD) is an umbrella term for several chronic conditions including primary snoring (PS), Upper Airway Resistance Syndrome (UARS) and Obstructive Sleep Apnea Syndrome (OSAS). SRBD are characterized by abnormal breathing during sleep with the symptoms being snoring, breathing effort or pauses, arousal, and sleep disruption, which occur on a regular basis and have an impact on a child's daytime wellbeing.

If not treated, SRBD can lead to neurological, metabolic, and cardio-vascular alterations which may impair children's growth and development.

1.1 Definition and Epidemiology

SRBD is a general term that refers to a continuum spectrum of clinical entities with variable severity of intermittent partial (hypopnea) or complete (apnea) upper airway obstruction during sleep. SRBD are characterized by snoring, respiratory effort, and sleep disruption with or without hypoventilation and an alteration in oxygen (SaO_2) and carbon dioxide (PCO_2) blood levels. (1)

Epidemiological data on the prevalence of SRBD in children and adolescents vary widely depending on the heterogeneity of the populations studied, diagnostic method, and clinical and instrumental threshold used for diagnosis. (2)

Overall, the prevalence of SRBD reported in the literature is between 4%-11%: the most frequent and mildest type is primary snoring with a prevalence up to 24%, while the least frequent is OSAS, the most harmful clinical entity which affects 1-5% of children. (2–5)

SRBD can also worsen overtime as it has been reported that up to 10-30% of children with primary snoring may progress to OSAS in the long-term. (1,6)

Children can be affected at all ages but two peaks of incidence can be identified: one in preschoolers (aged 3-to-6), which coincides with the peak age of adeno-tonsillar hypertrophy; and a second one in adolescents (aged 12-to-18), which is mostly related to being overweight and to obesity and is pathophysiologically more similar to adults' SRBD.(7) Nonetheless, also infants and toddlers can be affected by SRBD

which are often associated with earaches, tonsil and upper airway infections, and sometimes to life-threatening events such as sudden death.(8)

The prevalence of SRBD is similar between females and males in pre-pubertal ages, while males are more often and more severely affected after puberty: a larger adenoid size and the role their different hormonal status plays might explain these findings, but the evidence is still weak. (7)

1.2 Aetiology

SRBD and OSAS occur when the balance between the factors maintaining airway patency and those promoting airway collapse is altered. This balance is determined by the interactions of the upper-airway neuromuscular tone, central ventilatory responses to hypoxia, hypercapnia and airway occlusion, the effects of being in a sleeping state, and the anatomical size and resistance of the upper airway. (5) SRBD are caused by an upper airway disfunction which leads to intermittent partial or total upper airway obstruction and is caused by increased upper airway resistance and/or pharyngeal collapsibility. (1)

The aetiology of SRBD is multifactorial and it has been demonstrated that its onset is usually related to the interaction of two or more risk factors rather than a specific cause, especially in non-syndromic children. (2,9)

The current body of evidence indicates that different genetic and/or acquired conditions are involved in the development of SRBD and they can be divided into three main categories according to their pathogenetic mechanism of obstruction: anatomical, inflammatory, and neuro-muscular risk factors. (2,10,11)

The most frequent anatomical risk factor for SRBD and OSAS is adeno-tonsillar hypertrophy, which refers to an abnormal enlargement of the adenoids and/or tonsils that reduces the upper airway pathway. (1,12) This condition is common in pre-schoolers due to the physiological hypertrophy of Waldeyer's Lymphatic Ring at this age.

The action mechanism creates a reduction in upper airway patency, especially at the level between the posterior pharyngeal wall and the soft palate and tongue. This condition becomes critical at night due to the further reduction in airway pathway caused by

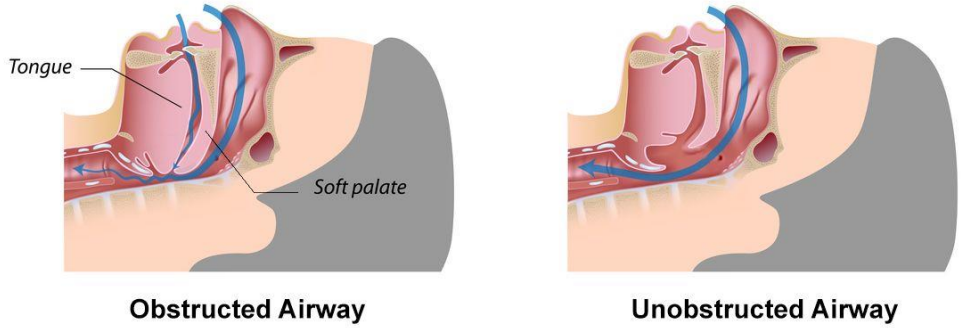

Figure 1.1 Normal and obstructed upper airway pathway during sleep (from https://www.news-medical.net/health/Obstructive-Sleep-Apnea-in-Children.aspx).

a decrease in the pharyngeal muscular tone and a supine position during sleep: this may lead to pharyngeal collapse and obstruction (Fig.1.1).

Alterations of skeletal and soft tissue cranio-facial structures surrounding and/or anatomically proximal to the upper airway tract are recognised risk factors for SRBD: particularly malocclusion and oral-facial dysfunctions have been proven to be frequent risk factors for SRBD and OSAS. (2,11)

The upper airway tract is delimited by the palate, the tongue and the mandible and those structures are also functionally linked together *via* the masticatory and pharyngeal muscles during breathing, mastication, swallowing, and speech.

Malocclusion and/or oral dysfunctions, which have been associated and proven to be risk factors for SRBD, consist of having a narrow palate, mandible hypoplasia, maxilla and/or mandibular retrusion, micrognathia, Class II malocclusion, Class III malocclusion with maxilla retrusion, a deep and retrusive bite, an open bite, a steep mandibular plane, oral breathing, atypical swallowing and altered tongue position. (1,2,11,13)

The mechanism of obstruction can be related to a transverse reduction of the palate and, consequentially, of the nasal widths and/or to an increased collapsibility of the soft palate and tongue over the posterior pharyngeal wall.

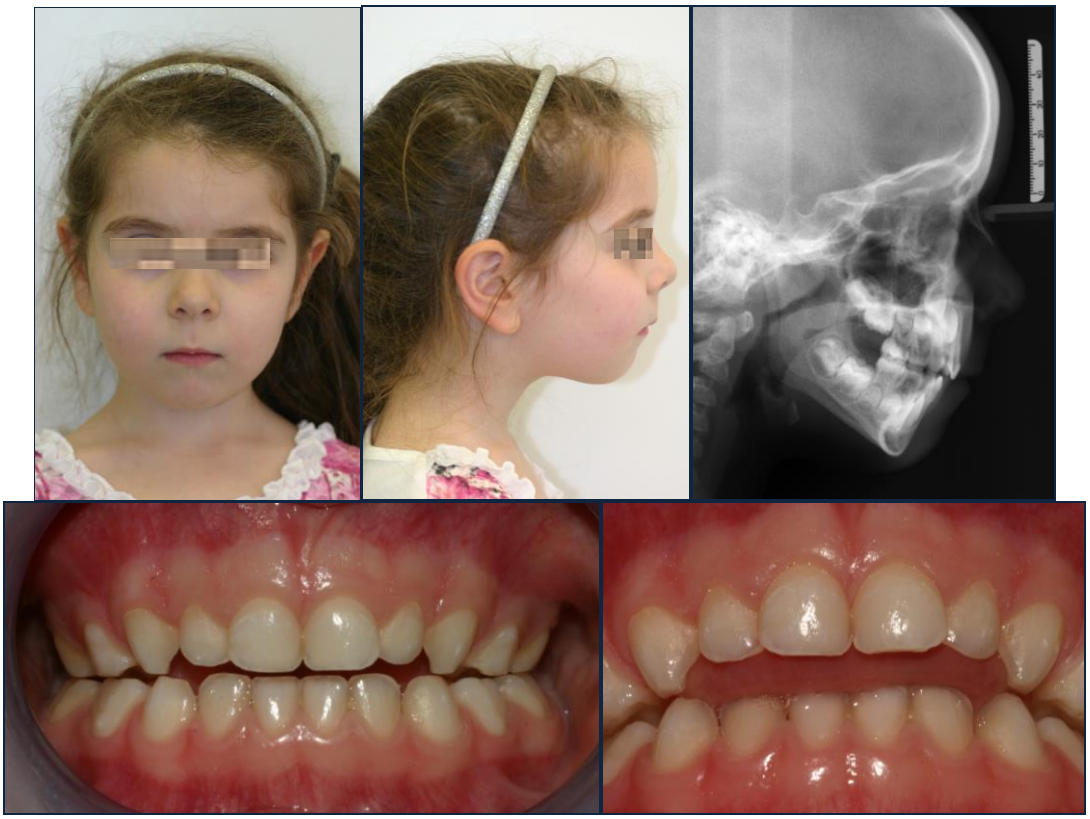

Figure 1.2 A 5-year-old patient affected by mild OSAS (AHI=1), skeletal and occlusal open bite malocclusion with visceral swallowing. Clockwise from top left: extraoral frontal and profile photographs; lateral cephalogram; intraoral frontal and overbite photographs. The reduction of the upper airways is well documented in the lateral cephalogram.

Children with oral breathing such as those with OSAS and SRBD are at a higher risk of dental caries and gingivitis due to the reduction of saliva and its buffer and protective immunological effects. (14,15)

Recurrent chronic infections and inflammatory/dysfunctional conditions such as upper airway respiratory infections, Eustachian tube dysfunctions, asthma, allergic rhinitis, and gastroesophageal reflux disease (GERD) may produce inflammation of the pharyngeal mucosa and/or adenoids and tonsils, thus leading to a reduction in the airway pathway and increase the risk of SRBD and OSAS. (1,16)

Neuro-muscular disease are also risk factors for SRBD: respiratory muscle weakness with nocturnal hypoventilation is sometimes the first manifestation of conditions like Duchenne Muscular dystrophy, Spinal Muscular Atrophy (SMA), and Mucopolysaccharidoses. (17) SRBD and OSAS can also occur in neurological diseases such as cerebral palsy and epilepsy. (18)

Children affected by SRBD and OSAS are clinically classified into three phenotypes:

- *Classic*, associated with adeno-tonsillar hypertrophy with or without malocclusion. They typically present long face syndrome with chronic mouth breathing, low Body Mass Index (BMI), underdeveloped thin nostrils, short upper lip and, in the presence of malocclusion, a narrow palate, underdeveloped upper jaw bones and dental crowding of the front teeth (Fig.1.2). This type is typical during childhood.
- *Congenital*, due to major congenital/genetic syndromes such as Pierre-Robin sequence, Crouzon, Apert, Treacher-Collins, and Down syndromes. (9) In these children, respiratory impairment is usually particularly severe. (9) They typically present severe mandible hypoplasia and/or complex malocclusion and cranio-facial abnormalities. This type is already present during infancy.
- *Adult*, associated with high BMI and obesity. In these patients, visceral fat accumulation in the tongue, neck and abdomen leads to obstruction as a consequence of mechanical factors (upper airway collapse, lower diaphragmatic excursion, reduction of intrathoracic volume, or increased respiratory work during sleep) and inflammatory cytokine production (resistance to leptin action, high oxygen-derived free radicals, high adipokine levels and inflammatory markers). The pathogenesis and clinical features of such type of SRBD are like that of adults and are more frequent in adolescence.(6,19)

1.3 Pathogenesis

SRBD are syndromes of upper airway dysfunction during sleep characterised by snoring and/or increased respiratory effort that result from increased upper airway resistance and pharyngeal collapsibility. (1) There is still no complete understanding of the pathogenetic mechanisms underlying SRBD and OSAS in children. (20) The main characteristic is an anatomically narrow/highly collapsible upper airway tract that becomes critical for breathing at night-time. The middle part of the pharyngeal airway (oropharynx) plays a particular role since it is unsupported by

bony/cartilaginous structures making it susceptible to collapse with increased negative pressure generated during inspiration. (20)

Any alteration to the surrounding soft and hard tissue, such as adenoid and tonsil hypertrophy, a narrow palate, and a hypoplastic mandible, reduces pharyngeal intraluminal volume and increases resistance to airflow during inspiration. Inspiration effort is therefore made to achieve stable breathing, and pharyngeal space pressures become more and more negative. During wakefulness, the activity of the pharyngeal dilator muscles such as the genioglossus, the stylopharyngeus, the palatine and hyoid muscles (e.g., tensor veli palatini, elevator veli palatini, mylohyoid, and geniohyoid) properly balance the negative pressure, but at the onset of sleep, their activity is reduced: airways may therefore collapse with partial or complete obstruction.

The quick rising of CO_2 blood level and negative pharyngeal pressure increases the activity of the diaphragm and chest muscles which work harder to open the airway. Also, some pharyngeal dilator muscles, particularly the genioglossus, are activated, but this is not sufficient to open the airway for adequate ventilation to occur. Inspiratory effort, the rising of CO_2, a drop in oxygen saturation and respiratory drive continue to build until the central respiratory pattern generator in the brain stem is stimulated and induces a reflex that activates all the pharyngeal dilatator muscles: the airway dramatically re-opens and usually a cortical arousal from sleep or awakening occurs. (20) Ventilation increases resulting in a reversal of blood gas disturbances and sleep is re-initiated: the cycle begins again and is repeated several times during the night. (20)

As a consequence, the nocturnal respiratory pattern becomes very unstable with intermittent periods of reduced airflow / obstruction, increased respiratory effort, airflow reduction, breath recovery and arousals.

Based on the severity of intermittent airflow reduction and the occurrence of an obstructive event, four clinical entities are recognised among obstructive SRBD as reported by Kaditis et al: (1)

- **Primary Snoring (PS)**: snoring occurs ≥ 3 nights per week, without apnea, hypopnea, frequent arousals from sleep or gas exchange abnormalities.

- **Upper Airway Resistance Syndrome (UARS)**: snoring, increased breathing effort, frequent arousals, but no recognisable obstructive events or gas exchange abnormalities.
- **Obstructive hypoventilation**: snoring, abnormally elevated end-expiratory carbon dioxide partial pressure, absence of recognisable obstructive events.
- **Obstructive Sleep Apnea Syndrome (OSAS)**: recurrent events of partial or complete cessation of airflow (hypopnea, apnea) due to upper airway obstruction with disruption of normal oxygenation, ventilation, and sleep pattern.

According to the American Thoracic Society, an obstructive event is diagnosed when a reduction in airflow of 50% or more (**hypopneas)** or complete (<90%) airflow cessation (**apnea)** occurs for at least 10 seconds with out-of-phase movements of the rib cage and abdomen, often accompanied by hypoxemia (desaturation events >4%) or arousal. In children affected by OSAS, prolonged hypopnea episodes are more frequent, while apnea is shorter and less frequent compared to that occurring in adults. (21)

Apnea is characterized as obstructive, central, or mixed. In **Obstructive apnea/hypopnea**, airflow is absent, despite continuing respiratory effort. In **central apnea/hypopnea** there is a concurrent cessation of airflow and abdominal/chest movement due to the lack of respiratory effort. Central apnea can be found in children, particularly premature babies, at all ages and is usually without consequence when lasting less than 20 seconds, but it can be a sign of a serious neurological disease (brain injuries, brain masses, or Chiari malformation). In OSAS, child obstructive apnea/hypopnea can be associated with central apnea and this condition is called **mixed apnea**, in other words, when central and obstructive apnea occur sequentially.

