Tampere University

SAARA MARKKANEN

Children's Sleep Disordered Breathing, Tonsil Hypertrophy and Dentofacial Development

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To my sons

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ABSTRACT

Paediatric sleep disordered breathing (SDB) is a common cause of a visit to an otolaryngologist. The mildest form of paediatric SDB is primary snoring (PS) and it is estimated that up to 15% of all children snore frequently. The prevalence of paediatric obstructive sleep apnoea (OSA), which is thought to be more severe form of SDB, is suggested to be 1% to 5%. The pathophysiology of paediatric SDB is not fully understood, although tonsil hypertrophy is considered to be the primary pathophysiological factor. There is a distinct difference between paediatric and adult SDB, where overweight is a frequent but not the only cause. Furthermore, the symptoms and clinical features of SDB change along with growth. Paediatric SDB cannot be considered to be a stabile entity throughout childhood and adolescence. Therefore, it is important to obtain knowledge of the different features of children with SDB at different ages. Knowledge of these features enables early recognition and treatment and might prevent the long-term effects caused by poor sleep quality and increased night-time sympathicotonia. The consequences of SDB, such as behavioural and cognitive problems, poorer school performance, dentofacial morphology changes, growth impairment and cardiovascular effects, are widely recognised and studied.

The present study concentrates on SDB and OSA in two to three years old patients. Furthermore, a review and a meta-analysis of the contemporary literature on the influence of tonsillectomy and/or adenoidectomy (hereafter, tonsil surgery) on dentofacial development in children is included. These subjects integrate because tonsil surgery is a primary treatment method for paediatric OSA and paediatric OSA and SDB are connected to changes in dentofacial morphology.

In the present study, minor dentofacial morphology changes were already found in two to three years old children suffering from SDB. This is a significant finding because SDB has previously been associated with a variety of dentofacial morphology changes, and it could therefore be shown that these changes start to emerge at a young age. There is scarcity of previous studies which concentrate on patients this young, and therefore the results of the present study are notable. Furthermore, it was observed that total snoring time in polysomnography (PSG) was longer in children with OSA than in children with PS. The total snoring time is not

a well-researched parameter in paediatric SDB, and this finding can offer new opportunities when diagnosing paediatric OSA. In addition, it was observed that children with OSA were more likely to breathe through their mouth and have a larger adenoid size in contrast with children with PS. However, no difference in palatine tonsil size was found in this age group of two to three years old children.

A review and a meta-analysis of the contemporary literature of the influence of tonsil surgery on dentofacial development was conducted. The risk of bias in the review had to be considered high because the number of studies which fulfilled the inclusion criteria was low, the studies were methodically heterogenic, and the quality of the studies was moderate at best when estimating the risk of bias in individual studies. However, modest evidence that tonsil surgery has a positive effect on dentofacial development in children was found. The main finding in the review was that the growth direction of the mandible changed from vertical to more horizontal.

The findings of the studies in this dissertation add to the body of knowledge on paediatric SDB and OSA and their clinical and PSG features. Furthermore, they combine contemporary knowledge on SDB, mouth breathing, hypertrophied tonsils and dentofacial morphology. The evident strength of the studies is the young, two to three years old participants. There is a scarcity of knowledge of the consequences of SDB in this age group because most of the literature concentrates on older children or the age distribution in the studies is heterogeneous. Based on the results of this dissertation, it can be concluded that SDB symptoms in two to three years old children should be noticed and treatment opportunities considered because the first signs of long-term influences, such as changes in dentofacial morphology, could already be seen in this young age group. More research is needed to determine whether total snoring time could be a useful method in OSA diagnostics and whether adenoidectomy alone could be a sufficient treatment method for young OSA patients.

TIIVISTELMÄ

Lapsen kuorsaus on tavanomainen syy hakeutua korva-, nenä- ja kurkkutautilääkärin vastaanotolle. Unenaikaisen hengityshäiriön, jonka vaikeusaste vaihtelee säännöllisestä kuorsauksesta obstruktiiviseen uniapneaan, esiintyvyyden lapsiväestössä on arvioitu olevan 3 - 15%:a. Obstruktiivinen uniapnea todetaan noin 1-5 %:lla lapsista.

Lasten unenaikaisen hengityshäiriön tavanomaisin aiheuttaja on kita- ja nielurisojen liikakasvu. Aikuisilla keskeinen, joskaan ei ainoa, syy kyseisiin ongelmiin on ylipaino. Lasten unenaikaisen hengityshäiriön oireet ja löydökset eivät säily samankaltaisina läpi lapsuuden ja nuoruuden vaan ne muuttuvat kasvun myötä. Hengityshäiriön erityispiirteet eri-ikäisillä lapsilla on hyvä tuntea, jotta tila voitaisiin todeta ja hoitaa mahdollisimman varhaisessa vaiheessa. Varhaisella hoidolla pyritään ehkäisemään mahdollisia pitkäaikaishaittavaikutuksia, joita huonontunut unenlaatu ja lisääntynyt sympaattisen hermoston aktiivisuus aiheuttavat. Lasten unenaikaisen hengityshäiriön on todettu aiheuttavan muun muassa käytöshäiriöitä, kognitiivisen kehityksen häiriintymistä, huonontunutta koulumenestystä, kasvojen kasvun ja purennan kehityksen muutoksia, kokonaiskasvun hidastumista ja sydän-verisuonielimistön toiminnan muutoksia.

Tämä väitöskirja keskittyy unenaikaiseen hengityshäiriöön 2 – 3-vuotiailla lapsilla. Lisäksi väitöskirjaan sisältyy kirjallisuuskatsaus ja meta-analyysi kita- ja nielurisakirurgian vaikutuksista kasvojen ja purennan kehitykseen. Aihepiirit liittyvät toisiinsa, sillä kita- ja nielurisakirurgia on lasten obstruktiivisen uniapnean ensisijainen hoitomuoto. Lisäksi lasten unenaikaisella hengityshäiriöllä sekä kasvojen ja purennan kehityksen muutoksilla on aiemmassa kirjallisuudessa todettu selkeä yhteys.

Väitöskirjan tutkimuksissa havaittiin, että jo 2 – 3-vuotiailla unenaikaisesta hengityshäiriöstä kärsivillä lapsilla voidaan todeta vähäisiä muutoksia kasvojen mittasuhteiden kehityksessä. Tätä havaintoa voidaan pitää merkityksellisenä, sillä aiemmassa kirjallisuudessa unenaikainen hengityshäiriö on liitetty muutoksiin kasvojen ja purennan kehityksessä, ja nyt ensimmäisten muutosten havaittiin alkavan jo varhaisella iällä.

Lapsilla, joilla kuorsauksen lisäksi todettiin obstruktiivinen uniapnea, havaittiin pidempi kokonaiskuorsausajan kesto, kuin lapsilla, joilla todettiin ainoastaan kuorsausta. Kokonaiskuorsausaika on vähän tutkittu mittari lasten obstruktiivisen uniapnean diagnostiikassa. Tehty havainto voikin johtaa uusien diagnostiikkatapojen tutkimukseen ja kehitykseen. Lisäksi obstruktiivisesta uniapneasta kärsivillä lapsilla todettiin keskimäärin suurempi kitarisakoko ja useammin suuhengitystä kuin ainoastaan kuorsaavilla lapsilla. Nielurisojen koossa ryhmien välillä ei havaittu eroa.

Systemaattisessa kirjallisuuskatsauksessa löydettiin kohtalaista näyttöä kita- ja nielurisakirurgian suotuisasta vaikutuksesta lasten kasvojen mittasuhteiden ja purennan kehitykseen. Meta-analyysissa voitiin osoittaa kirurgian positiivinen vaikutus alaleuan kasvusuuntaan, joka vähensi kasvojen sivuprofiilin kuperuutta. Kirjallisuuskatsauksen luotettavuutta huononsivat vähäinen sisäänottokriteerit täyttävien tutkimusten määrä sekä matala kokonaispotilasmäärä. Lisäksi tutkimusten toteutustavat erosivat merkittävästi toisistaan ja yksittäisten tutkimusten laatu oli korkeintaan keskinkertainen.

Kokonaisuudessaan väitöskirja lisää tietoa lasten unenaikaisesta hengityshäiriöstä erityisesti vähäntutkitussa 2 – 3-vuotiaiden ikäryhmässä. Väitöskirjan tulosten perusteella voidaan todeta, että pienten lasten unenaikaiset hengityshäiriöoireet tulee huomioida ja hoitaa, sillä ensimmäisiä merkkejä pitkäaikaisvaikutusten ilmaantumisesta havaittiin jo tässä ikäryhmässä. Lisää tutkimusta tarvitaan kokonaiskuorsausajan käytöstä lasten unenaikaisen hengityshäiriön diagnostiikassa, sekä kitarisakirugian vaikuttavuudesta ainoana toimenpiteenä pienten lasten obstruktiivisen uniapnean hoidossa.

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ABBREVIATIONS

AHI	Apnoea-hypopnoea index
BMI	Body mass index
CPAP	Continuous positive airway pressure
NREM sleep	Non-rapid eye movement sleep
OAHI	Obstructive apnoea-hypopnoea index
OAI	Obstructive apnoea index
OSA	Obstructive sleep apnoea
PS	Primary snoring
PSG	Polysomnography
S%	Snoring time precentage from total sleep time
SDB	Sleep disordered breathing
SDSC	The Sleep Disturbance Scale for Children
REM sleep	Rapid eye movement sleep
UARS	Upper airway resistance syndrome

LIST OF ORGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I Niemi P, Markkanen S, Helminen M, Rautiainen M, Katila M, Saarenpää-Heikkilä O, Peltomäki T. Association between snoring and deciduous dental development and soft tissue profile in 3-year-old children. American Journal of Orthodontics and Dentofacial Orthopedics. 156(6);840-845, 2019.

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III Markkanen S, Rautiainen M, Himanen S-L, Satomaa A-L, Katila M, Peltomäki T, Saarenpää-Heikkilä O. Snoring toddlers with and without obstructive sleep apnoea differed with regard to snoring time, adenoid size and mouth breathing. Acta Paediatrica. 00:1-8, 2020.

IV Markkanen S, Rautiainen M, Niemi P, Helminen M, Peltomäki T. Is securing normal dentofacial development an indication for tonsil surgery in children? Systemic review and meta-analysis. International Journal of Pediatric Otorhinolaryngology. 133; 1100066, 2020.

The publications are referred to in the text by their roman numerals.

1 INTRODUCTION

Paediatric sleep disordered breathing (SDB) is a term used to describe children's upper airway dysfunction during sleep. It is characterised by snoring and/or increased respiratory effort in addition to increased upper airway resistance and pharyngeal collapsibility (Kaditis et al., 2016). SDB is a continuum from primary snoring (PS) to obstructive sleep apnoea (OSA). It is estimated that 3% to 15% of children snore frequently, and the prevalence of paediatric OSA is suggested to be 1% to 5% (Bixler et al., 2009; Liukkonen, Virkkula, Aronen, Kirjavainen, & Pitkäranta, 2008; Lumeng & Chervin, 2008; Marcus et al., 2012). The prevalence of snoring is challenging to determine because the definition of habitual snoring differs between studies. Furthermore, the diagnostic criteria for paediatric OSA have changed during recent decades. Nevertheless, SDB is not a rarity among children.

SDB disturbs a child's sleep and increases respiratory effort during sleeping time. Paediatric SDB, and especially OSA, is associated with various health consequences such as cognitive and neuropsychological problems, harmful cardiovascular effects and craniofacial and upper airway morphology changes (Gottlieb et al., 2004; Horne et al., 2011; Katyal et al., 2013; O'Brien et al., 2004; Xu, Li, & Shen, 2013). However, the diagnosis and treatment of SDB has been reported to have positive effects on these problems (Chervin et al., 2002; Gozal, 1998; Marcus et al., 2013). Hence, the early recognition and treatment of the condition is crucial. The gold standard method for the diagnosis is nocturnal laboratory polysomnography (PSG) (Aurora et al., 2011). However, due to the weak availability and high cost of paediatric PSG and the strain that in-hospital examination causes, the diagnosis of the condition is often made using anamnesis and clinical examination. Nevertheless, this practice has been proven to be inadequate in definitely identifying OSA (Brietzke, Katz, & Roberson, 2004; Carroll, McColley, Marcus, Curtis, & Loughlin, 1995).

Unlike in adult SDB in which obesity is a crucial pathophysiological factor, tonsil hypertrophy has been determined to be the primary cause of SDB in otherwise healthy children (Marcus et al., 2012). Furthermore, obesity, neuromuscular abnormalities and altered craniofacial morphology are also associated with SDB in children (Garg, Afifi, Garland, Sanchez, & Mount, 2017; Ikävalko et al., 2012; Katyal et al., 2013; Li et al., 2010; Verhulst et al., 2007). When tonsil hypertrophy is the main cause of SDB, the primary treatment modality is adenotonsillectomy (M. Friedman et al., 2009; Marcus et al., 2012, 2013). The treatment success of an adenotonsillectomy is estimated to be between 60% and 83% (Brietzke & Gallagher, 2006; M. Friedman et al., 2009). Consequently, persistent or recurrent symptoms after this primary treatment modality are frequent (Bhattacharjee et al., 2010; Ye et al., 2010). Other treatment modalities, such as orthodontic treatments, nasal corticosteroids, leukotriene antagonist and continuous positive airway pressure (CPAP), can be used if the results of the primary treatment are not sufficient, or the operation is not performed due to the small size of the tonsils or due to the risks involved in the operation related to the patient's pre-existing conditions (Brouillette et al., 2001; Machado-Júnior, Zancanella, & Crespo, 2016; Nazarali et al., 2015; Villa et al., 2007).

Dentofacial development, mouth breathing, tonsil hypertrophy and paediatric SDB have a multidirectional connection (Figure 1). Children with SDB aged 3 to 15 years have been observed to have changes in dentofacial morphology in contrast with healthy controls (Flores-Mir et al., 2013; Katyal et al., 2013), and children with hypertrophied tonsils or mouth breathing have been found to have similar unfavourable changes in dentofacial morphology (Becking et al., 2017; Peltomäki, 2007; Souki et al., 2009). Furthermore, mouth breathing and enlarged tonsils are more prevalent among children with SDB (Kang et al., 2016; Nieminen, Tolonen, & Lopponen, 2000). It is clear that enlarged tonsils cause upper airway narrowing which, in turn, can result in mouth breathing and SDB. To some extent, this can be thought of as being the daytime and night-time manifestations of the same condition. However, the connection between dentofacial morphology changes and paediatric SDB is more complex. After children with hypertrophied tonsils and SDB are treated with adenotonsillectomy, normalisation in dentofacial development, as in SDB, is seen (Zettergren-Wijk, Forsberg, & Linder-Aronson, 2006). This positive result indicates that tonsil hypertrophy and SDB can cause changes in dentofacial morphology. Furthermore, it has been speculated that not only enlarged tonsils but also, for example, SDB-induced impaired growth hormone secretion or changes in sleeping position can have an influence on dentofacial development in children with SDB (Peltomäki, 2007; Pirilä, Tahvanainen, Huggare, Nieminen, & Löppönen, 1995). In contrast, SDB is common in patients with syndromes such as congenital craniofacial abnormalities (Tan, Kheirandish-Gozal, Abel, & Gozal, 2016). In such cases, the impairments in dentofacial morphology can be the direct cause of the SDB symptoms. The same could be said to be true among children with no optimal dentofacial morphology, but without any syndrome. Thus, it cannot be stated conclusively whether paediatric SDB is the cause of the dentofacial morphology changes connected with it, or the other way around. The truth is likely to be somewhere in the middle.

In summary, paediatric SDB should be treated as a distinct condition from adult SDB with differences in pathophysiology, symptoms, consequences and treatment. Furthermore, the characteristics of paediatric SDB alter with growth. This dissertation aims to increase the existing knowledge, especially on SDB in two to three years old children and on the dentofacial growth changes connected with paediatric SDB and tonsil hypertrophy.

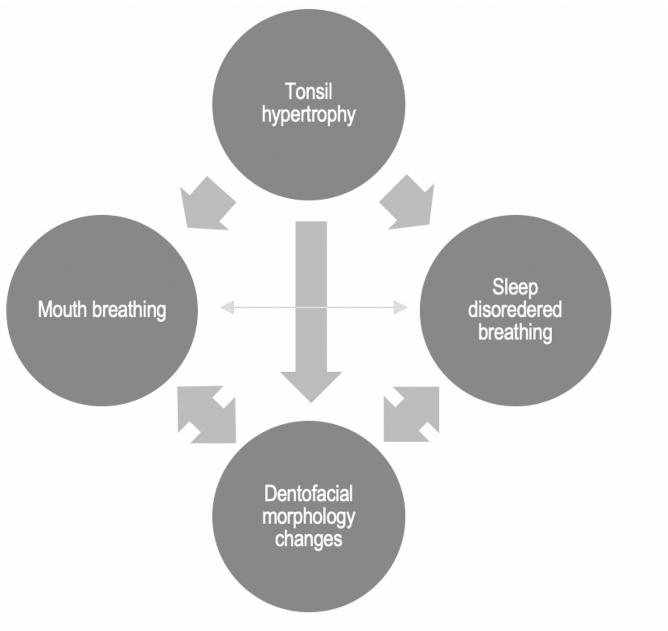

Figure 1. The multidirectional connection between SDB, tonsil hypertrophy, mouth breathing and changes in dentofacial morphology (S. Markkanen)

2 REVIEW OF THE LITERATURE

2.1 Sleep disordered breathing in children

Paediatric SDB is a general term used to describe children's breathing difficulties caused by upper airway dysfunction during sleep. It causes increased respiratory effort in addition to increased upper airway resistance and pharyngeal collapsibility (Kaditis et al., 2016). SDB can be thought of as a continuum from PS to OSA.

2.1.1 Primary snoring in children

Paediatric habitual snoring is defined as snoring at least three nights per week, and it is diagnosed based on caregivers' report (Kaditis et al., 2017). The prevalence of habitual snoring is proposed to be 3% to 14.8% (Liukkonen et al., 2008; Lumeng & Chervin, 2008; Marcus et al., 2012). However, not all studies use the criterion of three nights per week for habitual snoring, which complicates the assessment of the prevalence.

PS is snoring without obstructive events, arousals from sleep or gas exchange abnormalities (Kaditis et al., 2016). The prevalence of habitual snoring cannot be directly interpreted to be the prevalence of PS because some of the habitual snorers actually have OSA. The differential diagnosis between PS and OSA can only be definitely made using PSG, as described further in Chapter 2.1.3.3.2.

As previously stated, paediatric SDB is a continuum ranking from PS to OSA. Hence, the pathophysiology and risk factors of paediatric PS are mainly the same, although to a milder extent than in paediatric OSA (Chapter 2.1.3.1). Tonsil hypertrophy is thought to be the primary cause of snoring in children (Anuntaseree, Rookkapan, Kuasirikul, & Thongsuksai, 2001). However, obesity, nasal obstruction and parental smoking are also associated with snoring (Bixler et al., 2009; Corbo et al., 2001; Liukkonen et al., 2008). Snoring in children is reported to be more common in boys in some studies and to have no difference in prevalence by sex in others (Lumeng & Chervin, 2008).

Even though PS is considered to be a less harmful condition than OSA, it is nevertheless associated with various health risks. For instance, children with PS have been found to have more hyperactive and inattentive behaviour and poorer school performance compared with non-snoring children (Biggs, Nixon, & Horne, 2014; Brockmann, Urschitz, Schlaud, & Poets, 2012; Gottlieb et al., 2004; O'Brien et al., 2004; Rosen et al., 2004). The sleep architecture of children with PS has been observed to be disturbed in contrast to healthy controls and respiratory effort is increased during sleeping (Kheirandish-Gozal et al., 2007; Lopes & Guilleminault, 2006).

It has also been observed that if PS in children is left untreated, PS resolves in approximately one third of patients, in on third it persists and in one third it turns into OSA (Li et al., 2013; Tan, Alonso Alvarez, Tsaoussoglou, Weber, & Kaditis, 2017). On the other hand, there is evidence that as many as half of snorers do not snore after two years of follow-up (Ali, Pitson, & Stradling, 1994). The cause of the change in status might be a change in the size of the tonsils and adenoids with respect to the airway at different ages.

There are no coherent treatment guidelines for paediatric PS (Kaditis et al., 2016). However, while there is evidence that PS can have an influence on children's tiredness and might lead to health risks, PS is at times treated with adenotonsillectomy. Further, it has to be remembered that OSA and PS cannot be dependably distinguished from one another without PSG. In everyday practice, this leads to a situation where children with SDB symptoms are often treated without accurate diagnosis.

2.1.2 Upper airway resistance syndrome in children

Upper airway resistance syndrome (UARS) is described as the partial obstruction of the upper airway which leads to increased respiratory effort and arousals without apnoeas, hypopnoeas or gas exchange abnormalities. It can be thought that in the SDB continuum, UARS is situated somewhere between PS and OSA. In PSG, the increased respiratory effort is detected by using oesophageal pressure monitoring (Guilleminault, Pelayo, Leger, Clerk, & Bocian, 1996). However, because of co-operational reasons, oesophageal pressure monitoring is rarely used in paediatric PSG. Instead, the existence of UARS can be speculated from other measuring channels in PSG. For example, snoring with increased amounts of arousals can be a sign of UARS. Nevertheless, there is no uniform diagnostic criteria for UARS in children, and when there is lack of apnoeas and hypopnoeas, patients with UARS are usually diagnosed with PS.

2.1.3 Obstructive sleep apnoea in children

OSA is a breathing disorder during sleep, which is characterised by repeated complete or partial obstruction of the upper airway (apnoeas and hypopnoeas), that disturbs normal ventilation and normal sleep patterns (Kaditis et al., 2016; Loughlin et al., 1996).

2.1.3.1 Epidemiology and pathophysiology

The prevalence of paediatric OSA is estimated to be between 1% and 5% (Bixler et al., 2009; Marcus et al., 2012). OSA is found in children of all ages, but the peak prevalence occurs between the ages of 2 and 8 years (DelRosso, 2016; Marcus, 2001). It is challenging to estimate the prevalence because of the various diagnostic methods used to diagnose paediatric OSA between studies. The gold standard method used to diagnose OSA is nocturnal laboratory PSG, which will be discussed in more detail in chapter 2.1.3.3.2., but PSG is difficult to execute in large population studies. Moreover, the prevalence of paediatric OSA depends on the diagnostic PSG criteria used.

It has been suggested that there is equal prevalence of paediatric OSA between boys and girls (Sogut et al., 2005), but an increased prevalence in boys has also been reported (Katila, Saarenpää-Heikkilä, Saha, Vuorela, & Paavonen, 2019; Li et al., 2010). OSA has also been estimated to have a higher prevalence among African Americans and children born prematurely (Rosen et al., 2003).

The pathophysiology of paediatric OSA is complex and partly controversial. The anatomy and function of the upper airway are affected by a variety of factors. It can be said that the pathophysiological factors can be divided into two types – factors causing anatomical narrowing of the upper airways and factors causing increased collapsibility of the upper airways. Adenotonsillar hypertrophy (anatomical narrowing) is considered to be the most common cause of OSA in children. In addition, obesity (anatomical narrowing and increased collapsibility), craniofacial anatomy (anatomical narrowing) and neuromuscular abnormalities (increased collapsibility) play a notable role in the emergence of the disorder (Marcus et al., 2017).

2.1.3.1.1 Adeno-tonsillar hypertrophy

Adenotonsillar hypertrophy obstructs the upper airways and is considered to be the main cause of paediatric OSA in otherwise healthy children (Garg et al., 2017). It has been reported that paediatric OSA patients have larger palatine tonsils and adenoids compared with healthy children (Arens et al., 2001) and the peak incidence of paediatric OSA is coincident with the age of three to seven years, when the size of the tonsil tissue is largest (Jeans, Fernando, Maw, & Leighton, 1981; Papaioannou et al., 2013). Furthermore, adenotonsillectomy has been proven to have a significant positive effect on paediatric OSA (Mitchell, 2007), as described in more detail in chapter 2.1.3.4.1.

2.1.3.1.2 Obesity

Obesity has been reported to be an independent risk factor for paediatric OSA (Dayyat, Kheirandish-Gozal, Capdevila, Maarafeya, & Gozal, 2009; Ikävalko et al., 2018; Li et al., 2010; Verhulst, Van Gaal, De Backer, & Desager, 2008). Obesity decreases upper airway volume and, in addition, has an effect on the central nervous system ventilatory responses. Furthermore, is has been speculated that obesity has an influence on neuromotor function in the upper airways. Many obese children with OSA have enlarged tonsils in addition to being overweight. An adenotonsillectomy has also been proven to be an effective treatment choice for obese children (Marcus et al., 2013). Residual OSA after operation is, however, more common among these children (Mitchell & Kelly, 2007). In addition, obesity is an independent risk factor for many of the co-morbidities associated with OSA, such as cardiovascular disease risk and metabolic abnormalities (Marcus et al., 2012).

2.1.3.1.3 Dentofacial morphology

Unfavourable dentofacial morphology narrows the upper airways. In otherwise healthy children, OSA is associated with a variety of craniofacial and occlusal developmental changes, as described more detail in chapter 2.3.3.3. It is a matter of controversy whether OSA is the cause of the dentofacial morphology changes or whether these changes are defined by genetic and developmental factors; hence, they would be more a cause than a consequence. Furthermore, OSA is more common among children with craniofacial abnormalities related to other disorders (Garg et al., 2017; Tan et al., 2016).

Recently, paediatric OSA has been associated with short lingual frenulum, which is associated with oral dysfunction that can lead to oral-facial dysmorphosis and decrease the size of the upper airways (Guilleminault, Huseni, & Lo, 2016; Villa, Evangelisti, Barreto, Cecili, & Kaditis, 2020).

2.1.3.1.4 Neuromuscular abnormalities

The meaning of neuromuscular responses among specialists is contradictory. It is a fact that some children have residual OSA after obstruction of the upper airways is removed during surgery (Bhattacharjee et al., 2010). This leads to the question: which factors cause the residual OSA and are they part of the original aetiology of the disease or are they changes that the disease has caused. Children snore less than adults, even though they have anatomically narrower and smaller upper airways. It has been proposed that children have less tendency for upper airway collapsibility during sleep than adults, which explains this difference (Marcus, Lutz, Hamer, Smith, & Schwartz, 1999). The less collapsible upper airways are thought to result from increased ventilatory drive and upper airway neuromuscular tone. In the literature, it has been speculated whether children with OSA lack these upper airway neuromuscular responses to some extent (Marcus et al., 1999). Moreover, it is well-known that children with neuromuscular diseases are at high risk of OSA (Kaditis et al., 2016).

2.1.3.2 Symptoms and long-term influences

Paediatric OSA is associated with a variety of symptoms. The most described symptom is habitual snoring, which is usually defined as "snoring present often/frequently" or ">3–4 nights per week" (Goodwin et al., 2003; Lumeng & Chervin, 2008). Parent-reported breathing difficulties or witnessed apnoea are cogent signs of OSA (Certal et al., 2012), but they may be challenging to detect when a child is sleeping in a separate room from adults and when breathing pauses may only occur a couple of times per hour. Restless sleep, mouth-breathing tendency and nocturnal enuresis have all been described to be more common among children with OSA (Jeyakumar, Rahman, Armbrecht, & Mitchell, 2012; Nieminen et al., 2000). Excessive daytime somnolence is also often described (Certal et al., 2012; Goodwin et al., 2003), but it should be remembered that tiredness in children does not always present as excessive sleepiness. Furthermore, paediatric SDB is associated with conditions such as recurrent otitis media and paediatric asthma (Gozal, Kheirandish-Gozal, Capdevila, Dayyat, & Kheirandish, 2008; Malakasioti, Gourgoulianis, Chrousos, & Kaditis, 2011; Niemi et al., 2015).

