SNORING AND OBSTRUCTIVE SLEEP APNEA IN YOUNG CHILDREN
A 6-month follow-up study

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OULU 2002
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Academic Dissertation to be presented with the assent of the Faculty of Medicine, University of Oulu, for public discussion in the Auditorium 7 of the University Hospital of Oulu, on May 3rd, 2002, at 12 noon.

OULUN YLIOPISTO, OULU 2002
Nieminen, Peter, Snoring and obstructive sleep apnea in young children  A 6-month follow-up study
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Oulu, Finland
2002

Abstract
Seventy-eight prepubertal children 3 to 10 years old (mean age 5.67 years, range 2.4 - 10.5 years), with symptoms suggestive of obstructive sleep apnea syndrome (OSAS) were studied. Based on overnight polysomnography (PSG) results, 32 children were classified as having OSAS, whereas 46 children were considered as primary snorers (PSs’), when an obstructive apnea-hypopnea index (AHI\(_O\)) of over one was considered abnormal. Symptoms, signs and findings in these two groups were compared in a cross-sectional study. Fifty-eight of the children were retrieved for a follow-up visit, which was scheduled six months from the first visit. The children with an initial AHI\(_O\) of 2 or over (n = 21) had been subjected to adenotonsillectomy swiftly after the first visit, whereas the others (n = 37) were observed without intervention. The changes in symptoms, signs and findings were analysed within and between these groups.

Relative risk (RR) ratios were calculated in order to find clinical symptoms and signs predicting OSAS in snoring children. Observed apneas, restless sleep, constant snoring and tonsillar hypertrophy were significantly associated with an increased risk of OSAS.

Dental arch measurements indicated that AHI\(_O\) was significantly associated with the amount of overjet, suggesting that altered breathing may affect the dentofacial morphology.

Nasalance measurements revealed no group differences between the OSAS children and PSs’. Adenotonsillectomy had no significant influence on the nasalance scores. Measurements of nasalance seem to contribute little to the diagnostics of OSAS in children.

At the first visit the mean circulating concentrations of insulin-like growth factor-1 (IGF-1) were of the same magnitude in the OSAS children, the PSs’ and the age-matched control group, but both the OSAS children and the PSs’ had lower IGF-binding protein-3 (IGFBP-3) concentrations than the control subjects. At the second visit a significant increase of the peripheral concentrations of IGF-1 and IGFBP-3, along with increases in weight for height and BMI were observed in the surgically treated children, whose respiratory parameters and symptoms had improved highly significantly, as well. These results indicate that the growth of children with obstructed nighttime breathing is potentially affected through impaired growth hormone secretion.

None of the primary snorers developed OSAS during the observation period, which finding suggests a favorable prognosis for primary snoring in children.

Keywords: growth, children, snoring, obstructive sleep apnea, tonsillectomy
Acknowledgements

This work was carried out in the Departments of Otolaryngology, Clinical Neurophysiology, Pediatrics and the Institute of Dentistry, University of Oulu, during the years 1994-2002.

I wish to express my deep gratitude to Professor Kalevi Jokinen, M.D., Head of the Department of Otolaryngology for his encouraging interest in my work throughout the years, and to Emeritus Professor Antti Palva, M.D., who as the former Head of Department stimulated me in beginning of this study.

I am particularly grateful to the supervisor of my work, Docent Heikki Löppönen, M.D., my friend, who has excellently taught me the scientific way of thinking and writing. His patience has been enormous, when he has guided me through the up- and downhills of this project. In spite of many other urgent matters he has always found the time to discuss and help me with problems and he has considerably helped me in completing this work.

I wish to express my gratefulness to Docent Uolevi Tolonen, M.D., of the Department of Clinical Neurophysiology, who in addition to the enormous task of analyzing the sleep recordings has also taken the time to guide me in scientific writing. His kind attitude, constructive criticism and logic have made a great impression on me.

Docent Markku Partinen, M.D., University of Helsinki, the referee of this thesis, has shown positive interest in my research. In the final stages of this study he provided me with constructive criticism and advice, which I am deeply grateful for. I am indebted to Docent Henrik Malmberg, M.D., University of Helsinki, the referee of this thesis, for his thoroughness and constructive criticism in the process of reviewing.

I have been provided by very pleasant and skillful collaboration from my co-authors, which as specialists in different clinical fields have been of utmost importance for this study. I am deeply grateful to Dr. Tuija Löppönen, M.D., of the Department of Pediatrics, who performed the anthropometric measurements and supervised me in study V. I wish to express my sincere thankfulness to Kirsi Pirilä, DDS and Paula Tahvanainen, DDS, of the Institute of Dentistry, and Professor Jan Huggare, DDS, who made the study II possible. I also wish to thank phoniatricians Mirja Väyrynen, M.D., and Aulikki Tervonen, M.D., for
their supervision in study III. My warmest thanks go also to Docent Peter Lanning, M.D., for his assistance in study V. Professor Mikael Knip, M.D., helped me in designing and finishing study V, for which I am deeply grateful.

I wish to thank the highly qualified staff of the ward 21 of the Department of Otolaryngology for their excellent and unselfish collaboration during this study. My thanks go also to the Pediatric research laboratory and to the staff of the audiophoniatric department.

I sincerely thank all the children, parents and volunteers, who kindly participated in this study. Without them this work would not have been possible.

I wish to thank all the senior colleagues of the Department of Otolaryngology for teaching me in the field of Otolaryngology, and for fruitful comments and help with this study. Docent Jukka Luotonen, M.D., has encouraged me on several occasions, and he was one of the co-authors in study I.

My parents have supported and encouraged me during this work, for which I am grateful.

Finally, my dearest thanks go to my wife Anna-Lena and our daughters Erica and Henrietta. Thank you for all your patience with me during these years. Combining research, clinical work and family life is not easy. Anna-Lena has always supported and encouraged me, and she has never questioned the time I have needed for my work. Anna-Lena, I know you have had to carry out a lot of tasks without my help, besides your own studies. You have still managed to be a wonderful mother and a dear wife. Erica and Henrietta have been too young to understand the “book I am writing”, and are mainly eager to get more time on the computer. Their happy laugh has given me a lot of strength.

This research has financially been supported by Korvatautien tutkimussäätiö, Helsinki, Finland, the Alma and K.A Snellman foundation, Oulu, Finland, and The Finnish Medical Foundation, Helsinki, Finland.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHI</td>
<td>apnea-hypopnea index</td>
</tr>
<tr>
<td>AHIO</td>
<td>apnea-hypopnea index: obstructive</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
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<tr>
<td>ECG</td>
<td>electrocardiography</td>
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<td>EDS</td>
<td>excessive daytime somnolence</td>
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<td>EEG</td>
<td>electroencephalography</td>
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<tr>
<td>EMG</td>
<td>electromyography</td>
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<tr>
<td>EOG</td>
<td>electro-oculogram</td>
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<tr>
<td>IGF-1</td>
<td>Insulin-like growth factor-1</td>
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<tr>
<td>IGFBP-3</td>
<td>Insulin-like growth factor binding protein-3</td>
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<td>OSAS</td>
<td>obstructive sleep apnea syndrome</td>
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<tr>
<td>Pcrit</td>
<td>critical closing pressure</td>
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<tr>
<td>PSG</td>
<td>polysomnography</td>
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<tr>
<td>RDI</td>
<td>respiratory disturbance index</td>
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<tr>
<td>REM</td>
<td>rapid eye movement</td>
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<td>RIP</td>
<td>respiratory inductive pletysmography</td>
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<tr>
<td>SBD</td>
<td>sleep-related breathing disorder</td>
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<tr>
<td>SWS</td>
<td>slow-wave sleep</td>
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<tr>
<td>TST</td>
<td>total sleeping time</td>
</tr>
<tr>
<td>UARS</td>
<td>upper airway resistance syndrome</td>
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List of original communications

The thesis is based on the following communications which will be referred to in the text by their Roman numerals.


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1 Introduction

Sleep related obstructive breathing disorders are relatively common in children. They have a very large scale of symptoms, from plain harmless snoring to obstructive sleep apnea syndrome (OSAS), a condition related to snoring with nighttime repetitive airway patency disruptions. The mildest forms of sleep-related breathing disorders are probably quite harmless to the children, whereas OSAS can even lead to life-threatening complications in the pediatric population (1), hence there is a need for understanding the syndrome.

Many physicians are still unaware of OSAS and its potential complications in children, which may result in delayed diagnosis and unnecessary morbidity (2, 3). It may also be difficult to separate the various levels of sleep disorders without objective measurements, as there is a great deal of overlap of the symptoms across the continuum of sleep-related obstructive disorders. Diagnostic challenges of the syndrome still remain to be overcome.

Due to the state of ongoing development, OSAS may affect children in specific ways not encountered in adults. Some of the complications may have effects on later life and possibly predispose to reappearing OSAS in adulthood.

The pathophysiology and etiology of OSAS in children are inadequately understood. The complex process of airway closure during sleep is a dynamic phenomenon not explained by mechanical factors alone. The multifaceted etiology of OSAS in children explains why the method of choice - treatment, adenotonsillectomy, is not always curative.

The present investigation of snoring children with symptoms suggestive of OSAS was designed to increase our knowledge of this disease and further give guidelines for diagnostics and treatment of children suffering from OSAS.
2 Review of the literature

2.1 History of sleep apnea among children

Charles Dickens was probably the first to describe the features of sleep apnea in his famous comic narrative The Posthumous Papers of the Pickwick Club (4). The fat boy Joe was snoring heavily, he was falling constantly asleep and was described as having slow perception. Damn that boy...! In 1889, William Hill (5) recognized the symptoms of the syndrome, describing the stupid lazy-looking kid who frequently suffers from headaches at school, breathes through his mouth instead of his nose, snores and is restless at night. He speculated that some of their backwardness was secondary to some hampering of the cerebral functions rather than deafness. Hill also found adenotonsillectomy to be helpful for these children. In 1965 Menashe et al. (6) described two children with cor pulmonale and other typical symptoms of OSAS secondary to chronic upper airway obstruction formed by tonsils and adenoids, and regression of the symptoms after tonsillectomy and adenoidectomy. The same year Noonan (7) presented two children with right-sided ventricular hypertrophy, tremendous adenoids and tonsils and snorting respiration. Radiation therapy to the nasopharynx caused the lymphoid tissue to regress and the cardiopulmonary function to return to normal. Noonan stated that “cor pulmonale from hypertrophied tonsils and adenoids” seems to constitute a valid but rare medical indication for tonsillectomy and adenoidectomy. Further the same year, Cox et al. (8) described a child with typical OSAS-symptoms and cor pulmonale resulting from laryngomalacy, with clinical improvement after tracheotomy. All the authors saw the connection between noisy respiration and hypersomnolence and heart changes. In 1967 Levy et al. (9) described how the symptoms of respiratory obstruction could be alleviated by nasopharyngeal tubing.

The first continuous polygraphic night recordings of adult patients suffering from the Pickwickian syndrome were performed by Jung & Kuhlo in 1965 (10). Pickwickian syndrome, a terminological predecessor of OSAS, named after Dickens’ narrative of the features of the fat boy Joe in the Pickwick Club (4), was described as consisting of frequent diurnal episodes of spontaneous sleep with apnea, alveolar hypoventilation with hypercapnia, and obesity (10). Jung & Kuhlo showed that occurrence of apneic intervals
is a prominent feature also during nocturnal sleep, and may occur before development of obesity, so that the Pickwickian should have some central disturbance of respiration and arousal, as shown by the CO₂ tracing and EEG recordings of the sleeping subjects.

A further step towards the modern concept of OSAS was when Gastaut et al. (11) in 1966 also concluded that the loss of nocturnal sleep is responsible for diurnal somnolence. Daytime drowsiness was shown not to be a consequence of acquired hypoxia as was thought earlier. Polygraphic nocturnal recording showed heavily disturbed sleep architecture with arousals at the termination of apneas and resaturation of the arterial blood after resumption of breathing in an obese male.

The sleep apnea syndrome was described for the first time in 1973 in adults (12), and 1976 in children (13), in a pioneer article on the condition in the pediatric population with a series of eight children. The symptoms, signs and complications of the syndrome were described more thoroughly in a more comprehensive study with 50 children in 1981 (14), when the first diagnostic criteria were introduced as well. The diagnostic criteria resembled closely those developed for adults, but the adult criteria have later been found not to be suitable for children (15) and have hence been modified (16).

In Finland, none of the earlier theses on obstructive sleep apnea (17-22) has focused on OSAS in children from a surgical point of view.

2.2 Normal sleep in 3 to 10 year old children

The total amount of sleep needed by young children decreases annually with about one hour to be about 12 hours at the age of five, at which age the afternoon naps have started to disappear, and the frequency of night awakenings is low (23). By the age of ten, children sleep 8 to 10 hours, and the sleep is quieter with less body movements than at younger age. The sleep pattern usually follows a cycle of rapid movement through stages 1, 2 and 3, before remaining in stage 4 for a longer time. Stage 4 gives way to stages 3 and 2 and a short period of stage one before REM sleep appears. The cyclic pattern is repeated on the average four times during the night with less stage 4 sleep and increasing amounts of REM sleep in the later periods (24). The change in children's sleep stages occurs smoothly and regularly in contrast to adults' (24).

Between the first and fifth years of age, the percentage of REM sleep of the total amount of sleep decreases from 30% to the adult level between 20 to 25% (25). In 6 to 11-year-old children, the amount of REM sleep remains constant at the 20 to 25% level of sleep time (24, 26). The first REM period starts to appear somewhat earlier in older children, within the first two hours of sleep, being quite short, about 15 minutes, whereas the later periods have a tendency to become longer, up to 30 minutes, and more intense toward the end of the night (26). Most of stage 3 and 4 sleep (slow-wave sleep, SWS) is seen in the first third of the night (24), SWS accounting for ~ 22-26% of the total sleep time (26), while REM sleep is more concentrated in the latter two third parts of the night, especially in the latest part (24). With increasing age, the time spent in stage 2 non-REM
sleep increases at the expense of stage 4 non-REM sleep (slow-wave sleep), which declines from about 18% in six-year-olds to 14% in ten-year-olds (26). Most sleep is spent in stage 2, over 40% of the total sleeping time.

The breathing may be quite irregular during the night. Sighs, when a sharp increase of respiratory movement amplitude occurs, contribute to reopening unventilated zones (27). The respiratory frequency is highest during periods of wakefulness and in stage 1 non-REM sleep and lowest during stage 2 non-REM sleep of the last cycle of the night (28). The mean highest and lowest respiratory rates have been reported to be 17 and 15 breaths per minute accordingly (28). Later in childhood/adolescence the respiratory frequency and variability is highest in REM sleep and lowest in stages 3–4 of non-REM sleep (29).

Apneas (see definitions below) may occur in normal children. Central apneas are relatively common and normal phenomena, especially after movement (14, 28), occurring mainly in stage 1 and 2 of non-REM sleep, and less in REM sleep (28, 29). Even up to 25-second-long central apneas have been recorded in normal children (28–30). Obstructive apneas are less common, reported earlier as non-existent in normal children (14, 28, 29). Later, obstructive apneas have been found to exist also in normal children, but they are rare and only of short duration (16).

### 2.3 Definitions

#### 2.3.1 Primary snoring

Children who snore, but are not found to have apneas, hypoventilation or excessive arousals from sleep on polysomnography, have been called primary snorers (31, 32).

#### 2.3.2 Obstructive apneas

In an obstructive apnea there is a continuing respiratory effort despite cessation of gas exchange at the level of the mouth and nostrils. In Guilleminault et al.'s report from 1981 (14) the apnea as well as the hypopnea was defined to have to last at least 10 seconds to be important. The same 10-seconds criterion was also used by Brouilette et al. in 1982 (33) as a part of the diagnostic procedure, and later by many other research groups. There have been arguments against the adult criteria being extrapolated to children, since children have smaller respiratory capacity and a faster respiratory rate (15). The 10-second criterion has in many reports had to give way to shorter apneas, especially after Marcus et al. in 1992 (16) published normal polysomnographic values for children. They found no normal child to have obstructive apneas lasting more than ten seconds, and apneas lasting 5-10 seconds were rare, which results are supported by others (28).
Obstructive apnea occurrence is usually greatest in REM sleep (34, 35), with up to 55% of obstructive apneas occurring in REM sleep, and 36% in stage 2 sleep (35). Obstructive apneas in SWS account for only about 5% to 10% of the total occurrences of apneas during the night in children (35, 36). The apneas occurring in REM sleep are also more severe than apneas in other sleep stages (35). The apneas in REM sleep tend to increase in number and become more intense towards the latter part of the night (35), when the REM periods also become longer (26).

2.3.3 Obstructive hypopneas

In an obstructive hypopnea the gas exchange is reduced at the level of the mouth and nostrils despite breathing effort. For hypopneas there exists a wide range of recording techniques and definitions used in different sleep laboratories (37). In a survey study to different accredited sleep laboratories it was found that no two laboratories used the same definition and measures of hypopnea (37). In 54% (24/44) of the laboratories a 50% reduction in the airflow was required to define a hypopnea, while in the rest of the 20/44 laboratories the requirement was less strict. Thirty-seven laboratories also included oxygen desaturation as a part of their definition, but the degree of desaturation required to meet the criteria for hypopnea varied widely. In 33 laboratories a sleep arousal was needed to fulfil the definition of hypopnea, but there was no consistent definition of arousal in response to the question. In a study on adults a 50% reduction in thoracoabdominal movement lasting for 10 seconds was found to be the best definition of hypopnea (38).