SRBD and OSAS are associated with multiple and severe systemic long-term adverse outcomes. Chronic airflow reduction and respiratory effort impairs nocturnal ventilation and sleep patterns and lead to intermittent hypoxia and hypercarbia, sleep

disruption, and an increase in heart rate, thoracic pressure, and inflammatory oxidative stress. These alterations may lead to major cardio-vascular, metabolic, and neurological sequalae which can impair the life and growth of children. (22)

Patients with SRBD undergo strong cardio-vascular stress since they alternate periods of tachycardia and tachypnoea, because of catecholamine release after a respiratory event, and bradycardia and respiratory effort during obstruction resulting in complications such as hypertension, left ventricular hypertrophy, pulmonary heart, or arrhythmias.

Metabolic complications are associated with increased oxidative stress and a dysfunction in hormone release regulators such as Insulin-like Growth Factor-I, a Growth Factor Release Hormone, with the likelihood of occurrence of diabetes, dyslipidaemia, or growth failure.

Neuro-behavioral disorders are a consequence of prefrontal cortical and hippocampus dysfunctions and may cause a dysfunction of the cognitive executive system such as behavioral inhibition, working memory, self-regulation of affect and arousal, or set shifting analysis/synthesis. SRBD and OSAS children can thus show lower intellectual ability, attention deficit hyperactivity disorder (ADHD), rigid thinking, emotional lability, or poor judgment.

1.4 Clinical features and Diagnosis

There is no specific test to diagnose SRBD and OSAS in children, as well as in adults. SRBD are firstly suspected based on signs and symptoms referrals by patients and observations made during clinical examination. In case of a strong suspicion, further instrumental assessments are performed to confirm and grade the type of SRBD the patient presents.

1.4.1 Clinical assessment

Clinical assessment consists of collecting a patient's history and undergoing a clinical examination.

The main symptom of SRBD is habitual snoring which occurs as a result of vibration of the soft palate over the pharyngeal posterior wall due to increased resistance that the airflow encounters during inspiration. SRBD is suspected when snoring occurs ≥

3 nights per week constantly for at least three months and is associated with one or more of the following major nocturnal/diurnal symptoms:

- Respiratory effort.
- Wheezing.
- Pauses in breathing lasting from a few seconds up to a minute.
- Mouth breathing.
- Nocturnal *enuresis*.
- Nocturnal sweating.
- Bruxism and/or parasomnia.
- Restlessness during sleep.
- Daytime irritability or excessive sleepiness.
- Behavioral and/or learning disabilities.

In case a child is suspected of SRBD, further and more detailed anamnestic recordings are collected through *ad hoc* questionnaires: from the simpler Brouillette Questionnaire to investigate the presence of apnea, snoring and disturbed sleep in children with adeno-tonsillar hypertrophy, to the more detailed Pediatric Sleep Questionnaire (PSQ) and Sleep Disturbances Scale for Children (SDSC), which allow for associated neuro-behavioral symptoms to be assessed. (23–25) These questionnaires are validated to record the signs and symptoms referred by the parents/guardians and to assess the likelihood of SRBD.

Clinical examination is important to detect the presence of risk factors for SRBD and OSAS such as adenoid and/or tonsil hypertrophy, malocclusion (micrognathia, narrow palate, or long face syndrome), obesity, growth failure, recurrent chronic upper airway infections, gastro-esophageal reflux disease (GERD), and cardio-vascular and neuro-muscular diseases.

Careful inspection is essential also when assessing the site of obstruction (adenoid/tonsil hypertrophy; possible residual tonsil tissue; lingual tonsil hypertrophy; nasal obstruction). (22)

Clinical assessment in children has high sensitivity but low specificity and therefore is not sufficient for a conclusive diagnosis of SRBD. The reasons are multiple as the

following exist: high inter-individual variability of snoring intensity and reporting; difficulty in differentiating between disrupted or not snoring; apnea occurring late during sleep when parents are not awake; underestimation or overevaluation of sleep disorders based on parents' awareness of the problem.
The diagnostic process therefore requires instrumental assessments to fulfil a SRBD diagnosis.

1.4.2 Instrumental assessment

The gold standard for objective assessment of SRBD and OSAS is to conduct an overnight polysomnography (PSG) that allows for the diagnosis and grading of SRBD and OSAS to be objectively confirmed. (21) In addition, a flexible laryngoscopy on a patient that is awake may be performed or plain lateral neck films may be taken. (22)
PSG simultaneously records sleep state, snoring, ventilation, chest movements, heart rate, muscle activity, eye movements, blood oxygen levels, esophageal Ph, sleep behavior and snoring by means of an electroencephalogram (EEG), a respiratory inductive plethysmography (RIP), oronasal thermistors, an electrocardiogram (ECG), an electromyography (EMG), an electrooculogram (EOG), pulse oximetry, pH catheter, body position sensors, and infra-red cameras. (21)
The following variables and indices are assessed overnight during all sleep stages: (21)

- Respiratory variables:
  - Nasal airflow to assess if nocturnal ventilation is adequate.
  - Chest-abdomen movements to evaluate respiratory effort and distinguish central from obstructive apnea/hypopnea.
  - Oxygen saturation.
  - End Tidal CO_2.

- Non-respiratory variables:
  - EEG permits sleep staging.
  - EOG aids sleep staging *via* detection of rapid eye movements.
  - EMG aids sleep staging and assessment of arousals *via* recording of

submental and tibial muscles activity.

- ECG aids in cardio-vascular impairment and respiratory assessments.
- Supine/non supine position *via* a body position sensor since it affects nocturnal ventilation.

- PSG indices:
  - Apnea/Hypopnea Index (AHI): number of respiratory events (obstructive and/or central apnea/hypopnea) per hour of total sleep.
  - Respiratory Disorder Index (RDI): number of respiratory events with arousals per hour of total sleep.
  - Oxygen Desaturation Index (ODI): number of 4% or more oxygen desaturation events per hour of total sleep.

OSAS in children is classified, according to PSG indices, as:

- mild OSAS: 1<AHI<5
- moderate OSAS: 5<AHI<10
- severe OSAS: AHI>10

A PSG is recommended for OSAS assessment and should be performed before and after any intervention for OSAS (adenotonsillectomy, orthodontic treatment, ventilatory treatments), but it is also an expensive procedure that cannot always be performed. In fact, a PSG is usually performed at dedicated pediatric facilities in hospitals or specialized sleep centers and requires highly specialized technicians able to correctly perform and read it. (26) Moreover, high compliance is needed from children and parents, and clinicians frequently face difficulties.

A valid alternative is **nocturnal cardio-respiratory monitoring** that can be performed also at home and does not require supervision by an expert technician. Recording is reduced to assessing ventilation, heart rate, chest and leg movements, and blood oxygen levels by means of a portable machine with nasal cannula and a few channels for EMG and chest chain, and pulse oximetry. This method has low

sensitivity, so it is recommended that a PSG be performed in case of negative results in a patient with severe signs and symptoms of SRBD or OSAS.

Once the definitive diagnosis is established with a polysomnography (PSG), the site or sites of obstruction should be identified. **Cine magnetic resonance imaging (MRI)** and **sleep endoscopy** have been increasingly used since they allow the airway to be visualized during sleep or sedation and enable multiple sites of obstruction to be identified. (22,27) These procedures are particularly recommended in children that have a high risk of persistent SRBD/OSAS after adenotonsillectomy (AT), such as children with malocclusion and/or orofacial syndromes, obesity, and neurological diseases.

Sleep endoscopy, also known as drug-induced sleep endoscopy (DISE), allows for dynamic obstruction during sedated sleep to be assessed. DISE is usually performed in the operating room before AT and lasts approximately 15 minutes: the surgeon can observe dynamic airway obstruction at several levels and verify if resolution or improvement of obstruction occurs by pushing the patient's mandible forward. (27) Sleep endoscopy is useful to verify anatomic factors which worsen the obstruction provoked by enlarged tonsils and adenoids. This evaluation during a clinical examination when the patient is awake does not correlate well with disease severity or outcome of AT. (28)

In cine MRI images, consecutive images of the upper airway are acquired for 2 minutes and then displayed in a format that creates an active "movie". Cine MRI yields detailed information on both anatomy and dynamic airway motion: it allows for multiple pharyngeal levels to be simultaneously examined and it helps in identifying primary and secondary sites of obstruction. (29)

1.5 Treatment

SRBD and OSAS therapy require a multi-specialistic approach involving pediatricians, otolaryngologists, sleep medicine specialists, pneumologists, neuropsychiatrists, orthodontists, and speech therapists.

The multidisciplinary treatment may include monitored observation, adenotonsillectomy, orthodontic devices, medical treatments, weight loss, and non-invasive ventilation (continuous positive airway pressure, CPAP). (30,22)

Treatment is usually implemented in a stepwise fashion and planned case-by-case, based on the patient's age and phenotype (common, adult, or congenital), severity of obstruction and symptoms, comorbidities, and compliance. (30,22)

The patient is re-evaluated after each intervention to detect residual disease and to determine the need for additional treatment. (1)

AT is recommended as the first line of therapy for pediatric SRBD and OSAS especially when enlarged tonsils, a common phenotype, and severe symptoms are present. (1) It consists of the surgical removal of the adenoids and/or tonsils depending on individual assessment, and it is performed under general anaesthesia.

Adenotonsillectomy has nevertheless intrinsic risks and it is usually avoided in children under 3 years of age or with low body weight.

In patients without enlarged tonsils and moderate-to-severe symptoms, positive airway pressure, either continuous (c-PAP) or bi-level, is indicated. It consists of a machine to be used overnight that conveys positive airflow into the nose through a mask or a nasal thermistor and mechanically maintains the pharyngeal airway open during sleep. c-PAP applies constant airflow pressure, while a bi-level positive airway increases pressure during inspiration. In children, only nasal masks are preferred for they are less harmful to face growth. (31) The use of c-PAP in children is limited by the high prevalence of noncompliance: children frequently refuse to use the device for its adverse effects including mask leaks, dry mouth, awakening, and blocked nose. (31) Additionally, it has been noted that the pressure of the masks over the third mid-face has been associated to long-term alterations in orofacial growth. (31) Therefore, positive airway pressure is more often used as bridge therapy, before AT or other surgical procedures are performed in children with severe SRBD and/or life-threatening conditions.

In mild OSAS, other types of SRBD, and in patients with recurrence of apnea/hypopnea after AT, medical therapies (topical nasal steroids or antileukotriene used for 6-12 weeks to reduce inflammation and/or allergic patterns) and/or orthodontic procedures (palatal expansion, mandible advancement) are highly recommended.

In adult phenotypes, weight loss is the first line of treatment by means of a diet and/or endocrinal therapy in case of obesity, as a consequence of metabolic diseases.

c-PAP is usually indicated in severe OSAS patients, while adenotonsillectomy is recommended based on the individual situation.

In congenital SRBD and OSAS, immediate treatment is required since a rapid onset of pulmonary failure and hypertension may occur. Such patient is treated early on with a tracheostomy and c-PAP at birth, but poor compliance usually leads to the need for surgical procedures to be performed such as a maxillomandibular advancement (MMA) and/or epiglottis/nasal plastic surgery to target the upper airway more specifically. (11)

Myofunctional Therapy (MT) is also used in the treatment of children with SRBD and OSAS and consists of a combination of oropharyngeal exercises and sensorial stimulation. (32) Children with SRBD and OSAS always exhibit a certain degree of muscular hypotonia and abnormal patterns of breathing, mastication, and swallowing: the aim of MT is to increase sensorial stimulation through the nose and improve the muscular hypotonia of the tongue and muscles around the airways.

MT protocols may vary widely according to the patient's age, type of SRBD, and health system in which treatment is delivered (e.g., public or private).

Exercises must be repeated daily by the patient at home, at least three times a day for 3-5 minutes, and therapy sessions with a speech therapist are planned two to three times a week. This first intensive treatment phase can last 3-6 months, depending on the degree of functional impairment and cooperation. Once proper muscle activity is reached, patients are checked-up every 2 to 3 months to verify if recurrence occurs.

MT has proven to be effective in treating children with SRBD, but studies are limited by the very small number of patients and short follow-ups. (33) Although these exercises are easy to learn and teach, the child's cooperation and adherence is a potential limitation. (33)

Recent studies seem to corroborate these concerns and potentially advocate for passive myofunctional therapy via an intraoral appliance rather than the active exercise format.

Chapter 2
Orthodontic management of pediatric SRBD and OSAS

Craniofacial anomalies are recognised risk factors for SRBD and OSAS: they can reduce the volume of oral and nasopharyngeal cavities and trigger tongue falling into the oropharynx during the night. (5)

Not only are occlusal anomalies an anatomical risk factor: oral-facial growth plays an important role in the development of pediatric SRBD, particularly in non-obese children. (11)

In the last two decades, researchers have paid more attention to orthodontic treatment for pediatric SRBD: significant improvements in respiratory patterns have been observed after orthodontic treatment and a wider range of therapeutic tools have been developed for this purpose. (34–37)

2.1 Rationale of orthodontic treatment in children with SRBD

Despite the fact that adenotonsillectomy is still the first line of treatment for children with abnormal breathing during sleep, its application is limited by surgical risks and a high prevalence of recurrence is reported, ranging between 30 and 50%. (11,12,38)

Children undergoing tonsil and adenoid surgery are at risk of respiratory compromise. Risk factors for immediate post-operative adverse outcomes are: being below 3 years of age, weighing less than the fifth percentile, having severe respiratory impairment (AHI>5), and the presence of craniofacial anomalies. (38)

Many investigations revealed that prepubertal children treated with the surgical removal of adenoids and/or tonsils, and followed up with a polysomnogram, displayed incomplete resolution of PSG results and/or recurrence of symptoms 3 months post-operatively and even, years later, in adolescence.(39–42) Children that had an incomplete response to AT were frequently affected by cranio-facial and/or occlusal anomalies as revealed by clinical examination and 3D-CT (Computer Tomography) assessments.(11,42) In such patients, it is claimed that adenotonsillectomy is indicated to restore normal dentofacial development, but the evidence is modest.(43,44)

Two systematic reviews agreed that adenotonsillectomy seems to affect mandibular growth positively, enhancing its horizontal development, with negligible changes in the nasomaxillary complex. (43,44)

These findings were related to the earliest orthodontic findings and theories on the relationship between patterns of breathing, swallowing, chewing and dento-skeletal oral-facial growth.

Angle showed that Class II division 1 malocclusion is associated with obstruction of the PAS and mouth breathing, and suggested that soft tissue would play an important role in the development of malocclusion.(45) Later on, Moss described how soft tissue and functional factors can interfere with normal oral-facial growth in what he called the "*Theory of functional matrices"*.(46,47) Moss explained that oral-facial growth in some districts − such as the mid-palatal suture and the alveolar process of the mandible and the maxilla − is driven by genetic factors, but is largely influenced by the activity of surrounding soft tissues (tongue, masticatory and perioral muscles) and patterns of breathing, swallowing, chewing, and speech.(46) Normal functional patterns encourage correct oral-facial growth, which is conversely impaired by abnormal functional activities: force delivered by soft tissue during functional activities account for the position and the development of dentition and maxillomandibular bones.(46)

Between 1970 and 1980, crucial findings were discovered after a series of experiments that investigated the role of increased nasal resistance on oral-facial growth during the development period, and ultimately demonstrated the relationship between mouth breathing and dental malocclusion.