2.1.3.2.1 Sleep architecture changes

Revealing sleep architecture changes using conventional sleep stage classification has been challenging in children's OSA, and their sleep macrostructure is often found to be normal (Chervin, Fetterolf, Ruzicka, Thelen, & Burns, 2009; Goh, Galster, & Marcus, 2000; Kheirandish-Gozal et al., 2007; Scholle & Zwacka, 2001; Yang et al., 2010). In a more recent study with novel scoring rules, however, children with OSA presented less stage three non-rapid eye movement (NREM) sleep, often referred to as deep sleep, and longer rapid eye movement (REM) sleep latency than children with primary snoring (Miano et al., 2011). These findings resemble the sleep structure changes seen in adults with OSA who have a reduced amount of deep and REM sleep (Bianchi, Cash, Mietus, Peng, & Thomas, 2010). Adults' apnoeas/hypopnoeas more often end with arousal than children's respiratory events (Berry & Gleeson, 1997). Despite this, the sleep microstructure of children with OSA has been observed to change and more arousals and movements have been detected (Kheirandish-Gozal et al., 2007; Miano et al., 2011; Scholle & Zwacka, 2001).

2.1.3.2.2 Cognitive and neuropsychological problems

Paediatric OSA has been associated with poorer performance in cognitive tests compared with the performance of healthy children (Suratt et al., 2007). Furthermore, treatment of the disease has been observed to improve neurocognitive functions (B. C. Friedman et al., 2003; Gozal, 1998). Nevertheless, in some studies, mild paediatric OSA has not had an effect on neurocognitive and psychological functioning and OSA treatment has not improved this functioning (Calhoun et al., 2009; Waters et al., 2020). Consequently, the evidence on the subject is contradictory. Children with SDB have demonstrated more behavioural problems, hyperactivity and inattention than children without SDB, and treatment of the disease has normalised these problems (Chervin et al., 2002; Mulvaney et al., 2006; Sedky, Bennett, & Carvalho, 2014). It should be taken into consideration that cognitive and neuropsychological problems are also associated with, for example, ethnicity, socioeconomic status and obesity, which can all be risk factors for SDB (Marcus et al., 2012). Therefore, it is not straightforward to determine the causality of these factors. However, the improvement in cognitive and neuropsychological problems after treatment of SDB indicates that there is a direct relationship between SDB and these problems. Principally, it is thought that SDB may have an influence on children's cognitive and neuropsychological ability, and thus leads to poorer school performance and poorer economic success later in life. Early intervention, therefore, might lead to an interruption of this undesirable development.

2.1.3.2.3 Cardiovascular effects

Paediatric SDB is associated with elevated blood pressure compared with healthy controls (Horne et al., 2011; Xu et al., 2013). Nevertheless, there is heterogeneity among studies and a meta-analysis did not find a statistically significant connection between SDB and the risk of elevated blood pressure (Zintzaras & Kaditis, 2007). Despite the contradictory evidence, a published consensus statement on childhood hypertension recommended that the possibility of OSA should be taken into account when treating children with hypertension (Falkner & Daniels, 2004). Children with SDB have been observed to have increased levels of blood brain natriuretic peptide overnight compared with controls (Kaditis et al., 2006). This may indicate increased cardiac strain during the night-time. In addition, children with SDB have been observed to possess altered autonomic nervous system regulation and increased sympathetic vascular reactivity, which lead to strain on the cardiovascular system (O'Brien & Gozal, 2005). In summary, it can be said that paediatric SDB seems to have an influence on cardiovascular health, although the evidence is diverse. It has been speculated whether these effects on the cardiovascular system are long-term and whether they increase the risk of cardiovascular illnesses later in life. Furthermore, it has also been discussed if there is a connection between cardiovascular changes and cognitive problems.

2.1.3.2.4 Metabolic effects

Metabolic syndrome, which includes increased waist circumference, increased glucose level, increased triglyceride level, increased high-density lipoprotein cholesterol level and elevated blood pressure, is more common in children and adolescents who are overweight and have SDB (Redline et al., 2007; Verhulst et al., 2007). Furthermore, it has been suggested that SDB contributes to metabolic dysfunction over that of obesity (Redline et al., 2007). Non-obese children with SDB have not been observed to have similar metabolic consequences (Kaditis et al., 2005). It has therefore been speculated that the influence of SDB on metabolic syndrome is more significant in adolescents than in children due to the length of time that SDB has been present and hormonal changes in puberty (Marcus et al., 2012). Thus, the connection between obesity, SDB and metabolic abnormalities in the paediatric population is complex.

2.1.3.2.5 Growth

Traditionally, children with OSA have been assumed to grow to be small and skinny, which is not necessarily true at present, as discussed in Chapter 2.1.3.1.2. Nevertheless, OSA is associated with decreased growth hormone levels, and an improvement in growth and hormone levels is detected after treatment (Bonuck, Freeman, & Henderson, 2009; Esteller et al., 2018; Nieminen et al., 2002).

2.1.3.3 Diagnosis and diagnostic methods

The American Academy of Sleep Medicines states that paediatric OSA diagnostic criteria are 1) The presence of snoring; and/or laboured, paradoxical, or obstructed breathing during sleep; and/or sleepiness, hyperactivity, behavioural problems, or learning problems; and simultaneously 2) PSG demonstrates obstructed/mixed apnoeas or hypopnoeas ≥1/hour; and/or a pattern of obstructive hypoventilation, defined as at least 25% of total sleep time with hypercapnia in association with snoring; and/or flattening of the inspiratory nasal pressure waveform; and/or paradoxical thoracoabdominal motion (American Academy of Sleep Medicine, 2014) (Table 1).

In the European Respiratory Society statement (Kaditis et al., 2016), paediatric obstructive sleep apnoea syndrome is defined as follows: "SDB symptoms in combination with obstructive apnoea-hypopnoea index (OAHI) ≥2 episodes/hour or obstructive apnoea index (OAI) ≥1 episodes/hour" or "SDB symptoms and apnoea-hypopnoea index (AHI) ≥1 episode/hour (including central events)" (Table 1).

In clinical practice, a child considered to be healthy should have an OAHI <1. The severity of paediatric OSA is commonly classified as minimal with an OAHI ≥ 1.5 to 2, mild with an OAHI ≥ 2 to 5, moderate with an OAHI ≥ 5 to 10 and severe with an OAHI ≥ 10 (Stowe & Afolabi-Brown, 2019). Nevertheless, the OAHI alone is not the only parameter that should be considered when assessing the severity of paediatric OSA. For example, the severity of breathing effort, oxygen desaturation or hypercapnia should also be considered. The problems of using PSG as a primary diagnostic tool for OSA are the availability and high cost. Consequently, guidelines to estimate patients' need for PSG have been drawn up (Roland et al., 2011). According to the guidelines, PSG is not needed when diagnosing otherwise healthy, non-overweight and previously untreated child with large tonsils and SDB-symptoms, (Kaditis et al., 2016). By contrast, the American Academy of Sleep

Medicines states that PSG is always indicated when the clinical assessment suggests a diagnosis of OSA in children (Aurora et al., 2011).

Table 1. The paediatric OSA diagnostic criteria. PSG = polysomnography, SDB = sleep disordered breathing, OAHI = obstructive apnoea-hypopnoea index, OAI = obstructive apnoea index, AHI = apnoea-hypopnoea index

the American Academy of Sleep Medicines	the European Respiratory Society
The presence of (one or more) 1) snoring 2) laboured, paradoxical, or obstructed breathing during sleep 3) sleepiness, hyperactivity, behavioural problems, or learning problems; and simultaneously and PSG demonstrates (one or more) 1) obstructed/mixed apnoea or hypopnoea ≥1/h 2) a pattern of obstructive hypoventilation, defined as at least 25% of total sleep time with hypercapnia in association with snoring 3) flattening of the inspiratory nasal pressure waveform; and/or paradoxical thoracoabdominal motion	The presence of SDB symptoms and PSG demonstrates (one or more) 1) OAHI ≥2 episodes/h 2) OAI ≥1 episodes/h 3) AHI ≥1 episode/hour

2.1.3.3.1 Clinical history and physical examination

Clinical history and physical examination are widely used to estimate the likelihood of OSA. However, these measures alone have been proven to be unsuitable for this task (Carroll et al., 1995). Snoring history and tonsillar size are considered to have high sensitivity and excessive daytime somnolence or parent observed apnoea in sleep high specificity to predict the likelihood of OSA (Certal et al., 2012). It has been demonstrated, however, that a single symptom or sign will have poor diagnostic accuracy in predicting paediatric OSA. Questionnaires and models that combine both history and clinical parameters have been developed and tested (Chervin, Hedger, Dillon, & Pituch, 2000; Kang et al., 2016; Villa et al., 2013). To date, no model has been proven to satisfactorily perform an estimation of the likelihood of OSA that can be used in everyday practice (Certal et al., 2012). Perhaps the best diagnostic algorithm has been published by Villa et al. (2013) who reported their sleep clinical scale to have 96% sensitivity and 67% specificity when identifying children with OSA from children with mild forms of SDB. However, the prevalence of OSA was quite high, 72.8%, because the study population comprised children with SDB symptoms.

Moreover, attempts have been made to estimate OSA severity using clinical history and physical examination. Tonsil size estimation and OSA severity have been shown to have a weak association at best (Nolan & Brietzke, 2011). In addition, there are several clinical factors, such as obesity or the Paediatric Sleep Questionnaire total score, that are associated with OSA severity (Chervin et al., 2000; Mitchell et al., 2015). These measures are not capable, however, of diagnosing OSA, although they could be used to estimate the severity of the disease to some extent.

2.1.3.3.2 Laboratory polysomnography

Nocturnal in-laboratory PSG is the gold standard method used to diagnose paediatric OSA. PSG is used to measure cortical activity, respiratory patterns, muscle activity, and oxygenation and gas exchange in sleep. Conventional paediatric PSG includes the monitoring of electroencephalography, electro-oculography and electromyography with submental and bilateral tibial electrodes to score sleep stages and leg movements. To monitor airflow and respiratory effort, an oronasal thermal airflow sensor, a nasal pressure transducer, respiratory inductance plethysmography belts, and usually diaphragmatic and abdominal electromyography are used. Pulse oximetry and capnometry monitor oxygen saturation and end-tidal carbon dioxide, respectively. In addition, body position and electrocardiography are detected. Audio-visual recordings are made to assess, for example, snoring sound, neck position and mouth breathing (Stowe & Afolabi-Brown, 2019).

The American Academy of Sleep Medicines has determined the obstructive apnoea rule for scoring paediatric patient's PSG to be the following: "there is a drop in the peak signal excursion by ≥90% of the pre-event baseline and the duration of the drop is at least 2 breaths during baseline breathing and it is associated with the presence of respiratory effort throughout the entire period of absent airflow" and the hypopnoea rule to be: "the peak signal excursions drop by ≥ 30% of pre-events baseline and duration of the ≥ 30% drop lasts for at least 2 breaths and there is ≥ 3% desaturation from pre-event baseline or the event is associated with an arousal" (Berry et al., 2012). Nevertheless, in the older literature, other PSG scoring criteria have been used, which serves to complicate the comparison of study results.

2.1.3.3.3 Ambulatory polysomnography

The term ambulatory PSG is used to describe PSG that is executed at the home of the patient. Furthermore, it usually comprises only cardiorespiratory recordings and not the evaluation of sleep patterns. It is, however, a commonly used method to diagnose adult OSA. Currently, there is scarcity of studies that evaluate the usability of ambulatory PSG in diagnosing paediatric OSA and the existing knowledge is contradictory. It seems that ambulatory PSG can be dependably used to diagnose OSA in school-aged children, but it lacks specificity in younger children (Goodwin et al., 2001; Zucconi, Calori, Castronovo, & Ferini-Strambi, 2003).

2.1.3.3.4 Nocturnal oximetry

Nocturnal pulse oximetry has been shown to have a positive predictive value when used to evaluate the likelihood of OSA in children suspected of having OSA (Brouillette et al., 2000). However, the sensitivity and specificity of the method have been determined to be insufficient for diagnosing OSA (Kirk, Bohn, Flemons, & Remmers, 2003).

2.1.3.3.5 Drug-induced sleep endoscopy

Drug-induced sleep endoscopy is a technique used to guide the selection of treatment modality. Drug-induced sleep endoscopy is performed in the operating theatre and anaesthetics are used to induce sleep. During the procedure, the upper airways are evaluated with a flexible fibreoptic endoscope and the fixed and dynamic obstruction sites are detected. There is evidence that drug-induced sleep endoscopy could be a useful tool when considering a suitable treatment modality for paediatric OSA patients (Boudewyns, Verhulst, Maris, Saldien, & Van de Heyning, 2014). Nevertheless, it is considered to be an unnecessary examination for the majority of children, since the primary treatment for these children is an adenotonsillectomy and the need for this treatment can be evaluated by other, simpler means (Galluzzi, Pignataro, Gaini, & Garavello, 2015).

2.1.3.3.6 Other methods

A variety of other methods have been evaluated to be used to either clinically diagnose paediatric OSA or as a screening technique for the necessity of PSG. Snoring detection, day-time nap polysomnography, radiographic evaluation, different cardiorespiratory parameters, urinary and laboratory tests are some of the methods studied. None of these methods, however, have been proven to be applicable to everyday practice (Marcus et al., 2012).

2.1.3.4 Treatment

Paediatric OSA can be treated with different treatment modalities. However, an adenotonsillectomy is regarded as the primary treatment modality for otherwise healthy children, and the procedure is also often the first treatment choice for children with co-existing disorders (Marcus et al., 2012). AHI > 5 is often used as an indication for OSA treatment, but also lower cut-off values, such as OAHI ≥2 or OAI >1, have been justified, especially if there are coexisting conditions (Kaditis et al., 2016).

2.1.3.4.1 Tonsil surgery

An adenotonsillectomy is used as a primary treatment for paediatric OSA (M. Friedman et al., 2009; Marcus et al., 2012, 2013). In paediatric OSA patients, the procedure has been shown to improve quality of life, increase growth rate, decrease cardiovascular strain, improve cognitive skills and concentration, diminish sleepiness and reduce enuresis (Bonuck et al., 2009; Gozal, 1998; Jeyakumar et al., 2012; Marcus et al., 2013; Sedky et al., 2014; Teo & Mitchell, 2013). There is, however, a lack of evidence regarding the objective improvement of the attention and executive functions (Marcus et al., 2013).

The treatment success of an adenotonsillectomy is estimated to be between 60% and 83%, depending on which PSG diagnostic criteria are used to determine a positive outcome (AHI range 0.5 to 5 events/hour) (Brietzke & Gallagher, 2006; M. Friedman et al., 2009). Consequently, a significant number of operated patients have residual OSA, although milder in most cases. The risk for residual OSA is larger in specific subgroups, such as children with severe OSA and obese children

(Bhattacharjee et al., 2010; Marcus et al., 2013). In addition, children with concurrent congenital craniofacial abnormalities and/or neuromuscular disorders are at risk of persistent OSA after an adenotonsillectomy (Kaditis et al., 2016).

There is not a sufficient number of studies to compare adenoidectomy alone with adenotonsillectomy in the treatment of paediatric OSA, although the procedure is used in such a manner (Kaditis et al., 2016). There is, however, some evidence that adenoidectomy alone could be enough for younger patients, especially in children aged less than 12 months (Reckley et al., 2016).

Partial tonsillectomy/tonsillotomy has been shown to have a positive effect on OSA, and it has been compared with tonsillectomy (Wood, Cho, & Carney, 2014). Partial tonsillectomy is executed by subtotal removal of tonsillar tissue and leaving a margin of tissue on the tonsillar capsule (Sathe, Chinnadurai, McPheeters, & Francis, 2017). There is evidence that partial tonsillectomy could be an adequate treatment for paediatric OSA and the operation risks, such as postoperative bleeding, would be lower (Francis et al., 2017). Conversely, tonsillar regrowth is presumably more common, 0.5% to 17% between studies, after partial tonsillectomy than after traditional tonsillectomy (Çelenk et al., 2008; Solares et al., 2005).

2.1.3.4.2 Watchful waiting

Mild or moderate OSA has been observed to cease in some children without any treatment (Chervin et al., 2015; Fehrm, Nerfeldt, Browaldh, & Friberg, 2020; Marcus et al., 2013). Marcus et al. (2013) found that in 46% of the children aged five to nine years who were followed for seven months without any treatment, the AHI normalised. In the same study, the AHI normalised in 79% of the children who were treated with an adenotonsillectomy. Among children with only mild OSA, the amount of ceased OSA was between 65% and 86% in the watchful waiting and adenotonsillectomy groups, respectively. Consequently, when taking into account that any operative treatment is not without risks and costs, the treatment of mild OSA should be carefully considered. The problem lies in the fact that when PSG is not used, it is difficult to assess the severity of OSA using the current diagnostic methods.

2.1.3.4.3 Orthodontic treatments

Rapid maxillary expansion is an orthodontic treatment in which orthodontic appliances cause palatal widening and flattening of the upper dental arch. Rapid maxillary expansion is shown to have a positive effect on AHI when treating children aged under 13 years with OSA and a high arched and/or narrow hard palate (Machado-Júnior et al., 2016; Vale et al., 2017; Villa et al., 2007), and especially if children have previously undergone an adenotonsillectomy or have small tonsils (Camacho et al., 2017; Guilleminault et al., 2011). Consequently, rapid maxillary expansion should be considered, especially when treating residual or recurrent OSA.

Functional oral orthopaedic appliances, oral devices which alter the muscle force against the teeth and facial skeleton, have been studied in the treatment of OSA. There is low quality of evidence that these devices can have a mild positive effect (Carvalho, Lentini-Oliveira, Prado, Prado, & Carvalho, 2016; Nazarali et al., 2015).

2.1.3.4.4 Medications

Topical nasal corticosteroids and leukotriene antagonist (montelukast) have been studied in the treatment of paediatric OSA. There is evidence that nasal corticosteroids could have a positive effect on mild paediatric OSA (Brouillette et al., 2001). Montelukast is a less studied modality, but some positive developments have also been described in mild OSA, regardless of the existence of an asthmatic background. (Kheirandish-Gozal, Bandla, & Gozal, 2016).

2.1.3.4.5 Myofunctional therapy

Myofunctional therapy using oropharyngeal exercises has been studied to treat or prevent residual OSA and mouth breathing tendency after an adenotonsillectomy (Guilleminault et al., 2013; Lee, Guilleminault, Chiu, & Sullivan, 2015; Villa et al., 2015). There is some evidence of positive effects and, in some cases, it might be profitable to consider myofunctional therapy as an additive treatment with adenotonsillectomy.

2.1.3.4.6 Weight reduction

There is evidence that weight reduction can be an effective treatment in adolescents (Verhulst, Franckx, Van Gaal, De Backer, & Desager, 2009). However, the efficacy of weight reduction in overweight children has not been studied.

2.1.3.4.7 Continuous positive airway pressure

Continuous positive airway pressure (CPAP) is a positive airway pressure ventilator that creates continuous mild positive air pressure to keep the airways open during breathing. CPAP is used to treat paediatric OSA in special circumstances. These can be residual OSA after other treatment possibilities have been used, or OSA related to other comorbidities such as obesity, neuromuscular disorders or congenital craniofacial abnormalities. CPAP has been shown to be effective, but adherence can be a problem (Marcus et al., 2006).

2.1.3.4.8 Tracheostomy

A tracheostomy is extremely effective treatment modality for OSA because it bypasses the upper airways. However, because of morbidities and the complexity it causes, it is a method of last resort if other treatment methods fail and a child has severe OSA and often concurrent disorders (Kaditis et al., 2016).

2.1.3.4.9 Residual OSA after primary treatment

Persistent or recurrent OSA symptoms should be recognised after treatment. As in diagnosing OSA, PSG is the gold standard method for the evaluation of response to treatment. Naturally, is not possible nor necessary to perform PSG for every patient after treatment. It has been estimated that from 13% to as much as 73% of the operated children have residual OSA after adenotonsillectomy (Bhattacharjee et al., 2010; Ye et al., 2010). Dispersion of the estimates depends on the features of the studied population and on the criteria used to assess the recovery from OSA. Risk factors for residual OSA are obesity, high baseline AHI and underlying disorders, such as neuromuscular diseases and craniofacial abnormalities (Costa & Mitchell, 2009; Mitchell, 2007). Accordingly, the response to treatment should be assessed, but this does not necessarily mean a new PSG. It has been observed that absence of snoring after adenotonsillectomy usually indicates a good response to the treatment (Mitchell, 2007; Nieminen et al., 2000; Suen, Arnold, & Brooks, 1995). PSG should be re-performed only if the patient has a high risk of residual OSA or has distinct and continuing symptoms after primary treatment.

2.2 Tonsil hypertrophy in children

2.2.1 Anatomy and classification

2.2.1.1 Pharynx

The pharynx is a muscular tube that connects the oral and nasal cavities to the oesophagus and larynx. It comprises the nasopharynx, the oropharynx and the hypopharynx. The nasopharynx encompasses the space posterior to the nasal cavity between the cranial base and the soft palate. The nasopharynx includes the pharyngeal tonsil. The oropharynx is situated inferior to the nasopharynx and is limited to the posterior part of the oral cavity and the superior border of the epiglottis. The oropharynx includes the palatine tonsils, the posterior third of the tongue, the lingual tonsil and the soft palate. The hypopharynx lies inferior to the oropharynx and it is limited to the superior border of the epiglottis and the inferior border of the cricoid cartilage.

The walls of the pharynx are composed of circular and longitudinal muscles. The three circular muscles are the superior, middle and inferior pharyngeal constrictor. The patency of the pharynx is mainly maintained by these circular muscles, and they constrict the lumen of the pharynx when swallowing. They are innervated by the vagus nerve (the cranial nerve X). The longitudinal muscles are the stylopharyngeus, the palatopharyngeus and the salpingopharyngeus. The stylopharyngeus is innervated by the glossopharyngeal nerve (the cranial nerve IX) and the other two by the vagus nerve. The longitudinal muscles shorten and widen the pharynx and lift the larynx when swallowing.

The pharyngeal lymphoid tissue, also known as Waldeyer's ring, comprises the pharyngeal tonsil, the palatine tonsils and the lingual tonsil.

2.2.1.2 Pharyngeal tonsil

The pharyngeal tonsil is situated at the roof and posterior wall of the nasopharynx. When the pharyngeal tonsil is enlarged, it can also be called adenoids.

The pharyngeal tonsil cannot be examined by just looking into the oral cavity because it is hidden behind the soft palate. A mirror can be used to get a view into the nasopharynx (posterior mirror rhinoscopy), but this examination method can be problematic when used with non-cooperative child patients. Therefore, other methods to estimate the size of the pharyngeal tonsil should be used.

The size of the pharyngeal tonsil can be estimated from a lateral cephalometric radiograph when the co-operation ability of the child allows it. The method of Cohen and Konak (1985) can be used in classification. This method is based on measuring the airway immediately behind the upper part of the soft palate. If the airway is narrower than the width of the soft palate, it is considered to be markedly obstructed; if it is narrower than half of the soft palate, it is severely obstructed; and if it is the same width as the soft palate, it is not narrowed. A systematic review by Major et al. (2006) concluded that lateral cephalometric radiography is an acceptable preliminary imaging method to assess the size of the pharyngeal tonsil. Lateral cephalometric radiographs have been compared to magnetic resonance imaging (MRI). However, MRI did not prove to be a better tool for measuring the dimensions of the nasopharyngeal region (Pirilä-Parkkinen et al., 2011).

A flexible nasofiberoscope can be used to estimate pharyngeal tonsil size, and it has been proven to be a reliable method to assess paediatric adenoid size when compared with radiographic assessment methods (Kindermann, Roithmann, & Neto, 2008). A distinct advantage of nasofiberoscopy compared to lateral cephalometric radiographies is that it does not expose children to radiation, and it is possible to execute during otorhinolaryngological examination.

2.2.1.3 Palatine tonsils

The palatine tonsils are seen in the oropharynx in clinical examination of the mouth and throat, and they are situated on the posterolateral wall of the oropharynx in the tonsillar fossa.

The size of the palatine tonsil can be classified using specific scales. The most commonly used classification method in children is the Brodsky scale (Brodsky, 1989; Brodsky & Koch, 1992). The palatine tonsil size is determined in the following manner: grade 0 = tonsils limited to the tonsillar fossa; grade 1 = tonsils occupying up to 25% of the space between the anterior pillars of the tonsillar fossae; grade 2 = tonsils occupying 25% to 50% of the space between the anterior pillars of the tonsillar fossae; grade 3 = tonsils occupying 50% to 75% of the space between the anterior pillars of the tonsillar fossae; grade 4 = tonsils occupying 75% to 100% of the space between the anterior pillars of the tonsillar fossae. The Friedman scale is more often used when evaluating the palatine tonsil size in adults (M. Friedman et al., 1999). Palatine tonsil size is determined in the Friedman scale as follows: grade 0

= no tonsils, tonsillectomy has been performed, grade 1 = tonsils are hidden between the palatoglossal and the palatopharyngeal arch, grade 2 = tonsils extend to the arches, grade 3 = tonsils extend beyond the arches, but not to the midline, grade 4 = tonsils extend to the midline (Figure 2).

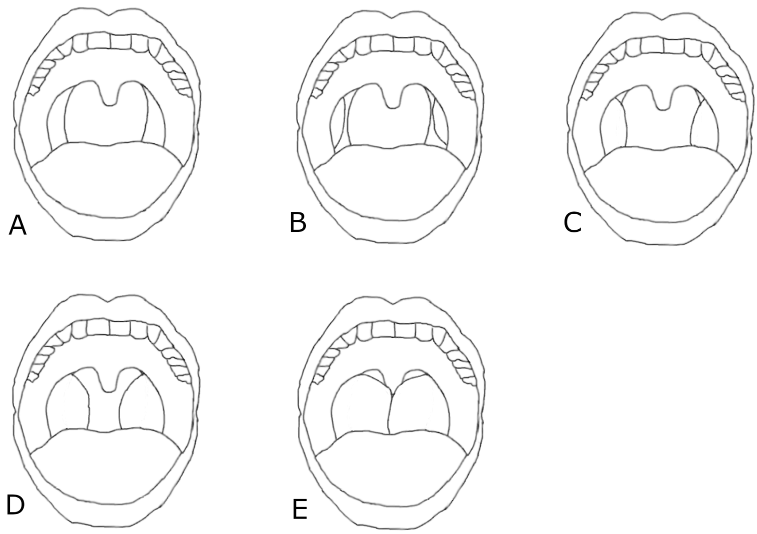

Figure 2. Friedman tonsil scale. A = grade 0, B = grade 1, C = grade 2, D = grade 3 and E = grade 4. Redrawn from Friedman M. et al. (1999).

2.2.1.4 Lingual tonsil

The lingual tonsil is located at the posterior third of the tongue. It can be examined with a mirror, a flexible nasofiberoscope or evaluated from radiologic images. The classification of lingual tonsils is used more rarely, and no established grading system is used (Costello, Prabhu, & Whittet, 2017; N. R. Friedman, Prager, Ruiz, & Kezirian, 2015).

2.2.2 Pathophysiology

The size of the tonsil in contrast with the pharyngeal volume changes during childhood (Linder-Aronson & Leighton, 1983). Figure 3 shows the size of the lymphoid tissue during childhood in contrast with general growth. It should be noted that the lymphoid tissue also includes organs other than the Waldeyer's ring, such as the thymus and spleen, and the size of the lymphoid tissue of the pharynx does not precisely follow Scammon's growth curve of lymphoid tissue. The size of the tonsil tissue is normally largest in contrast with the pharyngeal space at about the age of 5 years (Linder-Aronson & Leighton, 1983; Papaioannou et al., 2013)

In addition to the fact that lymphoid tissue size is at its largest in childhood, the tissue can be hypertrophied due to other reasons. The increase in lymphoid elements in the tissue enlarges the size of the tonsil tissue, and the size of the tonsils are shown to be associated with bacterial load and the number of B and T cell in the tissue (Brodsky, Moore, Stanievich, & Ogra, 1988). The bacteria Haemophilus influenzae and Staphylococcus aureus are especially associated with hypertrophied tonsils in children (Brodsky, Moore, & Stanievich, 1988; Kuhn et al., 1995). In addition, viral infections are also associated with tonsil hypertrophy in childhood. Especially infections, such as Epstein-Barr virus infection, can cause rapid lymphoid hyperplasia (Ganzel, Goldman, & Padhya, 1996). The association between tonsil hypertrophy and allergy is a matter of debate and a clear association has not been shown (Ameli, Brocchetti, Tosca, Schiavetti, & Ciprandi, 2014; Carr, Obholzer, & Caulfield, 2007). Additionally, in rare cases, malignant diseases, such as lymphoma, can be the cause of tonsil hypertrophy.

