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SURGICAL TREATMENT OF OBSTRUCTIVE SLEEP APNEA – RANDOMIZED CONTROLLED STUDIES IN CHILDREN AND ADULTS

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Karolinska Institutet

Stockholm 2020

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Published by Karolinska Institutet.
Printed by Universitetsservice US-AB

ISBN 978-91-7831-901-5

SURGICAL TREATMENT OF OBSTRUCTIVE SLEEP APNEA – RANDOMIZED CONTROLLED STUDIES IN CHILDREN AND ADULTS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

This thesis will be publicly defended in lecture hall B64, at Karolinska University Hospital, Huddinge, Friday, 2 October 2020, 9:00 am.

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For Rut and Iris. Knowing I have you makes me sleep better.

ABSTRACT

Obstructive sleep apnea (OSA) is a common disorder in both children and adults. In adults, OSA is a major health concern because it is highly prevalent and increases the risk for hypertension, cardiovascular disease, and mortality. The primary treatment for adults is continuous positive airway pressure (CPAP), but surgery with uvulopalatopharyngoplasty (UPPP) is an alternative in selected cases. Although CPAP has been shown to successfully improve a patient's respiratory sleep parameters, this treatment only modestly improves their blood pressure. The treatment effect of UPPP in improving blood pressure has been less understood, and this effect was evaluated in **Paper I**.

Surgery is the primary treatment for children with OSA, and adenotonsillectomy (ATE), the removal of the tonsils and adenoid, is the first choice of treatment. While ATE is effective in improving quality of life and respiratory sleep parameters, residual OSA after surgery is not uncommon, especially in children with obesity or severe OSA. A modified ATE with closure of the tonsillar pillars, called adenopharyngoplasty (APP), has been suggested to improve the surgical outcome. This surgical method was evaluated in **Papers II and III**. Although OSA occurs frequently in children that are between two and four years of age, there are no randomized controlled trials (RCT) evaluating the efficacy of surgery in this population of children; therefore, this was studied in **Paper IV**.

Randomized controlled trials are the optimal study design to evaluate cause-effect relationships between different treatments and outcomes, but there are few RCTs evaluating surgical treatment of OSA. This thesis aims to use RCTs to evaluate surgical treatment of OSA in children and adults.

Paper I evaluated changes in morning blood pressure from an RCT that compared patients who received modified UPPP (n = 32) with a control group (n = 33). The control group also received surgery six months after their first follow-up. The results showed that UPPP improved both systolic and diastolic blood pressure after six months. The results in all operated patients also indicated that there still was an improvement in both systolic and diastolic blood pressure after 24 months.

Papers II and III reported on an RCT in children, two to four years of age, with severe OSA. The patients were randomly assigned to APP (n = 36) or ATE (n = 47) and had a follow-up after six months. Respiratory sleep parameters, which were measured with polysomnography (PSG), and quality of life, which was measured with a questionnaire called OSA-18, were evaluated in **Paper II**. This study did not show that APP was more effective than ATE. Postoperative morbidity, such as pain, infection, bleeding, satisfaction with treatment, swallowing, and speech, was assessed by a logbook, questionnaire, and medical records. The results, presented in **Paper III**, showed only small differences between the groups, in favor of ATE. The combined results of these studies suggest that ATE should still be considered as the primary treatment for otherwise healthy children with severe OSA.

Paper IV reported on an RCT in children, two to four years of age, with mild to moderate OSA. The patients were randomly assigned to ATE (n = 29) or watchful waiting (n = 31) and were evaluated with PSG and the OSA-18 questionnaire after six months. The results showed only small differences regarding respiratory sleep parameters, but children with moderate OSA showed greater improvement after ATE. There were also large differences in quality of life between the groups, which increased more after ATE. These results suggest that children with moderate OSA should be considered for early ATE, whereas children with low OSA-18 scores and mild OSA might benefit from a period of watchful waiting.

LIST OF SCIENTIFIC PAPERS

I. Fehrm J, Friberg D, Bring J, Browaldh N. **Blood pressure after modified uvulopalatopharyngoplasty: results from the SKUP3 randomized controlled trial.** *Sleep Med. 2017;34:156-161.*

II. Fehrm J, Nerfeldt P, Sundman J, Friberg D. **Adenopharyngoplasty vs adenotonsillectomy in children with severe obstructive sleep apnea: a randomized clinical trial.** *JAMA Otolaryngol Head Neck Surg. 2018;144(7):580-586.*

