

Department of Otorhinolaryngology – Head and Neck Surgery
University of Helsinki
Finland

Katja Liukkonen

SNORING AND SLEEP APNEA IN CHILDREN

To be presented, with the permission of the
Medical Faculty of the University of Helsinki,
for public examination in Lecture Hall 2 of Biomedicum Helsinki,
Haartmaninkatu 8, on December 9th, 2011, at 12 noon.

Helsinki 2011

Supervised by

Professor Anne Pitkäranta
Department of Otorhinolaryngology – Head and Neck Surgery
Helsinki University Central Hospital
University of Helsinki, Faculty of Medicine, Finland

Docent Turkka Kirjavainen
Department of Pediatrics
Helsinki University Central Hospital
University of Helsinki, Finland

Reviewed by

Professor Olli Polo
Department of Respiratory Diseases
University of Tampere
Tampere, Finland

Docent Pirkko Ruoppi
Institute of Clinical Medicine – Otorhinolaryngology
University of Eastern Finland
Kuopio, Finland

Opponent

Professor Elisabeth Hulcrantz
Department of Clinical and Experimental Medicine
Division of Otorhinolaryngology
University of Linköping
Linköping, Sweden

ISBN 978-952-10-7306-9 (paperback)

ISBN 978-952-10-7307-6 (PDF)

<http://ethesis.helsinki.fi>

Layout Olli Eloranta

Unigrafia Oy, Helsinki 2011

CONTENTS

LIST OF ORIGINAL PUBLICATIONS	5
ABSTRACT	6
TIIVISTELMÄ	8
ABBREVIATIONS	10
INTRODUCTION	11
REVIEW OF THE LITERATURE	13
Pediatric sleep-related breathing disorders	13
Terminology and classification	13
Epidemiology	14
Pathophysiology and risk factors	14
Snoring and obstructive sleep apnea	19
Diagnosis	19
Consequences	28
Management	36
AIMS OF THE STUDY	41
SUBJECTS AND METHODS	42
Subjects	42
Methods	44
Statistical methods	49
RESULTS	50
Epidemiology of snoring (I)	50
Parental smoking, rhinitis and nasal resistance in children (III)	51
Risk factors and consequences of snoring and sleep apnea (II and IV)	51
Feasibility and normal nasal volume values of acoustic rhinometry in children (V)	56
DISCUSSION	57
Prevalence of snoring	57
Risk factors for snoring and sleep apnea	57
Nasal measurements and cephalometry	58
Polysomnography	59
Neurobehavioral consequences	60
LIMITATIONS OF THE STUDY	61
CONCLUSIONS	62
ACKNOWLEDGMENTS	63
REFERENCES	67
ORIGINAL PUBLICATIONS	76

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles, which are referred to in the text by Roman numerals I - V.

- I Liukkonen K, Virkkula P, Aronen ET, Kirjavainen T, Pitkäranta A. All snoring is not adenoids in young children. *Int J Pediatr Otorhinolaryngol.* 2008;72;879-84.
- II Aronen ET, Liukkonen K, Simola P, Virkkula P, Uschakoff A, Korkman M, Kirjavainen T, Pitkäranta A. Mood is associated with snoring in preschool-aged children. *J Dev Behav Pediatr.* 2009;30;107-14.
- III Virkkula P, Liukkonen K, Suomalainen AK, Aronen ET, Kirjavainen T, Pitkäranta A. Parental smoking, rhinitis and nasal resistance in children. *Acta Paediatr.* 2011;100;1234-8.
- IV Liukkonen K, Virkkula P, Suomalainen AK, Haavisto A, Aronen ET, Pitkäranta A, Kirjavainen T. Symptoms at presentation in children with sleep-related disorders. Submitted.
- V Liukkonen K, Virkkula P, Pitkäranta A. Acoustic rhinometry in small children. *Rhinology* 2006;44;160-3.

These publications are reproduced with the permission of their copyright holders.

ABSTRACT

Snoring is a primary and major clinical symptom of upper airway obstruction during sleep. Sleep-disordered breathing ranges from primary snoring to significant partial upper airway obstruction, and obstructive sleep apnea. Adult snoring and obstructive sleep apnea have been extensively studied, whereas less is known about these disorders in children. Snoring and more severe obstructive sleep apnea have been shown to have a harmful effect on the neurobehavioral development of children, but the mechanisms of this effect remains unknown. Furthermore, the correlation of this effect to objective sleep study parameters remains poor.

This study evaluated the prevalence of snoring in preschool-aged children in Finland. Host and environmental risk factors, and neurobehavioral and neurocognitive symptoms of children suffering from snoring or obstructive sleep apnea were also investigated. The feasibility of acoustic rhinometry in young children was assessed.

The prevalence and risk factors of snoring (I) were evaluated by a questionnaire. The random sample included 2100 children aged 1-6 years living in Helsinki. All 3- to 6-year-old children whose parents reported their child to snore always, often, or sometimes were categorized as snorers, and invited to participate to the clinical study (II-IV). Non-snoring children whose parents were willing to participate in the clinical study were invited to serve as controls.

Children underwent a clinical ear-nose-throat examination. Emotional, behavioral, and cognitive performances were evaluated by Child Behavioral Checklist (CBCL), Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R) and NEPSY-A Developmental Neuropsychological Assessment (NEPSY). Nasal volume was measured by acoustic rhinometry, and nasal resistance by rhinomanometry. Lateral and posteroanterior cephalometry were performed. A standard overnight ambulatory polysomnography was performed in the home environment. Twenty-six healthy children were tested in order to assess the feasibility of acoustic rhinometry in young children (V).

Snoring was common in children; 6.3% of children snored always or often, whereas 81.3% snored never or occasionally. No differences were apparent between snorers and non-snorers regarding age, or gender. Pediatric snoring was associated with recurrent upper respiratory infections, otitis media, and allergic rhinitis. Exposure to parental tobacco smoke, especially maternal smoking, was more common among snorers. Rhinitis was more common among children who exposed to tobacco smoke.

Overnight polysomnography (PSG) was performed on 87 children; 74% showed no signs of significant upper airway obstruction during sleep. Three children had obstructive apnea/hypopnea index (OAHI) greater than 5/h. Age, gender, or a previous adenoidectomy or tonsillectomy did not correlate with OAHI, whereas tonsillar size did correlate with OAHI. Relative body weight and obesity correlated with none of the PSG parameters. In cephalometry, no clear differences or correlations were found in PSG parameters or between snorers and non-snorers. No correlations were observed between acoustic rhinometry, rhinomanometry, and PSG parameters.

Psychiatric symptoms were more frequent in the snoring group than in the non-snoring group. In particular, anxious and depressed symptoms were more prevalent in the snoring group. Snoring children frequently scored lower in language functions. However, PSG parameters correlated poorly with neurocognitive test results in these children.

This study and previous studies indicate that snoring without episodes of obstructive apnea or SpO₂ desaturations may cause impairment in behavioral and neurocognitive functions. The mechanism of action remains unknown. Exposure to parental tobacco smoke is more common among snorers than non-snorers, emphasizing the importance of a smoke-free environment. Children tolerated acoustic rhinometry measurements well.

TIIVISTELMÄ

Unenaikainen ylähengitystieahtauma käsittää jatkumon ajoittaisesta hiljaisesta kuorsaamisesta vaikea-asteiseen obstruktiiviseen uniapneaan, jossa koko uni on toistuvien tukoksellisten hengitystaukojen rikkoma. Vaikea-asteisen obstruktiivisen uniapnean tiedetään voivan vaikuttaa sekä lapsen henkiseen että fyysiseen kehitykseen, mutta yleisemmin on osoitettu kuorsaavien lasten pärjäävän verrokkeja huonommin koulussa.

Selvitimme 1 - 6-vuotiaiden helsinkiläisten lasten kuorsauksen yleisyyttä kyselykaavakkeella. Aineiston valinta perustui satunnaistettuun otantaan väestörekisterikeskuksesta (n=2100). Vastanneista (n=1471, 71%) lapsista 92 (6,3%) kuorsasi aina tai lähes aina, ajoittain kuorsasi 183 lasta (12,4 %) ja 1196 (81,3%) lapsista ei kuorsannut koskaan tai kuorsasi satunnaisesti.

Kutsuimme kaikki 3 - 6-vuotiaat aina tai lähes aina kuorsaavat lapset sekä halukkaat terveet verrokki, jatkotutkimuksiin. Jatkotutkimuksiin osallistui 45 kuorsaava lasta ja 52 ei-kuorsaavaa lasta. Tavoitteenamme oli selvittää kuorsauksen riskitekijöitä, minkä asteisista unenaikaisista hengityshäiriöstä lapsen kärsivät ja millaisia päiväoireita kuorsaus aiheuttaa lapselle. Lisäksi selvitimme terveillä vapaaehtoisilla lapsilla (n=26) jo aiemmin aikuisilla käytössä olevan mittausmenetelmän, akustisen rinometrian käyttökelpoisuutta lasten nenän tilavuuden arvioinnissa.

Kyselytutkimuksen perusteella kuorsaavien ja ei-kuorsaavien lasten välillä ei ollut eroja sukupuolen, iän eikä painon osalta. Sen sijaan vanhempien ja erityisesti äidin tupakointi olivat riskitekijöitä lapsen kuorsaukselle ($P < .01$). Ero kuorsaajien ja ei-kuorsaajien välillä oli merkittävä, vaikka lapsi ei altistunut tupakansavulle sisätiloissa. Kuorsaavilla lapsilla oli ei-kuorsaavia lapsia useammin ylempien hengitysteiden infektioita, välikorvan tulehduksia ja allergista nuhaa ($P < .001$). Nenän tilavuutta ja ilmapirtausta arvioitiin akustisen rinometrian avulla. Menetelmä soveltui hyvin jo alle kouluikäisillä lapsilla. Nenämittauksissa ei todettu eroja kuorsaavien ja ei-kuorsaavien lasten välillä.

Jatkotutkimukseen osallistuneille lapsille tehtiin koko yön kestävä unirekisteröinti (n=87). Kolmella kuorsaavalla lapsella unirekisteröinti oli selkeästi poikkeava (OAH $>5/h$). Lapsen ikä, sukupuoli, paino tai nenämittaukset tulokset eivät korreloineet unirekisteröinnin tuloksiin. Nielurisojen koko sen sijaan korreloi obstruktiivisten hengitystukosten määrään (OAH) ja voimistuneeseen hengitystyöhön ($P < .01$).

Lapsen tunne-elämää, käytöshäiriöitä ja älykkyyttä mitattiin neuropsykologisilla testeillä (CBCL, WPPSI-R ja NEPSY-A). Psykkiset oireet, erityisesti ahdistus ja masennus ($P = .04$) olivat yleisempiä kuorsaavilla lapsilla verrattuna ei-kuorsaaviin lapsiin. Lisäksi kuorsaavilla lapsilla oli huonommat kielelliset valmiudet ($P < .01$). Kokonaisälykkyudessa ei ollut eroja ryhmien välillä. Unirekisteröinnin tulokset eivät korreloineet neuropsykologisten ja käyttäytymistä mittaavien testien kanssa.

Kuorsaus on suhteellisen yleinen oire lapsella. Se aiheuttaa jo alle kouluikäisellä ahdistus- ja masennusoireita sekä vaikeuksia kielellisissä taidoissa. Tarkka mekanismi, miksi kuorsaus aiheuttaa lapselle päiväoireita, on epäselvä. Terveystieteiden tutkimuksissa on tärkeää tunnistaa lasten kuorsaus ja ohjata lapsi jatkotutkimuksiin ja hoitoon. Lapsen altistuminen vanhempien tupakoinnille lisää lapsen riskiä kuorsaukselle, jonka vuoksi kuorsaavien lasten hoidossa tulisi kiinnittää huomiota myös vanhempien mahdolliseen tupakointiin.

ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AHI	Apnea/hypopnea index
ARM	Acoustic rhinometry
BMI	Body mass index
BP	Blood pressure
CBCL	Child Behavior Checklist
CPAP	Continuous positive airway pressure
ECG	Electrocardiogram
EDS	Excessive daytime sleepiness
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
MRI	Magnetic resonance imaging
MSLT	Multiple sleep latency test
NEPSY	NEPSY-A Developmental Neuropsychological Assessment
OAHl	Obstructive apnea/hypopnea index
OSA	Obstructive sleep apnea
PS	Primary snoring
PSG	Polysomnography
PTT	Pulse transit time
QoL	Quality of life
RIP	Respiratory inductance/inductive plethysmography
RME	Rapid maxillary expansion
RMM	Rhinomanometry
SDB	Sleep-disordered breathing
SDSC	Sleep Disturbance Scale
SpO ₂	Arterial oxyhemoglobin saturation
SPT	Skin prick test
TEA	Adenotonsillectomy
TT	Tonsillotomy
URI	Upper respiratory tract infection
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence, Revised

INTRODUCTION

Sleep-disordered breathing (SDB) ranges from primary snoring to significant partial upper airway obstruction and obstructive sleep apnea (OSA) (American Thoracic Society 1999). Snoring is a primary and major clinical symptom of SDB. Adult snoring and sleep apnea have been extensively studied, whereas less is known about these disorders in children with similar night-time symptoms. Snoring and more severe OSA have been shown to have a harmful effect on the neurobehavioral development of children, but the correlations with objective sleep study parameters are poor. Considering the importance of sleep in the growing and developing child, information on sleep and sleep disorders needs to be updated.

Snoring is common in children, with the prevalence reaching 16% in children aged 5-12 years (Ali *et al.* 1993, Liukkonen *et al.* 2008, Bixler *et al.* 2009). Clinical history cannot distinguish primary snoring from OSA in children, and polysomnography (PSG) has been acclaimed as the "gold standard" for diagnosis (Carroll *et al.* 1995). The estimated prevalence of OSA in otherwise normal, healthy children is 0.7-3% in the pediatric population (Ali *et al.* 1993, Gislason and Benediktsdottir 1995, Bixler *et al.* 2009). Upper airway obstruction is supposedly mostly caused by upper airway narrowing due to the lymphoid tissue, i.e. adenoids and tonsils, in otherwise normal children.

One of the unique features in pediatric OSA is the high prevalence of different syndromes affecting facial appearance, facial growth, and muscle tone. These include the Pierre Robin, Crouzon, Apert, Pfeiffer, Robin sequence and Treacher-Collins syndromes. (Arens and Marcus 2004.) In addition, unlike in adults, OSA is not clearly linked to obesity in early childhood, but obesity may contribute to severity of SDB in older children (Kaditis *et al.* 2008). No clear associations of overweight or obesity with increased prevalence of SDB in children have been found (Kohler and van den Heuvel 2008).

Associations between sleep problems, psychiatric symptoms and disorders, and cognitive functions have been increasingly recognized in child populations (Beebe *et al.* 2004, O'Brien *et al.* 2004a). Associations between childhood disordered breathing and behavioral problems, including hyperactivity, inattention, moodiness, aggression, and delinquent behavior, as well as associations between SDB and decreased performance in neurocognitive tasks measuring attention, intellectual development, and memory have been found. (Gottlieb *et al.* 2004, O'Brien *et al.* 2004a, Rosen *et al.* 2004, Halbower *et al.* 2006.)

The purpose of this study was to evaluate the prevalence of snoring in preschool-aged children in Finland, to determine host and environmental risk factors, as well neurobehavioral and neurocognitive symptoms of children suffering from snoring or OSA, and to test the feasibility of acoustic rhinometry in young children.

REVIEW OF THE LITERATURE

Pediatric sleep-related breathing disorders

Terminology and classification

SDB = Sleep-disordered breathing. Snoring is a common symptom in children with SDB, which comprises a wide spectrum of abnormalities ranging from primary snoring to significant partial upper airway obstruction and further to obstructive sleep apnea (American Thoracic Society 1999). The spectrum of SDB is suggested to represent a continuum of symptoms of differing severity, with primary snoring at one end and obstructive sleep apnea at the other. Thus, the symptoms overlap between these entities, and one patient could have all of the symptoms.

PS = primary snoring. Snoring is a primary and major clinical symptom of SDB. PS refers to snoring every night or almost every night without any objective pathologies or major upper airway limitations, i.e. apnea, hypoventilation, hypoxemia, hypercapnia, or sleep disturbance. PS was previously thought not to be associated with daytime symptoms, but this assumption has been repealed in several studies (Blunden *et al.* 2000, Urschitz *et al.* 2003a, O'Brien *et al.* 2004a).

OSA = obstructive sleep apnea. OSA is a recognized condition associated with upper airway obstruction during sleep. Breathing is marked by periods of significant restriction or cessation in airflow, often interrupted by arousals during which normal respiration is restored. In (PSG), OSA is characterized by intrathoracic pressure swings, increased respiratory effort, sleep fragmentation, and intermittent hypoxemia and hypercapnia. (American Thoracic Society 1996, Gozal 2001.)

An obstructive apneic episode is defined as complete cessation of the oronasal airflow lasting more than two respiratory cycles and the presence of continuous breathing efforts. Hypopnea is defined as a reduction of at least 50% in the airflow signal, flattened airflow shape, and central apnea as cessation of the airflow in the absence of breathing efforts. Commonly, episodes of apnea and hypopnea are counted together and divided by total sleep time, giving an index, i.e. events per hour, obstructive apnea index (OAH).

Epidemiology

Occurrence of PS and OSA is difficult to interpret because the criteria and definitions of snoring and OSA vary markedly, and accurate identification of habitually snoring children who have OSA is particularly challenging, considering that clinical history and physical examination are poor predictors of the condition (Carroll *et al.* 1995).

All of the prevalence estimates are based on questionnaire studies, i.e. parent-reported snoring prevalence, and no recording-based data exist. Snoring is common in children, with the prevalence reaching up to 16% (Teculescu *et al.* 1992, Ali *et al.* 1993, Gislason and Benediktsdottir 1995, Hultcrantz *et al.* 1995, Lu *et al.* 2003, O'Brien *et al.* 2003, Kaditis *et al.* 2004, Liu *et al.* 2005, Kuehni *et al.* 2008, Liukkonen *et al.* 2008, Bixler *et al.* 2009). (Table 1). All of the OSA prevalence studies are performed as two phase studies, where a selected population has been chosen for PSG based on history of snoring. The prevalence of OSA in otherwise normal, healthy children is 0.7-3% in the pediatric population (Ali *et al.* 1993, Gislason and Benediktsdottir 1995, Bixler *et al.* 2009).

Table 1. Representative epidemiological studies of the prevalence of snoring in under school-aged children.

Author	No. of children	Age (years)	Habitual snoring	Obstructive sleep apnea
Teculescu (Teculescu <i>et al.</i> 1992)	190	5-6	10 %	ND
Ali (Ali <i>et al.</i> 1993)	782	4-5	12.1%	0.7%
Hultcrantz (Hultcrantz <i>et al.</i> 1995)	500	4	6.2%	ND
Gislason (Gislason and Benediktsdottir 1995)	454	0.5-6	3.2%	2.9%
O'Brien (O'Brien <i>et al.</i> 2003)	5728	5-7	11.7%	ND
Lu (Lu <i>et al.</i> 2003)	974	2-5	10.5%	ND
Kaditis (Kaditis <i>et al.</i> 2004)	581	1-6	5.3%	ND
Liu (Liu <i>et al.</i> 2005)	2636	2-5	5.3%	ND
Kuehni (Kuehni <i>et al.</i> 2008)	6811	1-4	7.9%	ND
Liukkonen (Liukkonen <i>et al.</i> 2008)	1471	1-6	6.3%	ND
Bixler (Bixler <i>et al.</i> 2009)	700	5-12	15.5%	1.2%

ND= no data provided

Pathophysiology and risk factors

The pathophysiology of SDB is a complex interaction between an airway predisposed toward collapse and neuromuscular support (Katz and D'Ambrosio 2008). Factors that decrease pharyngeal size or increase pharyngeal compliance predispose to SDB. (Figure 1).

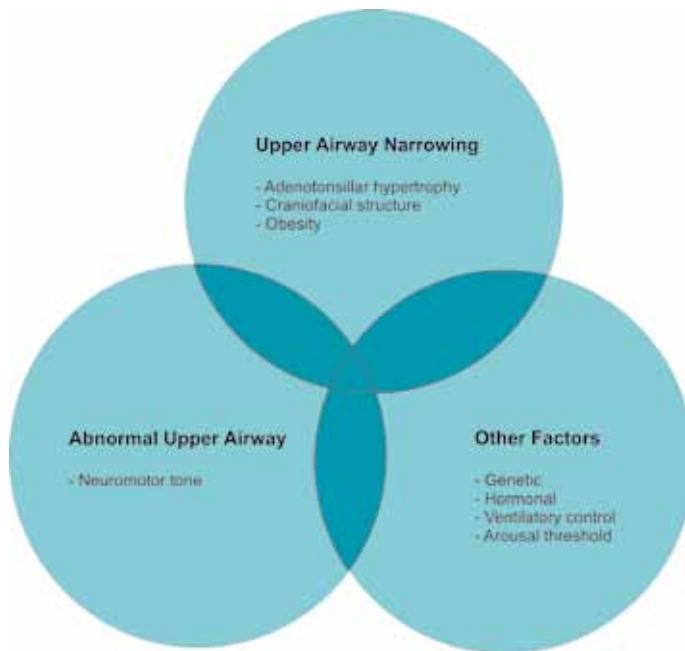


Figure 1. Obstructive sleep apnea including children may result from a combination of factors. Modified by Brooks LJ. Principles and practice of pediatric sleep medicine (Sheldon et al. 2005).

SDB occurs in children of all ages, from neonates to adolescents. Snoring frequency is slightly more common among preschool-aged children than among older children (Kaditis *et al.* 2004). This could result from adenoidal hypertrophy being higher in young children, thus causing obstruction more easily in these individuals than in older children. In prepubertal children, the prevalence of snoring seems to be similar between genders (Teculescu *et al.* 1992, Ali *et al.* 1993), but a slight overrepresentation of snoring or apnea episodes among young boys has also been described. This discrepancy has been proposed to be due to boys having more upper respiratory infections. (Gislason and Benediktsdottir 1995.)

Children with SDB have larger adenoids, tonsils, or soft palates than healthy non-snoring children. Most otherwise healthy children respond well to adenotonsillectomy (TEA) (Brietzke and Gallagher 2006). However, obstruction is not caused by adenotonsillar hypertrophy alone. In several studies, no correlations between adenotonsillar size and SBD were found (Brooks *et al.* 1998, Joshua *et al.* 2006). In addition, 10-20% of children suffering from snoring are not cured by TEA (Wolfensberger *et al.* 2000, Ameli *et al.* 2007).