Newborn rhesus monkeys were artificially induced to mouth breathing after blocking the nasal passage using a small silicone head placed in the nostrils. After 6 months, several consequences were observed: narrowing of dental arches and cranial skeleton; restriction of the nose and the maxilla; increased overjet; increased anterior facial height; downward and backward displacement of the mandible with persistent mouth opening posture; modification of tongue firing patterns, geniohyoid, genioglossus, suprahyoid, upper lip elevator and digastric muscles at the EMG assessment.(48,49) The changes were reversible if nasal breathing was restored when the monkeys were still in their developmental phase.(11,48,49)

The experiments proved that nasal obstruction led to important adverse effects on the morphology of the nose, the maxilla, and the mandible: the modification of the tongue activation patterns and all the muscles around the airways was responsible for the morphometric changes observed. (11)

These findings, suggesting that orthodontic treatment may be beneficial to children affected by SRBD and OSAS, led to further investigations on this topic. The aim of orthodontic treatment in children with SRBD is not only to improve respiratory parameters, as in adults, but rather to normalize oral-facial growth, and achieve permanent and stable anatomical changes that prevent further recurrence of SRBD.

2.2 Rapid Maxillary Expansion

Rapid Maxillary Expansion (RME) has been extensively studied in children with mouth breathing, and it is the first orthodontic strategy applied in children with abnormal breathing during sleep since the first recognition of OSAS in children was made in 1974 by Guilleminault et Al. (50)

RME consists of applying heavy orthopaedic forces that widen the mid-palatal suture, increase the transversal width of the maxilla and reduce palatal vault depth.(51) Other modifications were described during RME such as a slight anterior displacement of the maxilla, a clockwise rotation and advancement of the mandible, and a slight expansion of the lower dental arch.(52,53) These changes aid in increasing the volume of the oropharyngeal tract.(54) RME is effective in reducing AHI and improving oxygen saturation in the short-term and long-term follow-ups: the expansion of the palate results in an increase in nostril width and increased airflow path and reduced nasal resistance (Fig. 2.1).(55)

RME is indicated whenever a narrow maxilla is present and this may occur in posterior/anterior crossbite, Class II malocclusion, Class III malocclusion, openbite, or moderate-to-severe crowding. (56)

Custom-made devices called palatal expanders are used for this purpose, and feature bands anchored to second deciduous upper molars or first permanent upper molars, a central expansion screw, two frontal arms and two back arms.

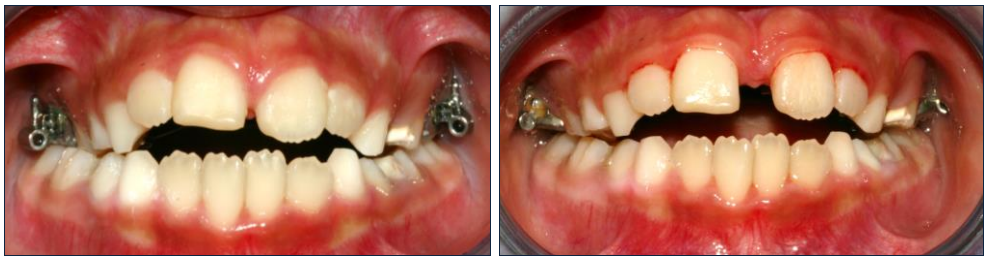

Fig. 2.1 Rapid maxillary expansion performed in a 7-year-old girl with moderate OSAS (AHI=2), posterior crossbite, and anterior open bite. Intraoral photographs before and after the active phase of palatal expansion. After 2 months, the AHI normalized at cardiorespiratory monitoring.

Many types of palatal expanders are available and have been used in SRBD patients, depending on the degree and type of expansion needed (Fig. 2.2). The screw is activated once or twice a day for 3-4 weeks and can cause the palatal width to increase by a total of 5-to-8 mm. The appliance is then left in position for a further 6-8 months to allow the bone to fill the gap between the two halves of the maxilla.

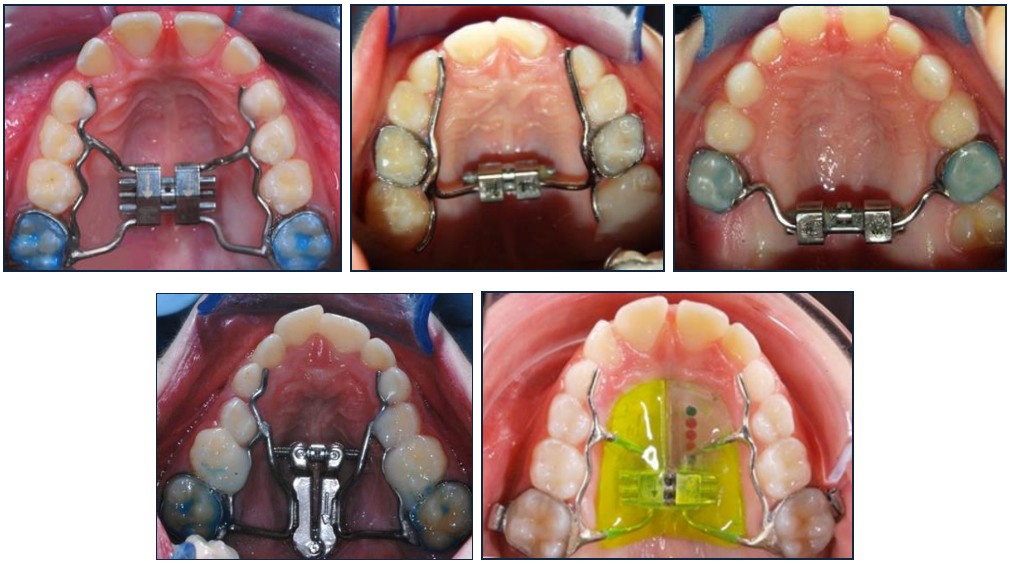

Fig. 2.2 Rapid palatal expanders are fabricated in several design types. Clockwise from top left: The Hyrax expander is displayed in three designs, the first with bands on the first permanent molars, the second with bands on the second deciduous molars, the third without arms. It is indicated in posterior crossbites; The Fan type expander presents a fan median screw. It widens the anterior maxillary arch while maintaining the posterior transversal diameter unchanged. It is indicated in “V” shaped arches; The Haas expander has double acrylics which come into contact with the palatal mucosa. It is used in deep palatal depth.

2.3 Functional devices

Functional orthodontic treatment is based on the use of orthopaedic mandibular advancement devices (MAD) that work by protruding the mandible forward and ultimately increasing the pharyngeal airway space volume. (31,34,57,58)

They are more often used in Class II, deep bite and or retrusive bite malocclusions.

Functional devices can be either active or passive, depending on whether the position of the mandible is maintained by the appliance itself or because of the activation of soft tissues and muscles. They are removable appliances that could be tooth (e.g., Andreasen's monobloc, Twin-Block) or tissue anchored (Fränkel, Bionator), and can be built with additional features such as expansion screws, and lip-bumpers based on clinical requirements (Fig. 2.3).

Passive functional devices have been studied in recent years for children with SRBD and OSAS.

The patient must wear the appliance at night-time and at least 3-4 hours during the daytime for 12-18 months, depending on the degree of correction needed.

They are effective in children in the short-term by improving respiratory parameters (AHI, oxygen saturation) and snoring, and in the long-term by enhancing mandibular growth because of the activation of the perioral soft tissues and masticatory muscles and a remodelling of the condylar region. (34,37,59–61) An increase in mandibular length of up to 3-6 mm can be achieved if treatment is performed during the active growth phase.

Active functional appliances are fixed devices made of custom-made stainless-steel

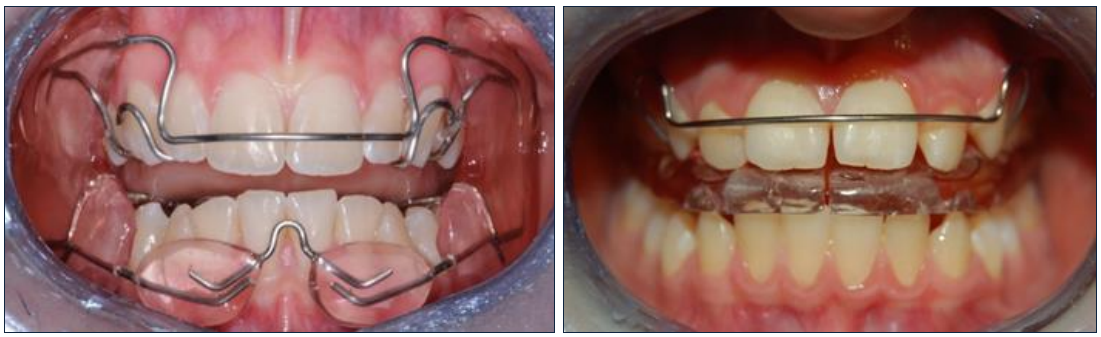

Fig. 2.3 Functional appliances used in Orthodontics for mandibular advancement. On the left: the Fränkel type II appliance is a tissue borne functional device. On the right: Andreasen's monobloc is a tooth anchored functional device.

frameworks that are cemented to the first permanent molars in all four corners of the patient's mouth and upper and lower splints. These frameworks are connected by telescoping mechanisms that exert an upward/backward force on the upper jaw and a forward force on the lower jaw.

Therapy with fixed active functional devices lasts 12 months and is usually performed in late mixed and permanent dentition before comprehensive orthodontic treatment. The effectiveness of such appliances in children with SRBD and OSAS has been investigated in case reports, and in few randomized controlled trials. (34,37,59–61)

2.4 Oral myofunctional therapy with oral devices

This approach combines orthodontic treatment and myofunctional therapy to optimize improvements of oral growth and functions, reduce treatment time, and partly overcome poor cooperation frequently seen during myofunctional treatment alone. (33)

The rationale is to passively produce myofunctional effects with an intraoral device at night-time, and actively with oropharyngeal exercises to be performed with and/or without the device in the mouth during the daytime, and concurrently achieve correct sagittal and vertical occlusal relationships.

Oral devices that have become popular for this purpose are Prefabricated Myofunctional Appliances (PMA) as they are comfortable, easy to use and cost-effective. (62–64)

They are single-block prefabricated devices made of soft silicon-like material, are available in different models and sizes, and simultaneously act onto the lower and upper jaws (Fig. 3.4). The orthodontist chooses the appliance according to the patient's age and type of malocclusion: the patient is asked to wear the appliance at night-time and 2-3 hours during the daytime.

PMA combine the effect of a functional device, together with passive myofunctional and dental effects: they forward the mandible to maintain correct sagittal relationships, and aid in limiting and/or enhancing molar eruption thus improving vertical dimension; and have labial flanges to avoid tongue thrusting, while vestibular bumpers stretch the perioral muscles; dental niches are present in the

anterior dental arch segments and promote alignment of the incisors. (65)

Myofunctional intervention consists of increasing children's sensorial experiences and teaching patients several combinations of isotonic and isometric oropharyngeal exercises. (31,32)

The sensorial stimulation elicits activation of the sensory receptors to induce a feedback response of the muscles: this promotes the use of nasal breathing as the preferred respiratory route and aids in achieving a more favourable positioning of the tongue within the oral cavity (Fig. 2.5). (33)

Oropharyngeal exercises consist of mouth and throat exercises which strengthen the tongue, the orofacial muscles, and the upper airway dilator muscles which are essential to maintaining pharyngeal patency. (32)

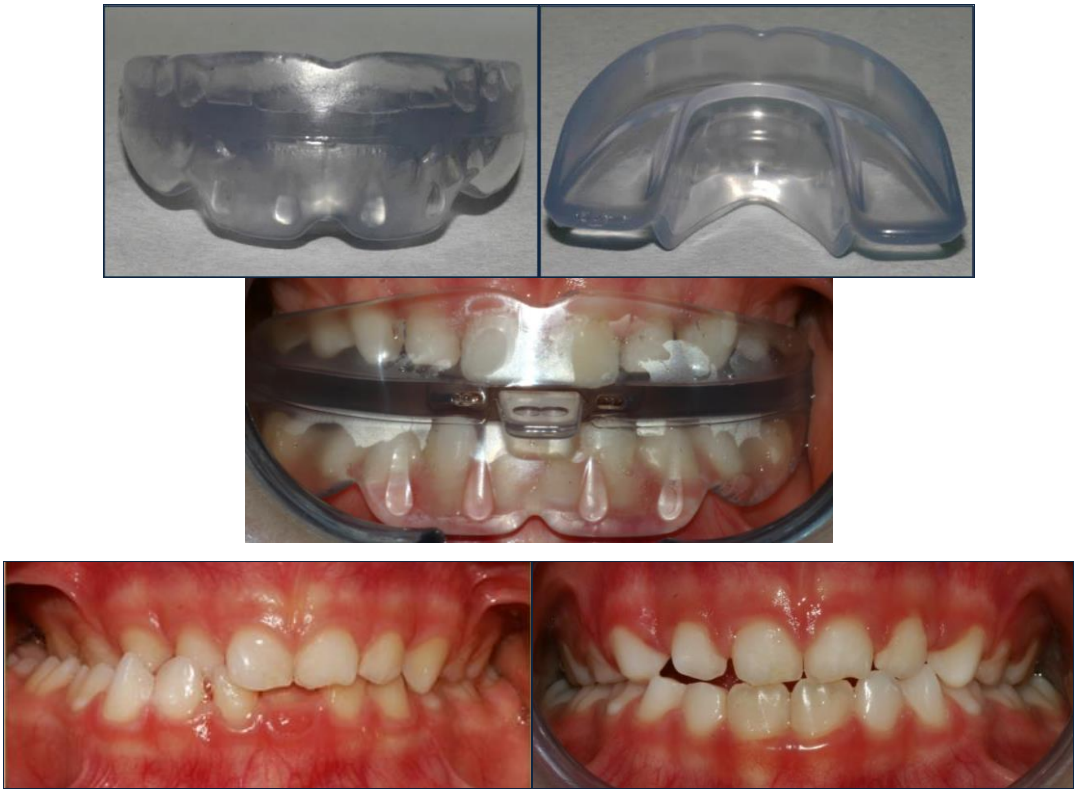

Fig. 2.4 Prefabricated Myofunctional Appliance (PMA). Top left: The PMA presents frontal bumpers that stretch the lower lip away from the lower incisors. Top right: The PMA has a lingual flange to avoid tongue thrusting, and double occlusal paths for the dentition. Central: PMA worn by the patient (EF line®, Orthoplus, France). Bottom left: posterior left crossbite in a 6-year-old girl. Bottom right: the same patient after 8 months of treatment with a PMA (EF Start®, Orthoplus, France).

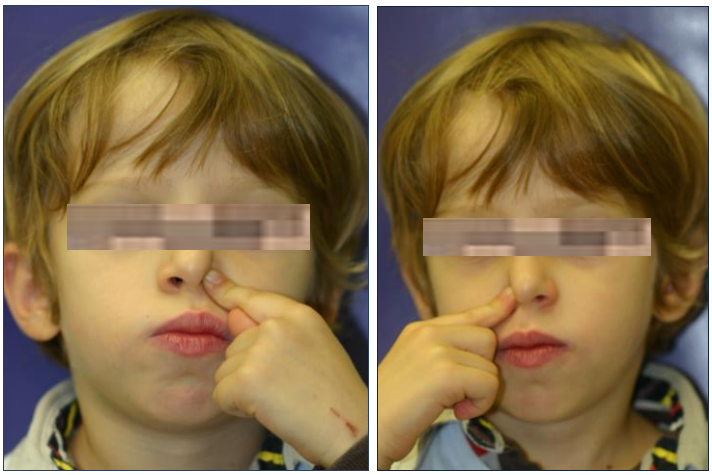

Fig. 2.5 Sensorial stimulation of nasal breathing. The patient is asked to alternatively close one nostril and breathe through the other one while maintaining the mouth closed and avoiding oral breathing. The session is supervised by a guardian at home who can actively maintain the mouth closed.