III. Fehrm J, Borgström A, Nerfeldt P, Friberg D. **Postoperative morbidity after adenotonsillectomy versus adenopharyngoplasty in young children with obstructive sleep apnea: an RCT.** *Eur Arch Otorhinolaryngol, published online May 16, 2020.*

IV. Fehrm J, Nerfeldt P, Browaldh N, Friberg D. **Effectiveness of adenotonsillectomy vs watchful waiting in young children with mild to moderate obstructive sleep apnea: a randomized clinical trial.** *JAMA Otolaryngol Head Neck Surg. 2020;146(7):647–654.*

CONTENTS

LIST OF ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AHI	Apnea-hypopnea index
APP	Adenopharyngoplasty
ATE	Adenotonsillectomy
CHAT	Childhood Adenotonsillectomy Trial
CI	Confidence interval
CPAP	Continuous positive airway pressure
DBP	Diastolic blood pressure
DISE	Drug induced sleep endoscopy
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
ESS	Epworth sleepiness scale
FPS-R	Faces Pain Scale – Revised
ITT	Intention to treat
MRD	Mandibular retaining device
OAHI	Obstructive apnea-hypopnea index
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
PG	Polygraphy
PSG	Polysomnography
QoL	Quality of life
RCT	Randomized controlled trial
RDI	Respiratory disturbance index
RERA	Respiratory effort-related arousals
SBP	Systolic blood pressure
SD	Standard deviation
SKUP^3	Sleep apnea Karolinska UPPP
UPPP	Uvulopalatopharyngoplasty
VAS	Visual analogue scale

1 AIMS

This thesis aims to evaluate surgical treatment of obstructive sleep apnea (OSA) in children and adults.

Specifically, this thesis evaluates

- the effect that modified uvulopalatopharyngoplasty has on blood pressure in adult patients with OSA (**Paper I**);

- whether children with severe OSA improved more after adenopharyngoplasty than adenotonsillectomy by analyzing polysomnography data and OSA-18 scores (a quality of life questionnaire) (**Paper II**);

- postoperative morbidity (e.g. postoperative pain, bleeding, infection, satisfaction with treatment, and impaired speech and swallowing) after adenopharyngoplasty compared to adenotonsillectomy (**Paper III**); and

- whether adenotonsillectomy is more effective than watchful waiting for treating mild to moderate OSA in children by analyzing polysomnography data and OSA-18 scores (**Paper IV**).

2 INTRODUCTION

2.1 ADULT OBSTRUCTIVE SLEEP APNEA

2.1.1 Background

Obstructive sleep apnea (OSA) is a common type of sleep-disordered breathing that is characterized by partial or complete upper airway obstruction during sleep. The prevalence of this disorder is rising and is estimated to be 26%, and around 13% of men and 6% of women are diagnosed to have moderate to severe OSA[1]. However, recent studies have suggested that the prevalence of moderate to severe OSA is even higher at 50% in men and 23% in women[2]. OSA is becoming a major health concern due to its high prevalence, its independent association with hypertension[3,4], and the higher risk it carries for cardiovascular disease and mortality[5–8]. Untreated OSA also results in increased health care costs[9].

2.1.2 Etiology and risk factors

Obstructive sleep apnea is caused by a complete or partial repetitive collapse of the upper airway during sleep[10]. The loss of upper airway patency is multifactorial and cannot be explained only by the anatomy of the patient's upper airway. Poor upper airway muscle function, narrow upper airway due to craniofacial and soft tissues structures, low arousal threshold, small lung volume, and respiratory instability are all believed to be causative factors of OSA[11].

Unlike in children, the major risk factors for OSA as an adult are not tonsillar or adenoid hypertrophy but obesity and being of the male sex[1,12]. Other important risk factors are increasing age, genetic predisposition, drinking alcohol, smoking and menopause[1,11,13–15].

2.1.3 Morbidity

The recurrent asphyxia, fragmented sleep, increased sympathetic nervous system activity, and increased intrathoracic pressure that result from episodes of airway obstruction are associated with substantial negative health consequences[11]. Studies have shown that OSA is an independent risk factor for hypertension[3,4], and the prevalence of OSA is between 30% and 83% among patients with hypertension[16]. There is also a high prevalence of unrecognized OSA among patients with drug-resistant hypertension[17]. Furthermore, OSA increases the risk of cardiovascular diseases, such as congestive heart failure, fatal and non-fatal myocardial infarction, and stroke[5,7,18]. An increased risk for cancer, metabolic disorders, cognitive dysfunction, and all-cause mortality[6,8,19], as well as impaired quality of life (QoL) and a higher risk for motor vehicle accidents[20,21] have also been reported.