Although obstruction is supposedly mostly caused by upper airway narrowing due to lymphoid tissue in otherwise normal children, one of the unique features in pediatric SDB is the high prevalence in different syndromes affecting facial appearance, facial growth, and muscle tone. Children with abnormal bony facial structure, hypoplasia, retropositioning of the mandible or maxilla, or cleft deformities frequently have symptoms of SDB. (Zettergren-Wijk *et al.* 2006, Katz and D'Ambrosio 2008, Maclean *et al.* 2009.)

An association between race or ethnicity and prevalence of SDB among children indicates that the prevalence may be two- to fourfold higher in blacks. Symptoms of OSA also appear to be increased in Hispanic children and those of African-American origin. (Redline *et al.* 1999, Goodwin *et al.* 2003, Rosen *et al.* 2003.) Prematurity with very low birth weight (Paavonen *et al.* 2007) and low birth weight siblings are known risk factors for SDB (Friberg *et al.* 2009).

The relationship between upper airway obstruction and obesity in children is ambiguous. Obesity may narrow the pharynx due to the deposition of adipose tissue within muscles and soft tissue around the airway. Obesity seems to be a risk factor for snoring in some older children (Redline *et al.* 1999, Chng *et al.* 2004), and moderate or severe obesity appears to be a predictor of upper airway obstruction (Kohler *et al.* 2008). In the prospective study of Bixler (2009), 700 randomly chosen 5- to 12-year-olds were investigated. Measurements of height, weight, waist circumference, and neck circumference were recorded. All children underwent overnight PSG. The authors found a relationship between waist circumference and BMI across all degrees of severity of SDB, suggesting metabolic factors may be important risk factors for SDB in children. (Bixler *et al.* 2009.) An Australian retrospective study included 190 children aged 4-12 years who had been referred for evaluation of upper airway obstruction. These children underwent overnight PSG. Those with confirmed OSA had a greater BMI than children with either intermittent or habitual snoring. (Kohler *et al.* 2008.) Conflicting findings have been reported among younger children (Kuehni *et al.* 2008). The association between obesity and snoring may change with age, and BMI may play only a minor role in the etiology of snoring in preschool children, in contrast to adolescent (Ievers-Landis and Redline 2007). In a large review, Kohler *et al.* (2008) evaluated the evidence linking increased adiposity to risk or severity of SDB in children and adolescents. Their conclusions were that SDB is not associated in a straightforward manner with overweight or obesity, unlike in adults (Kohler and van den Heuvel 2008).

Snoring is associated with symptoms caused by viral infections, the common cold, and otitis media infections (Kuehni *et al.* 2008). Asthma or atopy has also

been shown to be associated with snoring (Lu *et al.* 2003, Chng *et al.* 2004). The mechanism of how recurrent upper respiratory infections (URI) increase the risk of upper airway obstruction has been a target of research in recent years. Children with respiratory syncytial virus (RSV) bronchiolitis as infants had a higher OAH than their age- and sex-matched controls. These children also had larger tonsillar size, indicating that adenotonsillar hypertrophy plays a significant role in the occurrence of pediatric OSA. (Snow *et al.* 2009.)

The specific factors mediating the proliferation of adenotonsillar tissue remain unclear, but increasing evidence of the presence of inflammation in the upper airways of children with OSA has recently been published, revealing increased levels of leukotrienes in exhaled breath (Goldbart *et al.* 2006), adenotonsillar tissues (Goldbart *et al.* 2005a), and tonsillar proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and interleukin-1 alpha (IL-1 α) (Kim *et al.* 2009), as well as increased levels of C-reactive protein (Tauman *et al.* 2004, Gozal *et al.* 2007) among children with SDB. These findings support the contention of recruitment of inflammatory pathways within upper airway tissues in the context of OSA.

The upper airway of a child is smaller than that of an adult. In children, the maximal airway narrowing corresponds to areas where the tonsils and adenoids overlap (Arens *et al.* 2003). Acoustic studies show that women have a relatively stiff pharynx compared with men (Brooks and Strohl 1992). Children have different pharyngeal pressure characteristics, suggesting a more rigid upper airway than in adults (Marcus *et al.* 1999). Thus, in some cases, the anatomical size of the pharynx may not be the only cause of OSA, leaving a role for other determinants of airway patency such as neuromuscular tone, ventilatory control, and arousal threshold (Katz and D'Ambrosio 2008).

During wakefulness neural input maintains the pharyngeal muscle tone and airway patency. During sleep, an increased resistance to airflow normally accompanies relaxation of these pharyngeal muscles. The mechanism for increases in pharyngeal collapsibility is that such increases are related to disturbances in pharyngeal neuromuscular control. This increase in pharyngeal collapsibility is recognized to lead to airflow obstruction during sleep. Similar to adult OSA, the collapsibility of upper airway in children with OSA is greater than in healthy children (Marcus *et al.* 2005), as evidenced by reduced upper airway dimensions detectable by acoustic reflectometry and magnetic resonance imaging (MRI) (Monahan *et al.* 2002, Arens *et al.* 2003).

Parental smoking and exposure to cigarette smoke are related to SDB in childhood. Corbo *et al.* showed a dose-response effect between snoring in children and the number of cigarettes smoked by their parents (Corbo *et al.* 1989). Ali *et al.* (Ali *et al.* 1993) demonstrated a dose-response relationship between passive smoking and habitual snoring, especially for maternal smoking. Similar findings have been reported in other studies (Marshall *et al.* 2007, Kuehni *et al.* 2008). Children with exposure to tobacco smoke suffered from more rhinitis and poorer sleep than children without exposure (Johansson *et al.* 2008). Chronic exposure to tobacco smoke may augment upper airway inflammation in children due to reduced cilia regeneration (Atef *et al.* 2009), increasing airway resistance (Kooi *et al.* 2004) and decreasing nasal volume (Zavras *et al.* 1997). Road traffic, having a single parent, and socioeconomic deprivation have also been demonstrated to be risk factors for SDB in children (Spilsbury *et al.* 2006, Kuehni *et al.* 2008).

Cotinine is the major metabolite of nicotine found in biological fluids. It is considered to be the best marker of environmental tobacco smoke exposure because its biologic half-life in body fluids is much longer than that of nicotine (approximately 20 h vs. 2 h) (Benowitz *et al.* 1982, Benowitz *et al.* 1983, Florescu *et al.* 2009). Numerous studies have measured cotinine in blood, urine, saliva, and hair to estimate exposure to passive smoke. In children, collection of hair is an easy and preferred technique of data collection compared with such invasive methods as collection of blood, urine, and saliva (Florescu *et al.* 2009). The levels of cotinine in the body are dependent on nicotine metabolism, which in turn is affected by factors such as age and race, making comparison between children's exposure to tobacco smoke difficult (Wilson *et al.* 2007). Due to subjects' different metabolism, objective measurement of cotinine concentrations from room air may be advisable (Wilson *et al.* 2007, Yolton *et al.* 2010).

Snoring and obstructive sleep apnea

Diagnosis

History and physical examination

A sleep history of nocturnal snoring every night or almost every night is a hallmark of primary snoring. However, a history of snoring cannot distinguish between children with OSA and those with primary snoring (Carroll *et al.* 1995). Bedtime struggles, sleep-onset delays, increased need for comforting activities, requiring a night-light to fall asleep, being afraid of sleeping alone, teeth grinding, frequently changing sleep positions, hyperextension of the neck, episodes of observed apnea, night awakenings, sleep-talking, and nightmares are more frequently noted in children with SDB (Stradling *et al.* 1990, Nieminen *et al.* 1997, Ferreira *et al.* 2000, Eitner *et al.* 2007). Snoring and OSA have also been associated with enuresis and bed-wetting in children. This may be related to the increased release of natriuretic peptides. (Sans Capdevila *et al.* 2008.)

The physical findings on examination of a child with SDB are variable. These children appear to have mildly to moderately enlarged tonsils or adenoids and do not necessarily demonstrate breathing difficulties. Therefore, a normal physical examination does not exclude SDB. Mouth breathing and adenoidal face are noteworthy as they may indicate impaired nasal breathing. Hyponasal voice is also a clue of nasal obstruction and suggestive of adenotonsillar enlargement. The Mallampati classification or the Brodsky scale are useful in evaluating pharyngeal or tonsillar size (Mallampati *et al.* 1985, Brodsky 1989). In addition, the presence of allergic rhinitis, chronic rhinosinusitis, turbinate hypertrophy, rhinorrhea, nasal polyps, nasal septum deviation, or any other factor likely to increase nasal airflow resistance are more predominant in children with SDB sleep symptoms (Ng *et al.* 2006, Bixler *et al.* 2009).

Questionnaires

In epidemiologic studies, a number of questionnaires are used. These questionnaires are usually self-made, including questions about a child's behavioral patterns while asleep or while wake. Furthermore, information about the medical history of a child is sought. Several studies have tried to develop questionnaires that can detect children with clinically significant SDB (Chervin *et al.* 2000, Chervin *et al.* 2007).

Brouillette and coworkers used a specific OSA score to investigate a total of 92 children, including those with OSA or suspected OSA and healthy children (Bro-

uilette *et al.* 1984). They argued that the use of the OSA score should decrease the need for PSG monitoring. A standardized questionnaire covers family history for atopy, child medical history, snoring and episodes of apnea (frequency and duration), presence of symptoms that could be related to breathing disorders (troubled sleep, enuresis, thirst, sweating, oral breathing, need for afternoon rest, daily sleepiness, poor school achievements), and smoking habits in the family and during pregnancy.

In 1996 Bruni *et al.* published the Sleep Disturbance Scale for Children (SDSC), which is an instrument for assessing the frequency of sleep problems and snoring in school-aged children on a 5-point scale. (Bruni *et al.* 1996). The SDSC appears to be a useful tool in evaluating the sleep disturbances of school-aged, children in clinical and nonclinical populations. It can be used in population-based studies to screen for upper airway obstruction in children. This questionnaire has been used extensively around the world and is translated into numerous different languages (Eitner *et al.* 2007, Ferreira *et al.* 2009, Paavonen *et al.* 2009). The SDSC consists of 26 items grouped into six subscales: 1) disorders of initiating and maintaining sleep (*sleep latency, going to bed reluctantly, difficulty in falling asleep, anxiety in falling asleep, night awakenings, difficulty in falling asleep after awakenings*), 2) sleep breathing disorders (*breathing problems, sleep apnea*), 3) disorders of arousal/nightmares (*sleep-walking, sleep terrors, nightmares*), 4) sleep-wake transition disorders (*hypnic jerks, rhythmic movement disorders, hypnagogic hallucinations, nocturnal hyperkinesia, sleep-talking, bruxism*), 5) disorders of excessive somnolence (*difficulty in waking up, tiredness upon waking up, daytime somnolence, sleep paralysis, bed-wetting*), and 6) sleep hyperhydrosis (*night sweating, falling asleep sweating*).

A systematic review conducted by Briezke in 2004 concluded that clinical findings are generally not reliable for diagnosing OSA in children (Brietzke *et al.* 2004).

Imaging and laboratory evaluation

To evaluate the upper airway in children with SDB, several radiologic techniques are available, including lateral neck radiographs (Fujioka *et al.* 1979), cephalometrics (Kawashima *et al.* 2000), and MRI (Arens *et al.* 2001, Arens *et al.* 2003).

Lateral neck radiography was first published by Fujioka in 1979 (Fujioka *et al.* 1979). The ratio of the absolute size of the adenoid and the size and shape of the nasopharynx was termed the adenoidal nasopharyngeal ratio (AN ratio). In this method, the adenoidal measurement (A) represents the distance from the point of maximal convexity of the adenoid shadow to a line along the anterior margin of the basiocciput. The nasopharyngeal measurement (N) is the distance between the

posterior border of the hard plate and the antero-inferior edge of the sphenobasioccipital synchondrosis. The AN ratio is obtained by dividing the measurement for A by the value for N. The study group disclosed that an AN ratio greater than 0.80 may be considered indicative of enlarged adenoids (Fujioka *et al.* 1979). This method is widely used clinically to evaluate nasopharyngeal size. Brooks and coworkers studied 33 children with suspected OSA. Lateral neck radiography as well as overnight polysomnography were performed. No healthy controls were included. They found a relationship between the AN ratio and the duration of obstructive episodes of apnea, although adenoid size did not correlate with the number of respiratory events. (Brooks *et al.* 1998.) The upper airway of children with SDB sleep appears to be smaller on average than that of healthy children (Orji and Ezeanolue 2008).

Cephalometry is a two-dimensional radiograph that examines soft tissue and craniofacial structures bounding the upper airways. Upper airway craniofacial structures can be accurately measured with a cephalometric radiograph. The angles between these craniofacial structures can also be identified with cephalometry. However, standardized imaging and analysis parameters must be utilized in making a cephalometric radiograph. The head needs to be placed in a rigid structure for stabilization with a cephalostat. (Kawashima *et al.* 2000.)

Several studies have been published to investigate soft tissue and craniofacial structures of the upper airways in children. In these studies, SDB children were compared with healthy children: they have a narrower upper airway, an inferiorly positioned hyoid bone, a longer vertical airway length from the posterior nasal spine to the base of the epiglottis, a more protruding maxilla, and anterior-posterior discrepancy of the maxilla and mandible (Zucconi *et al.* 1999, Finkelstein *et al.* 2000, Kulnis *et al.* 2000, Zettergren-Wijk *et al.* 2006, Banabilh *et al.* 2008).

Rhinometric measurements

In 1989, a new method, acoustic rhinometry (ARM), was introduced for assessment of nasal geometry. ARM measures cross-sectional areas and volume of the nasal cavity. It helps to define objectively the dimensions and pathology of the nasal passage (Hilberg *et al.* 1989, Hilberg and Pedersen 2000). The method involves measurements of acoustic reflections from the nasal cavity. A sound pulse produced by a spark in a sound tube enters the nasal cavity via a nosepiece. The method is noninvasive, requires little cooperation of the subject, and has been recommended for use even in small children (Hilberg *et al.* 1989, Djupesland and Pedersen 2000, Hilberg and Pedersen 2000, Liukkonen *et al.* 2006, Haavisto and Sipila 2008).

The experience of ARM among small children is scant, although the method has been used to demonstrate changes in the volume the nasopharynx and nasal cavities of children (Riechelmann *et al.* 1993, Zavras *et al.* 1994, Riechelmann *et al.* 1999, Marques and Anselmo-Lima 2004). ARM has been used to evaluate nasal airway resistance during rapid maxillary expansion (RME) (Enoki *et al.* 2006), allergic rhinitis and asthma in children (Kobayashi *et al.* 2001, Steinsvag *et al.* 2007). The method is also suitable for the evaluation of septal deviations and surgical success in school-aged children (Can *et al.* 2005) and for the diagnosis of congenital choanal malformations in neonates (Djupestrand *et al.* 1997). In these studies, ARM has been valuable for interindividual comparisons, but not for assessment of different groups or adenoidal size in preschool-aged children (Marques and Anselmo-Lima 2004).

Rhinomanometry (RMM) is a physiologic noninvasive method for the evaluation of nasal airway patency. In active anterior RMM, nasal airway resistance is measured in one nasal passage at a time during normal breathing, while the contralateral nostril is taped. Total nasal resistance is then calculated from the unilateral measurements. Successful recordings require some cooperation with breathing rhythm and acceptance of increased work in breathing, especially if the nose is blocked. RMM among children was first described by Sorensen *et al.* in 1980 (Sorensen *et al.* 1980). They suggested that RMM could be performed on all snoring children aged over five years referred to the hospital for adenoidectomy. Both radiography and rhinomanometry give valuable parameters for the indication of adenoidectomy (Sorensen *et al.* 1980).

Nasal resistance has been found to decline with increasing age and is elevated in the presence of mucosal swelling and adenoidal enlargement (Parker *et al.* 1989, Zapletal and Chalupova 2002). In addition, RMM has been deemed suitable for evaluating allergic inflammation (Ciprandi *et al.* 2005) and the effect of RME treatment in children (Monini *et al.* 2009). Rizzi *et al.* (2002) studied a total of 73 children (mean age 5.4 years) with RMM. OSA was confirmed for 60% of these children with polysomnography (apnea/hypopnea index, AHI ≥ 1). In this Italian study, total nasal resistance correlated with AHI ($P = .0001$), and snoring ($P = .005$). Thus, RMM was concluded to be a useful tool in evaluating SDB in children. (Rizzi *et al.* 2002.) A similar finding has been published in another Italian study among OSA children treated with inferior turbinotomy and adenotonsillectomy (Mora *et al.* 2003), showing decreasing total resistance in RMM after surgical treatment.

Overnight polysomnography

Carroll *et al.* (Carroll *et al.* 1995) stated that clinical history cannot distinguish primary snoring from OSA in children, and overnight PSG has since been acclaimed as the "gold standard" for OSA diagnosis. The combination of PSG signals

varies, but most often PSG includes recordings of sleep using continuous recordings of the electroencephalogram (EEG), submental electromyogram (EMG), and electrooculogram (EOG). Respiration is monitored for effort (thoracoabdominal belts, diaphragmatic EMG), airflow (thermistors or pressure transducers), and gas exchange (arterial oxyhemoglobin saturation (SpO₂), end-tidal or transcutaneous carbon dioxide). Often PSG also includes measurements of electrocardiogram (ECG), body position, limb movements and video recordings, but may also include more uncommonly used extra sensors such as esophageal pressure measurement or body movement sensor (static-charge-sensitive bed, SCSB).

Respiratory parameters are used to diagnose sleep apnea. An obstructive apnea episode is defined as complete cessation of the oronasal airflow lasting for more than two respiratory cycles and the presence of continuous breathing efforts. Hypopnea is defined as a reduction of at least 50% of the airflow signal and a flattened airflow shape, accompanied by a 3% (or 4%) decrease in SpO₂ or termination by an arousal. Central apnea is defined as cessation of airflow in the absence of breathing efforts and is separate from obstructive events. Obstructive apnea/hypopnea indices (OAHI/AHI) are calculated as the number of obstructive apnea/hypopnea events per hour of sleep time.

Childhood SDB has traditionally been defined according to adult criteria, summing up the total number of upper airway obstructions per hour as the apnea index, or including partial obstructions as the apnea-hypopnea index (AHI). It is noteworthy that different studies use different values of OAHI/AHI, and the criteria for child OSA varies between clinical practice and research studies. Recently, the new American Academy of Sleep Medicine (AASM) rules and the old Rechtschaffen and Kales (R&K) criteria for sleep scoring have been shown to produce different results also in children (Novelli *et al.* 2010). Today, an abnormal value for OAHI in children is considered above 1/h (Iber *et al.* 2007), although it seems clear that one event/hour likely cannot have any significant effect by itself.

Measuring the airflow

The measurement of airflow is part of the diagnostic criteria for episodes of apnea and hypopnea as well as for respiratory-related arousals. Many new devices designed for airflow measurement have become available for use during PSG. Airflow can be evaluated either by measuring it with nasal cannula with pressure transducer, or facial mask connected to a pneumotachograph or by detecting temperature differences between expired air and ambient air.

A pneumotachometer provides a quantitative measurement, and although rarely used, is the “gold standard” for the measurement of flow rate during breathing. The

breath is passed through a short tube and cylinder in which there is a fine mesh that serves as a small resistance laminar airflow. The resulting pressure drop across the mesh is in proportion to the flow rate. The pressure drop is very small (e.g. 2 mmHg) and a differential pressure transducer is normally used. In research setups, the pneumotachograph is usually connected to a facemask.

A temperature difference exists between air coming from the respiratory system and air going into the respiratory system. In the past, thermistors have been commonly used. They detect fluctuations in temperature with respiration and provide a qualitative signal. By definition, thermistors and thermocouples are not airflow sensors, but simply detect the temperature oscillation as a qualitative indicator of airflow. A thermistor does not properly detect the flow rate, and therefore, it poorly displays decreases in airflow. However, total cessation of airflow is detected because of the lack of temperature variation. Despite the limitations of the thermistors and thermocouples, scoring of hypopnea has evolved to events of reduced airflow being first identified from the thermistor signal, then validated as true episodes of hypopnea by desaturation or arousal on EEG. However, if the thermal sensor does not detect a candidate respiratory event and there is no desaturation, arousals remain “unexplained”. Although thermistors are accepted as precise in identifying apnea, detection of hypopnea is controversial. Up to 70% of respiratory events may be missed in adult patients with symptoms consistent with OSA, but without frank apnea and hypopnea. (Kryger *et al.* 2005.)

During inspiration airway pressure is negative relative to the atmosphere and positive during expiration. The measurement of these changes in the nasal airway may be used to estimate air flow. Nasal cannula pressure systems generate this respiratory waveform signal by detecting these fluctuations in pressure caused by inspiration and expiration. Unlike the inspiratory and expiratory fluctuations recorded as temperature changes with a thermistor, these signals are more proportional to flow. Recommended devices for monitoring airflow are nasal pressure transducers, which have improved the diagnostic sensitivity of the PSG. To record respiratory events, new standards for measuring airflow have been initiated to include the combination of thermistor with recordings from nasal pressure transducers, to better detect and count partial airway obstruction events (Griffiths *et al.* 2005). Artifacts are caused by dislodged cannula, mouth breathing, nasal obstruction, and obstruction of the cannula from secretions, all of which are particularly common in children.

Measuring respiratory effort

Measures of respiratory effort are important to differentiate between central and obstructive events, to categorize episodes of hypopnea or respiratory effort-relat-

ed arousal. There are three primary methods of noninvasive chest and abdominal plethysmography (measurement of change in volume) in current use: measurement of changes in elastic belt tension, changes in electrical impedance, or changes in electrical inductance.

An elastic belt fastened around the chest or abdomen will exhibit a change in tension as the chest or abdomen expands or contracts. This change in tension can be easily measured and converted to a voltage by a variety of methods. The most common method in current use is Piezo crystal belts that directly generate a voltage when compressed or stretched. This method, while simple and inexpensive, is subject to trapping artifact: it is fairly easy to imagine how a portion of elastic belt may become “trapped” as a person turns from one side to another, resulting in variable tension along the belt circumference. Thus, this method can both under-, and/or overestimate the actual degree of chest or abdominal movement in addition to creating a false signal when belt tension suddenly changes with altered body position. Elastic bands with Piezo crystal show only the motion itself and is not calibrated to the direction of motion, i.e. the signal direction during inward and outward thorax movement may vary even during the same recording, and it is not proportional to the size of the movement. In 1999, the AASM consensus discouraged the use of Piezo crystal belts for scoring respiratory events (American Thoracic Society 1999).