Oropharyngeal exercises improve the labial seal and lip tone and improve the tension and activity of the oropharyngeal muscles by working on several functions such as breathing, sucking, chewing, blowing, speaking, and swallowing (Fig. 2.6). (32,33)
In a recent study undertaken by Levrini et Al., myofunctional therapy performed with oral devices was studied for the treatment of children with mild-to-moderate OSAS: a significant decrease of AHI was observed in the 3-month follow-up. (62)

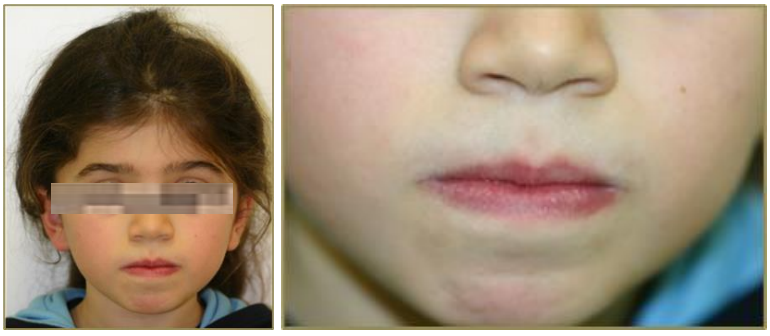

Fig. 2.6 Myofunctional exercises: the monkey exercise. The patient is asked to fill the lower lip with air for one minute. This exercise is indicated in children with lower lip trap.

2.5 Limits and side effects of orthodontic treatment in SRBD

Overall, orthodontic treatment is well tolerated in children with SRBD and is a valid alternative to more invasive and less acceptable tools such as c-PAP. Minor and temporary side effects were reported such as excessive salivation, tooth and/or masticatory muscle pain, and discomfort with wearing the oral appliance: all these complaints usually self-resolve after 1-2 weeks and are limited with proper counselling. (34,62)

Although many investigations have been performed, evidence on the effectiveness of orthodontic treatment on children with abnormal breathing during sleep is modest: this is mainly due to the poor quality of the studies, and a high heterogeneity of clinical protocols and outcomes used for benefits assessment.

Orthodontic treatment is more often used as a complementary therapy to adenotonsillectomy and/or a second treatment option for residual SRBD/OSAS in children. (33)

RME and functional appliances alone proved to be effective in relieving signs and symptoms of children with OSAS in some studies, but in others they were not curative, and it was necessary to recur to tonsil and adenoid surgery to reach complete restoration of normal nocturnal breathing. (34,62)

The effect of orthodontic treatment on snoring and quality of life is also a topic of interest that requires more investigation.

A limitation of mandibular advancement devices is the high cooperation required by the patients and possible side effects on the teeth and periodontium. (57,58,66) It must be said that serious and permanent side effects on the teeth and gums are more likely in adults due to the inevitable aging of these structures.

Chapter 3
Research study

3.1 Introduction and Rationale of the study

Sleep-Related Breathing Disorders (SRBD) is a general term that refers to a continuing spectrum of clinical entities, in which intermittent partial (hypopnea) or complete (apnea) upper airway obstruction during sleep occurs.(1,2) They are characterized by snoring, respiratory effort and sleep disruption with or without hypoventilation and alteration in oxygen (SaO2) and carbon dioxide (PCO2) blood levels.(1,2) SRBD are frequent in pre-school children with a prevalence of 11-24% for Primary Snoring, which is the mildest type, and of 1-5% for Obstructive Sleep Apnea Syndrome (OSAS), which is the most harmful entity. (2–5) Although adenotonsillectomy (AT) is still the first line of treatment for children with abnormal breathing during sleep, its application is limited by surgical risks and a high prevalence of recurrence ranging between 30 and 50%.(11,12,38) Based on these considerations, alternative and/or complementary treatment options to AT have been advocated especially in SRBD, as opposed to OSAS and/or mild-to-moderate OSAS where benefits of AT are questioned.(34)

Craniofacial anomalies are recognised risk factors for both the onset and recurrence of SRBD and OSAS, particularly in those malocclusions associated with mandibular retrusion, mandibular hypoplasia, and narrow maxilla.(9,34) They can reduce the volume of oral and nasopharyngeal cavities and promote tongue falling into the oropharynx during the night.(5) Moreover, SRBD are frequently associated with oral dysfunctions such as oral breathing, visceral swallowing, and speech disturbances that are considered risk factors for the development of malocclusion. The effectiveness of orthodontic treatment in children with mild-to-moderate OSAS was investigated in the short-term follow-up study, but there is still no conclusive evidence. (5,34,61,62)

Among the wide variety of oral devices that have been proposed for the treatment of childhood SRBD, Preformed Myofunctional Appliances (PMA) are of particular interest for their ease of use and low cost. PMA are single block preformed devices made of soft silicon material, available in gradual sizes and different models, and

simultaneously act on the upper and lower jaws. They are used to promote nasal breathing, correct tongue posture, and regular soft tissue activity while improving overjet, overbite, and slightly enhancing skeletal mandibular growth. (65,67–69) PMA proved to produce mild-to-moderate dento-skeletal changes while correcting oral habits and re-educating oral functions. (70)

The present study aims to evaluate the effectiveness of PMA in children affected by SRBD and/or mild-to-moderate OSAS and the associated outcomes on oral functions and cranio-facial structures.

3.2 Materials and Methods

3.2.1 Study objectives

The primary outcomes were:

- frequency of oral dysfunctions and occlusal anomalies.
- signs and symptoms of risk for SRBD and OSAS, measured with a validated tool (the Sleep Clinical Score, SCS).
- Apnea/Hypopnea Index (AHI), Oxygen Desaturation Index (ODI), and total sleep time spent with SaO2 < 90% (T90), measured objectively using nocturnal polygraphy.

The secondary outcomes were:

- frequency of sleep and neuro-behavioral disturbances, assessed using validated scales (the Sleep Disturbances Scale for Children, SDSC; the Child Behavior Checklist, CBCL).
- changes in dento-skeletal variables and upper airway dimensions, measured on lateral cephalogram.
- changes in upper and lower dental arches, measured *via* a digital morphometric analysis of dental casts.

3.2.2 Participants and settings

The study took place between November 2018 and October 2021 and was conducted at the Department of Pediatric Dentistry and the Sleep Medicine Center of ASST Santi Paolo e Carlo Hospital, Milan, Italy. The study protocol was carried out in accordance with the Ethical Principles for Medical Research Involving "Human Subjects", adopted by the Helsinki Conference, June 1964, and informed consent was obtained from each participant's parents.

3.2.3 Recruitment

Participants were recruited from among those patients reporting snoring, restless sleep, or apnea (≥ 3 nights a week) and referred for malocclusion and/or oral-facial dysfunctions.

Clinical history was obtained from parent/guardian interviews during which they were also administered a questionnaire about the child's health problems, use of medications, and occurrence of mouth breathing, sucking and/or harmful habits, speech defects, allergies, snoring, tonsillitis, or stuffy nose, among others.

All eligible patients underwent a thorough orthodontic, ENT and neurological physical examination that comprised clinical interviews, dental casts, lateral cephalograms, anterior rhinoscopy and otoscopy, and nasal fibroscopy.

All children underwent a home-based unattended overnight cardiorespiratory polygraphy at baseline to grade SRBD according to a standardized protocol (see Material and Methods).

Patients were enrolled if they met the following inclusion criteria:

- aged less than 6 years old.
- SRBD or mild-to-moderate OSAS (AHI<5), with no previous treatment in the past 6 months or recurrence after AT.
- presence of malocclusion with evident alteration of overjet, overbite and/or presence of posterior/anterior crossbite.
- presence of at least one oral dysfunction such as oral breathing, atypical swallowing, lip strain, hypotonia of the lips, hypertonia of mental muscle.

Patients presenting at least one of the followings were excluded:

- severe OSAS (AHI>5).
- Mallampati Tonsil Size score equal to 4.
- Hereditary and/or acquired cranio-facial syndromes.
- Acute and/or chronic upper airway infections.
- Major cardio-vascular, pulmonary, or neuromuscular disorders.
- Body Mass Index (BMI) ≥ 85° percentile.

3.2.4 Study design

This study was carried out as a before and after comparison study.

Within the framework of this study, primary and secondary outcomes were grouped consistently, and all participants underwent the following:

- Baseline (T0): sleep pattern assessment, cardiorespiratory polygraphy, orthodontic clinical assessment, cephalometric and dental measurements.
- 12-month follow-up (T1): sleep pattern assessment.
- 18-month follow-up (T2): orthodontic clinical assessment, cephalometric and dental measurements.

Patients who were diagnosed with OSAS underwent an additional mid-term cardiorespiratory polygraphy after 6 months of treatment.

3.2.5 Sleep pattern assessment

The following scales and questionnaires validated in 3-to-6-year-olds were collected for all participants at baseline (T0) and after 12 months (T1) of treatment:

- the Sleep Clinical Record (SCR);(26)
- the Sleep Disturbance Scale for Children (SDSC);(71)
- the Child Behaviour Checklist (CBCL);(72)

The SCR is a PSG-validated tool developed by Villa et al. in 2013 to assess OSAS risk in children.

SCR consists of three items that yielded data from clinical examinations, patient's history, and neuro-behavioral assessments (see Appendix 1). The first item reports

data regarding ENT and orthodontic examinations such as: presence of oral dysfunctions (oral breathing, nasal obstruction), malocclusion (deepbite, retrusive bite, narrow palate, facial phenotype); assessment of nostril patency, grading of adenoid and tonsil hypertrophy, palate position according to the Friedman classes, and BMI (see Appendix 1.1).(26) The second item investigates the patient's subjective symptoms and their clinical history based on the Brouillette questionnaire regarding weekly occurrence of apnea, snoring, agitated sleep, or daytime headache.(25) The response to each question can be "yes" or "no", then the Brouillette score is calculated. A score equal to or higher than −1 is considered positive (see Appendix 1.1). The third item investigates the presence of symptoms of ADHD *via* the ADHD Rating Scale adapted to the Italian population: it consists of 18 items grouped into two sections named "Scale A" for attention deficiency and "Scale B" for hyperactivity (see Appendix 1.2).(73) Responses to each question indicate how frequently a particular symptom occurs: "never", "sometimes", "often", "very often". A score equal to or higher than 14 is considered positive.
The results of the three items are converted using a fixed factor and then summed up to obtain the final SCS score (see Appendix 1.3). SCS > 6.5 have an 89% positive predictive value for OSAS.

SDSC is a questionnaire that assesses quality of sleep, occurrence of sleep disorders and comorbidities such as obesity, ADHD, epilepsy and/or cerebral palsy (see Appendix 2).(71) It consists of 26 items that assess the occurrence of various sleep disorders in the last 6 months (sleep initiation and maintenance, sleep disordered breathing, disorders of arousal, sleep awake transition disorders, disorders of excessive somnolence and sleep hyperhidrosis).(23,71) Responses to each question are scored on a 5-point Likert scale (1=never; 2=rarely, one or two times per month; 3=sometimes, one or two times per week; 4=often, three or four times per week; 5=every day).(23,71)
SDSC ≥ 70 is considered from borderline up to pathological.

CBCL were developed by Achenbach et al. in 1991 to assess children's mental health and social functioning. (72) The CBCL for 3-to-5 year-old children consists of

100 items grouped into 8 syndromic scales which include anxiety, aggression, social problems, and depression. (72)
CBCL ≥ 65 is considered from borderline up to pathological.

All children underwent sleep studies at baseline (T0), while only OSAS children underwent it again after 6-months to verify changes in respiratory patterns.
A sleep study was performed with a home-based unattended overnight cardiorespiratory polygraphy. A portable sleep monitoring unit was used (Embletta®, Natus Neurology Incorporated, Ontario, Canada) and parents were instructed on proper positioning. The polygraphy was repeated if less than 85% of total recording time was of good quality and/or temporary loss of more than one channel occurred (except for nasal airflow).
Multi-channel derivations were recorded continuously during night sleep: nasal airflow, pulse oximetry, snoring, body position, chest and abdominal effort, heart rate, and haemoglobin oxygen saturation ($HbSaO_2$). Parents were properly instructed on how to position the device, and tracing was checked to verify appropriate recording: in case of doubt, the exam was repeated. Sleep variables were scored according to standard definitions reported by previous studies.(74,75) The following variables were considered for the purpose of the study: Apnea/Hypopnea events per hour (AHI), Oxygen Desaturation Index (ODI), and total sleep time spent with arterial oxygen saturation SaO2 < 90% (T90).

The sleep/behavioral questionnaires and cardiorespiratory polygraphy were evaluated by the specialized Pediatric Sleep Medicine team which consisted of a trained Neurologist, Neuropsychiatrist, and Neurophysiopathology technician.

3.2.6 Orthodontic clinical assessment

The orthodontic examination covered an oral function evaluation, extraoral and intraoral findings, and patient and parent interviews.
All participants underwent a thorough orthodontic examination at T0 and T2, and routine clinical check-ups during orthodontic treatment every 4-6 weeks.

Functional assessment was performed with the patient sitting in a comfortable position, with head straight. The following functional findings were assessed: habitual lip and perioral muscle posture; tongue, lip, and perioral muscle activity during swallowing; respiratory pattern at rest; respiratory tests including dental mirror test and reflex of the alar muscles; speech tests. According to chair-side evaluations, patients were diagnosed with nasal or mouth breathing; normal or atypical swallowing; normal or abnormal tongue posture; tongue thrusting; normal, hypotonic, or hypertonic perioral muscle tone; lower lip trap; competent or incompetent lip closure; absence or presence of oral habits; absence or presence of speech defects. Presence and number of oral-facial dysfunctions were recorded.

Intraoral orthodontic findings were reported as presence of overjet/overbite alterations and posterior crossbites. Overjet and overbite measurements were taken directly in the mouth of the patient with a metal calliper at T0 and T1. Overjet was defined as: "normal", when within 0−3 mm; "increased", if more than 3 mm; "decreased", if less than 0 mm. Overbite was defined as: "normal", when within 1−2 mm; "deepbite", if more than 2 mm; "openbite", if less than 1 mm. Presence of posterior crossbite was diagnosed when the buccal cusps of at least 2 posterior maxillary teeth were > 0 mm lingual to the buccal cusps of the opposing teeth.

Patient's compliance and any adverse effects that occurred during orthodontic treatment were recorded at the routine check-ups based on participant and parents/guardian interviews, and then confirmed at the clinical examination if a visible change in the color of the appliance and presence of gum, oral mucosa or tongue abrasion or decubitus ulcer occurred.