The connection between OSA and these negative health consequences is complex (Figure 1), although, the intermittent hypoxemia is believed to promote oxidative stress, increased sympathetic activation, and systemic and vascular inflammation with endothelial dysfunction. These

factors are believed to affect cardiovascular disease, metabolic dysfunction, cognitive impairment and cancer[19,22].

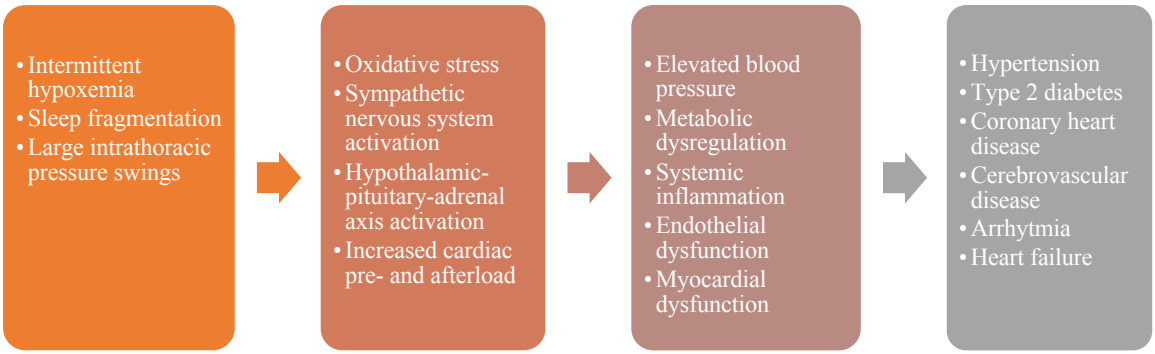


Figure 1 Possible explanations for the connection between OSA and negative health consequences.

2.1.4 Diagnosis

In adults, both a clinical evaluation and an objective sleep study are required to diagnose OSA[23]. Common symptoms of OSA are snoring, apneas, nocturnal choking, restless sleep, and excessive daytime sleepiness[24]. The most common symptom of adult OSA is excessive daytime sleepiness, but the severity of sleepiness does not seem to correlate to the severity of OSA[25]. The most widely used questionnaire to assess sleepiness is the Epworth Sleepiness Scale (ESS)[26], and Functional Outcomes of Sleep Questionnaire (FOSQ) is also frequently used[27]. There are also objective tests to measure sleepiness, such as the multiple sleep latency test (MSLT)[28] and the Oxford sleep resistance (OSLER)[29] test. While questionnaires for screening for OSA have also been designed, such as the Stop-Bang Questionnaire, they are not sufficiently reliable to diagnose OSA[30].

2.1.4.1 Polysomnography

Polysomnography (PSG) is the gold standard method to diagnose adult OSA. PSG is performed overnight in a sleep laboratory and measures both sleep stages and respiratory functions. A standard PSG includes an electroencephalogram (EEG), electrooculogram (EOG), electrocardiogram (ECG), and electromyogram (EMG); monitors oronasal airflow, oxygen saturation, respiratory movements of the abdomen and thorax, body position, and transcutaneous carbon dioxide; and records audio and video during sleep. These data are used to generate several parameters, the most common of which is the apnea-hypopnea index (AHI), which measures the number of apneas and hypopneas per hour of sleep. The AHI is scored according to the manual of 2012 from American Academy of Sleep Medicine (AASM)[31].

The scoring of apneas and hypopneas is similar in children and adults, but the time for a respiratory event in adults is ≥ 10 seconds and in children it is defined as the time equivalent of two missed breaths (Figure 2). The AHI in adults includes not only obstructive episodes, but

also mixed and central respiratory events[31]. The AHI is used to classify the severity of OSA: mild OSA, AHI ≥ 5 and < 15; moderate OSA, AHI ≥ 15 and < 30; and severe OSA, AHI ≥ 30.

Apnea (all criteria must be satisfied)

- The respiratory event lasts for at least two missed breaths in children, determined by the baseline breathing pattern, OR ≥ 10 seconds in adults.
- The event is associated with a ≥ 90% drop in the airflow signal amplitude.
- To qualify as an obstructive apnea, the event must be associated with the presence of respiratory effort throughout the entire period of absent airflow.

Hypopnea (all criteria must be satisfied)

- The event is associated with a ≥ 30% drop in airflow signal amplitude.
- The respiratory event lasts for at least two missed breaths in children, determined by the baseline breathing pattern, OR ≥ 10 seconds in adults.
- There is a ≥ 3% desaturation, or the event is associated with an arousal.

Figure 2 Criteria for scoring respiratory events as apneas and hypopneas, according to AASM.