Esophageal manometry is a technique used to detect abnormal sleep-related respiratory events (Guilleminault *et al.* 2004). However, it is limited in a clinical setting due to its invasiveness and it is not widely used among children. The human body is a fairly poor conductor of electricity. In other words, it presents a fairly high impedance to the electrical current flowing through it. This impedance changes as the cross-section of the body expands and contracts, allowing qualitative measurement of thoracic and abdominal movement during breathing. Respiratory inductance/inductive plethysmography (RIP) is a promising diagnostic tool measuring respiration from body surface movements. It is usually taken as respiratory effort for clinical diagnostic purposes. Two (or sometimes four or more) electrodes are attached to the skin and a weak alternating electrical current is passed through these electrodes, allowing the impedance to be measured.

Calibrated RIP seems to provide semiquantitative information on ventilation, which is generally comparable with that achieved with nasal pressure monitoring (Redline *et al.* 2007). However, the number of studies that have addressed the validity of RIP is small, and in the future prospective studies should be encouraged to evaluate the utility of RIP as a measure of respiratory effort.

Measuring gas exchange

Although the most accurate method of diagnosing OSA is nocturnal PSG, such testing is expensive, time-consuming, and thus other methods of investigation are being sought. Previously, SpO₂ were widely used in sleep apnea trials in children. Brouillette *et al.* (2000) studied almost 350 children (median age 4.5 years), 60% of these children had OSA, as defined by PSG. Conclusions were that oximetry was thought to have a 97% positive predictive value for OSA if periodic clusters of desaturations of less than 90% were found. (Brouillette *et al.* 2000.) Oximetry can quickly and inexpensively identify children with a history suggestive of SDB. However, a negative oximetry result cannot be used to rule out OSA (Brouillette *et al.* 2000, Kirk *et al.* 2003).

In standard PSG, desaturation is usually assessed by finger or ear pulse oximetry because directly measurement from an indwelling arterial catheter is highly invasive. Pulse oximetry gives an estimate of SpO₂, which is a major ventilatory feature defining OSA. Its severity is usually reported as mean SpO₂, or lowest SpO₂, and the amount of 4% or more SpO₂ drops per hour during sleep. A pitfall with oximeters is the use of averaging time, which is, however, usually adjustable. A long time window for averaging may cause episodes of hypoxemia to be missed.

A mild desaturation (90–93%) is relatively common in children during sleep (Urschitz *et al.* 2003b). Verhulst *et al.* (2007) reported a mean overnight SpO₂ value of 97% (SD 0.6, range 96–98) and a mean minimum SpO₂ value of 92% (SD 2.7, range 82–96) in 60 European children aged 6–16 years with no polysomnographic evidence of SDB (Verhulst *et al.* 2007). Traeger *et al.* (2005) reported similar values in 66 North American children aged 2–9 years: mean SpO₂ 97% (SD 1.0, range 95–98) and minimum SpO₂ 92% (SD 3.0, range 81–95) (Traeger *et al.* 2005). These results support the view that the basal SpO₂ values range from 95% to 100%.

In a prospective British study, 61 children with a history of snoring were investigated. The children were evaluated with PSG. Using these SpO₂ criteria, 12 children screened positive with oximetry. However, these SpO₂ parameters failed to identify seven children with a clinical diagnosis of OSA confirmed by PSG (using an AHI of ≥ 5). (Sproson *et al.* 2009.) Thus, an oximetry measurement does not appear to be a reliable measure for diagnosis of children's sleep apnea.

Measuring sleep stages and arousals

The AASM completed a new manual for the scoring of sleep and associated events in 2007 (Iber *et al.* 2007). The rules and specifications in the visual scoring, however, retain much of the framework of the rules of Rechtschaffen and Kales (Rechtschaffen and Kales 1968), but in the new AASM system, the distinction between

wakefulness (W), rapid eye movement (REM) sleep (R) and non-REM sleep (N) is maintained, although the non-REM stages are reduced to three: N1 (previous stage 1), N2 (previous stage 2), N3 (previous stages 3 + 4).

The pediatric task force (Grigg-Damberger *et al.* 2007) also made several modifications to the scoring criteria for infant sleep. One of the main changes is in terminology: in the AASM manual, sleep stages S1, S2, S3, and S4 are referred to as N1, N2, and N3, with N3 reflecting slow-wave sleep (R&K stages S3 + S4) and Stage REM is referred to as stage R.

The measurement of arousals during sleep is useful for quantifying sleep fragmentation. Arousals are markers of detrimental and harmful sleep disruption. An EEG arousal is defined as an abrupt shift in EEG frequency, lasting at least 3 s, which may include theta, alpha, or other frequencies greater than 16 Hz, but not spindles. Since alpha activity is common in REM in children, these shifts must be accompanied by an increase in submental muscle activity in order to indicate arousal (American Sleep Disorders Association 1992). In normal healthy children with aged 3-9 years, arousals do not differ according to age, and overall arousals occurs every 6 minutes throughout the night (Montgomery-Downs *et al.* 2006).

Respiratory events during sleep can potentially lead to an increase in the number and duration of arousals that may cause sleep fragmentation and disruption of normal sleep architecture. However, while obstructive sleep apnea episodes regularly end with an arousal that disturbs the sleep structure in adults (Berry and Gleeson 1997), in children this is not as evident and many obstructive respiratory events are resolved without obvious EEG arousal (McNamara *et al.* 1996). Although children may not manifest cortical arousals, evidence suggests that they do have a subcortical central nervous system or autonomic response to most obstructive episodes of apnea. Many obstructive episodes of apnea in children terminate with movement, as represented by enhanced number of movements and periodic leg movements (Praud *et al.* 1989, Mograss *et al.* 1994) in the absence of EEG arousals. The lack of cortical arousal in children with OSA may explain why children can go on to have extended uninterrupted periods of obstructive hypoventilation, and sleep architecture is preserved in these children (American Thoracic Society 1996, Goh *et al.* 2000). Although SDB-related EEG arousals are less common in children than adults, subcortical arousals, as demonstrated by movement or autonomic changes, seem to occur frequently. Katz *et al.* (2003) studied pulse transit time (PTT), an indicator of autonomic function, in children (Katz *et al.* 2003). The PTT is a measure of respiratory effort and arousal that has shown promise in the diagnosis of SDB in adults (Pitson and Stradling 1998). The PTT is the interval between the R-wave of the ECG and the arrival of the photoplethysmographic pulse at the finger (Geddes

et al. 1981). The travel time of the pulse wave is inversely proportional to arterial wall stiffness, which is determined by blood pressure (BP). Therefore, the PTT is a noninvasive index that is inversely related to BP. Katz *et al.* (2003) demonstrated that EEG arousals occurred with 55% of obstructive episodes of apnea, similar to the results shown by McNamara (McNamara *et al.* 1996), but that pulse transit time arousals were present in 91% of obstructions. Thus, subcortical activation of the brain in children appears to take place in response to upper airway obstruction (Katz *et al.* 2003).

Heart rate variability is commonly used to investigate autonomic control. Changes in autonomic function, such as changes in heart rate, PTT or BP, have been noted. These seem to be more frequent than EEG arousals and may be more sensitive measures for detecting subcortical arousals, predicting neurocognitive and/or cardiovascular outcomes in children with OSA (Katz *et al.* 2003, Chaicharn *et al.* 2009). Chaicharn *et al.* (2009) found that parasympathetic activity remains relatively normal, but baseline cardiovascular sympathetic activity and reactivity to autonomic challenges are impaired in pediatric OSA (Chaicharn *et al.* 2009). In addition, high urine levels of norepinephrine due to increased sympathetic tone have been published (Kaditis *et al.* 2009).

Consequences

Morbidity of snoring and obstructive sleep apnea

Although many sleep and neuropsychological studies among children have already been conducted, the mechanism by which OSA causes neuropsychological and cardiovascular morbidity remains unclear. The cognitive deficits seen in children with OSA may be secondary to prefrontal cortex dysfunction caused by intermittent hypoxia and disruption of sleep architecture. While intermittent hypoxemia appears to be the major contributor to consequences of SDB, with lesser roles played by sleep fragmentation, increased breathing effort, and hypercapnia (Gottlieb *et al.* 2000, Beebe and Gozal 2002, Gozal and Kheirandish 2006). These physiological disturbances are thought to cause neuronal injury to the hippocampus and frontal cortex, leading to impaired cognitive execution (O'Brien and Gozal 2002, Halbower *et al.* 2006). It is unclear which of the multiple physiologic perturbations account for neuropsychological dysfunction, and in fact, it is difficult to separate them since one or all of these perturbations are demonstrated in patients with SDB. Evidence suggests, that even habitual snoring alone, in the absence of any other gas exchange or sleep architecture abnormality, may be associated with an increased risk for neurobehavioral disturbances (O'Brien *et al.* 2004a).

Intermittent hypoxemia and alveolar hypoventilation

In rats, intermittent hypoxia during sleep is associated with increases in neuronal cell loss and adverse effects on spatial memory tasks in the absence of sleep fragmentation or deprivation (Gozal *et al.* 2001, Row *et al.* 2002).

In previous studies, frequent oxyhemoglobin desaturations during sleep have been common in children with OSA (Stradling *et al.* 1990, Gislason and Benediktsdottir 1995). Even a mild desaturation (90–93%) is relatively common (Urschitz *et al.* 2003b). However, in recent years, intermittent hypoxemia with or without OSA, even brief episodes of mild decreases in saturation from baseline, has been speculated to cause of neuropsychological dysfunction in children (O'Brien *et al.* 2004a). In children aged up to 14 years with SDB, intermittent or chronic hypoxemia was conducted to produce adverse cognitive effects (Bass *et al.* 2004). Urschitz *et al.* studied behavioral problems in 1144 snoring children and clarified the role of intermittent hypoxia with pulse oximetry. Habitual snoring was associated with hyperactive and inattentive behavior, daytime tiredness, and sleepiness, but was not dependent on intermittent hypoxia (Urschitz *et al.* 2003a, Urschitz *et al.* 2004a). Nighttime SpO₂ decreases were considered not to explain the daytime symptoms in snoring children.

Intermittent elevations in partial pressure of carbon dioxide manifesting as alveolar hypoventilation, is frequent in pediatric OSA during sleep. It can exacerbate the effects of intermittent hypoxia on neural tissue, but can also affect cerebral circulation, vasomotor or sympathetic activities (Sheldon *et al.* 2005).

In children, episodic hypoxia and sleep fragmentation may lead to alterations in the neurochemical substrate of the prefrontal cortex, with resultant executive dysfunction (Beebe and Gozal 2002, Bass *et al.* 2004). Intermittent hypoxia during the night may produce increased sympathetic neural activity in children with OSA and contribute to the overall elevation of BP (Marcus *et al.* 1998, Baharav *et al.* 1999, Amin *et al.* 2004). Increased sympathetic activity can cause neurocognitive deficits in children as a result of a variety of responses, including increased oxidative stress, systemic inflammatory responses, and endothelial dysfunction (Bhattacharjee *et al.* 2009, Gozal 2009).

Sleep fragmentation

Sleep disruption and fragmentation without hypoxemia is another major mechanism that may cause impairment in neurobehavioral functioning. The physiologic and behavioral effects of sleep loss have been investigated in adults, but the effects of OSA on sleep in children remain poorly understood. In adults, OSA is known to

cause sleep fragmentation due to multiple arousals. Children with OSA do not experience sleep-fragmented arousals like adults (Goh *et al.* 2000). The arousal index increases linearly from childhood to old age, but remains unchanged during adolescence (Boselli *et al.* 1998, Tapia *et al.* 2008).

O'Brien *et al.* (2004) published an article in which 70 children with a mean age of 6.7 years were studied. They showed that the total arousal index correlated negatively with neurocognitive abilities, suggesting a role for sleep fragmentation in cognitive dysfunction in OSA children compared with healthy children (O'Brien *et al.* 2004b). Neurobehavioral deficits in SDB children may be related to increased susceptibility to sleep fragmentation (O'Brien *et al.* 2004a) or a combination of hypoxemia and sleep fragmentation (Kennedy *et al.* 2004). Both sleep fragmentation and intermittent hypoxia are believed to lead to a variety of responses, including increased oxidative stress and systemic inflammatory responses, and are important in the context of OSA to elicit neurobehavioral morbidity (Kheirandish and Gozal 2006).

Many factors appear to affect child's daytime behavior and neurocognition, but independently of the currently available polysomnography markers for pediatric OSA. Therefore, it is necessary to provide better markers, such as those of heart rate variability or inflammation.

In 2007, Gozal and colleagues investigated children with OSA and compared them with snoring children aged 5-7 years. Polysomnography and neurocognitive studies were performed, and high-sensitivity C-reactive protein was measured. Higher C-reactive protein correlated with poor cognitive performance. Also high-sensitivity C-reactive protein levels were higher in the OSA group than in the snoring group. The body of research inferred that the inflammatory responses induced by OSA are a major determinant of increased risk for neurocognitive dysfunction. (Gozal *et al.* 2007.)

During apnea there may be slowing of heart rate, and during arousal an acceleration of heart rate. Such arousals are characterized by a stimulation of the sympathetic nervous system. In adults, the autonomic nervous system plays a key role in mediating cardiovascular changes during sleep apnea. Hemodynamic changes, including hypertension and cardiovascular morbidity, are the most important complications (Smith *et al.* 1998, Phillips and Somers 2003, Bassetti *et al.* 2006). In children with OSA, increased heart rate is also present (Aljadeff *et al.* 1997, Baharav *et al.* 1999), and after TEA both pulse rate and pulse rate variability decrease (Constantin *et al.* 2008). Possibly abnormal sympatheticotony during sleep in OSA children could lead to abnormal daily symptoms, including impaired behavior or neurocognition, but thus far there is no research to support this.

Quality of life

Several outcome measures have recently been published to assess quality of life (QoL) in pediatric sleep disturbance populations. Information is most commonly collected in the form of a questionnaire completed by the parent of the child. SDB appears to have an impact on health-related quality of life, as measured by both global and health-related quality of life instruments. The Child Health Questionnaire is a validated and considered instrument for measuring global QoL in children. Children with SDB have scores that are worse than normal healthy children (Stewart *et al.* 2000, Georgalas *et al.* 2004). The Child Health Questionnaire has 12 subsets that evaluate family cohesion, family activities, parental impact, general health, mental health, self-esteem, behavior, bodily pain, and social limitations caused by physical and emotional problems.

The most common QoL instruments are specific disease-specific QoL questionnaires. The disease-specific questionnaire is practical, validated, and reliable. Disease-specific QoL surveys allow for evaluation of changes in a child's sleep disturbance and daytime symptoms after TEA. However, these forms do not seem appropriate to distinguish sleep apnea in pediatric populations (Constantin *et al.* 2010). Several disease-specific QoL instruments, including the Obstructive Sleep Disorders-6 (de Serres *et al.* 2000), Child Health Questionnaire Version PF28 (Stewart *et al.* 2000), and the OSA-18 (Franco *et al.* 2000), have been developed for children with OSA.

Improvements in QoL scores after TEA for SDB have been shown in a number of studies. These improvements were comprehensive and included all domains of QoL. (Goldstein *et al.* 2002, Sohn and Rosenfeld 2003, Mitchell *et al.* 2004a, Mitchell *et al.* 2004b, Mitchell and Kelly 2005, Tran *et al.* 2005.)

Excessive daytime sleepiness

Excessive daytime sleepiness (EDS) is the major and most frequent presenting complaint in adults with OSA. The exact prevalence of EDS in the pediatric population with OSA is unclear. Several studies have thus far examined this particular issue. Carroll *et al.* suggested that only a small minority of these children (7%) presented with symptoms consistent with EDS (Carroll *et al.* 1995). However, in recent years, questionnaires that include more specific questions on behaviors associated with EDS indicate that the frequency of EDS among OSA children may be much higher, up to 43% (Melendres *et al.* 2004, Chervin *et al.* 2006). Also, daytime napping is more prevalent in snoring children than in non-snorers (Wasilewska *et al.* 2009).

Night-time symptoms

SDB is associated with several sleep problems, including sleep-onset delay, increased need for comforting activities to fall asleep, bedtime problems, night-awakenings, sleep-talking, teeth-grinding, nightmares, sleep-wake transition, and sleep hyperhidrosis (Ferreira *et al.* 2000, Eitner *et al.* 2007, Sans Capdevila *et al.* 2008).

The Sleep Disturbance Scale for Children (SDSC) was developed by Bruni *et al.* (Bruni *et al.* 1996). The scale contains 26 items, e.g. '*The child goes to bed reluctantly*' or '*The child has difficulty in breathing during the night*'. These are rated on a Likert-type scale (1, never; 2, occasionally [once or twice or less/month]; 3, sometimes [once to twice/week]; 4, often [three to five times/week]; 5, always [daily]). Based on their research, Bruni *et al.* (Bruni *et al.* 1996) presented a total disturbance scale and six subscales reflecting different types of common sleep problems.

Neurocognition, behavior, and school performance

Associations between sleep problems, psychiatric symptoms, disorders and cognitive functions have been increasingly recognized in child populations (Blunden *et al.* 2000, Beebe *et al.* 2004, Kennedy *et al.* 2004, O'Brien *et al.* 2004a). In children, the associations between childhood SDB and behavioral problems, including hyperactivity, inattention, mood, aggression, and delinquent behavior (O'Brien *et al.* 2004a, Rosen *et al.* 2004, Aronen *et al.* 2009), as well as the associations between SDB and decreased performance in neurocognitive tasks measuring attention, intellectual development, and memory (Gottlieb *et al.* 2004, Halbower *et al.* 2006) have been the main findings.

The Child Behavioural Checklist (CBCL) (Achenbach and Rescorla 2000) is a widely used parental questionnaire for the evaluation of childhood psychiatric symptoms. The checklist includes 99 problem items rated on a three-point scale with response alternatives 0 for not true, 1 for somewhat true or sometimes true, and 2 for very true or often true. In item 100, the respondent can add any problems not previously listed. The questionnaires are scored using the Achenbach scoring program, which gives an empiric-based broad-band symptom scale for total problems, and separately for internalizing and externalizing problems. The narrow-band symptoms scales for *Emotionally Reactive*, *Anxious/Depressed*, *Somatic Complaints*, and *Withdrawal* are included in the internalizing broad-band scale; *Attention Problems* and *Aggressive Behavior* are included in the externalizing broad-band scale. Items reflecting sleep problems are usually not included in either internalizing or externalizing scales.

The Wechsler Preschool and Primary Scale of Intelligence, revised (WPPSI-R) (Wechsler 1989) is used to evaluate children's cognitive capacity. Verbal Intelligence Quotient (VIQ) and Performance Intelligence Quotient (PIQ) are each estimated on the basis of four subscales from the verbal scale, these being the information, arithmetic, similarities, and sentences subscales, and the object assembly, block design, picture completion, and animal pegs subscales, respectively. VIQ, PIQ, and Full-Scale Intelligence Quotient (FSIQ) were compiled. These measures have a mean of 100 (SD 15) in the normal population.

NEPSY-A Developmental Neuropsychological Assessment (NEPSY) was designed to be a neuropsychological assessment tool for 3- to 12-year-old children and is used to evaluate more specific neuropsychological functions (Korkman *et al.*) (Table 2). The Finnish version of the NEPSY was standardized in Finland simultaneously with the U.S. standardization. It is equivalent to the American version and its validity has been demonstrated in several studies, as reported in the NEPSY manual. It consists of 27 subtests that assess neuropsychological functions in five domains: *attention and executive functions, language functions, sensorimotor functions, visuospatial processing, and memory and learning*. Subtests are usually chosen to provide age-appropriate measures for attention, language skills, sensorimotor functions, and memory and learning. The subtests have a mean score of 10 (SD 3) in the normal population.

O'Brien *et al.* compared snoring children with non-snoring children; 118 children aged 5-7 years underwent overnight PSG at hospital. Neurobehavioral tests were performed. Children with suspected OSA were excluded. Snoring children performed worse on measures related to attention, social problems, and anxious/depressive symptoms. In addition, overall cognitive abilities, certain language and visuospatial functions were lower for the snoring group than for the controls (O'Brien *et al.* 2004a).

In a recent study, 78 children with SDB and 26 control children without SDB were evaluated with overnight PSG, pediatric sleep questionnaire, and neuropsychological test. The results revealed greater difficulties in cognitive measurements for SDB children compared with controls. Somewhat surprisingly, the divergences were larger in children without OSA than in children with OSA relative to controls. (Gior-dani *et al.* 2008.) In fact, according to reports, daytime sleepiness, hyperactivity, and aggressive behaviors can also develop, albeit to a lesser extent, in children who habitually snore but in the absence of OSA (Blunden *et al.* 2000).

Table 2. NEPSY-A Developmental Neuropsychological Assessment (NEPSY) - subtests descriptions by domains.

Domain	Subtest	Description
Attention and Executive Functions	<i>Auditory attention</i>	The subtest was constructed to assess the child's ability to maintain vigilance and selective auditory attention. The child is to respond to the word "red" out of a set of words presented on an audiotape that lasts three minutes. The child is instructed as follows: When you hear the word <i>Red</i> , put a red square in the box.
	<i>Visual attention</i>	The subtest was constructed to assess the child's ability to scan and locate targets presented on a sheet with figures as quickly and as accurately as possible, by marking them with a red pencil.
	<i>Statue</i>	The subtest is designed to assess motor persistence and inhibition. The child is asked to maintain a body position with eyes closed during a 75-second period and to inhibit the impulse to respond to sound distracters.
Language Functions	<i>Speeded naming</i>	The child is to name visual stimuli presented on a sheet as quickly as possible. Items are named by size, color, and shape.
	<i>Comprehension of instructions</i>	The subtest assesses the ability to process and respond to verbal instructions of increasing complexity. The child points to figures on a sheet according to instructions.
	<i>Body Part Naming</i>	This subtest is designed to assess confrontation naming and name recognition, basic components of expressive and receptive language. For naming items, the child names the parts of the body on a figure of a child or on his or her own body.
Sensorimotor Functions	<i>Visuomotor Precision</i>	The subtest assesses fine motor skills and hand-eye coordination by having the child draw a line inside a curvilinear track as quickly and as precisely as possible.
Memory and Learning	<i>Memory for Faces</i>	The child is shown a series of faces and is asked to identify gender. The child is then shown a series of three-face arrays, from which to select the faces shown previously. The recognition procedure is repeated after a delay of 30 minutes, with new distracters.
	<i>Memory for Names</i>	The names of six children, shown in line drawings, are learned and reproduced by the child over three trials. The child is to name the children again after 30 minutes.
	<i>Narrative Memory</i>	The child listens to a story and is then asked to repeat the story. The child is then asked questions to elicit missing details from his or her recall of the story.