2.3.4 Obstructive hypoventilation

In children hypopneas often account for the most part of obstructive events (39, 40); obstructive events are often periods of partial airway obstruction and prolonged hypoventilation instead of clear-cut apneas (40), which are rather a culmination of the “hypopnea”-syndrome (38). This is why many consider it important to measure the amount of hypoventilation (16, 41, 42), rather than quantify the hypopneas. Brouilette et al. (33) considered obstructive hypoventilation to be present when signs of partial airway obstruction (paradoxical inward chest movement, snoring and use of accessory muscles) were accompanied by hypercarbia. When Marcus et al. 1992 (16) introduced their normal polysomnographic values for children and adolescents, they recommended that a peak end-tidal CO₂ over 53 mmHg, or end-tidal CO₂ over 45 mmHg for more than 60 % of total sleeping time (TST) should be considered abnormal. They also observed that the peak end-tidal CO₂ was frequently over 45 and occasionally even over 50 mmHg in normal non-apneic children.
2.3.5 Central apneas

A central apnea occurs when there is a lack of breathing effort concomitant with loss of gas exchange. Stradling et al. (43) have suggested that any event, regardless of the duration, with an over 4% decrease in arterial oxygen saturation exceeding the frequency of 3/hour should be considered abnormal. The role of the central apneas in OSAS is, however, unclear (44), and many different standards have been applied. To be scored, there may be a demand of co-joint deep desaturation (below 90%) (16), a lower time limit (20 sec) with co-incident desaturation (45) and/or bradykardia (32), or central apneas may be ignored (31). It seems that central apneas are more common in OSAS-children than in primary snorers (46).

2.3.6 Mixed apneas

A mixed apnea begins with a central apnea proceeding with an obstructive component. Mixed apneas are usually included in the category of obstructive apneas.

2.3.7 Desaturation

A decrease in the blood oxygenation level, desaturation, may follow all types of apnea. Desaturations may also occur in non-snoring children. The mean arterial oxygen saturation during the night in normal children is ~ 96% (43, 47). Brief over 4% desaturations may occur in normal children at a rate less than 3 times per hour (43), and occasional deep desaturations below 90 % in normal children have been reported (48), even below 80% (30). As for normative criteria, Marcus et al. (16) recommended that saturation values below 92% should be considered abnormal in the pediatric population. In their study population with normal children there were nevertheless found desaturations below this level. However, many children with clear apneas never desaturate below 92% (31, 49).

2.3.8 Arousals and sleep architecture

An EEG-arousal in sleep is defined as an abrupt shift in EEG frequency, lasting for 3 seconds or more, which may include theta, alpha and/or frequencies greater than 16Hz but not spindles (50). The adult criteria have been modified for children so that EEG frequency shifts greater than 1 second are considered (51). An arousal is usually linked with the termination of obstructive apnea in adults, whereas this is often not the case in children (15, 52, 53). There are no standardized criteria for arousal detection in infants and children (51, 53), and only few reports have documented regular occurrence of
arousal at the end of sleep-related obstructive events in infants and children (51, 54). EEG arousals are probably not an important mechanism in the termination of respiratory events in children (31, 35, 46, 53, 55, 56), as less than 40% of the respiratory events are terminated with an arousal, and the EEG arousal index has been found to be relatively alike between OSAS-children and normal controls (31, 53, 55), or only slightly higher (46). It has, however, been pointed out that spontaneous arousals (movement or EEG arousals) without any relation to apneas should be assessed as respiratory arousals, since they are possibly associated with aggravated inhalation (57).

The percentages of REM sleep and slow-wave sleep seem to be quite equal in OSAS children compared with normal subjects (35, 51, 52), so the sleep macrostructure in OSAS children is preserved compared with normal children (35, 56, 57). Bandla et Gozal (58) demonstrated that in apneas not associated with an arousal, the delta frequency was decreased during the apnea followed by increase after the termination of the apnea. The authors speculated that this phenomenon might represent subtle evidence of arousal and sleep fragmentation. According to the Atlas Task Force (1992) (50) the delta wave bursts might be indicative of arousals, but the evidence is limited.

### 2.3.9 Autonomic arousals

It is possible that arousals not detected by current definitions can occur without visible EEG changes. Nocturnal sound provocations causing increase in blood pressure but no visible EEG changes have been shown to cause increased daytime sleepiness in adults (59). Instead of EEG arousals, children rather tend to have movement arousals. Mograss et al. (51) reported that the majority of apneas in children were terminated by a short movement arousal, which often did not result in sleep-stage change, but did re-establish airway patency. The arousals were often shorter than 3 seconds. Praud et al. (60) reported that 88% of non-REM apneas were terminated by movement arousal, 12% with an EEG arousal. All the apneas in REM sleep were ended with a movement arousal, which was defined as an increase in EMG on any channel, accompanied by a change in pattern on any additional channel lasting for at least 2 seconds.

Overnight ECG monitoring in OSAS children has revealed reduced R-R intervals beginning a few seconds after initiation of obstruction, followed by increased R-R intervals when breathing resumed (61). Mograss et al. (51) found that 84% of all movement arousals in children could be detected using cardio-respiratory montage. The movement arousal is identified with tachycardia, increased amplitude and irregularity of respiratory inductive plethysmography signals, and distortion of the pulse waveform. A pulse increase linked to the obstructive event evidently indicates subcortical reactions (62). Children with OSAS have also been found to have higher sympathetic activity throughout the night than normal children (63).
2.4 Classification of sleep-related airway obstruction

The severity of upper airway obstruction can be considered to have a spectrum with increasing severity, from mild obstruction causing only snoring to the culmination of repetitive complete closures of the upper airways (apneas) (Fig. 1) (64). Primary snoring, UARS and OSAS seem to lie on a continuum (46), with a great deal of syndrome overlap (65). Due to the resembling symptomatology, the syndromes are hardly separated based on the symptoms and orocraniofacial information (65).

![Schematic spectrum of the severity of airway obstruction in children.](image)

**Fig. 1. The schematic spectrum of the severity of airway obstruction in children.**

2.4.1 UARS

Fragmented sleep due to repetitive arousals secondary to increased inspiratory effort has been blamed as the cause of the daytime symptoms of children with snoring but no apneas. In adults this is called the upper airway resistance syndrome (UARS), where inspiratory negative pressure increase causes a cortical arousal leading to an abrupt opening of the airways before an apnea occurs (66). However, excessive daytime somnolence, personality changes and neurocognitive impairments have been shown to occur in children with heavy snoring, restless sleep and large negative esophageal
pressure changes in the absence of apneas, desaturations or cortical arousals (67). Downey et al. (46) found no significant difference in the arousal index between snorers and children they felt to have UARS, whereas Guilleminault et al. (65) found no significant difference in the number of arousals in children with UARS and OSAS. The role of arousals in pediatric UARS is unclear (56), as is the best method of identifying UARS, since many children will not tolerate the esophageal catheter used to monitor the esophageal pressure required for detecting respiratory effort-related arousals, which method has been thought to be the best for recognizing abnormal breathing patterns during sleep (65). A recent finding suggests that a nasal cannula/pressure transducer could be a non-invasive reproducible detector of all events in sleep-disordered breathing, detecting also the same events as esophageal manometry (68), which can help to clarify the role of this syndrome in children.

2.4.2 OSAS

OSAS can be considered as the culmination of sleep-related obstructive disorders in children. OSAS arises from a series of events which repeat themselves during the night, and which can lead to daytime symptoms and development of health-related complications. A total collapse of the upper airway leads to an obstructive apnea, with no gas exchange at the level of mouth and nostrils. If the collapse is incomplete, an obstructive hypopnea with reduced gas exchange or a prolonged hypoventilation period occurs. Instead of repetitive discrete obstructive apneas, children often exhibit a pattern of partial obstructive hypoventilation characterized by snoring, paradoxical ribcage motion, phasic desaturations and hypercapnia (33, 40, 69). Though sometimes called the obstructive hypoventilation syndrome, this type of obstruction pattern is included under OSAS in children.

2.5 Diagnostic criteria for OSAS

Diagnostics of pediatric OSAS is difficult at least for two reasons: lack of universally accepted criteria for the syndrome and the unique demands of the children. Children will not always easily tolerate complex recording apparatus in and around them, which obviously is a problem from the technical point of view. For most of the information regarding the child’s symptoms one has to rely on the parents, who perhaps do not notice their child’s nocturnal symptoms unless their own sleep is disturbed.

The most accurate and comprehensive method of diagnosing OSAS is nocturnal polysomnography (70). The diagnostic criteria used for adults are found not to be suited for children (15, 16, 40). Basically in the studies of pediatric OSAS the children have the same clinical symptomatology, but may be differently classified due to different criteria and the recording methods used. The diagnostic criteria are usually based on a certain apnea/hypopnea index (AHI), but desaturations, hypercapnic episodes, and arousals may
be included in the criteria, then often called the respiratory disturbance index (RDI), either as their own parameters or in association with apnea or hypopnea. Different approaches to measuring RDIs may contribute to substantial variability in the identification and classification of the disorder.

Marcus et al. (16) have studied 50 normal children and adolescents and given recommendations for normal polysomnographic criteria (Table 1). Marcus et al. (16) found obstructive apneas to be very rare in normal children, whereas in older (pubertal) children are apneas perhaps not as uncommon. Most authors use lower indexes and shorter apnea times as criterion for pediatric OSAS than the index 5 and apnea duration 10 seconds originally presented by Guilleminault et al. (14).

Table 1. Abnormal polysomnographic criteria for children according to Marcus et al. (1992)

<table>
<thead>
<tr>
<th>Abnormal polysomnographic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) more than one obstructive apnea of any length per hour of sleep</td>
</tr>
<tr>
<td>b) central apneas associated with desaturation below 90% irrespective of the length of the apnea</td>
</tr>
<tr>
<td>c) peak end-tidal CO2 pressure &gt; 53mmHg or end-tidal CO2 pressure &gt; 45 mmHg for more than 60% of total sleeping time</td>
</tr>
<tr>
<td>d) arterial oxygen saturation values &lt; 92%</td>
</tr>
</tbody>
</table>

In the consensus statement of the American Thoracic Society (70) for standards and indications for cardiopulmonary sleep studies in children, only broad guidelines to determine abnormality for the respiratory events could be given.

2.6 Diagnostic methods

2.6.1 Polysomnography

(PSG) is the gold standard recommended for diagnostic investigation also in children (41). In the consensus statement of the American Thoracic Society (70), PSG is recommended to differentiate between primary (benign) snoring and snoring associated with either partial or complete airway obstruction, hypoxemia and sleep disruption. According to the consensus statement, polysomnography is indicated as a diagnostic tool in a variety of situations, most importantly: 1) for evaluating the child with disturbed sleep patterns, excessive daytime sleepiness, cor pulmonale, failure to thrive, or polycythemia unexplained by other factors or conditions, especially if the child also snores; 2) in the child who has clinically significant airway obstruction during sleep as observed by medical personnel, or documented by audiovideo recording. 3) Since children with OSAS are at a higher risk of postoperative complications (72), PSG is recommended if the surgeon is uncertain whether the clinical observation of obstructed breathing is sufficient to warrant surgery.
The exceptional demands of children make the pediatric PSG perhaps more demanding than for adults. Pediatric PSG should be as little invasive as possible so as not to disrupt the child’s usual sleeping pattern. Also, the surroundings should be appropriate for age and to accommodate a parent.

The measurements are obtained to assess the adequacy of ventilation, to differentiate between the obstructive and central apneas and to evaluate the severity and physiological consequences of the breathing disturbance (70). Usually a central apnea is scored when there are flat tracings simultaneously from strain gauges and the thermistor, and an obstructive apnea when continuous deflections are obtained from strain gauges while there is a simultaneous flat recording from the thermistor (23).

There are several parameters measured with PSG. The airflow is usually measured with an oro-nasal thermistor and/or a nasal CO₂ sampling catheter, which both can provide a qualitative airflow signal (42). The thermistor registers the airflow both from the mouth and the nostrils, but in order to do this, it must be attached to the upper lip. Quantitative measurements of airflow require an oro-nasal mask (pneumotachograph), or tracheotomy tube, and are therefore used mainly in research settings. The limitations of both methods can perhaps be circumvented with a recently introduced system for detection of respiratory events, the nasal cannula/pressure transducer (73).

The ventilation can be measured semiquantitatively with respiratory inductive plethysmography (RIP), where two bands measure the separate contributions of chest and abdomen to the tidal volume. When compared with pneumotachographic airflow measurement, RIP has been shown to have a 0.96 or greater correlation coefficient (74). Calibrated RIP can detect obstructive apneas and hypopneas (38). RIP may also prove to be useful in non-invasive diagnostics of UARS (75). The advantage of RIP is that it does not require attachments to the face.

The oxygenation of blood is usually measured with pulse oxymetry, which rapidly responds to changes in the blood oxygen partial pressures, with only the circulation time to the periphery as a systemic artifact. The oxymetry sensor is convenient but sensitive to movement artifacts and may easily be pulled off. The pulse waveform should also be monitored on a separate channel adjacent to the ECG signal to help to determine the accuracy of the saturation reading (70). Transcutaneous oxygen tension measurement has a long response time to rapid decrease in arterial oxygen saturation, so the decrease of oxygen tension with apnea may be difficult to quantitate (76).

The effective way to detect periods of hypoventilation is to measure the end-tidal CO₂, which is thought to reflect the alveolar CO₂ (42). The CO₂ pressure may also be measured transcutaneously, but then only a trend rather than transient changes can be measured (42).

Electroencephalogram should be included in PSG for sleep staging, together with electrooculogram to record rapid eye movements (70). Scoring arousals from an all-night EEG recording is a laborious manual process, so a recent finding suggests that an automated analysis of arousals implied from blood pressure rises could be a convenient alternative to EEG scoring (77). Submental or chin electromyogram (EMG) discharges can indicate changes in respiratory effort, whereas intercostal EMG used by some may allow monitoring of the diaphragmatic effort (41). Tibialis EMG monitoring is used to detect periodical leg movements. It can also help to quantitate movement arousals during PSG assessment of cardiopulmonary function (70).
The cardiac rate and rhythm should be monitored with electrocardiogram (70) to reveal cardiac consequences of obstructed breathing (39, 61).

Daytime nap studies should be interpreted with caution due to the circadian rhythm of many functions and the relative lack of REM sleep (41), as obstructive apneas and hypopneas are more common during REM than non-REM sleep (35, 53, 78). Nap studies seem to underestimate the degree of obstructed breathing, though they may have a screening value, since the positive predictive value of nap studies compared with overnight studies has been found to be 100% and the negative predictive value 17% (79).

There is often big discrepancy between PSG results and the clinical diagnosis score in children with strongly suspected OSAS (49), and it has been suggested that the diagnosis should be based on a combination of factors gathered from these forms of assessment (49). Reliance on EEG as an indicator may also be misleading by giving an underestimate of the clinical severity of sleep-disordered breathing in children (53). PSG is perhaps not necessary in all children with strong clinical evidence of OSAS, since PSG is so expensive and the availability may be poor (80). Sleep studies do, however, contribute to the clinical impression when assessing the need for operation or possible postoperative complications (81).

The first-night effect or night-to-night variability may influence the PSG-results (82), but there is no data on the reproducibility, sensitivity and specificity of a single-night PSG for children of different ages. In adults, the first-night effect on apneas and hypopneas is not significant (83).

The automated sleep analyses or computer-based scoring systems are not yet very reliable, and tend to overestimate the respiratory disturbances (84). The smaller oro-nasal airflow and respiratory movement signals as well as a displaced thermistor may be misinterpreted by the computer as apneas/hypopneas (84).

### 2.6.2 Clinical diagnosis

Many physicians have to base their diagnosis of OSAS on the clinical symptoms and signs of the children. The accuracy of clinical diagnosis of pediatric OSAS has been evaluated in a series of studies (31, 85-88), in which only half or less of the children proved to have OSAS despite symptoms strongly suggesting the condition. The results are fairly constant in spite of slightly different criteria used for OSAS in the studies. Scoring and screening methods for guidelines of diagnosis-making have been developed, both for the pediatric (89) and adult population (90, 91). Brouilette et al. (89) derived a symptom score which according to their research classified correctly all controls and 22 out of 23 OSAS patients. Observed apneas, constant snoring and difficulty in breathing during sleep were found to be fairly predictive of OSAS. Later the OSA score has been shown to misclassify a substantial number of patients (31), and to be even less accurate than clinical subjective impression (92). Goldstein et al. (88) found clinical diagnosis to have a 92% sensitivity and 29% specificity for right diagnosis of OSAS, and a 50% positive predictive value and 83% negative predictive value when compared to PSG-results. Parental information of apneas is reported to have high specificity (94%), but...
relatively low sensitivity (44%) (93), and the predictive accuracy of witnessed apneas was in one study found to be only 32% (85). A health-related quality of life (HRQL) survey has been proposed as a mean of determination of OSAS severity in children (94). In the study, the scores of the survey were significantly associated with the apnea-hypopnea score.

Some orofaciocranial features are found to be highly suggestive of breathing disorders during sleep when associated with specific clinical symptoms: a small chin, a steep mandibular plane, a retroposition of the mandible, a long face, a high hard palate, and an elongated soft palate (65). Guilleminault et al. (65) found a high score on a visual clinical orocraniofacial scale to be equally common in UARS and OSAS children, but if a child also scored high on tonsil-size grading OSAS was a more likely diagnosis than UARS.

