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PEDIATRIC OBSTRUCTIVE SLEEP APNEA – EVALUATION OF QUESTIONNAIRE AND SURGICAL TREATMENT

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To my family

“The good life is one inspired by love and guided by knowledge”

Bertrand Russell

ABSTRACT

Obstructive sleep apnea (OSA) is a major pediatric health problem and is associated with potentially severe consequences if left untreated. Diagnosing OSA in children can be challenging since the clinical symptoms are very non-specific. A full-night polysomnography is recommended as the gold standard to establish the diagnosis, but it is not possible to perform this for every child where suspicion of OSA has arisen. Other diagnostic instruments such as questionnaires have been used, and one of these, the OSA-18, was evaluated in **Paper I**. The dominant cause of OSA in children is tonsil hypertrophy and treatment is surgical with removal of tonsils. Tonsillectomy is one of the most common surgical procedures performed on children throughout the world. The trends of Swedish tonsil surgery in recent decades were described in **Paper II**. In recent years, tonsillotomy (partial tonsillectomy) has gained popularity as an option for surgery in Sweden. It has been unclear whether tonsillotomy is as effective as tonsillectomy in treating OSA, and this was investigated in a randomized study. The overall aim of the thesis was to contribute to the improvement of the diagnostic process and surgical treatment of OSA for children.

Paper I considers the diagnostic process of pediatric OSA and evaluates the disease-specific questionnaire OSA-18. 225 children were included. They all performed a full-night PSG and their parents responded to OSA-18. The scores of the OSA-18 were compared to the apnea-hypopnea index from PSG, and the results showed poor predictivity of the OSA-18 to detect and correctly grade the severity of OSA.

Paper II is a longitudinal description of the trends in the clinical practice of tonsil surgery in Sweden between 1987 and 2013. The study was based on the Swedish National Patient Register, and all children aged 1-17 years who were registered with a tonsil surgery procedure were included, totaling 167 894 individuals. The results demonstrated substantial shifts in the trends of tonsil surgery over the period, with an overall increase in incidence of tonsil procedures, consisting mainly of tonsil surgery due to sleep disordered breathing/OSA, especially among the youngest children (1-3 years). Moreover, a gradual increase in the incidence of tonsillotomy since it was introduced in the late 1990s was observed, and since 2011 tonsillotomy has been more common than tonsillectomy.

Papers III and IV are a randomized trial with the aim of comparing adenotonsillotomy (ATT) with adenotonsillectomy (ATE) regarding the effect of treating pediatric OSA measured by polysomnography(**Paper III**). The RCT included 79 children aged 2-6 years, with moderate to severe OSA, randomized to either ATT or ATE. All children performed a PSG at baseline, with follow-up one year after surgery. **Paper III** primarily evaluated the polysomnographic outcomes, showing that ATT was non-inferior to ATE. However, five cases in the ATT-group needed repeated surgery due to re-growth of tonsils and return of OSA-symptoms, and thus considered as failures of ATT. All children were also evaluated concerning postoperative pain and bleeding (**Paper IV**), showing that ATT is associated with less postoperative pain than ATE, but the differences were modest. Two cases of postoperative bleeding were seen in the ATE group and no cases of postoperative bleeding in the ATT group, indicating a lower risk of bleeding after ATT than ATE, but a larger study population would have been needed for better evaluation.

LIST OF PUBLICATIONS

This thesis is based on the following studies, which will be referred to in the text by their roman numerals:

I. Borgström A, Nerfeldt P, Friberg D
Questionnaire OSA-18 has poor validity compared to polysomnography in pediatric obstructive sleep apnea
International Journal of Pediatric Otorhinolaryngology 2013; 77: 1864-1868

II. Borgström A, Nerfeldt P, Friberg D, Sunnergren O, Stalfors J
Trends and changes in paediatric tonsil surgery in Sweden 1987- 2013: a population-based cohort study
BMJ Open. 2017 Jan 13;7(1):e013346. doi: 10.1136/bmjopen-2016-013346

III. Borgström A, Nerfeldt P, Friberg D
Adenotonsillotomy vs Adenotonsilletomy in pediatric obstructive sleep apnea: An RCT
Pediatrics, accepted for publication, Jan 12 2017

IV. Borgström A, Nerfeldt P, Hessén-Söderman A-C, Friberg D
Postoperative pain and bleeding after adenotonsillotomy vs adenotonsillectomy in pediatric obstructive sleep apnea: an RCT
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

AAP	American Academy of Pediatrics
AASM	American Association of Sleep Medicine
AHI	Apnea-hypopnea index
ATE	Adenotonsillectomy
ATT	Adenotonsillotomy
AUC	Area under the curve
BMI	Body mass index
CAHI	Central apnea-hypopnea index
CI	Confidence interval
CPAP	Continuous positive airway pressure
ECG	Electrocardiogram
EEG	Electroencephalogram
EOG	Electrooculogram
HRQL	Health-related quality of life
IQR	Interquartile range
ITT	Intention to treat
NPV	Negative predictive value
OAHI	Obstructive apnea-hypopnea index
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
QoL	Quality of life
PG	Polygraphy
PSG	Polysomnography
RCT	Randomized clinical trial
RDI	Respiratory disturbance index
RME	Rapid maxillary expansion
RPSGT	Registered polysomnographic technologist
PPV	Positive predictive value
ROC	Receiver operating characteristics
SD	Standard deviation
SDB	Sleep disordered breathing
TE	Tonsillectomy
TSS	Total symptom score
TT	Tonsillotomy

1 BACKGROUND

"The stupid-lazy child who frequently suffers from headaches at school, breathes through his mouth instead of his nose, snores and is restless at night, and wakes up with a dry mouth in the morning, is well-worthy of the solicitous attention of the school medical officer."

This was how William Hill characterized the manifestations of a child with sleep disordered breathing in the British Medical Journal in 1889. These symptoms have thus been well recognized in history, but it was not until the mid-1970s that Christian Guilleminault described the disease obstructive sleep apnea (OSA) in children[1]. Since then, the awareness of OSA has increased and it is now known to be an important and common disorder in the pediatric population, encountered by most clinicians meeting pediatric patients. The most common cause of OSA in children is hypertrophy of tonsils and adenoid and first-line treatment is surgery. Tonsil surgery is one of the most commonly performed surgical procedures in children, and considered the "bread and butter" of ENT-surgeons' work.

This thesis was based on studies addressing different aspects of childhood obstructive sleep apnea: challenges involved in the diagnostic process and tonsil surgery.

1.1 PEDIATRIC SLEEP DISORDERED BREATHING AND OBSTRUCTIVE SLEEP APNEA

Sleep-disordered breathing (SDB) is characterized by an abnormal respiratory pattern or abnormal ventilation during sleep. SDB is most commonly used to describe disorders of an obstructive character, caused by a partial or complete obstruction of the upper airway. To be accurate, the term SDB also includes other disorders, such as those of central neurological origin with an affected central ventilatory drive. These are less common and will not be discussed further in this thesis, where the focus instead lies on obstructive SDB.

SDB varies in severity and includes a spectrum of clinical entities with primary snoring at one end to the most severe from, obstructive sleep apnea (OSA), at the other end, ***Figure 1***. OSA is a disorder of disturbed breathing during sleep characterized by prolonged incomplete and/or intermittent complete upper airway obstruction[2]. This obstruction causes decreased or interrupted airflow despite continual respiratory effort, disrupting normal ventilation and

sleep patterns. OSA has been recognized as a probable cause of morbidity among children and is associated with severe complications if left untreated. Further, it entails increased health care utilization, with more hospital visits and higher health care costs compared to children without OSA[3].

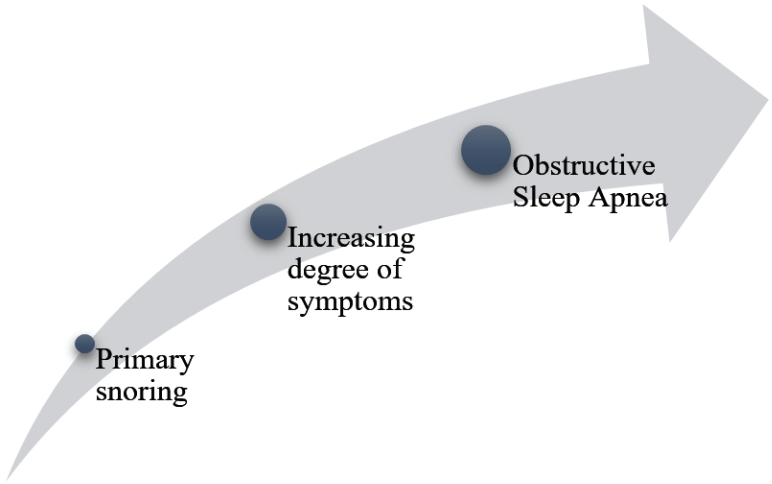


Figure 1. *The spectrum of sleep disordered breathing with increasing degree of upper airway obstruction.*

1.1.1 Epidemiology

The prevalence of SDB has been estimated in several studies and varies from 0.7% to 13.0%, depending on the populations studied, the methods used for assessment and the diagnostic criteria[4-7]. Of these, 1-5% are diagnosed with OSA[6,8,9], with a peak prevalence at 2-5 years of age, when the lymphoid tissue of the tonsils and adenoid are largest in relation to airway size[10-12]. There are epidemiologic studies indicating that pediatric SDB/OSA display familial clustering[13], and an increased risk of OSA if a parent or sibling is affected by the disease[14]. Also, there seems to be an association between OSA severity and socioeconomic factors[15,16].

1.1.2 Etiology and mechanisms of pediatric OSA

OSA is caused by upper airway collapse, complete or partial, during inspiration. By far the most common cause in children is hypertrophy of tonsils and adenoid, structurally narrowing the upper airway. However, the etiology is multifactorial and besides anatomical and structural factors, there are also functional and neuromotor factors affecting the collapsibility of the upper

airway[17]. It has been reported that children with OSA have more collapsible upper airways than children with no OSA[18].

The sleep stage is also of importance. In children the respiratory events occur more frequently during rapid eye movement (REM) sleep than in non-REM[19], due to muscle atonia and reduced arousal threshold[20]. It has also been seen that the pharyngeal dilator activity decreases more during REM sleep in children than in adults[21].

1.1.3 Co-morbidities and risk groups

Several medical conditions can increase the risk of OSA in children. Obesity is recognized as a major risk factor for OSA and OSA has a prevalence of up to 40% of obese children[22]. For this group the clinical presentation more closely resembles adult OSA[23].The mechanisms are multiple: fatty infiltrate in the soft tissue narrows the airway and increased visceral fat of the thorax and abdomen is entailed by reduced functional lungcapacity[24]. Oxygen desaturation is more pronounced in obese children with OSA, with the degree of obesity associated with the severity of desaturation[25]. It is estimated that 45% of obese children with OSA have adenotonsillar hypertrophy[26], and therefore could benefit from surgery, but obese children are at risk of residual OSA after surgery[27]. Asthma and allergic rhinitis are also associated with OSA[28]. A common inflammatory pathway of the upper airway has been suggested as the underlying pathophysiological mechanism[29]. Gastroesofageal reflux often coexists with OSA but it is not fully clear how they are interrelated. It has been observed that treatment with proton pump inhibitor reduce the obstructive respiratory events[30].

Other groups with high risk of OSA include children with neuromuscular disorders (e. g. congenital muscular dystrophies[31], cerebral palsy[32]), craniofacial abnormalities[33] (e g Pierre Robin, sequence, Treacher Collins syndrome, cleft palate[34]), sickle cell disease[35], prematurity[36], laryngomalacia[37] and some other complex abnormalities such as Down syndrome[38], Prader Willi syndrome[39], mucopolysaccharidoses[40], achondroplasia[41], Chiari malformation/myelomeningocele[42] and more.

1.1.4 Morbidity

OSA is associated with significant negative health consequences if left untreated. The most commonly reported of these are neurocognitive dysfunction and behavioral disturbances, with hyperactivity, aggressive behavior, moodi-

ness, learning problems and concentration difficulties[43]. Even mild OSA and primary snoring (defined as habitual snoring > three nights a week, without apneas, hypopneas, frequent arousals from sleep or gas exchange abnormalities[44]) are associated with affected neurocognitive function[45]. There are studies demonstrating that treatment of OSA (usually adenotonsillectomy, ATE) improves the neurocognitive and behavioral functioning[46-48]. Systolic hypertension is also correlated to pediatric OSA[49]. Other severe adverse outcomes are cardiovascular complications such as pulmonary hypertension leading to right-sided heart failure[50]. There are also studies showing a higher mortality rate in children with OSA than in controls[51].

Systemic inflammation has been proposed as a possible mechanism of the development of both neurobehavioral and cardiovascular morbidity in OSA and a higher level of C-reactive protein has been observed in children with OSA[52,53]. Interestingly, treatment of OSA (ATE) seems to reduce the CRP levels[54].

Complications of metabolic character include nocturnal enuresis[55] and failure to thrive[56]. The latter can be the consequence of the excessive work of breathing during sleep, but imbalance in hormonal levels is also thought to contribute to failure to thrive in OSA children[57]. The association between OSA and insulin resistance and diabetes is not as robust as for adults, but is seen in obese children with OSA[58].

The mechanisms leading to the negative consequences of OSA are not clearly established. It has been discussed whether it is the sleep fragmentation and frequent arousals or the intermittent hypoxemia that causes the end-organ effect, or a combination of both. It has also been suggested that there are specific developmental periods of higher vulnerability and differences in individual susceptibilty. Moreover, genetic and environmental factors could play a role in the phenotypic expression of OSA and its adverse outcomes[59].

1.1.5 Symptoms

Daytime symptoms of OSA in children are very unspecific and can include mouth breathing, concentration difficulties, behavioral disturbances as mentioned above, and excessive daytime sleepiness. However, sleepiness is not as common in children with OSA as it is in adult OSA. Examples of nighttime symptoms are snoring (nearly all children with OSA snore[60]), restless sleep, excessive sweating, nocturnal enuresis, apneas and cervical hyperextension. Altogether, there are no distinctive symptoms of OSA in children and the diagnosis requires a high level of suspicion to detect[26].

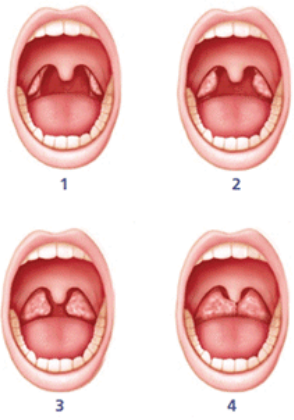
The physical finding mostly associated with OSA in children is hypertrophy of tonsils and adenoid. However, the tonsil size is not predictive of OSA severity[61,62].

Other physical findings that can be associated with OSA include poor growth, abnormal craniofacial morphology, high arched palate, mouth breathing, nasal septum deviation, swollen nasal mucosa, pectus excavatum and macroglossia[63,64].

1.2 DIAGNOSIS OF PEDIATRIC OSA

1.2.1 History and clinical examination

Early recognition and treatment of pediatric OSA is required to prevent long-term complications and a proper diagnosis is the basis for correct and effective treatment. The American Academy of Pediatrics(AAP) issued guidelines in 2012 recommending that all children and adolescents should be screened for snoring[65]. If snoring is present, a more extensive evaluation of SDB-related symptoms should be prompted, starting with a patient history and physical examination with a focus on the symptoms and signs listed above. In many cases this is considered to be sufficient to diagnose OSA and decide on treatment. However, clinical evaluation has not been shown to be reliable for diagnosing OSA compared with PSG[66]; the positive predictive values of history and physical examination have been reported as 65% and 46% respectively[9, 67]. The child might not present any abnormal clinical findings, and tonsil size cannot predict the presence of OSA in the individual child[61]. Clinical assessment of tonsil size in children is performed by using the 1-4 Brodsky scale[68] (***Figure 2***). There are several reasons why the correlation between tonsil size and OSA is unclear. First, the nature of the Brodsky scale is subjective, although with acceptable intra-and inter-rater reproducibility[69]. Second, there are difficulties in obtaining a clear visual assessment when examining small children. Videorecording or photographing the tonsils and pharynx may help in this situation. Also, large tonsils may not always be protruding, they can be deeply positioned lateral to the tonsillar pillars and thus misjudged. Studies have shown that the tonsil volume correlates to OSA severity, regardless of how much they protrude medially from the tonsillar pillars[70,71]. In summary, the clinical evaluation is challenging and both the AAP and the European Respiratory Society recommend that children at risk of SDB should be referred for further investigation[44, 65], preferably PSG.