In 2001 Gozal and Pope studied children aged 13-14 years. The questionnaire was sent to students who ranked either in the top 25% or in the bottom 25% of their class. The survey included items about the frequency and loudness of previous snoring in childhood. The results revealed that those with lower academic performance are more likely to have snored during childhood. (Gozal and Pope 2001.) Urschitz et al reported similar results for 9-year-old schoolchildren (Urschitz *et al.* 2003a).

In the large population-based study of Calhoun et al (2009), 571 school-aged children were investigated with full-night PSG and comprehensive neuropsychological

logical tests. Children with mild SDB showed no neuropsychological impairment relative to children without SDB. The findings suggest that children with mild SDB are not at risk for neuropsychological impairment. The coexistence of mild SDB with any neuropsychological impairment should be considered co morbid and not causal (Calhoun *et al.* 2009). Noteworthy in this study that children who had sleep apnea were few (AHI>5, six children); however, the diagnosis of sleep apnea was based on AHI. It has previously been shown that even a simple snoring can cause attenuation in neuropsychological tests. This raises the possibility that the AHI is a poor indicator. In the future, a measurement other than AHI or OAHl may be considered to be more useful.

Somatic growth

In children with OSA may have a failure to thrive (Brouillette *et al.* 1982, Everett *et al.* 1987), whereas some studies show no growth retardation in children with OSA (Nieminen *et al.* 2002) Potential mechanisms implicated in growth deceleration include dysphagia resulting from adenotonsillar hypertrophy (Stradling *et al.* 1990), reduced systemic levels of insulin-like growth factor-1 (IGF-1) with disruption of growth hormone cumulative pulsatile circadian release (Waters *et al.* 1996, Bar *et al.* 1999, Nieminen *et al.* 2002) or increased energy expenditure during sleep as a consequence of increased breathing effort during sleep (Marcus *et al.* 1994). Also children undergoing TEA for SDB seems to have lower iron stores than children in the normal pediatric population (Kerstein *et al.* 2009), which may cause growth retardation.

However, there have been reports of catch-up growth after TEA among normal and underweight children (Stradling *et al.* 1990, Ersoy *et al.* 2005), unlike obese children with OSA, who demonstrate accelerations in weight gain after treatment of OSA (Soultan *et al.* 1999).

Cardiovascular consequences

Previous studies in children have suggested a positive association between OSA and elevated systemic BP (Marcus *et al.* 1998, Li *et al.* 2008, Li *et al.* 2009). Studies comparing BP in children with and without habitual snoring have reported conflicting results. In a study using a community-based sample, Kaditis *et al.* (2005) found no relationship between BP and snoring (Kaditis *et al.* 2005). By contrast, the study of Kwok *et al.* (2003) among snorers and age-, sex-, and body size-matched controls found increased systolic, diastolic, and mean BP in habitually snoring children (Kwok *et al.* 2003). In addition, a study with PSG and ambulatory BP measurement among non-obese children showed increasing daytime and nighttime BP across the severity spectrum of SDB in snorers and OSA children

relative to healthy controls (Li *et al.* 2009). Disruption of sleep and gas exchange may thus induce alterations in vasomotor tone, leading to vascular remodeling and inducing cardiovascular morbidity.

Hypertension is a well-recognized mechanism underlying remodeling of the myocardium and generation of left ventricular hypertrophy, dysfunction, and cor pulmonale (Amin *et al.* 2005). OSA remodels the right ventricle, resulting in right ventricle systolic and diastolic dysfunction (Tavil *et al.* 2007). If left untreated, OSA may lead to cor pulmonale (Brouillette *et al.* 1982).

Management

In the early stages of a child's life, sleep is the predominant activity. The smaller the child, the more important undisturbed sleep. Disturbed night sleep causes problems in child growth and development. Children's sleep disturbances occur differently than those in adults. Physicians are not always aware of a child's sleep disorders or may have insufficient knowledge about adequate investigations and treatments.

Habitual snoring tends to persist during adolescence if no intervention is undertaken to modify its natural history (Sanchez-Armengol *et al.* 2008). By contrast, in children aged 9–13 years a decrease up to 50–65% occurred in the prevalence of habitual snorers by the end of the follow-up without any treatment (Urschitz *et al.* 2004b, Anuntaseree *et al.* 2005). In these studies, no PSG measurements were taken.

In a longitudinal study, children with an average age of nine years (n=14), with PSG-confirmed mild OSA without any therapeutic intervention were re-examined after six years. The mean OAHl dropped from 7.5 to 2.5 ($P < .0001$). OAHl dropped in all but three children (79%). On the contrary, the body mass index (BMI) percentile was higher in almost 80% of children after six years. The main finding was that in most of the children apnea symptoms disappear as the child grows, despite a substantial increase in BMI. The authors speculated that the decrease in OAHl is related to somatic growth of the pharynx, coupled with regression of tonsillar tissue with age. (Rice *et al.* 2010.)

Nonsurgical management

It is generally accepted that corticosteroids may have some limited useful in the management of pediatric OSA (Marcus 1997). Demain and Goetz showed that topi-

cal nasal corticosteroids over a 24-week treatment reduced adenoidal size and improved symptoms of nasal airway obstruction (Demain and Goetz 1995). However, these investigators did not evaluate the efficacy for OSA. Topical nasal steroids most likely affect the anatomic component by decreasing inspiratory upper airway resistance at the nasal level, in allergic and non-allergic children or at the adenoidal (Demain and Goetz 1995) or tonsillar (Brouillette *et al.* 2001) level in hypertrophied patients.

The recently reported increase in the expression of glucocorticoid receptors in upper airway lymphoid tissues would globally predict favorable outcomes when using intranasal corticosteroids in pediatric OSA (Goldbart *et al.* 2005b). In children with mild obstruction, topical corticosteroid treatment may prove to be the treatment of choice (Kheirandish-Gozal and Gozal 2008).

In a randomized, triple-blind, placebo-controlled study showed that topical corticosteroids may be helpful in ameliorating pediatric obstructive sleep apnea (Brouillette *et al.* 2001). PSG, clinical, and radiographic assessments were performed at baseline and after 6 weeks on fluticasone or placebo treatment. All children had baseline OAH1 >1 and adenoidal hypertrophy assessed on radiography. The authors found that a 6-week treatment of nasal fluticasone decreased the severity of pediatric OSA, as demonstrated by reduced frequencies of obstructive airway events (mean OAH1 from 10 to 5.0/h). (Brouillette *et al.* 2001.)

Oral therapy with a leukotriene modifier appears to be associated with improved breathing during sleep. Goldbart *et al.* studied 24 snoring children with mild OSA (OAH1 1-5/h). Treatment included daily montelukast 4-5 mg for 16 weeks. Sixteen children with mild OSA but receiving no treatment served as controls. After treatment, the adenoidal/nasopharyngeal ratio decreased from 0.76 to 0.56 ($P < .001$). OAH1 decreased with treatment from 3.0/h to 2.0/h, $P = .02$). No adverse drug reactions were reported throughout the study. By contrast, children who received no therapy displayed no changes in any of the anatomic polysomnographic measures during the 16-week period. (Goldbart *et al.* 2005a.) In addition, children with residual SDB who have already undergone TEA for treatment of OSA would seem to benefit from montelukast and intranasal budesonide compared with children without any further medical treatment (Kheirandish *et al.* 2006). The downside to these therapies are the unknown long-term duration of response or the length of medical therapy required, and randomized, double-blind, placebo-controlled trials are needed to confirm findings.

Among overweight children, aerobic exercise may also be effective improving snoring, and aerobic exercise programs may be valuable for prevention and treatment of SDB in overweight children (Davis *et al.* 2006). In addition, weight loss seems to be effective in obese teenagers suffering from SDB (Verhulst *et al.* 2009).

Several reports have highlighted the ability to use continuous positive airway pressure (CPAP) in children and infants with SDB (Waters *et al.* 1995, Downey *et al.* 2000, Harrington *et al.* 2003), especially in children with gross craniofacial anomalies (e.g. Pierre Robin sequence, Treacher-Collins syndrome), Down syndrome, morbid obesity, or upper airway muscle weakness (e.g., cerebral palsy). Hence, CPAP increasingly replaces surgery and tracheotomy in children with severe SDB. The remaining problems are related to the lack of optimal equipment for young children and frequent difficulties with regard to initial adaptation to the nasal mask and compliance with treatment. Furthermore, CPAP can be used in children with severe SDB or persisting SDB after TEA.

A palatal expander, also known as a rapid palatal expander, RME appliance or palate expander is an orthodontic procedure that uses a fixed appliance with an expansion screw anchored on selected teeth, usually to first molars or permanent molars in the upper jaw. The developmental impact of abnormal nasal resistance related to septal deviation early in life, is abnormal maxillary development. The goal of RME is to increase the transversal diameter of the hard palate and, thus, improve nasal airflow. Radiographs indicate that RME moves nasal and palatal bones. The total expansion effect consists of a downward and forward movement of the maxillary complex with a resulting increase in the nasal canal and an improvement in nasal airflow. The device is usually kept in place for 6-12 months. RME improves nasal resistances and cross-sectional areas in children (Bicakci *et al.* 2005, Compadretti *et al.* 2006, Enoki *et al.* 2006, Doruk *et al.* 2007).

Pirelli *et al.* (2004) studied 31 children with RME with a mean age of 8.7 years. Inclusion criteria were the absence of adenotonsillar hypertrophy, presence of malocclusion, oral breathing, and OSA based on PSG monitoring. After 6-12 months of RME therapy, nasal resistances had decreased and PSG indicated an AHI <1 in all cases, with mean OAH1 from 12.2/h to 0.4/h. None of the children presented with any problems with RME. (Pirelli *et al.* 2004.) The study of Villa *et al.* (2007) in 14 OSA children with a mean age of 6.6 years also showed after 12 months of REM therapy resolution in sleep parameters and obstructive episodes of apnea indices, from 3.1 to 0.9/h. In these children, orthodontic assessment detected the presence of jaw deviation from normal occlusion; i.e. deep bite, retrusive bite, and cross-bite. 40% of children had a tonsillar size of 3-4 on the Brodsky scale. (Villa

et al. 2007.) RME seems to be effective in SDB children with malocclusion and/or the presence of nasal disturbances, i.e. septal deformities.

Surgical management

TEA is an effective treatment for snoring and obstructive sleep apnea; snoring resolves after adenoidectomy or TEA in 60-90% of children (Bahadir *et al.* 2006, Joshua *et al.* 2006, Arrarte *et al.* 2007). The prospective study of Mitchell *et al.* (2007) in children aged 3-14 aged showed, that TEA was effective for 90% of children. All children with mild OSA, were cured after TEA, while 12-36% of children with moderate or severe OSA had persistent OSA in PSG after TEA (Mitchell 2007). In the study of Tauman (2006), complete normalization after TEA occurred in 25% of children with OSA and 29% of children had persistent OSA (OAHI >5/h) after treatment (Tauman *et al.* 2006). Guilleminault *et al.* (2007) reported that almost 48% of children still had persistent abnormal sleep recording after surgery. They concluded that TEA may not resolve obstructive sleep apnea in children. In multivariate analysis, they showed that Mallampati scale scores of 3 and 4, retropositioning of the mandible, enlargement of nasal turbinates, and deviated septum were associated with a greater risk for persistent OSA in sleep studies. (Guilleminault *et al.* 2007.)

In obese children, the TEA is effective in less than 40% of children, and most obese patients still have residual OSA requiring further treatment after TEA (Shine *et al.* 2006, Tauman *et al.* 2006).

Tonsillotomy (TT) has been advocated in the last few years as an effective and safer method than tonsillectomy for treating airway obstruction. In TT, the tonsillar capsule and some tonsillar tissue are left during surgery into the tonsillar pit, preventing injury and inflammation. This results in less post-operative pain and a more rapid recovery (Hultcrantz *et al.* 1999). Since the post-operative recovery is often painful and tonsillar surgery is associated with a reasonably high risk of postoperative bleeding, TT has been studied as an alternative surgical treatment to the traditional tonsil surgery in snoring and OSA children (de la Chaux *et al.* 2008). The long-term success of TT is unclear, but some evidence shows that snoring may recur more frequently in children who have undergone TT compared with those receiving tonsillectomy (Vlastos *et al.* 2008). At least in children who do not have recurrent tonsillitis, snoring can be treated with TT.

A small jaw pushes the tongue into the back of the throat, causing blockage of breathing. Mandibular distraction is a method used to increase the length of the jaw bone in congenital micrognathia or midface hypoplasia in children (Bouchard *et al.* 2009). Most children treated with mandibular distraction have either unilateral or bilateral mandibular hypoplasia due to hemifacial microsomia, other syndromic disorders, or the Pierre Robin syndrome. Children with upper airway obstruction from craniofacial anomalies and mandibular hypoplasia treated with mandibular distraction, demonstrated clinical improvement of obstructive sleep apnea (Lin *et al.* 2006).

Tracheostomy is indicated for severe and chronic airway obstruction. However, tracheostomy is not without risks. Long-standing tracheostomy produces an increased risk for tracheal granuloma, stomal stenosis, and chronic bronchitis (Conway *et al.* 1981, Zeitouni and Manoukian 1993). Decreased QoL, intellectual and physical impairments, compromised social interactions, and requirements for complex nursing care and parental education have also been demonstrated (Puhakka *et al.* 1992, Cohen *et al.* 1998). Historically, tracheostomy was the only safe, long-term treatment option for infants.

AIMS OF THE STUDY

The purpose of this study was to assess snoring and sleep apnea in children in Finland.

Specific aims were:

- 1) To evaluate the prevalence of snoring in Finnish preschool-aged children
- 2) To investigate host and environmental risk factors for snoring and sleep apnea in children
- 3) To determine divergences in rhinometric and cephalometric measurements between healthy children and children with snoring and SDB
- 4) To evaluate neurobehavioral and neurocognitive symptoms in children with snoring and SDB
- 5) To test the feasibility of acoustic rhinometry in young children

SUBJECTS AND METHODS

Subjects

All studies were prospectively conducted in 2005-2008. A flow chart of the children's examinations is presented in Figure 2.

In the epidemiology part (I) of the study, the prevalence and risk factors of snoring were evaluated by questionnaire. A sample of 2100 children aged 1-6 years and born between September 1998 and August 2005 was randomly picked from the Population Register Center, Helsinki. The sampling represented 7% of all children living in Helsinki. All children aged 3-6 years who were reported by their parents to snore always, often, or sometimes were invited to participate in the clinical study (II-IV) and were categorized as snorers. Non-snoring children whose parents expressed their willingness to participate in the clinical part of the study were also invited to serve as controls. Based on the questionnaire in Study I, a total of 97 children participated in the clinical part of the study.

For Study V, 26 children aged 1-6 years were recruited via voluntary parents of employees of the Department of Otorhinolaryngology. All of these healthy children were investigated with acoustic rhinometry.

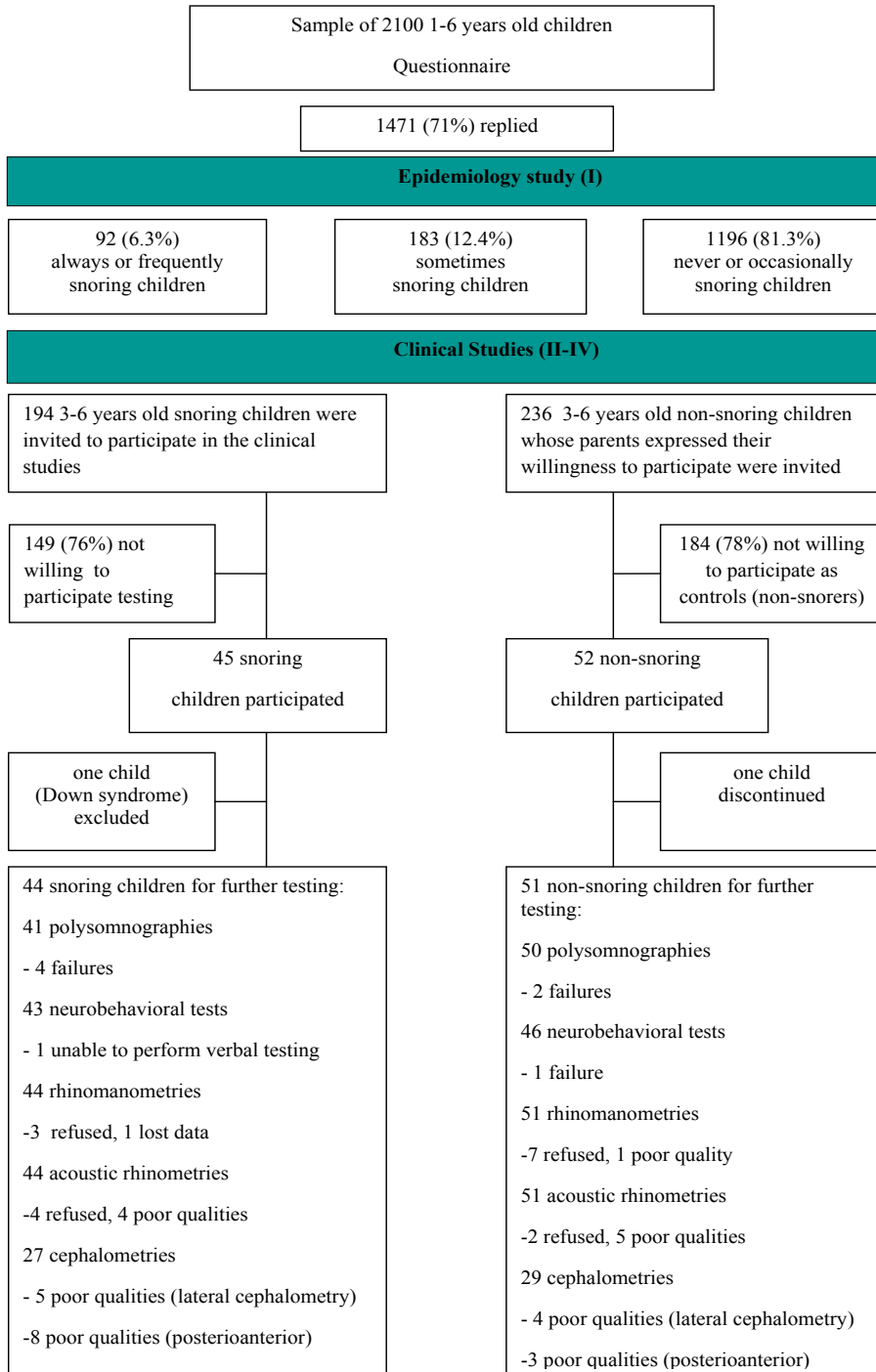


Figure 2. Flow chart of the children who participated in Studies I-IV.

Methods

Study I

The epidemiology and risk factors of snoring and sleep problems were evaluated by a parental questionnaire describing the sleep of their children (Appendix A). The frequency of snoring was identified based on parents' response to the item "*How often does your child snore?*". Symptoms during the past 6 months were described. Children were classified as snorers if they were reported to snore always, often, or sometimes (scores 3-5) or as non-snorers if the answer was occasionally or never (scores 1 and 2). History of allergic rhinitis was assessed with a question "*Does your child have allergic rhinitis?*". Respiratory infections were assessed with the question "*Does your child have upper respiratory infection (URI) episodes?*" (common colds, cough, or sore throat during the last 6 months). A response of often or always (scores 4 and 5) was defined as having recurrent URI. The number of acute otitis media episodes was determined with the options none, one, two, three, or over four during the last 6 months. Children having four or more episodes of acute otitis media during the past 6 months were classified as having recurrent otitis media. Child's age, height, weight, and previous surgeries were recorded.

All children reported by their parents to snore always, often, or sometimes were invited to participate in the clinical study. Non-snoring children whose parents expressed their willingness to participate in the clinical part of the study were also invited to serve as controls (Studies II-IV).

Study II

The Finnish version of the WPPSI-R was used to evaluate children's cognitive capacity, and NEPSY was used to evaluate more specific neuropsychological functions. The assessment took 2-2.5 h, and the examiner was blind to the subject's group status. During the assessment the parent completed the CBCL questionnaire in a separate room.

Helsinki city socioeconomic status classification was used. Socioeconomic class I includes persons with an academic degree, business managers, and professionals (engineers, teachers, doctors, lawyers); class II includes administrative personnel, owners of small businesses, and minor professionals (graduate nurses, photographers, merchants); class III includes skilled manual employees (laboratory assistants, children's nurses, shop assistants); class IV includes unskilled employees (trainees, domestic maids, office messengers). The highest socioeconomic class of the parents was used to describe the family's socioeconomic status.

Studies III and IV

All snoring and non-snoring children underwent a clinical ear-nose-throat examination. The clinical status included the examination of the ears and mouth as well as anterior and posterior rhinoscopy. The tonsils were graded according to Brodsky *et al* (Brodsky 1989). Child's age, height, and weight were recorded, and BMI z-scores were calculated using an online BMI z-score calculator provided by the Centers for Disease Control and Prevention (CDC).

Measurement of nasal resistance was performed with active anterior rhinomanometry (Figure 3). Inspiratory nasal resistance at radius 200 was calculated according to the method of Broms (1982), and total nasal resistance was calculated from the left- and right-side recordings (Broms *et al.* 1982). The measurements were performed according to recommendations of the Standardization Committee on Objective Assessment of the Nasal Airway (Clement 1984, Clement *et al.* 2005). Logarithmic transformation of rhinomanometric data in the statistical analysis was used.



Figure 3. Rhinometry in a 5-year-old boy.

Skin prick tests (SPT) included the following 10 common aeroallergens related to allergic symptoms in the Helsinki area: birch, timothy grass, common alder, meadow fescue, mugwort, dander of cat, dog, and domestic guinea pig, and *Dermatophagoides farinae* and *pteronyssinus*. A positive SPT was defined as a wheal of at least 3 mm, when control solutions gave the expected results (European Academy of Allergology and Clinical Immunology 1989). Atopy was defined as the presence of at least one positive SPT.

A standard overnight multichannel ambulatory PSG (Siesta Compumedics®, Australia) was performed at home. The child had to be free of infection, i.e. no URIs over the last 2 weeks.