**2.6.3 Pulseoximetry**

In adults, starting treatment based on results of nocturnal oxymetry suggestive of sleep apnea hypopnea syndrome has been suggested to be a way of decreasing the need for PSG (95). The clear disadvantage of the method is though, that it cannot differentiate between central and obstructive apneas and hypopneas. Lately, Brouilette et al. (96) demonstrated that a positive nocturnal oximetry trend graph including at least three or more desaturation clusters and at least three desaturations to under 90%, had at least a 97% positive predictive value in a child suspected of having OSAS. According to the authors oxymetry could be used as a definitive diagnostic test for straightforward OSAS attributable to adenotonsillar hypertrophy or for identifying children with obstructive symptoms who could require PSG. A negative oxymetry cannot rule out OSAS, so a high clinical suspicion warrants further investigations (97).

**2.6.4 Sleep sonography**

Sleep sonography, where the breathing sounds are recorded and analysed through computer processing, cannot differentiate between central and obstructive apnea, which is clearly a drawback of the method (98). Still, sonography may have value as a cheap screening method (98). Lamm et al. (99) found in their study of 29 children that findings on a home audiotape, where the presence of struggled sound and respiratory pauses are analysed manually, can be suggestive of OSAS, but they are not sufficiently specific to reliably distinguish between OSAS and primary snoring. Tracheal sound recordings together with O₂ measurement have been reported to be a reliable method of detecting respiratory events in adults (100). This method is not suitable for children either, as children often exhibit continuous snoring with hypoventilation/hypopneas instead of clear apneas (stop in breathing and sound) (40, 101).
2.6.5 Video and cardiorespiratory monitoring

Video-recording of the first 60 minutes of a child’s sleep has been suggested to be helpful in demonstrating sleep apnea (43, 102). Video recording can also be used to evaluate the time spent moving to measure sleep disturbance (43). Video-recording has been shown to be valuable as a part of cardiorespiratory video montage, where movement/arousals can be identified sensitively with the aid of cardiovascular channels and video recording, which helps to delete induced arousals (51) and to distinguish sleep from wakefulness, thereby reducing the need for EEG recording in pediatric polysomnography (78).

2.6.6 Radiology

Anteroposterior and lateral radiographs of the airway are the most common radiological examinations of children with suspected airway obstruction (103). But the airway obstruction is a dynamic phenomenon, and lateral neck radiography does not provide sufficient information on which to base a decision to perform adenotonsillectomy to relieve airway obstruction during sleep in children (104). The plain radiographs will nevertheless reveal anatomic abnormalities (103).

(Video)fluoroscopy has been performed on children to study the pathophysiology of OSAS (33, 105, 106). Videofluoroscopy can provide additional information to lateral radiographs and PSG in children with minor adenotonsillar enlargement or with predisposing factors (101).

Virtual endoscopy has proved to effectively show fixed lesions in the upper airways, but it is not sensitive enough to detect dynamic movements leading to obstruction (107).

Magnetic resonance imaging of the upper airways may reveal structural abnormalities in OSAS children (108).

2.6.7 Endoscopy

Flexible fiberoscopy has been shown to identify reliably the site of obstruction in children with anomalous upper airways with obstructive symptoms even when awake (109). Sleep nasoendoscopy combined with rigid laryngo-bronchoscopy has been suggested to be valuable in detecting the site of obstruction in children with residual symptoms after adenotonsillectomy (110).
2.6.8 Nasal cannula/pressure transducer

A recent finding suggests that a nasal cannula/pressure transducer could be a non-invasive reproducible detector of all events in sleep disordered breathing, detecting also the same events as esophageal manometry (68). The nasal cannula system consists of a standard oxygen cannula placed in the nares and attached to a sensitive pressure transducer that detects pressure fluctuations caused by inspiration and expiration. The pressure reading is taken from the distal end of the oxygen cannula with prongs that extend into the nose, thus measuring the pressure inside the nose. The flow signal is measuring a pressure drop across a relatively constant resistance at the inlet of the nose (73). The nasal cannula system permits the analysis of both flow and its morphology (111, 112), and may even detect snoring (112). The nasal cannula system seems to be more sensitive in detecting apneas and hypopneas than the thermistor (73). The system may be especially useful in identifying increased upper airway resistance and the presence of flow limitation (68, 73, 113). In conjunction with EEG, analysis of the shape of the nasal cannula flow signal, when transient inspiratory flattening suggests flow limitation, can be used to replace esophageal manometry in detecting respiratory-related arousals (68).

2.7 Prevalence

The prevalence of regular snoring in children is reported to vary between 3.2 and 11% (114-118). Irregular snoring is present in 17 to 27% of all children (116, 119). The prevalence of OSAS in the pediatric population has been reported to be 0.7–3.4 % in the epidemiological studies of the subject (114-116, 120).

The prevalence estimates may be affected by variability in respiratory event identification across laboratories (71). In groups of children with predisposing factors, such as morphological anomalies (ex. Mb Down) (121), allergy (122), and obesity (92, 123-125) the prevalence of sleep-related breathing disorders (SBD) is often higher. Passive smoking and smoking in pregnancy seem also to increase the risk for OSAS (118). Racial differences may also influence the prevalence of SBD’s, Afro-American and far-east Asians being at higher risk (120, 125-127). In contrast to adults, OSAS is equally common in both genders (15, 116, 120). More studies assessing the prevalence seem to be needed.

The prevalence of UARS is unclear, though it has been suggested that it may be as common as or more common than OSAS, based on a study where children with anomalies/syndromes were included (65).
2.8 Pathophysiology

The upper airway area, which is controlled by 30 muscles, has to serve many functions: it must enable speaking and swallowing and it must keep an open airway. The key force causing the closure of the upper airway is the suction pressure created by the inspiratory effort (128). A narrowed airway leads to higher inspiratory effort to maintain airflow into the lower airways, and when a so-called critical closing pressure (Pcrit) is reached (129), the muscle contraction force keeping the airway patent in the collapsible upper airway is overcome by the pharyngeal suction force, and subsequently a closure occurs (130). As in adults (131), the upper airway in children has been shown to behave in accordance with the Starling resistor model; when a collapsible segment is situated between two non-collapsible segments with fixed diameters, resistances and pressures (nasal and tracheal), closure in the collapsible segment occurs when the pressure surrounding the airway becomes greater than the pressure in the airway (Pcrit) (Fig. 2) (129). The model predicts that under conditions of flow limitation the maximal inspiratory airflow is determined by the pressure changes upstream (nasal) to a collapsible locus of the upper airway and is independent of the downstream (tracheal) pressure generated by the diaphragm. In adults it has been shown that Pcrit is higher in patients with OSAS than in primary snorers (132), and decreases after treatment (uvulopalatoplasty) in those who respond in a clinically favourable way (133). There is some evidence that this would also be the case in children, as Marcus et al. (129) found in a study with a small material that Pcrit for OSAS children declined after treatment and clinical improvement, but was still higher than in primary snorers. The Pcrit is similar in children and adults with OSAS (129, 132), but markedly lower in children than adults with primary snoring, suggesting a less collapsible upper airway in children (129, 134). Children seem to respond to subatmospheric pressure loading by neuromuscular activation far better than adults, preventing airway collapse (135). Isono et al. (134) found children with sleep-disordered breathing to have positive closing pressures, while normal control children had subatmospheric closing pressures when fully paralysed with muscle relaxant. The closing pressure was found to be highest at adenoidal/tonsillar level, whereas in control children the soft palate and retroglossal areas were the primary sites of closure. These areas also closed with higher pressures in the obstructed than in the control children. In adults it has been shown that normal men develop obstructive apneas of different intensity in sleep when subjected to application of subatmospheric pressures (136), whereas children seem to be able to better maintain the upper airway patency when subjected to subatmospheric pressures (135).
Fig. 2. The Starling resistor model of upper airway. The airway is represented by a tube with a collapsible segment (pharynx) between two rigid segments with fixed diameters, resistances and pressures (nasal and tracheal segments). The airway collapses when the pressure surrounding the airway becomes greater than the pressure within the airway.

Despite the fact that the adenoids and tonsils have been pointed out as the cause of OSAS in children in the majority of cases (14, 33, 36), there must be an underlying tendency to airway obstruction, as reviewed above, since many children with enormous tonsils have no respiratory problems, while some children with OSAS without exceptionally large tonsil and adenoid tissue (101, 137) with perhaps subtle predisposing conditions (138) get cured with tonsillectomy (139), but may have underlying predisposing conditions. Airway obstruction and OSAS are dynamic phenomena resulting from a combination of structural and neuromotor abnormalities that may occur in some children. Loss in sleep of neuromuscular control reflexes of upper airway muscles that are intact during wakefulness has been shown to happen in adult OSAS patients significantly more than in controls (140), and is obviously the case also in children, as they do not snore while awake.

In normal children (infants) there is very little movement of the pharyngeal soft tissues in sleep (141). Videofluoroscopy has demonstrated how the inspiratory obstruction may involve forward movement of the retropharyngeal soft tissues, medial movement of the lateral pharyngeal walls, inferior and posterior displacement of tonsils, posterior displacement of tongue and posterior movement of the mandible (33, 101, 105). In some children the soft palate is found to be sucked into the airway, though less constantly (101). These same changes have been demonstrated through endoscopy during sleep in children with anomalous upper airways (109). Genioglossus hypotonia is unlikely pathogenesis for OSAS in children, as genioglossus activation increases during partially obstructed breathing (142). Praud et al. (143) found no decrease in genioglossus or diaphragmatic EMG activity in children with obstructed breathing due to enlarged tonsils at the onset of obstructive apnea, but instead a significant increase in the genioglossus EMG activity preceding the end of the apneas.
The pharyngeal dilating muscles, which relax in sleep, are controlled by various reflexes and stimuli. What is the main reason for imbalance in these reflexes in OSAS children is unknown. Increased neuromotor tone of the pharyngeal dilating muscles has been shown to be a compensatory mechanism for narrowing of the upper airways in adults, but due to the invasive methods required, similar studies have not been performed on children (144). The upper airway muscles are muscles accessory to respiration, and have in animal models proved to be prone to activation by chemical stimuli (145). The ventilatory drive in children seems to be fairly normal in contrast to adults (135), in whom the ventilatory responses to hypercapnia and hypoxia are significantly decreased in OSAS patients (146), but normalized after treatment (147). Breathing responses to exposed hypoxia and hypercarbia have been compared between OSAS children and healthy controls, and no significant difference was found between the children during wakefulness (148) nor during sleep (55). The sleeping children had slightly blunted arousal response to hypercapnia, correlating with the apnea index (55). Hypoxia was found to be a poor stimulus to arousal. Artificial CO₂ increase resulted in decreased airway obstruction. OSAS children have also been found to have blunted arousal threshold to inspiratory resistive loading, suggesting together with the responses to hypercapnia that children with OSAS may have a generalised deficit of arousal in response to respiratory stimuli (149).

Functional magnetic resonance imaging has revealed respiratory loading to cause significant signal increase in discrete brain regions (150).

In OSAS children sympathetic activity has been found to be higher and the parasympathetic activity lower throughout the night when compared with normal children (63). It is unknown, whether obstructive apneas cause increased sympathetic activity or increased sympathetic activity is the predisposing factor for development of apneas.

### 2.9 Etiology

In most reports, hypertrophy of the tonsils and adenoids is considered as the major cause of OSAS in children (14, 33, 36, 93, 101, 151). The size of the palatine tonsils is not necessarily decisive, though usually children with OSAS have larger adenoids and tonsils compared with other children (108, 152). Magnetic resonance imaging of the upper airways has shown that OSAS children have smaller volume of the upper airways than matched control children (108). There exists no study where the relationship between the tonsils and adenoids in order of importance as the etiological factor of OSAS would have been systematically studied. The adenoids and tonsils are often considered as a “bulk”, and the treatment has then been described in many reports as tonsillectomy or adenoidectomy or both. The role of the adenoid in producing nighttime apneas and hypventilation is probably smaller than that of oropharyngeal tissues; bare adenoidectomy is not always a curative treatment of OSAS in otherwise normal children, even if it can give temporary relief, while tonsillectomy then relieves the obstruction (116). Croft et al. (93) found no relationship between the nasal airway patency and the degree of snoring/apneas, whereas there was a significant relationship between tonsillar
position and size and sleep grade. The thickness of the pad of adenoids in lateral
cephalometry was not important. Mahboubi et al. (104) stated that the radiologically
assessed adenoidal size would not give much information about the degree of airway
obstruction, whereas Fernbach et al. (101) found hardly any OSAS-children to have an
adenoidal-nasopharyngeal ratio greater than two standard deviations above the mean
value of normal controls. In one study has the adenoid size been found to correlate to the
severity of apneic periods but not to the number of episodes of obstructive apnea in
children (153). Brodsky et al. (154) reported that the velopharyngeal sphincter, one of the
key sites of obstruction in adult OSAS, seems to be enlarged in children with large
obstructing tonsils due to a shorter soft palate. The authors concluded that the obstruction
is not at the nasopharyngeal level, but rather in a small diameter oropharynx, which gets
crowded with low density/high volume tonsils. In another study Brodsky et al. (151)
demonstrated that much of the smaller distance between the medial tonsillar surface in
children with obstruction compared with those without obstruction is explained by the
smaller diameter between the lateral pharyngeal walls.

Any anatomical abnormality which can affect the upper airway may potentially impair
nocturnal respiration. In the early report by Guilleminault et al. (14) 26 out of the 50
children had so-called secondary OSAS; 14 children had either micrognathia-
retrognathia, Pierre-Robin syndrome, Crouzon disease, Treacher-Collins syndrome,
trismy 21 (Downs syndrome), webbed pharynx or obstruction secondary to surgery for
cleft palate. Other contributing underlying diseases may be arthrogryposis multiplex,
temporomandibular joint ankylosis, Larsen syndrome (33) or Goldenhar syndrome (155).
Hypoplasia of the skeletal and cartilaginous tissues and/or hyperplasia and hypotonia of
soft tissues such as relative macroglossia and glossoptosis (156), and lingual tonsil
hypertrophy (157) may also contribute to upper airway obstruction. Bower et Gungor
(158) have listed 48 syndromes/diseases which may predispose to OSAS. Any
neurological or muscular (neuromuscular) deficiency affecting the muscle tone in the
upper airways or the breathing muscles can also predispose to OSAS (14, 33, 159).

In contrast to adults, only the minority of OSAS children are obese (15). Obesity may
increase the risk of OSAS (92, 120, 123, 124, 153, 160), especially in morbidly obese chil-
dren (ideal body weight exceeded by 200%) (161). In a study of 32 massively obese chil-
dren, 93% had abnormal sleep study (nap study)(161). In another study with a similar type
of patients, 32% (13/41) of the obese children had mildly abnormal PSG, while two had
seriously abnormal PSG (160). In unselected material are OSAS children, however, not
markedly more obese than children with primary snoring (31).

Allergy seems to be associated with an increased risk of snoring and OSAS in children
(117, 122). Children with sinus problems and persistent wheeze as an indication of asthma
are also at increased risk of developing obstructive sleep disorders (120).

The importance of familial predisposition in developing OSAS in adults has been
pointed out (3, 120, 162-164). There has also been seen increased risk of OSAS in infants
with familial predisposition (165).

Ethnicity may be a risk factor in OSAS. Redline et al. (120) have found Afro-American
children to be at higher risk of developing obstructive sleep disorders. Far-East-Asian men
seem to have more severe OSAS than white men though being usually non-obese, probably
due to craniofacial anatomical differences (127).
Though tonsillar and adenoidal hypertrophy is the major cause of OSAS in children, it is important to be aware of the possible predisposing factors when inspecting and examining children with suspected OSAS. The natural history of OSAS may be different in children with underlying conditions and treatment modalities may be more demanding (155).

### 2.10 Morphological and odontological considerations

The developing facial skeleton may be influenced by obstruction and mouth breathing caused by adenoidal and tonsillar hypertrophy (166). By the age of four, the facial skeleton has attained 60% of adult size and by the age of 12, 90%. There is a continuous interaction between airway patency during sleep and maxillo-mandibular growth (167). Obstructed breathing leading to an extended position of the head has been shown to affect even the morphology of the first vertebra (atlas) (168). Children with obstructed nocturnal breathing seem to alter the posture of the head to improve the airflow (54), which affects the soft tissues which mould the facial skeleton. Children with OSAS seem to have a narrower width of maxilla and longer dental arches than non-obstructed children (169). Guilleminault et al. (65) found that a small chin, a steep mandibular plane, a retroposition of the mandible, a long face, a high hard palate, and an elongated soft palate were common among children with obstructed breathing. In addition to significantly reduced mandibular protrusion, the hyoid bone has been found to be significantly lower in OSAS children than in age matched controls (152).

It has been shown that children with tonsillar obstruction have a lot of bite anomalies, like open bite and lateral cross bite, which diminish or disappear over two years after treating the obstruction (170). The authors speculated that early treatment of obstruction might development of OSAS in adulthood. The dental/facial irregularities seem to worsen during periods of fast growth and rarely reverse spontaneously (171).