Brodsky Table

(Degree of Tonsils Blockage)	Ratio of the Tonsil in the Oropharynx
Degree 1	Tonsil occupies less than 25% of the Oropharynx
Degree 2	Tonsil occupies from 25 to 50% of the Oropharynx
Degree 3	Tonsil occupies from 50 to 75% of the Oropharynx
Degree 4	Tonsil occupies more than 75% of the Oropharynx

Figure 2. *The Brodsky scale for clinical tonsil size grading in children*[68].

1.2.2 Polysomnography

The gold standard for evaluating pediatric SDB and OSA is overnight, attended polysomnography (PSG) performed in a sleep laboratory[65]. PSG is a noninvasive test, where both sleep stage and respiratory functions are measured. Standard PSG includes recordings of several physiological variables: electroencephalogram (EEG), electrooculogram (EOG), electrocardiogram (ECG), oronasal airflow (cannula), oxygen saturation (SaO_2), respiratory movements (abdomen and thorax), body position, transcutaneous carbon dioxide (pCO_2), and video and sound recordings during sleep. PSG has been shown to have a good test-retest reliability and consistency[63] and no significant first-night effect when diagnosing OSA in children[72]. PSG also determines the severity of OSA, and this is helpful when planning treatment and perioperative and postoperative management. The disadvantages of PSG are that it could give a delay in treatment and that it is an expensive, time-consuming and resource-demanding procedure, which is only performed in a few centers and thus not widely accessible. In the US, less than 10% of children treated with adenotonsillectomy due to symptoms of OSA undergo PSG before surgery[73]. In Sweden, PSG for children is only available at very few centers, the largest of which is at the ORL Department at Karolinska University Hospital in Stockholm, the setting

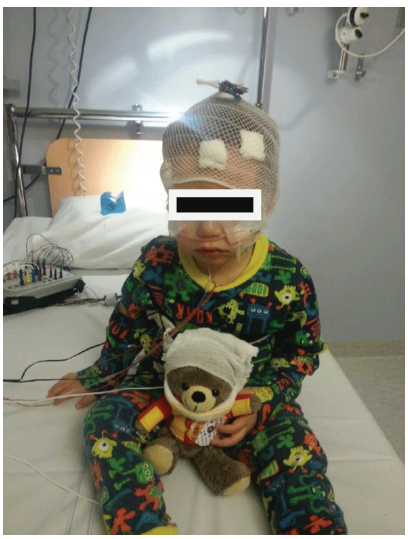


Figure 3. *Child attending the sleep laboratory.*

for three of the studies in this thesis (**papers I, III** and **IV**), in which all the included children have had PSGs performed.

Because of the limited availability, the expense, and the inconvenience, it is not practically possible to perform a PSG on every individual child with suspected OSA. Therefore, children with co-morbidity indicating a high risk of OSA (e. g. children with obesity, neuromuscular disorders, Down syndrome, Prader-Willi syndrome or craniofacial deformities) have been prioritized and in these groups it is recommended to perform PSG prior to performing tonsil surgery[74]. PSG is also recommended when the need for treatment is unclear, when there is a discrepancy between the reported OSA history and tonsillar size, or as a postoperative control in some cases with a high risk of persistent OSA[44,74].

The clinical interpretation and scoring of PSG should be performed according to the American Academy of Sleep Medicine (AASM) manual, published in 2007[75] and updated in 2012[76].

- *According to the American Academy of Sleep Medicine (AASM) a respiratory event is scored as an **obstructive apnea** if it meets the following criteria:*
  - *The event lasts for at least two missed breaths (or the duration of two breaths as determined by baseline breathing pattern)*
  - *The event is associated with a >90% fall in the signal amplitude*
  - *The event is associated with continued or increased inspiratory effort throughout the entire period of decreased airflow*
  - *The duration of the apnea is measured from the end of the last normal breath to the beginning of the first breath that achieves the pre-event baseline inspiratory excursion*
- *Score a respiratory event as **hypopnea** if it meets all of the following criteria:*
  - *The event is associated with a ≥ 30% decrease in the amplitude of the nasal pressure or alternative signal compared to the pre-event baseline excursion*
  - *The event lasts at least two missed breaths (or the duration of two breaths as determined by baseline breathing pattern) from the end of the last normal breathing amplitude*
  - *The event is associated with an arousal, awakening, or ≥ 3% desaturation from pre-event baseline*

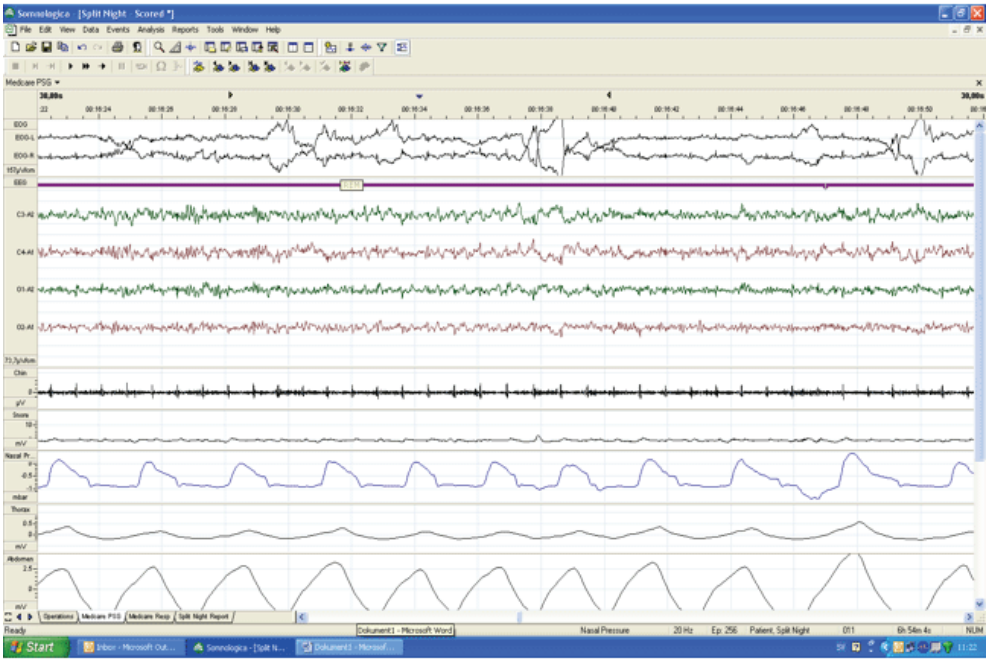


Figure 4. *Normal polysomnographic recording. From the top: Electrooculogram (left + right), electroencephalogram (here four channels), Electromyogram (chin), snoring, nasal airflow, thoracical and abdominal movements.*

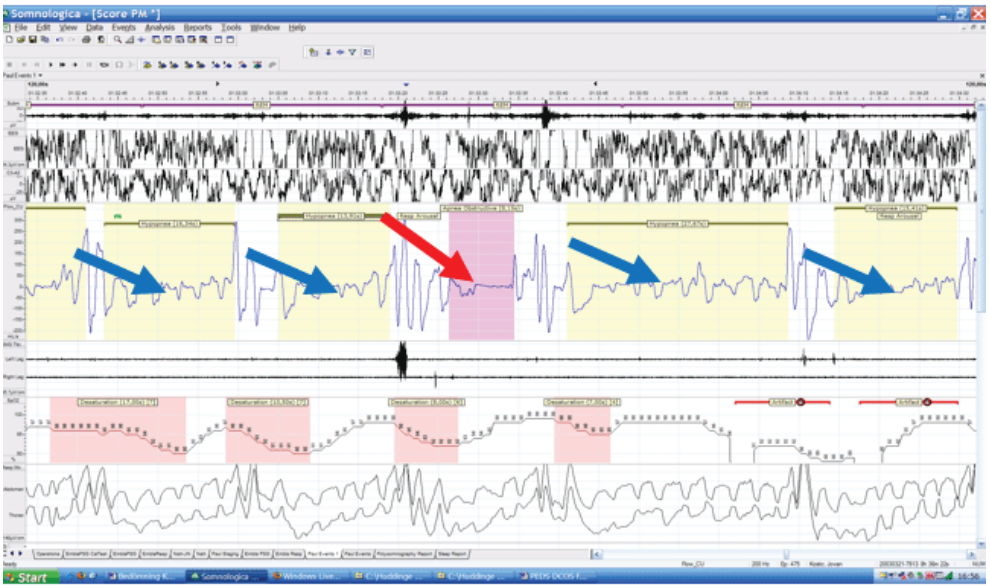


Figure 5. *Polysomnographic recording from a child with obstructive sleep apnea. From the top: Electromyogram (chin), Electroencephalogram, nasal airflow, Electromyogram (tibialis left + right), oxygen saturation, abdominal and thoracical movements. Both apnea (red arrow)and hypopneas (blue arrows) are seen. Also note the decreases in* SaO_2 *and paradoxical respiratory movements.*

Examples of a normal PSG recording and a PSG recording in a child with OSA are seen in ***Figures 4*** and ***5***.

The Apnea-Hypopnea Index (AHI) is the most commonly reported PSG parameter as a measure of SDB/OSA severity. It is derived from the total number of apneas and hypopneas divided by hours of total sleep time. There is still no international consensus on which AHI cut-off values to use when grading pediatric OSA, but according to widespread clinical practice the following cut-offs are used[77]:

AHI 1 - <5	Mild OSA
AHI 5- <10	Moderate OSA
AHI ≥ 10	Severe OSA

These AHI cut-off values differ from the values for adult patients, where a higher number of respiratory events are required for the different degrees of OSA. The pediatric scoring rules applies to children <18 years, but for children ≥13 years adult criteria can be used[76]. All children included in the PSG-studies in this thesis (**Papers I, III** and **IV**) were younger than 13 years and scored according to the pediatric rules.

According to the AASM, central apneas (apnea without inspiratory effort[76]) are included in the AHI. It can sometimes be helpful to divide the AHI into obstructive AHI and central AHI (this was done in **Paper III**, even if the main outcome was total AHI). Interestingly, both central and obstructive apnea index have been observed to improve after adenotonsillectomy[78,79]. Examples of polygraphic recordings of obstructive apnea and hypopnea are seen in ***Figures 6*** and *7*.

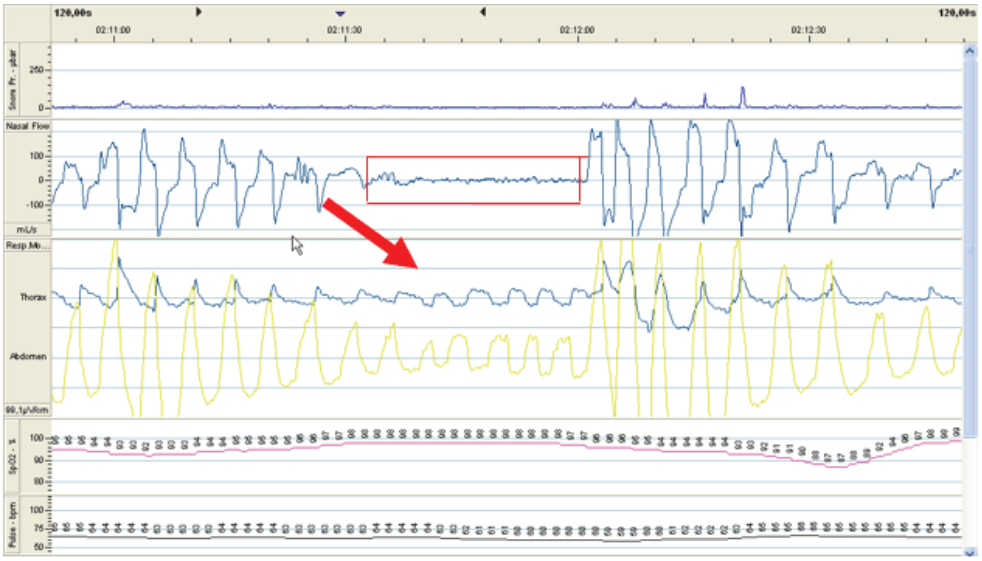


Figure 6. *Example of an obstructive apnea with absence of nasal airflow (red rectangle) and continued respiratory effort (red arrow). This is a polygraphic recording, with no EEG registrations.*

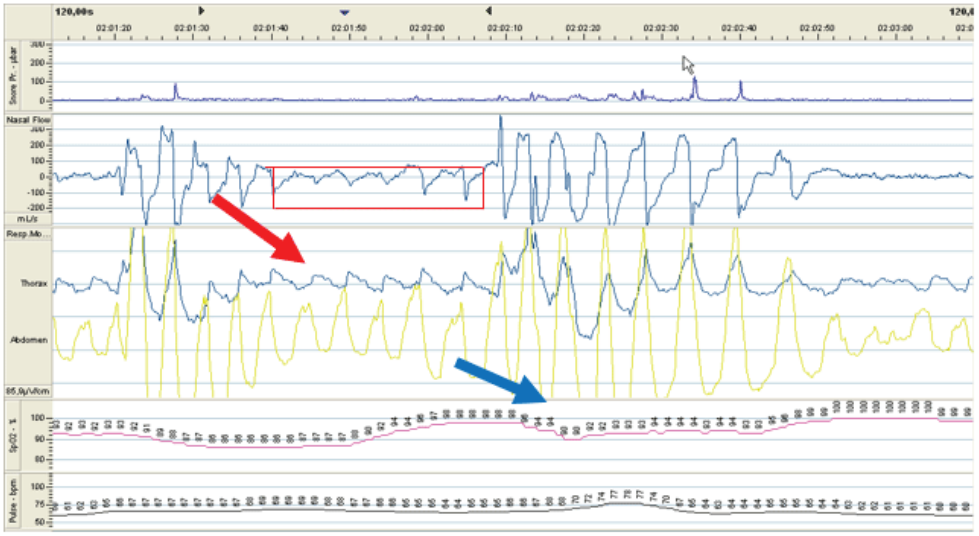


Figure 7. *Example of an obstructive hypopnea with reduction of the amplitude of the nasal airflow (red rectangle) and paradoxical thoracical and abdominal movements (red arrow) and associated with a decrease in* SaO_2 *(blue arrow). EEG and EMG channels are not shown, hence this recording gives no information of arousals.*

1.2.3 Other objective methods for diagnosis of OSA

There are some other objective methods for detecting and measuring OSA in children, which are used in some parts of Sweden. They will be briefly mentioned here.

Polygraphy (PG). PG measures cardio-respiratory variables: respiratory effort and airflow, heart rate or ECG and oxygen saturation (pulse oximetry), but gives no information about sleep stages or arousals since no EEG is included. PG-devices are portable and can be used at home or in a hospital setting. A few previous studies of children have been performed, with variable sensitivity and specificity[80,81]. There is a risk of underestimation of AHI in PG compared to PSG, especially in children with mild to moderate OSA[81,82].