PSG included EEG, EOG, submental and diaphragmatic EMG, ECG, airflow (pressure transducer), respiratory bands, SpO₂, and body motion. The transducers and lead wires allowed normal positional changes during sleep (Figure 4).

Each signal was manually scored in 30-s epochs, and respiratory parameters obstructive apnea/hypopnea indices (OAHI/AHI), sleep architecture, and arousals from sleep were analyzed using standard pediatric criteria (Iber *et al.* 2007, Montgomery-Downs *et al.* 2006, Verhulst *et al.* 2007). An obstructive apnea episode was defined as complete cessation of the oronasal airflow lasting >2 respiratory cycles as detected by the nasal pressure transducer and the presence of continuous breathing efforts in the submental and diaphragmatic EMG. Hypopnea was defined as a reduction of at least 50% in the airflow signal, flattened airflow shape followed by either respiratory arousal, EEG arousal, or SpO₂ desaturation of more than 2%. Central apnea was defined as cessation of the airflow in the absence of breathing efforts. Mean SpO₂, as measured by pulse oximetry (SpO₂), together with SpO₂ nadir were determined.



Figure 4. Overnight polysomnography measurement in a 3-year-old boy at home.

ODI was defined as the average number of oxyhemoglobin desaturations of 2% (ODI2) or 4% (ODI4), below the baseline level, per hour. Respiratory effort was measured from submental and diaphragmatic EMG with a 3-point scale: 1; normal, 2; mildly increased, 3; clearly increased. Oronasal airflow flattening was also evaluated on a 3-point scale: 1; normal, 2; mild flattening, 3; severe flattening.

Cephalometry

Standardized lateral and posteroanterior cephalometric radiographs were taken in a cephalostat (Cranex C, Soredex Co., Tuusula, Finland), with children in an upright position and using a Frankfort horizontal line parallel to the floor (Kawashima *et al.* 2003). The landmarks identified from lateral and posteroanterior cephalograms were digitized and recorded in the computer software program, after which variables describing nasopharyngeal dimension were calculated (Viewbox 3.1, Cephalometric Software; dHal Software, Kifissia, Greece).

Table 3. Angular (degrees) and linear (millimeters) variables related to both craniofacial skeletal and soft tissue.

Cranial base dimensions		
	S-N	Anterior cranial base length (mm)
	S-Ba	Posterior cranial base length (mm)
	NSBa	Cranial base angle between S-N and S-Ba (°)
Maxillary dimensions and relationships		
	PNS-ANS	Palatal length, distance from anterior nasal spine to posterior nasal spine (mm)
	ANS-Me	Lower anterior facial length, distance from ANS to mandibular menton (mm)
	SNA	Angle from sella to the nasion to the subspinal point (°)
Mandibular dimensions and relationships		
	Cd-Gn	Mandibular length of base, distance between condylion and gnathion points (mm)
	SNB	Angle from sella to the nasion to the supramental point (°)
	SN/MP	Facial divergence, angle determined by S-N and mandibular plane (°)
	Gonial angle	Angle determined by Go-Cd and Go-Gn lines (°)
Pharyngeal airway		
	S-PNS	Posterior midfacial length, distance between sella and posterior nasal spine (mm)
	AA-PNS	Bony oropharynx, distance between anterior atlas and PNS (mm)
	PNS-ad1	Distance between posterior nasal spine and posterior pharyngeal wall measured along the line from PNS to basion (mm)
	PNS-ad2	Distance between PNS to posterior pharyngeal wall measured along the line from PNS perpendicular to sella basion line (mm)(S-BA) line
	p-p2	Minimal distance from the tip of the uvula to the posterior pharyngeal wall (mm)
	PNS-p	Distance between PNS and P; the most inferior tip of the soft palate (mm)
	PAS-PAS	Thickness of posterior airway space measured on a line from supramentale (B) to the most inferior point at the angle of mandible (GOinf) (mm)
	ve1-ve2	Minimal distance from velum to posterior pharyngeal wall (mm)
	Ph1-Ph2	Minimal distance between base of the tongue and posterior pharyngeal wall (mm)
Posterior-anterior cephalometry		
	lo-lo	Latero-orbitale distance (mm)
	um-um	Upper first molar width (mm)
	lap-lap	Internasal distance (mm)
	lm-lm	Lower first molar width (mm)
	ag-ag	Mandibular width (mm)

The radiographic magnification of 10% was corrected. The effect of growth was taken into account in the statistical comparisons by dividing nasopharyngeal measurements with distance from the sella to the nasion (S-N) in lateral cephalogram measurements and lo-lo (latero-orbitale) distance dimension in anteroposterior measurements (Kirjavainen and Kirjavainen 2003).

Study V

Measurement of nasal volume with acoustic rhinometry was performed on 26 healthy children. The measurement was performed at a minimum of 15 min after arrival, following a period of acclimatization to the test room temperature and humidity according to the current recommendations (Hilberg and Pedersen 2000) before and 20 min after decongestion (xylometazolin 0.5mg/ml, one spray, 0.07 ml per nostril). Measurements were performed in a seated position and after at least a 2-week period without symptoms of upper airway infection. ARM volumes were measured at distances of 0-5 cm (VOL 0-5) and 1-4 cm (VOL 1-4) from the nostrils, and the minimal nasal cross-sectional area (MCA, cm²) and its distance (DCA, cm) from the nostrils were recorded. The success of obtaining this measurement among young children and the normal values for healthy children of this age group were studied (Figure 5).



Figure 5. Measurement with acoustic rhinometry in a 5-year-old boy.

Statistical methods

The analyses were conducted with statistical software (NCSS and PASS 2004; Number Cruncher Statistical Systems, Kaysville, UT). Group contrasts for continuous variables were subjected to Student's *t*-test or Mann-Whitney U-test. For contrasts of dichotomous variables, such as nonclinical range of internalizing symptoms/ borderline and clinical range of internalizing symptoms in snoring and non-snoring groups, Chi-Square or Fisher's exact test values were computed. All probabilities are reported as two-tailed. Spearman rank correlation coefficients served to evaluate behavioral symptoms and neurocognitive impairment.

In Study II logistic regression analysis was used to control for the effects of socioeconomic status, age, gender, and verbal IQ while investigating the association between snoring and the number of internalizing symptoms. For internalizing scale symptoms, a cut-off of 60 T-points was used to form the nonclinical group and the borderline/clinical group of children.

P-values of less than .05 were considered to indicate statistical significance.

Ethics

The study protocol was approved by the local ethics committee of Helsinki University Central Hospital. Parents signed a written informed consent and oral consent was obtained from the children. All studies were performed under the Declaration of Helsinki and good clinical practices.

RESULTS

Epidemiology of snoring (I)

In the epidemiology study, the age range of the study subjects was 12-84 (median 46) months. Boys comprised 719 subjects (48.1%). Children who always or often snored accounted for 6.3%, children who sometimes snored for 12.4%, and children who never or occasionally snored for 81.3% of all subjects. No differences were apparent between snorers and non-snorers regarding age or gender. Snoring children were heavier ($P = .02$) and longer ($P = .01$) than did non-snorers. The number of adenoidectomies ($P < .001$) and tympanostomies ($P < .001$) were higher in the snoring group than in the non-snoring group. Allergic rhinitis ($P < .001$), recurrent URIs ($P < .001$), and otitis media ($P < .001$) were more common among snorers. Smoking of either or both parents was reported in 32.5% of families. Among snoring children, parental smoking, especially maternal smoking ($P < .01$), was more common than among non-snorers. Parental snoring was higher in the snoring group than in the non-snoring group (Table 4).

Table 4. Demographic and epidemiologic data for 275 snoring (at least once a week) and 1196 non-snoring (never or less than once a week) children.

	Snorers (n = 275)	Non-snorers (n = 1196)	<i>p</i> value
Male gender	141 (51)	578 (48)	.39
Age (months, median)	48.2	45.9	.06
Median height, (m, SD)	1.05 (± 0.14)	1.02 (± 0.14)	.01
Median weight, (kg, SD)	17.0 (± 4.9)	16.0 (± 4.7)	.02
Adenoidectomy	63 (24)	151 (13)	< .001
Tympanostomy	61 (22)	154 (13)	< .001
Tonsillectomy	16 (6)	35 (3)	.01
Allergic rhinitis	65 (24)	171 (14)	< .001
Recurrent respiratory infections ^a	58 (21)	109 (9)	< .001
Acute otitis media ^b	105 (38)	307(26)	< .001
Snoring ^c			
mother	103 (37)	235 (20)	< .001
father	201 (73)	701 (59)	< .001
Smoking			
mother	27 (14)	71 (8)	< .01
father	42 (20)	202 (20)	.03
both	40 (20)	96 (10)	< .001

Data presented as number of children/parents (%), unless otherwise noted

^aUpper airway infections > 5 episodes in the previous 6 months

^bFour or more episodes of acute otitis media in the previous 6 months

^cParents snoring sometimes, often, or always

Parental smoking, rhinitis and nasal resistance in children (III)

The smoking group included 35 children, with 19 girls (54%), and the non-smoking group included 60 children, with 28 girls (47%). Children in non-smoking families were younger than those in smoking families (71 vs. 63 months, $P = .01$). Age was a confounding factor in comparison of these groups only in the number of adenoidectomies ($P = .04$). No differences between groups were found for gender.

Perennial rhinitis was more common in children with a smoking parent (37%) than in children without a smoker in the household (15%) (adjusted OR 2.76). Smoking in the family was not associated with increased nasal resistance ($P = .18$).

Atopy appeared in 35% of the children, but was not associated with smoking in the family (adjusted OR 0.31). Neither tonsil size (adjusted OR 0.88), number of adenoidectomies (adjusted OR 0.76), nor number of tonsillectomies (adjusted OR 1.09) was higher in children with smoking parents. Cephalometric measurements reflecting the width of the nasopharyngeal airway at the level of the adenoidal tissue were not associated with smoking in the family.

Risk factors and consequences of snoring and sleep apnea (II and IV)

Neurobehavioral and cognitive symptoms were investigated among snorers and non-snorers in Studies II and IV. No differences between groups were found for gender or age. The median BMI z-score was 0.7 (SD 1.3) in the snoring group and -0.2 (SD 1.1) in the non-snoring group ($P = .45$). Recurrent URIs were more common among the snoring than non-snoring children (27% vs. 11%, $P = .01$). One snoring child had chronic illness (migraine). In the non-snoring group one child had von Willebrand disease, one hypothyroidism (euthyroid after medication), one child had undergone heart operation and one suffered from constipation. Subjects' characteristics and examination distributions of variables in snoring and non-snoring children are seen in Table 5.

Table 5. Children characteristics and examination distributions of variables in snoring and non-snoring children.

	Snorers (n = 44)	Non-snorers (n = 51)	p value
Age, median, years	5.3 (1.6)	5.2 (1.2)	.94
Female/male	23/21	24/27	.61
Frequency of snoring			
never		21	
sporadically (1-2 nights a month)		30	
sometimes (1-2 times a week)	25		
often (3-5 times a week)	12		
always	7		
Height, median, m	1.15 (0.1)	1.15 (0.1)	.52
Weight, median, kg	20.7 (4.7)	20.0 (4.1)	.27
Body mass index, median, Z score	0.7 (1.3)	-0.2 (1.1)	.45
Brodsky score 3-4 ^a	18 (18.4%)	12 (12.2%)	.09
Recurrent upper airway infections ^b	12 (26.7%)	6 (11.3%)	.01
Tonsillectomy	2 (4.4%)	2 (3.8%)	.88
Adenoidectomy	15 (33.3%)	12 (22.6%)	.26

Data presented as number of children (SD), or (%), unless otherwise noted

^aTonsillar size 3-4, scored by Brodsky scale (Brodsky 1989)

^bUpper airway infections > 5 episodes in the previous 6 months

Psychiatric symptoms were more frequent in the snoring group than in the non-snoring group. Internalizing symptoms, in particular, were more prevalent in the snoring group. Of the narrow-band subscale of the CBCL internalizing symptoms, the Anxious/Depressed ($P = .04$) subscale scores were higher in snoring children than in non-snoring children. Externalizing symptoms were no more frequent in snorers than in non-snorers.

The two groups did not differ in IQ scores. In the NEPSY subtests, a divergence between the groups was found in language function: Comprehension of instructions ($P = .01$), Speeded naming ($P < .01$), and attention test, Statue ($P = .03$). Sensorimotor functions tests and memory and learning tests revealed no differences between the groups (Table 6).

Table 6. Behavioral and cognitive symptoms in snoring and non-snoring children according to the Child Behavior Checklist (CBCL), Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R), and NEPSY-A Developmental Neuropsychological Assessment (NEPSY).

	All	Snoring (n = 42)	Non-snoring (n = 45)	95% CI of the mean difference	p value
CBCL					
Total Problems	47.3 (10.3)	50.0 (10.6)	45.1 (9.5)	(-9.2, -0.6)	.03
Internalizing Problems	47.9 (10.9)	50.7 (10.8)	45.6 (10.6)	(-9.4, -0.3)	.04
Anxious or Depressed	52.3 (4.3)	53.5 (5.3)	51.6 (3.3)	(-3.5, 0.1)	.04
Somatic Complaints	56.2 (7.2)	57.4 (7.4)	55.0 (6.8)	(-5.5, 0.6)	.11
Emotional Reactive	53.5 (5.4)	54.7 (6.4)	52.5 (4.3)	(-4.3, 0.3)	.09
Withdrawn	53.6 (4.5)	53.8 (5.0)	53.3 (4.0)	(-2.5, 1.4)	.56
Externalizing Problems	46.0 (9.9)	47.9 (10.4)	44.3 (9.1)	(-7.8, 0.5)	.08
Attention Problems	51.7 (3.0)	51.9 (3.2)	51.6 (2.7)	(-1.6, 0.9)	.61
Aggressive Behavior	52.9 (5.6)	53.9 (7.2)	51.9 (3.6)	(-4.4, 0.4)	.10
WPPSI-R					
Total IQ	110.7 (12.9)	109.0 (14.2)	112.5 (11.4)	(-2.2, 8.7)	.23
Verbal IQ	109.0 (12.8)	106.2 (13.5)	111.8 (11.7)	(-0.0, 10.6)	.05
Performance IQ	108.8 (12.0)	108.9 (14.2)	108.9 (11.6)	(-5.3, 4.9)	.95
NEPSY - A					
Attention/Executive Functions					
Visual Attention	11.2 (3.0)	11.4 (3.2)	11.0 (2.9)	(-1.7, 0.9)	.63
Auditory Attention#	12.0 (3.4)	11.2 (3.3)	13.2 (3.0)	(-1.6, 1.0)	.08
Statue##	11.2 (2.5)	12.1 (0.9)	10.5 (3.1)	(-3.3, 0.3)	.03
Language Functions					
Comprehension of Instruction	11.2 (2.6)	10.5 (2.3)	11.9 (2.7)	(0.3, 2.4)	.01
Speeded Naming#	10.7 (2.9)	9.7 (2.4)	12.0 (2.9)	(0.6, 3.7)	.007
Body Part Naming##	11.2 (2.5)	10.9 (3.2)	11.4 (1.9)	(-1.2, 2.2)	.57
Sensorimotor Functions					
Visuomotor Precision	9.7 (3.2)	9.5 (3.3)	9.8 (3.2)	(-1.0, 1.8)	.57
Memory and Learning					
Memory for Faces#	10.8 (2.8)	10.9 (2.8)	10.8 (2.9)	(-1.6, 1.6)	.99
Memory for Names#	11.4 (2.7)	11.0 (2.8)	11.7 (2.6)	(-0.9, 2.2)	.38
Narrative Memory##	10.8 (3.1)	11.4 (3.8)	10.2 (2.5)	(-3.4, 0.9)	.25

Data presented as means (SD)

CI; Confidence Interval

IQ; Intelligence Quotient

only 5- to 6-year-olds included (n=50), ## only 3- to 4-year-olds included (n=37)

Overnight PSG were performed on 90 children. SpO₂ recording was successful in all children; however, three recordings ultimately failed because of wire or sensor disconnection. Eighty-seven children attended the clinical study.

Sixty-six children (74%) had OAHl of less than 0.9/h, 18 children had OAHl of 1.0-4.9/h, and three children had OAHl of more than 5/h. One child had OAHl of 19.2/h, which was considered to be clinical. Children's age, gender, and previous adenoidectomy or tonsillectomy did not correlate with OAHl. Relative body weight or obesity did not correlate with any of the PSG parameters. Tonsillar size correlated with OAHl ($P < .01$) as well as with respiratory effort, measured from submental muscles ($P < .01$) or diaphragm muscles ($P = .01$), and respiratory airflow ($P < .01$). Sleep architecture, respiratory variables, and SpO₂ values for snoring and control children are seen in Table 7. The differences in OAHl, AHI, airflow flattening, and respiratory effort reached statistical significance.

Table 7. Sleep architecture, sleep-related respiratory variables, and arterial oxyhemoglobin desaturation parameters for 39 snoring and 48 non-snoring children.

Variables	Snoring (n = 39)	Non-snoring (n = 48)	p value
Total sleep time, min	452 [400-513]	504 [414-552]	.26
Sleep latency, min	10 [5-20]	16 [9-23]	.38
Arousal index	11.9 [7.9-12.9] (0.9-17.0)	12.3 [10.2-14.8] (1.8-20.8)	0.16
Obstructive apnea/hypopnea index	0.7 [0.0-1.0] (0-19.2)	0.3 [0.0-0.2] (0-4.3)	.002
Central apnea index	1.6 [1.2-2.9] (0.1-5.1)	1.7 [1.3-1.9] (0.1-4.7)	.82
Apnea hypopnea index	2.9 [1.7-3.6] (0.1-20.5)	1.8 [1.5-2.3] (0.1-5.5)	.02
2% oxygen desaturation index	0.8 [0.5-1.3] (0-9.5)	0.6 [0.5-0.9] (0-4.1)	.20
4% oxygen desaturation index	0.1 [0-0.2] (0-3.1)	0.0 [0-0.1] (0-1.3)	.23
Pulse oximetry haemoglobin saturation			
Mean lowest(%)	98.0 [98-98] (99-97)	98.0 [98-98] (99-96)	.98
lowest (%)	95.0 [94-95] (98-84)	95.0 [93-96] (98-78)	.99
Heart rate (/min)	73 [67-81]	76 [70-78]	.94
Respiratory effort			
Submental ^a	0.3 [0-0.7] (0-1.3)	0.0 [0-0.3] (0-1.3)	.02
Diaphragm ^b	0.7 [0-1] (0-2.7)	0.4 [0.3-0.6] (0-2.3)	.54
Respiratory airflow ^c	0.6 [0.3-0.6] (0-2)	0.0 [0-0.3] (0-1)	.003

Data is presented as medians with confidence interval [CI 95%], and (ranges)

^a Respiratory effort as measured from electromyography electrodes on submental muscles; scores: 1 = normal, 2 = mildly increased, 3 = clearly increased

^b Respiratory effort as measured from electromyography electrodes on diaphragm muscles; scores 1 = normal, 2 = mildly increased, 3 = clearly increased

^c Oronasal airflow flattening as measured from nasal cannula; scores 1 = normal, 2 = mild flattening, 3 = severe flattening

In NEPSY and PSG parameters, correlations were presented between OAH1 and *Auditory Attention* ($P < .05$, $r = .29$), OAH1 and *Comprehension of Instructions* ($P < .05$, $r = .24$), ODI2 and *Body Part Naming* ($P < .05$, $r = .47$), and respiratory effort and *Memory* ($P < .05$, $r = .34$). No correlation was observed between the CBCL, WPPSI-R, and sleep study parameters.

In cephalometry, the minimal distance from the velum to the posterior wall (velum1-velum2) was shorter for snorers relative to non-snorers (5.5 mm vs. 6.6 mm) ($P < .05$). In PSG data, the velum1-velum2 had a weak correlation with AHI ($P = .05$). No correlations were found between ARM, RMM, and PSG parameters.

In neurobehavioral tests, children suffering from recurrent URIs have more somatic complaints than children without recurrent URIs ($P < .01$). The presence of recurrent URIs did not correlate with any PSG parameters or rhinometric values.

Feasibility and normal nasal volume values of acoustic rhinometry in children (V)

Twenty-six children, 13 girls and 13 boys aged 1-6 years participated in this study. Their median age was 48 months. Children were grouped into three subgroups based on age: 1-2 years, 3-4 years, and 5-6 years. Accepted recordings of ARM included measurements before and after decongestion of nasal mucosa. The overall success rate of ARM was 69%, being the highest (78%) among children aged 5-6 years.

DISCUSSION

Prevalence of snoring

Snoring in young children is common, with no changes occurring in the prevalence with age; 19% of young Finnish children snore at least sometimes, and 6.3% always or often. These results are in line with previous surveys, with reported prevalence reaching 16% (Teculescu *et al.* 1992, Ali *et al.* 1992, Bixler *et al.* 2009)

The sample included 2100 children aged 1-6 years in the Helsinki region based on the random sampling of Population Register Center data. The overall response rate (72%) was good. Reliability of the study can also be considered good.

Risk factors for snoring and sleep apnea

In children with small upper airways, mucosal inflammation is an important risk factor for snoring (Gozal and Kheirandish 2006). Many authors have reported an association between snoring, allergic rhinitis (Anuntaseree *et al.* 2001), and URIs (Hultcrantz *et al.* 1995, Urschitz *et al.* 2004b), suggesting the presence of increased inflammation in the upper airway of children in relation to the severity and frequency of obstructive episodes during sleep (Goldbart *et al.* 2006). Our study supports previous research on the risk factors of snoring.

No significant difference in snoring prevalence between young boys and girls was seen, in agreement with some previous literature (Teculescu *et al.* 1992). Snoring frequency varies slightly among different age groups, being a bit more common among preschool-aged children than older ones (Kaditis *et al.* 2004, Liu *et al.* 2005). In our study, all children were preschool-aged, and the age discrepancy was small. This is likely to explain why no age related differences were noted.

The importance of large adenoids and tonsils, and a narrow upper airway structure are well documented causes of sleep-related breathing obstruction in children. Adenotonsillar hypertrophy is a known as a risk factor for children's snoring (Ferreira *et al.* 2000, Anuntaseree *et al.* 2001, Zhang *et al.* 2004, Au and Li 2009). In this study, the normal cohort was slightly biased, and snoring children (24%) had undergone adenoidectomy more often than non-snoring children. The overall adenoidectomy rate was 15% among the study population. Most of the adenoidec-

tomies were performed because of recurrent ear infections, not because of snoring. In Finland, the adenoidectomy rate for young children has been high relative to other countries (Van Den Akker *et al.* 2004, Karevold *et al.* 2007). These findings suggest that removal of adenoids might be often insufficient in treating snoring, and may reflect the importance of tonsils as a cause of snoring. (Liukkonen *et al.* 2008).