3.2.7 Cephalometric measurements

Baseline (T0) and 18-month (T2) lateral cephalograms at natural head position were obtained using the same X-ray machine (Orthophos® XG 5/Ceph, Sirona Dental System GmbH, Bensheim, Germany). Cephalometric tracings were digitally performed using Ortho TP® software (Microlab, Vimercate, Italy). A custom cephalometric analysis consisting of 18 landmarks, 10 angular and 15 linear

measurements was used to assess skeletal and dento-alveolar relationships, pharyngeal upper airway (PAS) dimensions and hyoid bone position as previously described by other authors (Fig. 3.1, Table 3.1). (76–79)

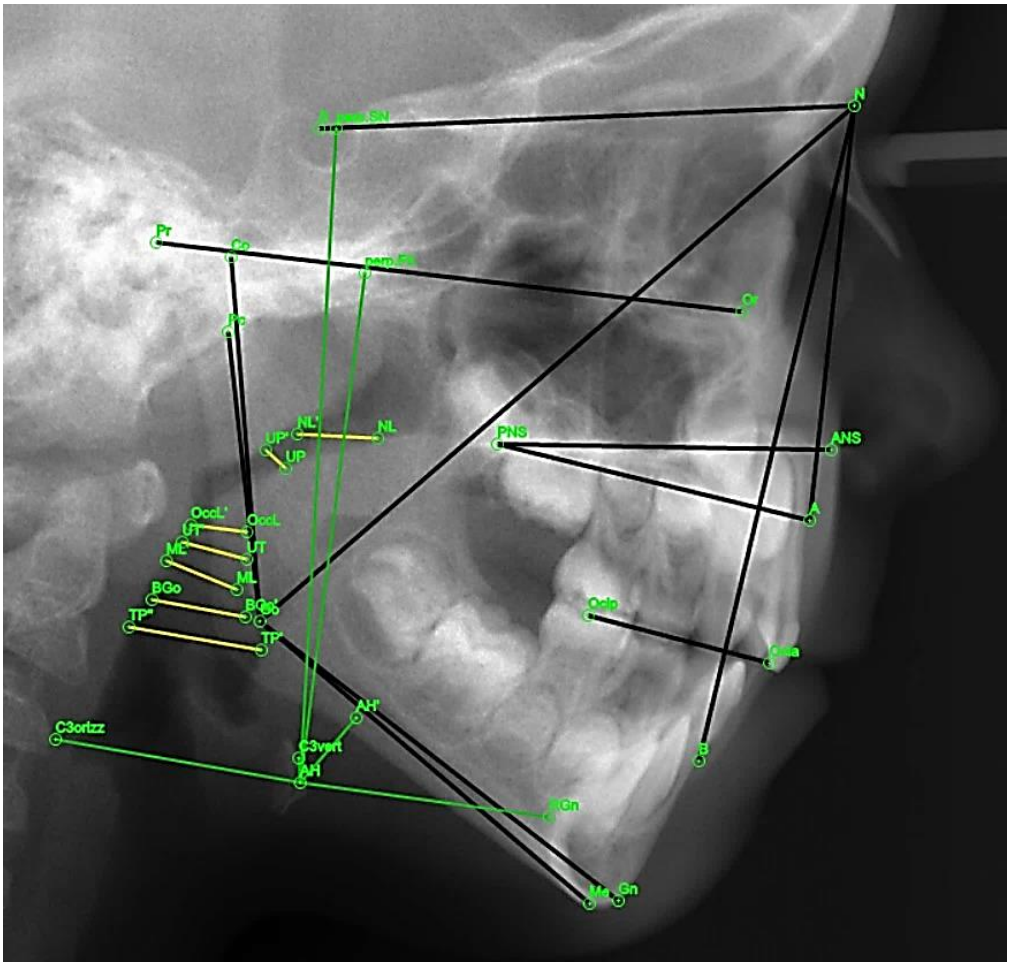

Fig. 3.1 Landmarks and reference lines used in the cephalometric analysis. Definitions of skeletal landmarks: N-Nasion, S-Sella, A-Subspinal, B-Submental, Pc-Condilar, Co-Condylion, Go-Gonion, Me-Menton, Gn-Gnation, Pr-Porion, Or-Supraorbital, ANS-Anterior nasal spine, PNS-Posterior nasal spine, AH-Anterior superior hyoid bone, AH'-Hyoid Bone perpendicular to mandibular plane, RGn-Retrognation, perp.SN-Intersection of AH perpendicular to SN, perp.FK-Intersection of AH perpendicular to Frankfurt Plane (Or-Pr). Definition of PAS reference lines: PAS-NL (NL-NL'), PAS-UP (UP-UP'), PAS-OccL (OccL-OccL), PAS-UT (UT-UT), PAS BGo (BGo-BGo'), PAS-ML (ML-ML'), PAS-TP (TP-TP').

Table 3.1 List of linear and angular measurements made on lateral cephalograms to evaluate modifications to the skeletal and dento-alveolar relationships, PAS dimensions and hyoid bone position in the sagittal plane induced by PMAs in children affected by SRBD and OSAS.

Abbreviation	Definition
Sagittal skeletal relationship	
SNA (°)	Sagittal position of the maxilla
SNB (°)	Sagittal position of the mandible
ANB (°)	Sagittal relationship between the maxilla and the mandible
SNP−A (mm)	Maxillary Length
Go−Me (mm)	Mandibular Length
Vertical skeletal relationships	
SN/GoGN (°)	Inclination of the mandible to the anterior cranial base
SN/SNPSNA (°)	Inclination of the maxilla to the anterior cranial base
SNPSNA/GoGn (°)	Intermaxillary angle
Craniofacial growth pattern	
PcGoGn (°)	Total gonial angle
NGoGn (°)	Lower gonial angle
PcGoN (°)	Upper gonial angle
Co−Go−Me (°)	Condylion – Gonion – Menton angle
Pharyngeal Airway Space (76–78)	
PAS−NL (mm)	Pharyngeal airway space along SNP-SNA line
PAS−UP (mm)	Minimal pharyngeal airway space between the uvula and the posterior pharyngeal wall
PAS−OccL (mm)	Pharyngeal airway space on occlusal line
PAS−UT (mm)	Minimal pharyngeal airway space between the uvula tip and the posterior pharyngeal wall
PAS–Bgo (mm)	Pharyngeal airway space on B-Go line
PAS–ML (mm)	Pharyngeal airway space on mandibular line
PAS−TP (mm)	Minimal pharyngeal airway space between the back of the tongue and the posterior pharyngeal wall
Hyoid Bone (79)	
AH−AH’ (mm)	Vertical distance from hyoid bone to mandibular plane
AH−RGn (mm)	Horizontal distance from hyoid bone to retrognation
AH−FH (mm)	Perpendicular line from hyoid bone to Frankfort Horizontal
AH−SN (mm)	Perpendicular line from hyoid bone to cranial base
AH−C3 ORIZZ. (mm)	Horizontal distance from hyoid bone to third cervical vertebra
AH−C3 VERT. (mm)	Vertical distance from hyoid bone to third cervical vertebra

3.2.9 Dental measurements

Baseline (T0) and 18-month (T2) digital dental casts in maximum intercuspal position were obtained. Eight landmarks were located on the digital dental casts using Mirror® Vectra Software (Canfield Scientific, Fairfield, NJ) and 4 linear measurements were calculated, 2 for each dental arch: inter-canine width and inter-premolar width (Fig. 3.2, Table 3.2).

Inter-canine width was measured as the linear distance between the crown tips of the primary canine. Inter-premolar width was obtained by measuring the distance between the centroid on the occlusal surface of the second primary molars and its antimere (Fig. 3.2, Table 3.2).(80) The centroid was visually identified on 3D models as the point of intersection of two lines, one passing through the facial-medial and the linguo-distal crown tips and one through the facial-distal and the palatal/lingual-mesial crown tips of the upper and lower second primary molars.

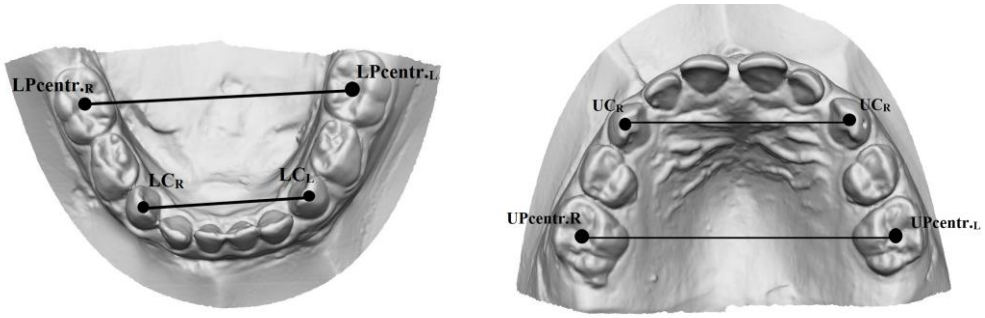

Fig.3.2 Landmarks and linear measurements evaluated on digital dental casts using Mirror® Vectra Software (Canfield Scientific, Fairfield, NJ). LPcentr.$_R$, Lower Posterior Centroid Right; LC$_R$, Lower Canine Right; LPcentr.$_L$, Lower Posterior Centroid Left; LC$_L$, Lower Canine Left; UPcentr.$_R$, Upper Posterior Centroid Right; UC$_R$, Upper Canine Right; UPcentr.$_L$, Upper Posterior Centroid Left; UC$_L$, Upper Canine Left.

Table 3.2 List of linear measurements made on digital dental casts to evaluate arch width modifications after orthodontic treatment with PMAs in children affected by SRBD and OSAS.

Abbreviation	**Definition**
LC$_R$-LC$_L$	Lower Inter-canine width
LPcentr.$_R$-LPcentr.$_L$	Lower Inter-premolar width (80)
UC$_R$-UC$_L$	Upper Intercanine width
UPcentr.$_R$-UPcentr.$_L$	Upper Inter-premolar width (80)

3.2.10 Treatment protocol

Each participant underwent orthodontic treatment with a PMA for 18 months in accordance with a clinical protocol previously validated over a sample of 5 patients followed for 6 months.

All children received orthodontic treatment with EF Start® (EF Line®, Orthoplus, Igny, France), a PMA made of medical PVC. EF Start® is a removable device and has lingual flanges to avoid tongue thrusting, drop-shaped bumpers to condition activity of the lips, slight upper and lower indentation in the inter-canine segment, and double occlusal paths that stretch away the cheeks and the tongue.

Participants were instructed to wear the appliance at night-time and during the daytime for 2 hours which were divided into 3-4 sessions lasting 20-30 minutes each. When using the appliance during the daytime, patients were asked to alternatively bite the device while keeping lips in contact and perform myofunctional exercises to enhance the restoration of normal patterns of swallowing, nasal breathing, and tongue and peri-oral muscle activity (see Appendix 3). The active treatment period lasted for at least 12 months to guarantee full recovery of oral functions. Then the appliance was worn only at night-time for a following 6-month retention.

3.2.11 Blinding

All sleep records, questionnaires, and cephalometric and dental measurements were performed by blinded outcome assessors who were not aware of and were not involved in the participants' treatment.

Two trained operators performed all measurements on lateral cephalograms and dental casts.

3.2.12 Method error

Intra-class correlation coefficients (ICC) with 95% CI based on a two-way random effects model were calculated to determine intra-operator and inter-operator reliability for six repeated (at 3-week intervals) digitized measurements of dental casts and lateral cephalograms (n=20).

Intra- and inter-operator agreements were also calculated using a Bland-Altman analysis. An *a priori* intra-operator limit of agreement was set at 0.5 mm for dental

cast measurements, and at 2 degrees and 2 mm for angular and linear cephalometric measurements respectively. An *a priori* inter-operator limit of agreement was set at 1.5 for dental cast measurements, and at 3 degrees and 3 mm for angular and linear cephalometric measurements respectively.

3.2.13 Data collection and statistical analysis

Based on sample size calculations, a sample of at least 9 participants was necessary to allow a 90% chance of detecting a difference of 1.0 unit for sleep parameters between T0 and T1 time points, considering a double-tailed test, a power of 0.95, and a significance level (alpha) of 0.05.

Data were input into a Microsoft Excel® 2020 spreadsheet (Microsoft Corporation, Washington, USA) and statistical analysis was performed using GraphPad Prism® Version 9.3.0 (© 1995-2021 GraphPad Software, LLC). Means and standard deviations were calculated for continuous variables at T0, T1, and T2. The D'Agostino-Pearson and Shapiro-Wilk tests were used to check for normal distribution of the data. Given the non-normal distribution, variables were analysed with non-parametric tests. Differences between pre-treatment (T0), 12-month (T1) and 18-month (T2) follow-ups were analysed using the Wilcoxon matched-pair signed rank test. Subgroup comparisons between SRBD non-OSAS and OSAS children were performed at T0, T1, and T2 using the Mann-Whitney signed rank test. The Chi-square test was used to perform multiple comparisons of categorical variables. Fisher's exact test was performed when a cell had a value of less than 5. The significance level was set at $p < 0.05$.

3.3 Results

Twelve consecutive patients (4 females, 8 males) aged 5.0±0.47 years were initially recruited for the study. One child refused to wear the appliance and was therefore excluded after 2 months and considered as a drop-out (Fig. 3.3). The final sample consisted of eleven patients (4 females, 7 males) aged 5.04±0.60 years who underwent orthodontic treatment with PMAs and completed the 18-month follow-up study (Fig. 3.3).

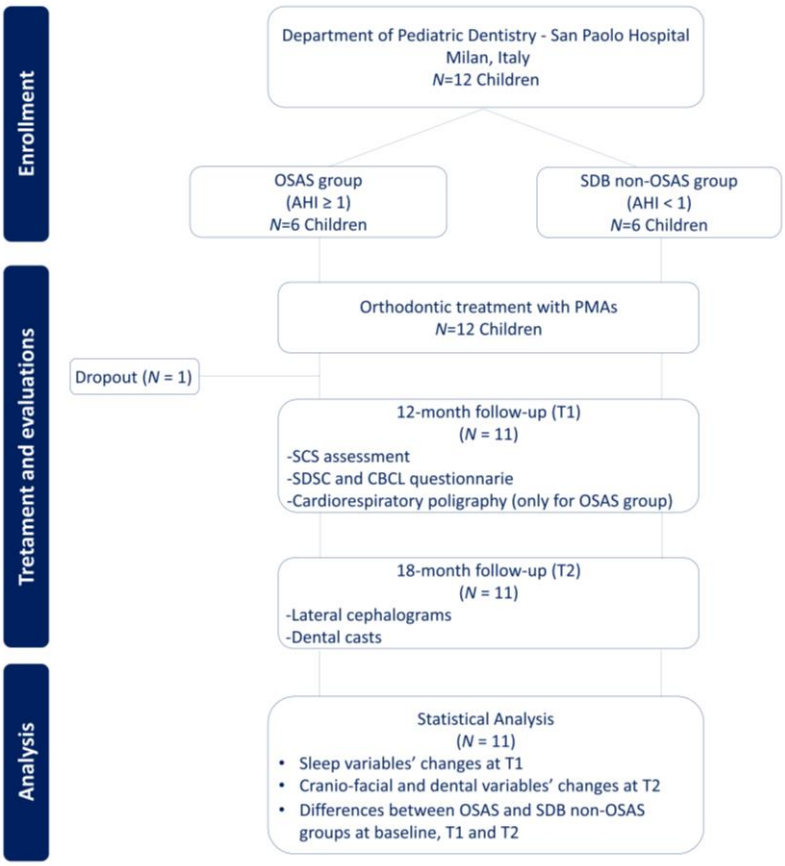

Fig. 3.3 Study Flow chart

3.3.1 Results of sleep pattern assessment

The mean Sleep Clinical Score (SCS) was high at baseline and significantly decreased (p<0.001) after 12 months (Table 3.3). However, the mean SCS was still above the range of normal values (cut-off = 6) at T2. The reduction of the SCS was mainly due to a reduction in frequencies of malocclusion, in adenoid and tonsil hypertrophy, in hyperactivity symptoms and due to an increase in day-time concentration.