Nocturnal oximetry. Measuring oxygen saturation continuously over night is easy and much less expensive than performing a PSG. Desaturations are detected, however, movements can give false positive results. A recent review by Kaditis and co-workers found that clusters of desaturation are predictive of moderate to severe OSA, and concluded that nocturnal oximetry can be a valuable tool when polysomnography is not available[44].

Videorecording. It is relatively common for parents to bring a cell phone recording to the physician to demonstrate their child's breathing problems during sleep. One study comparing home videotaping with PSG found a sensitivity of 94% and a specificity of 68%, suggesting this to be a useful screening test for OSA[83]. However this study used only obstructive apneas (OAI), not hypopneas as criteria for diagnosis. The use of videorecording needs to be further evaluated.

In conclusion, these methods seem have an acceptable sensitivity, at least for detecting severe OSA, but specificity is lower[84]. A high specificity is required, since an OSA diagnosis often leads to surgical intervention. None of the aforementioned methods can be a substitute for PSG, but can be used when pediatric PSG is not available as a complement to the clinical evaluation of SDB/OSA in otherwise healthy children. Awareness of the limitations of the methods is important.

1.2.4 Questionnaires

The limited availability of PSG and the poor prediction of history and physical examination have led to the search for other less costly and simpler instruments to evaluate OSA in children. In this search, various questionnaires have been developed, but so far none of these has been shown to have any

diagnostic power[85]. One of these questionnaires is OSA-18, a disease-specific quality-of-life instrument that is validated in Swedish[86] and has been commonly used by pediatric otorhinolaryngologists in Sweden and elsewhere. OSA-18 was developed as a disease-specific quality-of-life questionnaire in 2000 by Franco et al[87]. Many studies on pediatric OSA have used the OSA-18 as an outcome measure[88-90]. It has been suggested as a replacement for PSG in the evaluation of OSA in children[91], and as an aid when determining treatment[92]. However, several studies (including **Paper I**) have found OSA-18 to be a poor predictor of OSA[93,94]. The OSA-18 is more thoroughly described in the methods section of this thesis (**Paper I**, methods).

1.3 TREATMENT OF PEDIATRIC OSA – TONSIL SURGERY

1.3.1 Tonsil surgery – a brief history

Tonsil surgery has a long history, with descriptions in documents dated as early as 700 BC[95].Prior to 1900, tonsil surgery was performed as tonsillotomy or subtotal tonsillectomy, leaving the tonsil capsule. This could be performed with for example a knife or a tonsillar "guillotine"; with the lack of proper anesthesia it was important to make the procedure as quick as possible. In the late 1800s it was recognized that the results of tonsillotomy were suboptimal, with patients having persistent infections (tonsil infections were the primary indication of tonsil surgery at this time) and re-growth of tonsil tissue[96]. This led to the technique for total tonsillectomy (removal of the whole tonsil including the capsule) being developed, and one of the earliest descriptions of this was published by the American otorhinolaryngologist Griffin in 1906[97]. Around the1930s, with further development of anesthesiological techniques, tonsillectomy had become common practice and the method of tonsillotomy was abandoned, However, adenotonsillectomy has been associated with postoperative pain and a significant risk of intraoperative and postoperative bleeding, and an alternative surgical method has therefore been desired and tonsillotomy has had a revival and gained increasing popularity since the 1990s.

1.3.2 Tonsil surgery today

Tonsil surgery remains one of the most common surgical procedures performed on children. For example in the US more than 500 000 tonsillectomies are performed annually[98]. In Sweden, 14 000 tonsil operations are performed annually and of these more than 9000 are done in pediatric patients[99]. The most common indication for tonsil surgery in children is OSA and for child-

ren under 3 years of age OSA is the indication in 95% of all cases of tonsillectomy[100,101]. There have been many changes in the clinical practice of tonsil surgery over the past decades in Sweden. These are described and discussed in **Paper II**.

1.3.3 Adenotonsillectomy

Adenotonsillectomy (ATE) with complete removal of the tonsils and adenoid is the first-line therapy for children with OSA[102]. In otherwise healthy, non-obese children of young ages, and with enlarged tonsils, ATE is considered highly effective[65]. However, ATE is not uniformly curative; persistent OSA is reported in 19-73% when using AHI ≤1 as a criterion, and when AHI <5 is used as a criterion, 13-29% have persistence of OSA[9]. Residual OSA after ATE is more common in children with severe OSA, in older children and in children in the risk groups previously mentioned, including obesity and asthma[27]. For children with severe OSA, co-morbidity, African American ethnicity or age under 3 years there is also an increased risk of respiratory complications in the immediate postoperative period[103-105], and guidelines from the American Academy of Pediatrics and the European Respiratory Task Force recommend postoperative admission for those groups of patients[44,65].

It is well known that ATE is associated with postoperative dysphagia and a temporarily decreased oral intake for a period after surgery. Acute pain is the most common reason for revisits following pediatric ATE[106]. Severe complications of ATE are fortunately rare; these include dehydration, secondary infection, velopharyngeal insufficiency, and, perhaps most importantly, postoperative bleeding, which can arise at any time several days after surgery and can be life-threatening[107,108]. A meta-analysis including 23 studies of pediatric ATE showed a bleeding prevalence of 2.4% (primary bleeding) and 2.6% (secondary bleeding)[109]. ATE can be performed with different surgical techniques, such as cold steel dissection, electrocautery dissection or ultracission. Studies have reported a higher frequency of bleeding complications when ATE is performed with hot techniques[110].

1.3.4 Adenotonsillotomy

Tonsillotomy (TT or adenotonsillotomy – ATT - if the adenoid is removed), also called partial, subtotal or intracapsular tonsillectomy, means partial excision of the tonsillar tissue leaving some tonsil tissue in the fossa and keeping the lateral tonsillar capsule intact, as protection for underlying vessels and nerves. ATT can be performed with different surgical devices, such as coblation®, CO_2-laser or radiofrequency. In Sweden ATT has been a widely accepted surgical method to treat pediatric OSA during the past decade[95]. Windfuhr

and colleagues have performed a systematic literature review of 86 articles to clarify what has been validated concerning indications, surgical techniques, complications and outcome after ATT. In this review they concluded that there is evidence that pain is less after ATT compared to ATE, but large, well-designed trials are necessary to determine whether ATT can replace ATE to resolve OSA in children[111]. Also, there is a risk of re-growth of tonsils and adenoid after ATT, with the literature reporting re-growth risks of 1-17%[112,113].

1.3.5 Adenotonsillectomy versus adenotonsillotomy

In 2003, the first large study comparing TT vs TE in children with OSA was published. It was a retrospective study, showing faster recovery and reduced postoperative pain in the TT group[114]. Since then there have been several other studies comparing the two methods in pediatric OSA populations showing the advantages of ATT concerning intraoperative and postoperative morbidity[115,116]. The major disadvantage of ATT is the aforementioned risk of re-growth of tonsils and recurrence of OSA with need for repeated surgery. A Swedish study, including >28 000 patients, compared the risk of reoperation of tonsils after TE vs TT in children with SDB/OSA and found a seven times higher risk after TE, with the highest risk difference among the youngest children[117]. Both ATE and ATT show similar improvement of short-term and long-term quality of life following surgery[118]. Moreover, in 2012, Walton and colleagues performed a systematic review of level1 evidence studies comparing TE vs TT in children with SDB[115]. They included 16 RCTs and concluded that TT was equivalent or superior to TE concerning recovery-related outcomes (postoperative pain, secondary bleeding rate, return to normal diet). The included RCTs had a great variation in follow-up time (1month – 3years) and none of the studies reported preoperative and postoperative polysomnographic data. The lack of such studies was noted in a Cochrane report from 2009[119], in which the authors concluded that *"there is a need for high quality randomized controlled trials to be carried out in the field of surgery for the treatment of OSA in childhood"*, and this was the background to the randomized trial reported in **Papers III** and **IV** in this thesis.

1.3.6 Non-surgical treatment options in pediatric OSA

There are some alternatives to tonsil surgery in the treatment of pediatric OSA. These will be only briefly described here, since they are not within the immediate scope of this thesis.

1.3.6.1 CPAP

For children who are not suitable for surgery or for children where OSA persists postoperatively, CPAP (continuous positive airway pressure) is a non-

surgical treatment alternative[120]. By maintaining constant positive airway pressure during the breathing cycle CPAP can correct the complete or partial collapse of the upper airway during sleep. It has been shown that CPAP is highly effective in treating sleep-related breathing disorders including OSA in children[121-123]. However, CPAP is also associated with technical/equipment problems and side effects, such as nasal symptoms (e g congestion, nasal bleeding)[122] or dentofacial problems[124,125]. Also there are problems with poor adherence[122].

1.3.6.1.1 Orthodontic treatment

In selected patient populations orthodontic procedures have been suggested. An example of this is rapid maxillary expansion, RME, providing a possible treatment for children with a narrow maxilla, a high -arched palate and malocclusion. RME aims to widen the maxillary arch, reduce maxillary constriction and to reduce mouth breathing[126].

1.3.6.2 Medication

Some anti-inflammatory agents have been tried as a treatment, primarily in children with mild to moderate OSA. Intranasal steroids have been shown in placebo-controlled studies to improve AHI, reduce symptoms and also to give a decrease in adenoid size[127]. Other anti-inflammatory drugs that have been tried are leukotriene-receptor antagonists. These have also shown a significant reduction in respiratory-related sleep disturbances and adenoid size in children with mild disease[128]. A study of the combination of intranasal steroid and oral leukotriene-receptor antagonist for twelve weeks as treatment for mild OSA in children showed beneficial effects in >80% of the cases and normalized sleep parameters in >60%[129]. These medications have a favorable safety profile with no significant side effects, and have been discussed as an alternative to tonsil surgery in mild pediatric OSA. However, the optimal duration of therapy is not yet known.

2 AIMS

The overall aims of this thesis were to contribute to more accuracy in the diagnostic process and to evaluate and optimize tonsil surgery as a treatment for OSA in children.

The specific aims of the four papers were:

- To evaluate the accuracy of the questionnaire OSA-18 for assessing and detecting OSA in children, compared to objective data from gold standard polysomnography (**Paper I**).

- To describe tonsil surgery in Swedish children longitudinally in recent decades regarding incidence, surgical method and indications, as well as age- and gender differences (**Paper II**).

- To compare adenotonsillotomy versus adenotonsillectomy as treatment of pediatric OSA, evaluated by polysomnography and OSA-18 after one year (**Paper III**).

- To compare adenotonsillotomy and adenotonsillectomy concerning the postoperative morbidity of pain and bleeding (**Paper IV**).

3 SUBJECTS AND METHODS

3.1 DESIGN AND STUDY SUBJECTS

3.1.1 Paper I

This was a retrospective, cross-sectional study using an existing clinical database. Data were collected from a mixed population of children, all referred to the sleep laboratory at the Department of Otorhinolaryngology at Karolinska University Hospital in Stockholm. The inclusion criteria were: 1) age 1-12 years, 2) having undergone a full-night PSG during 2009-2010, 3) the parent/caregiver having responded to questionnaire OSA-18.

3.1.2 Paper II

Paper II was a retrospective, longitudinal, population-based, cohort study based on register data. The study population was based on a national cohort and consisted of all children aged 1-<18years who had been subject to tonsil surgery between 1987 and 2013 and who were registered in the Swedish National Patient Register (NPR).

3.1.3 Papers III and IV

These were randomized, blinded, parallel-group intervention trials performed at the Department of Otorhinolaryngology (ORLD) at Karolinska University Hospital, Huddinge, Stockholm, Sweden. Those eligible for enrollment were all children referred to the ORLD with a history of OSA. First, there was a run-in period for which the inclusion criteria were: 1) age 2-6 years, 2) tonsil hypertrophy 3-4 according to Brodsky[68]. Patients with co-morbidities (e g neuromuscular disease, craniofacial abnormality, mb Down), history of recurrent tonsillitis, bleeding disorder, previous adenotonsil surgery and obese patients (BMI z-score>1.67) were excluded.

3.2 METHODS

Paper I

All children underwent an over-night PSG and their parents/caregivers responded to questionnaire OSA-18. The OSA-18 contains 18 questions grouped into five subscales: sleep disturbance, physical symptoms, emotional distress, daytime function and caregiver concerns, see ***Figure 8***. These 18 items are scored using a Likert-type scoring system with a seven-point scale, where the parent answers the 18 questions by grading the child's symptoms over the past four weeks on the following scale: *(1) none of the time, (2)*

hardly any of the time, (3) a little of the time, (4) some of the time, (5) a good bit of the time, (6) most of the time and (7) all of the time. From this a total symptom score (TSS) is calculated that can range from 18 to 126. The sleep disturbance domain consists of four questions (loud snoring, breath-holding spells or pauses in breathing at night, choking or gasping sounds while asleep and restless sleep or frequent awakenings) and the score can range from 4-28. Also, parents responded to a question about the SDB related Health Related Quality-of-Life (HRQL), with a 10 point visual analogue scale graded from 1 (worst quality of life possible) to 10 (best quality of life possible).

OSA18-18 Survey on Quality of Life
Sleep Respiratory Disorder Assessment

Instructions. For each of the questions below, please circle the number that best describes the frequency with which each symptom or problem has occurred within the past four weeks (or since the last survey, if more recently).

	None	Almost None	Few times	Some times	Many times	Most of the time	Every times
Sleep disorders							
For the past 4 weeks, how often has your child...	1	2	3	4	5	6	7
... snored loudly?							
... held his or her breath or stopped breathing at night?	1	2	3	4	5	6	7
... choked or had difficulty breathing during sleep?	1	2	3	4	5	6	7
... had agitated sleep or woken up frequently from sleep?	1	2	3	4	5	6	7
Physical distress							
For the past 4 weeks, how often has your child...							
... mouth-breathed due to nasal obstruction?	1	2	3	4	5	6	7
... had colds or upper airway infections?	1	2	3	4	5	6	7
... had nasal secretion or runny nose?	1	2	3	4	5	6	7
... had difficulty feeding?	1	2	3	4	5	6	7
Emotional distress							
For the past 4 weeks, how often has your child...							
... had mood swings or anger episodes?	1	2	3	4	5	6	7
... behaved aggressively or hyperactively?	1	2	3	4	5	6	7
... had discipline problems?	1	2	3	4	5	6	7
Diurnal problems							
For the past 4 weeks, how often has your child...							
... been sleepy or napped excessively during the day?	1	2	3	4	5	6	7
... had difficulty focusing or paying attention?	1	2	3	4	5	6	7
... had difficulty getting up in the morning?	1	2	3	4	5	6	7
Caretaker preoccupation							
For the past 4 weeks, how often did the troubles above...							
... leave you worried about your child's overall health?	1	2	3	4	5	6	7
... lead you to believe your child was not breathing well enough?	1	2	3	4	5	6	7
... interfere with you ability to perform your daily duties?	1	2	3	4	5	6	7
... make you feel frustrated?	1	2	3	4	5	6	7

Figure 1

Above all, how would you rate your child's quality of life given the troubles mentioned above?
(Circle a number)

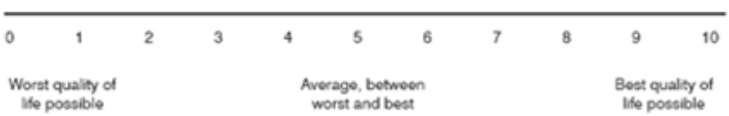


Figure 8. *The OSA-18 questionnaire, including the Health Related Quality of Life question.*

For all the included children the TSS and the score from the sleep disturbance domain were evaluated at different cut-off levels and compared to the AHI from PSG and analyzed using several different statistical methods.

A TSS ≥60 has been considered as abnormal and suggested as correlating to moderate OSA, while a TSS > 80 has been suggested to correlate to severe OSA. Therefore, these were the cut-offs used when comparing to the different levels of OSA according to AHI.