Although SDB obstruction is supposedly mostly caused by upper airway narrowing due to the lymphoid tissue in otherwise normal children, one of the unique feature in pediatric OSA is the high prevalence of different syndromes affecting facial appearance, facial growth, and muscle tone (Spier *et al.* 1986, Lo and Chen 1999, Hoeve *et al.* 2003, Pijpers *et al.* 2004, de Jong *et al.* 2010). Such children were not part of the cohort. Only one child had high OAH of 19.2/h. This girl snored sometimes and had large tonsils. Our study shows that sleep-related breathing disorder with clear PSG changes is rare in otherwise healthy preschool children. Although parents have reported nocturnal breathing cessation, PSG studies are usually normal without significant obstructive sleep apnea.

In our study, 33% of children had a smoking parent. Smoking, even passive smoking, is an independent risk factor for snoring in adults (Franklin *et al.* 2004). Children suffering from snoring are more likely to live in smoking households (Gozal and Pope 2001, Ersu *et al.* 2004). Ali *et al.* (1993) demonstrated a dose-response relationship between passive smoking and habitual snoring in children, especially for maternal smoking (Ali *et al.* 1993). Although a history of parental snoring indicates the role of heredity in development of snoring in young children (Redline *et al.* 1999, Kalra *et al.* 2006), the relationship we found between parental snoring and snoring in children could be explained at least in part by parental smoking.

Nasal measurements and cephalometry

Rhinomanometry is rarely used in the pediatric population. Rizzi *et al.* (Rizzi *et al.* 2002) found a clear correlation between apnea/hypopnea indices and nasal resistances in children with adenotonsillar hypertrophy. Acoustic rhinometry has been deemed suitable for the evaluation of nasal volumes in children (Qian *et al.* 2007, Haavisto and Sipila 2008). Upright nasal cavity and pharyngeal cavity measurements obtained by acoustic rhinometry were larger in the OSA group than in snorers (Okun *et al.* 2010). To date, large comparative studies between healthy children and children with SDB have not been published.

Cephalometric analyses are valuable tools in the comprehensive diagnosis of malocclusions and skeletal malformations in orthodontics (Athanasίου and Van der Meij 1995). Cephalometry has been used to some extent in studies of obstructive breathing in children, showing abnormal craniofacial growth in snoring and OSA children compared with healthy controls (Zucconi et al. 1999).

However, in this study, we found no evident correlations between PSG values and nasal rhinometric measurements or cephalometric measurements. In 2004, the European Commission released the guidelines on radiation protection in dental radiology. Individual risks in dental radiography are small, but are greater in the younger age groups (<30 years). Based on these guidelines, cephalometry cannot be recommended for children without adequate justification (European Guidelines on Radiation Protection in Dental Radiology 2004.) Our results do not give grounds for recommending rhinometric or cephalometric measurements when investigating SDB in children.

Polysomnography

Ambulatory polysomnography was performed at home. All cables were fixed at the hospital pediatric ENT unit. The child arrived in the evening with his/her parent to the pediatric unit. Attaching the device and cables took 1.5 h. After securing the device for a wireless connection, the family returned to their home. Parents were instructed to turn off the power the next morning, after which the child came back to the pediatric unit for the removal of the cables and the device. Overnight PSG was performed on 90 children; three recordings failed because of wires or sensors disconnection. SpO₂ recording was successful for all children, and the overall success for the recordings was estimated as good.

In general, the PSG of these snoring children revealed no major sleep-related breathing disorder, including partial upper airway obstruction. The results question the importance of PSG in the first-line management of suspected sleep-related upper airway obstruction in preschool children. PSG is a relatively expensive and sparsely available. Since adenotonsillectomy is a basic surgery that effectively treats snoring in otherwise healthy children, the study results with previously published literature supports this approach as first-line management; 80-90% of children recover from snoring and upper airway obstruction after adenotonsillectomy. (Brietzke and Gallagher 2006). PSG should be performed primarily if severe or more complicated sleep-related breathing disorder is suspected, or in children who remain symptomatic after TEA.

Neurobehavioral consequences

This study and previous studies indicate that snoring without episodes of obstructive apnea or SpO₂ desaturations may cause impairment in behavioral and neurocognitive functions (Blunden *et al.* 2000, Gottlieb *et al.* 2004). Similar findings were published by Barnes *et al.* (Barnes *et al.* 2009), who showed that occasionally snoring children scored higher, indicating more behavioral problems than their healthy age- and sex-matched controls. Beebe (Beebe *et al.* 2004) enrolled 17 snorers, 13 children with mild to severe OSA, and 17 healthy controls aged 6-12 years for PSG and neuropsychological tests. Their study failed to show clear correlations between PSG values and neuropsychological tests.

Snoring may impair neurocognitive functions and behavior in a several ways even without major sleep disruption, sleep deprivation, or SpO₂ desaturations. Partial upper airway obstruction might interfere with sleep homeostasis and increase energy consumption. However, since reliable measurement of partial upper airway obstruction requires measuring of breathing effort, this link remains largely unverified. We attempted to measure respiratory effort with a semi-quantitative diaphragm EMG, which has proved to be of clinical value. Partial upper airway obstruction was also estimated by using airflow shape and chin EMG muscle activity. However, the estimated ventilatory effort or the presence of partial upper airway resistance correlated poorly with the neurocognitive and behavioral test results, and thus, we failed to establish a link between partial airway obstruction and neurobehavioral consequences.

Another potential impairment is the presence of recurrent upper airway infections. PSG studies are normally performed during an infection-free period, as in our study. An upper airway obstruction is likely to become more severe during infection. If infections appear frequently, the breathing situation may actually be much worse than that observed during an infection-free period, where the child's breathing is non-obstructed. As a result, information on obstruction during sleep can be missed. We further tested the hypothesis that recurrent URIs might cause the observed neurocognitive and behavioral impairment. We found only minor differences showing children with recurrent URIs suffering more somatic problems. In the future, this hypothesis should be retested in larger patient populations. The PSG should also be performed during a period of upper respiratory infection.

LIMITATIONS OF THE STUDY

The clinical part of our study was conducted in subgroups of snoring and non-snoring children who had volunteered to participate. This may have biased the samples. Parents of children with more problems likely were more eager to volunteer for this type of study. However, this bias was probably present in both groups. Moreover, both groups had an overrepresentation of higher socioeconomic status families relative to the general population structure of Helsinki, and the snoring group included more families than the non-snoring group from socioeconomic class I. This limits the generalization of our results to populations with lower socioeconomic status families.

Our data on snoring frequency were based on parental reports and were not confirmed with objective measures. Also an important cultural context is that children in Finland usually do not sleep in the same room as their parents, and thus, some parents may be unaware of their child snoring. Discrepancies in parental perception of what snoring constitutes might be a confounding factor, but this factor would be present in both groups.

Obstructive sleep apnea seems to be rare in otherwise healthy children, in contrast to neurobehavioral symptoms, which are more common in snoring children. We believe that one of the reasons for limited correlations in our neurobehavioral studies was that PSG differences between the groups were small, with only 3 of 87 children having OAH1 over 5.0/hour. This might limit the results.

CONCLUSIONS

- 1) Snoring is common in preschool children in Finland and may persist after adenoidectomy. Obstructive sleep apnea is very rare among otherwise healthy children.
- 2) No correlation was observed between a child's age, gender, or obesity and SDB in normal cohort of children. Snoring children have more upper respiratory infections and acute otitis media infections. Snoring is associated with allergic rhinitis, parental snoring, and exposure to tobacco smoke.
- 3) Children with SDB do not have abnormal facial growth or abnormal nasal volume or resistance values compared with non-snoring children.
- 4) Snoring itself without PSG findings is related to impaired neurocognitive and behavioral function. The mechanism of action remains unknown.
- 5) Acoustic rhinometry is feasible and well tolerated among young children.

ACKNOWLEDGMENTS

This study was conducted at Helsinki University Hospital, Department of Otorhinolaryngology - Head and Neck Surgery in 2005-2010. My sincere gratitude is owed to everyone who guided and helped me during these years. I owe a debt of gratitude to the former head of the Department of Otorhinolaryngology - Head and Neck Surgery, Docent Hans Ramsay, now Chief of the Clinic Group, and to the present head, Docent Heikki Rihkanen.

My sincere gratitude is owed to my supervisors. Professor Anne Pitkäranta is thanked for her interest in my work, her invaluable advice, and her kind support throughout the study period. Docent Turkka Kirjavainen I warmly thank for guidance and unfailing encouragement. It has been a great privilege to share your vast knowledge in medicine and research. Thank you for your time, optimism, and patience.

I thank the official reviewers of this thesis, Professor Olli Polo and Docent Pirkko Ruoppi, for their prompt and constructive criticism, which greatly improved the content of the manuscript. Carol Ann Pelli is thanked for editing the language of the text.

I am very grateful to my coauthors, Eeva Aronen, MD, PhD, Paula Virkkula, MD, PhD, Anni Suomalainen, DDS, PhD, Petteri Simola, MA, and Anu Haavisto, MPs for valuable collaboration and for tutoring me in all practical matters connected to these studies. I would not have been able to perform the clinical and scientific work without their encouraging and skillful guidance.

My warmest thanks are extended to Heini Liukkonen for her devoted assistance as a research nurse in recruiting volunteers and organizing data collection, to Riitta Heino, Leena Juvonen and Eija Nenye for excellent technical assistance, to Timo Pessi for statistical advice, and to Olli Eloranta for helping me with the layout of this thesis.

I thank my present and former colleagues at the Department of Otorhinolaryngology for their help and encouragement during this project. It has been a great pleasure to work in the friendly and inspirational atmosphere of the unit. I am particularly grateful to Riitta Saarinen and Hanna Tervonen for down-to-earth discussions that always swept away anxiety and for their endless support. Without their positive attitude towards research, this thesis would not have been possible. I warmly thank all children and families for their participation in this study.

Finally, to my family, a resounding thank-you for supporting me and providing backup in everyday tasks during the course of this study. I especially thank my mom for taking care of my home and family when my hands were full. My husband Anssi and boys Miko and Santtu are thanked for bottomless patience. I am really looking forward to a summer without the computer!

This study was financially supported by the Helsinki University Central Hospital Funds (EVO), the Päivikki and Sakari Sohlberg Foundation, the Sigrid Juselius Foundation, and the Korvatautien tutkimussäätiö.

Helsinki, December 2011

A handwritten signature in black ink, consisting of a large, sweeping initial 'K' followed by a series of loops and a final flourish.

Katja Liukkonen

PARENTS AND SIBLINGS

35. Fathers snores
10b. Loudness of snoring (1 very quiet – 5 very loud)
36. Mother snores
10b. Loudness of snoring (1 very quiet – 5 very loud)
37. Siblings snore
10b. Loudness of snoring (1 very quiet – 5 very loud)
38. Father, mother or sibling have a diagnose of sleep apnea
39. Father, mother or sibling have nCPAP for treatment of sleep apnea
40. Are the parents smoking on a regular bases?
41. Child exposed to tobacco smoke regularly at home

1	2	3	4	5
1	2	3	4	5
1	2	3	4	5
1	2	3	4	5
1	2	3	4	5

☐ Father ☐ Mother

☐ Sibling

☐ Father ☐ Mother

☐ Sibling

☐ Father ☐ Mother

☐ Yes ☐ No

OTHER DISEASES AND CONDITIONS

42. Child has undergone adenoidectomy
42b. Indication for adenoidectomy
- 42c. Child's age at the time of the operation _____
43. Child has undergone tonsillectomy
43b. Indication for tonsillectomy
- 43c. Child's age at the time of the operation _____
44. Your child has recurrent upper airway infections (more than 5 infections/past 6 months) (flu, cough, sore throat: (never - often)
45. How many otitis media infections your child has had?
45b. How many tympanostomy tubes your child has had?
46. Has your child had any sinusitis?
47. Does your child have allergic rhinitis?
47b. Your child snores during allergic rhinitis
47c. Loudness of snoring during allergic rhinitis (1 very quiet – 5 very loud)
48. Child has a syndrome or facial abnormality
- Syndromes like Down, Crouzon, Robin, etc.
48b. Syndromes name: _____
49. The child has a chronic disease
- ADHD, diabetes, asthma, atopy, allergy, etc.
49b. Name _____
50. The child has regular medication
50b. Names : _____

☐ Yes ☐ No

☐ Infections

☐ Snoring

☐ Other

☐ Yes ☐ No

☐ Infections

☐ Snoring

☐ Other

1	2	3	4	5
0	1	2	3	≥4
0	1	2	3	≥4
0	1	2	3	≥4

☐ Yes ☐ No

☐ Yes ☐ No

1	2	3	4	5
---	---	---	---	---

☐ Yes ☐ No

☐ Yes ☐ No

☐ Yes ☐ No

ARE YOU WILLING TO CONTINUE FURTHER WITH THIS RESEARCH PROJECT?

51. In the case your child is not snoring, are you willing to participated further with this research project and continue with sleep recording at home?

☐ Yes ☐ No

Parents names: _____

Tel: _____ E-mail: _____

Address: _____

REFERENCES

- Achenbach, T. M. and Rescorla, L. A. (2000). Manual for the ASEBA preschool forms & profiles. Burlington, VT: University of Vermont, Research Center of Children, Youth & Families
- Ali, N. J., Pitson, D. J. and Stradling, J. R. (1993). Snoring, sleep disturbance, and behaviour in 4-5 year olds. *Arch.Dis.Child.*, vol. 68, 3: 360-6
- Aljadeff, G., Gozal, D., Schechtman, V. L., *et al.* (1997). Heart rate variability in children with obstructive sleep apnea. *Sleep*, vol. 20, 2: 151-7
- Ameli, F., Brocchetti, F., Semino, L., *et al.* (2007). Adenotonsillectomy in obstructive sleep apnea syndrome. Proposal of a surgical decision-taking algorithm. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 71, 5: 729-34
- American Thoracic Society (1999). Cardiorespiratory sleep studies in children. Establishment of normative data and polysomnographic predictors of morbidity. *Am.J.Respir.Crit.Care Med.*, vol. 160, 4: 1381-7
- Amin, R. S., Kimball, T. R., Kalra, M., *et al.* (2005). Left ventricular function in children with sleep-disordered breathing. *Am.J.Cardiol.*, vol. 95, 6: 801-4
- Amin, R. S., Carroll, J. L., Jeffries, J. L., *et al.* (2004). Twenty-four-hour ambulatory blood pressure in children with sleep-disordered breathing. *Am.J.Respir.Crit.Care Med.*, vol. 169, 8: 950-6
- Anuntaseree, W., Kuasirikul, S. and Suntornlohanakul, S. (2005). Natural history of snoring and obstructive sleep apnea in Thai school-age children. *Pediatr.Pulmonol.*, vol. 39, 5: 415-20
- Anuntaseree, W., Rookkapan, K., Kuasirikul, S., *et al.* (2001). Snoring and obstructive sleep apnea in Thai school-age children: prevalence and predisposing factors. *Pediatr.Pulmonol.*, vol. 32, 3: 222-7
- Arens, R. and Marcus, C. L. (2004). Pathophysiology of upper airway obstruction: a developmental perspective. *Sleep*, vol. 27, 5: 997-1019
- Arens, R., McDonough, J. M., Corbin, A. M., *et al.* (2003). Upper airway size analysis by magnetic resonance imaging of children with obstructive sleep apnea syndrome. *Am.J.Respir.Crit.Care Med.*, vol. 167, 1: 65-70
- Arens, R., McDonough, J. M., Costarino, A. T., *et al.* (2001). Magnetic resonance imaging of the upper airway structure of children with obstructive sleep apnea syndrome. *Am.J.Respir.Crit.Care Med.*, vol. 164, 4: 698-703
- Aronen, E. T., Liukkonen, K., Simola, P., *et al.* (2009). Mood is associated with snoring in preschool-aged children. *J.Dev.Behav.Pediatr.*, vol. 30, 2: 107-14
- Arrarte, J., Lubianca Neto, J. F. and Fischer, G. B. (2007). The effect of adenotonsillectomy on oxygen saturation in children with sleep breathing disorders. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 71, 6: 973-8
- Atef, A., Zeid, I. A., Qotb, M., *et al.* (2009). Effect of passive smoking on ciliary regeneration of nasal mucosa after functional endoscopic sinus surgery in children. *J.Laryngol.Otol.*, vol. 123, 1: 75-9
- Athanasiou, A. E. and Van der Meij, A. W. (1995). Possibilities and limitations of various cephalometric variables and analyses. In: *Orthodontic cephalometry*.
- Au, C. T. and Li, A. M. (2009). Obstructive sleep breathing disorders. *Pediatr.Clin.North Am.*, vol. 56, 1: 243,59, xii
- Bahadir, O., Caylan, R., Bektas, D., *et al.* (2006). Effects of adenoidectomy in children with symptoms of adenoidal hypertrophy. *Eur.Arch.Otorhinolaryngol.*, vol. 263, 2: 156-9
- Baharav, A., Kotagal, S., Rubin, B. K., *et al.* (1999). Autonomic cardiovascular control in children with obstructive sleep apnea. *Clin.Auton.Res.*, vol. 9, 6: 345-51
- Banabilh, S. M., Asha'ari, Z. A. and Hamid, S. S. (2008). Prevalence of snoring and craniofacial features in Malaysian children from hospital-based medical clinic population. *Sleep Breath*, vol. 12, 3: 269-74
- Bar, A., Tarasiuk, A., Segev, Y., *et al.* (1999). The effect of adenotonsillectomy on serum insulin-like growth factor-I and growth in children with obstructive sleep apnea syndrome. *J.Pediatr.*, vol. 135, 1: 76-80
- Barnes, M. E., Huss, E. A., Garrod, K. N., *et al.* (2009). Impairments in attention in occasionally snoring children: an event-related potential study. *Dev.Neuropsychol.*, vol. 34, 5: 629-49
- Bass, J. L., Corwin, M., Gozal, D., *et al.* (2004). The effect of chronic or intermittent hypoxia on cognition in childhood: a review of the evidence. *Pediatrics*, vol. 114, 3: 805-16
- Bassetti, C. L., Milanova, M. and Gugger, M. (2006). Sleep-disordered breathing and acute ischemic stroke: diagnosis, risk factors, treatment, evolution, and long-term clinical outcome. *Stroke*, vol. 37, 4: 967-72
- Beebe, D. W., Wells, C. T., Jeffries, J., *et al.* (2004). Neuropsychological effects of pediatric obstructive sleep apnea. *J.Int.Neuropsychol.Soc.*, vol. 10, 7: 962-75
- Beebe, D. W. and Gozal, D. (2002). Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. *J.Sleep Res.*, vol. 11, 1: 1-16
- Benowitz, N. L., Kuyt, F., Jacob, P., 3rd, *et al.* (1983). Cotinine disposition and effects. *Clin.Pharmacol.Ther.*, vol. 34, 5: 604-11
- Benowitz, N. L., Jacob, P., 3rd, Jones, R. T., *et al.* (1982). Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. *J.Pharmacol.Exp.Ther.*, vol. 221, 2: 368-72
- Berry, R. B. and Gleeson, K. (1997). Respiratory arousal from sleep: mechanisms and significance. *Sleep*, vol. 20, 8: 654-75