Other common parameters are the oxygen desaturation index (ODI), which is the number of desaturations of more than 3% or 4% per hour, respiratory effort-related arousals (RERA), respiratory disturbance index (RDI), and lowest oxygen saturation (saturation nadir).

Polysomnography is expensive and resource demanding, and it is, therefore, not always available**.** Polygraphy (PG) is more widely available and allows the patient to perform the sleep study at home. However, the true sleep time, arousals, and sleep stages cannot be assessed with PG as it lacks EEG, EOG, and EMG. Consequently, true sleep time, some hypopneas, and sleep fragmentation are missed by PG, resulting in missed diagnosis of OSA or misdiagnosis of its severity. Consequently, it is important to perform PSG on patients that have excessive daytime sleepiness, a high clinical suspicion of OSA, and a normal PG[32]. However, PSG also has its limitations, and night-to-night variability has been reported[33,34]. A second PSG could, therefore, be of value if the PSG result is in conflict with the clinical assessment.

2.1.5 Treatment

2.1.5.1 Continuous positive airway pressure

Continuous positive airway pressure (CPAP) is a treatment that uses air pressure to keep the airway open and is the primary treatment for adult OSA. If accepted, CPAP has a positive effect on nocturnal respiratory parameters, excessive daytime sleepiness, and QoL[35,36]. However,

studies have shown that patients have difficulties adhering to CPAP and have reported long-term compliance of around 50-68%[37–39].

2.1.5.2 Mandibular retaining device

A mandibular retaining device (MRD) is also a common treatment option and it prevents the collapse of the upper airway by repositioning the lower jaw forwards. While studies have shown improvements in respiratory parameters and sleepiness, this treatment is not as effective as CPAP and is recommended for less severe forms of OSA[40]. As with CPAP, there are challenges with patient adherence, and MRDs have a compliance rate around 56-68%[41].

2.1.5.3 Surgery

Before the introduction of CPAP and MRDs, palate surgery, such as uvulopalatopharyngoplasty (UPPP), was the primary therapy for OSA. UPPP enlarges the oropharyngeal airway and reduces the collapsibility by adjusting the pharyngeal soft tissue (tonsils, uvula and soft palate)[42]. The efficacy and safety of UPPP have been questioned[43,44], but recent studies using modified UPPP in a selected group of patients have shown the surgery to be both safe and effective to improve respiratory parameters, QoL and sleepiness[45–49].

To select candidates for surgery it is important to assess the pharyngeal anatomy and patient obesity. The Friedman staging system is the most common clinical assessment method and is based on palate position, tonsil size and body mass index[50]. It has shown correlations between preoperative examination and surgical outcome[50,51], but low inter-examiner agreement might limit the value of this staging system[52]. Drug induced sleep endoscopy (DISE) is another tool for preoperative evaluation of adult patients with OSA and can be used to assess the level of obstruction. DISE evaluates the specific site and character of the upper airway obstruction during a pharmacological sleep. Although some studies have indicated a higher surgical success rate after DISE[53], there is insufficient evidence to claim that this approach leads to a better surgical outcome compared to a normal clinical evaluation of the upper airway in fully awake patients[54,55].

2.1.5.4 Other treatments

There are several alternative treatment options for OSA, including weight loss, bariatric surgery, sleep positioning, and upper airway stimulation. Obesity is a major risk factor for OSA, and meta-analyses have shown that weight loss through lifestyle changes or bariatric surgery can improve OSA parameters[56,57]. Furthermore, sleeping in the supine position often contributes to the collapse of the upper airway, so it is generally recommended that OSA patients sleep in a lateral position. However, even if patients have primarily positional OSA, studies have shown that positional therapy is inferior to CPAP[58]. Upper airway stimulation, through stimulation of the hypoglossal nerve, has shown promising results in patients with moderate to severe OSA and could become an alternative to CPAP[59,60].

2.1.5.5 Treatment effect on blood pressure

Hypertension is a known consequence of OSA, but both CPAP and MRDs show only a slight improvement in systolic (SBP) and diastolic blood pressure (DBP). Systematic reviews of CPAP showed a mean decrease of 2.6 and 2.0 mmHg in SBP and DBP, respectively[61,62]. A systematic review of MRDs had similar results, with a decrease of 2.7 mmHg in both SBP and DBP[63]. While drug resistant hypertension is common in patients with OSA[17,64], antihypertensive medication (angiotensin II receptor blocker) is still almost four times more effective than CPAP in patients with OSA[65]. There are studies that indicate that UPPP can improve blood pressure in patients with, but the overall evidence is weak. Randomized controlled trials (RCT) evaluating the effect UPPP has on blood pressure and other cardiovascular endpoints are needed and have been requested[66]. In this thesis, the effect of modified UPPP on blood pressure was evaluated in **Paper I**.