Paper II

Two data sources were used: the Swedish National Patient Register (NPR) and Statistics Sweden (Statistiska Centralbyrån). All relevant medical data from the NPR were collected. The first search was based on surgical codes for tonsillectomy and tonsillotomy (with or without adenoidectomy) from the Nordic Medico-Statistical Committees of Surgical Procedures and all patients 1-<18 years registered with a tonsil surgical procedure were included. Diagnosis codes (ICD-codes) linked to the surgical procedure for the included patients were then collected from the NPR. The diagnosis codes were categorized into two main groups: 'obstructive/SDB' and 'infectious'. All other indications were referred to as 'other'. The second data source, Statistics Sweden, contains population data on the Swedish population, and from this population statistics for all individuals in Sweden aged 1->18 years during the study period were collected. Descriptive statistical analyses were then performed regarding tonsil surgery incidence, gender, age, indication and surgical method.

Paper III

176 patients were enrolled for the run-in period and underwent a full-night, attended, in-lab PSG. Thereafter, the patients who met the final inclusion criteria of AHI 5-30 (moderate to severe OSA) were included. At the time of their night at the sleep lab, they also responded to the OSA-18 questionnaire. Thereafter, they were randomized to one of the following surgical interventions: adenotonsillotomy (ATT) or adenotonsillectomy (ATE). ATT was performed using the coblation® technique, with partial removal of tonsils to the level between the anterior and posterior tonsillar pillars. ATE was performed using the cold steel technique. See ***Figure 9 a+b***.

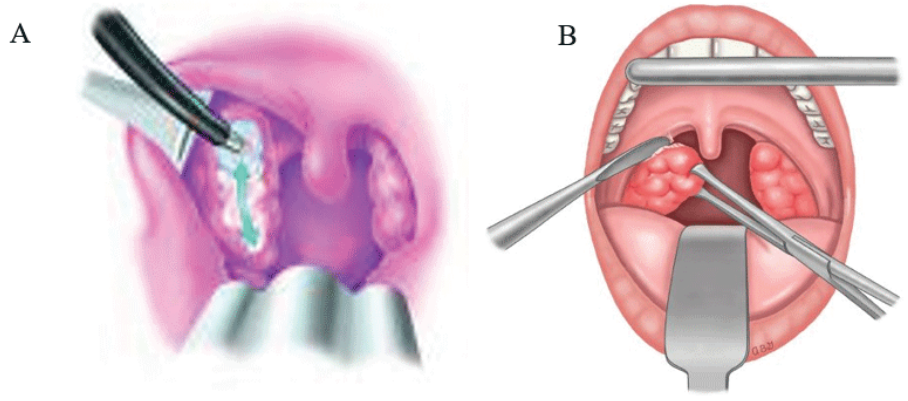


Figure 9. *Schematic illustration of tonsillotomy performed with coblation® (A), and tonsillectomy performed with cold steel (B).*

Follow-up was done one year after surgery with a new PSG and response to OSA-18. The flow chart for study participants is illustrated in ***Figure 10***.

The primary outcome was the difference in total AHI changes between the two intervention groups after one year. Secondary outcomes were differences in changes in other PSG variables on respiration and sleep, and differences in changes in scores from the OSA-18. The need for repeated surgery was also evaluated.

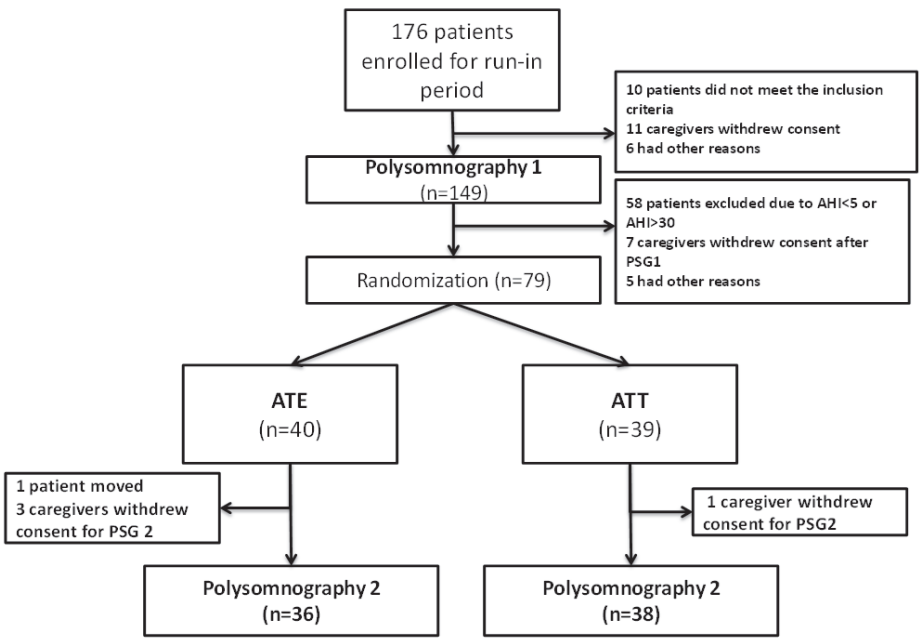


Figure 10. *Flow of participants in paper III.*

Paper IV

This was a continuous report of the study population from **Paper III**, with the same intervention. In this paper, the included children were evaluated with respect to postoperative pain, intraoperative and postoperative bleeding and this was compared between the two intervention groups. Children and parents were blinded for intervention method, as were the researchers when analyzing the data; hence the study was double-blinded. On discharge the day after surgery, caregivers were given a standardized schedule for analgetics, with total treatment time recommended to be as long as the child had signs of pain. No restrictions on food intake were given.

All parents received a log book for pain registration during the ten first days after surgery. In the log book, parents were asked to grade their child's pain in a visual analogue scale (VAS) from 1 to 10, from 1=no pain, through 10=worst possible pain. The log book also registered the child's assessment of pain, using the Faces Pain Scale-Revised (FPS-R), a standardized self-report pain scale for children validated for children four years and older[130,131], shown to be a useful tool in the quantification of post-tonsillectomy pain in children[132] (***Figure 11***). Both parents and children performed a grading of pain three times daily. In addition, analgetic consumption and food intake were registered. Altogether, six pain-related outcomes were obtained from the log book and compared between the ATE and ATT groups: first day when child and caregivers estimated pain free (FPS-R 0 and VAS 1), first day when child and caregiver estimated a reduction of pain to (FPS-R <6 and VAS ≤5), first day without analgetic use and first day with return to normal diet. Intraoperative blood loss was also registered and evaluated, as were cases of postoperative bleeding.

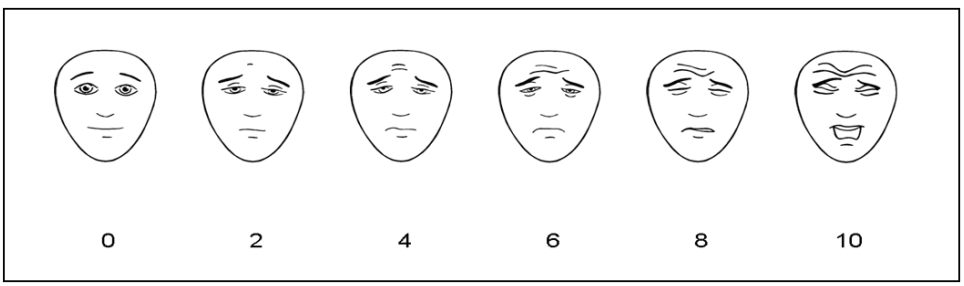


Figure 11. *Faces Pain Scale - Revised (FPS-R). www.iasp-pain.org/fpsr. Copyright ©2001, International Association for the Study of Pain®. Reproduced with permission.*

Table 1. *Overview of the general design of the doctoral project.*

Paper	Design	Data collection	Participants	Outcome measures
I	Retrospective, cross-sectional study.	Polysomnographic data and questionnaire OSA-18 from a clinical database at the ORL-depatrment at Karolinska University Hospital	225 children, 1-12 years, who underwent in-lab polysomnography 2009-2010	Sensitivity, specificity, predictive values and correlations of the OSA-18 in comparison to PSG.
II	Retrospective, longitudinal, descriptive cohort study	Data on tonsil surgery procedures from the Swedish National Patient Register and population data from Statistics Sweden	A national cohort of 167, 894 children 1-<18 years, who underwent tonsil surgery 1987-2013	Longitudinal incidence of tonsil surgery with descriptions of age and gender distribution, indications and surgical methods.
III	Randomized, blinded, parallel group, intervention trial	Clinical and polysomnographic data from patient records at the ORL-department, Karolinska University Hospital	79 children, 2-6 years, with moderate to severe OSA, randomized to ATT or ATE	The difference in AHI change between the groups. Differences in changes of other PSG variables and OSA-18 scores.
IV	Randomized, double-blinded, parallel group intervention study	Clinical data from patient records and log books.	Same study population as in paper III	Six pain-related outcomes. Evaluation of intra- and postoperative bleeding

4 STATISTICAL ANALYSES

Statistical analyses were performed using Statistica 5.0 (**Paper I**), IBM SPSS version 18, (**Paper I**), SAS System Version 9 (**Paper II**), Joinpoint Regression program, version 4.3.1.0 (**Paper II**) and IBM SPSS statistics version 20 (**Papers III** and **IV**). Statistical analyses for **Paper II** were performed by a professional statistician and for **Papers III** and **IV** the statistical methods were chosen in collaboration with a professional statistician.

4.1 PAPER 1

Statistical measures of sensitivity, specificity, PPV and NPV were calculated for different levels of OSA-18 total symptom scores (TSS) compared to AHI from PSG. The Spearman rank correlation coefficient was used for correlations between OSA-18 scores and AHI. Receiver operating characteristics (ROC) curves were used to assess the predictive capacity of the TSS.

4.2 PAPER II

Descriptive statistics were used. The denominator used for incidence rate calculations was the sum of the end-of-year population estimates for each year and age. Gender differences regarding event rate and indication for surgery in specific age groups were tested. The incidence trends were tested by using Joinpoint regression analyses; these were performed for boys and girls separately.

4.3 PAPER III

The study was designed to test the hypothesis that ATT would be non-inferior to ATE for the primary outcome (differences in changed scores, ΔAHI), with an upper limit of the 95% confidence interval (CI) of AHI 5. Prior to study start a power analysis was performed, based on 80% power with an α level of 0.05 to detect a difference in changed AHI score of 5 between groups, considered to be a clinically relevant difference. The power analysis yielded a sample size of 66 patients (33 in each group), but to cover for possible dropouts the sample size was increased to 79.

For secondary outcome PSG data, parametrical tests were used for comparisons, since PSG variables are continuous data and the sample size was >30. These included the paired t-test for within-group comparisons of preoperative

and postoperative PSG variables, and the unpaired t-test for between-group comparisons. To compare the distribution of success rates (ordinal data) between the groups, the Chi-Square test was used. For OSA-18 outcomes (ordinal data), non-parametrical tests were used for comparisons. These included the Wilcoxon signed-rank test within groups and the Mann-Whitney U test between groups.

Sensitivity analysis with intention-to-treat (ITT) was performed for the primary outcome variable ΔAHI; this included the five dropouts with missing values being imputed by using the baseline carried forward.

4.4 PAPER IV

Kaplan-Meier analyses were performed to determine the outcomes regarding postoperative pain and return to normal diet. These analyses showed time-to-event for all pain-related outcomes, where events were defined as "free from pain", "reduced pain", "no analgetics needed" or "normal diet". Log-rank tests were used for comparison between groups. Intraoperative blood loss in milliliters was analyzed by t-test for independent samples. The difference in cases of postoperative bleeding was analyzed using Fisher's exact test.

5 ETHICAL APPROVALS AND CONSIDERATIONS

Studies I, III and **IV** were approved by the regional Ethical Review Board in Stockholm, Sweden (Dnr: 2011/333-31/4, 2011/925-32, 2013/2274-32). **Study II** was approved by the regional Ethical Review Board in Gothenburg, Sweden (Dnr: 534-14).

Studies III and **IV** were both based on a randomized clinical trial, which was registered at www.clinicaltrials.gov (Trial Registration Number: NCT01676181). All the caregivers of children included in the trial gave their written informed consent to participate in the study.

Ethical considerations prior to study start concerned the young age (2-6 years) of the study participants in the RCT. The children could therefore not be regarded as being capable of making their own decisions to participate in the study. Instead consent was obtained from the parents/caregivers after detailed information. A summarized appraisal was that both for the participating indi-

viduals as well as from a wider perspective, the benefits outweighed the risks, since the aim of the trial was to optimize and improve the surgical treatment of pediatric OSA.

The author has no conflicts of interest regarding this thesis.

6 RESULTS

6.1 PAPER I

Results
Data were obtained from 225 children; 139 (62%) boys and 86 (38%) girls. Their median age was 4.5 (range 1-12) years. 83% of the children were <6 years. 13% of the children had some co-morbidity for OSA. 93% of the children had AHI>1.

For the study patients, different levels of TSSs from OSA-18 were compared with different degrees of OSA by polysomnographic AHI levels. Calculations were made to determine the sensitivity, specificity, positive predictive value and negative predictive value. The results are shown in ***Table 2***. These comparisons showed a sensitivity of 32.1-59.3%, with the lowest sensitivity for those with TSS>80 compared to AHI≥10 (the children with the most severe OSA). Specificity values were somewhat higher.

Moreover, separate calculations were performed for the subgroups of children aged 1-6 years (n=186) and 7-12 years (n=39), but still with low specificity and sensitivity.

Table 2. *The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with different levels of the OSA-18 total symptom score (TSS) and the apnea-hypopnea index (AHI).*

	TSS≥60 AHI>1	TSS≥60 AHI≥5	TSS>80 AHI≥5	TSS>80 AHI≥10
Sensitivity	55.2%	59.3%	24.6%	32.1%
Specificity	40.9%	48.4%	88.4%	88.4%
PPV	89.6%	60.3%	74.4%	59.5%
NPV	9.0%	47.5%	46.1%	71.0%

Correlations were estimated using the Spearman rank correlation, showing a significant, but weak, correlation: R=0.17 (p<0.005), ***Figure 12***.
The score from the domain of Sleep disturbance of OSA-18 (4 questions, score 4-28), was also correlated to the AHI values, demonstrating a correlation with R=0.34 (p<0.05), ***Figure 13***.