### 2.11 Clinical symptoms

Symptoms of OSAS in children differ in several ways from those in adults, and may be only nocturnal (Table 2). Despite a troublesome struggle throughout the night, the children may be quite symptomless in the daytime, at least in the initial stages of the syndrome. Excessive daytime somnolence, the hallmark of OSAS in adults, is encountered only in a minority of children with OSAS (15, 172).
Table 2. Comparison of the symptoms and some other features of OSAS in adults and children

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snoring</td>
<td>Often continuous, snorting</td>
<td>Loud, alternating with pauses</td>
</tr>
<tr>
<td>Predominant respiratory pattern</td>
<td>Mixture of obstructive, mixed and central apneas and hypoventilation</td>
<td>Obstructive apneas predominate</td>
</tr>
<tr>
<td>Sleep structure</td>
<td>Normal macrostructure</td>
<td>Sleep pattern disruption</td>
</tr>
<tr>
<td>Arousal on apnea termination</td>
<td>Usually not</td>
<td>Nearly always</td>
</tr>
<tr>
<td>Nighttime mouth-breathing</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Restless sleep</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Sweating during sleep</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Odd sleeping positions</td>
<td>Common</td>
<td>Not common</td>
</tr>
<tr>
<td>Excessive daytime sleepiness (EDS)</td>
<td>Minority of patients, rather hyperactivity, behavioral changes</td>
<td>Main presenting symptom</td>
</tr>
<tr>
<td>Daytime mouth breathing</td>
<td>Common</td>
<td>Not common</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>May be present, poor school</td>
<td>May be present</td>
</tr>
<tr>
<td></td>
<td>performance</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>Minority of patients</td>
<td>Majority of patients</td>
</tr>
<tr>
<td>Growth or weight retardation</td>
<td>Not rare</td>
<td>No</td>
</tr>
<tr>
<td>Gender</td>
<td>Male-female 1:1</td>
<td>Male-female 8:10:1</td>
</tr>
<tr>
<td>Enlarged tonsils and adenoids</td>
<td>Most common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Complications</td>
<td>Cardiopulmonary, growth,</td>
<td>Mainly cardiopulmonary and complications of EDS</td>
</tr>
<tr>
<td></td>
<td>behavioral, developmental</td>
<td></td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>Adenotonsillectomy curative in</td>
<td>Only in selected cases</td>
</tr>
<tr>
<td></td>
<td>most cases</td>
<td></td>
</tr>
</tbody>
</table>

2.11.1 Nighttime symptoms

Snoring has in most studies been found to be the most common symptom of pediatric OSAS (Table 3). While in all reports most OSAS children are found to snore every night, only in the early report by Guilleminault et al. (14) were all children observed to snore constantly. The snoring is typically interrupted by pauses and associated by snorts. The respiratory effort is frequently increased during obstructed breathing, observed as retractions, use of accessory muscles and paradoxical breathing (158). Detected apneas by the parents have been found to have high specificity (94%), but relatively low sensitivity (44%) (93), which last number is fairly well in line with the figures in Table 3. The other common symptoms mentioned in many reports are restless sleep, mouth breathing, profuse sweating, nightmares and enuresis (Table 3). Some of these symptoms, at least enuresis, may be influenced by age. Reappearing enuresis after toilet training probably has greater significance as a significant symptom than enuresis per se (14).
Table 3. Most common nighttime symptoms of pediatric OSAS and their prevalence in various reports.

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Snoring (every/most nights) (%)</th>
<th>Difficulty breathing in sleep (%)</th>
<th>Observed apneas (%)</th>
<th>Restless sleep (%)</th>
<th>Sweating (%)</th>
<th>Enuresis (%)</th>
<th>Night terror/mares (%)</th>
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<tr>
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<td>50</td>
<td>100</td>
<td>84</td>
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<td>75/87</td>
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<td>88</td>
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Other nighttime symptoms reported are awakenings, cyanosis, insomnia (1, 31, 87, 89). Sometimes the symptoms connected with bedtime, such as struggling, bed resistance, sleep-walking, sleep-talking, nightmares and restless sleep, may be due to behavioural disorders, which can accompany OSAS (173).

### 2.11.2 Daytime symptoms

Excessive daytime sleepiness (EDS), the hallmark of OSAS in adults, is not common in children (15, 36, 126, 172). Though reported in many papers as a possible symptom of pediatric OSAS (1, 87, 89, 174, 175), only in two studies by Guilleminault et al. (14, 65) has EDS been the most commonly presented complaint (84% and 86%). In a recent study, where a multiple sleep latency test was performed on 54 prepubertal OSAS children, less than 15% of the children exhibited EDS (172). In a survey study with 782 pre-school-age children regular snorers were found to have higher risk of EDS, but over the two-year follow-up period daytime overall sleepiness decreased from 20.7 to 11.2%, though the prevalence of snoring remained constant (114, 115). This indicates perhaps some age dependency of sleepiness in children. The children must also often follow the hectic time schedules of their parents, which may lead to an insufficient amount of sleep, especially in the younger ones, which can be a difficult parameter to control in clinical trials. Anyhow, in the study, daytime sleepiness increased significantly across the snoring categories (115).
The characteristics of pediatric OSAS with periods of prolonged hypoventilation or hypopneas with no necessity of abundant EEG arousals is probably one explanation for the relative rarity of EDS in pediatric OSAS. The possible autonomic reactions seem not to disturb the macrostructure of sleep (57). However, obesity and very high apnea indexes seem to increase the risk for EDS (172). Another explanation is that sleepiness in young children may be difficult to distinguish. Rather than being sleepy, children may show behavioural deterioration or outbursts, and increased activity (176). Indeed, externalizing behaviour problems such as hyperactivity, irritability, bizarre behaviour, personality changes, bed resistance, school and learning problems and morning headaches are frequently reported symptoms of OSAS in children, but none is patognomonous for OSAS, and the reported prevalence of these symptoms is usually well below 50% (14, 89, 174). Authors who have reported the highest incidence of these symptoms in OSAS children have included children with serious facial dysmorphism, neuromuscular disorder or general medical problems in their study material (14), which obviously explains the difference in reported frequency of daytime symptoms compared with other reports. Goldstein et al. (177) reported abnormal behaviour in 28% of children scheduled for adenotonsillectomy due to chronic upper airway obstruction, with obvious improvement after treatment.

Even in mild forms of obstructive sleep disturbances, aggression, inattention and hyperactivity have been found to improve after adenotonsillectomy, along with a positive effect on vigilance, reflectiveness and impulsivity (178). On the other hand, Harvey et al. (179) did not find successful treatment of OSAS to result in any significant changes in overall development or temperament.

Sometimes the daytime symptoms in OSAS children may be secondary to primary behavioural sleep disorders, as children with OSAS and co-morbid behavioural sleep disorders have been found to have significantly more daytime behaviour problems than OSAS-children without the accompanying condition (173). Children with adenotonsillar hypertrophy and signs of upper airway obstruction have also been found to have less daytime behavioural problems than children with attention-deficit disorder (180).

School problems may lead educators to request clinical investigations of abnormally behaving children (14). Besides behavioural problems, obstructive sleep disorders may also adversely affect learning performance; poor academic scores of first-grade children with nighttime obstructed breathing have also been found to improve significantly after treatment (181). In obese children, the number of apneic/hypopneic events has been found to significantly and inversely correlate with memory and learning abilities (123).

Most of the studies concerning neurocognitive and behavioural functions in sleep-related breathing disorders lack objective measurements, and are mainly based on parental reports. Professional educators may also have a different evaluation of the child’s behaviour than the parents. Ali et al. found (178) found children with obstructed nighttime breathing to, after adenotonsillectomy, improve statistically significantly in all three behaviour subscales (aggressiveness, inattention and hyperactivity) on Conner’s behaviour scale of the parent questionnaire, while the teachers, who completed the same questionnaire, had not observed any obvious changes, despite a significant improvement was found in the children postoperatively when objective tests measuring attention,
reflectiveness and impulsivity were performed. Interestingly, the children considered as plain snorers scored also significantly better on the objective tests 3 to 6 months after surgery.

It has been mentioned in many reports, that children with OSAS suffer from frequent upper airway infections (89, 167, 174). In fact, Brouilette et al. (89) found a highly significant difference in the frequency of upper airway infections in children with OSAS and the control group, with 83% of the children having frequent infections, and increased difficulty breathing during the infections. Carroll et al. (31) found no difference in the frequency of “runny nose” between OSAS children and primary snorers (33% each).

### 2.12 Complications

OSAS may lead to serious, even life-threatening complications in children (182). What is the level of apneic events and duration of OSAS needed to increase the risk leading to complications is unknown. Evidence exists that even mild forms of sleep disturbance may have deleterious effects affecting the daytime functioning of the child (178). On the other hand, PSG-defined severity of apneas or development of cardiovascular complications has not been found to have a clear relationship with the duration of symptomatology (36). Frank et al. (36) reported that many OSAS children had had symptoms lasting up to five years without progression in severity or development of complications, whereas some children developed severe symptoms and complications in just a few weeks.

### 2.12.1 Failure to thrive

Children with OSAS may show slowed weight- and height-gain. Typically children start falling from their weight and height curves, and after the relief of their airway obstruction they experience a rapid “catch-up growth”, the weight increase being especially rapid (8, 33, 43, 67, 102, 183-186). High prevalence of failure to thrive, 52% (67) and 27% (33), have been found in studies where children with anatomic abnormalities or other handicaps have been included in the study material. The causes of poor growth are not known. Suggested causes for underheight and -weight are poor appetite and recurrent tonsillitis (43), difficulties in feeding, increased work of respiration and of caloric expenditure (102, 186), abnormal nocturnal growth hormone secretion (1, 187), and nocturnal acidemia impairing end-organ response to growth factors (183). In a recent study it was shown that the respiratory improvement after adenotonsillectomy in children with OSAS is associated with a significant increase both in serum Insulin-like growth factor-1 (IGF-1) levels and weight (188). IGF-1 is thought to be the main mediator of the growth-promoting actions of GH (189), reflecting the daily mean GH levels, and is thought to correlate well with physiological changes in GH secretion (190).
Probably depleted GH-secretion is not the only cause of failure to thrive, since OSAS-children may also be obese (14, 160, 161), but, in contrast to adults, only the minority (15). On the other hand, obesity has been found to be linked with higher risk of obstructive sleep disorders in children also (120).

2.12.2 Cardiovascular complications

2.12.2.1 Cor pulmonale

Cor pulmonale due to chronic upper airway obstruction in children has been well reported (14, 33, 183, 191-193). Already before OSAS was recognized as a clinical entity, case reports of children with obstructing tonsils and adenoids who had cor pulmonale were published (6-9). Children with apparent OSAS suffering from congestive heart-failure and even pulmonary oedema, which resolved after treatment, have been described (9, 192).

The prevalence, the needed severity or duration of the syndrome leading to cor pulmonale is not known. Most of the reports of pediatric cor pulmonale secondary to OSAS are case-reports, with only the early reports presenting a high incidence in bigger series (14, 33). In a study with stringent criteria for OSAS no abnormal electro- or echocardiograms were found in any of the studied 30 OSAS children (88).

Cardiac changes may take place without evident clinical features, with reversal after treatment (194, 195). The right ventricular ejection fraction has been found to be reduced in some children with clinically diagnosed OSAS, despite normal physical examination, chest radiography and ECG (194). Changes in the internal ventricular dimensions correlating with the degree of peak negative inspiratory pressure have also been found in snoring children without daytime evidence of cardiovascular complications (195).

2.12.2.2 Hypertension

In adults hypertension is a common complication of OSAS. As regards children there exist somewhat controversial findings. Only the minority seem to have clearly abnormal blood pressure (14, 88). Marcus et al. (196) found the mean blood pressure to be elevated in OSAS-children compared to primary snorers and age-appropriate normative data. The diastolic blood pressure, especially in sleep, was found to be significantly higher in OSAS children than in primary snorers, who both had relatively high blood pressure compared with normative data, though the majority of the children were within the normative range. Tracheotomy has been found to eliminate hypertension in children with OSAS (197).
The etiology for hypertension secondary to OSAS has been widely studied in adults, with sympathetic nervous system activation secondary to arousal and/or hypoxemia and changes in cardiac output secondary to increased intrathoracic pressure as the probable causes (196). Parasympathetic dysfunction in OSAS patients may also be linked with cardiovascular morbidity (198). Cardiac reactions due to autonomic nervous system changes triggered by subcortical arousals (51) have been suggested as the cause of development of OSAS-related arterial hypertension in children (196).

2.12.2.3 Arrhythmias

Serious cardiac arrhythmias in OSAS-children are found to be infrequent (39, 44). In the study by D’Andrea et al. (39), no evidence of life-threatening cardiac arrhythmias were found among 12 children with serious desaturations. The average heart rate during obstructive periods decreased statistically significantly, but the change was small, only about 5%. In another study OSAS was found to alter the beat-to-beat variation in a characteristic fashion, more pronounced at slow heart rates, but in this study either no serious arrhythmias were found (61). OSAS-children have in one study been found to have significantly higher overnight pulse frequency than matched children, presumably due to hypoxemia rather than arousals, according to the authors (43). Baharav et al. (63) found changes in heart rate variability in power spectrum analysis of instantaneous fluctuations, with low frequency power being higher in OSAS patients than controls for all sleep stages. The differences were less obvious on visual inspection.

2.12.3 Developmental aspects

Behavioural disorders, which have been reported in OSAS children (14, 33, 173), may have negative long-term consequences for the children, if they last for a longer period (199). Learning problems may occur at school age. In a study by Gozal (181), first-grade pupils with academic scores ranked in the lowest 10th percentile with sleep-associated gas exchange abnormalities, were found to get clearly improved grades after adenotonsillectomy, while those not operated on had no change in their grades. There is also a risk of “learning debt”, since based on a large survey study there are indications that young children who snore loudly and frequently during their sleep are at higher risk of exhibiting lower grades in school several years after the snoring has resolved (200). Aggression, inattention and hyperactivity have been found to improve after adenotonsillectomy in children with mild sleep disturbance according to a parent questionnaire. Surgery also had a positive effect on vigilance, reflectiveness and impulsivity. (178) In a preliminary study of obese children, the number of apneic/hypopneic events was found to be significantly and inversely correlated with memory and learning abilities (123).
2.13 Treatment

2.13.1 Surgery

2.13.1.1 Adenotonsillectomy

Tonsillectomy and/or adenoidec-tomy has proved to be a curative treatment of pediatric OSAS in most cases of normally developed children, where the most likely cause is adenotonsillar hypertrophy (14, 33, 39, 56, 86, 88, 93, 139, 170, 174, 201), even if the tonsils and/or adenoids would not be seemingly enlarged (101, 139, 174, 202). As mentioned earlier, different anomalies or concomitant diseases may predispose to OSAS, and in such cases adenotonsillectomy is not necessarily a satisfactory treatment (33, 155, 156, 203), though in many cases of “secondary OSAS” adenotonsillectomy has proved to be effective (14, 159). Relapses may nevertheless occur in adolescence, probably due to morphological causes and hormonal changes in boys (204). Persistent or reappearing OSAS later in childhood/adolescence seems to be strongly correlated with obesity and Afro-American ethnicity (125).

Adenotonsillectomy has also been shown to be an effective treatment of children suspected of having UARS (67).

Adenoidec-tomy is not always a curative treatment even though the adenoid is enlarged and a supposed site of obstruction (116, 183). Levy et al. (9) reported that the symptoms of a child with obvious OSAS were alleviated by adenoidec-tomy, but the pulmonary pressure remained abnormally high. The authors did not consider tonsillectomy.

Tonsillotomy has recently been advocated as an alternative to tonsillectomy due to less postoperative pain and shorter convalescence, with results fairly well comparable to conventional tonsillectomy (205, 206).

The predominant cause of adenoidec-tomy and tonsillectomy is recurrent infections (207), but there has been a dramatic increase in OSAS as a significant indicator for surgery (208). Tonsillectomy is reluctantly performed on children under three years of age: sleep apnea seems to be the leading cause for operation in this age group (209, 210). The incidence of OSAS in children is feared to increase, as the total amount of these operations is declining due to increased use of antibiotics (211), although tonsillectomy and adenoidec-tomy currently are the most common pediatric surgical procedures performed. Tonsillectomy decreases effectively the frequency of throat infections (207), during which the prevalence of snoring has been shown to increase, and obstructive symptoms are expected to worsen (119). The prevalence of pediatric OSAS is probably regionally unequal, as there are great regional differences in tonsillectomy rates due to different criteria for surgery (207). Interestingly, all ear, nose and throat-consultants or general practitioners do not recognize OSAS as indication for tonsillectomy (2, 3). Parental pressure may also sometimes influence decisions about surgery (2).
2.13.1.2 Maxillo-facial and related surgery

Obstructed breathing may affect the development of facial morphology just as the abnormal facial morphology may be the etiology explaining obstructed breathing. Treatment of OSAS has been shown to improve dentofacial deformities (138, 202). Maxillofacial surgery is rare in children, and obviously applied only in OSAS cases with upper airway anomalies, where adenotonsillectomy is either insufficient or contraindicated. Possible operations are mandibular and/or maxillary osteotomy, tongue-hyoid suspension, maxillary expansion combined with soft-tissue reduction procedures (44, 155, 212).

In children with anomalies or neuromuscular compromises, methods shown to be effective in adults have been applied to children with good results (155, 156, 212). Burnstein et al. (155) launched the “Airway zone concept” stressing the importance of recognizing the multifactorial etiology of OSAS in these children. Since the treatment is usually quite straightforward in children, adenotonsillectomy is still usually the preliminary procedure before more advanced surgical procedures (tongue reduction, tongue-hyoid suspension and jaw surgery). It is important to be aware of anatomical abnormalities, such as long soft palate, subclinical mandibular or lingual displacements, which may explain residual symptoms seen in some after tonsillectomy (34). Recurrence of symptoms requiring treatment occurring in adolescence in some boys is probably due to underlying craniofacial morphological changes (204). A small percentage of children with adenotonsillar hypertrophy but no other risk factors for OSAS are not cured by adenotonsillectomy (86), and may require further treatment, for example CPAP (213).