- Bhattacharjee, R., Kheirandish-Gozal, L., Pillar, G., *et al.* (2009). Cardiovascular complications of obstructive sleep apnea syndrome: evidence from children. *Prog.Cardiovasc.Dis.*, vol. 51, 5: 416-33
- Bicakci, A. A., Agar, U., Sokucu, O., *et al.* (2005). Nasal airway changes due to rapid maxillary expansion timing. *Angle Orthod.*, vol. 75, 1: 1-6
- Bixler, E. O., Vgontzas, A. N., Lin, H. M., *et al.* (2009). Sleep disordered breathing in children in a general population sample: prevalence and risk factors. *Sleep*, vol. 32, 6: 731-6
- Blunden, S., Lushington, K., Kennedy, D., *et al.* (2000). Behavior and neurocognitive performance in children aged 5-10 years who snore compared to controls. *J.Clin.Exp.Neuropsychol.*, vol. 22, 5: 554-68
- Boselli, M., Parrino, L., Smerieri, A., *et al.* (1998). Effect of age on EEG arousals in normal sleep. *Sleep*, vol. 21, 4: 351-7
- Bouchard, C., Troulis, M. J. and Kaban, L. B. (2009). Management of obstructive sleep apnea: role of distraction osteogenesis. *Oral Maxillofac.Surg.Clin.North.Am.*, vol. 21, 4: 459-75
- Brietzke, S. E. and Gallagher, D. (2006). The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: a meta-analysis. *Otolaryngol.Head Neck Surg.*, vol. 134, 6: 979-84
- Brietzke, S. E., Katz, E. S. and Roberson, D. W. (2004). Can history and physical examination reliably diagnose pediatric obstructive sleep apnea/hypopnea syndrome? A systematic review of the literature. *Otolaryngol.Head Neck Surg.*, vol. 131, 6: 827-32
- Brodsky, L. (1989). Modern assessment of tonsils and adenoids. *Pediatr.Clin.North Am.*, vol. 36, 6: 1551-69
- Broms, P., Jonson, B. and Lamm, C. J. (1982). Rhinomanometry. II. A system for numerical description of nasal airway resistance. *Acta Otolaryngol.*, vol. 94, 1-2: 157-68
- Brooks, L. J., Stephens, B. M. and Bacevice, A. M. (1998). Adenoid size is related to severity but not the number of episodes of obstructive apnea in children. *J.Pediatr.*, vol. 132, 4: 682-6
- Brooks, L. J. and Strohl, K. P. (1992). Size and mechanical properties of the pharynx in healthy men and women. *Am.Rev.Respir.Dis.*, vol. 146, 6: 1394-7
- Brouillette, R., Hanson, D., David, R., *et al.* (1984). A diagnostic approach to suspected obstructive sleep apnea in children. *J.Pediatr.*, vol. 105, 1: 10-4
- Brouillette, R. T., Manoukian, J. J., Ducharme, F. M., *et al.* (2001). Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea. *J.Pediatr.*, vol. 138, 6: 838-44
- Brouillette, R. T., Morielli, A., Leimanis, A., *et al.* (2000). Nocturnal pulse oximetry as an abbreviated testing modality for pediatric obstructive sleep apnea. *Pediatrics*, vol. 105, 2: 405-12
- Brouillette, R. T., Fernbach, S. K. and Hunt, C. E. (1982). Obstructive sleep apnea in infants and children. *J.Pediatr.*, vol. 100, 1: 31-40
- Bruni, O., Ottaviano, S., Guidetti, V., *et al.* (1996). The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *J.Sleep Res.*, vol. 5, 4: 251-61
- Calhoun, S. L., Mayes, S. D., Vgontzas, A. N., *et al.* (2009). No relationship between neurocognitive functioning and mild sleep disordered breathing in a community sample of children. *J.Clin.Sleep Med.*, vol. 5, 3: 228-34
- Can, I. H., Ceylan, K., Bayiz, U., *et al.* (2005). Acoustic rhinometry in the objective evaluation of childhood septoplasties. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 69, 4: 445-8
- Carroll, J. L., McColley, S. A., Marcus, C. L., *et al.* (1995). Inability of clinical history to distinguish primary snoring from obstructive sleep apnea syndrome in children. *Chest*, vol. 108, 3: 610-8
- Centers for Disease Control and Prevention (<http://www.cdc.gov/>)
- Chaicham, J., Lin, Z., Chen, M. L., *et al.* (2009). Model-based assessment of cardiovascular autonomic control in children with obstructive sleep apnea. *Sleep*, vol. 32, 7: 927-38
- Chervin, R. D., Weatherly, R. A., Garetz, S. L., *et al.* (2007). Pediatric sleep questionnaire: prediction of sleep apnea and outcomes. *Arch.Otolaryngol.Head.Neck.Surg.*, vol. 133, 3: 216-22
- Chervin, R. D., Weatherly, R. A., Ruzicka, D. L., *et al.* (2006). Subjective sleepiness and polysomnographic correlates in children scheduled for adenotonsillectomy vs other surgical care. *Sleep*, vol. 29, 4: 495-503
- Chervin, R. D., Hedger, K., Dillon, J. E., *et al.* (2000). Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. *Sleep Med.*, vol. 1, 1: 21-32
- Chng, S. Y., Goh, D. Y., Wang, X. S., *et al.* (2004). Snoring and atopic disease: a strong association. *Pediatr. Pulmonol.*, vol. 38, 3: 210-6
- Ciprandi, G., Tosca, M. A., Marseglia, G. L., *et al.* (2005). Relationships between allergic inflammation and nasal airflow in children with seasonal allergic rhinitis. *Ann.Allergy Asthma Immunol.*, vol. 94, 2: 258-61
- Clement, P. A., Gordts, F. and Standardisation Committee on Objective Assessment of the Nasal Airway, IRS, and ERS. (2005). Consensus report on acoustic rhinometry and rhinomanometry. *Rhinology*, vol. 43, 3: 169-79
- Clement, P. A. (1984). Committee report on standardization of rhinomanometry. *Rhinology*, vol. 22, 3: 151-5
- Cohen, S. R., Suzman, K., Simms, C., *et al.* (1998). Sleep apnea surgery versus tracheostomy in children: an exploratory study of the comparative effects on quality of life. *Plast.Reconstr.Surg.*, vol. 102, 6: 1855-64
- Compadretti, G. C., Tasca, I. and Bonetti, G. A. (2006). Nasal airway measurements in children treated by rapid maxillary expansion. *Am.J.Rhinol.*, vol. 20, 4: 385-93
- Constantin, E., Tewfik, T. L. and Brouillette, R. T. (2010). Can the OSA-18 quality-of-life questionnaire detect obstructive sleep apnea in children? *Pediatrics*, vol. 125, 1: e162-8

- Constantin, E., McGregor, C. D., Cote, V., *et al.* (2008). Pulse rate and pulse rate variability decrease after adenotonsillectomy for obstructive sleep apnea. *Pediatr.Pulmonol.*, vol. 43, 5: 498-504
- Conway, W. A., Victor, L. D., Magilligan, D. J., Jr, *et al.* (1981). Adverse effects of tracheostomy for sleep apnea. *JAMA*, vol. 246, 4: 347-50
- Corbo, G. M., Fuciarelli, F., Foresi, A., *et al.* (1989). Snoring in children: association with respiratory symptoms and passive smoking. *BMJ*, vol. 299, 6714: 1491-4
- Davis, C. L., Tkacz, J., Gregoski, M., *et al.* (2006). Aerobic exercise and snoring in overweight children: a randomized controlled trial. *Obesity (Silver Spring)*, vol. 14, 11: 1985-91
- de Jong, T., Bannink, N., Bredero-Boelhouwer, H. H., *et al.* (2010). Long-term functional outcome in 167 patients with syndromic craniosynostosis; defining a syndrome-specific risk profile. *J.Plast.Reconstr. Aesthet.Surg.*, vol. 3,10: 1635-41
- de la Chaux, R., Klemens, C., Patscheider, M., *et al.* (2008). Tonsillotomy in the treatment of obstructive sleep apnea syndrome in children: polysomnographic results. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 72, 9: 1411-7
- de Serres, L. M., Derkay, C., Astley, S., *et al.* (2000). Measuring quality of life in children with obstructive sleep disorders. *Arch.Otolaryngol.Head.Neck.Surg.*, vol. 126, 12: 1423-9
- Demain, J. G. and Goetz, D. W. (1995). Pediatric adenoidal hypertrophy and nasal airway obstruction: reduction with aqueous nasal beclomethasone. *Pediatrics*, vol. 95, 3: 355-64
- Djupesland, P. and Pedersen, O. F. (2000). Acoustic rhinometry in infants and children. *Rhinol.Suppl.*, vol. 16, : 52-8
- Djupesland, P., Kaastad, E. and Franzen, G. (1997). Acoustic rhinometry in the evaluation of congenital choanal malformations. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 41, 3: 319-37
- Doruk, C., Sokucu, O., Bicakci, A. A., *et al.* (2007). Comparison of nasal volume changes during rapid maxillary expansion using acoustic rhinometry and computed tomography. *Eur.J.Orthod.*, vol. 29, 3: 251-5
- Downey, R., 3rd, Perkin, R. M. and MacQuarrie, J. (2000). Nasal continuous positive airway pressure use in children with obstructive sleep apnea younger than 2 years of age. *Chest*, vol. 117, 6: 1608-12
- Eitner, S., Urschitz, M. S., Guenther, A., *et al.* (2007). Sleep problems and daytime somnolence in a German population-based sample of snoring school-aged children. *J.Sleep Res.*, vol. 16, 1: 96-101
- Enoki, C., Valera, F. C., Lessa, F. C., *et al.* (2006). Effect of rapid maxillary expansion on the dimension of the nasal cavity and on nasal air resistance. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 70, 7: 1225-30
- Ersoy, B., Yuceturk, A. V., Taneli, F., *et al.* (2005). Changes in growth pattern, body composition and biochemical markers of growth after adenotonsillectomy in prepubertal children. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 69, 9: 1175-81
- Ersu, R., Arman, A. R., Save, D., *et al.* (2004). Prevalence of snoring and symptoms of sleep-disordered breathing in primary school children in istanbul. *Chest*, vol. 126, 1: 19-24
- European Comission (2004). European guidelines on radiation protection in dental radiology. http://ec.europa.eu/energy/nuclear/radioprotection/publication/doc/136_en.pdf
- Everett, A. D., Koch, W. C. and Saulsbury, F. T. (1987). Failure to thrive due to obstructive sleep apnea. *Clin.Pediatr.(Phila)*, vol. 26, 2: 90-2
- Ferreira, A. M., Clemente, V., Gozal, D., *et al.* (2000). Snoring in Portuguese primary school children. *Pediatrics*, vol. 106, 5: E64
- Ferreira, V. R., Carvalho, L. B., Ruotolo, F., *et al.* (2009). Sleep disturbance scale for children: translation, cultural adaptation, and validation. *Sleep Med.*, vol. 10, 4: 457-63
- Finkelstein, Y., Wexler, D., Berger, G., *et al.* (2000). Anatomical basis of sleep-related breathing abnormalities in children with nasal obstruction. *Arch.Otolaryngol.Head.Neck.Surg.*, vol. 126, 5: 593-600
- Florescu, A., Ferrence, R., Einarson, T., *et al.* (2009). Methods for quantification of exposure to cigarette smoking and environmental tobacco smoke: focus on developmental toxicology. *Ther.Drug Monit.*, vol. 31, 1: 14-30
- Franco, R. A., Jr, Rosenfeld, R. M. and Rao, M. (2000). First place--resident clinical science award 1999. Quality of life for children with obstructive sleep apnea. *Otolaryngol.Head.Neck.Surg.*, vol. 123, 1 Pt 1: 9-16
- Franklin, K. A., Gislason, T., Omenaas, E., *et al.* (2004). The influence of active and passive smoking on habitual snoring. *Am.J.Respir.Crit.Care Med.*, vol. 170, 7: 799-803
- Friberg, D., Sundquist, J., Li, X., *et al.* (2009). Sibling risk of pediatric obstructive sleep apnea syndrome and adenotonsillar hypertrophy. *Sleep*, vol. 32, 8: 1077-83
- Fujioka, M., Young, L. W. and Girdany, B. R. (1979). Radiographic evaluation of adenoidal size in children: adenoidal-nasopharyngeal ratio. *AJR Am.J.Roentgenol.*, vol. 133, 3: 401-4
- Geddes, L. A., Voelz, M. H., Babbs, C. F., *et al.* (1981). Pulse transit time as an indicator of arterial blood pressure. *Psychophysiology*, vol. 18, 1: 71-4
- Georgalas, C., Tolley, N. and Kanagalingam, J. (2004). Measuring quality of life in children with adenotonsillar disease with the Child Health Questionnaire: a first U.K. study. *Laryngoscope*, vol. 114, 10: 1849-55
- Giordani, B., Hodges, E. K., Guire, K. E., *et al.* (2008). Neuropsychological and behavioral functioning in children with and without obstructive sleep apnea referred for tonsillectomy. *J.Int.Neuropsychol.Soc.*, vol. 14, 4: 571-81

- Gislason, T. and Benediktsdottir, B. (1995). Snoring, apneic episodes, and nocturnal hypoxemia among children 6 months to 6 years old. An epidemiologic study of lower limit of prevalence. *Chest*, vol. 107, 4: 963-6
- Goh, D. Y., Galster, P. and Marcus, C. L. (2000). Sleep architecture and respiratory disturbances in children with obstructive sleep apnea. *Am.J.Respir.Crit.Care Med.*, vol. 162, 2 Pt 1: 682-6
- Goldbart, A. D., Krishna, J., Li, R. C., *et al.* (2006). Inflammatory mediators in exhaled breath condensate of children with obstructive sleep apnea syndrome. *Chest*, vol. 130, 1: 143-8
- Goldbart, A. D., Goldman, J. L., Veling, M. C., *et al.* (2005a). Leukotriene modifier therapy for mild sleep-disordered breathing in children. *Am.J.Respir.Crit.Care Med.*, vol. 172, 3: 364-70
- Goldbart, A. D., Veling, M. C., Goldman, J. L., *et al.* (2005b). Glucocorticoid receptor subunit expression in adenotonsillar tissue of children with obstructive sleep apnea. *Pediatr.Res.*, vol. 57, 2: 232-6
- Goldstein, N. A., Fatima, M., Campbell, T. F., *et al.* (2002). Child behavior and quality of life before and after tonsillectomy and adenoidectomy. *Arch.Otolaryngol.Head.Neck.Surg.*, vol. 128, 7: 770-5
- Goodwin, J. L., Kaemingk, K. L., Fregosi, R. F., *et al.* (2003). Clinical outcomes associated with sleep-disordered breathing in Caucasian and Hispanic children--the Tucson Children's Assessment of Sleep Apnea study (TuCASA). *Sleep*, vol. 26, 5: 587-91
- Gottlieb, D. J., Chase, C., Vezina, R. M., *et al.* (2004). Sleep-disordered breathing symptoms are associated with poorer cognitive function in 5-year-old children. *J.Pediatr.*, vol. 145, 4: 458-64
- Gottlieb, D. J., Yao, Q., Redline, S., *et al.* (2000). Does snoring predict sleepiness independently of apnea and hypopnea frequency? *Am.J.Respir.Crit.Care Med.*, vol. 162, 4 Pt 1: 1512-7
- Gozal, D. (2009). Sleep, sleep disorders and inflammation in children. *Sleep Med.*, vol. 10 Suppl 1, : S12-6
- Gozal, D., Crabtree, V. M., Sans Capdevila, O., *et al.* (2007). C-reactive protein, obstructive sleep apnea, and cognitive dysfunction in school-aged children. *Am.J.Respir.Crit.Care Med.*, vol. 176, 2: 188-93
- Gozal, D. and Kheirandish, L. (2006). Oxidant stress and inflammation in the snoring child: confluent pathways to upper airway pathogenesis and end-organ morbidity. *Sleep Med.Rev.*, vol. 10, 2: 83-96
- Gozal, D., Daniel, J. M. and Dohanich, G. P. (2001). Behavioral and anatomical correlates of chronic episodic hypoxia during sleep in the rat. *J.Neurosci.*, vol. 21, 7: 2442-50
- Gozal, D. (2001). Morbidity of obstructive sleep apnea in children: facts and theory. *Sleep Breath.*, vol. 5, 1: 35-42
- Gozal, D. and Pope, D. W., Jr. (2001). Snoring during early childhood and academic performance at ages thirteen to fourteen years. *Pediatrics*, vol. 107, 6: 1394-9
- Griffiths, A., Maul, J., Wilson, A., *et al.* (2005). Improved detection of obstructive events in childhood sleep apnoea with the use of the nasal cannula and the differentiated sum signal. *J.Sleep Res.*, vol. 14, 4: 431-6
- Grigg-Damberger, M., Gozal, D., Marcus, C. L., *et al.* (2007). The visual scoring of sleep and arousal in infants and children. *J.Clin.Sleep Med.*, vol. 3, 2: 201-40
- Guilleminault, C., Huang, Y. S., Glamann, C., *et al.* (2007). Adenotonsillectomy and obstructive sleep apnea in children: a prospective survey. *Otolaryngol.Head.Neck.Surg.*, vol. 136, 2: 169-75
- Guilleminault, C., Li, K., Khrantsov, A., *et al.* (2004). Breathing patterns in prepubertal children with sleep-related breathing disorders. *Arch.Pediatr.Adolesc.Med.*, vol. 158, 2: 153-61
- Haavisto, L. E. and Sipila, J. I. (2008). Acoustic rhinometry in children: some practical aspects and influence of age and body surface area on results. *Am.J.Rhinol.*, vol. 22, 4: 416-9
- Halbower, A. C., Degaonkar, M., Barker, P. B., *et al.* (2006). Childhood obstructive sleep apnea associates with neuropsychological deficits and neuronal brain injury. *PLoS Med.*, vol. 3, 8: e301
- Harrington, C., Kirjavainen, T., Teng, A., *et al.* (2003). nCPAP improves abnormal autonomic function in at-risk-for-SIDS infants with OSA. *J Appl Physiol.*, vol. 95, 4: 1591-7
- Hilberg, O. and Pedersen, O. F. (2000). Acoustic rhinometry: recommendations for technical specifications and standard operating procedures. *Rhinol.Suppl.*, vol. 16, : 3-17
- Hilberg, O., Jackson, A. C., Swift, D. L., *et al.* (1989). Acoustic rhinometry: evaluation of nasal cavity geometry by acoustic reflection. *J.Appl.Physiol.*, vol. 66, 1: 295-303
- Hoeve, L. J., Pijpers, M. and Joosten, K. F. (2003). OSAS in craniofacial syndromes: an unsolved problem. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 67 Suppl 1, : S111-3
- Hultcrantz, E., Linder, A. and Markstrom, A. (1999). Tonsillectomy or tonsillotomy? A randomized study comparing postoperative pain and long-term effects. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 51, 3: 171-6
- Hultcrantz, E., Lofstrand-Tidestrom, B. and Ahlquist-Rastad, J. (1995). The epidemiology of sleep related breathing disorder in children. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 32 Suppl, : S63-6
- Iber, C., Ancoli-Israel, S. and Chesson, A. L. and Quan, S. F. (2007). *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications*, 1st edn.
- Ievers-Landis, C. E. and Redline, S. (2007). Pediatric sleep apnea: implications of the epidemic of childhood overweight. *Am.J.Respir.Crit.Care Med.*, vol. 175, 5: 436-41
- Johansson, A., Ludvigsson, J. and Hermansson, G. (2008). Adverse health effects related to tobacco smoke exposure in a cohort of three-year olds. *Acta Paediatr.*, vol. 97, 3: 354-7
- Joshua, B., Bahar, G., Sulkes, J., *et al.* (2006). Adenoidectomy: long-term follow-up. *Otolaryngol.Head Neck Surg.*, vol. 135, 4: 576-80

- Kaditis, A. G., Alexopoulos, E. I., Damani, E., *et al.* (2009). Urine levels of catecholamines in Greek children with obstructive sleep-disordered breathing. *Pediatr.Pulmonol.*, vol. 44, 1: 38-45
- Kaditis, A. G., Alexopoulos, E. I., Hatzi, F., *et al.* (2008). Adiposity in relation to age as predictor of severity of sleep apnea in children with snoring. *Sleep Breath*, vol. 12, 1: 25-31
- Kaditis, A. G., Alexopoulos, E. I., Kostadima, E., *et al.* (2005). Comparison of blood pressure measurements in children with and without habitual snoring. *Pediatr.Pulmonol.*, vol. 39, 5: 408-14
- Kaditis, A. G., Finder, J., Alexopoulos, E. I., *et al.* (2004). Sleep-disordered breathing in 3,680 Greek children. *Pediatr.Pulmonol.*, vol. 37, 6: 499-509
- Kalra, M., Lemasters, G., Bernstein, D., *et al.* (2006). Atopy as a risk factor for habitual snoring at age 1 year. *Chest*, vol. 129, 4: 942-6
- Karevold, G., Haapkyla, J., Pitkaranta, A., *et al.* (2007). Otitis media surgery: Large variability between Finland and Norway. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 71, 7: 1035-9
- Katz, E. S. and D'Ambrosio, C. M. (2008). Pathophysiology of pediatric obstructive sleep apnea. *Proc. Am.Thorac.Soc.*, vol. 5, 2: 253-62
- Katz, E. S., Lutz, J., Black, C., *et al.* (2003). Pulse transit time as a measure of arousal and respiratory effort in children with sleep-disordered breathing. *Pediatr.Res.*, vol. 53, 4: 580-8
- Kawashima, S., Peltomaki, T., Sakata, H., *et al.* (2003). Absence of facial type differences among preschool children with sleep-related breathing disorder. *Acta Odontol.Scand.*, vol. 61, 2: 65-71
- Kawashima, S., Niikuni, N., Chia-hung, L., *et al.* (2000). Cephalometric comparisons of craniofacial and upper airway structures in young children with obstructive sleep apnea syndrome. *Ear Nose Throat J.*, vol. 79, 7: 499,502, 505-6
- Kennedy, J. D., Blunden, S., Hirte, C., *et al.* (2004). Reduced neurocognition in children who snore. *Pediatr. Pulmonol.*, vol. 37, 4: 330-7
- Kerstein, R., Stimpson, P., Caulfield, H., *et al.* (2009). Iron deficiency and sleep disordered breathing in children--cause or effect? *Int.J.Pediatr.Otorhinolaryngol.*, vol. 73, 2: 275-80
- Kheirandish, L., Goldbart, A. D. and Gozal, D. (2006). Intranasal steroids and oral leukotriene modifier therapy in residual sleep-disordered breathing after tonsillectomy and adenoidectomy in children. *Pediatrics*, vol. 117, 1: e61-6
- Kheirandish, L. and Gozal, D. (2006). Neurocognitive dysfunction in children with sleep disorders. *Dev.Sci.*, vol. 9, 4: 388-99
- Kheirandish-Gozal, L. and Gozal, D. (2008). Intranasal budesonide treatment for children with mild obstructive sleep apnea syndrome. *Pediatrics*, vol. 122, 1: e149-55
- Kim, J., Bhattacharjee, R., Dayyat, E., *et al.* (2009). Increased cellular proliferation and inflammatory cytokines in tonsils derived from children with obstructive sleep apnea. *Pediatr.Res.*, vol. 66, 4: 423-8
- Kirjavainen, M. and Kirjavainen, T. (2003). Maxillary expansion in Class II correction with orthopedic cervical headgear. A posteroanterior cephalometric study. *Angle Orthod.*, vol. 73, 3: 281-5
- Kirk, V. G., Bohn, S. G., Flemons, W. W., *et al.* (2003). Comparison of home oximetry monitoring with laboratory polysomnography in children. *Chest*, vol. 124, 5: 1702-8
- Kobayashi, M., Ukai, K., Tatematsu, M., *et al.* (2001). Late phase responses after nasal challenges with allergen and histamine in asthmatic children with perennial nasal allergy. *Auris Nasus Larynx*, vol. 28, 4: 305-10
- Kohler, M., Lushington, K., Couper, R., *et al.* (2008). Obesity and risk of sleep related upper airway obstruction in Caucasian children. *J.Clin.Sleep Med.*, vol. 4, 2: 129-36
- Kohler, M. J. and van den Heuvel, C. J. (2008). Is there a clear link between overweight/obesity and sleep disordered breathing in children? *Sleep Med.Rev.*, vol. 12, 5: 347,61; discussion 363-4
- Kooi, E. M., Vrijlandt, E. J., Boezen, H. M., *et al.* (2004). Children with smoking parents have a higher airway resistance measured by the interruption technique. *Pediatr.Pulmonol.*, vol. 38, 5: 419-24
- Korkman, M., Kirk, U. and Kemp, S. (1998). NEPSY – A developmental neuropsychological assessment manual. U.S.: The Psychological Corporation.
- Kryger, M. H., Roth, T. and Dement, W. C. (2005). Principles and Practice of Sleep Medicine. , vol. , 117: 1378
- Kuehni, C. E., Strippoli, M. P., Chauliac, E. S., *et al.* (2008). Snoring in preschool children: prevalence, severity and risk factors. *Eur.Respir.J.*, vol. 31, 2: 326-33
- Kulnis, R., Nelson, S., Strohl, K., *et al.* (2000). Cephalometric assessment of snoring and nonsnoring children. *Chest*, vol. 118, 3: 596-603
- Kwok, K. L., Ng, D. K. and Cheung, Y. F. (2003). BP and arterial distensibility in children with primary snoring. *Chest*, vol. 123, 5: 1561-6
- Li, A. M., Au, C. T., Ho, C., *et al.* (2009). Blood pressure is elevated in children with primary snoring. *J.Pediatr.*, vol. 155, 3: 362-8
- Li, A. M., Au, C. T., Sung, R. Y., *et al.* (2008). Ambulatory blood pressure in children with obstructive sleep apnoea: a community based study. *Thorax*, vol. 63, 9: 803-9
- Lin, S. Y., Halbower, A. C., Tunkel, D. E., *et al.* (2006). Relief of upper airway obstruction with mandibular distraction surgery: Long-term quantitative results in young children. *Arch.Otolaryngol.Head.Neck.Surg.*, vol. 132, 4: 437-41
- Liu, X., Ma, Y., Wang, Y., *et al.* (2005). Brief report: An epidemiologic survey of the prevalence of sleep disorders among children 2 to 12 years old in Beijing, China. *Pediatrics*, vol. 115, 1 Suppl: 266-8
- Liukkonen, K., Virkkula, P., Aronen, E. T., *et al.* (2008). All snoring is not adenoids in young children. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 72, 6: 879-84