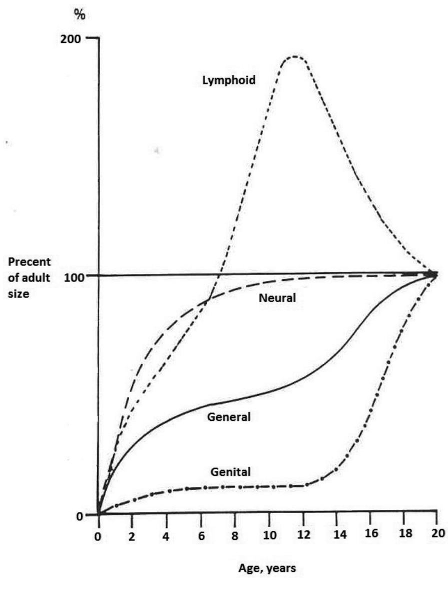

Figure 3. Scammon curves for growth of the tissues. Redrawn from Scammon RD (1930). The measurement of the body in childhood.

2.3 Dentofacial growth and development in children

2.3.1 Anatomy and normal development

The facial anatomy of a child and of an adult is clearly different. The size of the face in contrast to the size of the head is smaller in childhood. In infants, the cranium-face-ratio is approximately 3:1 and in adults 1:2 (Figure 4). Consequently, dentofacial morphology changes radically during childhood. The majority of the growth of the facial structures in transversal dimension occurs before the age of ten years (Kozak & Ospina, 2010), but thereafter a significant amount of growth takes place in the sagittal and particularly in the vertical direction.

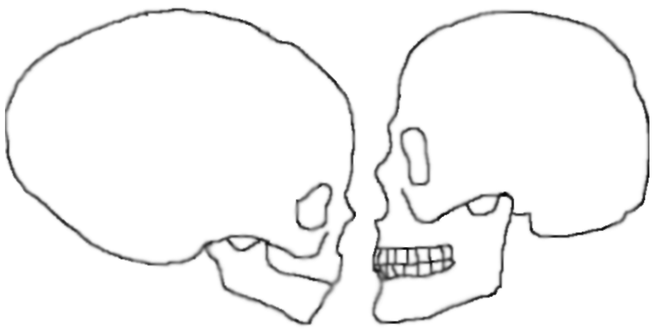

Figure 4. The proportion of the face in contrast with head size. Redrawn from Lowery GH. Growth and Development of Children (1973).

The craniofacial complex can be divided into three components: the neurocranium, the nasomaxillary complex and the mandible. The neurocranium is further divided into the calvarium and the cranial base. About 90% of the volume of the brain and the associated calvarium is completed by the age of 7 years. The cranial base (parts of the occipital, temporal, sphenoid and ethmoid bones) grows more slowly, and the majority of the growth is accomplished by the age of 10 years. The cranial base does not only grow in size but also changes in shape as well. The nasomaxillary complex (the nasal, lacrimal, maxillary, zygomatic, pterygoid and vomer bones) is displaced forwards and downwards in relation to the cranial base as the growth of the face proceeds. The development of the nasomaxillary complex is at its largest before the age of 10 years, but especially the nose region develops further during puberty. Before puberty, a convex facial profile is a typical characteristic because the mandible is still situated further back in relation to the maxilla. At birth, the mandible comprises two bones that are fused together by the age of 6 months. Like the maxilla, the mandible is displaced downwards and forwards during the growth with great individual variability (Kozak & Ospina, 2010; Proffit, 2013a). The growth of the mandible occurs in two growth spurts: a juvenile growth spurt between the ages of 5 to 7 years and a pubertal growth spurt between the ages of 10 to 15 years (Miller & Kerr, 1992; Patcas, Herzog, Peltomäki, & Markic, 2016). The deciduous dentition eruption takes place between 6 and 30 months and the permanent dentition eruption between 6 and 20 years (Proffit, 2013a) (Table 2&3).

Table 2. Average eruption timing and sequence of primary teeth (Proffit, 2013a).

Tooth	Age in months
Lower central incisors	8
Upper central incisors	10
Upper and lower lateral incisors	12
Upper and lower 1st molars	16
Upper and lower canines	20
Upper and lower 2nd molars	28

Table 3. Average eruption timing and sequence of permanent teeth (Proffit, 2013a).

Tooth	Age in years
Lower 1st molars	6
Upper 1st molars	6 ¼
Lower central incisors	6 ¼
Upper central incisors	7 ¼
Lower lateral incisors	7 ¼
Upper lateral incisors	8 ¼
Lower canines	10 ½
Upper 1st premolars	10 ¼
Lower 1st premolars	10 ½
Upper 2nd premolars	11
Lower 2nd premolars	11 ¼
Upper canines	11 ½
Lower 2nd molars	12
Upper 2nd molars	12 ½
Upper and lower 3rd molars	20

Facial growth is modulated by a variety of factors, and both genetic and environmental factors play a role in the development. The facial bones grow in connection with the other tissues in the head region (Moss, 1997). For example, the bones of the cranium grow when the brain tissue is growing. It has been theorised that the major determinant of growth of the maxilla and mandibula is the upper airway's functional need to grow. From this perceptive, environmental factors, such as mouth breathing, tonsil hypertrophy and sucking habits in early childhood, that alter the function of the upper airways can have an effect on dentofacial growth (Behlfelt, Linder-Aronson, & Neander, 1990; Karjalainen, Rönning, Lapinleimu, & Simell, 1999; Souki et al., 2009). Furthermore, it should be noted that gender and ethnicity cause variation in growth and dentofacial morphology (Proffit, 2013b).

2.3.2 Evaluation of occlusion and facial structures

The evaluation of occlusion and facial structures is a process that combines orthodontic clinical evaluation and diagnostic records. Photographs can be used to document clinical evaluation and to register and measure soft tissue landmarks. Dental casts (made by alginate impression or intraoral scanning) and lateral cephalometric radiographs are the most conventionally used diagnostic methods. A dental cast is a three-dimensional copy of the teeth, and it is made to evaluate dental alignment and occlusion. Additionally, different measurements, such as upper and lower dental arch length, width and perimeter, can be obtained. Cephalometric radiographs are used to evaluate dentofacial proportions and to clarify the anatomic basis of malocclusion. The face can be divided into five components, whose relation is assessed. The components are (1) the cranium and the cranial base; (2) the maxilla and nasomaxillary complex; (3) the mandible; (4) the maxillary teeth and alveolar process and (5) the mandibular teeth and alveolar process (Proffit, 2013c).

When evaluating dentofacial traits, five different characteristics should be considered – dentofacial appearance, teeth alignment, and the transverse, sagittal and vertical plane of space. The evaluation of dentofacial appearance includes assessing facial asymmetry, anteroposterior and vertical facial proportions and lip-tooth relationships. The alignment evaluation includes assessing the symmetry of the dental arches and observing the crowding and/or spacing of the teeth (Figure 5). These characteristics can be evaluated using clinical evaluation and photographs.

Figure 5. Crowding and spacing of the teeth (T. Peltomäki)

The evaluation of the transverse plane of space is performed using clinical evaluation, dental cast and radiographs. The presence or absence of posterior crossbite is assessed (Figure 6). Crossbite is palatal, when the upper molars, premolars and sometimes canines are situated more palatinally from their normal position with respect to their lower counterparts. Further, the origin of crossbite should be assessed. It can be dental, when a dental arch is narrow, or skeletal, when the width of the maxilla is narrowed.

Figure 6. Crossbite (T. Peltomäki)

The Angle's classification is used to describe dental relationship in the sagittal plane of space. (Angle, 1899). The classification is based on the relationship of the first molar teeth and the alignment of the teeth relative to the line of occlusion. The classification includes four classes: Normal occlusion with normal molar relationship; Class I malocclusion (normal molar relationship, but teeth crowded, rotated, etc.); Class II malocclusion (lower molar distal to upper molar, relationship of other teeth to the line of occlusion not specified) and Class III malocclusion (lower molar mesial to upper molar, relationship of other teeth to the line of occlusion not specified) (Figure 7) (Proffit, 2013c). After assessing the class of malocclusion, the cause of the malocclusion should be further evaluated. The cause can be either skeletal, when there is discrepancy between the jaws, or dental, when the problem lies with displaced teeth, or a combination of both. To determine the class of malocclusion and the cause of it, both dental casts and radiographs are needed. Overjet is a term used to describe the sagittal overlap of the maxillary central incisors beyond the ridges of the mandibular central incisors when the jaws are closed normally.

Figure 7. Class I, II & III malocclusion (T. Peltomäki)

In the evaluation of the vertical plane of space, the attention is drawn to bite depth, in other words, overbite. The term overbite describes the vertical overlap of the maxillary central incisors over the mandibular central incisors. Anterior open bite means the failure of the incisors teeth to overlap and anterior deep bite, that is, negative overbite, means excessive overlap of these teeth (Figure 8 & 9). The term posterior open bite describes the condition when the posterior teeth of the upper and lower jaw do not touch each other when the jaws are closed normally. In children, however, it should be remembered that the unfinished eruption state of the teeth can cause a similar situation. As in evaluating the transverse and sagittal plane of space, it is important to observe whether the detected problems arise from dental or skeletal changes. The excessive or insufficient eruption of posterior teeth can lead to an anterior open bite or an anterior deep bite, respectively. On the other hand, the rotation changes between the upper and lower jaws can cause similar problems. Pure dental anterior open bite can be found in childhood if the child has prolonged pacifier use or a finger sucking habit (Karjalainen et al., 1999). However, the cause of the problem is almost always a combination of changes in both dental and skeletal components. Consequently, dental casts and radiographs are needed for proper analysis.

Figure 8. Open bite (T. Peltomäki)

Figure 9. Deep bite (T. Peltomäki)

2.3.3 Dentofacial morphology changes associated with upper airway obstruction

2.3.3.1 Mouth breathing

Breathing through the nose is considered to be the normal respiratory pattern (Linder-Aronson, 1970; Proffit, 2013d) Mouth breathing due to upper airway obstruction is believed to affect dentofacial development and occlusion (Peltomäki, 2007; Souki et al., 2009). This changed development is explained by upper airway obstruction altering the position of the head and tongue when nasal breathing turns to mouth breathing. In nasal breathing the tongue gives support to the upper dental arch, which secures normal transversal growth of the upper dental arch. In mouth breathing, the tongue takes a lower position in the oral cavity and support to the upper dental arch is lost. This reshapes the musculature balance and the pressure on the dentition.

The most commonly described changes are an increase in anterior facial height and an increase in mandibular plane inclination, convex profile, and upper incisor protrusion, narrow upper arch and high palate, class II malocclusion, anterior open bite and posterior crossbite (Bresolin, Shapiro, Shapiro, Chapko, & Dassel, 1983; Cheng et al., 1988; Linder-Aronson, 1970; Löfstrand-Tideström, Thilander, Ahlqvist-Rastad, Jakobsson, & Hultcrantz, 1999). This combination of facial and occlusion features is referred to as “the long-face syndrome” or “the adenoid face”, which indicates the conventional reason for mouth breathing.

The influence of mouth breathing on dentofacial morphology has been questioned among experts (Vig, 1998). The difficulty lies in the fact that mouth breathing is rarely complete and the mode of breathing changes from nasal to oral and vice versa depending on, for example, whether the person is awake or asleep.

2.3.3.2 Tonsil hypertrophy

Enlarged adenoids and palatine tonsils are suggested to be the main reason for mouth breathing and head and tongue posture changes in children (Behlfelt et al., 1990; Linder-Aronson, 1970). The effect of tonsil surgery on dentofacial development has been studied to ascertain the effect of hypertrophied tonsils on the same subject. Recent reviews suggest that there is evidence of normalisation towards a more labial inclination of the upper and lower incisors, normalisation towards a more horizontal maxilla-mandibular growth pattern and horizontal catch-up growth of the mandible after tonsil surgery (Becking et al., 2017; do Nascimento, Masterson, Mattos, & Vilella, 2018). In some studies, the width of the upper dental arch is reported to increase (Linder-Aronson, Woodside, Hellsing, & Emerson, 1993; Vieira et al., 2012) and in one study the incidence of crossbite is reported to decrease (Hultcrantz et al., 1991).

2.3.3.3 Sleep disordered breathing

Two reviews have concentrated on the craniofacial changes in children with SDB and state that there is evidence of craniofacial disharmony with respect to paediatric SDB (Flores-Mir et al., 2013; Katyal et al., 2013). The most commonly described changes are a more convex facial profile (Ikävalko et al., 2012; Katyal et al., 2013), increased values of anterior facial height and a vertical reduction in posterior facial height (Löfstrand-Tideström et al., 1999; Zucconi et al., 1999). Additionally, SDB is associated with changes in dental arch morphology such as crossbite, narrower upper dental arch and shortened lower dental arch (Hultcrantz & Löfstrand Tideström, 2009; Ikävalko et al., 2012; Löfstrand-Tideström et al., 1999; Pirila-Parkkinen et al., 2009; Zucconi et al., 1999).

Tonsil hypertrophy is thought to be the main etiological reason for paediatric SDB. Further, it has been stated that tonsil hypertrophy is the main cause of mouth breathing. Hence, the dentofacial changes that are associated with tonsil hypertrophy and mouth breathing are also associated with SDB. It has, however, been suggested that changes in dentofacial development in children with SDB are not only due to tonsil hypertrophy but also to more complicated environmental and endocrinologic mechanisms. For example, children with SDB have been reported to have abnormal nocturnal growth hormone secretion (Nieminen et al., 2002), and it is proposed that changes in hormonal status have an influence on facial growth (Peltomäki, 2007). It has also been speculated that sleeping position could have an effect on the dentofacial morphology in children with SDB (Pirilä et al., 1995). Additionally, children with congenital unfavourable craniofacial morphology are at higher risk for SDB. Therefore, the causality of the SDB and the dentofacial morphology changes is not simple to determine and it is likely to be bidirectional.

3 AIMS OF THE STUDY

1. To study whether snoring two to three years old children have changes in dentofacial morphology compared to non-snoring same-aged children. (I)

2. To study whether two to three years old children with OSA have changes in dentofacial morphology compared to non-snoring same-aged children. (II)

3. To identify specific clinical, anamnestic and PSG features that are characteristic for two to three years old children with OSA in contrast to snoring children without OSA. (III)

4. To analyse the contemporary literature to assess the changes in dentofacial morphology after tonsil surgery and to clarify whether tonsil surgery is needed to attain normal dentofacial development in children with hypertrophied tonsils. (IV)

4 MATERIAL AND METHODS

4.1 Child-Sleep project (I, II, III)

4.1.1 Study design and participants

The present studies were executed as part of the Child-Sleep project, which is a longitudinal birth cohort study that involves 1673 children born between April 2011 and February 2013 at Tampere University Hospital, Finland. The Child-Sleep project is a research project jointly undertaken by Pirkanmaa Hospital District, the Finnish Institute for Health and Welfare, Tampere University, the University of Eastern Finland and the University of Helsinki.

The inclusion criteria for the cohort study were living in the Pirkanmaa Hospital District catchment area and that the native language in the family was Finnish. The families were recruited to the study prenatally in maternity clinics after the 32nd week. Questionnaires, which concentrated on sleep, somatic and mental health, behaviour, temperament and family relations, were filled out prenatally, at the birth of the child and at 3, 8, 18 and 24 months after the birth (Paavonen et al., 2017).

The present studies concentrated on snoring children in the Child-Sleep cohort. The Sleep Disturbance Scale for Children (SDSC) (Bruni et al., 1996) was used to estimate snoring frequency at the ages of 8 and 24 months. The SDSC is a validated rating scale developed for the evaluation of sleep disorders in children. The question from the sleep-disordered breathing subscale, which was used for patient selection, was "Does the child snore?" and the answer options were "always (daily)", "often (3–5 times per week)", "sometimes (once or twice per week)", "occasionally (once or twice per month or less)" and "never."

The inclusion criteria for the present studies were parent-reported snoring "always" or "often". A snoring minimum of three night per week was selected to be the cut-off point because a reported snoring minimum of three nights per week has been used to indicate a significant amount of snoring in children in previous studies (Kaditis et al., 2017). The exclusion criteria were severe illnesses/disabilities or snoring only during respiratory infections.

Those families who had reported their child to snore a minimum of three nights per week at 8-month questionnaire (41 of 1291 families) or 24-month questionnaire (24 of 947) were contacted and offered the opportunity to take part in further clinical examinations. Parents were interviewed via telephone to ensure the occurrence of snoring before enrolment to the study. The opportunity to take part in the study was also offered to families whose child did not snore regularly to recruit control patients.

Based on the 8-month questionnaire, 22 snoring and 13 non-snoring children were recruited to participate in the study. Seven snoring and nine non-snoring children dropped out of the study before the age of 24 months. Based on the 24-month questionnaire, 17 new snoring and 16 new non-snoring children were recruited. In total, 52 children from the cohort were recruited to the present study (Figure 10). Moreover, 32 of the children (14 boys and 18 girls) were snorers and 20 (14 boys and 6 girls) were controls.

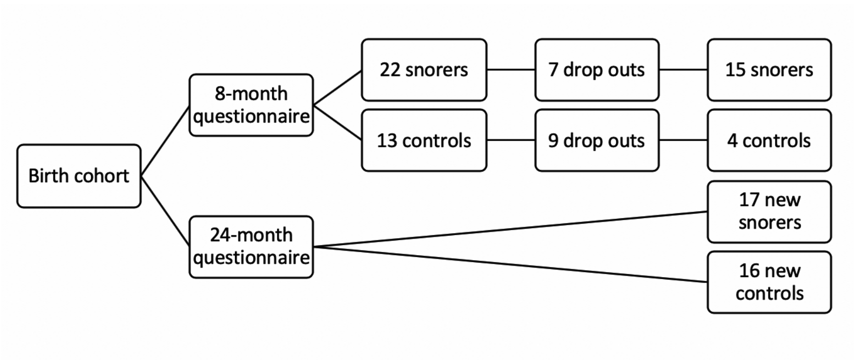

Figure 10. Study design (S.Markkanen)

4.1.2 Outcome measures

At the mean age of 27 months (min 23, max 34), otorhinolaryngological and paediatric examinations were carried out for snorers and controls. A full-night polysomnography was performed on average 19 days (range 0-99) after the clinical examinations. At the mean age of 33 months (min 28, max 42), a dental examination was performed. The dental examination time was chosen to be around the time when primary dentation had just been completed. Otorhinolaryngological examination was carried out by one specialist in otorhinolaryngology, paediatric examination by three specialists in paediatrics and dental examination by two dentists.

The otorhinolaryngological examination was successfully performed on 52 children (32 snorers and 20 controls). The examination included inspection of the oral cavity and oropharynx, anterior rhinoscopy and nasal flexible fibre optic endoscopy of the nasopharynx, hypopharynx and larynx. To induce local anaesthesia, 4% lidocaine was sprayed in one nostril. Palatine tonsil size was assessed using Friedman's tonsil classification (0 = no tonsils, tonsillectomy has been made, 1 = tonsils are hidden between the palatoglossal and palatopharyngeal arch, 2 = tonsils extend to the arches, 3 = tonsils extend beyond the arches but not to the midline, 4 = tonsils extend to the midline) (M. Friedman et al., 1999). A four-class scale to determine the adenoid size with respect to the nasopharyngeal volume was used (tissue filling 0% to 25%, 26% to 50%, 51% to 75% or 76% to 100% of the nasopharyngeal volume). Dominant mouth breathing was assessed visually during the clinical examination.

The paediatric examination was successfully performed on 49 children (30 snorers and 19 controls). The examination included measurements of weight and height and a general paediatric and neurologic assessment. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared.

Questionnaires, which concentrated, for example, on sleep, nutrition, behavioural problems, infections and allergies, were filled out during the otorhinolaryngological and paediatric examinations. The SDSC questions: "How often does your child gasp for breath or is unable to breath during sleep?", "Does the child snore?" and "How often does your child experiences daytime somnolence?" were used for analysis. In addition, the parents were asked about their child's breathing habits and nasal symptoms.

A full night polysomnography was successfully performed on 49 children (31 snorers and 18 controls). Two children did not arrive for the polysomnography and one registration failed because of the child's respiratory infection. The polysomnographies were performed at the sleep laboratory of Tampere University Hospital. The following signals were recorded: eight channels of electroencephalography, two channels of electro-oculography, submental electromyography, airflow by oronasal thermistor and nasal pressure transducer signal, oxygen saturation by two pulse oximeters, thoracoabdominal inductance plethysmography, diaphragmatic and abdominal electromyography, Emfit mattress sensor, electrocardiography, end-tidal partial pressure of carbon dioxide, video, sleeping position and snoring. The recordings were manually analysed by two independent clinical neurophysiologists. The sleep stages and respiratory events were scored according to the paediatric rules in the American Academy of Sleep Medicine manual (Berry et al., 2012). Snoring periods were selected based on piezo and nasal pressure signal and verified by listening. The percentage of time spent snoring from the total sleep time was calculated for each child. A diagnosis of OSA was made if the OAHI was more than one per hour.

The dental examination was successfully performed on 51 children (32 snorers and 19 controls) and included the sagittal relationship of the second primary molars (mesial step/flush/distal step), overjet (normal/increased ≥3 mm), overbite (open bite ≤0 mm/normal/deep bite ≥3 mm), crowding and spacing (yes/no), and anterior and lateral crossbite (yes/no). Occlusal bite index was obtained to measure the inter canine width between the upper primary canines (dd. 53–63) and the intermolar width between the upper second primary molars (dd. 55–65). No study models were made, but measurements were made directly from the wax bite indexes (Yellow Bite Wax Sheets, 0.18-0.22 cm thick, Modern Materials) with a digital sliding calliper (Somet PM160 digi s hl.d 1.6 TYP:14016458KS). For the measurement, the tips of the sliding calliper were placed on the right and left sides in the wax bite grooves, indicating the upper canine cusp tip and the mesiopalatal cusp of the upper second primary molar. A profile photograph of the face was then taken with a digital camera. The children stood at rest and were asked to bite their teeth together when the photograph was taken. The photographs were printed, and the soft tissue landmarks (glabella, subnasale, and pogonion) were identified to measure facial convexity (Figure 11). Upper dental arch and soft tissue measurements were made twice by one researcher and the mean of the measurements was used in the statistical analysis.

Figure 11. The profile measurement points. Glabella (G), subnasale (Sn) and pogonion (Pg). (S.Markkanen)

4.1.2.1 Snorers and controls (I)

In publication I, 32 snorer children, whose parents reported them snoring a minimum of three nights per week at 8- or 24-months questionnaire, and 19 controls were compared in order to evaluate the differences between mouth breathing tendency, occlusal characteristics, upper dental arch dimensions and soft tissue profile measurements. In early childhood, snoring status fluctuates naturally (Luo, Schaughency, Gill, Dawes, & Galland, 2015). At the time of the examinations, 56% of children in the snorer group were still snoring frequently (≥ 3 night/week). All the control children were still non-snoring. Consequently, the snorer group represents children who have a history of remarkable snoring between the ages of 8 and 24 months, with the control group representing non-snoring children.

The parameters outlined above were further compared between those snorer children whose parents reported current snoring to be a minimum of 3 nights per week at the age of 24 months (n = 18) and the controls (n =19), and inside the snorer group to distinguish differences between mainly mouth breathing snoring children (n=10) and mainly nasal breathing snoring children (n=22).

4.1.2.2 Children with OSA and non-snoring children (II)

An OSA diagnosis was given to 9 children. In PSG, the snoring time of 18 children was less than 1% of the total sleeping time, and they were interpreted to be PSG-verified non-snoring children.

In publication II, the children with OSA and PSG-verified non-snoring children were compared to evaluate the differences between tonsillar size, mouth breathing tendency, occlusal characteristics, upper dental arch dimensions, soft tissue profile measurements and BMI. In addition, it was examined whether palatine tonsil size, adenoid size or breathing habit could independently have an influence on occlusal characteristics, upper dental arch dimensions or soft tissue profile measurements. For this analysis, palatine tonsil size was regrouped into two classes: ‘small palatine tonsil size’ (Friedman classes 1–2) and ‘large palatine tonsil size’ (Friedman classes 3–4). Adenoid size was also regrouped into two classes: ‘small adenoid size’ (tissue filling 0% to 50% of the nasopharyngeal volume) and ‘large adenoid size’ (tissue filling 51% to 100% of the nasopharyngeal volume).

4.1.2.3 Snoring children with or without OSA and controls (III)

In publication III, the 32 snorer children, whose parents reported them to snore a minimum of three nights per week at 8- or 24-months questionnaire, and 20 controls were compared to evaluate the differences between currently reported snoring and PSG parameters.

The snorer group was further divided into two groups according to OSA-diagnosis. The OSA-diagnosis was given to 9 children. In addition, 22 children from the snorer group did not have OSA and were labelled no OSA-group. One child's PSG was unsuccessful.

The children with OSA and the snoring children without OSA were compared to evaluate the differences between parent-reported information (current snoring, night-time breathing difficulties, daytime somnolence, daytime mouth breathing, rhinitis and nasal stuffiness), PSG parameters and clinical findings (sex, age, palatine tonsil size, adenoid size, mouth breathing, secretion and swelling of the nasal mucosa, BMI).

4.1.3 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (version 22 or newer) (SPSS Inc. Chicago, Illinois, USA). Mann-Whitney U-test and Kruskal-Wallis test were used to compare quantitative variables between groups. Bonferroni correction was used when the Mann-Whitney U-test was used to compare differences pairwise after the Kruskal-Wallis test. Crosstabulation was used to compare qualitative variables and the strength of the association was evaluated with Fisher exact test. $P<0.05$ was considered statistically significant.

4.1.4 Ethical considerations

The Child-Sleep study protocol was approved by the Ethical Committee of Pirkanmaa Hospital District in March 2011 (approval number R11032). The families were personally asked to participate in the present studies. Written informed consent was obtained from at least one parent. All research was performed in accordance with relevant guidelines and regulations.

4.2 Systematic review and meta-analysis (IV)

4.2.1 Strategy of the literature search and eligibility criteria

The aim of the systematic literature review was to clarify the effects of tonsil surgery on the dentofacial development of children. Studies which included an evaluation of both the palatine tonsils and the adenoid were included. The null hypothesis for the review was "Tonsil operations do not change dentofacial development in children aged between 3 and 10 years".

Search strategies were planned for specific databases. The databases used were Medline, PubMed, Embase, Cochrane Central Register of Controlled trials, Cochrane Database of Systematic Reviews and Web of Science Core Collection. The original searches were conducted on June 13 and 14, 2016. All studies published up to that date were included. Update searches were subsequently conducted on October 23, 2019. References published from 1.1.2016 onwards were searched.

The eligibility criteria for the review were defined using the PICOS format as follows: P (population): 3- to 10-years-old (mean intervention age) children with obstructed tonsils. Both palatine tonsil size and adenoid tissue size had to have been evaluated; I (intervention): Adenoidectomy and/or tonsillectomy (total or partial); C (comparison): Children not undergoing adenoidectomy or tonsillectomy; O (outcome): Dentofacial parameters measured before and at least one year after intervention; and S (study design): Prospective clinical comparative studies with at least 20 participants. The language was not restricted.

4.2.2 Data extraction

Three separate investigators reviewed the titles and abstracts of the papers. Articles that could not be excluded based on titles and abstracts were analysed full-text by the same three investigators. If unanimous agreement could not be reached, the situation was resolved with discussion between the investigators. Data from the studies were collected by two investigators using a specially designed data extraction form. The following information was collected: author, year of publication, country, study design, sample size, age of the subjects, gender of the subjects, description of the test and control groups, intervention, follow-up period, methods of assessment and outcome measures. The most complete data with the longest follow-up period were accepted.