2.13.1.3 Uvulo-palato-pharyngoplasty

The initially very promising treatment of OSAS in adults (214) has later been shown to require accurate diagnosis to be effective treatment of OSAS. In children this operation is rare, but obviously effective, when the criteria are right, though usually preceded by (adeno)tonsillectomy (44, 138, 155).

2.13.1.4 Tracheotomy

Tracheotomy is hardly an alternative in cases where adenotonsillar hypertrophy is the leading cause of OSAS, due to risks of substantial decreases in the quality of life (215). In the early reports of pediatric OSAS, tracheotomy was not an uncommon therapeutic alternative (13, 14, 33). Tracheotomy to a child is a heavy treatment, and problems like inaccurately fitting tubes, granulation, infections and depression have to be overcome (14). The need for tracheotomy has diminished due to developed new treatments, such as CPAP (203, 213, 216), and vigorous surgery (155). According to Cohen et al. (215), parents of children with performed tracheotomy due to OSAS found 95% of the
controlled parameters worse than the parents of children who had undergone even extensive surgery for OSAS. In serious cases of OSAS where nothing else gives a satisfactory result, tracheotomy is curative, since the obstruction is by-passed.

2.13.1.5 CPAP

Continuous positive airway pressure (CPAP) is an effective treatment of OSAS also in children, especially in cases of congenital malformations, when in the past tracheotomy usually had to be performed, if adenotonsillectomy failed to relieve a serious obstruction (203). Many of the technical problems with the device and poorly fitting nasal masks (203) have been overcome (213), and nasal CPAP has been found to be an effective and generally well-tolerated therapy (216). In the multicenter retrospective study by Marcus et al. (213), data was obtained from 94 patients evenly divided between different age categories. The compliance rate to CPAP treatment was estimated to be between 50 to 100%, the younger children being more compliant. Of the patients with adequate compliance, CPAP was effective in treating OSA in all but one case.

In the multicenter study the main reasons for CPAP treatment was associated obesity (27%), craniofacial anomalies (25%), idiopathic OSAS (persisting after adenotonsillectomy) (18%) and Down syndrome (13%). All centres still recommended adenotonsillectomy as primary treatment, in case contraindications to surgery did not exist. In the study by Waters et al. (216) only 5% of the 82 children needing CPAP after adenotonsillectomy had idiopathic OSAS, whereas upper airway structural and functional abnormalities accounted for 62% of the cases where CPAP was used. The success rate for treatment was 86%. CPAP therapy may be of value when preparing children with serious OSAS for operation (216, 217).

2.13.2 Other

OSAS-children are rarely seriously overweight (15). Obesity is, however, shown to be linked with higher incidence of PSG abnormalities (160, 161), and possibly even higher prevalence of OSAS (92, 126), so, in case of overweight, reduction will not be harmful.

Radiofrequency volumetric tissue reduction of the soft palate is a promising method of treating snoring in adults (218, 219). The method has few adverse effects, but there is no experience of its use on children.

Supplemental oxygen has been shown to improve the oxygenation of OSAS children with significant hypoxemia without necessarily blunting the hypoxic ventilatory drive (220), though the number or duration of apneas is not affected (221). This method is suggested to be used temporarily when waiting for definitive treatment in children in a serious situation (220).

Corticosteroids have been shown to be ineffective in the treatment of OSAS; prednison did not diminish the adenotonsillar hypertrophy nor symptomatology (201).
Radiation therapy, used to regress the lymphoid tissue in the two cases presented by Noonan (7), belongs inevitably to the past.

2.14 Treatment complications

The most common complication after pediatric adenotonsillectomy is local bleeding, with a reported incidence 2–4%, requiring operative re-intervention in 0.06–2% of all the children operated on (222, 223). The more serious complication is airway obstruction, occurring in ~1%–2% of unselected operative child material (209, 223). Rosen et al. (217) found the risk of postoperative airway complications to be very high among OSAS-children with underlying medical conditions in addition to enlarged tonsils and adenoids to explain the presence of OSAS. The high-risk clinical characteristics were found to be young age, craniofacial anomalies, failure to thrive, hypotonia, morbid obesity, large extent of operation, high RDI and serious desaturations. McCollery et al. (72) found 23% (16/69) of OSAS-children to have severe respiratory compromise after adenotonsillectomy, defined as intermittent or continuous desaturation to 70% or less and/or hypercapnia. Young age (under three years) and high obstructive event index (>10) were found to be the most important risk factors. In one study children with mild OSAS were found to have a small improvement rather than worsening of their respiratory status on the night following adenotonsillectomy (224). The results should not be extrapolated to children with more serious OSAS though, since they were not studied.

Pulmonary oedema has been reported as a possible complication following relief of acute (225) or chronic airway obstruction (226). In chronic airway obstruction there is probably an underlying cardiac complication (cor pulmonale, even right cardiac failure) predisposing to oedema when the airway obstruction is suddenly relieved (226). Inhalation halothane anesthesia induction may provoke airway obstruction, so intravenous access should be established even before the child is asleep (224). Extreme caution has been warranted after surgery for children with serious OSAS (224), and in general children with OSAS should undergo inpatient surgery (32, 102).

2.15 Natural history

The natural history of OSAS is unknown (44). In severe cases it may be poor, with serious complications developing (33, 36). What is the level of obstructive disorders and the needed time for serious complications to develop are so far unknown. The PSG-defined severity of apneas or the development of cardiovascular complications have not been found to have a clear relationship with the duration of symptomatology (36). Many OSAS children may have symptoms lasting up to five years without progression in severity or development of complications, whereas some children developed severe symptoms and complications in just a few weeks (36). Recent studies indicate though that even mild forms of sleep disturbance have measurable effects on children’s daytime
behaviour and neurocognitive functions (178, 227). There may often be a long delay between the onset of symptoms and treatment, during which time the children/parents can experience severe and discomforting symptoms (3, 36). In Richards & Ferdman’s study (3) 82% of the children had a delay over one year, 51% over two years and 13% over as many as six years.

Is there a trend in children that snoring and obstruction tends to get worse over time as in adults? Snoring has been shown to have a stable prevalence in preschool-age children in two studies by Ali et al. (114, 115). In their studies initially four to five-year-old children were studied two years later. Twelve per cent of the children snores regularly at both times, but half of the children who had snored regularly at the time of the first study no longer did so at the time of the second study. This would suggest that as snoring may be self-limiting in children, also obstructive disorders could be at least in some cases temporary. In children primary snoring seems rarely to progress to OSAS over the years, and if so, the syndrome is mild (32, 228). Guilleminault et al. (204) noticed that in some boys the obstructive disorders reappear in puberty, despite initially successful treatment with adenotonsillectomy. The reason was thought to be hormonal changes linked with puberty. However, the prevalence of OSAS seems not to be significantly higher in 12 to 16-year-old adolescents than in younger children (229).

It might be that early treatment of obstruction could prevent and reverse facial morphology changes and inhibit development or recurrence of OSAS in adulthood (204). As there seems to be familial aggregation of OSAS (163), early recognition and treatment of children with SBD and familial tendency to disproportionate facial morphology could be important in a preventive sense (65).
3 Aims of the present study

The investigation was undertaken to increase the knowledge about OSAS in children, focusing on symptoms, signs, etiology, diagnosis, effects of treatment, prognosis and complications. The ultimate goal is to find children at risk of serious OSAS.

Six hypotheses were studied based on prior knowledge derived from the literature.

1. Certain symptoms and signs in snoring children are more prevalent in children with OSAS.
   Children with OSAS may have few daytime symptoms and therefore receive a delayed diagnosis, predisposing them to sneaking complications. The symptoms may resemble those of children with primary snoring. Finding factors linked with increased risk of OSAS would be clinically valuable.

2. Dentofacial differences exist between children with and without OSAS.
   Occlusal and morphological abnormalities have been recognized in children with abnormal night time breathing. Some of these changes seem not to be inherited. Obstructed breathing and abnormal sleeping positions can be suspected to affect the development of the dentofacial skeleton.

3. Children with OSAS have a different ratio of acoustic energy emitted through the nose and mouth (nasalance) compared with children without OSAS.
   Hyponasality is often considered as a sign of adenotonsillar hypertrophy. Accordingly, children with OSAS could be assumed to have lower nasalance scores than other children.

4. Adenotonsillectomy is a curative treatment of OSAS in children.
   The main etiology of OSAS in children is adenotonsillar hypertrophy. Adenotonsillectomy should therefore cure OSAS in the absence of underlying predisposing conditions. If successful treatment leads to the reversal of symptoms, will complications already developed also be reversed?
5. **Primary snoring will progress to OSAS if untreated.**
   
   The natural history of less severe obstructive sleep disorders in children has been little studied. Whether children with primary snoring tend to develop OSAS, and whether mild OSAS has a tendency to progress to more serious stages needs to be studied.

6. **Growth hormone secretion is impaired in children with OSAS.**
   
   Growth failure is a reported complication of pediatric OSAS. Growth hormone and its mediators are the strongest growth-promoting factors in humans. Therefore, disturbed growth hormone secretion could be thought to cause the growth impairment in children with OSAS.
4 Subjects and methods

4.1 Subjects

The study population consists of prepubertal (3–10-year old) children with regular nighttime obstructive symptoms suggestive of OSAS. The lower age-limit was chosen for technical reasons and the higher to avoid pubertal hormonal changes possibly affecting the results (study V). The children were in the first phase selected from the referrals from primary health care to the Department of Otorhinolaryngology in the Oulu University Hospital during the years 1994-1997 regarding the necessity of treatment due to nighttime snoring, apneas or difficult breathing. At this point, children with known upper airway anomalies, abnormal development, chronic infections, asthma or perennial allergy were excluded. Children with seasonal allergy were accepted for the study if they had obstructive nighttime breathing disorders also outside the allergy season.

Secondly, the parents of all children with OSAS completed a detailed questionnaire regarding their child’s diurnal symptoms. The parents were asked to follow their child’s sleep for two weeks before completing the questionnaire.

After a review of the questionnaires, children with regular obstructive symptoms for more than six months were invited for an ear, nose and throat evaluation and a thorough update of patient history. The facial morphology was controlled. Earlier adenoidectomy was not an exclusion criterion.

Seventy-eight snoring children constituted the source of subjects for five separate studies. They all had symptoms suggestive of OSAS, they were regular snorers and/or were observed to have apneas during sleep. Due to co-operation problems, non-availability of some laboratory functions at times or technical reasons the number of subjects is unequal in the different studies (Studies I–V, Table 4). Of the 78 children in studies III–V 43 were boys. One girl assessed in the study I did not participate in further studies, while a boy was included in the study material after study I. The mean age of the study subjects was 5.67 years, median 5.4 years, range 2.4–10.5 years.
Table 4. The number of OSAS children and primary snorers successfully measured and evaluated in the diverse studies. PS = primary snorers.

<table>
<thead>
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<th>Study</th>
<th>Visit I</th>
<th>Visit II</th>
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<tr>
<td></td>
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<td>PS n</td>
<td>OSAS n</td>
</tr>
<tr>
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<td>49</td>
<td></td>
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<tr>
<td>Study II</td>
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<td>Study III</td>
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<td>Study IV</td>
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<td>31</td>
<td>27</td>
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<tr>
<td>Study V</td>
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Thirty normal subjects, (17 of them boys), mean age 7.1 years, range 4.2–10.9 years, offspring of hospital personnel, were recruited to constitute a control group for the establishment of normative data for PSG measurements.

4.2 Methods

4.2.1 Questionnaire

The questionnaire completed by the parents included 31 questions. The questionnaire included questions concerning the regularity and duration of snoring, detected apneas, sleeping disturbances, oral breathing day- and nighttime, eating habits and daytime symptoms described as being typical of OSAS. The answering alternatives were formulated in the same manner as in the Basic Nordic Sleep Questionnaire (230) as: always (every night/day), every other night/day (3 to 5 times a week), weekly, less than weekly or never. When possible, the alternatives yes or no were used.

4.2.2 Clinical evaluation

A thorough clinical ear, nose and throat examination was done. Previous adenoidectomy was registered. The palatine tonsils were graded on a scale from I to IV on a clinical basis slightly modified from the standardised evaluation system recommended by Brodsky et al. (231) as follows: Grade (Gr.) I tonsils within tonsillar fossa, Gr. II tonsils not reaching the midline between anterior faucial pillar and uvula, Gr. III tonsils medially from the midline and Gr. IV tonsils with maximally four millimetres in between. Tonsils graded III and IV were considered enlarged in this study.
In all studies the children were subjected to overnight polysomnography. The PSG-monitoring was performed in the hospital under the surveillance of a trained nurse. The children were accompanied by a parent through the night in the room.

A six-channel computerised polygraph developed by the Department of Clinical Neuropsychology with leads for an oronasal thermistor (qualitative measurement of oronasal airflow), a thoracoabdominal strain gauge (measurement of thoracoabdominal movement), a pulseoximeter (oxygen saturation, pulse, pulse waveform), a body-position sensor, leg EMG (exclusion of myoclonus) and a static charge-sensitive bed (SCSB) was used (Figure 3). The children’s sleep was also videotaped to ascertain their sleep in addition to the nurse’s diaries. Although the analysis programme included a possibility of automatic analysis of the night’s events, all recordings were manually checked by a clinical neurophysiologist. All obstructive apneas, hypopneas and mixed apneas were scored, as well as central apneas. An obstructive apneic episode was defined as total cessation of oronasal airflow as detected by the thermistor in the presence of continuous breathing efforts revealed by the thoracoabdominal strain gauge or the SCSB, and hypopnea as at least 50% reduction in the airflow signal. A central apnea was defined as a cessation of airflow in the absence of breathing efforts. Central apneas preceded by a deep sigh were disregarded. The apneas lasting 5–10 seconds and apneas lasting more than 10 seconds were scored separately. Mixed apneas were included into the obstructive episodes category. The baseline oxygen saturation was determined at the beginning of sleep. The number of oxygen desaturation events to below 4% from the baseline value per hour of sleep was calculated, as well as the number of over 10% desaturations. The saturation distribution was analysed as the width of the saturation range of the night when the time spent with the highest and lowest values (10% each) had been cut off. This parameter describes the variability of the oxygen saturation during the night. Obstructive apnea-hypopnea index (AHI O) of one or higher with events lasting 10 seconds or more was considered pathological in this study according to normative data (16), (study IV). Mixed apneas were included in the index, whereas central apneas were not. Children with an AHI O of one or higher were considered as having OSAS, while children with an AHI O of less than one were considered as primary snorers. Successful PSG recording was mandatory for all children in order to be evaluated in the study. Due to the lack of EEG, EOG or chin EMG-tracing sleep staging or recording of cortical arousals could not be performed. Tachycardic episodes linked to the termination of intervals of periodic hypopneas with less than 50% decrease in oronasal signal amplitude were scored. These respiratory-induced pulse increases likely indicate subcortical arousals (144) and may be linked to the increased upper airway resistance syndrome (UARS).
4.3 Symptoms and signs (studies I & IV)

As the first task the questionnaire answers were used to compare the symptoms between the children with OSAS and primary snoring. In order to find symptoms and signs linked with increased risk of OSAS, cumulative relative risk (RR) ratios of having OSAS were calculated for each level of the answer alternatives with 95% confidence intervals (CI). Relative risk ratios for predicting OSAS were also calculated for the tonsillar size and previous history of adenoidectomy.

The OSA-score developed and presented by Brouilette and co-workers (89) was also tested in this study (Study IV). There is one reservation about the analysis of the OSA-scores in this study, since we used laborious breathing instead of breathing difficulties during sleep as in the original formula.
4.4 Dental arch dimensions (study II)

Dental impressions were taken using alginate impression material and cast in blue dental stone. The wax index was used to record the intercuspal relationship. The linear dimensions of the dental arches were measured manually. Nine variables were measured from the plaster casts using a calibrated digital sliding calliper. In this part of the study children with AHI of 4 or more were categorised as having OSAS.

4.5 Nasalance studies (study III)

The objectively measured nasal air escape in speech, nasalance, was assessed as a nasalance score obtained with a commercially available Nasometer, Model 6200 (Kay Elemetrics, Pine Brook, NJ, USA). The Nasometer uses a sound separator to differentiate between oral and nasal acoustic waveforms, after which each waveform is filtered with a 300-Hz band-pass filter that has a centred frequency at 500Hz. The separator plate rests against the upper lip with microphones on both sides for measuring the acoustic energy emitted through the nasal and oral passages. The intensity of the filtered energy is then converted into a ratio (nasal/nasal+oral), which is, after multiplication by 100, expressed as a nasalance percentage that reflects the relative proportion of nasal to nasal + oral acoustic energy. Four standardised sentences in Finnish, for which reference values for mean nasalance and its standard deviation in normal Finnish speech have been developed (232), were used to obtain the nasalance scores. One sentence only contains nasal consonants, with high nasalance score in normal speech. The three other sentences contain mainly oralised sound segments with low nasalance scores in normal speech. The nasalance scores of the OSAS children and primary snorers were compared with the Finnish reference values (232). A mean of three consecutive measurements was calculated when the coefficient of variation was approximately 20% or less. The children had to produce the test phrases in a natural manner.