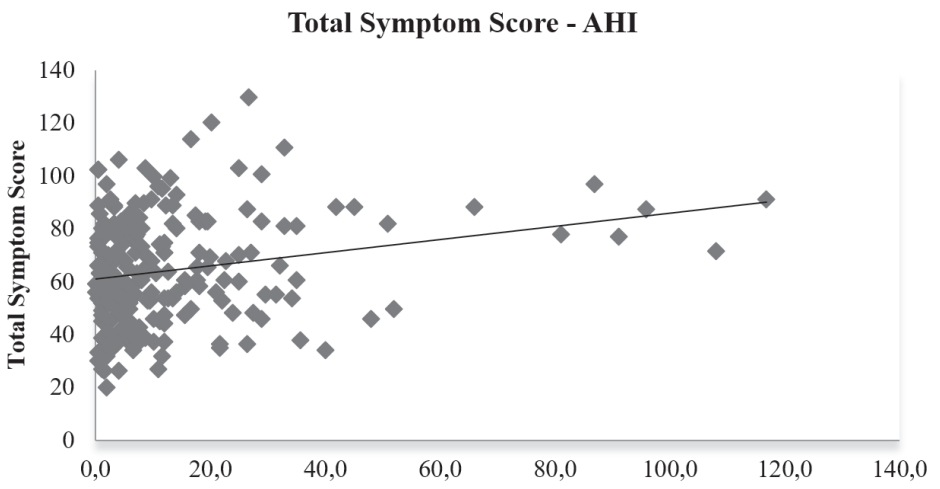


Figure 12. *Scatterplot illustrating the correlation between the Total Symptom Score (TSS) and the Apnea Hypopnea Index (AHI).*

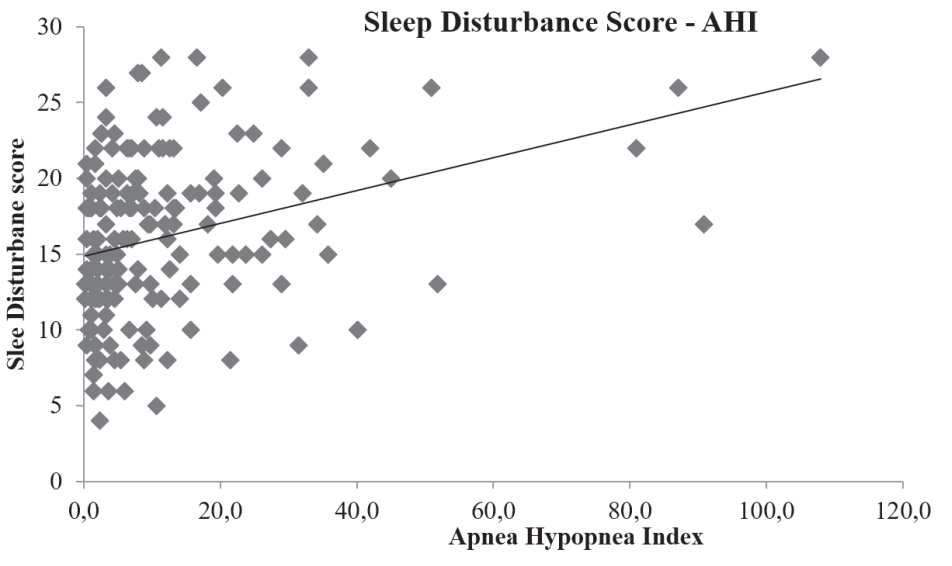


Figure 13. *Scatterplot illustrating the correlation between the score from the domain Sleep Disturbance (SD) and the Apnea Hypopnea Index (AHI).*

ROC curves were also performed, with area under the curve (AUC) close to 0.5 for all three levels of AHI (***Figure 14 a-c***).

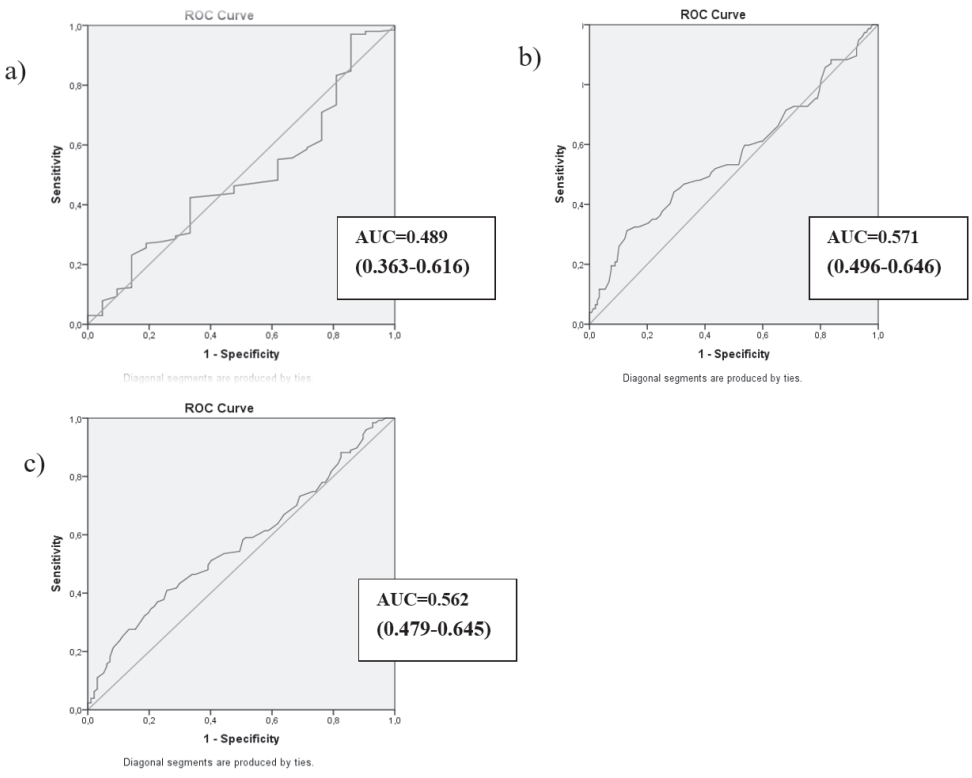


Figure 14. *Reciever Operating Characteristics (ROC) curves for Total Symptom Score (TSS) and three different cut-offs for Apnea Hypopnea Index: a)AHI>1, b) AHI≥5 and c) AHI≥10. Area under the curve (AUC) and 95% confidence intervals are shown.*

6.2 PAPER II

In total, 167 894 children (82 398 girls and 85 496 boys) were registered in the NPR as having undergone tonsil surgery (with or without adenoidectomy) during the observed period (1987-2013). Several trends and changes regarding the practice of tonsil surgery were observed, with a near doubling of the overall incidence rate, increasing from 22/10 000 person years in 1987 to 47/10 000 person years in 2013. The increase was continuous, with the exception of a period of decrease from 1996 through 2001. The proportion undergoing tonsil surgery for obstructive/SDB indications has increased over the same period (***Figure 15***).

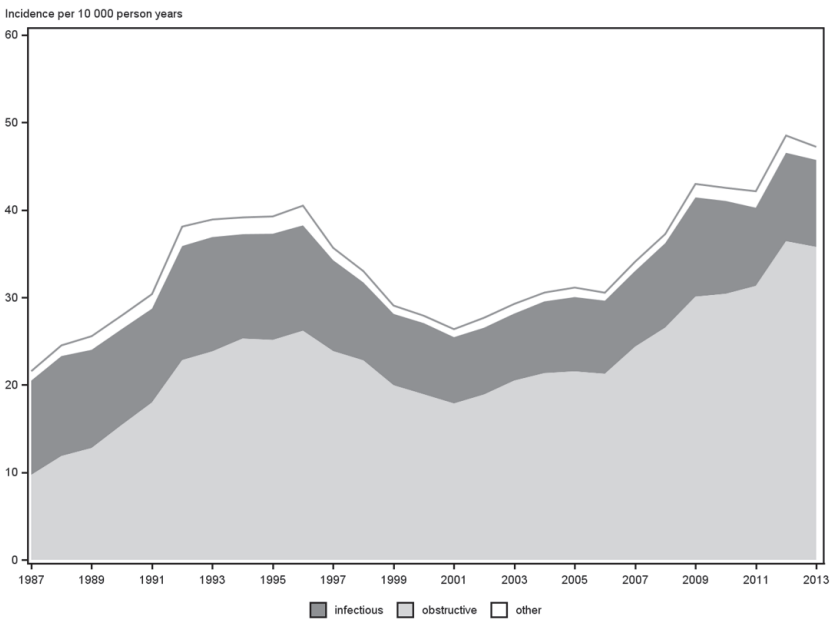


Figure 15. *The incidence and indications of tonsil surgery in children aged 1-<18 years from 1987 to 2013. Incidence/10 000 person years. Dark grey shadow represents infectious indications, light grey shadow represents obstructive/SDB indications and white represents other indications.*

The most marked increase was observed in the youngest children, 1-3-year-olds, increasing from 17 to 73/10 000 person years over the study period.

Significant differences between the genders were observed for the total period, showing a slight dominance for boys (p=0.0011). For both genders the indication 'obstructive/SDB' was most common in the younger age groups, peaking between ages 2 and 6. The highest incidence, 113/10 000 person years, was seen in 3-year-old boys with obstruction, during the period 2008-

2013 (***Figure 16 a+b***). 'Infectious' indications were more common for teenagers for both genders, where teenage girls showed a three to four times higher incidence than teenage boys.

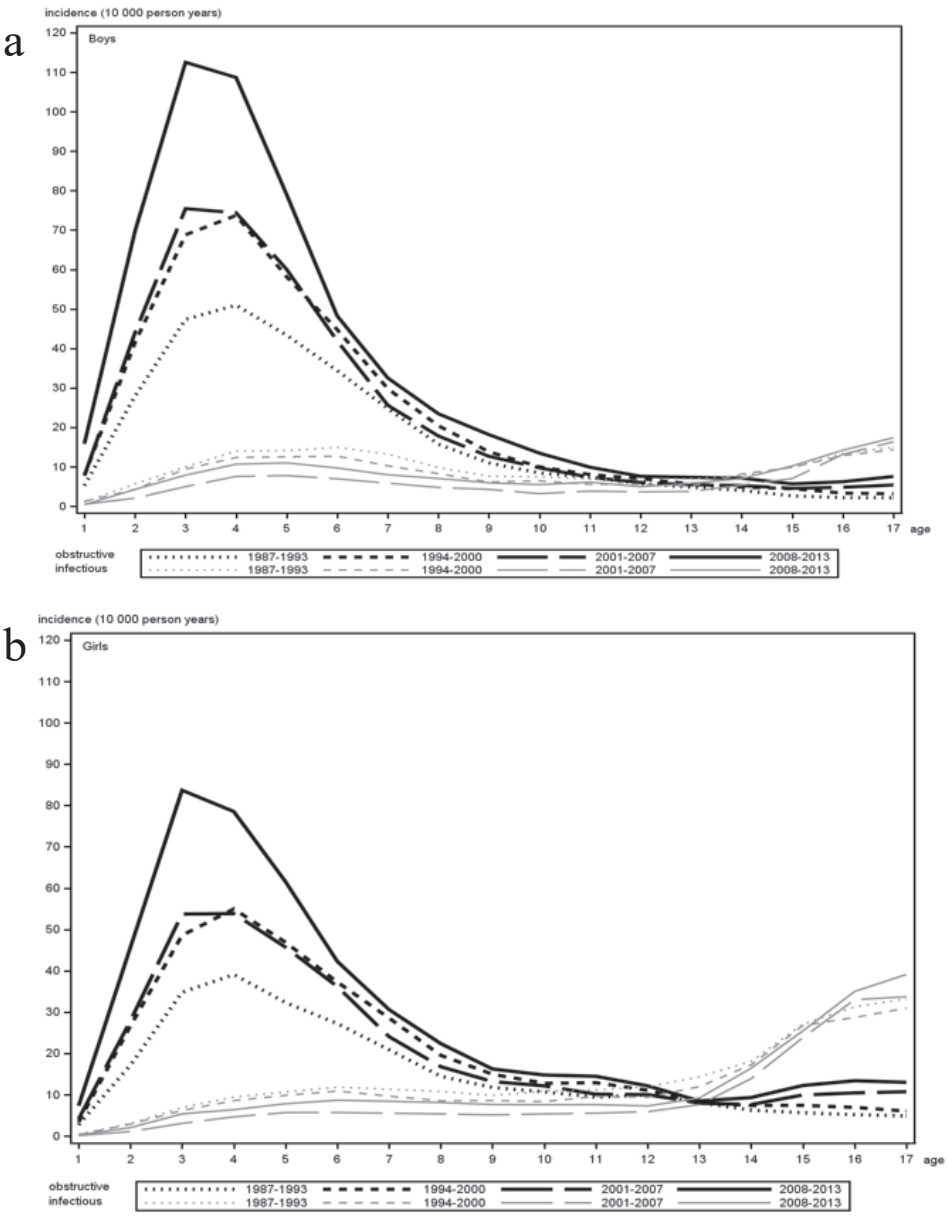


Figure 16. *Incidence of tonsil surgery procedures for boys (a) and girls (b) aged 1-<18 years between 1987-2013 separated by age and indication. Black lines represent obstructive/SDB indications and gray lines represent infectious indications. Each curve represents a 6-year or 7-year period.*

Surgical methods. From 1996, a change in surgical methods was observed, with TT gradually replacing TE, see ***Figure 17***. Thereafter an increasing trend has been seen, with a sharp increase from 2006. From 2011 onwards, TT was more common than TE. The major indication for TT was 'obstruction/SDB', and in 2013 >96% of all TTs were performed for this indication. For the youngest children (1-3 years), TT was the most common procedure, with 71% of all tonsil procedures in this age group being TTs.

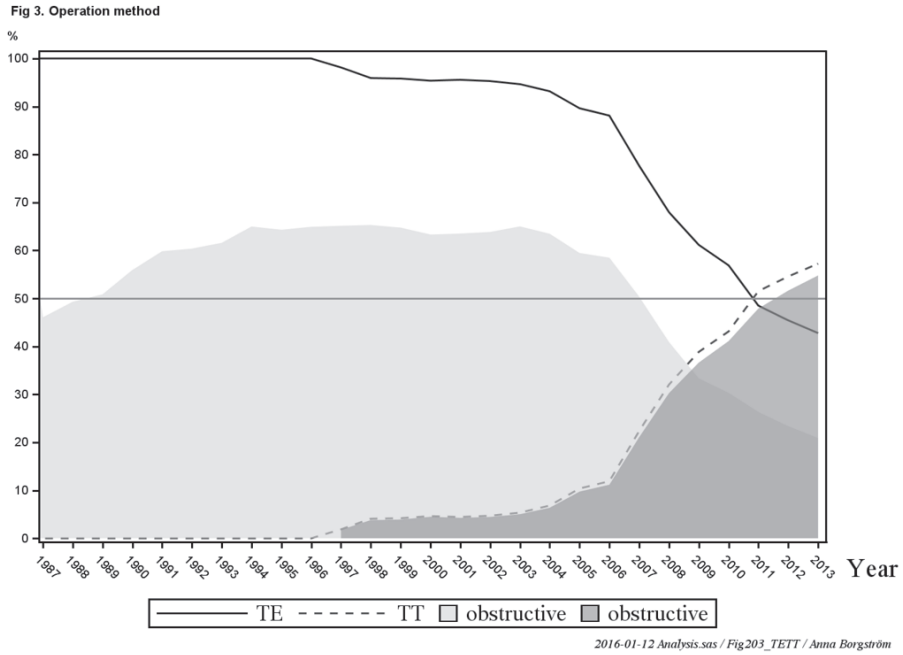


Figure 17. *Distributions of the percentage of TE and TT procedures, with or without simultaneous adenoidectomy, performed between 1987 and 2013. The proportion due to an obstructive/SDB indication is shaded for each method. TE, tonsillectomy. TT, tonsillectomy.*

6.3 PAPER III

79 children, 53(67%) boys and 26 (33%) girls were included and randomized to either ATE (n=40) or ATT (n=39). 74 (93%) children completed the follow-up PSG one year after surgery (dropout rate 6.3%). The mean time from intervention to PSG2 was 12.1±1.5 months in the ATE group and 11.8 ±1.7 months in the ATT group. The groups showed well-balanced baseline characteristics, ***Table 3***.

Table 3. *Baseline characteristics.*

	ATE n=40	**ATT n=39**
Age at intervention (months)	47 (15)	45 (15)
Male gender n (%)	29 (73)	24 (62)
Length (cm)	98 (13)	99 (10)
Weight (kg)	15.7 (3.1)	15.3 (3.3)
Tonsil size (1-4)	3.3 (0.6)	3.5 (0.6)
Adenoid size (1-4)	2.7 (0.8)	3.0 (0.7)
Apnea Hypopnea Index	14.5 (7.3)	15.4 (7.3)

Values are mean (SD), except for gender.