- Liukkonen, K., Virkkula, P. and Pitkaranta, A. (2006). Acoustic rhinometry in small children. *Rhinology*, vol. 44, 2: 160-3
- Lo, L. J. and Chen, Y. R. (1999). Airway obstruction in severe syndromic craniosynostosis. *Ann.Plast.Surg.*, vol. 43, 3: 258-64
- Maclean, J. E., Waters, K., Fitzsimons, D., *et al.* (2009). Screening for obstructive sleep apnea in preschool children with cleft palate. *Cleft Palate.Craniofac.J.*, vol. 46, 2: 117-23
- Mallampati, S. R., Gatt, S. P., Gugino, L. D., *et al.* (1985). A clinical sign to predict difficult tracheal intubation: a prospective study. *Can.Anaesth.Soc.J.*, vol. 32, 4: 429-34
- Marcus, C. L., Katz, E. S., Lutz, J., *et al.* (2005). Upper airway dynamic responses in children with the obstructive sleep apnea syndrome. *Pediatr.Res.*, vol. 57, 1: 99-107
- Marcus, C. L., Lutz, J., Hamer, A., *et al.* (1999). Developmental changes in response to subatmospheric pressure loading of the upper airway. *J.Appl.Physiol.*, vol. 87, 2: 626-33
- Marcus, C. L., Greene, M. G. and Carroll, J. L. (1998). Blood pressure in children with obstructive sleep apnea. *Am.J.Respir.Crit.Care Med.*, vol. 157, 4 Pt 1: 1098-103
- Marcus, C. L. (1997). Management of obstructive sleep apnea in childhood. *Curr.Opin.Pulm.Med.*, vol. 3, 6: 464-9
- Marcus, C. L., Carroll, J. L., Koerner, C. B., *et al.* (1994). Determinants of growth in children with the obstructive sleep apnea syndrome. *J.Pediatr.*, vol. 125, 4: 556-62
- Marques, V. C. and Anselmo-Lima, W. T. (2004). Pre- and postoperative evaluation by acoustic rhinometry of children submitted to adenoidectomy or adenotonsillectomy. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 68, 3: 311-6
- Marshall, N. S., Almquist, C., Grunstein, R. R., *et al.* (2007). Predictors for snoring in children with rhinitis at age 5. *Pediatr.Pulmonol.*, vol. 42, 7: 584-91
- McNamara, F., Issa, F. G. and Sullivan, C. E. (1996). Arousal pattern following central and obstructive breathing abnormalities in infants and children. *J.Appl.Physiol.*, vol. 81, 6: 2651-7
- Melendres, M. C., Lutz, J. M., Rubin, E. D., *et al.* (2004). Daytime sleepiness and hyperactivity in children with suspected sleep-disordered breathing. *Pediatrics*, vol. 114, 3: 768-75
- Mitchell, R. B. (2007). Adenotonsillectomy for obstructive sleep apnea in children: outcome evaluated by pre- and postoperative polysomnography. *Laryngoscope*, vol. 117, 10: 1844-54
- Mitchell, R. B. and Kelly, J. (2005). Quality of life after adenotonsillectomy for SDB in children. *Otolaryngol.Head.Neck.Surg.*, vol. 133, 4: 569-72
- Mitchell, R. B., Kelly, J., Call, E., *et al.* (2004a). Quality of life after adenotonsillectomy for obstructive sleep apnea in children. *Arch.Otolaryngol.Head.Neck.Surg.*, vol. 130, 2: 190-4
- Mitchell, R. B., Kelly, J., Call, E., *et al.* (2004b). Long-term changes in quality of life after surgery for pediatric obstructive sleep apnea. *Arch.Otolaryngol.Head.Neck.Surg.*, vol. 130, 4: 409-12
- Moggras, M. A., Ducharme, F. M. and Brouillette, R. T. (1994). Movement/arousals. Description, classification, and relationship to sleep apnea in children. *Am.J.Respir.Crit.Care Med.*, vol. 150, 6 Pt 1: 1690-6
- Monahan, K. J., Larkin, E. K., Rosen, C. L., *et al.* (2002). Utility of noninvasive pharyngometry in epidemiologic studies of childhood sleep-disordered breathing. *Am.J.Respir.Crit.Care Med.*, vol. 165, 11: 1499-503
- Monini, S., Malagola, C., Villa, M. P., *et al.* (2009). Rapid maxillary expansion for the treatment of nasal obstruction in children younger than 12 years. *Arch.Otolaryngol.Head.Neck.Surg.*, vol. 135, 1: 22-7
- Montgomery-Downs, H. E., O'Brien, L. M., Gulliver, T. E., *et al.* (2006). Polysomnographic characteristics in normal preschool and early school-aged children. *Pediatrics*, vol. 117, 3: 741-53
- Mora, R., Salami, A., Passali, F. M., *et al.* (2003). OSAS in children. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 67 Suppl 1, : S229-31
- Ng, D. K., Chan, C. H., Hwang, G. Y., *et al.* (2006). A review of the roles of allergic rhinitis in childhood obstructive sleep apnea syndrome. *Allergy Asthma Proc.*, vol. 27, 3: 240-2
- Nieminen, P., Lopponen, T., Tolonen, U., *et al.* (2002). Growth and biochemical markers of growth in children with snoring and obstructive sleep apnea. *Pediatrics*, vol. 109, 4: e55
- Nieminen, P., Tolonen, U., Lopponen, H., *et al.* (1997). Snoring children: factors predicting sleep apnea. *Acta Otolaryngol.Suppl.*, vol. 529, : 190-4
- Novelli, L., Ferri, R. and Bruni, O. (2010). Sleep classification according to AASM and Rechtschaffen and Kales: effects on sleep scoring parameters of children and adolescents. *J.Sleep Res.*, vol. 19, : 238-47
- O'Brien, L. M., Mervis, C. B., Holbrook, C. R., *et al.* (2004a). Neurobehavioral implications of habitual snoring in children. *Pediatrics*, vol. 114, 1: 44-9
- O'Brien, L. M., Mervis, C. B., Holbrook, C. R., *et al.* (2004b). Neurobehavioral correlates of sleep-disordered breathing in children. *J.Sleep Res.*, vol. 13, 2: 165-72
- O'Brien, L. M., Holbrook, C. R., Mervis, C. B., *et al.* (2003). Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder. *Pediatrics*, vol. 111, 3: 554-63
- O'Brien, L. M. and Gozal, D. (2002). Behavioural and neurocognitive implications of snoring and obstructive sleep apnoea in children: facts and theory. *Paediatr.Respir.Rev.*, vol. 3, 1: 3-9
- Okun, M. N., Hadjiangelis, N., Green, D., *et al.* (2010). Acoustic rhinometry in pediatric sleep apnea. *Sleep Breath*, vol. 14, 1: 43-9

- Orji, F. T. and Ezeanolue, B. C. (2008). Evaluation of adenoidal obstruction in children: clinical symptoms compared with roentgenographic assessment. *J.Laryngol.Otol.*, vol. 122, 11: 1201-5
- Paavonen, E. J., Raikkonen, K., Lahti, J., *et al.* (2009). Short sleep duration and behavioral symptoms of attention-deficit/hyperactivity disorder in healthy 7- to 8-year-old children. *Pediatrics*, vol. 123, 5: e857-64
- Paavonen, E. J., Strang-Karlsson, S., Raikkonen, K., *et al.* (2007). Very low birth weight increases risk for sleep-disordered breathing in young adulthood: the Helsinki Study of Very Low Birth Weight Adults. *Pediatrics*, vol. 120, 4: 778-84
- Parker, L. P., Crysedale, W. S., Cole, P., *et al.* (1989). Rhinomanometry in children. *Int.J.Pediatr. Otorhinolaryngol.*, vol. 17, 2: 127-37
- Phillips, B. G. and Somers, V. K. (2003). Hypertension and obstructive sleep apnea. *Curr.Hypertens.Rep.*, vol. 5, 5: 380-5
- Pijpers, M., Poels, P. J., Vaandrager, J. M., *et al.* (2004). Undiagnosed obstructive sleep apnea syndrome in children with syndromal craniofacial synostosis. *J.Craniofac.Surg.*, vol. 15, 4: 670-4
- Pirelli, P., Saponara, M. and Guilleminault, C. (2004). Rapid maxillary expansion in children with obstructive sleep apnea syndrome. *Sleep*, vol. 27, 4: 761-6
- Pitson, D. J. and Stradling, J. R. (1998). Value of beat-to-beat blood pressure changes, detected by pulse transit time, in the management of the obstructive sleep apnoea/hypopnoea syndrome. *Eur.Respir.J.*, vol. 12, 3: 685-92
- Praud, J. P., D'Allest, A. M., Nedelcoux, H., *et al.* (1989). Sleep-related abdominal muscle behavior during partial or complete obstructed breathing in prepubertal children. *Pediatr.Res.*, vol. 26, 4: 347-50
- Puhakka, H. J., Kero, P., Valli, P., *et al.* (1992). Tracheostomy in pediatric patients. *Acta Paediatr.*, vol. 81, 3: 231-4
- Qian, W., Chen, W., Chen, J. M., *et al.* (2007). Acoustic rhinometry in preschool children. *Otolaryngol.Head. Neck.Surg.*, vol. 137, 1: 39-42
- Rechtschaffen, A. and Kales, A. (1968). *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subject*. US Government Printing Office, National Institute of Health Publication.
- Redline, S., Budhiraja, R., Kapur, V., *et al.* (2007). The scoring of respiratory events in sleep: reliability and validity. *J.Clin.Sleep Med.*, vol. 3, 2: 169-200
- Redline, S., Tishler, P. V., Schluchter, M., *et al.* (1999). Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory problems. *Am.J.Respir.Crit.Care Med.*, vol. 159, 5 Pt 1: 1527-32
- Rice, A., Costy-Bennett, S., Goodwin, J. L., *et al.* (2010). Control of breathing in children with mild sleep apnoea: a 6-year follow-up study. *Eur.Respir.J.*, vol. 35, 1: 124-31
- Riechelmann, H., O'Connell, J. M., Rheinheimer, M. C., *et al.* (1999). The role of acoustic rhinometry in the diagnosis of adenoidal hypertrophy in pre-school children. *Eur.J.Pediatr.*, vol. 158, 1: 38-41
- Riechelmann, H., Rheinheimer, M. C. and Wolfensberger, M. (1993). Acoustic rhinometry in pre-school children. *Clin.Otolaryngol.*, vol. 18, 4: 272-7
- Rizzi, M., Onorato, J., Andreoli, A., *et al.* (2002). Nasal resistances are useful in identifying children with severe obstructive sleep apnea before polysomnography. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 65, 1: 7-13
- Rosen, C. L., Storfer-Isser, A., Taylor, H. G., *et al.* (2004). Increased behavioral morbidity in school-aged children with sleep-disordered breathing. *Pediatrics*, vol. 114, 6: 1640-8
- Rosen, C. L., Larkin, E. K., Kirchner, H. L., *et al.* (2003). Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. *J.Pediatr.*, vol. 142, 4: 383-9
- Row, B. W., Kheirandish, L., Neville, J. J., *et al.* (2002). Impaired spatial learning and hyperactivity in developing rats exposed to intermittent hypoxia. *Pediatr.Res.*, vol. 52, 3: 449-53
- Sanchez-Armengol, A., Ruiz-Garcia, A., Carmona-Bernal, C., *et al.* (2008). Clinical and polygraphic evolution of sleep-related breathing disorders in adolescents. *Eur.Respir.J.*, vol. 32, 4: 1016-22
- Sans Capdevila, O., Crabtree, V. M., Kheirandish-Gozal, L., *et al.* (2008). Increased morning brain natriuretic peptide levels in children with nocturnal enuresis and sleep-disordered breathing: a community-based study. *Pediatrics*, vol. 121, 5: e1208-14
- Sheldon, S. H., Kryger, M. H. and Ferber, R. (2005). *Principles and practice of pediatric sleep medicine*.
- Shine, N. P., Lannigan, F. J., Coates, H. L., *et al.* (2006). Adenotonsillectomy for obstructive sleep apnea in obese children: effects on respiratory parameters and clinical outcome. *Arch.Otolaryngol.Head.Neck.Surg.*, vol. 132, 10: 1123-7
- Smith, R. P., Veale, D., Pepin, J. L., *et al.* (1998). Obstructive sleep apnoea and the autonomic nervous system. *Sleep Med.Rev.*, vol. 2, 2: 69-92
- Snow, A., Dayyat, E., Montgomery-Downs, H. E., *et al.* (2009). Pediatric obstructive sleep apnea: a potential late consequence of respiratory syncytial virus bronchiolitis. *Pediatr.Pulmonol.*, vol. 44, 12: 1186-91
- Sohn, H. and Rosenfeld, R. M. (2003). Evaluation of sleep-disordered breathing in children. *Otolaryngol. Head Neck Surg.*, vol. 128, 3: 344-52
- Sorensen, H., Solow, B. and Greve, E. (1980). Assessment of the nasopharyngeal airway. A rhinomanometric and radiographic study in children with adenoids. *Acta Otolaryngol.*, vol. 89, 3-4: 227-32
- Soultan, Z., Wadowski, S., Rao, M., *et al.* (1999). Effect of treating obstructive sleep apnea by tonsillectomy and/or adenoidectomy on obesity in children. *Arch.Pediatr.Adolesc.Med.*, vol. 153, 1: 33-7

- Spier, S., Rivlin, J., Rowe, R. D., *et al.* (1986). Sleep in Pierre Robin syndrome. *Chest*, vol. 90, 5: 711-5
- Spilsbury, J. C., Storfer-Isser, A., Kirchner, H. L., *et al.* (2006). Neighborhood disadvantage as a risk factor for pediatric obstructive sleep apnea. *J.Pediatr.*, vol. 149, 3: 342-7
- Sproson, E. L., Hogan, A. M. and Hill, C. M. (2009). Accuracy of clinical assessment of paediatric obstructive sleep apnoea in two English centres. *J.Laryngol.Otol.*, vol. 123, 9: 1002-9
- Steinsvag, S. K., Skadberg, B. and Bredesen, K. (2007). Nasal symptoms and signs in children suffering from asthma. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 71, 4: 615-21
- Stewart, M. G., Friedman, E. M., Sulek, M., *et al.* (2000). Quality of life and health status in pediatric tonsil and adenoid disease. *Arch.Otolaryngol.Head.Neck.Surg.*, vol. 126, 1: 45-8
- Stradling, J. R., Thomas, G., Warley, A. R., *et al.* (1990). Effect of adenotonsillectomy on nocturnal hypoxaemia, sleep disturbance, and symptoms in snoring children. *Lancet*, vol. 335, 8684: 249-53
- Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology (1989). Skin tests used in type I allergy testing Position paper. *Allergy*, vol. 44 Suppl 10, : 1-59
- Tapia, I. E., Karamessinis, L., Bandla, P., *et al.* (2008). Polysomnographic values in children undergoing puberty: pediatric vs. adult respiratory rules in adolescents. *Sleep*, vol. 31, 12: 1737-44
- Tauman, R., Gulliver, T. E., Krishna, J., *et al.* (2006). Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. *J.Pediatr.*, vol. 149, 6: 803-8
- Tauman, R., Ivanenko, A., O'Brien, L. M., *et al.* (2004). Plasma C-reactive protein levels among children with sleep-disordered breathing. *Pediatrics*, vol. 113, 6: e564-9
- Tavil, Y., Kanbay, A., Sen, N., *et al.* (2007). Comparison of right ventricular functions by tissue Doppler imaging in patients with obstructive sleep apnea syndrome with or without hypertension. *Int.J.Cardiovasc. Imaging*, vol. 23, 4: 469-77
- Teculescu, D. B., Caillier, I., Perrin, P., *et al.* (1992). Snoring in French preschool children. *Pediatr. Pulmonol.*, vol. 13, 4: 239-44
- Traeger, N., Schultz, B., Pollock, A. N., *et al.* (2005). Polysomnographic values in children 2-9 years old: additional data and review of the literature. *Pediatr.Pulmonol.*, vol. 40, 1: 22-30
- Tran, K. D., Nguyen, C. D., Weedon, J., *et al.* (2005). Child behavior and quality of life in pediatric obstructive sleep apnea. *Arch.Otolaryngol.Head.Neck.Surg.*, vol. 131, 1: 52-7
- Urschitz, M. S., Eitner, S., Guenther, A., *et al.* (2004a). Habitual snoring, intermittent hypoxia, and impaired behavior in primary school children. *Pediatrics*, vol. 114, 4: 1041-8
- Urschitz, M. S., Guenther, A., Eitner, S., *et al.* (2004b). Risk factors and natural history of habitual snoring. *Chest*, vol. 126, 3: 790-800
- Urschitz, M. S., Guenther, A., Eggebrecht, E., *et al.* (2003a). Snoring, intermittent hypoxia and academic performance in primary school children. *Am.J.Respir.Crit.Care Med.*, vol. 168, 4: 464-8
- Urschitz, M. S., Wolff, J., Von Einem, V., *et al.* (2003b). Reference values for nocturnal home pulse oximetry during sleep in primary school children. *Chest*, vol. 123, 1: 96-101
- Van Den Akker, E. H., Hoes, A. W., Burton, M. J., *et al.* (2004). Large international differences in (adeno) tonsillectomy rates. *Clin.Otolaryngol.Allied Sci.*, vol. 29, 2: 161-4
- Verhulst, S. L., Franckx, H., Van Gaal, L., *et al.* (2009). The effect of weight loss on sleep-disordered breathing in obese teenagers. *Obesity (Silver Spring)*, vol. 17, 6: 1178-83
- Verhulst, S. L., Schrauwen, N., Haentjens, D., *et al.* (2007). Reference values for sleep-related respiratory variables in asymptomatic European children and adolescents. *Pediatr.Pulmonol.*, vol. 42, 2: 159-67
- Villa, M. P., Malagola, C., Pagani, J., *et al.* (2007). Rapid maxillary expansion in children with obstructive sleep apnea syndrome: 12-month follow-up. *Sleep Med.*, vol. 8, 2: 128-34
- Vlastos, I. M., Parpounas, K., Economides, J., *et al.* (2008). Tonsillectomy versus tonsillotomy performed with scissors in children with tonsillar hypertrophy. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 72, 6: 857-63
- Wasilewska, J., Kaczmarek, M., Citko, D., *et al.* (2009). Sleep-wake schedules in preschool children who snore. *Adv.Med.Sci.*, vol. 54, 2: 256-63
- Waters, K. A., Kirjavainen, T., Jimenez, M., *et al.* (1996). Overnight growth hormone secretion in achondroplasia: deconvolution analysis, correlation with sleep state, and changes after treatment of obstructive sleep apnea. *Pediatr. Res.* vol. 39, 3: 547-53
- Waters, K. A., Everett, F. M., Bruderer, J. W., *et al.* (1995). Obstructive sleep apnea: the use of nasal CPAP in 80 children. *Am.J.Respir.Crit.Care Med.*, vol. 152, 2: 780-5
- Wechsler D. (1989). Wechsler Preschool and Primary Scale of Intelligence-Revised. San Antonio. The Psychological Corporation.
- Wilson, S. E., Kahn, R. S., Khoury, J., *et al.* (2007). The role of air nicotine in explaining racial differences in cotinine among tobacco-exposed children. *Chest*, vol. 131, 3: 856-62
- Wolfensberger, M., Haury, J. A. and Linder, T. (2000). Parent satisfaction 1 year after adenotonsillectomy of their children. *Int.J.Pediatr.Otorhinolaryngol.*, vol. 56, 3: 199-205
- Yolton, K., Xu, Y., Khoury, J., *et al.* (2010). Associations between secondhand smoke exposure and sleep patterns in children. *Pediatrics*, vol. 125, 2: e261-8

- Zapletal, A. and Chalupova, J. (2002). Nasal airflow and resistance measured by active anterior rhinomanometry in healthy children and adolescents. *Pediatr.Pulmonol.*, vol. 33, 3: 174-80
- Zavras, A. I., al-Bultan, T., Jackson, A., *et al.* (1997). Exposure to passive smoking and other predictors of reduced nasal volume in children 7 to 12 years old. *J.Clin.Pediatr.Dent.*, vol. 21, 4: 295-303
- Zavras, A. I., White, G. E., Rich, A., *et al.* (1994). Acoustic rhinometry in the evaluation of children with nasal or oral respiration. *J.Clin.Pediatr.Dent.*, vol. 18, 3: 203-10
- Zeitouni, A. and Manoukian, J. (1993). Tracheotomy in the first year of life. *J.Otolaryngol.*, vol. 22, 6: 431-4
- Zettergren-Wijk, L., Forsberg, C. M. and Linder-Aronson, S. (2006). Changes in dentofacial morphology after adeno-/tonsillectomy in young children with obstructive sleep apnoea - a 5-year follow-up study. *Eur.J.Orthod.*, vol. 28, 4: 319-26
- Zhang, G., Spickett, J., Rumchev, K., *et al.* (2004). Snoring in primary school children and domestic environment: a Perth school based study. *Respir.Res.*, vol. 5, : 19
- Zucconi, M., Caprioglio, A., Calori, G., *et al.* (1999). Craniofacial modifications in children with habitual snoring and obstructive sleep apnoea: a case-control study. *Eur.Respir.J.*, vol. 13, 2: 411-7