4.6 Growth characteristics (study V)

The children were subjected to anthropometric measurements. Height was measured to the nearest 1.0 mm with a Harpenden wall mounted stadiometer (Holtain Limited, Crymch, Dyfed, Britain), and weight with an electronic scale to the nearest 0.1 kg. Relative height and relative weight were assessed from Finnish growth charts (233). Target height representing the relative midparental height was calculated as follows: \[ \text{TH (standard deviation score, SDS)} = \frac{[\text{height (cm) of mother + father}/2 - 171]}{10} \] (234). The target height deficit was target height minus relative height at final evaluation. The data on parental height was collected by means of a questionnaire (235). The biceps, triceps and subscapular skin folds were measured to the nearest 0.1 mm with a Harpenden skin fold calliper (John Bull, British Indicators Ltd., St. Albans, Herts, UK) (236). The
body mass index (BMI) was calculated (weight (kg) divided by height squared (m²)). Finnish age- and gender-matched references were used to assess the relative BMI in SDS' (237). The body density was calculated from the combined triceps and subscapular skin fold thickness results according to the method devised by Parizkova (238). The percentage of body fat was calculated by the method described by Keys and Brozek (239). All the anthropometric measurements were performed three times and the mean value was subsequently used.

The stage of puberty (Tanner I) was ascertained according to Tanner and Whitehouse (240). The radiological bone age was determined according to Greulich and Pyle (1959).

Insulin-like growth factors were measured from peripheral blood samples. Circulating concentrations of insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGFBP-3) are strongly related to diurnal GH secretion, reflecting mean daily GH levels, and thought to correlate well with physiological changes in GH secretion (190, 241). IGF-1 is perceived as the main mediator of the growth-promoting actions of GH (189). The samples were taken in the morning following the PSG. Plasma IGF-I concentrations were analyzed with a radioimmunoassay using commercial reagents (Instar Corporation, Stillwater, Minnesota, USA), with a sensitivity of 1.0 nmol/l. The serum IGFBP-3 concentrations were determined radioimmunologically (Diagnostic Systems Laboratories Inc, Webster, Texas, USA), with a sensitivity of 30 µg/l. The methods have intra-assay coefficients of variation less than 5%. Both samples from the same individual were analyzed in the same assay to exclude the effect of interassay variation.

4.7 Protocol

The study was prospective, with aimed two visits six months apart. At the first visit polysomnographically verified children with OSAS and primary snorers were compared for symptoms, clinical findings, acoustic airway patency and growth parameters. Age-matched control groups were generated or existing normative data applied (Studies II–V).

At the second visit six months later (visit two) PSG and all the other studies were repeated for all children available (Studies III–V), except for the odontological studies. The parents completed the same questionnaire regarding their child’s symptoms. 58 children had a successful second PSG study. Fifteen children did not participate in the second part of the study, in four cases there was a protocol violation and in one case technical problems. As for visit 1, the number of subjects is unequal in the different studies due to co-operation problems, non-availability of some laboratory functions at times or technical reasons (Table 4). According to the study protocol, children with AHİO of two or higher underwent surgical therapy (adenotonsillectomy), unless there were contraindications, shortly after the first visit. Children with AHİO of less than two constituted the follow-up group. Two children with AHİO over 2 were included in the follow-up group due to contraindications for surgery. The effect of adenotonsillectomy as treatment of OSAS was assessed subjectively through the symptoms as reported by the parents, OSA-score and symptom score, as well as objectively with PSG (study IV). The effects of surgery on
acoustic airway patency (study III) and on growth parameters (study V) were also assessed. The same parameters were also assessed in the follow-up group to obtain natural history in children with primary snoring or mild OSAS. In both groups the children served as their own controls, and the children were compared within and between the groups.

4.8 Statistics

The data was stored and processed with the SPSS for Windows software® (SPSS Inc., Chicago, Ill., USA). Students t-test for two independent samples and paired samples were applied for normally distributed data. The non-parametric Mann-Whitney U-test and Wilcoxon’s signed rank tests were utilized for data with skewed distribution. Chi-square analyses were used for nominal and ordinal variables. Correlation coefficients were calculated with the Pearson 2-tailed test. Regression analysis was applied when the dependent and independent variables were continuous, and the residuals ranged from –3 to 3 without obvious skewness.

Relative risk (RR) ratios with 95% confidence intervals were calculated using CIA software (242).

4.9 Ethical aspects

The study protocol was approved by the Ethics Committee, Medical Faculty, University of Oulu. The study was conducted according to the Declaration of Helsinki.
5 Results and comments

5.1 First visit

5.1.1 Polysomnography results

Thirty-two children were classified as having OSAS whereas 46 children were considered as primary snorers based on the PSG results (Table 5). Of all the obstructive events lasting 10 seconds or more, hypopneas accounted for 78.6% in the OSAS- and 92.5% in the primary snorers group. Short obstructive events (5 to 10 seconds) were much less common than those lasting for 10 seconds or more in both groups. Inclusion of the shorter apneas in the AH\textsubscript{I}O would not have changed the grouping. The main PSG-results are given in Table 5, where the OSAS children and the primary snorers are also compared with the control group. Significant differences could be noted between the OSAS children and primary snorers for all the main parameters except for the mean saturation distribution ($p = .11$) and the central apnea index ($p = .07$). The primary snorers had significantly higher mean obstructive indexes than the control children, whereas the total apnea index was not significantly higher in the primary snorers due to equal central apnea indexes.
Table 5. The polysomnography findings of the whole study material. The data are mean, (SD)(range).

<table>
<thead>
<tr>
<th></th>
<th>OSAS (n = 32)</th>
<th>Primary snorers (n = 46)</th>
<th>Controls (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive apnea-hypopnea index (&gt;10 sec)</td>
<td>5.15 (5.2) (1.0–14.6)</td>
<td>.00 0.14 (0.26) (0–0.89)</td>
<td>.001 0 .00</td>
</tr>
<tr>
<td>Obstructive hypopnea index (&gt;10 sec)</td>
<td>4.15 (3.7) (0.41–14.48)</td>
<td>.00 0.12 (0.23) (0–0.79)</td>
<td>.001 0 .00</td>
</tr>
<tr>
<td>Obstructive apnea-hypopnea index (&gt;5 sec)</td>
<td>6.28 (4.91) (1.1–19.1)</td>
<td>.00 0.18 (0.28) (0–0.95)</td>
<td>.002 0 .00</td>
</tr>
<tr>
<td>Central apnea index (&gt;10 sec)</td>
<td>0.66 (1.1) (0–5.78)</td>
<td>.07 0.29 (0.3) (0–1.28)</td>
<td>.96 0.28 (0.26) (0–0.86)</td>
</tr>
<tr>
<td>Total apnea index (&gt;10 sec)</td>
<td>5.73 (4.4) (0.26–16.77)</td>
<td>.00 0.43 (0.4) (0–1.8)</td>
<td>.13 0.28 (0.26) (0–0.86)</td>
</tr>
<tr>
<td>Saturation distribution % (90 - 10)</td>
<td>3.17 (1.6) (0.8–10.2)</td>
<td>.11 2.7 (0.7) (1.7–4.5)</td>
<td>.27 2.4 (0.7) (0.3–3.7)</td>
</tr>
<tr>
<td>4% desaturation index</td>
<td>3.9 (6.4) (0–30)</td>
<td>.002 0.8 (2.0) (0–13)</td>
<td>.03 0.12 (0.22) (0–1.0)</td>
</tr>
<tr>
<td>Periods with tachycardia associated with partial hypopnea (min/hour)</td>
<td>1.2 (1.1) (0.2–4.6)</td>
<td>.00 0.57 (0.6) (0–2.37)</td>
<td>.00 0.16 (0.24) (0–1.2)</td>
</tr>
</tbody>
</table>

*p1* indicates the statistical difference between the children with OSAS and the primary snorers, *p2* the statistical difference between the primary snorers and the control children and *p3* the statistical difference between the OSAS children and the controls. Total apnea index includes obstructive apneas, hypopneas and central apneas. The saturation distribution refers to the width of the saturation range of the night when the time spent with the highest and lowest values (10 % each) have been cut off.

5.1.1.1 Comments

Less than half of the children, 41%, suspected of having OSAS proved to have the condition according to the criteria used in this study. This finding is well in line with other reports, where half or less of the children suspected of having OSAS actually proved to have the state (31, 85-88). Despite the resemblance of obstructive symptoms between the OSAS children and primary snorers, they had distinctly different nighttime sleep characteristics based on the PSG findings, when an AH\(_I\) of one or more was considered abnormal. This criterion is supported by the findings of others (16) and own findings in the control group of 30 children, where there were found only two single periods of obstructive hypopneas and no apneas in all of the children. The respiratory frequency of children is much faster than that of adults, so the length of apneas and hypopneas considered abnormal should probably be shorter than in adults (56). In the present study the 10-seconds criterion used. The separately counted apneas lasting 5–10 seconds should correlate fairly well with the criterion of missed 2-3 breaths proposed by
many (16, 31), but the use of the shorter apneas as criterion of abnormality would not have affected the results of this study. Limitations of the sleep monitoring were the lack of EEG, EOG and chin EMG-tracing, which did not allow sleep staging or detection of cortical arousals. The role of arousals in terminating respiratory events in children is unclear though, as EEG arousals are probably not an important mechanism in the termination of respiratory events (31, 35, 46, 53, 56), and even if the microstructure of sleep might be changed the macrostructure is not (57). Partial obstructive episodes were scored quantitatively as hypopneas, as no end-tidal CO₂ tracing was performed.

The OSAS children showed the typical obstructive pattern described in the literature (39, 40), as the vast majority of the obstructive episodes were found to be partial. The OSAS children had significantly more desaturations than the primary snorers, but some OSAS children never had over 4% drops in the oxygen saturation despite complete over ten-second apneas.

There are some indications that the children considered as primary snorers had other abnormalities in nighttime respiration in addition to plain snoring, as they had a significantly higher mean 4% desaturation index than the control children. It is possible that some of the children classified as primary snorers could have been classified differently based upon the hypoventilation criterion (16), despite the lack of significant apneas and hypopneas. The primary snorers had also more tachycardic episodes connected with the termination of partial obstructive hypoventilation than the control children did. These tachycardic episodes are thought to indicate subcortical arousals (144) and could be assumed to be a reaction to increased respiratory resistance.

### 5.1.2 Symptoms and signs

Statistically there could be found significant differences between the OSAS children and primary snorers for many of the symptoms and signs inquired and examined (Table 6). Both groups differed statistically from the controls for all the symptoms and signs except for excessive daytime somnolence (Table 6). There was no significant gender difference between any of the groups.
Table 6. General information about the OSAS children, primary snorers and the controls and of their symptoms and signs. Linear- by linear association test has been applied for the symptoms with more than two answering alternatives. p1 indicates the statistical difference between the OSAS children and the primary snorers, p2 the difference between the primary snorers and the controls and p3 the difference between the OSAS children and the controls.

<table>
<thead>
<tr>
<th></th>
<th>OSAS (n = 32)</th>
<th>p1</th>
<th>Snorers (n = 46)</th>
<th>p2</th>
<th>Controls (n = 30)</th>
<th>p3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>5.5 (1.8)</td>
<td>.55</td>
<td>5.8 (1.7)</td>
<td>.002</td>
<td>7.1 (1.8)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>(2.4–10.5)</td>
<td></td>
<td>(3.1–10.0)</td>
<td></td>
<td>(4.3–10.9)</td>
<td></td>
</tr>
<tr>
<td>Sex, boys/girls</td>
<td>15/17</td>
<td>.25</td>
<td>28/18</td>
<td>ns</td>
<td>17/13</td>
<td>ns</td>
</tr>
<tr>
<td>Earlier adenoidectomy %</td>
<td>63 (20)</td>
<td>.04</td>
<td>37 (17)</td>
<td>1.0</td>
<td>37 (11)</td>
<td>.07</td>
</tr>
<tr>
<td>(number)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3–4 tonsils, %</td>
<td>91 (29)</td>
<td>.02</td>
<td>65 (30)</td>
<td>.00</td>
<td>3 (1)</td>
<td>.00</td>
</tr>
<tr>
<td>(number)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every night</td>
<td>23</td>
<td>.03</td>
<td>24</td>
<td>.00</td>
<td>0</td>
<td>.00</td>
</tr>
<tr>
<td>Every other night</td>
<td>8</td>
<td>12</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once a week</td>
<td>1</td>
<td>10</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detected apneas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every night</td>
<td>17</td>
<td>.001</td>
<td>7</td>
<td>.00</td>
<td>0</td>
<td>.00</td>
</tr>
<tr>
<td>Every other night</td>
<td>2</td>
<td>9</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once a week</td>
<td>12</td>
<td>12</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less or never</td>
<td>1</td>
<td>15</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime mouthbreathing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most part of the day</td>
<td>9</td>
<td>.78</td>
<td>14</td>
<td>.00</td>
<td>0</td>
<td>.00</td>
</tr>
<tr>
<td>Daily</td>
<td>7</td>
<td>12</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occasionally</td>
<td>11</td>
<td>16</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>2</td>
<td>4</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nighttime mouthbreathing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every night</td>
<td>27</td>
<td>.82</td>
<td>39</td>
<td>.00</td>
<td>3</td>
<td>.00</td>
</tr>
<tr>
<td>Every other night</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once a week</td>
<td>2</td>
<td>3</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less or never</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odd sleeping positions %</td>
<td>69 (22)</td>
<td>.48</td>
<td>59 (27)</td>
<td>.00</td>
<td>10 (3)</td>
<td>.00</td>
</tr>
<tr>
<td>(number)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restless sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every night</td>
<td>14</td>
<td>.057</td>
<td>11</td>
<td>.00</td>
<td>0</td>
<td>.00</td>
</tr>
<tr>
<td>Every other night</td>
<td>8</td>
<td>9</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once a week</td>
<td>6</td>
<td>24</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less or never</td>
<td>3</td>
<td>2</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive daytime somnolence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every day</td>
<td>6</td>
<td>.05</td>
<td>4</td>
<td>.056</td>
<td>0</td>
<td>.00</td>
</tr>
<tr>
<td>Some days</td>
<td>21</td>
<td>28</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>4</td>
<td>14</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
While the OSAS children and the primary snorers had more often excessive daytime somnolence than the control children, in this respect they did not differ significantly from each other. For other symptoms reported as typical of OSAS children, such as morning headache, bed-wetting, abnormal nighttime sweating, sleep walking or concentration difficulties the OSAS children and the primary snorers were not statistically different.

The children with OSAS had undergone significantly more often adenoidectomy than the primary snorers prior to entering the study. The causes of adenoidectomy were retrospectively difficult to compile, but in most cases the procedure had been performed for infectious reasons, though the majority seemed also to have snored. The mean AHI0 among the OSAS children with previous adenoidectomy was significantly higher compared with those with intact adenoid (6.4 vs. 3.1, p = 016).

The OSA score was assessed for 58 children (Study IV). Twenty-seven children had an AHI0 of one or more, while 31 were primary snorers. The mean OSA-score for the OSAS-children was 3.1 (SD1.7) (range –0.3 to 4.0), for the PS-children 2.1(1.4)(-3.1 to 4.0), (p = .03) and for the control-group 3.7(1.3)(-3.8 to 0.4), (p < 0.01), compared with the OSAS children. The difference in OSA-scores was also significant between the primary snorers and control children (p < .01). Sixteen OSAS children had an OSA score over 3.5, which value is according to Brouilette et al. (89) highly suggestive of OSAS. All other OSAS children belonged to the intermediate range between –1 and 3.5, when polygraphic monitoring is recommended. Of the primary snorers five had an OSA score over 3.5, while 23 had an intermediate score, and three children had a score under –1, which would indicate absence of OSAS.

5.1.2.1 Comments

Substantial overlap of symptoms could be noticed between the OSAS children and primary snorers, as has been noticed earlier (46, 65). Mouth breathing was equally common in both groups. For many symptoms a clear difference could be observed between the groups. The children in both groups had clearly more symptoms than the control children. Many symptoms that have been found typical of OSAS in children (14, 31, 65, 85-87, 89, 96, 175) were frequently encountered also in the present study. None of the symptoms were, however, only present in the OSAS children. Excessive daytime somnolence was not found to be common, as pointed out by others (15, 36, 126).

Tonsillar hypertrophy, present in most of the studied children, is the principal etiology of airway obstruction in sleeping children (14, 33, 36, 93, 101, 151). OSAS is not explained by tonsillar hypertrophy alone, since all children did not have significant tonsillar enlargement, as has been found by others (139, 174, 202). Many of the primary snorers had also very large tonsils, as had a few of the control children. The relative size and structure are more important than absolute size (56), as a small distance between the lateral pharyngeal walls (151) may lead to protrusion of tonsils with lesser volume (243). The shape of the tonsils is also important (211), as is their mobility and rotability (137).
The importance of the adenoid in causing nighttime airway obstruction in children is unsettled. In the present study the majority of the OSAS children had been subjected to adenoidectomy before entering the study, and they had in general higher AHI:s than the children with intact adenoids. The adenoidectomy had been performed at a young age, at a mean age of 2.7 years. It is possible that these children had an overall strong tendency to lymphoid tissue hypertrophy and were therefore more affected when they reached an older age when tonsillar hypertrophy is most prominent.

The overlap of symptoms between OSAS children and primary snorers was also obvious in the light of the OSA score. Despite the significant differences in the scores between the groups, five primary snorers were misclassified, as they had an OSA score highly predictive of OSAS. Only three primary snorers had strong evidence of absence of OSAS (89). Though being an interesting method of trying to clinically screen children with obstructive symptoms, OSA score seems not to be reliable enough to reduce the need for sleep monitoring (31, 96).

5.1.3 Risk factors (Study I)

For symptoms and signs with a statistically significant difference between the OSAS children and the primary snorers, relative risk (RR) ratios for predicting OSAS with 95% confidence intervals (CI) were calculated (Table 7). Apneas detected by the parents were found to be the most important risk factor, the more regularly detected the higher the risk. If apneas were detected every night, the RR was 3.3 (CI 1.5 to 6.9). Restless sleep and regular snoring were also found to be significant risk factors for OSAS in this study (Table 7).
Table 7. Relative risk ratios for symptoms and signs predicting OSAS in snoring children are expressed at various levels with cumulative number of cases.