The mean Sleep Disturbances Scale for Children (SDSC) score was "borderline" at baseline and significantly decreased (p<0.01) after 12 months of treatment (Table 3.3). A general reduction in occurrence of parasomnia and disorders of sleep initiation and maintenance was responsible for SDSC improvement.

The mean Child Behavior Checklist (CBCL) score was "normal" at baseline, but

Table 3.3 Mean values (in scores) and standard deviations of SCS, SDSC and CBCL in the study sample (*N*=11) of children affected by SRBD and OSAS at baseline (T0) and after 12 months of treatment (T1). The Wilcoxon test was used for comparison between T0 and T1.

	Baseline (T0)	**12-month (T1)**	*P* value
	(Mean±SD)		
SCS score	18.52±3.48	13.20±2.98	***
SDSC score	43.45±4.17	39.64±5.20	**
CBCL score	31.91±4.95	28.18±5.33	**

Definition of abbreviations: SD= standard deviation; ns= not significant
* p<0.05; ** p<0.01; *** p<0.001

significantly decreased (p<0.01) at T1 because of a reduction in symptoms of anxiety and depression (Table 3.3).

OSAS children showed significantly (p<0.05) higher SCS and CBCL scores compared to SRBD non-OSAS children at baseline, while no significant differences were detected at T1 (Table 3.6). SDSC scores were not significantly different between OSAS and SRBD non-OSAS children at T0 and T1 (Table 3.4).

All the five children affected by OSAS normalized their AHI, ODI, and T90 after 6 months at the mid-term cardiorespiratory monitoring (data not in tables).

Table 3.4 Mean values (in scores) and standard deviations of SCS, SDSC, and CBCL in OSAS (*N*=5) and SRBD non-OSAS (*N*=6) subgroups at baseline (T0) and after 12 months of treatment (T1). The Mann-Whitney test was used for comparison between OSAS and SRBD non-OSAS subgroups at T0 and T1.

	OSAS	**SRBD non-OSAS**	*P* value
	(Mean±SD)		
SCS score			
Baseline (T0)	21.05±2.48	16.42±2.76	*
12-month (T1)	13.65±3.41	12.83±2.86	ns
SDSC score			
Baseline (T0)	41.80±2.77	44.83±5.77	ns
12-month (T1)	37.40±4.04	41.50±5.65	ns
CBCL score			
Baseline (T0)	35.20±3.11	29.17±4.62	*
12-month (T1)	30.60±6.88	26.17±2.85	ns

Definition of abbreviations: SD= standard deviation; ns= not significant

*p<0.05

3.3.2 Results of orthodontic clinical assessment

Demographic and orthodontic characteristics at baseline were slightly different between OSAS and SRBD non-OSAS subgroups, but not significantly ($p>0.05$), as displayed in Table 3.5.

All children recovered from oral dysfunctions after 18 months of treatment ($p<0.001$) as shown in Table 3.6. Most children displayed alterations in overjet/overbite (Table 3.4): the most frequent types were increased overjet (55%) and openbite (55%). A reduction in frequencies of malocclusion was observed at the T0-T2 interval, but was not significant.

Table 3.5. Frequencies of malocclusion traits and Oral-facial dysfunctions in OSAS (*N*=5) and SRBD non-OSAS (*N*=6) subgroups at baseline (T0). Fisher's exact test was used to compare frequency distributions between OSAS and SRBD non-OSAS at T0.

	OSAS	**SRBD non-OSAS**	*P* value
	Frequency n (%) *		
Sex			
Female	0 (0%)	4 (67%)	ns
Male	5 (100%)	2 (33%)	
Overjet			
Increased Overjet	2 (40%)	4 (67%)	ns
Normal	3 (60%)	2 (33%)	
Overbite			
Deepbite	1 (20%)	2 (33%)	
Openbite	3 (60%)	3 (50%)	ns
Normal	1 (20%)	1 (17%)	
Posterior crossbite			
Present	2 (40%)	2 (33%)	ns
Absent	3 (60%)	4 (67%)	
Oral-facial dysfunction (n)			
1 dysfunction	1 (20%)	2 (33%)	
2 dysfunctions	1 (20%)	3 (50%)	ns
≥ 3 dysfunctions	3 (60%)	1 (17%)	
Adenotonsillectomy (AT)			
Yes	1 (20%)	0 (0%)	ns
No	4 (80%)	6 (100%)	

Definition of abbreviations: SD= standard deviation; ns= not significant

*Data are expressed as a percentage of the total category subject (OSAS vs. SRBD non-OSAS)

Table 3.6 Frequency of malocclusion traits and Oral-facial dysfunctions in the study sample (*N*=11) of children affected by SRBD and OSAS at baseline (T0) and after 18 months of treatment with PMAs (T2). Fisher's exact test was used to compare frequency distributions between T0 and T2.

	Baseline (T0)	**18-months (T2)**	*P* value
	Frequency n (%) *		
Overjet			
Increased Overjet (>3 mm)	6 (55%)	4 (36%)	ns
Normal Overjet (0-3 mm)	5 (45%)	7 (64%)	
Overbite			
Deepbite (>3 mm)	3 (27%)	1 (9%)	
Openbite (<1 mm)	6 (55%)	4 (36%)	ns
Normal Overbite (1-2 mm)	2 (18%)	6 (55%)	
Posterior Crossbite			
Present	4 (36%)	3 (27%)	ns
Absent	7 (64%)	8 (73%)	
Oral-facial dysfunction			
1 dysfunction	3 (28%)	0 (0%)	
2 dysfunctions	4 (36%)	0 (0%)	<0.001 ***
≥ 3 dysfunctions	4 (36%)	0 (0%)	
Absent	0 (0%)	11 (100.00%)	

Definition of abbreviation: ns= not significant
* Data are expressed as a percentage of the total category subject (Baseline–18-months)
*** p<0.001

Overall, children tolerated the treatment well reporting only minor and temporary side effects such as excessive salivation (45.45%), masticatory muscle pain (9.10%), and discomfort at wearing the oral appliance (72.72%). All the above-mentioned side effects lasted briefly and were solved within the first month of treatment, except for the one drop-out.

3.3.3 Results of cephalometric and dental measurements

Intra-operator reliability ICC values were excellent: 0.967 for SNA ($_{95\%}$ CI = 0.917-0.9879), 0.996 for SNB ($_{95\%}$CI = 0.99-0.999), 0.999 for PAS-NL ($_{95\%}$CI = 0.997-0.999), 0.926 for AH-RGn ($_{95\%}$CI = 0.823-0.97), 0.998 for inter-canine width ($_{95\%}$CI = 0.995-0.999), and 0.998 for inter-premolar width ($_{95\%}$CI = 0.995-0.999). Inter-operator reliability ICC values were 0.988 for SNA ($_{95\%}$CI = 0.969-0.995), 0.985 for SNB ($_{95\%}$CI = 0.964-0.994), 0.99 for PAS-NL ($_{95\%}$CI = 0.975-0.996), 0.995 for AH-

RGn ($_{95\%}$CI = 0.988-0.998), 0.991 for inter-canine width ($_{95\%}$CI = 0.978-0.996), and 0.985 for inter-premolar width ($_{95\%}$CI = 0.949-0.995), indicating excellent reliability among operators. Inter and intra-operator agreements were good to excellent. Mean biases were close to zero and ranged from −0.31 to 0.25 mm/degrees; 95% limits of agreement were within those *a priori* clinical limits defined for dental cast measurements (from -0.37 to 1.32 mm), and for linear (from -0.35 to 1.12 mm) and angular (from -0.31° to 1.48°) cephalometric measurements (Table 3.7).

Sagittal and vertical skeletal and dento-alveolar relationships were little affected by orthodontic treatment: mean changes in T0-T2 were less than 1.5-2 degrees, which can be considered clinically irrelevant (Table 3.8).

Regarding cranio-facial growth pattern, the Co-Go-Me was significantly ($p<0.05$) reduced by an average of 2.5 degree at T2 while the other variables remained substantially unchanged (Table 3.8). Maxillary and mandibular length significantly ($p<0.001$) increased at T2 by an average of 2 mm and 6 mm, respectively (Table 3.8).

All pharyngeal airway space widths increased significantly ($p<0.01$), except for PAS-OccL, by an average 2-3 mm after 12 months (Table 3.8).

All hyoid bone variables increased, particularly AH−FH and AH−SN (mm) which showed a significant ($p<0.001$) increase of 10 mm at T1 (Table 3.8).

No differences were seen between OSAS and SRBD non-OSAS subgroups at T0 and T2 for all cephalometric variables (Table 3.9).

Table 3.7 Bland-Altman analysis for intra and inter-operator agreement (n=20) for cephalometric and dental measurements. All measurements were within the limit of agreements established at baseline.

	Intra-operator			**Inter-operator**		
		95% w/in limits of agreement			*95% w/in limits of agreement*	
	Mean bias	Lower	Upper	Mean bias	Lower	Upper
Inter-canine width	0.01	−0.48	0.49	0.13	−0.94	1.20
Inter-premolar width	0.05	−0.37	0.47	−0.31	−1.32	0.69
SNA	0.25	−0.99	1.48	0.14	−0.62	0.89
SNB	0.09	−0.31	0.48	0.11	−0.74	0.96
PAS-NL	0.03	−0.35	0.40	0.14	−0.85	1.12
AH-RGn	0.18	−0.62	0.97	0.10	−0.64	0.84

Table 3.8 Mean values (in mm or degrees) and standard deviations of cephalometric variables in the study sample (*N*=11) of children affected by SRBD and OSAS at baseline (T0) and after 18 months of treatment with PMAs (T2). The Wilcoxon test was used to compare T0 and T2.

Cephalometric variables	Baseline (T0) (Mean±SD)	18-month (T2) (Mean±SD)	*P* value
Sagittal relationship			
SNA (°)	81.76±2.31	80.33±2.67	**
SNB (°)	78.35±3.10	77.53±2.93	ns
ANB (°)	3.41±2.23	2.86±2.36	ns
Vertical relationships			
SN/GoGN (°)	34.08±3.92	35.95±4.07	*
SN/SNPSNA (°)	6.03±2.30	7.20±3.20	ns
SNPSNA/GoGn (°)	28.05±5.34	28.75±4.48	ns
Craniofacial growth pattern			
PcGoGn (°)	132.50±6.61	130.90±3.63	ns
NGoGn (°)	73.57±3.14	74.74±2.94	ns
PcGoN (°)	58.95±5.34	56.15±3.66	*
Co−Go−Me (°)	126.36±5.15	123.84±3.80	*
Maxillary length			
SNP−A (mm)	39.08±1.83	41.43±2.55	***
Mandibular length			
Go−Me (mm)	53.46±4.07	59.54±3.47	***
Pharyngeal Airway Space			
PAS−NL (mm)	9.58±3.63	13.69±2.35	***
PAS−UP (mm)	4.11±1.70	7.19±1.30	***
PAS−OccL (mm)	8.40±2.56	10.24±2.36	ns
PAS−UT (mm)	7.44±3.14	10.28±2.45	**
PAS−Bgo (mm)	8.61±2.65	10.47±3.00	**
PAS−ML (mm)	8.71±3.20	10.86±3.15	***
PAS−TP (mm)	8.26±3.00	9.90±3.06	**
Hyoid Bone position			
AH−MP (mm)	11.87±3.39	14.74±3.35	*
AH−RGn (mm)	29.55±4.08	31.19±3.98	ns
AH−FH (mm)	59.98±3.90	69.17±4.81	***
AH−SN (mm)	78.02±5.07	88.65±7.47	***
AH−C3 ORIZZ. (mm)	28.11±4.93	30.55±4.05	*
AH−C3 VERT. (mm)	4.66±3.40	6.38±7.80	ns

Definition of abbreviations: SD= standard deviation; ns= not significant
* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Table 3.9 Mean values and standard deviations of cephalometric variables in treated OSAS (*N*=5) and SRBD non-OSAS (*N*=6) subgroups at baseline (T0) and after 18 months of treatment (T2). The Mann-Whitney test was used to compare the OSAS and SRBD non-OSAS subgroups at T0 and T2.

	Baseline (T0)			*18-month (T2)*		
Cephalometric variables	**OSAS**	**SRBD non−OSAS**	*P* value	**OSAS**	**SRBD non−OSAS**	*P* value
	(Mean±SD)			(Mean±SD)		
Sagittal relationship						
SNA (°)	82.16±2.50	81.43±2.32	ns	80.00±3.40	80.60±2.20	ns
SNB (°)	79.10±2.47	77.72±3.63	ns	77.42±1.90	77.62±3.78	ns
ANB (°)	3.06±1.78	3.70±2.68	ns	2.72±2.20	2.97±2.71	ns
Vertical relationships						
SN/GoGN (°)	34.96±2.19	33.35±5.05	ns	36.62±3.03	35.40±4.91	ns
SN/SNPSNA (°)	5.58±2.64	6.40±2.12	ns	6.04±4.34	8.17±1.66	ns
SNPSNA/GoGn (°)	29.38±4.03	26.95±6.39	ns	30.60±3.83	27.20±4.69	ns
Craniofacial growth pattern						
PcGoGn (°)	133.40±4.66	131.80±8.28	ns	130.7±4.37	131.10±3.31	ns
NGoGn (°)	73.96±2.10	73.25±4.00	ns	74.78±3.11	74.70±3.09	ns
PcGoN (°)	59.38±5.47	58.58±5.72	ns	55.88±4.82	56.37±2.86	ns
Co−Go−Me (°)	126.40±3.84	126.30±6.42	ns	124.00±3.77	123.7±4.16	ns
Maxillary length						
SNP−A (mm)	39.64±1.79	38.62±1.89	ns	42.50±3.47	40.53±1.13	ns
Mandibular length						
Go−Me (mm)	54.26±5.42	52.80±2.90	ns	59.88±2.52	59.25±4.33	ns
Pharyngeal Airway Space						
PAS−NL (mm)	9.44±3.45	9.70±4.10	ns	13.48±2.37	13.74±2.83	ns
PAS−UP (mm)	4.68±1.96	3.63±1.45	ns	7.38±1.60	7.03±1.13	ns
PAS−OccL (mm)	8.60±3.24	8.23±2.15	ns	10.28±2.30	10.20±2.62	ns
PAS−UT (mm)	7.96±3.77	7.00±2.79	ns	10.14±3.22	10.40±1.91	ns
PAS−Bgo (mm)	8.72±3.38	8.52±2.21	ns	10.24±3.89	10.67±2.41	ns
PAS−ML (mm)	8.64±3.93	8.77±2.86	ns	10.48±4.01	11.18±2.58	ns
PAS−TP (mm)	8.66±3.52	7.93±2.77	ns	9.68±3.55	10.08±2.92	ns
Hyoid Bone position						
AH−MP (mm)	13.14±4.60	10.82±1.78	ns	14.76±3.66	14.72±3.43	ns
AH−RGn (mm)	30.56±4.31	28.70±4.07	ns	31.40±3.37	31.02±4.75	ns
AH−FH (mm)	62.40±3.92	57.97±2.73	ns	70.44±5.29	68.12±4.58	ns
AH−SN (mm)	80.90±5.89	75.62±2.88	ns	90.16±8.71	87.40±6.84	ns
AH−C3 ORIZZ. (mm)	29.50±7.32	26.95±1.52	ns	31.12±5.33	30.07±3.07	ns
AH−C3 VERT. (mm)	6.02±4.16	3.53±2.41	ns	6.96±6.31	5.90±9.45	ns

Definition of abbreviations: SD= standard deviation; ns= not significant

Inter-canine width significantly increased both in the mandible (p<0.001) and in the maxilla (p<0.05) by an average of 2.5-3 mm; inter-premolar width increased significantly only in the maxilla (p<0.001) by an average of 1.5 mm (Table 3.10).
None of the dental variables showed significant differences between OSAS and non-OSAS patients at baseline and at T2 (Table 3.11).