The principal summary measures used were difference in means/medians between case and controls before and after the intervention. In part of the studies, the means/medians at both timepoints were not reported. Instead, only the changes between the timepoints was reported and these were used as a summary measure in those cases.

4.2.3 Study selection and characteristics

The searches on June 13-14, 2016 retrieved 1447 references, and 921 references remained for screening after deduplication. After the titles and abstracts of the papers were reviewed, 882 papers were excluded and 39 were analysed full-text. In total, 8 papers fulfilled the inclusion criteria and were accepted to this review.

On October 23, 2019, the update searches retrieved 592 references, and 309 references remained for screening after deduplication. After the titles and abstracts of the papers were reviewed, no new papers fulfilling the inclusion criteria were found.

The eight studies accepted to the review were published between 2006 and 2016. Seven of the studies were executed in Brazil and one in Sweden. Three of the Brazilian articles were from the University of Sao Paulo at Ribeirao Preto and had the same research ethics committee number (Mattar, Matsumoto, Valera, Anselmo-Lima, & Faria, 2012; Mattar, Valera, Faria, Matsumoto, & Anselmo-Lima, 2011; Vieira et al., 2012). Three other Brazilian articles were from the Federal University of Minas Gerais (Brunelli et al., 2016; Petraccone Caixeta et al., 2014; Souki, Pimenta, Franco, Becker, & Pinto, 2010) and one from the Federal University of Sao Paulo (Pereira, Bakor, Louis, & Weckx, 2011). The two sets of three studies were both considered to involve potentially the same population and were therefore not treated as independent studies.

In one study, the inclusion criteria for the cases were obstructive sleep apnoea and enlarged tonsils and/or adenoids (Zettergren-Wijk et al., 2006). In the other studies, the inclusion criteria were mouth breathing and enlarged tonsils and/or adenoids. In all studies, both palatine tonsil and adenoid size were evaluated. All but one study classified palatine tonsil size using the classification of Brodsky (Brodsky, 1989; Brodsky & Koch, 1992). Adenoid size was evaluated using lateral skull radiography and the method of Cohen and Konak (Cohen & Konak, 1985) in three studies (Mattar et al., 2012, 2011; Vieira et al., 2012). Four studies used endoscopic assessment of the adenoid tissue (Brunelli et al., 2016; Petraccone Caixeta et al., 2014; Souki et al., 2010; Vieira et al., 2012). One study did not describe the specific method used to evaluate palatine tonsil or adenoid size (Zettergren-Wijk et al., 2006).

The controls in four studies were nasal breathing children (Mattar et al., 2012, 2011; Vieira et al., 2012; Zettergren-Wijk et al., 2006). In two studies, the controls, were mouth breathing children and had enlarged tonsils and/or adenoids, but did not undergo any intervention (Brunelli et al., 2016; Souki et al., 2010). In one study, there was both a mouth breathing and a nasal breathing control group (Petraccone Caixeta et al., 2014). Taking into account the fact that that there were only four separate materials in the eight studies, the total number of cases and controls in the review were 107 and 140, respectively.

At the time of the intervention, the mean age among cases was 4.25 to 6.9 years and 5.08 to 6.7 among controls. In one study, the cases and controls were further divided into deciduous and mixed dentation groups, with mean ages of 4.7/5.1 and 7.5/7.9, cases/controls, respectively (Souki et al., 2010). In one study, the mean age was not reported, but the age range was from 7 to 11 years (Pereira et al., 2011).

In five of the studies, the intervention was adenotonsillectomy (Brunelli et al., 2016; Pereira et al., 2011; Petraccone Caixeta et al., 2014; Souki et al., 2010; Vieira et al., 2012), in two studies either adenotonsillectomy or adenoidectomy (Mattar et al., 2012, 2011) and in one study adenotonsillectomy, adenoidectomy or tonsillectomy (Zettergren-Wijk et al., 2006).

In seven of the studies, the preoperative breathing pattern of the patients was evaluated (Brunelli et al., 2016; Mattar et al., 2012, 2011; Pereira et al., 2011; Petraccone Caixeta et al., 2014; Souki et al., 2010; Vieira et al., 2012). In five of them, it was reported that the mouth breathing pattern was normalised after the operation (Brunelli et al., 2016; Mattar et al., 2012, 2011; Souki et al., 2010; Vieira et al., 2012).

In all studies, the follow-up time after intervention was from 1 to 5 years. The assessment of the outcome measures was made from cephalometric radiographs and/or dental study casts.

4.2.4 Quality assessment and risk of bias

All of the selected studies were nonrandomised and consequently the risk of bias in the review in its entirety should be considered high. The Newcastle-Ottawa scale (Wells et al.) for assessing the quality of nonrandomised studies in meta-analyses was used to assess the quality of the individual studies. Two authors independently assessed each article. Disagreements were resolved by consensus.

The mean Newcastle-Ottawa scale score was 5.5 SD 1.51 when the maximum score was 9. Consequently, it can be said that the overall quality of studies was moderate. In case-control studies, the Newcastle-Ottawa scale comprehends three categories: selection, comparability and exposure. In all studies, the selection of the cases and controls was the weakest category. In one study, the cases were chosen by primary record source (polysomnography) (Zettergren-Wijk et al., 2006), in one study it was reported that otorhinolaryngological examination was executed by two doctors (Petraccone Caixeta et al., 2014). In other studies, the validation of the cases was not described precisely, or it was made based on only one person's opinion. None of the studies described whether the sample was truly random. In addition, none of the studies used true community controls or the selection of the controls was unclear. In one study, part of the controls were selected from a longitudinal cephalometric growth study (Zettergren-Wijk et al., 2006). The definition of the controls was clear in all studies. In all but one study (Pereira et al., 2011), the age of the cases and controls was matched. The ascertainment of exposure was clear in every study and the methods for assessing outcomes were the same for both cases and controls. The evaluation of non-responders was difficult in almost every study.

In five studies, neither the cases nor controls had undergone previous orthodontic treatments. In three studies, this was not clearly reported (Brunelli et al., 2016; Souki et al., 2010; Zettergren-Wijk et al., 2006). The sucking habits of the children – pacifier or thumb sucking – were reported in three studies (Petraccone Caixeta et al., 2014; Souki et al., 2010; Zettergren-Wijk et al., 2006). These features can be considered as confounders because they can have an effect on dentofacial development.

4.2.5 Statistical analysis

A meta-analysis was conducted when the data were methodologically homogenous enough to be pooled. The data, which were not applicable for the meta-analysis, were described and a summary of the findings was presented.

The meta-analysis of the parameters with continuous measure was performed using the function 'metacont' with R software (R Core Team, 2016). Depending on the heterogeneity, a random or fixed effect model was used. The heterogeneity was assessed with the I^2 statistics. The values of 25%, 50% and 75% were considered to indicate low, moderate and high heterogeneity, respectively (Grant & Hunter, 2006). The standardised mean difference and 95% confidence intervals were calculated. Forest plots were generated.

5 RESULTS

5.1 Snoring and dentofacial development in 2 to 3 years old children (I)

Those children whose parents had reported them to snore had a statistically significantly more convex profile than the control children (Table 4). The occurrence of mouth breathing was also statistically more common among snorer children (Table 4). Statistical analysis did not reveal significant differences between snorers and controls in any of the studied occlusal characteristics or in the measurements of maxillary dental arch dimensions (Table 4).

The same parameters were compared between those snorer children whose parents reported current snoring to be a minimum of 3 nights per week at the age of 24 months (n = 18) and the controls (n =19). Snoring children were found to have a mouth breathing preference statistically more frequently than the controls. No other statistically significant differences were found.

The same parameters were likewise compared inside the original snorer group (n = 32) to distinguish differences between mainly mouth breathing snoring children (n = 10) and mainly nasal breathing snoring children (n = 22). No statistically significant differences were found.

The duration of exclusive breastfeeding was 3.8 and 3.9 months among snorers and controls, respectively. No statistically significant difference was found.

Table 4. Otorhinolaryngological and dental findings compared between snorers and controls. Crosstabulation and Fisher's exact test used to compare qualitative variables and strength of association. Mann-Whitney U-test was used to compare quantitative variables. ¤median and interquartile range 0.25-0.75 presented.

	Snorer (n = 32)	**Control (n = 19)**	**p**
Mouth breathing			**0.035**
Yes	10 (31.3%)	1 (5.3%)	
No	22 (68.8%)	18 (94.7%)	
Sagittal relationship of 2nd primary molars			0.360
Mesial step			
Normal	21 (65.6%)	9 (50.0%)	
Distal step	5 (15.6%)	6 (33.3%)	
	6 (18.8%)	3 (16.7%)	
		Missing 1	
Overjet ≥3 mm			0.765
Yes	14 (46.7%)	7 (38.9%)	
No	16 (53.3%)	11 (61.1%)	
	Missing 2	Missing 1	
Overbite			0.766
Open bite ≤ 0 mm	4 (12.5%)	1 (5.6%)	
Normal	15 (46.9%)	10 (55.6%)	
Deep bite ≥ 3mm	13 (40.6%)	7 (38.9%)	
		Missing 1	
Crowding			0.295
Yes	8 (25.0%)	2 (11.1%)	
No	24 (75.0%)	16 (84.2%)	
		Missing 1	
Lateral crossbite			0.623
Yes	2 (6.3%)	2 (10.5%)	
No	30 (93.8%)	17 (89.5%)	
Inter canine width (mm)¤	27.4 (26.8-28.8) Missing 4	27.9 (27.0-29.3) Missing 2	0.394
Inter molar width (mm)¤	32.9 (31.7-34.2) Missing 11	33.8 (31.9-35.3) Missing 8	0.331
Arch length (mm)¤	28.5 (27.9-29.2) Missing 17	28.9 (27.1-29.9) Missing 15	0.796
Soft tissue profile (degrees)¤	166.2 (164.3-170.2) Missing 4	170.2 (167.9-173.9) Missing 7	**0.044**

5.2 OSA and dentofacial development in 2 to 3 years old children (II)

Statistically significant differences were found between children with OSA and PSG-verified non-snoring children in adenoid size, mouth breathing tendency and inter canine width. Children with OSA had larger adenoid size with respect to the nasopharyngeal volume and a stronger tendency to mouth breathing (Table 5). Children with OSA had narrower inter canine width than non-snoring children, median 27.0 versus 28.2 mm, respectively. No statistically significant differences were found when comparing occlusal characteristics, soft tissue profile measurements, BMI or palatine tonsil size (Table 5).

The occlusal characteristics, upper dental arch dimensions and soft tissue profile measurements were tested separately between palatine tonsil size, adenoid size and breathing habit. The only statistically significant finding ($p = 0.047$) was that inter canine width was slightly narrower among mouth breathing children than nasal breathing children, 27.0 (25.5–27.2) and 27.7 (27.1–29.5), median and interquartile range 0.25–0.75, respectively.

In total, 55.6% ($n = 5$) of children with OSA and 72.2% ($n = 13$) of PSG-verified non-snoring children used or had used a pacifier. The duration of exclusive breastfeeding was 5.0 months (3.5–6.0) among children with OSA and 4.0 months (2.5–5.0) among PSG-verified non-snoring children, median and interquartile range 0.25–0.75, respectively. These differences were not statistically significant.

Table 5. Otorhinolaryngological and dental findings compared between children with OSA and PSG verified non-snoring children. Crosstabulation and Fisher's exact test used to compare qualitative variables and strength of association. Mann-Whitney U-test was used to compare quantitative variables. ¤median and interquartile range 0.25-0.75 presented.

	Children with OSA (n=9)	**PSG verified non-snoring children (n=18)**	**p**
Mouth breathing			**0.002**
Yes	6 (66.7%)	1 (5.6%)	
No	3 (33.3%)	17 (94.4%)	
Adenoid size			**0.020**
0-25%	2 (22.2%)	13 (72.2%)	
26-50%	3 (33.3%)	4 (22.2%)	
51-75%	2 (22.2%)	1 (5.6%)	
76-100%	2 (22.2%)	0 (0.0%)	
Palatine tonsil size (Friedman classification)			0.268
1	2 (22.2%)	8 (44.4%)	
2	3 (33.3%)	7 (38.9%)	
3	4 (44.4%)	3 (16.7%)	
Sagittal relationship of 2nd primary molars			1.000
mesial step	6 (66.7%)	10 (58.8%)	
normal	2 (22.2%)	5 (29.4%)	
distal step	1 (11.1%)	2 (11.8%) Missing 1	
Overjet ≥3 mm			1.000
yes	4 (50.5%)	9 (52.9%)	
no	4 (50.5%) Missing 1	8 (47.1%) Missing 1	
Overbite			1.000
open bite	1 (11.1%)	1 (5.9%)	
normal	4 (44.4%)	8 (47.1%)	
deep bite	4 (44.4%)	8 (47.1%) Missing 1	
Crowding			0.628
Yes	3 (33.3%)	3 (17.6%)	
No	6 (66.7%)	14 (82.4%) Missing 1	
Lateral crossbite			1.000
Yes	1 (11.1%)	1 (5.6%)	
No	8 (88.9%)	17 (94.4%)	
Upper inter canine width (mm)¤	27.0 (25.9-27.2)	28.2 (26.2-29.6) Missing 2	**0.032**
Upper inter molar width (mm)¤	32.6 (29.4-33.8) Missing 4	32.4 (31.6-33.1) Missing 6	0.442
Upper dental arch length (mm)¤	28.8 (27.9-29.6) Missing 5	28.1 (27.1-29.5) Missing 12	0.762
Soft tissue profile (degrees)¤	167.3 (164.8-169.5) Missing 1	172.3 (168.8-174.8) Missing 4	0.297
BMI (kg/m2)¤	16.0 (15.5-17.0)	16.7 (16.0-17.8) Missing 1	0.164

5.3 Clinical and PSG features in 2 to 3 years old children with OSA (III)

Based on the 24-month questionnaire, the prevalence of snoring in the birth cohort was 2.5%.

At the time of the otorhinolaryngological and paediatric examinations (mean age 27 months), the parents of the control children still reported that their children never snored (one answer missing). The reported current snoring was distinctly more common ($p < 0.001$) in the snorer group, but the frequency varied within the group. Currently, 24.1% of the snorer children snored always; 37.9% 3 to 5 nights per week; 20.7% 1 to 2 nights per week; 10.3% 1 to 2 nights per month; and 6.9% never (three answers missing).

The PSG parameters were compared between the snorer and control group. Significant differences were found between OAHI and snoring time percentage from the total sleep time (S%), but not between the sleep parameters (Table 6). A total of 9 children (5 boys and 4 girls) from the snorer group were diagnosed to have OSA. Moreover, in the snorer group, 22 children did not fulfil the diagnostic criteria for OSA, and one child's PSG was missing. Consequently, the prevalence of OSA in the snorer group was 29%. None of the children in the control group were diagnosed with OSA.

When comparing the PSG parameters between the children with OSA and snoring children without OSA, significant differences were found between AHI, OAHI, S%, total sleep time and sleep stage N1 (Table 6). In the OSA-group, OAHI was 1.2 to 6.3/h (median 1.5/h) and S% was 16.0% to 94.7% (median 63.6%). In the no OSA-group, OAHI was 0.0 to 0.9/h (median 0.1/h) and S% was 0.0% to 87.8% (median 6.9%). In the control group, OAHI was 0.0 to 0.9/h (median 0.0/h), and S% was 0.0% to 34.5% (median 0.0%). The differences in S% between these three groups separately were statistically significant.

Table 6. The sleep and respiratory parameters. Snorer group compared with control group and OSA-group compared with no OSA-group. Median and interquartile range 0.25-0.75 presented. AHI = apnoea/hypopnoea index, OAHI = obstructive apnoea/hypopnoea index, ODI3 = oxygen desaturation index 3%, S% = snoring time % from total sleep time, TRT = total recording time, TST = total sleep time, N1 = sleep stage N1, N2 = sleep stage N2, N3 = sleep stage N3, REM = rapid eye movement sleep, REMlat = REM latency, ARI = arousal index

	Snorer group (n = 31)	**Control group (n=18)**	**p**	**OSA-group (n=9)**	**no OSA-group (n=22)**	**p**
AHI (n/h)	1.7 (1.1-3.0)	1.8 (1.1-3.4)	0.841	3.6 (2.2-5.0)	1.2 (0.7-1.9)	**<0.001**
OAHI (n/h)	0.3 (0.0-1.3)	0.0 (0.0-0.1)	**0.003**	1.5 (1.3-3.1)	0.1 (0.0-0.4)	**<0.001**
ODI3 (n/h)	1.0 (0.4-2.2)	1.6 (0.7-3.0)	0.367	2.2 (0.2-6.3)	0.9 (0.5-0.19)	0.513
S% (%/TST)	19.5 (2.3-58.6)	0.0 (0.0-12.2)	**<0.001**	63.6 (30.0-84.0)	6.9 (0.6-27.7)	**0.001**
TRT (min)	598.0 (570.5-630.5)	617.9 (575.8-640.7)	0.206	602.0 (591.0-634.0)	585.5 (563.0-615.5)	0.132
TST (min)	505.5 (464.0-551.5)	533.5 (487.4-593.0)	0.084	555.5 (504.0-569.5)	477.8 (458.4-516.4)	**0.005**
N1 (%/TST)	4.1 (2.6-7.2)	3.1 (1.4-6.3)	0.195	3.0 (1.4-3.6)	5.6 (3.2-8.4)	**0.005**
N2 (%/TST)	32.5 (28.3-39.3)	36.4 (34.2-41.1)	0.081	32.5 (26.7-38.7)	32.7 (28.7-39.8)	0.660
N3 (%/TST)	31.4 (26.2-38.8)	30.3 (24.3-36.0)	0.431	35.6 (26.5-41.3)	29.8 (25.8-35.3)	0.374
REM (%/TST)	28.8 (25.9-32.2)	27.2 (25.5-31.9)	0.548	31.0 (27.2-32.8)	27.8 (25.9-32.1)	0.249
REMlat (min)	71.0 (57.5-117.0)	63.5 (50.3-92.4)	0.238	69.5 (61.8-96.8)	75.8 (54.0-117.0)	0.773
ARI (n/h)	9.6 (8.7-11.2)	9.9 (8.3-11.3)	0.947	10.0 (9.2-12.7)	9.4 (8.4-11.1)	0.223

The parent-reported history was compared to find differences between children with OSA and snoring children without OSA. The prevalence of breathing difficulties while sleeping was not associated with OSA-diagnosis. In fact, none of the parents of children with OSA reported their child to have breathing difficulties during the night-time. In addition, the parent-reported frequency of current snoring or daytime somnolence did not statistically differ between the children with OSA and the snoring children without OSA. Breathing through the mouth in the daytime reported by parents was more common ($p = 0.015$) among the children with OSA (4 of the 9 children) than among the snoring children without OSA (1 of the 22 children). Nasal stuffiness did not differ statistically between the groups.

Clinical features were likewise compared to find differences between children with OSA and snoring children without OSA. Adenoid size was found to be larger in the OSA-group ($p = 0.008$). However, not all children with OSA had a large adenoid size. The size of the palatine tonsil was not found to differ significantly. Mouth breathing during the examination was found to be more common among the children with OSA (6 of the 9 children) than the snoring children without OSA (3 of the 22 children) ($p = 0.007$). None of the children had a nasal septum deviation or significant deformities in the upper respiratory track.

5.4 The effect of tonsil operations on dentofacial morphology – a systematic review and meta-analysis (IV)

5.4.1 Results of individual studies

The parameters studied in the studies can be divided into two categories: occlusion parameters and parameters associated with facial morphology.

5.4.1.1 Occlusion

Occlusion and dental arch morphology are reported in five studies (Brunelli et al., 2016; Mattar et al., 2012; Pereira et al., 2011; Petraccone Caixeta et al., 2014; Vieira et al., 2012)..

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5.4.1.1.1 Mouth-breathing cases versus nasal-breathing controls

In four studies, mouth breathing cases were compared to nasal breathing controls at the beginning of the study (Mattar et al., 2012; Pereira et al., 2011; Petraccone Caixeta et al., 2014; Vieira et al., 2012). Of these, the maxillary inter canine and second molar widths were evaluated in three studies. Two of them did not find differences between cases and nasal breathing controls (Mattar et al., 2012; Petraccone Caixeta et al., 2014). Vieira et al. (2012) reported lower inter canine width, but not second molar width in cases. It should be pointed out that two of the previously mentioned studies may have partly had the same study population, but Vieira et al. (2012) evaluated patients whose intervention was adenotonsillectomy and Mattar et al. (2012) patients whose intervention was adenoidectomy or adenotonsillectomy.

Petraccone Caixeta et al. (2014) found larger mandibular arch length and larger mandibular inter canine and second molar width in their studied cases. The morphology of the mandibular arch was not examined in the other studies.

The palatal vault was found to be deeper by Petracoccone Caixeta et al. (2014), but not by Viera et al. (2012). Pereira et al. (2011) also found that cases had a shallower overbite than controls, but Mattar et al. (2012) did not find any difference. The position of the maxillary and mandibular incisors was evaluated using different parameters in two studies (Mattar et al., 2012; Pereira et al., 2011). Perreira at al. (2011) found fewer orally tilted mandibular incisors, but Mattar et al. (2012) did not find any differences. Statistically significant differences in the other measured parameters, which included overjet (Mattar et al., 2012; Pereira et al., 2011); the presence of anterior open bite or posterior crossbite (Mattar et al., 2012); the terminal plane of the maxillary and mandibular second molars (Mattar et al., 2012); the length or perimeter of the maxillary dental arch (Petraccone Caixeta et al., 2014); and the perimeter of the mandibular dental arch (Petraccone Caixeta et al., 2014), were not found in any of the studies.

In two of the four studies, the differences that were observed between the cases and the nasal breathing controls prior to tonsil operation decreased after the operation (Pereira et al., 2011; Vieira et al., 2012). Mattar et al. (2012) did not find any differences prior to the operation, but the cases had larger overjet after the operation. Petraccone Caixeta et al. (2014) did not study the differences between the cases and the nasal breathing controls after the tonsil operation.

5.4.1.1.2 Mouth-breathing cases versus mouth-breathing controls

Two studies compared the cases and mouth breathing controls at the beginning of the study and after the operation (Brunelli et al., 2016; Petraccone Caixeta et al., 2014). At the beginning of the study, these groups did not have any differences in the outcome parameters in either of the studies. After the operation, however, Petraccone Caixeta et al. (2014) found that the change in maxillary inter canine and second molar width was larger in the positive direction in cases, but there was no actual difference between the groups. They also found that the change in palatal depth, to the direction of deeper shape, was larger in controls, yet there was no actual difference between groups in this parameter either. Brunelli et al. (2016) studied the change in maxillary inter canine and intermolar width, maxillary arch length, and perimeter and palatal depth. They further assessed the change in palatal volume. A statistically significant difference was found in only the change in palatal volume after the operation, and this change was significantly greater among cases. It should be noted that Petraccone Caixeta et al. (2014) and Brunelli et al. (2016) may have partly had the same study population, and the results should not therefore be evaluated as being independent from each other.

5.4.1.2 Facial morphology

Changes in facial morphology are described in four studies (Brunelli et al., 2016; Mattar et al., 2011; Souki et al., 2010; Zettergren-Wijk et al., 2006). The comparison of the results is complicated because different parameters and different measuring techniques are used to describe both facial morphology and facial development.

5.4.1.2.1 Mouth-breathing cases versus nasal-breathing controls

Two of the studies compared mouth breathing cases and nasal breathing controls before and after the intervention. Zettergren-Wijk et al. (2006) found a variety of differences between these groups. The cases had a more posteriorly inclined mandible, a more anteriorly inclined maxilla, a greater lower anterior face height, a shorter lower posterior face height, a shorter anterior cranial base, more retroclined upper and lower incisors, reduced airway space and less pronounced nose. After the operation, the majority of the differences had decreased, and the cases only had a shorter anterior cranial base and a less pronounced nose compared with the controls. Mattar et al. (2011) found that the cases had higher inclination of the mandibular plane when compared with the cranial base or the palatal plane, larger gonial angle and a decrease in total and inferior posterior facial height. Additionally, the cases demonstrated predominant dolichofacial development, meaning that the relation between face height and face depth changed towards a longer face. After the operation, the differences were no longer found, but the predominant dolichofacial development could still be seen.

5.4.1.2.2 Mouth-breathing cases versus mouth-breathing controls

Souki et al. (2010) compared the mouth breathing cases and mouth breathing, non-operated controls and further divided the participants into deciduous dentition and mixed dentition groups. At the beginning of the study, no differences were found between the deciduous dentition cases and controls nor between the mixed dentition cases and controls. The change in measured parameters between the beginning of the study and the time-point after operation and follow-up was evaluated between the cases and controls in the deciduous and mixed dentition groups. The actual difference in parameters at the same time-point was not evaluated. The statistical significance of the changes in parameters was similar among cases and controls in the deciduous and in the mixed dentition groups, with the exception of a statistically significant reduction in angle between the maxilla and mandibular plane seen among cases in the deciduous dentition group, but not among controls. In this study, the change in angle between the anterior cranial base/maxilla and the mandible plane was not significant between the cases and controls in either the deciduous or mixed dentition groups.

Brunelli et al. (2016) compared the cases and the mouth breathing, non-operated controls. This study may describe the same population as Souki et al. (2010), but no further division into subgroups was made and the measured parameters were different. Brunelli et al. (2016) found that mouth breathing cases showed a statistically significant change in those parameters that described the forward displacement of the maxilla, but the controls did not. However, the actual difference in these parameters was not reported.

5.4.2 Synthesis of the results

Because of the methodological diversity in the studies and the fact that some of the studies described the same population, only two studies and two parameters in them could be included in the meta-analysis when the changes between the time-point before the operation and after the follow-up in cases and in controls were analysed. The parameters used were the degree of mandible plane inclination in relation to the anterior cranial base and the degree of maxilla inclination in relation to the anterior cranial base from Zettergren-Wijk et al. (2006) and Mattar et al. (2011). The corresponding author of the first article was contacted to obtain details of the changes and the standard deviations of the mentioned parameters (Zettergren-Wijk et al., 2006). The same information was obtained directly from the second article (Mattar et al., 2011).

Heterogeneity between studies was considered low in the parameter "the degree of the mandible plane inclination" ($I^2 = 0.0\%$). Consequently, the fixed effects model was used. The degree of mandible plane inclination showed a significantly larger change in cases compared to controls, total standardised mean difference and 95% confidence interval -0.83 [-1.27; -0.39] ($p < 0.001$) (Figure 12 & 13). The angle between the mandible plane and the anterior cranial base was reduced in both groups, but significantly more in those cases approaching morphology normalisation.

Heterogeneity between studies in the parameter "the degree of the maxilla plane inclination" was found to be moderate ($I^2 = 57.9\%$). Hence, the random effect model was chosen. No significant difference between groups was found.

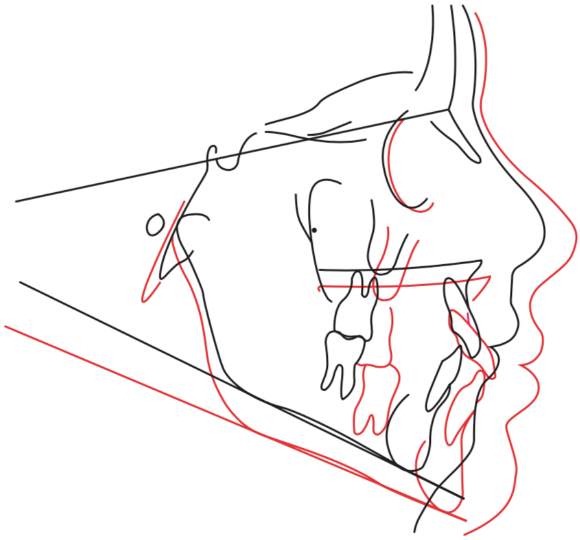

Figure 12. The mandibular growth direction changes from vertical (black) to more horizontal (red). (M. Ikävalko)

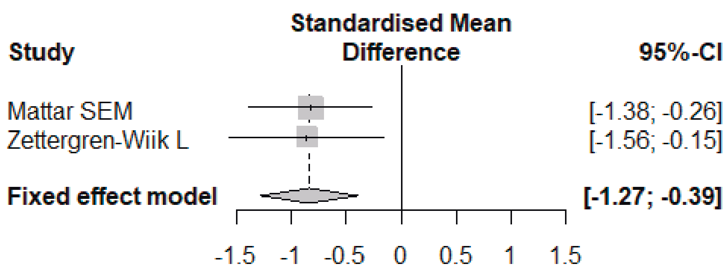

Figure 13. Forest plot of the degree of mandible plane inclination in relation to the anterior cranial base.