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>AI ≥ 1 (n = 32)</th>
<th>AI &lt; 1 (n = 46)</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected apneas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>every night</td>
<td>17</td>
<td>7</td>
<td>3.3</td>
<td>1.5 to 6.9</td>
</tr>
<tr>
<td>most nights</td>
<td>2</td>
<td>9</td>
<td>1.6</td>
<td>1.0 to 2.6</td>
</tr>
<tr>
<td>occasionally</td>
<td>12</td>
<td>12</td>
<td>1.4</td>
<td>1.2 to 1.8</td>
</tr>
<tr>
<td>never</td>
<td>1</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>every night</td>
<td>23</td>
<td>24</td>
<td>1.4</td>
<td>1.0 to 2.0</td>
</tr>
<tr>
<td>most nights</td>
<td>8</td>
<td>12</td>
<td>1.2</td>
<td>1.1 to 1.5</td>
</tr>
<tr>
<td>irregularly</td>
<td>1</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restless sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>every night</td>
<td>14</td>
<td>11</td>
<td>1.9</td>
<td>1.0 to 3.6</td>
</tr>
<tr>
<td>most nights</td>
<td>8</td>
<td>9</td>
<td>1.6</td>
<td>1.1 to 2.4</td>
</tr>
<tr>
<td>seldom or never</td>
<td>9</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odd sleeping positions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>22</td>
<td>27</td>
<td>1.2</td>
<td>0.8 to 1.6</td>
</tr>
<tr>
<td>no</td>
<td>10</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>daily</td>
<td>6</td>
<td>4</td>
<td>2.2</td>
<td>0.7 to 7.2</td>
</tr>
<tr>
<td>occasionally</td>
<td>20</td>
<td>30</td>
<td>1.2</td>
<td>1.0 to 1.6</td>
</tr>
<tr>
<td>never</td>
<td>3</td>
<td>15</td>
<td>0.4</td>
<td>0.1 to 1.2</td>
</tr>
<tr>
<td>Previous adenoidectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20</td>
<td>17</td>
<td>1.7</td>
<td>1.1 to 2.7</td>
</tr>
<tr>
<td>No</td>
<td>12</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size of tonsils</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>enlarged (gr 3 - 4)</td>
<td>29</td>
<td>30</td>
<td>1.4</td>
<td>1.1 to 1.8</td>
</tr>
<tr>
<td>normal (gr 1-2)</td>
<td>3</td>
<td>16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Regular excessive daytime sleepiness was not found to be a risk factor for having OSAS. A history of previous adenoidectomy in snoring children was found to increase the risk factor for having OSAS, RR 1.7 (CI 1.1 to 2.7). Also, snoring children with enlarged (Gr. III-IV) palatine tonsils have a greater risk of having OSAS than children with Gr. I-II tonsils, RR 1.4 (CI 1.1 to 1.8).
5.1.3.1 Comments

Significant risk factors for OSAS in snoring children were found from the symptoms and signs in the present study. Clearly the most important risk factor was witnessed apneas. The symptoms associated with the highest risk, witnessed apneas, restless sleep and chronic snoring, are in the literature reported as the most common symptoms of pediatric OSAS (14, 31, 65, 85-89, 139, 175). Still, none of the symptoms are patognomonic for OSAS, and the presence of symptoms with a high relative risk ratio can only have a predictive value. The knowledge of these risk factors is on the other hand valuable in the diagnostic work-up of children with obstructive nighttime symptoms.

Profound daytime somnolence in OSAS children is obviously not common. The finding that snoring children with regular or occasional EDS had slightly increased risk of having OSAS results from the lack of EDS in many of the primary snorers. This finding should be interpreted with caution, although it may be indicative.

Visually assessed tonsillar hypertrophy as a risk factor for OSAS seems logical, as the airway is potentially narrowed. Tonsillar volume alone is not the only important measurement though (137, 151, 211, 243).

Previous adenoidectomy in children with obstructive symptoms was found to be a risk factor for OSAS. This finding most probably indicates that the children who either had developed or had persistent OSAS after adenoidectomy had either an underlying tendency to OSAS or to significant lymphoid tissue hypertrophy.

The number of OSAS children vs. primary snorers is different in the results section than in the original article (Study I). A manual re-check of all the PSGs was performed after Study I, and two children considered as primary snorers were found to have an AHlO of over one. Also, one girl assessed in Study I was not participating in further studies whereas a boy who proved to have OSAS entered the study after Study I. Hence, the RRs and CIs presented in Table 7 are slightly different from those in Study I.

5.1.4 Dental arch dimensions (Study II)

Differences in dental arch dimensions were found among the studied 27 children (15 boys, 12 girls, mean age 5.8 years, range 3.6 to 9.9 years) depending on degree of obstruction and sleeping posture. In the multiple regression analysis when calculating the effect of age, AHlO and sleeping position, the AHlO was found to be significantly associated with increased overjet ($p = .007$). The AHlO was not significantly associated with intercanine width, whereas the time spent in supine position was ($p = .04$). When calculating the effects of age, AHlO and extended head posture, prolonged head extension and low AHlO were found to be correlated with reduced overjet ($p = .005$ & .03).
Children with obstructive sleep disorders have been recognized to have more malocclusion and craniofacial modifications than other children, such as open bite and lateral cross bite, deeper palatal height and retroposition and rotation of the mandible (169, 202, 244, 245). Children with OSAS have also been shown to have narrower width of maxilla than non-obstructed children (169), which according to the present results could be correlated with sleeping position rather than airway obstruction per se, presumably due to reduced moulding effect of the tongue. That the AH1O was found to be significantly associated with increased overjet confirms earlier results, that children with obstructed breathing tend to have longer maxillary dental arches and shorter lower dental arches than non-obstructed children (169). The unanswered question is whether these changes are genetically determined or results of abnormal breathing and altered head position, which could result in changes of the moulding effects of the soft tissues on the dental arches. Prolonged head extension, which has in the present study been found to be common (Table 6) was found to be correlated with reduced overjet. Again, the explanation might be reduced lingual moulding effect on the maxillary dental arches.

### 5.1.5 Nasalance scores (Study III)

Fifty-three children (31 boys), mean age 6.1, range 3.2 to 10.5 years, had successful nasalance measurements at the first visit. Nineteen children had OSAS, the mean AI for the OSAS group being 4.2 (1.1–11.6). Thirty-four children were primary snorers. Twenty-two children had had a previous adenoid operation, 10 of them in the OSAS group.

For all the studied children the mean score for the nasal sentence M, which contains only nasal consonants, was significantly higher than for normal Finnish children (76.3 ± 10(SD) vs. 69.9 ± 8.2(SD) (232). This means that more acoustic energy was omitted through the nasal passage than would have been expected. For the oral sentences the children in the present study did not differ from the normative data (232). The children with and without an earlier adenoid operation showed no significant differences in nasalance scores for either oralized or nasalized sentences. When comparing the OSAS children and the primary snorers, they did not differ statistically for any of the measured sentences.

### 5.1.5.1 Comments

Most children with nighttime obstructed breathing have enlarged palatine tonsils or adenoid or both. This could be assumed to alter the ratio of nasal/nasal+orally emitted acoustic energy. Indeed, this was found to be the case in the present study, but, perhaps unexpectedly, the children had higher values for the nasal sentences than normal Finnish children. This finding may be explained by hypertrophic tonsils with posterior placement.
of the upper poles of the tonsils into the oropharyngeal and nasopharyngeal airway (246), prohibiting the consonants from constricting the posterior oral cavity normally (247). That no significant differences in nasalance scores were found between children with OSAS and primary snorers is probably explained by the relatively similar tonsillar status, with functional differences causing airway obstruction in some children but not in others.

Measurement of nasalance has been suggested as an aid in selection of children for adenoidectomy, since words containing nasal consonants have been found to show large reductions in the Nasalance scores when the nostrils have been occluded (248). Different results have however been reported (249), as in the present study, where no differences were found between the children with preserved adenoids and those without.

5.1.6 Growth characteristics (Study V)

Seventy children (40 boys), mean age 5.8 years, range 2.4–10.5 years, completed the anthropometrical measurements at the first visit and comprised accordingly the initial study group (Table 8). Thirty of the studied children had OSAS, while 40 were considered as primary snorers. For anthropometric measurements and endocrinological studies 35 children (16 boys), mean age 6.45, range 1.5–10.2 years, recruited from child welfare clinics and schools, were used as control subjects (Table 8) (235, 250).
Table 8. Anthropometric measurements on the first visit in the children with OSAS, the children with primary snoring and the control group presented as mean values and their 95% confidence intervals.

<table>
<thead>
<tr>
<th></th>
<th>OSAS (n = 30)</th>
<th>Snorers (n = 40)</th>
<th>Controls (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>5.67</td>
<td>6.04</td>
<td>6.45</td>
</tr>
<tr>
<td>(9.93–6.30)</td>
<td>(5.50–6.58)</td>
<td>(5.63–7.27)</td>
<td></td>
</tr>
<tr>
<td>Relative height</td>
<td>0.23</td>
<td>0.13</td>
<td>0.36</td>
</tr>
<tr>
<td>(SDS) (-0.15–0.61)</td>
<td>(-0.25–0.51)</td>
<td>(0.03–0.69)</td>
<td></td>
</tr>
<tr>
<td>Target height</td>
<td>0.35</td>
<td>0.25</td>
<td>0.07</td>
</tr>
<tr>
<td>(SDS) (0.15–0.55)</td>
<td>(-0.07–0.43)</td>
<td>(-0.08–0.21)</td>
<td></td>
</tr>
<tr>
<td>Target height def-</td>
<td>-0.09</td>
<td>-0.13</td>
<td>0.29</td>
</tr>
<tr>
<td>(SDS) (-0.23)</td>
<td></td>
<td>(-0.44–0.17)</td>
<td>(-0.01–0.58)</td>
</tr>
<tr>
<td>Weight for height</td>
<td>101.9</td>
<td>101.2</td>
<td>100.3</td>
</tr>
<tr>
<td>(%) (97.2–106.7)</td>
<td></td>
<td>(98.2–104.2)</td>
<td>(97.2–103.3)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.9</td>
<td>15.7</td>
<td>16.0</td>
</tr>
<tr>
<td>(15.2–16.7)</td>
<td></td>
<td>(15.2–16.3)</td>
<td>(15.5–16.5)</td>
</tr>
<tr>
<td>IGF-1 (nmol/l)</td>
<td>11.02</td>
<td>12.15</td>
<td>11.11</td>
</tr>
<tr>
<td>(9.79–12.23)</td>
<td></td>
<td>(11.14–13.16)</td>
<td>(9.81–12.41)</td>
</tr>
<tr>
<td>IGFBP-3 (µg/l)</td>
<td>2.65</td>
<td>2.66</td>
<td>3.47</td>
</tr>
<tr>
<td>(2.46–2.85)</td>
<td></td>
<td>(2.49–2.83)</td>
<td>(3.17–3.78)</td>
</tr>
</tbody>
</table>

*p1* indicates the statistical difference between the OSAS children and primary snorers, *p2* the difference between the primary snorers and normal controls and *p3* the difference between the OSAS children and controls.

At the first visit the relative height and weight for height did not differ between the groups. The OSAS and PS children showed a similar trend towards a target height deficit compared with the controls. Mean relative height was lower in both groups than mean target height (Table 8).

The BMI’s were quite similar in the three groups, while the body fat mass was somewhat but not significantly higher in the OSAS children than in the two other groups (Table 8). All the children studied were prepubertal, and therefore the anthropometric data were not presented according to sex.

The bone age was available only from 27 children in the control group. Children with OSAS and the primary snorers had a retarded relative bone age, while the controls had an advanced bone age (Study V). As a consequence, the OSAS children and snorers had a significantly younger relative bone age than the control subjects.

The circulating concentrations of IGF-1 were of the same magnitude in all the three groups (Table 8). Both the OSAS and PS children had lower IGFBP-3 concentrations than the control subjects (*p = .001*) (Table 8). This was true also after adjustment for age.
OSAS in children is often associated with growth failure (14, 33, 43, 102, 183-186, 188, 251). In the present study no obvious growth retardation could be observed in OSAS children or primary snorers, when comparing the relative height and weight for height to the control children, but the children in both groups showed a target height deficit, which possibly indicates reduced growth potential compared with the control children. This interpretation is also supported by the finding that the children in the two groups had younger relative bone age than the controls, though individual growth patterns may explain some of the difference. The fact that no significant differences could be observed in the anthropometric data between the children with OSAS and those with primary snoring might be explained by sleep abnormalities, which may have been present in the children considered primary snorers as commented in chapter 5.1.1.

Obesity is not common in children with OSAS according to the present results, as has been stated by others (31). Only one OSAS child (AHI₀ 11.8) had a BMI slightly over 20.

The grounds of impaired growth in OSAS children are poorly understood, though many causes have been suggested (43, 102, 183, 186). Recent results (188) and earlier case reports (1, 187) indicate changes of the somatotrophic axis in children with OSAS. In the present study circulating concentrations of IGF-1 and IGFBP-3 were studied. IGF-1 is considered as the main mediator of the growth-promoting actions of GH (189), reflecting the daily mean GH levels, and it has been reported to correlate well with the physiological changes in GH secretion (190). GH stimulates the production of IGF-1 in the liver and other target tissues (252). IGFBP-3, the GH-dependent major carrier protein of IGF-1, has also been shown to correlate significantly with nocturnal GH secretion, but not as strongly as in the case of IGF-1 (241). Although IGFBP-3 probably exerts some functions of its own on cells, its major role is to prolong the half-life of IGF-1 (253). The major advantage of IGFBP-3 determinations in diagnostics is its relative stability over time (241), and it may therefore be a more reliable indicator of GH secretion over a longer time span than IGF-1. It is also less dependent on age than IGF-1 (253). This is perhaps the cause of the finding that the circulating concentrations of IGFBP-3 were in the present study found to be significantly lower both in the OSAS children and the primary snorers than in the controls, whereas there were no significant differences in the circulating concentration of IGF-1. That the concentrations of neither IGF-1 nor IGFBP-3 differed between the OSAS children and primary snorers may be explained by sleep disturbances in the primary snorers group not recognized by the present monitoring device.
5.2 Follow-up study

5.2.1 Polysomnography results

Fifty-eight children (31 boys) had a successful second sleep study and clinical appraisal. Twenty-one children with an AHIO of greater than two had been treated surgically shortly after the first visit. The other 37 children were subjected to follow-up without intervention. In this group were included two children with AHIO initially slightly above 2 (2.3 and 2.6) due to phoniatriac contraindications to surgery at the time, as well as four children with an AHIO of over one but less than two at the first visit.

Of the surgically treated children 73 % (16/21) had undergone adenoidectomy prior to entering the study, which operation had not resolved the obstructive symptoms, or the symptoms had begun after the adenoidectomy. By the time of tonsillectomy the epipharynx was controlled, and none of the children had any significant regrowth of the adenoidal tissue.

After tonsillectomy, or adenotonsillectomy in five cases, the mean AHIO had decreased significantly (Table 9). The AHIO was zero in 16 children, while three children had an AHIO of 1 or less. The other monitored parameters had all improved significantly as well, except for the central apnea index and the saturation distribution, which last was however narrower than prior to surgery, but not significantly (Table 9). One child’s AHIO was one, whereas one boy, who had an initial AHIO of 8.9, had still a clearly abnormal AHIO of 5.1. This boy had undergone adenoidectomy prior to entering the study, and he had got enormously enlarged tonsils removed, without showing any morphological abnormalities on clinical evaluation.
Table 9. Polysomnography results of the 21 children operated on. Unless otherwise indicated, data are mean (SD) (range). p1 indicates the statistical difference between the results from the first and second measurements.

<table>
<thead>
<tr>
<th></th>
<th>Visit 1</th>
<th></th>
<th>Visit 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>5.6 (2.1)</td>
<td>&lt;.01</td>
<td>6.3 (2.0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>(2.4–10.5)</td>
<td>(2.9–11.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Earlier adenoidectomy %</td>
<td>76 % (16/21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(number)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total apnea index</td>
<td>7.5 (4.4)</td>
<td>&lt;.01</td>
<td>0.7 (1.2)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>(2.1–16.8)</td>
<td>(0–5.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive apnea-hypopnea-index</td>
<td>6.9 (4.1)</td>
<td>&lt;.01</td>
<td>0.3 (1.1)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>(2.0–14.6)</td>
<td>(0–5.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive apnea index</td>
<td>1.4 (1.2)</td>
<td>&lt;.01</td>
<td>0.0 (0.03)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>(0.1–4.2)</td>
<td>(0–0.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive hypopnea index</td>
<td>5.5 (3.9)</td>
<td>&lt;.01</td>
<td>0.3 (1.1)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>(0.4–14.5)</td>
<td>(0–5.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central apnea index</td>
<td>0.7 (1.3)</td>
<td>.08</td>
<td>0.3 (0.4)</td>
<td>.08</td>
</tr>
<tr>
<td>(0–5.8)</td>
<td>(0–1.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short obstructive apnea index (5–10 sec)</td>
<td>1.6 (1.6)</td>
<td>.001</td>
<td>0.1 (0.1)</td>
<td>.001</td>
</tr>
<tr>
<td>(0–5.7)</td>
<td>(0–0.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4% desaturation index per hour</td>
<td>5.0 (7.4)</td>
<td>.04</td>
<td>0.2 (0.6)</td>
<td>.04</td>
</tr>
<tr>
<td>(0–29.6)</td>
<td>(0–2.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% desaturation index per hour</td>
<td>0.2 (0.4)</td>
<td>.02</td>
<td>0 (0)</td>
<td>.02</td>
</tr>
<tr>
<td>(0–1.4)</td>
<td>(0–0.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturation distribution %</td>
<td>3.4 (1.9)</td>
<td>.19</td>
<td>2.7 (0.5)</td>
<td>.19</td>
</tr>
<tr>
<td>(90–10)</td>
<td>(1.7–3.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periods with tachycardia associated with partial hypopnea (min/hour)</td>
<td>1.4 (1.3)</td>
<td>.001</td>
<td>0.4 (0.4)</td>
<td>.001</td>
</tr>
<tr>
<td>(0.2–4.6)</td>
<td>(0.0–1.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the non-treated group the mean AHI₀ had decreased insignificantly from 0.4 to 0.2. The AHI₀ had been normalized for all the four children with an AHI₀ of less than two but more than one, as well as for the one with an AHI₀ of initially 2.3, while for one the AHI₀ had remained the same at 2.6. None of the primary snorers had developed OSAS. The group mean values had changed insignificantly for all the monitored parameters (Study IV).