Table 3.10 Mean values (mm) and standard deviations of dental measurements performed on the dental casts of the study sample (*N*=11) of children affected by SRDB and OSAS at baseline (T0) and after 18 months of treatment (T2). The Wilcoxon test was used to compare T0 and T2.

Dental variables		**Baseline (T0)** (Mean±SD)	**18-month (T2)** (Mean±SD)	*P* value
Mandible	*Inter – canine*	22.85±2.68	26.17±1.68	***
	Inter – premolar	35.18±1.68	35.54±2.48	ns
Maxilla	*Inter – canine*	27.06±2.67	29.75±4.02	*
	Inter – premolar	36.59±3.82	38.09±3.98	***

Definition of abbreviations: SD= standard deviation; ns= not significant
* p<0.05; *** p<0.001

Table 3.11 Mean values (mm) and standard deviations of dental measurements performed on the dental casts of treated OSAS (*N*=5) and SRBD non-OSAS (*N*=6) subjects at baseline (T0) and after 18 months of treatment (T2). The Mann-Whitney test was used to compare the OSAS and SRBD non-OSAS subgroups at T0 and T2.

Dental variables		**OSAS** (Mean±SD)	**SRBD non-OSAS** (Mean±SD)	*P* value
Mandible	**Inter – canine**			
	Baseline (T0)	24.26±3.08	21.68±1.77	ns
	18-month (T2)	26.86±2.27	25.59±0.83	ns
	Inter – premolar			
	Baseline (T0)	35.48±2.04	34.94±1.46	ns
	18-month (T2)	35.83±2.71	35.31±2.50	ns
Maxilla	**Inter – canine**			
	Baseline (T0)	27.46±2.99	26.72±2.61	ns
	18-month (T2)	30.22±4.77	29.36±3.70	ns
	Inter – premolar			
	Baseline (T0)	37.58±4.63	35.76±3.19	ns
	18-month (T2)	38.69±4.92	37.59±3.39	ns

Definition of abbreviations: SD= standard deviation; ns= not significant

3.4 Discussion

Significant improvements in sleep and orthodontic patterns were observed in the present study: orthodontic treatment with PMAs performed in pre-schooled children may produce significant cranio-facial and dental changes that might aid in improving SRBD and mild-to-moderate OSAS.

Signs and symptoms of respiratory impairment improved after 12 months of treatment with PMAs, as revealed by the significant reduction in mean Sleep Clinical Score (SCS) ($p<0.001$) in the whole sample. Moreover, OSAS participants completely recovered from apnea episodes at the 6-month cardiorespiratory monitoring session. It should be noted that the mean SCS did not completely normalize and residuals were present after 12 months of treatment. These results confirm that orthodontic treatment may be effective in reducing signs and symptoms of abnormal nocturnal breathing, but it is unlikely curative and should be considered as part of a multidisciplinary approach, as reported by other authors.(34,62,81)

In the present sample, all participants except one did not undergo an adenotonsillectomy before the study's inception and a general reduction of adenoid and tonsil hypertrophy was reported at the ENT examination after 12 months. Orthodontic treatment may have improved pharyngeal airway flow by stimulation of nasal breathing and this could have helped in reducing inflammation and bacterial colonization (32,62).

Based on these findings, orthodontic treatment could therefore be considered before or immediately after AT to reduce surgical risks, improve respiratory patterns, and limit the recurrence of SRBD in the long-term.(11,40)

This is the first study investigating the effects that orthodontic treatment has on the sleep quality and neuro-behavioral patterns of children affected by SRBD and OSAS, to the author's best knowledge.

Sleep quality and neuro-behavioral patterns improved as revealed by the significant reduction in mean SDSC and CBCL scores after 12 months ($p<0.01$). Overall, the frequency of parasomnias, disturbances of sleep initiation and maintenance, and signs and symptoms of anxiety and depression perceived by the children's parents/guardians decreased after treatment. Even if SDSC and CBCL values were

not completely pathological at baseline, their reduction suggests that somehow they were altered and treatment improved them. These findings suggest that orthodontic treatment with PMAs may lead to multiple clinical benefits and positive outcomes for children's wellbeing.

Oral functions significantly improved and a notable, though not significant, reduction of occlusal anomalies occurred after 18 months of treatment: all children recovered from oral dysfunctions and most of them also reached acceptable occlusal relationships. The current body of evidence suggests that oral dysfunctions impair the growth of the oral cavity and promote the development of malocclusion.(82–84) These findings suggest that PMAs are effective tools for oral myofunctional therapy and may aid in restoring the physiological development of the jaw and dentition, as already reported in other studies. (85–87)

Success in harmonizing oral functions was indubitably influenced by the high cooperation rate of the participants involved in the study. Only one child dropped-out, as opposed to significant poor compliance rates reported in other studies.(32,33) Conventional myofunctional therapy is based on the concept that active exercises must take place and requires high patient and parent engagement and cooperation. PMAs act as an active training device to perform tongue and lip exercises in the day-time and as a passive continuous inducer of normal tongue positioning and nasal breathing at night-time.(85) This may have optimized patient's time and effort, as already suggested in previous studies which reported shorter treatment time when myofunctional therapy was associated to the use of an oral device.(69,85,88) The characteristics of the PMAs and the study setting may also have helped in achieving good cooperation: children tolerated the prefabricated oral device well since it is soft and comfortable compared to resin-based devices; treatment providers were all highly specialized and skilled dentists who routinely perform early orthodontic treatment, and children were checked-up at short time intervals of 4-6 weeks.

Cranio-facial growth patterns changed after orthodontic treatment, as revealed by the significant mean reduction of the Condylion-Gonion-Menton (Co-Go-Me) angle ($p<0.05$).

Co-Go-Me is commonly used to accurately evaluate mandibular rotational patterns since it is strongly related to mandibular morphology (the condylar axis and

mandibular plane) and hence it is not influenced by sagittal relationships and/or external structures.(89,90) Co-Go-Me values increase in hyperdivergent facial patterns that are frequently present in SRBD and OSAS children as a consequence of oral breathing and abnormal tongue posture.(5,34,89,90) The persistence of oral breathing during sleep leads to abnormal craniofacial and airway development.(30) The clinically significant reduction of 2.5 degrees, on average, in the Co-Go-Me angle might be considered a positive outcome of myofunctional therapy with PMAs: the oral environment improved and, accordingly, posterior rotational growth of the mandible was reduced. PMAs may be therefore effective in improving oral functions and craniofacial growth patterns in pre-schoolers with abnormal sleep breathing.

This finding is corroborated by the significant increase of 6 mm, on average, in mandibular length ($p<0.001$): PMAs enhanced and positively affected mandibular growth. One explanation for this successful result could be that the juvenile growth spurt occurred during treatment and thus increased the extent of clinical outcomes.(68,91)

Pharyngeal Airway Space (PAS) widths significantly increased ($p<0.01$) after 18 months of treatment, and this is consistent with respiratory findings reported after 12 months.

Patients with SRBD and OSAS usually display narrow PAS widths at cephalometric evaluation when compared to controls: the increase in PAS sagittal dimensions could help to improve airway patency.(2,92) These findings should be considered with caution since lateral cephalograms provide only bi-dimensional assessments and do not permit conclusions on the functionality of upper airways to be made.(2,27,93)

The hyoid bone moved downward and forward after treatment, as revealed by the significant increase in AH-FH, AH-SN, AH-MP and AH-C3 ORIZZ. distances.

In OSAS and SRBD children a distal and cranial position of the hyoid bone is present compared to controls.(59) This is due to alterations in activity of the upper airway muscles: negative airway pressure rises quickly during inspiration and the genioglossus muscle, which is the principal upper airway dilator, is not able to properly widen the PAS for adequate ventilation during sleep.(20) The forward and downward movement of the hyoid bone may represent a sign of reduction in negative

airway pressure and of increased efficiency of the airway dilator muscles including the genioglossus and suprahyoid muscles.

The position of the hyoid bone is strictly related to the position of the tongue by means of extrinsic and intrinsic tongue muscles: the hyoid bone shift seen in the present study likely contributes to forward the tongue and to prevent its collapse over the posterior pharyngeal wall during sleep.(20,59)

The dental arches were measured *via* morphometric analysis by means of digital technology as this improves measurement accuracy and allows for more precise and reliable assessments.(94) The dental arches were significantly affected by treatment with PMAs, particularly in the anterior region as revealed by the 2.5-3 mm expansion at the inter-canine level both in the mandible ($p<0.001$) and the maxilla ($p<0.05$).

Expansion of the dental arches is a favorable outcome in children with SRBD and OSAS, who are usually affected by a narrow maxilla and crowding.(95) PMAs used in primary and early mixed dentition feature tissue-borne anchorage systems such as buccal flanges and lingual ramps, that stretch away and screen buccinator and orbicularis muscles, and force the tongue into a slight backward and upward position over the premaxilla.(96) Expansion with elastodontic appliances is mainly induced by its myofunctional activity with little-to-negligible effects induced by direct orthopedic and/or orthodontic forces, as already observed with other functional appliances.(97,98) Functional re-education of the tongue and perioral soft tissue might therefore be able to restore correct tongue positioning and perioral muscle activities that ultimately remove any constriction to the development of the dental arches.(65,99)

A subgroup comparison between OSAS and SRBD non-OSAS children showed no significant differences at baseline and at the follow-ups. The exception being that mean SCS and CBCL scores at baseline were significantly higher in the OSAS group. This is not surprising since greater respiratory and neuro-behavioral impairment is expected in OSAS compared to other SRBD. Nevertheless, this difference was resolved after treatment.

Limitations of this study are the small sample size and the lack of a control group that would have allowed any spontaneous improvement to be detected and any modifications induced by growth and therapy to be differentiated.

It must be said that self-correction of SRBD and OSAS in children is unlikely according to existing evidence; the same applies for malocclusion associated with oral dysfunctions other than oral sucking habits.(87,100,101)

The results of the present study can be compared with those reporting changes in cephalometric and dental arch parameters in growing non-treated subjects. Previous studies which provide data on participants who were matched according to sex, age, and origin (north European) to those of our sample report the following changes during growth: Co-Go-Me reduction of approximately 1 degree/year; mandibular length increase of 2 mm/year; maxillary length increase of 1 mm/year, PAS width increase of 0.5-1.5mm/year; hyoid bone descent and anterior move of 3 mm/year and 0.3 mm/year respectively, and an inter-canine width increase of 0.6-0.8 mm/year.(102,103) Within the limits of comparing samples derived from different populations and time periods, these comparisons strengthen the results of the present study: changes occurring after treatment with PMAs were always bigger than those expected as a result of physiological cranio-facial development. These findings should be confirmed with further randomized controlled studies and a larger sample size.

Cranio-facial skeletal structures and pharyngeal widths were assessed on a lateral cephalogram which is a bi-dimensional method. This represent a limitation since anatomical structures are superimposed, soft tissue contrast is poor, and head posture might change overtime: this makes it difficult to classify different structures, to delineate soft tissue, and to obtain comparable images overtime. The application of 3D imaging would have overcome these limits, but their use was limited by ethical and radiological protection concerns related to higher X-ray exposition in young growing subjects. A very systematic protocol was used to obtain comparable X-ray images overtime: the same X-ray equipment was used, X-rays were performed by the same radiologist technician, and cephalograms were performed by the same operators on digital tracings to improve comparability and accuracy.

3.5 Conclusion

Cranio-facial and dental changes during orthodontic treatment with PMAs may improve signs and symptoms of SRBD and mild-to-moderate OSAS in pre-school aged children, as revealed by:

- the significant reduction in signs and symptoms of SRBD and in frequencies of sleep disturbances and neuro-behavioral impairments.
- the normalization of AHI, ODI, and T90 in mild-to-moderate OSAS.
- the significant increase in pharyngeal airway widths, mandibular length, and inter-canine widths.
- the significant improvement in mandibular rotational growth patterns and hyoid bone position.

Further studies are needed to confirm these findings and assess long-term stability.

Acknowledgments

These three years spent working on my PhD were particularly tough yet exciting at the same time, an undertaking which was also possible thanks to those who were by my side in this adventure.

I thank Prof. Eugenio Romeo and Prof. Massimo Del Fabbro for their kindness and for the precious advice they gave me.
I am particularly grateful to Prof. Maria Grazia Cagetti and Prof. Guglielmo Campus for involving me in their group, teaching me how to do good research, and always encouraging me.
I would like to acknowledge Prof. Laura Strohmenger: I will be forever grateful to her for the opportunities she gave me throughout the almost ten years we have being working together.
A special acknowledgement goes to prof. Chiarella Sforza for the time she granted me and for her wise teachings and suggestions.
I thank Prof. Maria Paola Canevini and Dr. Elena Zambrelli for their precious work and cooperation which has made this work possible.
I thank Debby Brecht for her precious work in the revision of my thesis.

A grateful acknowledgement goes to all the colleagues, residents, and students of the Pediatric Dentistry Department of San Paolo Hospital, who helped me over the years.
I also thank my PhD colleagues and all the members of the Council of Doctoral Students with whom I shared experiences, doubts, and fears: this made me feel part of a community. I learned a lot and enjoyed it.

I thank my mother Gemma, my father Roger, and my sisters, Anahid and Victoria Lucine, for always having encouraged and supported me.

Finally, I thank my husband Boštjan - who became my strength and my best friend – immensely.

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List of abbreviations

- **AHI:** apnea/hypopnea index
- **CBCL:** child behavior checklist
- **CI:** confidence intervals
- **CPAP:** continuous positive airway pressure
- **CT:** computer tomography
- **DISE:** drug-induced sleep endoscopy
- **ENT:** ear nose and throat
- **ICC:** intraclass correlation coefficients
- **MRI:** magnetic resonance imaging
- **MT:** myofunctional therapy
- **ODI:** oxygen desaturation index
- **OMT:** oral myofunctional therapy
- **OSAS:** obstructive sleep apnea syndrome
- **PCO_2:** blood carbon dioxide saturation
- **PAS:** pharyngeal airway space
- **PMA:** prefabricated myofunctional appliance
- **RME:** rapid maxillary expansion
- **SaO_2:** blood oxygen saturation
- **SCS:** sleep clinical score
- **SRBD:** sleep-related breathing disorders
- **SDSC:** sleep disturbances scale for children

Appendix

Appendix 1

Sleep Clinical Record and Sleep Clinical Score from Villa et al. (26)

Appendix 1.1 First and second items of the Sleep Clinical Record reporting ENT and orthodontic examination charts and Brouillette score calculation algorithm.