6 DISCUSSION

6.1 General discussion

Sleep and its effect on a person's physical and mental health is currently acknowledged to be an important part of well-being. In the case of children, it should be further considered what kind of impact sleep and its quality have on growth and mental development. Indeed, changes in these factors can have far reaching consequences. In some cases, paediatric OSA can be thought of as a precursor for adult OSA. Adult OSA further diminishes the quality of life in later years and is associated with cardiovascular diseases, metabolic consequences and increased mortality (Akashiba et al., 2002; Al Lawati, Patel, & Ayas, 2009; Bradley & Floras, 2009; Lavie, Lavie, & Herer, 2005). Further, the cognitive changes caused by paediatric OSA can lead to poorer school performance (Gozal, 1998), which might then lead to lower socioeconomic status in adulthood. The malocclusion and dentofacial changes associated with OSA can lead to symptoms later in life and increase the need for orthodontic treatments and orthognathic surgery. Furthermore, there is an increased risk of cardiovascular changes and metabolic syndrome already in childhood (Redline et al., 2007; Teo & Mitchell, 2013). Additionally, ongoing OSA symptoms, such as hyperactivity or bedwetting, cause stress and tiredness in the family and can lead to additive problems.

Paediatric OSA is different in many ways than adult OSA. In adult OSA, the key symptom is often tiredness, but in paediatric OSA the symptoms usually show up as behavioural problems such as inattention and hyperactivity (Chervin et al., 2002). In adults, being overweight is a major risk factor for OSA (Al Lawati et al., 2009). In the paediatric population, being overweight is also observed to be a risk factor, especially in adolescence (Li et al., 2010). However, the primary risk factor for paediatric OSA is obstruction in the upper airways caused by hypertrophic tonsils and adenoids. Because of the difference in the pathophysiology of adult and paediatric OSA, the primary treatment methods are also different. The primary treatment method for paediatric OSA is adenotonsillectomy, whereas soft palate surgery is currently rarely performed to treat adult OSA patients because of its poor outcomes (Shepard & Olsen, 1990). In adult OSA, weight reduction and CPAP are the first line treatments for many patients (Mannarino, Di Filippo, & Pirro, 2012).

Additionally, the OSA syndrome changes along with growth. Therefore, paediatric OSA cannot be considered to be a stabile entity throughout childhood and adolescence. Thus, it is crucial to have knowledge of the different features of different aged children's OSA. A knowledge of these features enables the early recognition and treatment of the syndrome and might prevent long-term influences. The present studies aimed to provide additional information on these features in two to three years old children.

Furthermore, the contemporary literature was reviewed to assess the changes in dentofacial morphology after tonsil surgery and to clarify whether tonsil surgery is required to secure normal dentofacial development in children with hypertrophied tonsils.

6.2 Principal findings

6.2.1 SDB in Child-Sleep project (I-III)

In the present study population, the prevalence of snoring was found to be 2.5% in 24-month-old children. The prevalence is quite low considering that in review articles the prevalence of snoring in children has been evaluated to be from 3% to 15% (Lumeng & Chervin, 2008; Marcus et al., 2012). In a previous Finnish study, the prevalence of snoring (always or ≥3/week) was 6.3%, but the mean age of the studied population was older (Liukkonen et al., 2008). The questionnaires in the present study were quite long and laborious to fill out, and therefore it can be expected that this might have resulted in a situation where the parents who participated in the study were more educated and represented a higher socioeconomical class compared to the whole Finnish population. This might have diminished the prevalence of snoring because paediatric SDB has been shown to be overrepresented in lower socioeconomical classes (Kuehni, Strippoli, Chauliac, & Silverman, 2008).

When considering the dentofacial development of snoring children (I, 32 children) and children with OSA (II, 9 children) in contrast to non-snoring controls (I, 19 children; II, 18 children), minor unfavourable changes could already be found in these young subjects. This is a remarkable finding considering that the obstructed breathing pattern cannot have been prevalent for years in such young patients. Additionally, it can be speculated that the unfavourable dentofacial development, which has been associated with SDB, begins at a young age. Further, it should also be considered that SDB in the study population was quite mild, PS or mild OSA, yet statistically significant differences were still found.

When comparing those children whose parents reported them to snore frequently to those children whose parents reported them to be non-snoring, the snoring children had a slightly more convex facial profile (I). Previously, a more convex facial profile has been associated with snoring in older children (Ikävalko et al., 2015; Katyal et al., 2013)

In study II, the PSG-verified children with OSA were compared to PSG-verified non-snoring children. The groups were chosen to represent opposite ends of the variety of sleep related breathing disorders to contribute to identifying any possible changes. All children with OSA were part of the snorer group and almost all control children were also verified by PSG to be non-snoring.

No difference in profile measurement could be found in this study. One reason for this could have been the smaller number of children studied (I 32 snorers/19 non-snorers vs. II 9 OSA/18 non-snorers).

Nevertheless, in study II, the upper inter canine width of the children with OSA were found to be narrower compared with the non-snoring children. Similar results have been previously detected in older children (Hultcrantz & Löfstrand Tideström, 2009; Löfstrand-Tideström et al., 1999; Pirila-Parkkinen et al., 2009). No changes in occlusion were found, but it can be speculated that narrower upper inter canine width could be a precursor for crossbite (Bell & Kiebach, 2014). As earlier mentioned, crossbite has been found to associate with SDB in older, four to 12 years old, children (Hultcrantz & Löfstrand Tideström, 2009; Ikävalko et al., 2012). Consequently, it could be concluded that the development of the characteristic occlusion changes in children with SDB will begin at a young age and proceed along with growth if the SDB persists. Previously, it has been shown that dentofacial abnormalities appear earlier and more often with children, aged two to 12 years, who have hypertrophied tonsils compared to children who do not (Kim, Rhee, Yun, & Kim, 2015). These findings further emphasise the importance of the early recognition and treatment of SDB.

The PSG, anamnestic and clinical features of the two to three years old children with OSA were investigated against the features of snoring children without OSA (III). It was observed that the snoring time percentage from total sleep time (S%) in PSG of children with OSA was longer than the S% of the snoring children without

OSA. This is an interesting observation because it might offer an easy screening method for paediatric OSA likelihood assessment. There is a scarcity of knowledge of S% in paediatric OSA, and S% has not been well researched in adults either. There is some evidence that among snoring adults with AHI <5 the S% is shorter than among adults with moderate (15≥AHI<30) or severe (30≥AHI<50) OSA. However, there was no statistically significant difference between the snoring adults with AHI<5 and adults with mild (5≥AHI<15) or very severe (30≥AHI<50) OSA (Hong et al., 2017). The scarcity of snoring in the very severe group can be explained by the number of apnoeas when there is no snoring sound. In the present study, the severity of OSA was generally mild (AHI median 3.6 and OAHI median 1.5), but there were still statistically significant differences between the OSA-, PS- and control children. Therefore, S% could be a better tool in paediatric OSA diagnostics than in adult OSA.

It was further observed that children with OSA are more likely to mouth breath and have a larger adenoid size compared to snoring children without OSA (III). However, the palatine tonsil was unlikely to be larger among children with OSA. These findings are in line with the age of the studied children, as it is generally accepted that adenoid hypertrophy is more likely in younger age groups than palatine tonsil hypertrophy. This leads to the question as to whether adenoidectomy alone could be a sufficient procedure for young OSA-patients. There have been some positive research results on the subject (Reckley et al., 2016). If adenoidectomy alone would serve as an effective and sustained treatment for young children with OSA, additional risks and expenses could be avoided. The risk of postoperative bleeding is markedly lower in respect of adenoidectomy than adenotonsillectomy (Gallagher, Wilcox, McGuire, & Derkay, 2010). Furthermore, recovery from an adenoidectomy is quicker than from an adenotonsillectomy. A quicker recovery would result in less discomfort for the child and lower costs to society by reducing the time parents are absent from work and lowering medicine costs. On the other hand, it has been suggested that between 2% and 29% of children who have undergone adenoidectomy because of airway obstruction will need tonsillectomy in the future (Black & Shott, 2014). The benefits achieved by using adenoidectomy alone would therefore be partly lost should there be a need for an additional operation later. Further research on the subject is needed.

6.2.2 Dentofacial development and tonsil surgery – a systematic review and meta-analysis (IV)

The contemporary literature indicates that children with hypertrophied tonsils have an alteration in their dentofacial development (Becking et al., 2017; do Nascimento et al., 2018). In addition, hypertrophied tonsils are firmly associated with mouth breathing and paediatric SDB, which are both further associated with dentofacial morphology changes. Tonsil surgeries, such as adenoidectomy, tonsillectomy, adenotonsillectomy and partial tonsillectomy, are used to relieve SDB, to change the mouth breathing habit towards normal nasal breathing and to secure normal dentofacial development or eventually to normalise an already altered morphology.

The systematic review and meta-analysis were conducted to clarify whether there is any dependable evidence on the effect of tonsil surgery on dentofacial development. However, knowledge on the subject was variable and partly controversial. Methodological differences between studies were common and the knowledge was difficult to compare or combine. It could be deduced, however, that tonsil surgery could have an effect on dentofacial development in children who have symptoms causing enlarged tonsils. Various positive effects, such as widening of the dental arches, increasing of the palatal volume and normalising of the facial proportions, were described in individual studies, but these effects could not be proven in all studies (Brunelli et al., 2016; Mattar et al., 2011; Petraccone Caixeta et al., 2014; Zettergren-Wijk et al., 2006). In meta-analysis, it was found that the degree of mandible plane inclination showed a significantly larger change in cases compared with controls. The angle between the mandible plane and the anterior cranial base reduced in both groups, but significantly more in those cases approaching morphology normalisation. Consequently, tonsil surgery can be an important procedure in securing normal dentofacial development.

It could not definitely be concluded in which situations or for which patients tonsil surgery would be indicated when the aim is dentofacial development. However, when children have enlarged tonsils, they are at further high risk of SDB and mouth breathing (Arens et al., 2001; Behlfelt et al., 1990; Linder-Aronson, 1970). Therefore, these features should not be considered to be separate entities but rather as an entirety. Tonsil surgery has a positive effect on OSA (Kaditis et al., 2016; Marcus et al., 2012), and often the indication for tonsil surgery is not only to secure normal dentofacial development.

6.3 Strengths and limitations

6.3.1 Child-Sleep project (I, II, III)

The strength of the study was the homogeneous group of two years old children. In various studies, the study population has been heterogeneous when considering the age of the children, and there is a scarcity of studies that concentrate on young children. The participants in the study were examined by experts from different medical fields and in-laboratory PSG was performed for all participants, including controls.

The study has evident limitations. The number of patients is low. Thus, the results of this study should be strengthened by a larger number of patients. Although the age of the children is the strength of the study, it also caused challenges in terms of examination. Co-operation, especially during the dental examination, was varied, and therefore all the planned measurements could not be collected. The assessment of the facial profile was made with photography analysis. No cephalometric radiographs were taken because of the age of the children. However, this kind of photography assessment has previously been used for the same purpose (Ikävalko et al., 2015). Furthermore, ensuring of the right head and jaw position (teeth together) for photography in this age-group can be challenging.

There are some confounding factors to be taken into account. First, three children had previously undergone an adenoidectomy and one an adenoidectomy and partial tonsillectomy, which can be interpreted as a confounder. Second, a finger sucking habit was not reported by parents in the questionnaires. Despite the fact that a finger sucking habit was not directly studied, the incidence of open bite would indirectly indicate a long-lasting/intensive non-nutritive sucking habit (Heimer, Tornisiello Katz, & Rosenblatt, 2008; Karjalainen et al., 1999). In the present material, only one subject in both groups had an anterior open bite.

6.3.2 Systematic review and meta-analysis (IV)

The risk of bias in the review has to be considered high. There are no randomised studies on the subject. Moreover, the number of studies that fulfilled the inclusion criteria was low, the studies were methodically heterogenic, the number of patients and controls was in general low, and the quality of the studies was moderate at best, when estimating the risk of bias in individual studies. Furthermore, the majority of studies were executed in Brazil, and therefore it can be questioned whether the results can be generalised when taking into account the fact that ethnicity has an impact on dentofacial morphology.

7 CONCLUSIONS

1. Snoring two to three years old children had on average a more convex facial tissue profile in contrast to non-snoring controls. Changes in occlusal features were not found.

2. Two to three years old children with OSA had on average narrower upper inter canine width in contrast to PSG-verified non-snoring children. Changes in occlusal features were not found.

3. Two to three years old children with OSA had longer total snoring time in PSG, larger adenoid size in respect of nasopharyngeal volume and greater mouth-breathing tendency when compared to snoring children without OSA. The palatine tonsil size did not have a statistically significant difference between groups in this age group.

4. There is modest evidence that tonsil surgery (tonsillectomy and/or adenoidectomy) has a positive effect on dentofacial development in children, especially on the growth direction of the mandible. Accordingly, tonsil surgery can be an important procedure to secure normal dentofacial development.

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ORIGINAL PUBLICATIONS

PUBLICATION
I

Association between snoring and deciduous dental development and soft tissue profile in 3-year-old children

Niemi P, Markkanen S, Helminen M, Rautiainen M, Katila M, Saarenpää-Heikkilä O, Peltomäki T

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Association between snoring and deciduous dental development and soft tissue profile in 3-year-old children

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Introduction: The aim was to study the association between snoring and development of occlusion, maxillary dental arch, and soft tissue profile in children with newly completed deciduous dentition. **Methods:** Thirty-two (18 female, 14 male) parent-reported snorers (snoring ≥3 nights/week) and 19 (14 female, 6 male) nonsnorers were recruited. Breathing preference (nose or mouth) was assessed at the mean age of 27 months by otorhinolaryngologist. At the mean age of 33 months, an orthodontic examination was performed, including sagittal relationship of second deciduous molars, overjet, overbite, and occurrence of crowding and lateral crossbite. Bite index was obtained to measure maxillary dental arch dimensions (intercanine and intermolar width, arch length). A profile photograph was obtained to measure facial convexity. **Results:** No significant differences were found between nonsnorers and snorers in any of the studied occlusal characteristics or in measurements of maxillary dental arch dimensions. Snorers were found to have a more convex profile than nonsnorers. Occurrence of mouth breathing was more common among snorers. **Conclusions:** Parent-reported snoring (≥3 nights/week) does not seem to be associated with an adverse effect on the early development of deciduous dentition, but snoring children seem to have more convex profile than nonsnorers. Snoring is a mild sign of sleep-disordered breathing, and in the present study its short time lapse may not have had adequate functional impact on occlusion. (Am J Orthod Dentofacial Orthop 2019;156:840-5)

Sleep-disordered breathing (SDB) describes a spectrum of conditions with increasing upper airway resistance. In its mildest form, patients exhibit a snoring habit without daytime symptoms. With the increase in airway resistance, this may gradually lead to a more severe disorder, ie, obstructive sleep apnea.[1] Snoring prevalence in the pediatric population has been found to vary greatly depending on the criteria used to judge snoring. In a Finnish study of 1- to 6-year-old children, the prevalence of snoring "always" or "often" was 6.3% and of snoring "sometimes", 12.4%.[2] In a systematic review and meta-analysis by Lumeng and Chervin,[3] the prevalence of parental reports that their child snored "always" was in the range of 1.5%-6.2%. But if including children who snored "often," the range was much greater: 3.2%-14.8%. Since occasional snoring is common in children, snoring during 3 nights per week or more frequently is generally considered a sign of SDB.[4]

Snoring is caused by obstruction in airways, which in small children is commonly due to increased adenoids and/or palatine tonsils, allergic rhinitis, respiratory infections, and parental snoring and smoking.[2] Furthermore, an association has been reported between body mass index and the severity of SDB in children.[5] Interestingly, breastfeeding has been found to be a protective factor in pediatric snoring.[6] Due to the increasing obstruction, the mode of breathing may change from normal nose breathing to partial or total mouth breathing. Since unrestricted breathing, particularly during sleep, is considered important for normal craniofacial

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and occlusal development,[7-10] snoring and mouth breathing may lead to a deviation from normal growth pattern. Maxillary transversal growth can be adversely affected, and mandibular forward displacement directed predominantly downwards, leading to increased lower facial height.[11-17] Most of the studies have, however, included subjects with significant variation in age, which also means significant variation in occlusal status.

The aim of the present study was to evaluate the association between snoring and the development of an occlusion, maxillary dental arch, and soft tissue profile in 3-year-old children with newly completed deciduous dentition. It was hypothesized that nonsnoring children would have more optimal development of deciduous dentition and a less convex soft tissue profile than snoring children.

MATERIAL AND METHODS

The present study is part of the Child-Sleep Birth Cohort research project, which is a longitudinal birth cohort study consisting of 1,673 children born between April 2011 and February 2013 at Tampere University Hospital. The inclusion criteria were a Finnish–speaking family and residing in the Pirkanmaa Hospital District. The families were recruited to take part of the project prenatally at the 32nd week of pregnancy in local maternity clinics. Questionnaires which concentrate on sleep, behavior, temperament, somatic and mental health, and family relations, were filled out prenatally at week 32, at the birth of the child, and at 3, 8, 18, and 24 months following birth. The study protocol was approved by the Ethics Committee of the Pirkanmaa Hospital District and the City of Tampere in March 2011.

Questions based on the Sleep Disturbance Scale for Children questionnaire[18] were used to assess snoring frequency. The question was "Does the child snore?" and the answer options were "always (daily)," "often (3-5 times per week)," "sometimes (once or twice per week)," "occasionally (once or twice per month or less)," and "never." This study focuses on children whose parents have reported their child to snore minimum of 3 nights per week at the age of 8 or 24 months. A child was excluded if snoring was detected only during respiratory infections. Controls were recruited among nonsnoring children. Patients' and controls' families were personally asked to participate in this substudy and were interviewed by phone to verify the occurrence of snoring. Duration of exclusive breastfeeding was also questioned at 24-months questionnaire. Written informed consent was obtained from the parents.

Based on the 8-months questionnaire, 22 snoring and 13 nonsnoring children were recruited to participate in the study. Seven snorers and 9 nonsnorers dropped out before the age of 24 months. Based on the 24-months questionnaire, 17 new snorers and 16 new nonsnorers were recruited, making a total of 32 (18 female, 14 male) snorers and 20 (14 female, 6 male) nonsnorers. At the mean age of 27 months (range 23-34 months), an otorhinolaryngological examination was performed, in all cases by the same researcher (S.M.). As a part of the examination, the child's breathing preference was assessed. A child was labeled to be a mouth or nose breather according to the principal breathing preference noticed by close observation during the examination.

One nonsnorer dropped out of the study before dental examinations. At the mean age of 33 months (range 28-42 months), when deciduous dentition is typically fully formed, orthodontic examination was performed. Examination included sagittal relationship of second deciduous molars (mesial step, distal step, or flush), overjet (increased $\geq$3 mm), overbite (open bite $\leq$0 mm, deep bite $\geq$3 mm), crowding (yes or no), and lateral crossbite (yes or no). In addition, occlusal bite index (Yellow Bite Wax Sheets, 0.18-0.22 cm thick, Modern Materials) was obtained to measure the maxillary dental arch dimensions. Measurements were made with a digital sliding caliper (Somet PM 160 digi s hl.d 1.6 Typ:14016458KS) and included intercanine width measured between maxillary deciduous canine cups tips (dd. 53–63), intermolar width measured between mesiopalatal cups of maxillary second deciduous molars (dd. 55–65), and arch length measured from the labial surfaces of the first deciduous incisors perpendicular to the line connecting the distal surfaces of the right and left maxillary second deciduous molars (Fig 1).

A profile photograph of the face was taken with a digital camera (Canon EOS 60D, DS126281 Canon Inc). Children were standing at rest and asked to bite their teeth together at the moment of taking the photo. The photographs were printed, and soft tissue landmarks-Glabella (G), subnasale, and Pogonion (Pg) were identified to measure facial convexity (Fig 2).

The maxillary dental arch and soft tissue profile angle measurements were made twice by one operator (PN) and mean values used in the statistical analysis. Statistical analysis was performed using IBM SPSS Statistics (version 22 or newer). Crosstabulation was used to compare occlusal characteristics between the groups and the strength of the association was evaluated with Fisher exact test. Differences in arch dimensions and soft tissue profile measurements between the groups were tested with Mann-Whitney U test. P value < 0.05 was considered statistically significant.

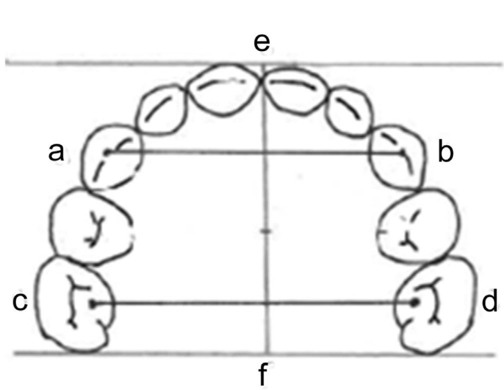

Fig 1. Deciduous dental arch measurements: a-b intercanine width (dd.53–63), c-d intermolar width (dd.55–65) and e-f arch length.

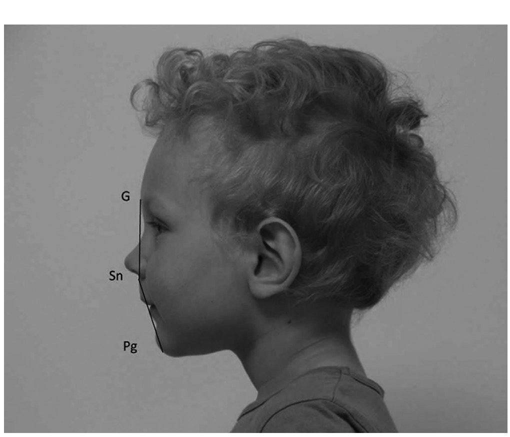

Fig 2. Soft tissue landmarks on lateral facial photographs. Soft tissue Glabella (G), Sn, and soft tissue Pogonion (Pg).

RESULTS

At the time of the otorhinolaryngological examination, all control children were still nonsnoring. Snoring status of the snoring children varied: 56% (n = 18) still snored minimum of 3 nights per week. A statistically significant difference was found between the groups in soft tissue profile in that, snorers had a more convex profile than nonsnorers (167°±4.5° vs 170°±4.8°, $P = 0.044$, Mann-Whitney U test). Occurrence of mouth breathing was also statistically more common among snorers (10/31.3% vs 1/5.0%, $P = 0.035$, Fisher exact test, Table I).

Statistical analysis did not reveal significant differences between nonsnorers and snorers in any of the studied occlusal characteristics ($P > 0.05$, Fisher exact test, Table II). No statistically significant differences were found between the groups in the measurements of maxillary dental arch dimensions. Intercanine width (dd. 53–63) was 27.8 mm and 28.1 mm, intermolar width (dd. 55–65) 32.9 mm and 33.8 mm, and arch length 28.8 mm and 28.6 mm in snorers and nonsnorers, respectively ($P > 0.05$, Mann-Whitney U test). Duration of exclusive breastfeeding was 3.8 and 3.9 months in the snoring and nonsnoring groups, respectively, ie, no statistically significant difference.

The same parameters were compared between the children whose parents reported them to snore minimum of 3 nights per week at the age of 24 months (n = 18) and the controls (n = 19). Snoring children were found to have mouth breathing preference statistically more frequently than the controls ($P = 0.04$). No other statistically significant differences were found ($P > 0.05$, Fisher exact test, data not shown). The same parameters were also compared inside the snorer group (n = 32) to distinguish differences between mainly mouth breathing snoring children (n = 10) and mainly nose breathing snoring children (n = 22). No statistically significant differences were found ($P > 0.05$, Fisher exact test, data not shown).

DISCUSSION

The strength of the present study is that, the children were studied at a younger age than in earlier studies and thus formed a homogenous group in terms of occlusal development. The examination time point was planned in children who had just completed deciduous dentition, which normally occurs by 30 months.[19] In 6 subjects, maxillary and/or mandibular second deciduous molars had not yet erupted, while all others had fully formed deciduous dentition. The age range of those without fully erupted dentition was 32-42 months. Gender difference has been found in dental arch measurements in that, boys tend to have larger values.[20] In the present study, however, no meaningful difference in the gender breakdown is noticed between the groups. Facial profile photographs, instead of radiological imaging (lateral radiographs), were used. This is an evident but ethically acceptable limitation and prevents direct comparison to most previous studies. Young age was also a challenge, and because of inadequate cooperation, not all planned information and measurements could be collected.

Habitual snoring status has been demonstrated to fluctuate naturally in the early childhood years.[21] In the current study, all controls were still nonsnoring and 56% of the snoring children were snoring minimum of 3 nights per week at the time of examination. The

Table I. Soft tissue profile measurements (mean, in degrees), occurrence of mouth breathing (n/%), and missing values in snorer and nonsnorer groups

	Snorers (n = 32)	*Snorer missing values*	*Nonsnorers (n = 19)*	*Nonsnorer missing values*	P *value*
Soft tissue profile (degrees)	167 ± 4.5	4	170 ± 4.8	7	0.044
Mouth breathing	10/31.3%	-	1/5.3%	-	0.035

Table II. Frequencies of occlusal morphological characteristics (n/%), and missing values in snorer and nonsnorer groups

	Snorer (n = 32)	*Snorer missing values*	*Nonsnorer (n = 19)*	*Nonsnorer missing values*	P *value*
Overjet ≥ 3 mm	14/46.7%	2	7/38.9%	1	0.77
Open bite ≤ 0 mm	4/12.5%	-	1/5.6%	1	0.77
Normal	15/46.9%		10/55.6%		
Deep bite ≥ 3 mm	13/40.6%		7/38.9%		
Crowding	8/25.0%	-	2/11.1%	1	0.30
Crossbite, lateral	2/6.3%	-	2/10.5%	-	0.62
Molar relationship					
mesial step	21/65.6%	-	9/50.0%	1	0.36
flush	5/15.6%		6/33.3%		
distal step	6/18.8%		3/16.7%		

groups can be interpreted to represent never snoring children (control group) and children who have had remarkable snoring between ages 8-24 months (snorer group).

Snoring children were found to have a more convex profile than nonsnorers, a finding that is in line with previous studies.[17,22] Systematic review and meta-analysis by Katyal et al[17] concluded that children with primary snoring have a statistically significantly increased ANB angle compared with nonsnorers, a difference that is mainly due to a more retrognathic mandible in snorers (1.4° decrease in SNB angle). The age range of the children included in the systematic review was however large: from 0 to 18 years. In a study of 6- to 8-year-old children by Ikävalko et al[22] a comparable profile photography method was used as in the present study. In SDB children, facial convexity was more remarkable than in healthy children. Unfortunately, as the authors indicated, use of facial convexity assessment is clinically challenging, since facial convexity is a normal characteristic of every healthy child. Minor difference, ie, 2°-3° is probably of marginal clinical significance. The tendency for increased facial height and a vertical growth pattern of the mandible have also been found in 4- to 8-year-old snoring children, using lateral cephalometry.[17,23,24] The current study methodology precluded assessment of these facial characteristics.