5.2.1.1 Comments

The present study confirmed the previously reported results (14, 33, 39, 56, 86, 88, 93, 139, 170, 174, 201) that adenotonsillectomy is efficient treatment of OSAS in children in most cases. Only one child had clearly abnormal AHI₀ even after surgery. The finding that most of the operated OSAS children were already free of adenoid tissue strongly
indicates that at least in many OSAS children the site of airway obstruction is at the oropharyngeal level, whereas nasopharyngeal obstruction is not so important (154). Further, based on this finding, adenoidectomy alone is not the perfect treatment of OSAS.

The course of obstructive sleep disorders in children is unpredictable (36). Habitual snoring often ceases by itself (114, 115) and has no obvious tendency to progress to OSAS (32), as was noticed in the present study, too. None of the primary snorers had a clearly abnormal second sleep study.

5.2.2 Symptoms (Study IV)

All the children were re-evaluated for the symptoms. Clinically, all the children operated on had benefited from the operation. All the symptoms disappeared completely from 16 children. Five children continued to have minor problems, mainly occasional snoring. None of these children had however any need for additional treatment. The mean OSA score had changed significantly from 3.4 (median 3.9) to −3.1 (median −3.8) (p < .01). The boy with the postoperative AHI_{O} 5.1 was snoring lighter, and he was more alert in daytime. Four children continued to snore irregularly, while one of them had at times labious breathing.

In the non-treated group (n = 31) six children had developed more symptoms, while 15 children had unchanged symptoms and 16 had reportedly decreased symptoms. One child had become totally symptomless. The mean OSA score had on the other hand decreased from 2.1 (median 2.5) to 0.5 (median 1.1), (p = .001).

5.2.2.1 Comments

In line with results from many other studies (14, 33, 39, 56, 86, 88, 93, 139, 170, 174, 201), (adeno)tonsillectomy of OSAS children was found to definitely improve the day- and nighttime symptoms. Five children were not totally free from symptoms though.

As noted earlier, primary snoring seems to have a favourable prognosis in children (32). In the present study the vast majority of the untreated children had unchanged or decreased symptoms, and the children with subjective worsening of symptoms had still PSG results within the normal range.

5.2.3 Impact on nasalance (study II)

Altogether 36 children were successfully measured at both the first and the second visit. The mean age of these children was 6.5 years, range 3.3 to 10.5 years of age, at the first visit. Twelve children had OSAS, of whom nine had an AHI_{O} of over 2 and had subsequently undergone (adeno) tonsillectomy. Twenty-four children were primary
snorers. Adenotonsillectomy had no statistically significant influence on the nasalance scores. Neither had the nasalance scores changed among the 27 non-treated children. No single parameter seems to have statistically significantly affected the nasalance scores between the measurements.

5.2.3.1 Comments

Adenotonsillectomy does not produce permanent changes in nasality in normal children (254), as seems be the case with OSAS children, too. The higher mean nasalance values than in normal Finnish children for the nasal sentence (232) were repeated in the surgically treated OSAS children. The lack of change in the nasalance scores of the non-treated children indicates diagnostic reliability of the measurements.

5.2.4 Effects on growth

Of the original 70 children, six did not participate in the follow-up study. In four cases there was a protocol violation, and in one case a technical problem. In six cases the laboratory or x-ray examinations could not be repeated. The result was that 53 children (27 boys), mean age 6.5 years, range 2.9–11.1 years, successfully completed the whole of this part of the study protocol. Nineteen of these children had had an AH1O of over two, and had been treated surgically shortly after the first visit. Among the 34 children not subjected to intervention two children were included with an AH1O of over two (2.3 and 2.6) due to contraindications to surgery.

Weight for height and BMI had increased significantly in the group which had undergone an operation ($p = .001$ and $p = .01$, respectively). The increase in the weight for height in this group seemed to be largely due to an increase of body fat ($p = .02$), since though the mean fat-free mass increased more in this group, the difference was not significant according to the linear regression model with age and intervention status as independent variables ($B = 0.59$, $r^2 = 0.21$, $p = .08$). Relative height increased significantly only in the non-surgery group ($p = .02$). There were no significant changes in bone age between the two visits in either group.

The peripheral concentrations of IGF-1 and IGFBP-3 were significantly higher on the second occasion in the surgically treated children ($p = .002$ and $p < .001$) (Fig. 4 and 5). In the non-treated group the changes in the circulating IGF-1 and IGFBP-3 levels were insignificant. The initially significant difference in IGFBP-3 levels between the children operated on and the controls ($p = .001$) had disappeared at the second visit (Fig. 4). Only in two cases out of 19 (10%) were the IGF-1 and IGFBP-3 concentrations lower at the second visit in the operated group, while in the non-operated group the IGF-1 and IGFBP-3 levels were lower at the second visit in 44% (15/34) and 29% (10/34) of the cases, respectively.
Fig. 4. Plasma IGF-1 levels in children treated surgically for OSAS and in primary snorers (non-operated) at the first and second visits 6 months apart and in the control subjects. Each box-plot represents the median (thick black band) and the 25th and 75th centiles. The error bars represent the smallest and largest observed values except the outliers.

Fig. 5. Serum IGFBP-3 levels in children treated surgically for OSAS and in primary snorers (non-operated) at the first and second visits 6 months apart and in the control subjects. Each box-plot represents the median (thick black band) and the 25th and 75th centiles. The error bars represent the smallest and largest observed values except the outliers.
That the normal growth pattern of children with night time airway obstruction is potentially affected was confirmed by the results of the follow-up study. A “catch-up growth phenomenon” after treatment of OSAS has been well reported (43, 102, 183, 186), when growth deceleration in OSAS children turns into growth acceleration, being especially fast for the weight. The findings of the present study support a growth pattern of this kind, as a significant increase in the weight for height and BMI was noticed in the surgically treated children, whereas the relative height did not increase significantly. The analysis of the different body mass components showed that the weight increase after treatment of OSAS was due to an increased amount of fat rather than an increase in fat-free mass. Increased energy consumption due to increased work of respiration has been suggested as a cause for growth failure in OSAS children (186), which could be thought to explain this finding, but a recent study showed that OSAS in children is not associated with increased energy requirements (251).

The findings of the present study indicate that changes in the somatotrophic axis can take place in OSAS children. The significant increase in the circulating IGF-1 and IGFBP-3 concentrations in the surgically treated OSAS children indicates an initially decreased nocturnal growth hormone secretion, followed by a significant increase after treatment. In line with the present findings, Bar et al. (188) have lately demonstrated, that IGF-1 concentrations increased significantly in surgically treated OSAS children. In contrast to their findings, in the present study there was observed a significant increase also in the IGFBP-3 concentrations along with the IGF-1 levels in the surgically treated children, implicating a decreased GH secretion in OSAS children over a longer time span prior to treatment. That the significant difference in the concentrations of IGFBP-3 between the OSAS children and controls had disappeared at the second measurement, indicates a normalisation of GH secretion after treatment of OSAS.

In this study, the children remained in prepuberty, when the peripheral IGF-1 levels increase fairly slowly (255), and since the time interval between the first and second measurements was relatively short in our study, the increase in age must have very modestly affected the circulating IGF-1 concentrations, as shown by the small increase observed in the children not operated on. Accordingly, the significant increase in peripheral IGF-1 levels observed in the surgically treated children suggests that the alleviated airway obstruction resulted in an increased GH secretion.

How the somatotrophic axis of OSAS children may be disturbed is unknown. As the main burst of growth hormone secretion takes place at the beginning of the night (252, 256), when apneas and hypopneas in children are rare (35), it seems likely that the somatotrophic axis is not necessarily disturbed by cortical arousals associated with obstructive apneas or hypopneas as in adults (257, 258), but rather by subcortical reactions or autonomic arousals linked to obstructed periods (51, 63, 259), as the macrostructure of sleep is little affected (57).
6 General discussion

In the light of current knowledge, some of the snoring children may be seriously affected, if the nature of their nighttime breathing obstruction passes the limit of harmless acoustic phenomena. As snoring is so common in children (114-117, 119), it is a big task to recognize the children with more serious sleep disorders among the snorers. There is a great deal of overlap between the different levels of seriousness of the sleep-related breathing disorders (46, 64), also as regards the symptoms. This is obvious from the results of many studies, where half or less of the children suspected of having OSAS actually proved to have it (31, 85-88), as was the case also in the present study.

Polysomnography is recommended to differentiate benign snoring from snoring associated with either partial or complete airway obstruction, hypoxemia and sleep disruption, i.e. pediatric OSAS (70). The nature of OSAS in children is different from that in adults, which necessitates its own diagnostic criteria (16, 31, 40). There exists however no consensus statement on PSG criteria for OSAS in children. Different approaches for measuring respiratory events may contribute to substantial variability to identification and classification of OSAS (71). Obstructive events are nevertheless rare in asymptomatic children, so the apnea-hypopnea index of one or more (16) was found to be statistically abnormal also in this study.

There is often a big discrepancy between PSG results and the clinical diagnosis score in children with strongly suspected OSAS (49). In the present study substantial overlap of symptoms could be noticed between the OSAS children and the primary snorers, which is obviously explained by the continuum of the sleep-related breathing disorders in children and the unsettled role of UARS in children (46, 64, 65). Some of the primary snorers were probably beyond the stage of a plain acoustic phenomenon, judged from the cardiac reactions to partial airway obstruction, which probably indicate subcortical arousals (62). The diagnosis of OSAS in children should therefore perhaps be based on a combination of factors gathered from PSG and clinical symptomatology (49). It has also been suggested that PSG is not necessary in all children with strong clinical evidence of OSAS, since PSG is rather expensive and the availability may be poor (80, 81). If one has to rely on clinical symptoms and signs in an attempt to make the diagnosis of OSAS, or has to screen candidates for limitedly available PSGs, the knowledge of symptoms and signs associated with
increased risk of having OSAS is important. Many symptoms have been found typical of OSAS in children (14, 31, 65, 85-87, 89, 96, 175), but none of the symptoms is pathognomonic for OSAS. The significant risk factors for predicting OSAS found in the present study can contribute to the diagnostic work-up of snoring children.

Anatomical abnormalities, often associated with different syndromes, may predispose to OSAS in children (14, 33, 121, 155-157). More subtle anatomic differences have been recognized to be correlated with increased incidence of OSAS in adults (260, 261). Adenotonsillar hypertrophy is the main etiology of OSAS in children (14, 33, 36, 93, 101, 151). The airway closure is a dynamic process though, and other underlying factors must be involved in the process, as tonsillar hypertrophy is not necessarily present in all children with OSAS (152, 202), and many children with tonsillar enlargement do not have OSAS, as was also the case in the present study. Children with obstructive disorders have been recognized to have more malocclusion and craniofacial modifications than other children (169, 202, 244, 245, 262). The unanswered question is whether these changes are genetically determined or the results of abnormal breathing and altered head position. Snoring and OSAS have been found to have a tendency to familial aggregation when studied in adults (162-164, 263), which can be a result of hereditary abnormal facial morphology, and to some extent increased obesity in the families (120). Obvious morphological differences between obstructed and non-obstructed children have been advocated to be results of altered breathing function (152, 167, 168), and many of the changes have been found to reverse after treatment (202, 244, 264, 265), which supports the idea that not all the differences are genetically determined. It is unknown whether the observed differences will stay permanent if they remain untreated or are treated late, and whether this can predispose to development of OSAS later in life (204), especially since the morphological modifications mentioned above may develop also in mouthbreathing children without OSAS (166, 171).

Soft tissues obstructing the upper airways could be thought to affect the air escape into the nose and nasal resonance, which can be objectively measured. Indeed, this was found to be the case, whereas the studied children showed abnormally high nasalance values compared with normal children. This unexpected result is most probably explained by impaired velopharyngeal closure secondary to tonsillar hypertrophy (246, 266).

The lack of change in the nasalance scores in the surgically treated OSAS children is an intriguing finding, since removal of large palatine tonsils might be expected to influence the nasal/oral acoustic ratio. Whether the lack of change is due to phonetic adaptation, or the persistent higher nasalance scores are secondary to other pharyngeal soft tissue abnormalities, such as a large velopharyngeal sphincter, which has been noted in OSAS children (154), is unsettled.

Adenotonsillectomy has been found to be curative treatment of OSAS in children in most cases (14, 33, 56, 86, 93, 101, 139, 170, 174, 201, 202), which finding was confirmed by the results of the present study. All children are however not cured or only partially cured by adenotonsillectomy, even some of those without obvious deviations in facial morphology (86), as was the case in the present study. Underlying subtle deviations in facial morphology or soft tissues may explain some of the residual symptoms (54) or relapses later in adolescence (204). As was mentioned earlier, functional changes may affect the facial morphology of OSAS children, which is mainly reversed after treatment, but perhaps not always. The dental/facial irregularities have been found to worsen during
periods of fast growth and rarely reverse spontaneously (171), so modifications of the continuous interaction between airway patency during sleep and maxillo-mandibular growth may be part of the explanation (167). In the present study none of the five children who were not totally free of symptoms, or were found to have some obstructive events left after surgery, had any obvious skeletal abnormalities, and they all had had removed grade-IV palatine tonsils, and had all been subjected to adenoidectomy already before entering the study. The children with residual symptoms were nevertheless among those with the initially highest AHI_{OSAS}, who were found to have increased overjet.

As the clinical presentation of OSAS in children differs from that in adults, so do also the complications, due to the specific state of ongoing development (259). Cardiovascular complications are the most serious ones, though obviously rare, with cor pulmonale and right-sided heart failure being potentially life threatening. OSAS in children is often associated with growth failure and a “catch-up” growth after treatment (14, 33, 43, 102, 183-186, 188, 251). The cause of this phenomenon has been unknown. In the present study it was observed that growth, especially weight gain, is improved after resolved OSAS in children. The somatotrophic axis is most likely to be affected by obstructive sleep disorders in children; resolved upper airway obstruction was seen to result in a significant increase in the circulating IGF-1 and IGFBP-3 concentrations, both factors being mediators of the growth-promoting actions of GH. The present results indicate an impaired GH secretion in OSAS children, which is normalized after treatment. A significant increase in the circulating concentrations of IGF-1 after surgical treatment of OSAS has also been verified by others (188). In the present study it was also found that the initially low IGFBP3 concentrations, indicating a reduced GH secretion over a longer time span, increased significantly in OSAS children after treatment to the level of those of the control children. This complication of OSAS in children seems to be reversible by successful treatment.

The prevalence of snoring seems quite stable in the pediatric population, as in many children snoring abates on its own while other children start snoring (114, 115). As in the study by Marcus et al. (32), the natural history of primary snoring was in the present study found to be favourable. This is an interesting finding, raising the question which children to treat and when. There exists no doubt about the necessity of prompt treatment of children with serious OSAS with severe symptoms and signs of complications. However, as our understanding and the public knowledge of sleep-related breathing disorders in children have improved, we find the children earlier, usually before serious complications have developed. In today’s clinical practice we often meet children with nocturnal symptoms of obstructive sleep disturbances, who may prove to have mild OSAS on overnight PSG, but have no daytime complaints or signs of complications. Should they all be treated? Surely, the treatment in these cases would not be addressed to the daytime symptoms as in adults, but rather to prevention of complications, since the natural course of OSAS may be unpredictable (36). Complications of OSAS can develop in children without any daytime complaints of OSAS (194, 195). The problem is that no test or PSG can predict in which of the children with mild OSAS complications will develop. Further, if the diagnosis and treatment are delayed (3), could the complications possibly developed be expected to be reversed by treatment? One of the main targets for future research is to find prognostic factors suggesting negative outcome of sleep related breathing disorders.
7 Conclusions

1. Snoring children have many typical symptoms and signs associated with an increased risk of having OSAS. However, PSG is needed to confirm the diagnosis of OSAS.
2. Dentofacial differences exist between children with OSAS and those without. These differences may be secondary to functional changes and sleeping positions.
3. Nasalance scores in children with nighttime obstructive symptoms are higher than in normal Finnish children. There does not seem to be differences in nasalance scores between snoring children with and without OSAS, neither are the scores affected by surgical treatment of OSAS. Nasometry is not useful in the prediction of OSAS.
4. Adenotonsillectomy is a curative treatment of OSAS in children in most cases, but some children may be left with residual symptoms.
5. Primary snoring in children seems seldom to progress to OSAS, and mild OSAS does not seem to have a tendency to progress to more serious stages during a six-month follow-up.
References


Original communications