Primary outcome (differences in AHI changes between groups). In the ATE group, the AHI decreased from median (IQR) 12.7 (8.3-19.1) at baseline PSG, to 2.0 (1.2-3.1) at follow-up PSG ($p<0.001$) and in the ATT group, the AHI decreased from median (IQR) 15.8 (8.5-21.2) to 4.0 (1.2-5.1) ($p<0.001$), see ***Figure 18***. The mean difference in AHI changes between the two groups was 0.83 with a 95% CI [-3.2 to 4.9].

No patients in the ATE group had increased their AHI, whereas one patient in the ATT group had a substantially increased AHI, as seen in ***Figure 18***. Analysis without the outlier in the ATT group showed a mean difference of -0.24, 95% CI [-3.7 to 3.2].

The ITT analysis with 79 patients for AHI changes did not change the results compared to the per-protocol analysis with 74 patients (mean difference -0.06, 95%CI [-4.01 to 3.92]).

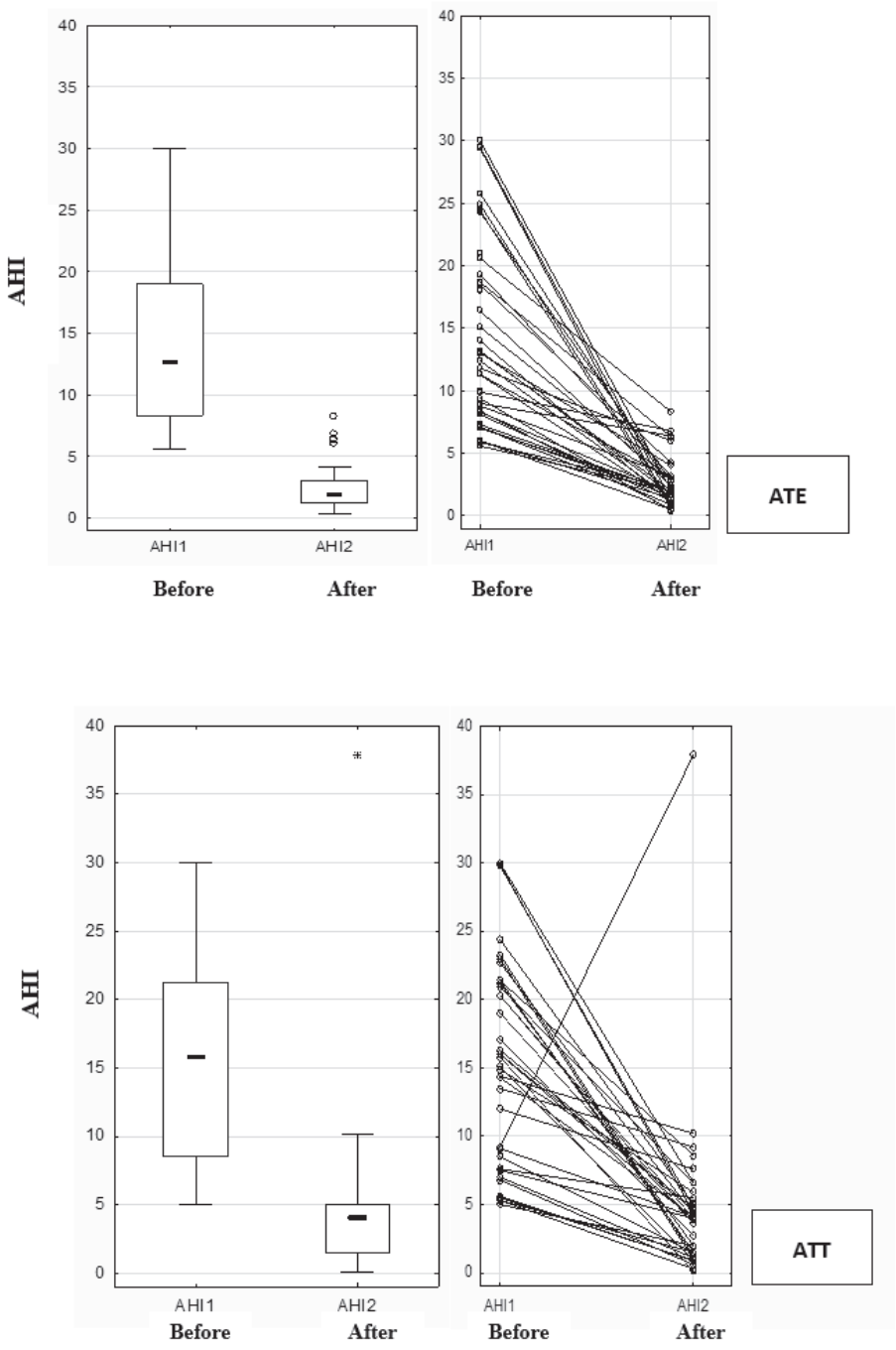


Figure 18. *Boxplots and lines showing the AHI 1 (before surgical intervention) and AHI 2 (one year after surgical intervention) in the ATE group and the ATT group. Boxes show the median, 25% and 75% values, whiskers show the non-outlier range and dots represent the outliers. P-values for the within group changes were p<0.001 for both the ATE group and the ATT group.*

Success rates for four different levels of AHI at PSG2 were analyzed, with no significant differences in the distribution of success rates between the groups, p 0.50 (Chi-Square test), see ***Table 4***.

Table 4. *The results from each group at four different levels of AHI at one-year follow-up.*

AHI at follow-up	ATE (n=36)	ATT (n=38)
≤1	**8 (22.2%)**	**8 (21.1%)**
1.1-4.9	**23 (63.9%)**	**21 (55.3%)**
5-10	**5 (13.9%)**	**7 (18.4%)**
>10	**0 (0%)**	**2 (5.3%)**

No significant difference in the distribution of success rates between the groups was found, p-value 0.50 (Chi-Square test).
AHI, Apnea-hypopnea index.

Secondary outcomes. Other PSG variables were also analyzed and compared between the groups. These all showed significant within-group reductions in both groups, with the exception of central AHI. No significant differences in change scores between groups were observed, see ***Table 5***. Likewise, for OSA-18 outcomes (TSS, Sleep Disturbance score and HRQL), significant reductions were observed within-groups and no significant differences between groups, ***Table 5***.

Table 5. *Results from the polysomnographic variables and OSA-18 scores before (PSG1) and after (PSG2) intervention, and mean difference in changed scores between groups.*

	n	ATE PSG1	ATE PSG2	p-value	n	ATT PSG1	ATT PSG2	p-value	Mean difference in changed scores between groups (95%CI)	p-value
AHI	36	14.2(7.6)	2.5(2.0)	**<0.001**	38	15.4(7.4)	4.5(6.1)	**<0.001**	0.83 (-3.23:4.88)	0.69
Obstructive AHI	36	12.8(7.9)	1.2(1.2)	**<0.001**	38	13.3(7.4)	2.3(4.6)	**<0.001**	0.66 (-3.39:4.70)	0.75
Central AHI	36	1.3(1.3)	1.3(1.4)	0.90	38	2.1(2.1)	2.2(2.3)	0.958	0.13 (-0.61:0.86)	0.73
ODI	36	5.1(5.2)	1.8(1.4)	**<0.001**	37	4.6(4.6)	2.0 (2.8)	**<0.001**	0.63 (-1.37:2.64)	0.53
RDI	36	16.4(7.5)	2.1(2.0)	**<0.001**	37	17.3(7.6)	3.8(5.0)	**<0.001**	0.84 (-3.11:4.78)	0.67
Mean SaO_2 (%)	36	95.5(1.0)	96.9(0.8)	**0.04**	37	96.7(0.8)	97.1(0.8)	**0.003**	0.00 (-0.45:0.45)	0.99
NadirO_2 (%)	32	86.5(6.1)	90.5(3.3)	**0.001**	37	86.7(7.2)	90.1(4.6)	**0.004**	-0.42 (3.58:2.74)	0.79
OSA-18 Total Symptom Score	34	60 (25-99)	31 (18-72)	**<0.001**	36	66 (29-103)	31 (20-61)	**<0.001**	-1.17 (-9.92:7.58)	0.66
OSA-18 Sleep Disturbance Score	34	17.5 (6-28)	5 (4-12)	**<0.001**	36	17 (7-28)	6 (4-24)	**<0.001**	1.07 (-3.77:1.63)	0.37
HRQL	34	7(2-10)	9(4-10)	**<0.001**	37	7(2-10)	9(5-10)	**<0.001**	0.53 (-0.72:1.79)	0.40

Data are mean (95%CI) for PSG variables and median(range) for OSA-18 scores. Between-group comparisons are differences in changed scores between groups and presented as mean (95%CI). For PSG variables, parametric tests (paired and unpaired t-tests) were used; for OSA-18 variables, non parametric tests (Wilcoxon signed-rank test and Mann-Whitney U test) were used for within- and between-group comparisons. Significant differences ($p<0.005$) are shown in bold type.

In the ATT group, five patients (13%), median age 32 (range 27-63) months, were deemed to be in need of repeated surgery (TE) during the follow-up period due to recurrence of OSA-symptoms, re-growth of tonsils or AHI≥5 at follow-up (or a combination of these factors). In the ATE group no patient needed this.

6.4 PAPER IV

The study population was the same as in **Paper III**, with 79 children included: 40 in the ATE group and 39 in the ATT group. 51 (65%) of the children were < 4 years old at the time of surgery. For pain-related outcomes, 63 patients (80%) returned the log book, 30 (75%) in the ATE group and 33 (85%) in the ATT group. All patients were included in the analysis of the bleeding parameters.

Pain-related outcomes. Two of the six pain-related outcomes showed significant differences between surgical technique (ATE compared to ATE); the first day when the children graded themselves as pain free (FPS-R 0), which occurred at day median (interquartile range) 8 (5-10) in the ATE group and day 5 (3-8) in the ATT group, p=0.021(log rank test), and also the first day the caregiver estimated the child's pain reduced to VAS≤5: 1 (0-4.5) after ATE and 0 (0-1) after ATT, p=0.007 (log rank test) (***Table 6***). For the other pain-related outcomes no significant differences between the groups were shown. Kaplan-Meier curves and p-values from log rank tests for pain outcomes are presented in ***Figure 19***.

Table 6. *Pain-related outcomes for adenotonsillectomy (ATE) versus adenotonsillotomy (ATT).*

	n	ATE	n	ATT	
First day when child estimates pain 0 at FPS-R	28	8 (5-9.7)	30	5 (3-8)	*
First day when caregiver estimates pain 1 at VAS	30	8 (5-9.2)	33	6 (3-9)	ns
First day when child estimates pain <6 at FPS-R	28	2 (1-6)	30	0 (0-1)	ns
First day when caregiver estimates pain ≤5 at VAS	30	1 (0-4.5)	33	0 (0-1)	*
First day with no analgetic use	31	8 (7->10)	33	7 (5-9)	ns
First day with return to normal diet	30	7 (5-9)	33	6 (4-8)	ns

Values are median(interquartile range).
** significant difference (p<0.05, log rank test).*
ns non-significant.

Bleeding. Intraoperative blood loss was significantly higher in the ATE group; (mean±SD) 55.1±33.9ml and 28.6±15.6ml in the ATT group, p<0.001 (***Table 7***). Postoperative bleeding occurred in two cases (5%) in the ATE group, one (2.5%) within 24 hours of surgery which needed repeated surgery, whereas the other was readmitted for 24 hours of observation seven days after surgery, but needed no surgical intervention. In the ATT group there were no cases of postoperative bleeding. The difference between groups was not statistically significant, (p=0.494), ***Table 7***.

Table 7. *Intraoperative and postoperative data of bleeding for adenotonsillectomy (ATE) versus adenotonsillotomy (ATT).*

	n	ATE	n	ATT	p
Intraoperative blood loss, ml, mean(SD)	39	55.1±33.9	39	28.6±15.6	<0.0011
Postoperative bleeding n(%)	40	2 (5%)	39	0 (0%)	0.4942

[1]*t-test for independent samples*
[2]*Fisher's exact test*
Significant difference (p<0.05) shown in bold type

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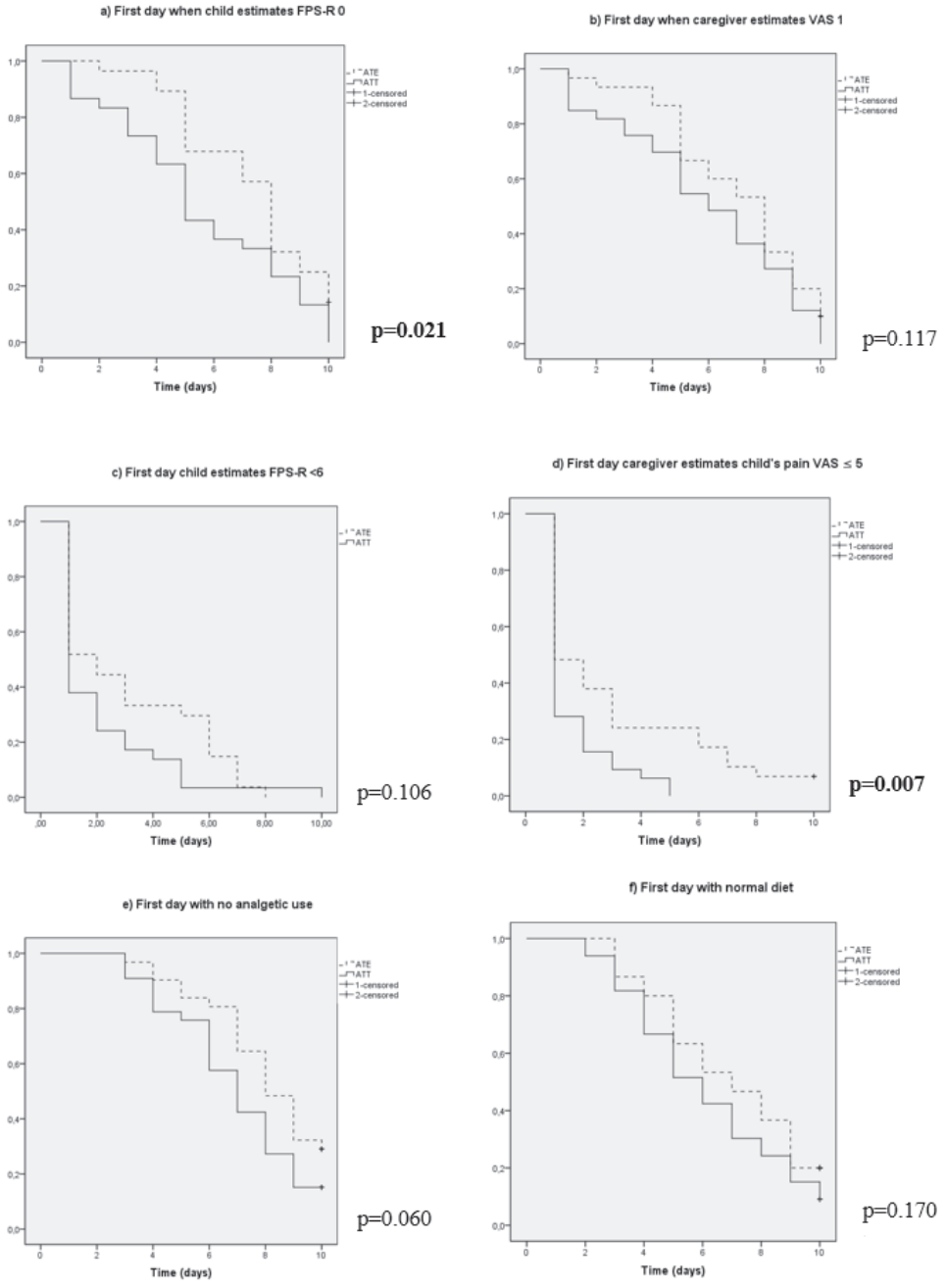

Figure 19. *Log-rank comparison of Kaplan Meier estimator for postoperative recovery for adenotonsillectomy (ATE ---dotted line) and adenotonsillotomy (ATT ─solid line), with estimates of time (days) to pain-related outcomes. For all figures, the y-axis represents the proportion of the patients who are estimated as pain free (a+b), in reduced pain (c+d), no longer in need of analgetics (e) and returned to normal diet (f), at a given time. Patients were censored after ten days since the log books contained no information thereafter. Two outcomes showed significantly lower pain in the ATT group compared to ATE (a and d).*

7 DISCUSSION

7.1 QUESTIONNAIRES AND PEDIATRIC OSA

The major finding in **Paper I** was that questionnaire OSA-18 has poor validity compared to gold standard PSG in diagnosing and grading OSA. Several statistical analyses were performed and they all showed the same results, low sensitivity and low positive predictive value, especially for the children with the most severe OSA. This indicates a high risk of missing the children with the most severe disease if relying on OSA-18 as a diagnostic tool. Separate calculations for children 1-6 years and 7-12 years were performed, showing similar findings as for the whole study population, indicating no age effect of the results. Not even for the score from the sleep disturbance domain of the OSA-18 was the correlation clear.