Sleep Clinical Record

DATE:

Patient

Date of birth_____

Age (years)_____ Weight (Kg)_____ Height (Cm)_____

BMI (Kg/h)_____percentile BMI_____

Age at symptom onset (years):_____Duration of disease (years):_____

Name:_____ Surname_____

NOSE

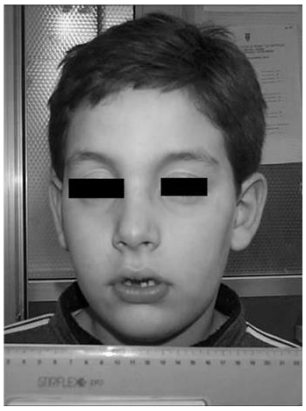
1) Septum nose deviation: YES/NO

2) Nasal cartilage hypotonia (see figure below): YES/NO

3) Orbicular muscle hypotonia (see figure below): YES/NO

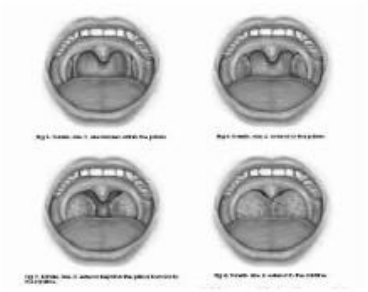
4) Nasal airway patency: YES/NO
Perform the "sniff test": obstruction of nasal airflow is based on physical examination by audible nasal congestion as a patient inhales forcibly 4 times through the right and left nostril, while the clinician compresses the contralateral nostril.

5) Habitual nose obstruction: Has your child an history of stuffy nose over the last 3 months, for 3 or more days per week?: YES/NO

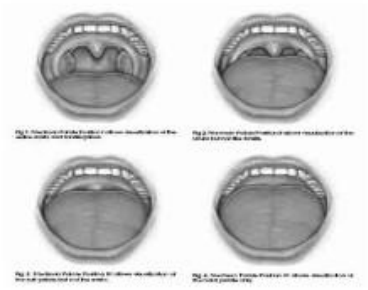


OROPHARYNX

TONSILLAR SIZE
I-II: no tonsillar hypertrophy
III-IV:yes tonsillar hypertrophy



FRIEDMAN PALATE POSITION
I-II: no, III-IV: yes



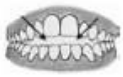
DENTAL / SKELETAL OCCLUSION

1. ANGLE CLASS

- I class (normal occlusion)
- II class (Retrognatic)
- III class (Prognatic)

2.BITE

OPEN-BITE



DEEP-BITE

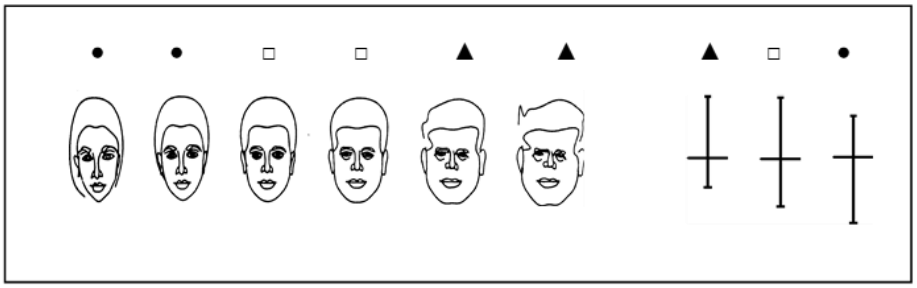
CROSS-BITE

3.OVERJET

4. NARROW PALATE
YES/NO

PHENOTYPE

- **adenoid phenotype: score 1**
- **□ normal: score 0**
- **▲ adult type: score 1**



Brouillette ** (AMERICAN ACADEMY OF PEDIATRICS Technical Report: Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome, Pediatrics 2002)

- **A** witnessed apneic episodes (0=NO; 1=YES);
- **S** habitual snoring (0=NEVER or OCCASIONALLY; 1=OFTEN or ALWAYS)
- **D** frequent awakenings or agitated sleep (0=NEVER; 1=OCCASIONALLY; 2=OFTEN; 3=ALWAYS)

1.42D +1.41A+0.71S-3.83=……..

negative: if <-1 positive: ≥-1 e ≤ 2.55

Appendix 1.2 Third item of the Sleep Clinical Record assessing symptoms of ADHD.

DSM IV: Modificato da: DMS IV APA 1995 e Scale SDAG Cornoldi, Gardinale, Masi, Pettenò 1996

Indicare con crocetta la casella che meglio descrive questo bambino in rapporto a coetanei dello stesso sesso.	**Mai**	**Qualche volta**	**Spesso**	**Molto spesso**
Scala A (Disattenzione)				
1. Incontra difficoltà nell'esecuzione di attività che richiedono una certa cura.	**0**	**1**	**2**	**3**
2. Ha difficoltà a mantenere l'attenzione nello svolgere incarichi, compiti o nelle attività varie, interrompendosi continuamente o passando ad attività differenti.	**0**	**1**	**2**	**3**
3. Quando gli si parla sembra non ascoltare.	**0**	**1**	**2**	**3**
4. Non segue fino in fondo le istruzioni e non porta a termine i compiti di scuola, le commissioni che deve fare o gli incarichi (ma non per comportamento oppositivo o incapacità a seguire le direttive).	**0**	**1**	**2**	**3**
5. Ha difficoltà a organizzarsi negli incarichi, nelle attività, nei compiti.	**0**	**1**	**2**	**3**
6. Evita, non gli piace o è riluttante ad affrontare impegni che richiedono uno sforzo mentale continuato (ad es. i compiti di scuola).	**0**	**1**	**2**	**3**
7. Non tiene in ordine le sue cose e perde spesso ciò che gli necessita per il lavoro o le attività (ad es. giocattoli, diario, matite, libri).	**0**	**1**	**2**	**3**
8. Si lascia distrarre facilmente da stimoli poco importanti.	**0**	**1**	**2**	**3**
9. E' sbadato, smemorato, nelle attività quotidiane.	**0**	**1**	**2**	**3**
Totale (pos ≥ 14)				
Scala B (Iperattività/Impulsività)				
1. Da seduto giocherella con le mani o con i piedi o non sta fermo o si dimena.	**0**	**1**	**2**	**3**
2. Lascia il suo posto in classe o in altre situazioni dove dovrebbe restare seduto.	**0**	**1**	**2**	**3**
3. Corre intorno e si arrampica di continuo, quando non è il caso di farlo (nell'adolescenza può trattarsi per lo più di irrequietezza).	**0**	**1**	**2**	**3**
4. Ha difficoltà a giocare o a intrattenersi tranquillamente in attività ricreative.	**0**	**1**	**2**	**3**
5. E' sempre "sotto pressione" o spesso si comporta come se fosse azionato da un motore.	**0**	**1**	**2**	**3**
6. Non riesce a stare in silenzio: parla troppo.	**0**	**1**	**2**	**3**
7. "Spara" le risposte prima che sia terminata la domanda.	**0**	**1**	**2**	**3**
8. Ha difficoltà ad aspettare il suo turno.	**0**	**1**	**2**	**3**
9. Interrompe o si intromette (per esempio nelle conversazioni o nei giochi degli altri).	**0**	**1**	**2**	**3**
Totale (pos ≥ 14)				

Appendix 1.3 Sleep Clinical Score algorithm.

SLEEP CLINICAL SCORE:

	0	1
ORAL BREATHING: Nasal cartilage hypotonia, muscles hypotonia	no	At least one yes
NASAL OBSTRUCTION: Nostril patency and habitual nose obstruction	no	At least one yes
	0	2
SEPTUM NOSE DEVIATION	no	Yes
TONSILLAR HYPETROPHY	no	Yes
DENTAL / SKELETAL MALOCCLUSIONs (Angle Class II, III; open-, deep-, cross-bite; overjet)	no	One or more maloccusions
FRIEDMANN PALATE POSITION	no	Yes
NARROW PALATE	no	Yes
PHENOTYPE	no	Yes
	0	0.5
[1]Other neurological symptoms (limb movements, EEG paroxysmal activity, daytime somnolence, headache, enuresis, nocturnal choking) and or positive ADHD rating scale	no	Yes
BROUILLETTE SCORE	negative	Positive
TOTAL SCORE		

[1]Daytime somnolence, enuresis and nocturnal choking according to International Classification of Sleep Disorders (2005)
[1]Headache: migraine or tension-type haedeache according to International Headache Society classification (2004).
[1]Limb movements: they are suspected when parents answer YES to one of the following questions with a frequency of one or more times per week: Does your child describe restlessness of the legs when in bed? Does your child have 'growing pains' that are worst in bed? At night, does your child usually get out of bed (for any reason)? Does your child wake up more than twice a night on average? Does your child wake up feeling unrefreshed in the morning? Does your child wake up with headaches in the morning?
[1]EEG paroxysmal activity: presence of spikes and/or sharp waves, either alone or accompanied by slow waves, occurring isolated or in bursts

Appendix 2

Sleep Disturbances Scale for Children sheet from Bruni et al. (71)

Appendix A. SLEEP DISTURBANCES SCALE FOR CHILDREN

***INSTRUCTIONS**: This questionnaire will allow to your doctor to have a better understanding of the sleep-wake rhythm of your child and of any problems in his/her sleep behaviour. Try to answer every question; in answering, consider each question as pertaining to the **past 6 months** of the child's life. Please answer the questions by circling or striking the number ① to ⑤.* Thank you very much for your help.

Name:_____ Age:_____ Date:_____

1. How many hours of sleep does your child get on most nights.	① *9-11 hours*	② *8-9 hours*	③ *7-8 hours*	④ *5-7 hours*	⑤ *less than 5 hours*
2. How long after going to bed does your child usually fall asleep	① *less than 15'*	② *15-30'*	③ *30-45'*	④ *45-60'*	⑤ *more than 60'*

					⑤ Always (daily)
				④ Often (3 or 5 times per week)	
			③ Sometimes (once or twice per week)		
		② Occasionally (once or twice per month or less)			
	① Never				
3. The child goes to bed reluctantly	①	②	③	④	⑤
4. The child has difficulty getting to sleep at night	①	②	③	④	⑤
5. The child feels anxious or afraid when falling asleep	①	②	③	④	⑤
6. The child startles or jerks parts of the body while falling asleep	①	②	③	④	⑤
7. The child shows repetitive actions such as rocking or head banging while falling asleep	①	②	③	④	⑤
8. The child experiences vivid dream-like scenes while falling asleep	①	②	③	④	⑤
9. The child sweats excessively while falling asleep	①	②	③	④	⑤
10. The child wakes up more than twice per night	①	②	③	④	⑤
11. After waking up in the night, the child has difficulty to fall asleep again	①	②	③	④	⑤
12. The child has frequent twitching or jerking of legs while asleep or often changes position during the night or kicks the covers off the bed.	①	②	③	④	⑤
13. The child has difficulty in breathing during the night	①	②	③	④	⑤
14. The child gasps for breath or is unable to breathe during sleep	①	②	③	④	⑤
15. The child snores	①	②	③	④	⑤
16. The child sweats excessively during the night	①	②	③	④	⑤
17. You have observed the child sleepwalking	①	②	③	④	⑤
18. You have observed the child talking in his/her sleep	①	②	③	④	⑤
19. The child grinds teeth during sleep	①	②	③	④	⑤
20. The child wakes from sleep screaming or confused so that you cannot seem to get through to him/her, but has no memory of these events the next morning	①	②	③	④	⑤
21. The child has nightmares which he/she doesn't remember the next day	①	②	③	④	⑤
22. The child is unusually difficult to wake up in the morning	①	②	③	④	⑤
23. The child awakes in the morning feeling tired	①	②	③	④	⑤
24. The child feels unable to move when waking up in the morning	①	②	③	④	⑤
25. The child experiences daytime somnolence	①	②	③	④	⑤
26. The child falls asleep suddenly in inappropriate situations	①	②	③	④	⑤
Disorders of initiating and maintaining sleep (sum the score of the items 1,2,3,4,5,10,11)					
Sleep Breathing Disorders (sum the score of the items 13,14,15)					
Disorders of arousal (sum the score of the items 17,20,21)					
Sleep-Wake Transition Disorders (sum the score of the items 6,7,8,12,18,19)					
Disorders of excessive somnolence (sum the score of the items 22,23,24,25,26)					
Sleep Hyperhydrosis (sum the score of the items 9,16)					
Total score (sum 6 factors' scores)					

Appendix 3

Oral Myofunctional Therapy (OMT) protocol

The following was the basic protocol for OMT which all patients performed during the study.

Patients were all asked to clean their nostrils before performing the myofunctional exercise and, if necessary, to clean them with nasal irrigation using a sterile physiological saline solution (0.9% NaCl).

First part

Exercises are repeated once for one session the first day and are then increased up to 10-12 times for two-three sessions. Exercises are repeated until the patient can wear the device for at least 1 minute, effortlessly and while nasal breathing.

1. Swallowing exercise: wear the PMA, elevate the pit of the tongue onto the palatal rugae, swallow saliva while keeping lips in contact.
2. Breathing exercise
    - Alar muscles stimulation: wear the PMA and massage the nostrils laterally and concurrently, while keeping lips in contact.
    - Alar muscles reflex stimulation: wear the PMA, maintain one nostril closed with a finger and breath through the other one, alternatively, while keeping lips in contact.

Second part

The exercises in the first session must be fully learned and well controlled before continuing. Exercises are repeated once for one session the first day and are then increased up to 12-15 times for two-three sessions.

1. Breathing exercises
    - Mirror exercise: wear the PMA, blow air out of the nose to mist up a mirror placed under the nose; try to increase the condensation area, gradually, over the mirror.
    - Tissue exercise: wear the PMA, blow air out of the nose and try to raise a tissue placed in front the nose as much as possible.
2. The monkey exercise: blow air into the lower lip, while mouth is closed, and keep it there for at least 10-12 seconds.

3. Pencil exercise n° 1: keep a pencil between the lips without dropping it.

Third part

The exercises in the previous sessions must be fully learned and well controlled before continuing. Exercises are repeated once for one session the first day and are then increased up to 12-15 times for two-three sessions.

1. Pencil exercise n° 2: keep a pencil between the lips, move it upward and downward without dropping it.
2. Tongue exercise n° 1: perform lingual snaps as loudly as possible.
3. Labial exercise: wear the PMA and send kisses while curling the lips.

Fourth part

The exercises in the previous sessions must be fully learned and well controlled before continuing. Exercises are repeated once for one session the first day and then increased up to 12-15 times for two-three sessions.

1. Tongue exercise n° 2: repeat at least 5 times the following words: “li”, “la”.
2. Tongue exercise n° 3: repeat at least 5 times the following words: “lalla”, “lilla”, “dadda”.
3. Labial exercise: wear the PMA and send kisses while curling the lips.

The treatment regimen must have been performed sequentially, without interruption. According to individual needs, the OMT protocol was adapted with the addition of further exercises to increase or decrease labial muscle tone and/or to treat complex visceral swallowing.

As part of OMT, parents/guardians were asked to gradually increase the consistency of food in the patient’s diet by adding small piece of celery, carrots or meat.