The present findings seem to contradict previous studies on dental arch measurements and occlusal characteristics. Löfstrand-Tideström et al[12] studied 4-year-old children and found that the maxillary dental arch width was smaller and lateral crossbite more frequent in snoring children than in nonsnorers. Pirilä-Parkkinen et al[15] reported that snoring children (mean age 7.2 years, range 3.8-10.8 years) had a larger overjet and narrower maxillary dental arch than the control children. They furthermore reported an increase in malocclusion prevalence with increased severity of the breathing disorder, from snoring to obstructive sleep apnea.[15] In the current study, no statistically significant differences were found in dental arch measurements or in any occlusal characteristics. Mouth breathing, as found in 30% of the snoring children, has been considered to have an impact on the muscular balance between the tongue and cheek muscles, and when long-lasting, on the occlusal relationships.[25] In the present study, this adverse effect may have not yet been at work sufficiently long to have an adverse effect on the maxillary dental arch or the occurrence of malocclusion, since no statistically significant difference was found between nose vs mouth breathing children in the snoring group. Souki et al[26] studied the association between mouth breathing and occlusal characteristics at different developmental stages (primary, mixed, and permanent dentition) and concluded that older children with mouth breathing tended to have increasing prevalence of malocclusions with great individual variation. They even stated that "using a young sample may explain the lack of association between the tested variables" as evidenced in our study. On the other hand, in our previous study, occlusal and dentoalveolar dimensions and features of snoring 5-year-old children did not differ compared with nonsnorers. In this study, the dichotomous question (yes or no snoring) may not have differentiated the groups adequately.[27]

The impact of breathing function on occlusal and craniofacial growth has been a controversial issue among orthodontists for longer than a century.[28] In many studies, the age range of the included subjects has been wide, meaning variable duration of the functional factor on the studied parameter(s). This has probably led to substantial variation in the response and unfounded conclusions on the association. During the first months after birth, feeding pattern seems to be an important factor: exclusive breastfeeding up to 3 months has been reported to be associated with lower SDB probability in later life. In our study this factor could not be properly studied, since duration of exclusive breastfeeding was equal in both groups. Carlson[29] has pointed out another probable confounding factor: normal variation in the individual genome, which means a different response to the same environmental factor; in this case, breathing function.

CONCLUSIONS

Within the limitation of the present small sample size, it can be concluded that parent-reported snoring (≥3 nights/week) does not seem to be associated with an adverse effect on the early development of deciduous dentition at the age of 2-3 years. Therefore, the hypothesis of the study has to be refuted concerning occlusion, but it cautiously supports the facial profile assumption. Snoring as the first and mild sign of SDB may not have adequate functional and environmental impact on the occlusion. Another explanation for the lack of association could lie in the short time lapse between completion of deciduous dentition and the snoring and mouth breathing. An ongoing, long-term study with the same study population will hopefully shed light on this issue.

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PUBLICATION
II

Craniofacial and occlusal development in 2.5-year-old children with obstructive sleep apnoea syndrome

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Original article

Craniofacial and occlusal development in 2.5-year-old children with obstructive sleep apnoea syndrome

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Summary

Objectives: Paediatric obstructive sleep apnoea syndrome (OSAS) is associated with a range of changes in craniofacial and occlusal development. There is, however, little knowledge of how early in life these changes can be found. The aim of the present study was to determine whether changes in dental arch morphology, occlusion, facial profile, tonsil size, breathing habit or body mass index (BMI) can already be found among 2.5-year-old children with OSAS.

Materials and Methods: Fifty-two children were recruited to the study. Of these, OSAS was diagnosed in 9 children and 18 children did not snore in polysomnography. These two groups were subsequently compared when evaluating polysomnographic, otorhinolaryngological and dental variables.

Results: Children with OSAS had narrower inter canine width than non-snoring children ($P = 0.032$). Furthermore, children with OSAS had larger adenoid size with respect to the nasopharyngeal volume ($P = 0.020$) and more tendency to mouth breathing ($P = 0.002$). No statistically significant differences were found when comparing palatine tonsil size, occlusal characteristics, soft tissue profile measurements or BMI.

Limitations: The limitation of the study is the small sample size.

Conclusion: Children with OSAS had narrower upper inter canine width than non-snoring children at the age of 2.5 years. Larger adenoid size and mouth breathing tendency were also more common among children with OSAS. Further studies with larger sample sizes are needed to determine if other changes in craniofacial and occlusal development can be found in this age group.

Introduction

Paediatric obstructive sleep apnoea syndrome (OSAS) is a relatively common disorder considering that prevalence in the paediatric population is estimated to be between 1 and 5% (1). Large tonsillar size is regarded as a sensitive positive marker when diagnosing OSAS in children (2). Accordingly, the primary cause of paediatric OSAS is thought to be the enlargement of the palatine and adenoid tonsils. However, that is not the only aetiology of the disorder. Paediatric

OSAS has additionally been associated with nasal stuffiness, obesity, neuromuscular diseases, and craniofacial anomalies (3–5).

Paediatric sleep-disordered breathing (SDB) problems are associated with a wide range of changes in craniofacial and occlusal development in otherwise healthy children (6). The most commonly described changes in dental arch morphology are crossbite (7–10), narrower upper dental arch (8, 10, 11), and shortened lower dental arch (10, 11). In addition, increased overjet and decreased overbite have also been associated with paediatric SDB (11). Furthermore, changes in craniofacial development are commonly found in children with SDB. More convex facial profile (7, 12), increased values of anterior facial height and vertical reduction in the posterior facial height (9) have all been described. It has been suggested that changes in craniofacial and occlusal development are due to upper airway resistance, large tonsil size, and mouth breathing tendency (13). However, genetics and multiple environmental factors are also believed to have an influence.

When congenital abnormalities are not considered, there is little to no knowledge of how early in life SDB related changes in craniofacial and occlusal development can be seen. The majority of previous studies have been executed among at least 4-year-old children, and the age-groups have frequently been heterogenous. The purpose of this investigation is to determine whether changes can already be found in the dental arch morphology, occlusion or facial profile of 2.5-year-old children with OSAS. A further aim is to determine if these changes are connected to tonsil size or mouth breathing tendency.

Materials and methods

This study was executed as part of the Child-Sleep research project, which is a longitudinal birth cohort study that comprises 1673 children born between April 2011 and February 2013 at Tampere University Hospital, Finland (14). The Child-Sleep study protocol was approved by the Ethical Committee of Pirkanmaa Hospital District in March 2011 (approval number R11032). The inclusion criteria for the cohort were Finnish-speaking family and living in the Pirkanmaa Hospital District. The families were recruited to the study prenatally at the 32nd week in local maternity clinics. Written informed consent was obtained from the parents. Questionnaires, which concentrated on sleep, somatic and mental health, behaviour, temperament, and family relations, were filled out prenatally at the 32nd week, at the birth of the child and at 3, 8, 18, and 24 months after the birth. The validated Sleep Disturbance Scale for Children (SDSC) (15) was used concerning sleep-related questions.

Families, who had reported their child to snore minimum of three nights per week at 8 months questionnaire (41 of 1291 answered families) or 24 months questionnaire (24 of 947), were contacted and offered opportunity to take part in further clinical examinations. Thirty-two families wanted to take part in the present study. Opportunity to take part in the study were also offered to families, who had reported their child not to snore regularly, to recruit 20 non-snoring participants. In total, 52 children from the cohort were recruited to the present study. At the mean age of 27 (min 23, max 34) months, a full night polysomnography and otorhinolaryngological examination were carried out successfully on 49 children. At the mean age of 33 months (min 28, max 42), a dental examination was performed on 48 of them. The dental examination time was chosen to be around the time when primary dentation had just been completed.

Polysomnographies were performed at the sleep laboratory of Tampere University Hospital. The following signals were recorded: eight channels of electroencephalography, two channels of electro-oculography, submental electromyography, airflow by oronasal thermistor and nasal pressure transducer signal, oxygen saturation by two pulse oximeters, thoracoabdominal inductance plethysmography, diaphragmatic and abdominal electromyography, Emfit mattress sensor, electrocardiography, end-tidal PCO_2, video, sleeping position, and snoring. The recordings were manually analysed by two independent clinical neurophysiologists (S-LH, A-LS). The sleep stages and respiratory events were scored according to the paediatric rules in the AASM manual (16). Snoring periods were selected based on piezo and nasal pressure signal and verified by listening. The percentage of time with snoring referred to total sleep time was calculated for each child.

The otorhinolaryngological examination included inspection of the oral cavity and oropharynx, anterior rhinoscopy and nasal flexible fibre optic endoscopy of the nasopharynx, hypopharynx, and larynx. To induce local anaesthesia, 4% lidocaine was sprayed in one nostril. Palatine tonsil size were assessed using Friedman's tonsil classification (0 = no tonsils, tonsillectomy has been made, 1 = tonsils are hidden between the palatoglossal and palatopharyngeal arch, 2 = tonsils extend to the arches, 3 = tonsils extend beyond the arches but not to the midline, 4 = tonsils extend to the midline) (17). A four-class scale to determine the adenoid size with respect to the nasopharyngeal volume was used (tissue filling 0 to 25%, 26 to 50%, 51 to 75% or 76 to 100% of the nasopharyngeal volume). Dominant mouth breathing was assessed visually during the clinical examination. Children's weight and height were measured. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Usage of pacifier and duration of exclusive breastfeeding was reported by parents. One researcher (SM) made all the otorhinolaryngological examinations.

Dental examination included sagittal relationship of second primary molars (mesial step/flush/distal step), overjet (normal/increased ≥3 mm), overbite (open bite ≤0 mm/normal/deep bite ≥3 mm), crowding (yes/no), and lateral crossbite (yes/no). Occlusal bite index was obtained to measure inter canine width between upper primary canines (dd. 53–63) and intermolar width between upper second primary molars (dd. 55–65) (Figure 1). No study models were made, but the measurements were made directly from the wax bite indexes with a digital sliding caliper (Somet PM160 digi s hl.d 1.6 TYP:14016458KS). To measure the tips of the sliding caliper were placed on the right and left sides in the wax bite grooves indicating upper canine cusp tip and mesiopalatal cusp of upper second primary molar. A profile photograph of the face was taken with a digital camera. The children stood at rest and were asked to bite

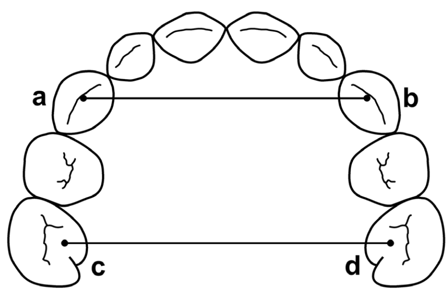

Figure 1. Primary dental arch measurements: (a–b) inter canine width (dd. 53–63) and (c–d) intermolar width (dd. 55–65).

their teeth together at the moment of taking the photo. The photographs were printed, and the soft tissue landmarks Glabella (G), Subnasale (Sn), and Pogonion (Pg) were identified to measure facial convexity (Figure 2). Upper dental arch and soft tissue measurements were made twice by one researcher (PN) and the mean of the measurements was used in the statistical analysis.

Based on the polysomnography results, an OSAS diagnosis was made if the obstructive apnoea-hypopnea index (OAHI) was ≥1/hour (18). Nine children met this criterion. OAHI in this group was 1.2 to 6.3/hour (median 1.5/hour) and snoring time was from 16.0 to 94.7% (median 63.6%) of the total sleeping time. The snoring time of 18 children was less than 1% of the total sleeping time, and they were interpreted to be polysomnography (PSG)-verified non-snoring children. OAHI in this group was 0.0 to 0.9/hour (median 0.0/hour) and snoring time 0.0 to 0.7% (median 0.0%).

We compared children with OSAS and PSG-verified non-snoring children to evaluate the differences between tonsillar size, mouth breathing tendency, occlusal characteristics, upper dental arch dimensions, soft tissue profile measurements, and BMI. In addition, we examined whether palatine tonsil size, adenoid size or breathing habit could independently have an influence on occlusal characteristics, upper dental arch dimensions or soft tissue profile measurements. For this analysis, palatine tonsil size was re-grouped into two classes: 'small palatine tonsil size' (Friedman classes 1–2) and 'large palatine tonsil size' (Friedman classes 3–4). Adenoid size was also regrouped into two classes: 'small adenoid size' (tissue filling 0 to 50% of the nasopharyngeal volume) and 'large adenoid size' (tissue filling 51 to 100% of the nasopharyngeal volume).

Statistical analysis was performed using IBM SPSS Statistics (version 22 or newer). Crosstabulation was used to compare qualitative variables and the strength of the association was evaluated with Fisher exact test. Mann-Whitney *U*-test was used to compare quantitative variables between groups. $P < 0.05$ was considered statistically significant.

Figure 2. Soft tissue landmarks on lateral facial photographs. Soft tissue Glabella (G), Subnasale (Sn), and Soft tissue Pogonion (Pg).

Results

Statistically significant differences were found between children with OSAS and PSG-verified non-snoring children in adenoid size, mouth breathing tendency and inter canine width. Children with OSAS had larger adenoid size with respect to the nasopharyngeal volume and more tendency to mouth breathing (Table 1). Furthermore, children with OSAS had narrower inter canine width than non-snoring children, median 27.0 versus 28.2 mm, respectively (Table 2). No statistically significant differences were found when comparing palatine tonsil size, occlusal characteristics, soft tissue profile measurements or BMI (Tables 1 and 2).

When the occlusal characteristics, upper dental arch dimensions, and soft tissue profile measurements were tested separately between palatine tonsil size, adenoid size, and breathing habit, the only statistically significant finding ($P = 0.047$) was that inter canine width was slightly narrower among mouth breathing children than nose breathing children, 27.0 (25.5–27.2) and 27.7 (27.1–29.5), median and interquartile range 0.25–0.75, respectively.

Pacifier usage did not differ significantly between the groups. 55.6% ($n = 5$) of children with OSAS and 72.2% ($n = 13$) of non-snoring children used or had used pacifier. The duration of exclusive breastfeeding was 5.0 months (3.5–6.0) among children with OSAS and 4.0 months (2.5–5.0) among non-snoring children, median and interquartile range 0.25–0.75, respectively. The difference was not statistically significant.

Discussion

We detected that minor changes in dental arch morphology can already be found in 2.5-year-old children with OSAS. Larger adenoid size and mouth breathing tendency were also more common among children with OSAS than PSG-verified non-snoring children.

The most interesting finding in our material was the narrower upper inter canine width among children with OSAS. In previous studies, a narrower upper dental arch has been found to be associated with paediatric SDB (8, 10, 11), and we were able to provide evidence that the change can already be seen at the age of 2.5 years. It should be further noted that even though the severity of OSAS in our material was quite mild, OAHI 1.2 to 6.3, the changes were still detectable. In a previous study, it was demonstrated that even primary snoring can affect dental arch morphology in children (11). We were not able to find other commonly described changes, such as crossbite or more convex facial profile, in this material. Whether this was because these changes had not yet developed, or the material was too limited to show them, remains unclear. Our finding regarding the significance of crossbite in our material could be explained by previous findings that narrower upper inter canine width could be a precursor for development leading to crossbite (19). It is also of note that pacifier use and duration of exclusive breastfeeding, which are possible confounding variables in terms of upper inter canine width, were not different between the groups.

Craniofacial development changes, which are connected to OSAS, are also connected to mouth breathing tendency and tonsil size (13). It is thought that obstructed nasal breathing, which can emerge because of large tonsils, leads to mouth breathing and to changes in head and tongue position and muscle balance. Subsequently, this imbalance leads to further changes in craniofacial growth. In our study, narrower upper canine width was associated with mouth breathing tendency, but not with adenoid or palatine tonsil size. This leads to the question is tonsil size the only determinant when considering OSAS in young, otherwise

Table 1. Qualitative variables. OSAS, obstructive sleep apnoea syndrome; PSG, polysomnography.

	Children with OSAS (*n* = 9)	PSG-verified non-snoring children (*n* = 18)	*P*
Sagittal relationship of second primary molars			1.000
Mesial step	66.7% (6)	58.8% (10)	
Flush	22.2% (2)	29.4% (5)	
Distal step	11.1% (1)	11.8% (2)	
		(Missing 1)	
Overjet ≥3 mm			1.000
Yes	50.0% (4)	52.9% (9)	
No	50.0% (4)	47.1% (8)	
	(Missing 1)	*(Missing 1)*	
Overbite			1.000
Open bite	11.1% (1)	5.9% (1)	
Normal	44.4% (4)	47.1% (8)	
Deep bite	44.4% (4)	47.1% (8)	
		(Missing 1)	
Crowding			0.628
Yes	33.3% (3)	17.6% (3)	
No	66.7% (6)	82.4% (14)	
		(Missing 1)	
Lateral crossbite			1.000
Yes	11.1% (1)	5.6% (1)	
No	88.9% (8)	94.4% (17)	
Palatine tonsil size (Friedman classification)			0.268
1	22.2% (2)	44.4% (8)	
2	33.3% (3)	38.9% (7)	
3	44.4% (4)	16.7% (3)	
4	0.0% (0)	0.0% (0)	
Adenoid size			**0.020**
0–25%	22.2% (2)	72.2% (13)	
26–50%	33.3% (3)	22.2% (4)	
51–75%	22.2% (2)	5.6% (1)	
76–100%	22.2% (2)	0.0% (0)	
Mouth breathing			**0.002**
Yes	66.7% (6)	5.6% (1)	
No	33.3% (3)	94.4% (17)	

Crosstabulation and Fisher's exact test used to compare variables and the strength of the association. $P < 0.05$ was considered statistically significant.

Table 2. Quantitative variables. BMI, body mass index; OSAS, obstructive sleep apnoea syndrome; PSG, polysomnography.

	Children with OSAS (*n* = 9)	PSG-verified non-snoring children (*n* = 18)	*P*
Inter canine width (mm)	27.0 (25.9–27.2)	28.2 (26.2–29.6) *(Missing 2)*	**0.032**
Inter molar width (mm)	32.6 (29.4–33.8) *(Missing 4)*	32.4 (31.6–33.1) *(Missing 6)*	0.442
Soft tissue profile (degrees)	167.3 (164.8–169.5) *(Missing 1)*	172.3 (168.8–174.8) *(Missing 4)*	0.297
BMI (kg/m^2)	16.0 (15.5–17.0)	16.7 (16.0–17.8) *(Missing 1)*	0.164

Mann-Whitney *U*-test used to compare variables. Median and interquartile range 0.25–0.75 presented.

healthy children. The limited sample size in our study should obviously be taken into consideration. However, it has previously been speculated that changes in craniofacial development are not only due to adenotonsillar hypertrophy, but also to a more complex genetic and/or environmental process (11, 13). For instance, supine sleeping position, which is a characteristic of patients with OSAS, is associated with narrower inter canine width among children with OSAS (20).

There is evidence that after treatment of OSAS with adenotonsillectomy (AT), changes in craniofacial and occlusal development normalize considerably (21). On the other hand, it has been shown that after AT up to 30 to 40% of children have residual OSAS (22). There are further indications that some children need both tonsil surgery and orthodontics for the complete resolution of OSAS (23). The early recognition of children with OSAS and changes in dental arch morphology leads to earlier treatment and hopefully has a positive influence on the growth of the craniofacial structures. Optimal craniofacial development may prevent sleep disordered breathing problems later in life.

Strengths and limitations

The strength of the present study is the age of the studied children and same-aged control children. There is a scarcity of knowledge of craniofacial and occlusal development in young children with OSAS. We were not able to find any other studies in which the whole group would have been under 4 years old. In the present study, the patients were examined just after they had completed primary dentation. PSG-verified non-snorer controls were a further strength of the study. In most studies, non-snoring controls have not been examined with PSG, and the snoring status has usually been defined based on the reports of parents. SDB is a continuum from slight primary snoring to severe OSAS. In this study, we have compared verified non-snoring children with OSAS-children, and this has made the differences more noticeable.

The evident limitation of the present study is a small sample size. The prevalence of snoring was generally lower in our cohort when compared to previous studies of infant and toddler aged children (24). Additionally, the study protocol was quite laborious for the families. This diminished the number of children able to participate in the study. Although the age of the children is the strength of the study, it also caused challenges in terms of examination. Co-operation, especially during the dental examination, was varied, and therefore all the planned measurements could not be collected (missing information in Tables 1 and 2).

Although pacifier usage and duration of exclusive breastfeeding was reported by parents, we did not ask about finger sucking habit. Despite the fact that finger sucking habit was not directly studied, incidence of open bite would indirectly indicate of long-lasting/intensive non-nutritive sucking habit (25, 26). In our material, one subject in both groups had anterior open bite, i.e. no statistically significant difference. There are also limitations concerning the assessment of facial profile. The assessment was made with photography analysis and, for ethical reasons considering the age of the patients, no cephalometric radiographs were taken. However, this kind of photography assessment has previously been used for the same purpose (27).

Conclusions

The present study showed that minor changes in dental arch morphology can already be found in 2.5-year-old children with OSAS. Further studies with larger sample size are needed to determine whether other changes in craniofacial and occlusal development can be found in this age group, and whether these changes are associated with tonsil size and mouth breathing tendency.

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Conflicts of interest

None to declare.

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PUBLICATION III

Snoring toddlers with and without obstructive sleep apnoea differed with regard to snoring time, adenoid size and mouth breathing

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REGULAR ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Snoring toddlers with and without obstructive sleep apnoea differed with regard to snoring time, adenoid size and mouth breathing

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Abstract

Aim: The difficulty of assessing the likelihood of obstructive sleep apnoea (OSA) in children who snore without full-night polysomnography is widely recognised. Our aim was to identify features that were characteristic of two-year-old children with OSA and evaluate whether this information could be used to assess the likelihood of OSA.

Methods: The study was carried out as part of the Child-Sleep Project, a longitudinal birth cohort study of children born at Tampere University Hospital, Finland. This part of the study focused on the children in the cohort who snored and was carried out between 2013 and 2015. The primary outcomes were measured using parental questionnaires, polysomnography and clinical examinations.

Results: In total, 52 children participated at a mean age of 27 months (range 23-34). Of these, 32 (44% male) snorers and 20 (70% male) controls. The most significant findings were that children who had OSA demonstrated longer snoring time ($P = .003$), a greater tendency for mouth breathing ($P = .007$) and bigger adenoid size ($P = .008$) than snorers without OSA.

Conclusion: Snoring time, adenoid tissue size and mouth breathing were important features that identified the likelihood of OSA in snoring toddlers.

KEYWORDS
adenoids, obstructive sleep apnoea, snoring time, toddlers, tonsils

Abbreviations: AHI, apnoea/hypopnoea index; OSA, obstructive sleep apnoea.

1 | INTRODUCTION

It has been estimated that 1.5%-15% of children snore regularly and 1%-5% have obstructive sleep apnoea (OSA).[1-4] OSA has been associated with many clinical morbidities, such as neurobehavioural problems and increased strain on the metabolism and cardiovascular organs.[1] Indeed, it has been suggested that early treatment of OSA would have a beneficial effect on behavioural changes and quality of life.[5] The great majority of children with OSA snore, but not all children who snore have OSA. The difficulty of distinguishing children with these two conditions is a widely recognised problem in the field of paediatric sleep medicine.

Full-night polysomnography is still the gold standard for diagnosing OSA.[6] However, paediatric polysomnography is limited in some centres because of a lack of availability and high cost. Other diagnostic methods, such as nocturnal pulse oximetry, video recording, nap-polysomnography and ambulatory polysomnography, have been estimated to have a poor predictive value when the result was negative.[1] Clinical findings and patient histories are often used as an alternative diagnostic method to assess the likelihood of OSA, although this method has many uncertainties.[7,8]

Present knowledge of the factors used for assessing the likelihood of paediatric OSA is controversial. The size of the child's tonsils and their snoring history are considered to have high sensitivity, whereas excessive daytime sleepiness and caregiver observed apnoeas during sleep have high specificity.[9] Nevertheless, it has been demonstrated that a single symptom or sign has poor diagnostic accuracy in predicting paediatric OSA.[9] The snoring status of children and the presence of OSA can change during childhood, regardless of whether any procedures are carried out.[10,11] The change in status may be caused be a change in the size of the tonsils and adenoids, with respect to the airway at different ages. Furthermore, the impact of adenotonsillar hypertrophy on paediatric OSA seems to change, as it has been reported to play a more significant role in preschool-aged children than in older children. In addition, the size of the adenoidal tissue seems to be a more important factor than palatine tonsil size in younger children.[12]

The appearance of symptoms and clinical findings of OSA vary at different ages, and paediatric OSA should not be considered as a stable disorder throughout childhood. Therefore, better tools are needed to determine which children need to be examined with polysomnography and whether there are other ways to reliably diagnose or exclude OSA. The aim of present study was to identify the polysomnographic features, patient history and clinical findings that were characteristic of two-year-old children with OSA. This age group was selected because there is scarcity of knowledge of these features in toddlers. The second aim was to determine whether the information that was gathered could be used to assess the likelihood of OSA in toddlers when parents had reported them snoring. It was hypothesised that toddlers with OSA would be more likely to snore more during polysomnography, have larger adenoids and palatine tonsils and demonstrate more mouth breathing than toddlers who snored but did not have OSA.

KEY NOTES

- The difficulty of assessing the likelihood of obstructive sleep apnoea (OSA) in children who snore without a full-night polysomnography is a widely recognised problem.
- Our study found that children with OSA snored for longer at night than children who snored, but did not have OSA.
- Adenoid tissue size and mouth breathing were important clinical factors when assessing the likelihood of OSA in toddlers at a mean age of 27 months.

2 | METHODS

2.1 | Study design and participants

The present study was carried out as part of the Child-Sleep Project, which is a longitudinal birth cohort study that comprises 1673 children born between April 2011 and February 2013 at Tampere University Hospital, Finland. The study protocol was approved by the Ethical Committee of the Pirkanmaa Hospital District in March 2011. The inclusion criteria were families who spoke Finnish and lived in the Pirkanmaa Hospital District. They were recruited by local maternity clinics during the prenatal period, once the pregnancy had reached 32 weeks. The first of a series of questionnaires that concentrated on sleep, somatic and mental health, behaviour, temperament and family relationships were filled out at this stage (n = 1673). The other were completed at three (n = 1427), eight (n = 1291), 18 (n = 1163) and 24 months (n = 947) after the birth.[13] The present study concentrated on children who snored in the Child-Sleep cohort.

The Sleep Disturbance Scale for Children,[14] which evaluates sleeps disorders in children, was used to estimate snoring frequency at the age of eight and 24 months. The question from the sleep-disordered breathing subscale, which asks how often the child snore, was used to select the patients. The children were included if their parents indicated they snored always or often, namely daily or three to five times a week. They were excluded if they snored sometimes or occasionally, defined as once or twice a week or once or twice a month, or never. Snoring for a minimum of three nights per week has been used to indicate a significant amount of snoring in children in previous studies.[15] The exclusion criteria also included children who only snored during respiratory infections or had severe illnesses and disabilities. Children who did not snore regularly were recruited as controls. They were recruited among the children whose parent indicated they snored never, occasionally or sometimes in the Sleep Disturbance Scale for Children at the age of eight or 24 months. The families were contacted and asked to participate in the study, and a parent was interviewed on the telephone to confirm the occurrence of snoring or lack of it. The parents provided written, informed consent so that their children and themselves could take part in the study. All research was performed in accordance with the relevant guidelines and regulations.

2.2 | Outcome measures

Some of the Sleep Disturbance Scale for Children questions were repeated at the time of the clinical examinations. These dealt with how frequently the child gasped for breath or was unable to breathe during sleep, how often the child snored and how often the child was tired during the daytime. Moreover, the parents were asked about the child's breathing habits and nasal symptoms. The questions, the possible answers and how the answers were grouped for the analysis are presented in Table 1.

The examination carried out by the paediatrician included measurements of weight and height and a general paediatric and neurological assessment.