A significant, albeit weak, correlation between TSS and AHI was shown with the Spearman rank test, but this statistical significance may be explained by some outliers with extremely high AHI values and may not reflect a true correlation. According to the ROC curves, the OSA-18 TSS was no better at predicting OSA than flipping a coin.

Prior to the study in **Paper I**, no other study had compared OSA-18 to PSG-AHI, but subsequent studies have demonstrated similar results, e. g. Ishman et al conducted a similar study in 2015, but in a more diverse population, where the results were comparable with ours and their conclusion was the same; the sensitivity and NPV were extremely low and OSA-18 is not a reliable substitute for PSG[93]. Yet another study supporting the suggestion that OSA-18 is a poor predictor of AHI was performed by Walter et al 2016[94].

One possible explanation for the findings is that OSA-18 was developed by Franco et al as a measure of quality of life, not as a diagnostic instrument[87]. Also, the PSGs in the original study were performed as nap studies and not full-night PSGs, and nap PSG has a poor sensitivity to OSA[120].

A weakness of the study in **Paper I** was that the study population was mixed including all children referred to the sleep lab, and this might somewhat affect the generalizability. 13% of the children had co-morbidities for OSA. The vast majority (93%) of the children in **Paper I** had an AHI>1 and thereby an OSA diagnosis. Another weakness is the retrospective design, with the inherent limitations of such studies.

Paper I illustrates the difficulties involved with questionnaires in the diagnostic process of pediatric OSA. Since history and physical examination alone do not predict pediatric OSA to a satisfying extent, the need for ”easy” screening tools has led to the development of numerous questionnaires of which none has been found to have diagnostic power[85]. There are some factors that might explain the problem with questionnaires. First, the responses rely on the parent's report. It is of importance if and when the parent watches the child sleep. Is the child watched during REM-sleep when most respiratory events occur?[19] If not, there is a risk of underestimating the symptoms. If the parent and child sleep in the same room, this could also affect how the child's sleep situation is interpreted. Likewise language skills and cultural factors could influence how the parent responds. Furthermore, there are parents who may underscore, for example if they are afraid of doctors and hospitals and the risk of their child needing surgery. On the other hand, some parents may overscore if they are eager to have their child operated on, or if they think that high scores can speed up the treatment planning. Also, there could be differences in scoring between the parents, and on different occasions.

With the limitations of existing questionnaires they cannot be considered reliable substitutes for PSG and are not recommended as diagnostic instruments or in treatment decision/planning.

Still, questionnaires can have a place when assessing OSA in children, for example as an aid supporting history-taking inquiry and as a complement to other tools used to measure OSA severity (e g PSG). More importantly, they can measure different relevant aspects of the disease to those measured by PSG, such as quality of life and caregiver concerns. Interestingly, it has been shown that the quality of life measured by OSA-18 significantly improves after adenotonsillectomy in children with OSA, regardless of disease severity[133]. Also, questionnaires can be of value to measure the effect of treatment, and in **Paper III** we used OSA-18 as a measure of quality of life before and after surgery, see below.

7.2 TRENDS IN THE CLINICAL PRACTICE OF TONSIL SURGERY

Paper II reveals significant shifts in the clinical practice of tonsil surgery carried out on Swedish children and adolescents in recent decades. A substantial increase in the total incidence is shown, with nearly a doubling of incidence over the period 1987 to 2013.

International comparisons reveal large differences in the rates of tonsil surgery in children. One study reporting from several European countries, the US, Canada and Australia showed a variation in incidence rates from 19 (in Canada) to 118/10 000 person years (in Northern Ireland)[134]. The Swedish rate of 47/10 000 person years can be considered relatively low in comparison. Possible explanations for the variations between countries are differences in attitudes regarding indications, differences in the availability of medical services and variations in reimbursement systems. Moreover, there are local geographic differences in tonsil surgery rates observed within countries[135]. Such differences might be affected by socioeconomic factors and local traditions. Local variations were not investigated in our study.

The majority of the increase in incidence rates consists of tonsil operations due to upper airway obstruction/SDB. This indication group increased nearly fourfold, from 10 to 36/10 000 person years and was most common in the younger age groups, peaking in children aged 2-6 years, corresponding to the peak in OSA prevalence[12]. OSA/SDB is now considered the primary indication for tonsil surgery in children, as reported in many studies[101,136,137]. This reflects the increasing awareness of pediatric SDB/OSA. Could it also represent an actual increase in the prevalence of OSA? This remains to be evaluated.

Regarding surgical method, there has been a large-scale shift, with TT gradually replacing TE. Since 2011, TT has been the most common method used for tonsil surgery in Swedish children and nearly all TTs are performed for OSA/SDB indications. One possible explanation for this might be that ATT is now performed where single adenoidectomy was chosen previously. The reason for this could be that surgeons consider the addition of the tonsillotomy to be safe, and minor in comparison with total tonsillectomy.

Sweden is one of the “early adopters” of TT, and this could be because several studies have been performed in Sweden showing the advantages of TT over

TE regarding postoperative complications and symptom relief[118,138]. These studies have had a relatively large impact on the Swedish tonsil surgery tradition[139].

Gender and age distributions in **Paper II** included one peak in incidence seen during pre-school ages with a dominance of boys with OSA/SDB. The overall highest incidence rate was seen in 1-3-year-old boys, during the period 2008 to 2013 incidence reached 113/10 000 person years for this subgroup. A less pronounced peak was observed in teenage girls operated on for infectious indications.

The NPR is generally considered to have high coverage[140], but like all clinical registers it has limitations such as inaccurate reported data and missing values, and this is the most important limitation of **Paper II**.

A decrease in incidence rate was observed between 1996 and 2001. One explanation for this could be the increased use of day-care surgery starting in this period and there may have also been a failure in reporting to the NPR during this period. Also, insufficient reporting to the NPR from private hospitals could explain the incidence decrease, with private hospitals having become more numerous during this period. However, there might have been an actual decrease in the number of surgeries, but the true extent of this cannot be determined.

To summarize, the findings in **Paper II** demonstrate overall increasing trends for tonsil surgery in children, especially those performed for the indication SDB/OSA. Given this, and the finding that TT is more common today than TE when operating on tonsils in Sweden, it is of high clinical interest to evaluate and compare these two methods, which was the aim of the randomized study in **Papers III** and **IV**.

7.3 POLYSOMNOGRAPHY

Polysomnography (PSG) plays a central role in **Papers I** and **III**, where the AHI serves as a measure of OSA severity. For research, as well as for clinical evaluations, a consensus in the polysomnographic scoring is of high importance. The AASM rules for pediatric scoring[76] are recommended and were used in the PSG studies in this thesis. Moreover, it is crucial that PSG has acceptable reliability and validity for characterizing OSA in children, and that patients benefit from a PSG being performed.

The reliability of PSG scoring for children has been evaluated, and the test-retest consistency is considered good to excellent[141 63]. Studies of night-to-night variability indicate no significant first-night effect regarding respiratory variables[142]. A few studies assessed the interscorer reliability, indicating no interobserver differences of significance, but data on this is limited[72,143]. A review from the AASM considers the overall reliability for pediatric PSG to be good[143].

Another large review, including 243 studies, has evaluated the validity, reliability and clinical utility of PSG in pediatric SDB[141]. This review compared PSG respiratory findings with other relevant measures of OSA in children and found a strong face validity and content validity. It also included several therapeutic intervention studies, for example pre- and post ATE, showing improvements in PSG variables after treatment, further supporting the validity of PSG as a measure of SDB/OSA. Moreover, the findings of the review indicated a strong clinical utility of PSG especially in children with high-risk co-morbidities for OSA.

Today, PSG remains the gold standard for pediatric OSA, and the reliability and validity seem strong. In addition, AHI and other PSG measures also serve as a universal "language" for researchers and clinicians evaluating children with SDB. Nonetheless, even if PSG is both reliable and valid, the AHI is not the whole "truth", and PSG variables need to be considered in combination with other aspects of OSA in each individual case.

7.4 WHO BENEFITS FROM TREATMENT? ARE THE AHI CUT-OFFS RELEVANT ?

All children in paper III had an AHI>5, and the indication for surgery was not controversial, since AHI>5 in combination with enlarged tonsils is considered in most cases as an indication for tonsil surgery. For mild pediatric OSA (AHI 1-5), treatment is recommended in the presence of symptoms of OSA-related morbidity[44]. However, there are studies concluding that children with primary snoring shows similar neurocognitive and behavioral dysfunctions to children with OSA[144], and some studies propose that primary snoring could affect the cardiovascular system[145]. ATE has been found to improve quality of life and neurobehavioral morbidity in both primary snorers and mild OSA[146, 147]. Today, there is no consensus on when to treat primary snorers, and more research is needed.

7.5 POLYSOMNOGRAPHIC OUTCOMES AFTER ATT VERSUS ATE

Paper III evaluated the polysomnographic outcomes after ATT versus ATE. The main finding was that, on a group level, ATT was non-inferior to ATE regarding the primary outcome, differences in changes in AHI-scores. Secondary outcomes were other PSG variables (ODI, nadir SaO_2 and more) and OSA-18 scores. For all these no significant differences were found between the groups. For all outcome measures significant improvements within groups were observed, with the exception of central AHI, but these values were already very low before intervention.

Overall, success rates for both ATT and ATE were high, with a rate of 76.4% for ATT and 86.1% for ATE when success was defined as AHI<5. In comparison, the results of a meta-analysis of 51 studies of ATE estimated an 81% success for AHI<5[148]. Success after ATT has been reported at 73% for AHI<5[149].

There is some controversy in terms of what to define as treatment “success”. In general, an AHI≤1 is considered as absence of OSA, and AHI >1 to <5 as mild OSA. Still, many studies define success as AHI<5 after intervention. When using the stricter criteria of AHI≤1, the success rates are markedly lower. In paper III, success defined as AHI≤ 1 had a success rate of 22.2% for ATE and 21.1% for ATT and these figures are consistent with other published studies[27,149]. Thus, only about 20% were completely “cured”, even if nearly all patients had a marked decrease in AHI.

One possible limitation of **Paper III** was the set criteria for the power analysis; a difference in AHI change scores of 5 was chosen as a clinically relevant difference, and this might be rather high given the AHI cut-offs for OSA. If a smaller difference had been chosen, a much higher sample size would have been needed, which would have been difficult in practical terms, although we partially compensated for this by adding extra patients.

For all PSG outcomes, the median and mean at follow-up were lower in the ATE group, even though no significant differences were observed. Moreover, there was a higher proportion of success (with success criterion AHI<5) in the ATE group, but no statistically significant differences between groups. It is possible that with a larger sample size significant differences in favor of ATE would have been observed.

Another weakness of paper III is that all included children were otherwise healthy, non-obese, with enlarged tonsils and none with an AHI > 30, and this limits the generalizability.

7.6 QUALITY OF LIFE

Paper III also evaluated the quality of life, as measured by OSA-18 scores, and it was found to have improved in both groups, with no significant difference between the groups. As discussed above, the OSA-18 is not a measure of OSA severity, but must still be considered clinically relevant, and this is probably one of the most important outcomes for the child and parents. The improvement of OSA-18 scores is congruent with several previous studies, including a meta-analysis comparing 20 studies of TT vs TE with no differences in OSA-18 improvement scores between the groups[150].

7.7 RE-GROWTH OF TONSILS AND REOPERATION AFTER ATT

Five patients (13%) in the ATT group, four boys and one girl, median age 32 months, were deemed to be in need of reoperation (TE) during the follow-up period of one year due to recurrence of OSA-symptoms, AHI>5 and/or tonsil re-growth. Reported re-growth rates after ATT vary widely in the literature, ranging from 0 to 17%[113,151]. A recent systematic review found a re-growth rate of 6% (needing TE)[152], comparable to the frequency of reoperations after ATT in **Paper III**, but with the difference that all study patients in **Paper III** were otherwise healthy, with no risk factors for residual OSA except for increased AHI.

In a large Swedish register-based cohort study including >27,000 patients followed for six years the risk of reoperation has been estimated seven times higher after TT than TE, with highest risk in the youngest children under three years, decreasing markedly with age[117].

It has been suggested that OSA-recurrence can occur later than one year after surgery[117], and the risk of repeated surgery could thereby be underestimated in **Paper II** with the follow-up time of one year. Follow-ups after three and five years are planned for the children in the RCT.

7.8 POSTOPERATIVE PAIN

All of the pain-related outcomes assessed in **Paper IV** showed a tendency towards faster recovery after ATT than ATE, but only two of the six pain-related outcomes showed significant differences between the groups: the first day when the child reported being pain free was day median (IQR) 8 (5-10) after ATE and day 5 (3-8) after ATT, and the first day the caregiver estimated a reduction of the child's pain to VAS≤5 was day median(IQR) 1 (1-4.5) for ATE and day 0 (1-2) for ATT. The findings are in line with previous studies showing the advantages of ATT over ATE[115,138], but the differences in **Paper IV** were minor. Walton and co-workers performed a review of 16 studies comparing TT vs TE regarding recovery-related outcomes[115]. Two of the included studies reported data on coblation TT vs coblation TE with results similar to **Paper IV**. One problem with direct comparisons to previous studies is the heterogeneity of techniques used for ATT and ATE, and diversity in how outcome was measured, and no previous studies have compared coblation ATT with cold steel ATE as in **Paper IV**. These are the most common methods used in Sweden. Moreover, the ATTs in **Paper IV** were performed with a technique that is more conservative than what is found in most previous studies, with dissection stopping at the level of the anterior and posterior pillar.

The main limitation of **Paper IV** is the difficulty in measuring self-reported pain in children. We used the faces scale FPS-R[130], which is validated for children from four years of age[131]. This might have affected the results since the majority of children (65%) were under 4 years. There are many other sources of bias in the reporting of pain from both children and parents, as these reports were all self-reported and thereby biased. For example, children under the age of five years tend to use only the extremes of scales[153]. Another limitation of **Paper IV** is the small sample size, based on a power analysis for the primary outcome in **Paper III**.

7.9 INTRAOPERATIVE AND POSTOPERATIVE BLEEDING

In **Paper IV** there was a significant difference in intraoperative blood loss, with 55.1±33.9ml for ATE and 28.6±15.6ml for ATT. Since volumes were small in both groups, the difference was considered to be of little clinical relevance.

There were two cases of postoperative bleeding in the ATE group, of which one needed a return to theatre. No case of postoperative bleeding was reported in the ATT group. The material was too small to detect any significant difference in postoperative bleeding, but the results indicate a higher risk after ATE than after ATT. The risk of bleeding after TE has been assessed in a recent review[154] estimating the bleeding frequency after TE (performed on indication OSA) in children at 2.5%, with a reoperation rate of 1.3%, and this is comparable to the results in **Paper IV**. Bleeding after TE due to infectious indications was higher, at 5.4% (reoperation 1.6%). The review also investigated bleeding after TT, at 1.3% with 0.6% reoperation, but few studies evaluated this and the data were sparse for TT. All ATEs in paper IV were performed using the cold steel technique, and this is associated with a decreased risk of readmission due to bleeding compared to warm techniques[155].

7.10 TONSILLECTOMY OR TONSILLOTOMY? OR NO SURGERY AT ALL?

Given the millions of tonsil surgical procedures performed on children with OSA throughout the world, it is of high importance to continue to optimize the method for surgery in order to diminish the risks and increase the effectiveness. Since ATT is currently the most common method for pediatric OSA-surgery in Sweden it is relevant to evaluate this method compared to traditional adenotonsillectomy. Several studies have compared ATE and ATT but our study (**Paper III**) was the first to report preoperative and postoperative polysomnographic data. The main finding was that regarding PSG outcomes, ATT is no less effective than ATE. Also when measuring the quality of life before and after intervention there were no significant differences between the groups. Thus, on a group-level, both techniques seem to have equally high efficacy in treating OSA in children.

Regarding postoperative pain and risk of bleeding ATT seems to be favorable to ATE, even though the differences seen in **Paper IV** were modest and of

doubtful clinical significance. There are several other studies comparing ATT and ATE showing advantages for ATT, but comparative analyses between studies are limited by the heterogeneity of compared operation techniques, how outcomes were measured and whether or not they were blinded. No study shows more pain or a higher risk of bleeding after ATT than after ATE.

One aspect of pain and postoperative recovery is that even small differences in postoperative pain can have an impact on health care cost. Children who need to stay home from daycare one or two days extra after ATE, and who need their parent to be home from work mean a cost for society. On the other hand, for coblation ATT there is a cost for the coblation device (approximately 200 USD per operation). Better analyses of the health economic aspects are needed.

Regarding postoperative bleeding, no conclusion could be drawn from **Paper IV** due to the small sample size. However previous studies, have showed a higher risk of bleeding for ATE than ATT[154], with bleeding rates after TE of around 2.5% for children operated on for OSA indications. The bleeding risk increases with age; one study showed an age-related odds ratio of 1.05, indicating a 5% higher risk for each year of increased age[155]. On the other hand, even though the general risk of bleeding after TE in children is very low, the risk of life-threatening bleeding is higher than for adults[156]. It is known that TE can have lethal complications. In a large Swedish population study covering 82 000 cases of tonsil surgery over eight years, two cases of death were identified, both boys, younger than five years, otherwise healthy and operated on the indication OSA/SDB and tonsil hypertrophy. Both deaths were related to bleeding[107]. In one of the cases surgery was intended as TT, but the autopsy showed no remaining tonsil tissue on the right side, where the bleeding source was located. The other boy underwent ATE. Reported TE-associated mortality rates vary in the literature, a recent report suggests a lower mortality rate of approximately 1/500 000 children[154]. Even though death after TE is extremely rare, it needs to be taken under consideration when planning for surgery.

The major disadvantage of ATT is the risk of tonsil re-growth. The five cases of repeated surgery after ATT in the RCT (**Paper III**) must be considered as failures of the treatment.

In clinical practice in Sweden today, we do not plan for a revisit after tonsil surgery. Thereby, potentially many children with tonsil re-growth and recurrence of OSA are never identified and there is a risk of underestimation of the problem. A reassessment of all patients is recommended by the American

Academy of Pediatrics 6-8 weeks after surgery[65]. Whether or not that is sufficient time to detect any tonsil re-growth can be questioned; for some children OSA recurrence may occur after a longer period of time.

Another aspect of the risk of reoperation after ATT is that the child then needs another general anesthesia. Wilder and colleagues showed an association between multiple anesthesias at early ages (<4 years) and learning disabilities[157]. Another large cohort study also found a similar association, where children exposed to two or more anesthesias before the age of 4 showed lower cognitive or academic performance in adolesence[158]. The differences were small, but interestingly children who had undergone anesthesia for ENT procedures were the group more likely display lower performance than children with other indications for surgery. OSA could thus have biased the results, since OSA is also associated with learning difficulties and poorer school performance than controls[159].

Parental preference is a factor that may affect the choice of surgical method, and it is important to carefully inform the parents. One study of parental preference found that they preferred tonsillectomy over tonsillotomy after having had both methods described in general terms[160].

Spontaneous resolution of OSA has been suggested to occur and a renowned large multicenter randomized trial (the CHAT-study)[161] evaluated the treatment efficacy of ATE versus watchful waiting in 464 children with OSA. The ATE group showed significant improvements in PSG parameters as well as behavioral, symptomatic and quality-of-life measures compared to the watchful-waiting group. However, the results showed no significant differences between the two study groups concerning attention and executive function, which was the primary outcome of the study[161]. In the watchful waiting group 42% had spontaneous resolution of OSA (after seven months)[162]. However, the CHAT study had some clear limitations; it included no children below five years when OSA is most prevalent, and the children had a low baseline AHI (median 4.5 in the watchful waiting group). Nonetheless, the results suggest a rather high possibility of resolution in children with mild sleep apnea, and further studies of this are ongoing.

To summarize, the results of the randomized study in this thesis indicate that ATT and ATE equally improve polysomnographic findings and quality of life in pediatric OSA. Postoperative pain is slightly reduced after ATT in comparison to ATE, but the differences are small. The risk of postoperative bleeding could not be fully evaluated in this RCT, but it seems clear from previous stu-

dies that ATE has a higher frequency of postoperative bleeding. Notwithstanding this, the risk of re-growth of tonsils is a major drawback after ATT, and this must be taken under careful consideration when planning surgery. The re-growth risk is especially high in the youngest children. Therefore, for children younger three years, the risk of re-growth may outweigh the advantages of ATT, and ATE could be the preferable alternative. However, the decision is complicated by the risk of severe postoperative bleeding after ATE, which is very small, but potentially fatal. Careful surgical technique and information to the parents both preoperatively and postoperatively are important. In older children (three years and older) with enlarged tonsils ATT could be favorable, but as always a delicate evaluation is needed for each individual child presenting with OSA.

8 CONCLUSIONS

- The validity of the OSA-18 questionnaire is low for detecting and diagnosing OSA in children. Therefore, The OSA-18 should not be considered to have diagnostic power and cannot replace objective measurements, such as polysomnography.

- There have been considerable changes in clinical practice for tonsil surgery in Swedish children in recent decades. Overall, a doubling in the total incidence rate was observed. This increase consisted mainly of an increase in surgical procedures due to obstructive/SDB indications, particularly among the youngest age group (1-3 years old). Tonsillotomy has gradually replaced tonsillectomy as the predominant method for tonsil surgery.

- Adenotonsillotomy (ATT) is not less effective than adenotonsillectomy (ATE) in treating pediatric OSA, evaluated by both objective polysomnography and subjective quality-of-life questionnaire. However, with ATT there is a non-negligible risk of tonsil re-growth, OSA recurrence and thereby repeated surgery, and this must be taken into account when deciding on the surgical method. Moreover, the long-term re-growth rate needs to be further studied before more widespread use of ATT.

- ATT is associated with less postoperative pain than ATE. However, the differences between the groups were minor in our double-blinded randomized study. Also, the study indicates a smaller risk of postoperative bleeding after ATT than after ATE, but the sample size was too small to evaluate this. Altogether, our conservative ATT can be considered a safe alternative technique to ATE in young children, regarding the short-term outcomes of pain and bleeding.

9 FUTURE PERSPECTIVES

The field of pediatric sleep medicine is relatively young, with about 20 years of active research time trying to figure out the basic questions. Much remains to be discovered and many questions about OSA need answers.

To start, improvement of the diagnostic process is needed. The problems with existing questionnaires and self-reporting of symptoms have been elicited in this thesis. It is essential to continue the effort to develop useful screening tools that are less costly and labor-intense than polysomnography, with acceptable sensitivity and predictive values. Not only tools to detect OSA and determine severity, but also to predict who will benefit from surgery and to assess the operative risk.

The trends in tonsil surgery and indications need to be continually followed and evaluated. In Sweden, the National Patient Register and the National Tonsil Surgery Register, in combination with easy accessible population data, provide unique possibilities for large-scale population based studies. It will be interesting to see in a couple of years if tonsillotomy will continue to increase as treatment of childhood OSA or if the pendulum swings back towards tonsillectomy.

Another topic warranted for future research is the re-growth of tonsils and recurrence of OSA. Why does this occur in some children after tonsillotomy? To identify patients at risk of re-growth would be highly interesting in order to optimally customize the method of tonsil surgery in each individual child with OSA.

Moreover, there is some ongoing research in the field of prognostic biomarkers as detectors of children at risk and as predictors of OSA severity. Also, what factors control the hypertrophy of the tonsils and adenoid? Biological samples (blood and tonsil tissue) have been collected from our study population in the RCT, and are waiting to be analyzed.

Longer follow-up after tonsil surgery is warranted, to better evaluate the long-term outcomes after tonsil surgery and to identify how late recurrence of OSA might occur. In the perspective of this thesis, further studies are planned regarding the study population in paper III and IV. New follow-ups with polysomnography will be performed after three and ten years, some of these have already been performed.

10 SAMMANFATTNING PÅ SVENSKA

Obstruktiv sömnapné (OSA) hos barn är en vanlig sjukdom som obehandlad kan medföra allvarliga komplikationer. OSA förekommer hos barn i alla åldrar men är vanligast i förskoleåldern. OSA innebär att andningen blir störd under sömnen på grund av trängsel i den övre luftvägen, och den allra vanligaste orsaken hos barn är förstorade tonsiller (halsmandlar) och en förstorad adenoid (körtel bakom näsan). Trängseln leder till att luftflödet minskar eller periodvis upphör helt – det uppstår en apné, ett andningsuppehåll. Den störda andningen kan i sin tur leda till syrebrist, inflammation och dålig sömnkvalitet. Detta stör bland annat hjärnans utveckling och kan leda till inlärningssvårigheter, koncentrationsproblem och hyperaktivitet. OSA kan även ge andra allvarliga komplikationer såsom hämmad tillväxt, högt blodtryck och i svåra fall hjärtsvikt. Symptomen på OSA hos barn är ospecifika och diagnosen är inte alltid lätt att ställa kliniskt. Det som anses vara bästa metoden för att diagnosticera OSA är att göra en polysomnografi (PSG), en fullständig sömnundersökning som görs över natten på sömnlaboratorium, med mätningar av luftflöde, syremättnad, sömnstadier (via EEG), med mera. En sådan undersökning kan dock inte alla barn med misstänkt OSA genomgå då resurserna är begränsade. Istället får den undersökande läkaren lita till sin kliniska undersökning och föräldrarnas berättelse om barnets sjukdomshistoria. Flera frågeformulär finns också tillgängliga, men att förlita sig alltför mycket på dem är inte oproblematiskt och detta visar delarbete I.

Behandlingen av OSA hos barn är i första hand kirurgisk med operation av adenoid och tonsiller. Tonsilloperation är ett av de allra vanligaste kirurgiska ingreppen på barn i världen. I Sverige opereras nästan 10 000 barn om året. Traditionellt har tonsillektomi (borttagande av tonsillerna i sin helhet) varit förstahandsval som behandling av OSA. På senare tid har en annan metod, tonsillotomi (borttagande av utbuktande del av tonsillerna, en del tonsillvävnad kvarlämnas), blivit populär i Sverige och på en del andra håll i världen. Det finns studier som jämför effekten av de båda metoderna, främst vad gäller förbättring av livskvalitet, där båda metoderna verkar förbättra livskvaliteten i samma utsträckning. Ingen tidigare studie har dock jämfört effekten att behandla OSA utvärderat med PSG, som anses vara ”golden standard” för att diagnosticera och mäta graden av OSA hos barn. Det är en sådan studie som nu genomförts och som ligger till grund för delarbete III.

Denna avhandlings fyra delarbeten studerar olika aspekter av barn-OSA: dess diagnostik och behandling med tonsilloperation:

Delarbete I berör diagnostiken och utvärderar ett frågeformulär, OSA-18, som tidigare använts flitigt bl. a. i Sverige som hjälp i den diagnostiska processen av OSA hos barn. Totalsumman från de olika delfrågorna i OSA-18 jämfördes med resultatet av polysomnografi hos 225 barn. Resultaten visar att OSA-18 inte är till någon hjälp i diagnostiken. De barn som hade allvarlig OSA enligt polysomnografin fångades endast upp på OSA-18 i ca en tredjedel av fallen. Risken att missa dessa barn med allvarlig sömnapné är allstå stor om man väljer att lita på resultatet av OSA-18.

Delarbete II beskriver hur tonsillkirurgin hos barn och ungdomar sett ut i Sverige under de senaste decennierna, och kan ses som en bakgrund till delarbete III och IV. En genomgång av det nationella patientregistret (NPR) har gjorts och alla barn 1-17 år som genomgått tonsillkirurgi under 1987 – 2013 har analyserats utifrån indikation, operationsmetod och fördelning vad gäller kön och åldrar. Studien visar att det skett avsevärda förändringar vad gäller klinisk praxis, med mer än en fördubbling av det totala antalet operationer 1987 - 2013. Den största delen av ökningen utgörs av barn som opereras på grund av OSA. För de yngsta barnen i åldern 1-3 år, har det skett mer än en fyrdubbel ökning. Vidare har andelen tonsillotomier ökat påtagligt sedan de introducerades i slutet av 90-talet och är sedan 2011 vanligare än tonsillektomi. Nästan alla tonsillotomier görs på indikationen OSA.

I **delarbete III**, en randomiserad studie, var syftet att jämföra adenotonsillotomi (ATT) med adenotonsillektomi (ATE) vad gäller effekten att behandla OSA hos barn. I studien ingick 79 barn i åldrarna 2-6 år med stora tonsiller och måttlig till allvarlig OSA. De lottades mellan ATT och ATE, och före operationen genomgick samtliga en polysomnografi. Effekten mättes med ny polysomnografi ett år efter operationen. Resultatet visade att båda grupperna kraftigt förbättrades och ATT föreföll på gruppnivå inte mindre effektivt än ATE. Däremot behövde fem av barnen i ATT-gruppen genomgå ny operation under uppföljningstiden på grund av att tonsillerna återväxt och att OSA-symptomen återkommit.

Det sista **delarbetet, IV**, utgick från samma grupp barn som delarbete III. Här utvärderades gruppskillnader vad gäller smärta och blödning efter operationen. Alla studiepatienters föräldrar fick fylla i en smärtdagbok under tio dagar efter operationen där de angav smärtgrad och behovet av smärtstillande medicin. Man fann små skillnader mellan grupperna, där ATT-gruppen verkade ha mindre smärta efter operationen. Dessa skillnader har dock sannolikt ingen avgörande klinisk betydelse. Två barn i ATE-gruppen drabbades av blödning

efter operationen, varav det ena barnet fick sövas på nytt för att kunna stilla blödningen. I ATT-gruppen noterades inget fall av efterblödning.

Några slutsatser som kan lyftas fram från detta avhandlingsarbete är följande:

- Frågeformulär OSA-18 bör inte användas i diagnostiskt syfte.

- Stora förändringar har skett de senaste åren vad gäller tonsillkirurgi på barn i Sverige, t ex är adenotonsillotomi nu vanligare än adenotonsillektomi.

- Adenotonsillotomi förefaller inte mindre effektivt än adenotonsillektomi att behandla OSA hos barn, men risken för reoperation efter tonsillotomi pga återfall i OSA är inte försumbar och måste noggrant beakttas.

- Adenotonsillotomi innebär mindre postoperativ smärta än adenotonsillektomi, men skillnaderna förefaller små och inte av avgörande klinisk betydelse.

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