The otorhinolaryngological examination included inspection of the oral cavity and oropharynx, anterior rhinoscopy and nasal flexible fibreoptic endoscopy of the nasopharynx, hypopharynx and larynx. Nasal flexible fibreoptic endoscopy has previously been determined to be a reliable method for assessing paediatric adenoid size, when compared to radiographic assessment methods.[16] A four-class scale was used to determine the adenoid size with respect to the nasopharyngeal volume, in which class one indicated that tissue filled 0%-25% of the nasopharyngeal volume, class two was 26%-50%, class three was 51%-75% and class four was 76%-100%. Palatine tonsil size was assessed using Friedman's tonsil classification.[17] Zero indicated no tonsils, one indicated that the tonsils were hidden between the palatoglossal and palatopharyngeal arch, two indicated that the tonsils extended to the arches, three indicated that the tonsils extended beyond the arches, but not to the midline, and four indicated that the tonsils extended to the midline. Furthermore, the breathing habit of the child, mainly through mouth or nose, was observed.

A full-night polysomnography was performed at the sleep laboratory at the Tampere University Hospital using an Embla N7000 device (Natus Medical Incorporated, Pleasanton, California, USA). The following signals were recorded: eight channels of electroencephalography, two channels of electro-oculography, submental electromyography, airflow by oronasal thermistor and nasal pressure transducer signal, oxygen saturation by two pulse oximeters, thoracoabdominal inductance plethysmography, diaphragmatic and abdominal electromyography. We also recorded electrocardiography, end-tidal partial pressure of carbon dioxide, sleeping position and snoring. An Emfit mattress sensor (Emfit Ltd, Finland) was used to detect breathing and body movements. The children were also video recorded. All of the recordings were manually analysed by two independent clinical neurophysiologists. The sleep stages and respiratory events were scored according to the paediatric rules in the American Academy of Sleep Medicine manual.[18] Snoring episodes lasting more than three consecutive breathing cycles were selected, based on piezo and nasal pressure signal and verified by listening. The percentage of time with snoring, referred to as total sleep time, was calculated for each child. A diagnosis of OSA was made if the obstructive AHI was more than one per hour.[19]

2.3 | Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics, version 22 or newer (IBM Corp). Cross-tabulation was used to compare qualitative variables, and the strength of the association was evaluated with Fisher's exact test. The Mann-Whitney *U* test and Kruskal-Wallis test were used to compare quantitative variables between the groups. Bonferroni correction was used when the Mann-Whitney *U* test was used to compare differences pairwise after the Kruskal-Wallis test. $P < .05$ was considered statistically significant.

3 | RESULTS

The prevalence of snoring in the cohort based on the questionnaire completed at 8 months after the birth was 3.2%, 41 snorers among 1291 children whose parents replied. At the timepoint of the

TABLE 1 Questions parents were asked during the clinical examinations

Questions for the parents	Group answers for the analysis
How often does your child gasp for breath or is unable to breath during sleep? How often does your child snore? How often does your child experience daytime somnolence? Never. Occasionally (1-2 times per month or less). Sometimes (1-2 times per week). Often (3-5 times per week). Always (daily)	Breathing difficulties during sleep: Yes or no. Snoring frequency: Maximum of two nights per week or minimum of three nights per week. Frequency of daytime sleepiness: Maximum of two days per week or minimum of three days per week
Does your child breathe through the nose or mouth when relaxed during the daytime? Mainly through nose. Mainly through mouth. Don't know.	Breathing habit: Mainly through nose. Mainly through mouth. Don't know.
Does your child have constant rhinitis or nasal stuffiness? Yes or no	Nasal rhinitis and stuffiness: Yes or no.

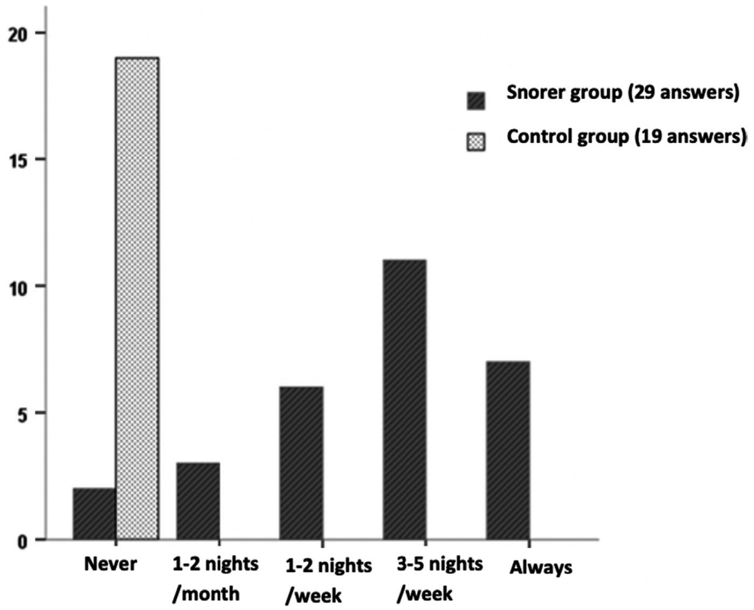

FIGURE 1 Frequency of snoring reported by parents at the time of the clinical examination in the snorer and control groups

24-month questionnaire, the prevalence was lower, 2.5%, 24 snorers among 947 children,

The total number of children who took part in the study at approximately 24 months was 52. Of these, 32 (44% male and 56% female) were snorers and 20 (70% male and 30% female) were controls. At the time of otorhinolaryngological examination, 19 of the parents of 20 children in the control group reported that their children currently never snore, and one did not answer the question. Current reported snoring was distinctly more common ($P < .001$) in the snorer group and the frequency varied within the group (Figure 1). The parents of three children from the snorer group did not answer the question. Consequently, the snorer group represents those children who had had remarkable snoring between the ages of 8 months and 24 months, although current snoring at the time of the clinical examinations varied. This is a common situation, because the snoring is not a stable feature in children.

At the time of clinical examination, the children had a mean age of 27 months (range 23-34). Their mean body mass index was 16.5 kg/m^2 (range 14.6-20.2), and their mean body mass index z-score was −0.02 (range −1.4-2.2). The body measurements of six children were missing. Three children had previously undergone an adenoidectomy, and one had received an adenoidectomy and partial tonsillectomy.

A full-night polysomnography was successfully performed on 49 children: 31 snorers and 18 controls. The time period between the otorhinolaryngological examination and the polysomnography was 19 days on average (range 0-99). Two children, one snorer and one control, did not arrive for the polysomnography and one registration failed in the control group because the child had a respiratory infection. The polysomnography findings of the snorers and controls are presented in Table 2. Significant differences were found between obstructive AHI and snoring time, but not between the sleep parameters. OSA was diagnosed in nine children (56% male) in the snorer group and in none in the control group. Consequently, 29% (9 of 31) of snorers examined with polysomnography had OSA.

The snorer group was further divided into two groups, according to the diagnosis of OSA. The polysomnography findings of the OSA group and the no OSA group are presented in Table 3. Significant differences were found between AHI, obstructive AHI, snoring time, total sleep time and sleep stage N1, which is the transition period from being awake to falling asleep. In the OSA group, obstructive AHI was 1.2 to 6.3 per hour (median 1.5 per hour) and the snoring time was 16.0%-94.7% (median 63.6%) of the total sleep time. In the no OSA group, obstructive AHI was 0.0-0.4 per hour (median 0.1 per hour) and snoring time was 0.0%-87.8% (median 6.9%) of total sleep time. In contrast, obstructive AHI was 0.0-0.9 per hour (median 0.0 per hour) in the control group and snoring time was 0.0%-34.5% (median 0.0%). The differences in snoring time between these three groups were statistically significant (Figure 2).

The parental reports (Table 4) and the clinical findings (Table 5) were analysed to find differences between the OSA group and the no OSA group. Mouth breathing, as reported by parents, was more common ($P = .015$) in the OSA group (4/9 children) than in the no OSA group (1/22 children). The prevalence of breathing difficulties while sleeping was not associated with the OSA diagnosis. In addition, the parent-reported frequency of current snoring, daytime tiredness and nasal stuffiness did not differ between the OSA group and the no OSA group.

During the clinical examination, mouth breathing observed by otorhinolaryngologist was more common in the OSA group (6/9 children) than in the no OSA group (3/22) ($P = .007$). Adenoid size was found to be larger in the OSA group ($P = .008$). However, not all

TABLE 2 Sleep and respiratory parameters between the snorer and control groups

	Snorer group (n = 31)	No snoring control group (n = 18)	*P* values
Total recording time (minutes)	598.0 (570.5-630.5)	617.9 (575.8-640.7)	.206
Total sleep time (TST) (minutes)	505.5 (464.0-551.5)	533.5 (487.4-593.0)	.084
Sleep stage N1 (%/TST)	4.1 (2.6-7.2)	3.1 (1.4-6.3)	.195
Sleep stage N2 (%/TST)	32.5 (28.3-39.3)	36.4 (34.2-41.1)	0.081
Sleep stage N3 (%/TST)	31.4 (26.2-38.8)	30.3 (24.3-36.0)	.431
Rapid eye movement (REM) sleep (%/TST)	28.8 (25.9-32.2)	27.2 (25.5-31.9)	.548
REM latency(minutes)	71.0 (57.5-117.0)	63.5 (50.3-92.4)	.238
Arousal index (number/hour)	9.6 (8.7-11.2)	9.9 (8.3-11.3)	.947
Apnoea/hypopnoea index (number/hour)	1.7 (1.1-3.0)	1.8 (1.1-3.4)	.841
Obstructive apnoea/ hypopnoea index (number/ hour)	0.3 (0.0-1.3)	0.0 (0.0-0.1)	**.003**
Oxygen desaturation index 3% (number/hour)	1.0 (0.4-2.2)	1.6 (0.7-3.0)	.367
Snoring time percentage (%/ TST)	19.5 (2.3-58.6)	0.0 (0.0-12.2)	**<.001**

Note: Median and interquartile ranges (0.25-0.75) are presented. *P* values <.05 bolded.

TABLE 3 The sleep and respiratory parameters between the OSA and no OSA groups

	OSA group (n = 9)	No OSA group (n = 22)	*P* values
Total recording time (minutes)	602.0 (591.0-634.0)	585.5 (563.0-615.5)	.132
Total sleep time (TST) (minutes)	555.5 (504.0-569.5)	477.8 (458.4-516.4)	**.005**
Sleep stage N1 (%/TST)	3.0 (1.4-3.6)	5.6 (3.2-8.4)	**.005**
Sleep stage N2 (%/TST)	32.5 (26.7-38.7)	32.7 (28.7-39.8)	.660
Sleep stage N3 (%/TST)	35.6 (26.5-41.3)	29.8 (25.8-35.3)	.374
Rapid eye movement (REM) sleep (%/TST)	31.0 (27.2-32.8)	27.8 (25.9-32.1)	.249
REM latency (minutes)	69.5 (61.8-96.8)	75.8 (54.0-117.0)	.773
Arousal index (number/hour)	10.0 (9.2-12.7)	9.4 (8.4-11.1)	.223
Apnoea/hypopnoea index (number/hour)	3.6 (2.2-5.0)	1.2 (0.7-1.9)	**<.001**
Obstructive apnoea/hypopnoea index (number/hour)	1.5 (1.3-3.1)	0.1 (0.0-0.4)	**<.001**
Oxygen desaturation index 3%(number/hour)	2.2 (0.2-6.3)	0.9 (0.5-0.19)	.513
Snoring time percentage (%/TST)	63.6 (30.0-84.0)	6.9 (0.6-27.7)	**.001**

Note: Median and interquartile ranges (0.25-0.75) are presented. *P* values <.05 bolded.

children with OSA had large adenoids. The size of the palatine tonsil did not differ significantly between the groups. None of the children had nasal septum deviations or significant deformities in the upper respiratory tract.

4 | DISCUSSION

Paediatric OSA is a relatively common disorder. Its epidemiology, symptoms and clinical features differ from those of adult OSA. Furthermore, it has also been demonstrated that there is a difference in clinical findings and risk factors between children of different ages with OSA [12,20] and that disorder can spontaneously resolve.[11] For this reason, we should consider paediatric OSA as a disorder that transforms as the child grows up, rather than a stable entity.

The polysomnography results showed that children with OSA had longer snoring time from the total sleep time than children who snored but do not have OSA. In future, it would be beneficial to consider whether snoring time could be a useful marker when distinguishing children with OSA from children who snore without OSA, and whether this might enable the development of a simple and valid screening method for paediatric OSA.

We clearly showed that parents could reliably evaluate whether the child snored when the questionnaire and polysomnography data were compared. However, there was no statistical difference between the parents' assessment of snoring frequency in the OSA group and in the no OSA group. None of the parents of the children with OSA reported their child having breathing difficulties while sleeping. Nevertheless, all of the children who were diagnosed with OSA were part of the snorer group. These findings confirm that patient histories on snoring frequency or remarkable breathing pauses cannot be reliably used to distinguish children with OSA from children who snore without OSA.[8] However, it seems to be beneficial to target diagnostics of OSA to those children whose parents report they snore.[21]

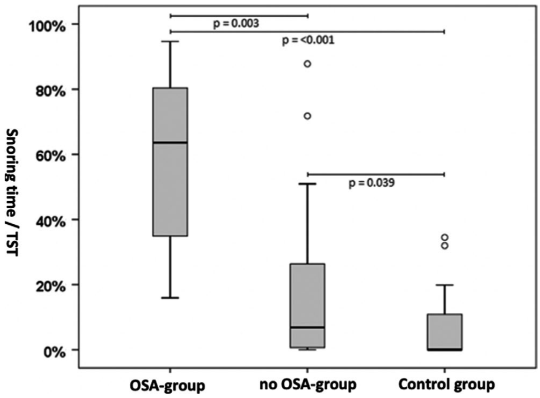

FIGURE 2 The snoring time from the total sleep time in the polysomnography between the OSA, no OSA and control groups

We observed that at the age of 2 years adenoid size and mouth breathing seemed to be important factors when assessing the likelihood of OSA, but palatine tonsil size was not. It has previously been reported that adenoid size seemed to influence the probability of OSA in younger children.[12,20] However, palatine tonsil size has not been seen as a significant factor. This raises the question about whether an adenoidectomy without tonsillectomy might be a sufficient procedure for young paediatric patients with OSA. Having an adenoidectomy on its own is not a well-researched procedure for treating paediatric OSA.[6] However, there is a evidence that it could be enough for young patients.[22] Moreover, adenoidectomy has been shown to have fewer complications than adenotonsillectomy.[23] Conversely, it has been suggested that between 2% and 29% of children who have undergone an adenoidectomy because of airway obstruction will need a tonsillectomy in the future.[24] Further research is needed on adenoidectomy alone as a treatment for paediatric OSA in young children. Perhaps, an adenoidectomy on its own, or combined with later myofunctional therapy, could be used to treat young children with OSA. Furthermore, myofunctional therapy has already been shown to reduce residual symptoms and mouth breathing after an adenotonsillectomy.[25,26]

TABLE 4 The anamnestic information reported at the time of the clinical examinations between the OSA and no OSA groups

Anamnestic information reported by parents	OSA group n = 9 (%)	no OSA- group n = 22 (%)	*P* values
Breathing difficulties during sleep			
No	9 (100)	17 (77)	.287
Yes	0 (0)	4 (18)	
Missing answers	0 (0)	1 (5)	
Snoring frequency			
Maximum of two nights per week	1 (11)	10 (45)	.110
Minimum of three nights per week	7 (78)	11 (50)	
Missing answers	1 (11)	1 (5)	
Frequency of daytime sleepiness			
Maximum of two days per week	9 (100)	15 (68)	.141
Minimum of three days per week	0 (0)	6 (27)	
Missing answers	0 (0)	1 (5)	
Breathing habit			
Mainly through nose	2 (22)	15 (68)	**.015**
Mainly through mouth	4 (44)	1 (5)	
Don't know	3 (33)	6 (27)	
Missing answers	0 (0)	0 (0)	
Nasal rhinitis or stuffiness			
No	7 (78)	18 (82)	1.000
Yes	2 (22)	4 (18)	
Missing answers	0 (0)	0 (0)	

Note: P values < .05 bolded.

TABLE 5 The clinical findings between the OSA and no OSA groups

	OSA group n = 9	no OSA group n = 22	*P* values
Sex			
Male	5 (56%)	8 (36%)	.433
Female	4 (44%)	14 (64%)	
Age (months, median, IQR 0.25-0.75)	27.5 (25.5 -29.5)	25.0 (23.0 -27.0)	.108
Body mass index (kg/m^2, median, IQR 0.25-0.75)	15.8 (15.4 - 16.4) Missing 1	15.7 (15.4 - 17.0) Missing 3	.969
Body mass index z-score (median, IQR 0.25-0.75)	-0.5 (−1.0-−0.2) Missing 1	-0.6 (−1.0 -0.4) Missing 3	1.000
Mouth breathing			
No	3 (33%)	19 (86%)	**.007**
Yes	6 (66%)	3 (14%)	
Palatine tonsil size(Friedman class)			
1	2 (22%)	6 (27%)	.531
2	3 (33%)	11 (50%)	
3	4 (44%)	5 (23%)	
4	0 (0%)	0 (0%)	
Adenoid size			
0%-25%	2 (22%)	13 (59%)	**.008**
26%-50%	3 (33%)	9 (41%)	
51%-75%	2 (22%)	0 (0%)	
76%-100%	2 (22%)	0 (0%)	
Secretion at nasal mucosa			
No	4 (44%)	5 (23%)	.385
Yes	5 (56%)	17 (77%)	
Swelling at nasal mucosa			
No or slight	9 (100%)	19 (86%)	.537
Moderate or severe	0 (0%)	3 (14%)	

Note: P values <.05 bolded.

4.1 | Strengths and limitations

The strength of the present study was that it focused on a homogeneous group of two-year-old children. In previous studies, the study populations have been heterogeneous with regard to the age of the children and few studies have focused on toddlers. We acknowledge the limitations of our study, including the low number of patients. A higher number could have strengthened our results. The prevalence of snoring was generally lower in our cohort, at 2.5%-3.2%, than previous studies of infants and toddlers, where the prevalence of snoring a minimum of three nights per week ranged from 5.3%-11%.[3,4] In addition, the study protocol was time-consuming for the families, and this reduced the number of families willing to participate in the study. There were only nine children with OSA and the severity of their OSA was generally mild, with obstructive AHI of 1.2-6.3. Despite this mild severity, we were still able to find detectable changes between the children with OSA and the children who snored without OSA. This strengthened the presumption that features that help assess the likelihood of OSA can be detected.

Three children had previously undergone an adenoidectomy and one had an adenoidectomy and partial tonsillectomy, which could be interpreted as a confounder. However, these children were not excluded because the regrowth of adenoid tissue after surgery is possible and the status of the tissue was evaluated during otorhinolaryngological examinations. Nevertheless, all the statistical analyses between the OSA and no OSA groups were repeated without the children who had received surgery and the significance of the results did not change when $P < .05$ was statistically significant.

5 | CONCLUSION

This study had two main findings that helped to assess the likelihood of OSA in toddlers. First, snoring time from total sleep time was longer in children with OSA than children who snored but did not have OSA. In future, it is possible that snoring time could be used as a diagnostic tool when distinguishing children who snore with and without OSA. Second, children with OSA breathed through their mouth more often and had bigger adenoid tissues than children who snored without OSA. In this age group, the size of the palatine tonsil did not seem to have a significant influence.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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PUBLICATION
IV

Is securing normal dentofacial development an indication for tonsil surgery in children? Systemic review and meta-analysis

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Review Article

Is securing normal dentofacial development an indication for tonsil surgery in children? A systematic review and meta-analysis

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ABSTRACT

Objective: Tonsil surgeries are common operations in the field of paediatric otorhinolaryngology. Often, the indication for these operations is hypertrophied tonsils. Paediatric sleep-disordered breathing and mouth-breathing are conventional situations caused by the hypertrophied tonsils. Both of these are further associated with dentofacial development alterations. Securing normal dentofacial development, or restoring it, is often used as an indication for tonsil surgery. In this review and meta-analysis, we assessed the contemporary literature to clarify whether tonsil surgery has an effect on dentofacial development in children.
Methods: Studies with children aged 3–10 years who underwent tonsil surgery and were compared to non-operated controls using dentofacial parameters were included to the review. Search strategies were planned for specific databases. The Newcastle-Ottawa scale was used to assess the risk of bias. A meta-analysis was performed when the data was methodologically homogenous enough to be pooled.
Results: The inclusion criteria for the review were fulfilled in 8 studies. The overall quality of the individual studies was judged to be moderate at best. The data were methodologically homogenous enough to be pooled for the meta-analysis in only 2 studies. The results of the meta-analysis revealed that tonsil surgery has a positive effect on the growth direction of the mandible ($p < 0.001$).
Conclusions: There is modest evidence that suggests that tonsil surgery has a positive effect on the dentofacial development in children with hypertrophied tonsils. Securing normal dentofacial development should be one component, but not the only one, when the indications for tonsil surgery in children are considered.

1. Introduction

1.1. Rationale

Adenotonsillectomy (AT), adenoidectomy (A) and tonsillectomy (T) are conventional operations in the field of otorhinolaryngology, especially in the treatment of the paediatric population. Indications for the operation, such as frequent or chronic tonsillitis, can be distinct, but remotely more complex conditions may also benefit from these operations. AT is the primary treatment when treating paediatric obstructive sleep apnea (OSA) and can be further used to treat other forms of sleep-disordered breathing (SDB) [1,2]. Hypertrophied tonsils and adenoids are considered to be the main cause of SDB in otherwise healthy children [3]. Furthermore, hypertrophied tonsils and adenoids have been suggested to be the main reason for mouth-breathing and the accompanying head and tongue posture changes in children [4,5]. Mouth-breathing, and the posture changes it causes, have been observed to also cause changes in dentofacial development [6,7]. Additionally, SDB and specific dentofacial features have been reported to be associated with each other and the causality between them is therefore not distinct [8,9]. It has been suggested that changes in dentofacial development in children with SDB are not only due to tonsil hypertrophy, but are also associated, for example, with SDB-related growth hormone changes and sleep position [7,10–12]. In summary, it can be stated that the connection between hypertrophied tonsils, mouth-breathing, paediatric SDB and dentofacial development is

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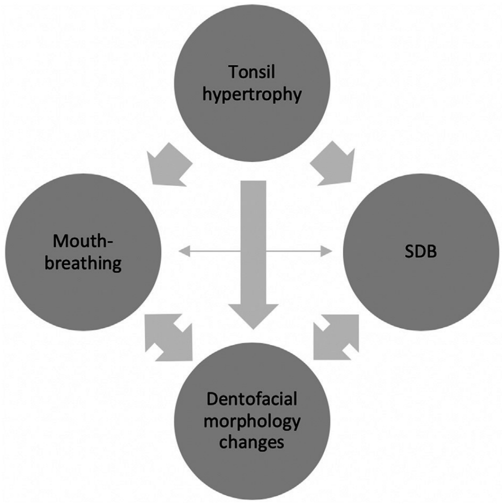


Fig. 1. The connections between hypertrophied tonsils, paediatric SDB, mouth-breathing and dentofacial development.

complex and multidirectional (Fig. 1).

Tonsil operations, like any other operative treatment, are not without risk [13]. The indications for operation should be carefully considered, especially when treating the vulnerable paediatric population. The indication for tonsil operation is clear when the child has OSA or clear symptoms of SDB and enlarged tonsils [2,14]. However, there is a significant number of paediatric patients who have no night-time symptoms, or the occurrence of these symptoms are unclear, but they still have obstructive tonsils and mouth-breathing. The gold standard method for diagnosing OSA is nocturnal laboratory polysomnography (PSG) [1,2]. Consequently, because there are limitations in the availability of paediatric PSG, it is not possible to execute it for every mouth-breathing child. Therefore, daytime mouth-breathing and the prevention of unfavourable dentofacial development are often used as indications for tonsil operations.

What is known about tonsil operations and their influence on the dentofacial development of children? A recent review aggregated the knowledge on the subject [15]. The key findings of the review were that after tonsil operations the incisors' inclination normalised towards a more labial position and mandibular growth became more horizontal. The disadvantage of the review was that half of the included studies concentrated only on the palatine tonsil or only on the adenoids and the other tonsil tissue was entirely ignored. From the perspective of the otorhinolaryngologist, the evaluation of obstructive tonsil tissue has to contain both palatine tonsil tissue and adenoid tissue and, less frequently in the paediatric population, lingual tonsil tissue.

1.2. Objectives

The objective in this systematic literature review was to clarify the effects of tonsil surgery on the dentofacial development of children with enlarged tonsils. Only studies which included an evaluation of both the palatine tonsils and the adenoids were included. In addition, the evaluation method for tonsil tissue size was also assessed. The null hypothesis for the review was as follows: "Tonsil operations do not change dentofacial development in children aged between 3 and 10 years".

2. Methods

2.1. Protocol and registration

The format of this review is based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16]. The review protocol was documented at the PROSPERO database (registration no. CRD42016037936).

2.1.1. Eligibility criteria

The eligibility criteria for the review were defined using the PICOS format as follows:

P (population): Children aged 3–10 years old (mean intervention age) with obstructed tonsils. Both palatine tonsil size and adenoid tissue size evaluated.

I (intervention): Adenoidectomy and/or tonsillectomy (total or partial).

C (comparison): Children who did not undergo adenoidectomy or tonsillectomy.

O (outcome): Dentofacial parameters measured before and at least one year after intervention.

S (study design): Prospective clinical comparative studies with at least 20 participants. The language not restricted.

2.1.2. Information sources

Medline, PubMed, Embase, Cochrane Central Register of Controlled trials, Cochrane Database of Systematic Reviews and Web of Science Core Collection comprised the information sources.

2.2. Search

Search strategies were planned for specific databases and can be seen in the attachments. The original searches were conducted on June 13 and 14, 2016. All studies published up to that time were included. On October 23, 2019, update searches were conducted. References published from 1.1.2016 onwards were searched.

2.3. Study selection

Three investigators (SM, PN and TP) separately reviewed the titles and abstracts of the papers. Articles that could not be excluded based on the titles and abstracts were analysed full-text by the same investigators. If unanimous agreement could not be reached, the situation was resolved with discussion between the investigators.

2.4. Data collection process

Data from the studies were collected by the two investigators (SM and PN) using a specially designed data extraction form. The most complete data with the longest follow-up period were collected.

2.5. Data items

The following information was collected: author, year of publication, country, study design, sample size, age of the subjects, gender of the subjects, description of the test and control groups, intervention, follow-up period, methods of assessment and outcome measures.

2.6. Risk of bias

All of the selected studies were nonrandomised. Consequently, the Newcastle-Ottawa scale for assessing the quality of nonrandomised studies in meta-analyses was used [17]. Two authors (SM & TP) independently assessed each article. Disagreements were resolved by consensus.

2.7. Summary measures

The principal summary measures were difference in means/medians between patients and controls before and after the intervention. In some of the studies, the means/medians at both time points were not reported. Instead, the studies reported the change between the time points, which was then used as a summary measure.

2.8. Synthesis of results

A meta-analysis was conducted when the data were methodologically homogenous enough to be pooled. The data which were not applicable for the meta-analysis were described and a summary of the findings presented.

A meta-analysis of parameters with continuous measure was performed using function 'metacont' with R software (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org). A random or fixed effect model, depending on the heterogeneity, was used. The heterogeneity was assessed with I^2 statistics. The values of 25%, 50% and 75% were considered to indicate low, moderate and high heterogeneity, respectively [18]. The standardised mean difference and 95% confidence intervals were calculated. Forest plots were generated.

3. Results

3.1. Study selection

The searches on June 13 and 14, 2016 retrieved 1447 references, and 921 references remained for screening after deduplication. After the review of the titles and abstracts of the papers, 882 papers were excluded and 39 were analysed full-text. Thereafter, 8 papers fulfilled the inclusion criteria and were accepted to this review.

On October 23, 2019, the update searches retrieved 592 references, and 309 references remained for screening after deduplication. After the titles and abstracts of the papers were reviewed, no new papers fulfilling the inclusion criteria were found (Fig. 2).

3.2. Study characteristics

The eight studies accepted to the review were published between 2006 and 2016. Seven of the studies were executed in Brazil and one in Sweden. Three of the Brazilian articles were from the University of Sao Paulo at Ribeirao Preto and had the same research ethics committee number [19–21]. Three other Brazilian articles were from the Federal University of Minas Gerais [22–24] and one from the Federal University of Sao Paulo [25]. The three studies from the University of Sao Paulo and the three studies from the Federal University of Minas Gerais were considered to potentially involve the same population, and therefore were not treated as independent studies.

In one study, the inclusion criteria for the cases were obstructive sleep apnea and enlarged tonsils and/or adenoids [26]. In the other studies, the inclusion criteria were mouth-breathing and enlarged tonsils and/or adenoids. In all studies, both palatine tonsil and adenoid size were evaluated. All but one study classified palatine tonsil size using the classification of Brodsky [27,28]. The adenoid size was evaluated using lateral skull radiography and the method of Cohen and Konak [29] in three studies [19–21]. Four studies used endoscopic assessment of the adenoid tissue [21–24]. One study did not describe the specific evaluation method for palatine tonsil or adenoid size [26]. We contacted the corresponding author of this study and obtained information that both the palatine tonsil size and the adenoid size was separately evaluated using 5 and 3 class classifications, respectively.

The controls in four studies were nasal-breathing children [19–21,26]. In two studies, both the patients and the controls were mouth-breathing and had enlarged tonsils and/or adenoids, but the controls did not undergo the intervention [22,23]. In one study, there was both a mouth- and a nasal-breathing control group [24]. Taking into account that there were only four separate materials in the eight studies, the total number of patients and controls in the review was 107 and 140, respectively.

The mean age of the patients was 4.3–6.9 years and 5.1 to 6.7 among the controls at the time of the intervention. In one study, the patients and controls were further divided into deciduous and mixed dentation groups, mean age 4.7/5.1 and 7.5/7.9, patients/controls respectively [23]. In one study, the mean age was not reported, but the age range was 7–11 years [25].

In five of the studies, the intervention was AT [21–25], in two either AT or A [19,20] and in one AT, A or T [26]. The follow-up time after intervention ranged from 1 to 5 years. In all studies, the assessment of outcome measures was made from cephalometric radiographs and/or dental study casts.

In seven of the studies the preoperative breathing pattern of the patients was evaluated [19–25]. In five of them it was mentioned that the mouth-breathing pattern was normalised after the operation [19–23].

All studies were prospective clinical comparative studies. One study was purported to be retrospective, but the study design, in our opinion, was prospective [22].

The study characteristics can be found in more detail in Table 1.

3.3. Risk of bias

The risk of bias in the review in its entirety should be considered high because there have been no randomised trials on the subject.

The Newcastle-Ottawa scale (NOS) was used to assess the study quality in the 8 studies included in this review (Table 2). The mean score was 5.5 SD 1.51 when the maximum score was 9. Consequently, it can be said that the overall quality of studies was moderate. In case-control studies, the NOS scale comprehends three categories: selection, comparability and exposure. In all studies, the selection of the patients and controls was the weakest category. In one study, the patients were chosen by primary record source (polysomnography) [26]. In one study, it was reported that otolaryngological examination was executed by two doctors [24]. In other studies, the validation of the patients was not described as precisely or it was made based on only one person's opinion. None of the studies described whether the sample was truly random. Furthermore, none of the studies used true community controls or the selection of the controls were unclear. In one study, some of the controls were selected from a longitudinal cephalometric growth study [26]. The definition of the controls was clear in all studies. In all but one [25] study, the age of the patients and controls was matched. The ascertainment of exposure was clear in every study and the methods used for assessing the outcomes were the same for patients and controls. The evaluation of non-responders was difficult in almost every study.

In five studies, neither the patients nor controls had had any previous orthodontic treatments. In three studies, this was not clearly reported [22,23,26]. The sucking habits, pacifier or thumb sucking, was reported in three studies [23,24,26]. These features can be considered as confounders as they can have an effect on dentofacial development.

3.4. Results of individual studies

The studied parameters in the studies can be divided into two categories: occlusion parameters and parameters associated with facial morphology. Next, the main outcomes of the studies are described in these categories. The aims of the specific studies, the main outcomes and conclusions are presented in further detail in Table 3.

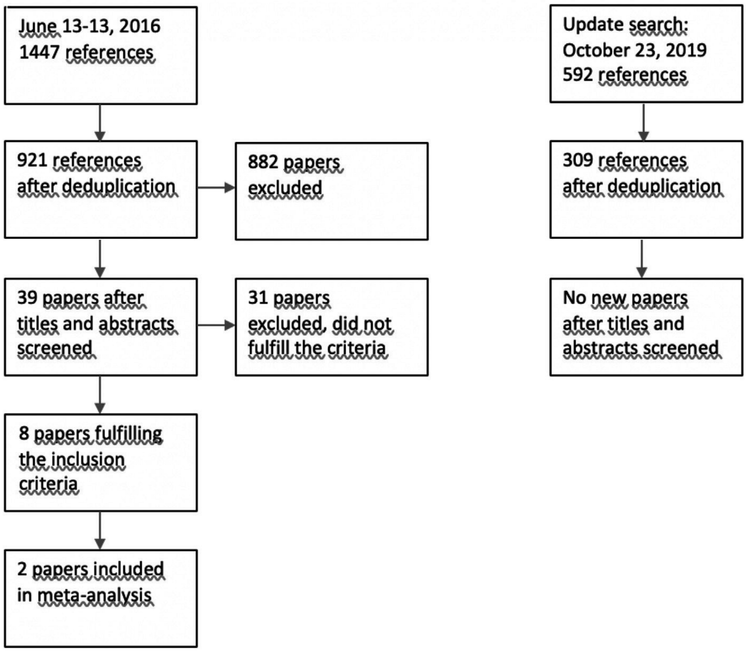


Fig. 2. The study selection flow chart.

3.4.1. Occlusion

Occlusion and dental arch morphology was discussed in five studies [19,21,22,24,25]. In four of them the used surgery method was AT and in one of them [19] it was AT or A.

In four studies, mouth-breathing patients were compared with nasal-breathing controls at the beginning of the study [19,21,24,25]. Of these, the maxillary inter canine and second molar width was evaluated in three studies. Two of them did not find differences between patients and nasal-breathing controls [19,24]. Vieira et al. reported the lower inter canine width but not the second molar width [21]. It should be pointed out that two of the aforementioned studies may in some part have had the same study population. However, in their study, Vieira et al. [21] evaluated patients whose intervention was AT and Mattar et al. [19] evaluated patients whose intervention was A or AT. The maxillary inter canine and second molar width were the only parameters that could be found in both of these studies.

Petraccone Caixeta et al. found a larger mandibular arch length and larger mandibular inter canine width and second molar width in patients [24]. The mandibular arch morphology was not examined in other studies. Palatal vault was found to be deeper by Petracoccone Caixeta et al., but not by Viera et al. [21,24]. Pereira et al. found that patients had a smaller overbite than controls, but Mattar et al. did not find any difference [19,25]. The position of the maxillary and mandibular incisors was evaluated using different parameters in two studies [19,25]. Perreira at al. found less lingually tilted mandibular incisors, but Mattar et al. did not find any differences. Statistically significant differences in other measured parameters, such as overjet [19,25], the presence of anterior open bite or posterior crossbite [19], terminal plane of the maxillary and mandibular second molars [19], maxillary dental arch length or perimeter [24] and mandibular dental arch perimeter [24]), were not found in any of the studies.

In two of the four studies, the differences that were observed between the patients and the nasal-breathing controls before operation decreased after the operation [21,25]. Mattar et al. did not find any differences before the operation, but the patients had larger overjet after the operation [19]. Petraccone Caixeta et al. did not study the differences between the patients and the nasal-breathing controls after the tonsil operation [24].

Two studies compared the patients with mouth-breathing controls at the beginning of the study and after the operation [22,24]. At the beginning of the study, these groups did not have differences in the outcome parameters in either of the studies. After the operation, Petraccone Caixeta et al. found that the change in maxillary inter canine and second molar width was larger in a positive direction in the patients, but there was no actual difference between the groups. They also found that change in palatal depth, to the direction of deeper shape, was larger in the patients, yet there was no actual difference between groups in this parameter [24]. Brunelli et al. studied the change in maxillary inter canine and intermolar width, maxillary arch length and perimeter, and palatal depth. They further assessed the change in palatal volume. The only statistically significant difference found was in the change in palatal volume after the operation, and the change was significantly greater among patients [22]. It should be noted that Petraccone Caixeta et al. and Brunelli et al. may have partly had the same study population, and therefore the results should not be evaluated as independent from each other.

3.4.2. Facial morphology

The changes in facial morphology are described in four studies [20,22,23,26]. In two of them the used surgery method was AT, in one of them AT or A [20] and in one of them AT, T or A [26]. A comparison of the results is complicated because different parameters and different measuring techniques were used to describe the facial morphology and development.

Two of the studies compared the patients and the nasal-breathing controls before and after the intervention. Zettergren-Wijk et al. found a number of differences between these groups. The patients had a more posteriorly inclined mandible, more anteriorly inclined maxilla, greater lower anterior face height, shorter lower posterior face height, shorter anterior cranial base, more retroclined upper and lower incisors,

Table 1
Study characteristics.

Author	Year	Country	Study group	Control group	Intervention	Patient Number (study/ control)	Mean age at the beginning, patient/ control (years)	Follow- up (years)
Zettergren-Wijkn et al.	2006	Sweden	Children with obstructed sleep apnea and enlarged tonsils/adenoids	Children with normal breathing pattern	AT, T or A	17/17	5.6/5.8	5
Souki et al.	2010	Brazil	Mouth-breathing children with enlarged tonsils/ adenoids, separated further into two groups: deciduous dentition and mixed dentition at the beginning of the study	Mouth-breathing children with enlarged tonsils/ adenoids, separated further into two groups: deciduous dentition and mixed dentition at the beginning of the study	AT	39/31	Deciduous dentition group: 4.7/5.1 Mixed dentition group: 7.5/7.9	1
Mattar et al.	2011	Brazil	Mouth-breathing children with enlarged tonsils/ adenoids	Nasal-breathing children	AT or A	33/22	4.67/5.08	2.3
Pereira et al.	2011	Brazil	Mouth-breathing children with enlarged tonsils/ adenoids	Children with normal breathing pattern	AT	18/20	NA Age range 7–11	1.2
Mattar et al.	2012	Brazil	Mouth-breathing children with enlarged tonsils/ adenoids	Nasal-breathing children	AT or A	33/22	4.67/5.08	2.3
Vieira et al.	2012	Brazil	Mouth-breathing children with enlarged tonsils/ adenoids	Nasal-breathing children	AT	29/15	4.25/5.08	2.3
Petraccone Caixeta et al.	2014	Brazil	Mouth-breathing children with enlarged tonsils/ adenoids	Two control groups: Mouth-breathing children with enlarged tonsils/adenoids and nasal-breathing children	AT	24/25 (mouth-breathing controls) & 46 (nasal-breathing controls)	6.2 (all mouth-breathing), 5.9 (nasal-breathing)	1
Brunelli et al.	2016	Brazil	Mouth-breathing children with enlarged tonsils/ adenoids	Mouth-breathing children with enlarged tonsils/ adenoids	AT	35/35	6.9/6.7	1

reduced airway space and less pronounced nose. After the operation, the majority of the differences had decreased and the patients only had a shorter anterior cranial base and less pronounced nose compared with the controls [26]. Mattar et al. found that the patients had a higher inclination of the mandibular plane when compared with the cranial base or the palatal plane, larger gonial angle and a decrease in total and inferior posterior facial height. Additionally, the patients demonstrated predominant dolicofacial development, meaning that the relation between face height and face depth was changed towards a longer face. After the operation, the differences were no longer found, except for the predominant dolicofacial development that could still be seen [20].

Souki et al. compared patients and mouth-breathing, non-operated controls and further divided the participants into deciduous dentition and mixed dentition groups. At the beginning of the study, no differences were found between the deciduous dentition patients and controls and the mixed dentition patients and controls. The change in measured parameters between the beginning of the study and the time point after operation and follow-up was evaluated between the patients and controls in the deciduous and mixed dentition groups. The actual difference in parameters at the same time point was not evaluated. The statistical significance of the changes in parameters was similar among patients and controls in the deciduous and mixed dentition groups. However, there was a statistically significant reduction of angle between maxilla and mandibular plane among patients in the deciduous dentition group but not among the controls [23]. In this study, the change in the angle between the anterior cranial base or maxilla and the mandible plane was not significant between the patients and controls either in the deciduous or mixed dentition groups.

Brunelli et al. compared the patients and the mouth-breathing, non-operated controls. Although this study may describe the same population as Souki et al., no further division into subgroups was made and the measured parameters were different. Brunelli et al. found that the patients had a statistically significant change in some of the parameters that described the forward displacement of the maxilla, but the controls did not. However, no actual difference in these parameters was reported.

3.5. Synthesis of results

Due to the methodological diversity in the studies and the fact that some of the studies described the same population, only two studies and two parameters in them could be included in the meta-analysis when the changes between the time point before the operation and after the follow-up in patients and controls was analysed. The parameters used were the degree of mandible plane inclination in relation to the anterior cranial base and the degree of maxilla plane inclination in relation to the anterior cranial base from the studies of Zettergren-Wijk et al. and Mattar et al. [20,26]. The corresponding author of the first article was contacted to obtain the changes and the standard deviations of mentioned parameters [26]. The same information was obtained straight from the other article [20].

Heterogeneity between studies was considered low in the parameter: "the degree of maxilla plane inclination", $I^2 = 0.0\%$ and a fixed effects model was used. The degree of mandible plane inclination showed a significantly larger change in patients compared with controls ($p < 0.001$) (Table 4) (Fig. 3). The angle between the mandible plane and the anterior cranial base reduced in both groups, but significantly more in patients, approaching morphology normalisation. Heterogeneity between studies in the parameter: "the degree of mandible plane inclination" was found to be moderate, $I^2 = 57.9\%$, and a random effect model was chosen. No significant difference between groups was found (Table 5).

Table 2
Newcastle-Ottawa scale of the studies.

	Selection max. 4	Comparability max. 2	Exposure max. 3	Total max 9
Zettergren-Wijk et al., 2006	★	★ ★	★ ★ ★	6
Souki et al., 2010	★ ★	★ ★	★ ★ ★	8
Mattar et al., 2011	★	★	★ ★ ★	5
Pereira et al., 2011	★		★ ★	3
Mattar et al., 2012	★	★	★ ★ ★	5
Vieira et al., 2012	★	★	★ ★ ★	5
Petraccone Caixeta et al., 2014	★ ★	★ ★	★ ★ ★	7
Brunelli et al., 2016	★	★ ★	★ ★	5

4. Discussion

4.1. Summary of evidence

Based on the current literature, it has been observed that mouth-breathing children have changed dentofacial morphology compared with nasal-breathing children. The classical mouth-breather is described to have an adenoid face, which means a narrow upper jaw, retroclined incisors, an increased anterior face height, a retrognathic mandible and an enlarged angle between the anterior cranial base and the mandibular plane [5,7]. The results of this review support this perception to some extent. All the aforementioned developmental changes were observed in mouth-breathing children when compared with nasal-breathing children [20,21,25,26]. However, all studies reported only some of these changes and none described the classical adenoid face.

When the individual studies were evaluated, a normalisation in the dentofacial morphology of the mouth-breathing children towards the morphology of nasal-breathing children was seen after tonsil surgery [19–21,26]. Moreover, a modest positive change towards more normal dentofacial development was observed when mouth-breathing controls and patients were compared after the patients had been operated [22,24]. Meta-analysis showed that tonsil surgery has a positive effect on the growth direction of the mandible. In the previous literature, the positive effects of tonsil surgery, especially on mandibular growth, has been described, yet many of the studies concentrated only on adenoidectomy [30–33].

The variability of the studies was a distinct problem when trying to combine the information across the studies. There were several methodological differences that made the comparison difficult. Some of the studies used nasal-breathing controls and some mouth-breathing controls. In addition, some studies had children with both deciduous and mixed dentition, and the follow-up times varied from one to five years. Furthermore, the methods used to evaluate the size of tonsils were diverse. Although the methods used to collect the dentofacial outcome parameters were similar, the parameters themselves or the methods used to measure the parameters differed. In addition, only four separate study populations could be defined among the eight studies.

Consequently, we only found two studies in which the definition of the control groups was similar, which did not use the same population and which used equivalent methods for measuring the outcome parameters [20,26]. The follow-up times in these studies were different and ranged from 2.3 to 5 years. This further complicated the comparison of the linear measurements while the impact of normal growth could not be eliminated between the studies. Therefore, we chose to only use angular measurements in the meta-analysis. It can be assumed that the increased change in angular dimensions is due to intervention or some other environmental change and is not due to normal growth [34,35]. Moreover, the angular changes between the anterior cranial base and the plane of the mandibula/maxilla cannot be achieved by means of orthodontic treatments as is the case with changes achieved among occlusal features. Hence, if tonsil surgery modifies these dimensions towards normalisation, the impact of the procedure can be more valuable than in those features that can be altered through other treatment modalities. The meta-analysis revealed that there was some evidence that tonsil surgery has a positive effect on the growth direction of the mandible in contrast to the anterior cranial base. This finding favours the use of tonsil surgery to secure normal dentofacial development. However, similar results were not found in the study by Souki et al., but this study could not be included in the meta-analysis due to the different outcome parameters used [23].

4.2. Application of the results to everyday practice

Based on the findings of this review, evidence on the effects of tonsil surgery on the dentofacial development of children with enlarged tonsils is scarce and the results are contradictory. It can be said therefore that the null hypothesis of the review, i.e: “Tonsil operations do not change the dentofacial development in children aged between 3 and 10 years”, can be rejected. However, based on the studies included in this review, it cannot be dependably concluded what all of the changes are and whether they are evident in all patients. The question “Is securing normal dentofacial development an indication for tonsil surgery in children?” cannot be fully answered based on the contemporary literature. However, there is evidence that mouth-breathing changes the dentofacial development of children and even more evidence that children with SDB undergo similar changes [9,36–40].

Souki et al. studied the effect of tonsil surgery in deciduous and mixed dentition groups. They concluded that the timing of the operation did not change the effect on facial morphology [23]. Previously, it had been speculated that dentofacial development would be more favourable if the obstructed tonsils were removed at a younger age. This speculation rises from the fact that significant facial growth occurs in early life [41]. In our own studies, we have noticed that children with SDB already have minor dentofacial changes at the age of 2.5 years [42,43]. Hence, children with obstructed upper airways should be monitored for dentofacial development, but it seems that the timing of the tonsil operation is not absolutely crucial from that perspective. On the other hand, there is evidence that the early treatment of SDB leads to better quality of life, and therefore supports early intervention [44].

Children with obstructer palatine tonsils and/or adenoid should be evaluated comprehensively and the connections between hypertrophied tonsils, mouth-breathing, SDB and dentofacial development, as seen in Fig. 1, should be carefully considered. Often, the desired positive effect on dentofacial development is not the only indication for the operation. The diagnostic value of PSG should be further considered when situations are unclear.

4.3. Application of the results to future research

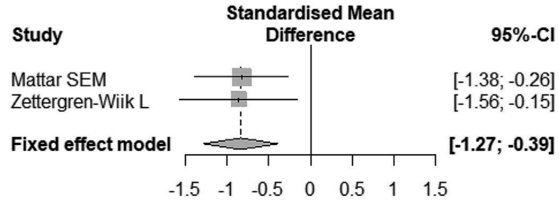
For future research, the outcome parameters and methods of measuring them should be standardised so that the study results can be combined and compared. The methods used to determine the size of the palatine tonsils and adenoids should be equally unified. In our review, no studies that grouped patients based on palatine tonsil and adenoid size were found. It could be speculated that the dentofacial changes in

Table 3
The study results. Studies 2, 4, 5 and studies 6, 7, 8 may have the same study population and the results should not be interpreted individual from each other.

Study	Aim of the study	Differences between the patients and controls at the beginning of the study	Differences between the patients and controls at the end of the study (follow-up time)	Conclusions
Studies with nasal-breathing controls				
1 *Zettergren-Wijk* et al. *2006*	To compare young children suffering from OSA syndrome with non-obstructed children, with respect of craniofacial morphology, soft tissue profile and airway space before and after tonsil surgery To longitudinally evaluate the development of these structures and to undertake a comparison with the normal development in non-obstructed children	Patients: more posteriorly inclined mandible, more anteriorly inclined maxilla, greater lower anterior face height, shorter lower posterior face height, shorter anterior cranial base, retroclined upper and lower incisors, reduced airway space, less pronounced nose	Patients: shorter anterior cranial base, less pronounced nose (5 years)	OSA in young children has an unfavourable effect on the development of several dental and facial components. If OSA is treated at an early age, an almost complete normalisation of dental morphology may be achieved
2 *Mattar* et al. *2011*	To examine the influence of mouth-breathing on children's facial morphology before and after adenoidectomy or adenotonsillectomy	Patients: larger inclination of mandibular plane when compared with cranial base or the palatal plane, larger gonial angle, dolichofacial morphology, decrease in the total and inferior posterior facial heights	Patients: dolichofacial morphology (2.3 years)	The difference between groups reached a significant similarity after tonsil surgery
3 *Pereira* et al. *2011*	To compare the cephalometric measurements before and after adenotonsillectomy in mouth- breathing patients	Patients: less lingually tilted mandibular incisors, smaller overbite	No difference (1.2 years)	Adenotonsillectomy brought about benefits in relation to dental occlusion, as it favours the morpho-functional development of the face
4 *Mattar* et al. *2012*	To evaluate mouth-breathing and nasal-breathing children before and after tonsil surgery, comparing the occlusal features	No difference	Patients: larger overjet (2.3 years)	Neither the breathing pattern nor the surgery had any effect on occlusal features in 3- to 6-year-olds
5 *Vieira* et al. *2012*	To evaluate the palate width and height in mouth-breathing children pre- and post-adenotonsillectomy	Patients: lower maxillary inter canine width	No difference (2.3 year)	The breathing pattern has little influence on palatal height and intramolar width. Intracanine width, which was found narrower in the mouth-breathing children, presented a significantly similar pattern to control group after AT
Studies with obstructed controls				
6 *Souki* et al. *2010*	To evaluate do children who have an early change in the mode of respiration, after TA, grow differently than late-treatment children.	Deciduous dentition group: no difference Mixed dentition group: no difference	Deciduous dentition group: reduction of angle between maxilla and mandibular plane in cases but not in controls Mixed dentition group: no difference (1 year)	Regarding the dentofacial vertical growth pattern, normalisation of the mode of respiration in young children is not more effective than in older children
7 *Brunelli* et al. *2016*	To measure the maxillary dentoskeletal and soft tissue changes of mouth-breathing young children after AT in comparison with a matched group of non-operated mouth-breathing children	No difference.	Cases: increase in palatal volume, increase in forward displacement of maxilla (1 year)	The palatal volume and forward displacement of maxilla increased after AT
Studies with nasal-breathing and obstructed controls				
8 *Petraccone Caixeta* et al. *2014*	To investigate the dental arch changes after AT in prepubertal children and to compare the dental arch dimensions of mouth-breathing and nasal-breathing children	Cases compared to nasal-breathing controls: deeper palatal vault, larger mandibular width and arch length Cases compared to obstructed controls: No difference	Cases compared to nasal-breathing controls: not compared Cases compared obstructed controls: Maxillary transverse dimensions increased significantly in cases; palatal vault increased significantly in controls (1 year)	The AT subgroup had a significantly different pattern of arch development compared to obstructed controls. Mouth-breathing children showed different dental arch changes in comparison to nasal-breathing children

Table 4
The change in the degree of the mandible plane inclination in relation to the anterior cranial base between the initial time point and the time point after the follow-up.

Study	Patients			Controls				Standardised mean difference
	Mean change	SD	Number of patients	Mean change	SD	Number of patients	Weight, Fixed	Fixed, 95% CI
Mattar et al., 2011	−2.30	2.60	33	0.00	3.00	22	61.2%	−0.82 [-1.38; −0.26]
Zettergren-Wijk et al., 2006	−3.55	2.02	17	−1.64	2.33	17	38.8%	−0.85 [-1.56; −0.15]
Total [95% CI]			50			39	100.0%	−0.83 [-1.27; −0.39]
Heterogeneity I^2 = 0.0%								
Test for overall effect: Z = −3.71 (p = 0.0002)								



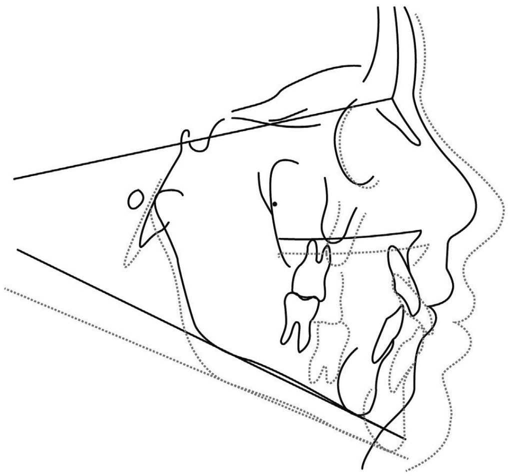


Fig. 3. The meta-analysis indicates that mandibular growth direction changes from vertical (solid line) to more horizontal (broken line) following tonsil surgery.

children who have a very large palatine tonsil and adenoid size would be more evident when compared with children who, for example, have a moderate palatine tonsil size and a moderate adenoid size. The effect of tonsil surgery could likewise be larger among those patients who have more obstructed upper airways. From an otolaryngologist perspective, it would be important to know whether there are indications to operate moderate size palatine tonsils and adenoids to secure dentofacial development or should the surgery only be performed if the upper airways are truly obstructed.

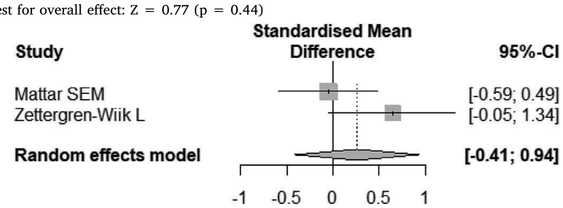
Previously, Peltomäki has hypothesised that tonsil surgery changes the mandibular plane angle not only due to the change in muscle balance but also to growth hormone secretion [7]. Our results support this hypothesis, but more research is still needed on the causal connections of the dental morphology normalisation.

4.4. Limitations

The risk of bias in the review has to be considered high. There have been no randomised studies on the subject. Moreover, the number of studies that fulfilled the inclusion criteria was low, the studies were methodically variable, and the quality of the studies was moderate at best when the risk of bias in the individual studies was estimated.

Table 5
The change in the degree of the maxilla plane inclination in relation to the anterior cranial base between the initial time point and the time point after the follow-up.

Study	Cases			Controls				Standardised mean difference
	Mean change	SD	Number of patients	Mean change	SD	Number of patients	Weight, Random	Random, 95% CI
Mattar et al., 2011	0.30	2.00	33	0.40	2.40	22	55.1%	−0.05 [-0.59; 0.49]
Zettergren-Wijk et al., 2006	1.46	1.70	17	0.29	1.84	17	44.9%	0.64 [-0.05; 1.34]
Total [95% CI]			50			39	100.0%	0.26 [-0.41; 0.94]
Heterogeneity I^2 = 57.9% [0.0%; 90,0%]								
Test for overall effect: Z = 0.77 (p = 0.44)								



5. Conclusion

There is modest evidence that tonsil surgery (tonsillectomy and/or adenoidectomy) has a positive effect on dentofacial development in children. It seems to have a particularly positive effect on the growth direction of the mandible. The other specific changes in the morphology cannot, however, be clearly determined based on the current literature. More quality research, with more homogenous execution, is therefore needed. When considering the indications for tonsil surgery in children, securing normal dentofacial development should be one component, but not the only one. Nevertheless, the normalisation of the breathing pattern from mouth-breathing to nasal-breathing should be considered to be important. Hypertrophied tonsils, mouth-breathing, SDB and dentofacial development should all be treated as an entirety and not as separate entities.

Declaration of competing interest

The authors have no conflict of interest to declare.

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