2.2 PEDIATRIC OBSTRUCTIVE SLEEP APNEA

2.2.1 Background

The prevalence of OSA in the pediatric population ranges from 1% to 6%[67–69] and the peak prevalence occurs between three and six years of age[70]. The obstructive episodes lead to recurrent asphyxia, fragmented sleep and increased sympathetic nervous system activity[71], and are associated with numerous morbidities and complications if left untreated[72,73]. Early diagnosis is not only important for the health of the child, but also from a socioeconomic perspective, as untreated OSA is associated with increased healthcare costs[74,75].

2.2.2 Etiology and risk factors

As in adults, OSA in children is caused by a narrowing of the upper airway, and the etiology of the obstruction is multifactorial[72,76]. Pediatric OSA is primarily caused by enlarged tonsils and adenoid, but neuromuscular factors may also affect the collapsibility of the upper airway[77,78]. Obesity, an increasing health problem, is another major risk factor for OSA[79,80]. Other groups with high risk of OSA include children with neuromuscular disorders[81], craniofacial abnormalities[78], prematurity[82], laryngomalacia[83], and chromosomal abnormalities, like Down syndrome[84,85]. There are also studies that have suggested an hereditary component to OSA [86,87].

2.2.3 Morbidity

OSA is associated with a wide array of disorders, such as neurocognitive dysfunction and behavioral disturbances, which are characterized by hyperactivity, aggressive behavior, learning problems and concentration difficulties[88–90]. Failure to thrive[91], cardiovascular complications with systolic and pulmonary hypertension[92,93], and increased mortality rates[73] have also been

reported for pediatric patients with OSA. There is also an association between OSA and asthma, and treatment of OSA seems to improve asthma control[94].

2.2.4 Diagnosis

The evaluation of a child with suspected OSA starts with an assessment of symptoms, risk factors, and a physical examination. Common nocturnal symptoms of OSA are snoring, apneas, restless sleep, enuresis, excessive sweating, and cervical hyperextension. Daytime symptoms are more difficult to distinguish and can include mouth breathing, excessive daytime sleepiness, concentration difficulties, hyperactivity, and failure to thrive[72,95,96].

2.2.4.1 Polysomnography

Clinical evaluation and medical history are not always reliable. As with adults (see chapter 2.1.4.1), the gold standard for diagnosing pediatric OSA is PSG[72,97]. Studies have shown a low night-to-night variability in children and a single PSG is considered sufficient to diagnose OSA[72,98].

In contrast to OSA in adults, an obstructive apnea-hypopnea index (OAHI) is mainly used, and this index does not include central or mixed events. The OAHI is used to determine the severity of OSA, and the following cut-offs are the most widely used[95]: mild OSA, OAHI ≥ 1 and < 5; moderate OSA, OAHI ≥ 5 and < 10; and severe OSA, OAHI ≥ 10.

Although PSG is the best available method to diagnose OSA, it is expensive, time consuming and not accessible for all patients. Furthermore, there are no strong correlations between PSG outcomes and QoL[99–102]. If PSG is not available, there are other objective methods that might help in the diagnosis of OSA, such as PG and nocturnal oximetry[72,103]. However, these methods have limitations in the diagnostic reliability that must be considered[104,105]. DISE can also be used in children, but it is not used in Sweden, and there are no studies that show improved surgical outcomes after DISE. However, DISE might be of value to children with persistent OSA after surgery[106].

2.2.4.2 OSA-18 Questionnaire

Numerous questionnaires have been developed to simplify the evaluation of pediatric OSA, but they are all limited when it comes to diagnosing OSA[107]. OSA-18 is the most common questionnaire used in Sweden, and, like other questionnaires, it has been shown to be a poor predictor of OSA and to evaluate the severity of OSA[102,108]. Even so, OSA-18 is useful to determine the QoL in pediatric patients with OSA, and to evaluate differences before and after surgery[109,110].

The OSA-18 questionnaire consists of 18 questions across five domains: sleep disturbance, physical symptoms, emotional distress, daytime function, and caregivers' concerns (Figure 3). Each question is scored on a 7-point Likert scale. Answers are summed to a total OSA-18 score

ranging from 18 to 126 points, where higher scores indicate a worse QoL. Scores less than 60 suggest a mild impact on QoL, scores between 60 and 80 suggest a moderate impact, and scores above 80 suggest a severe impact.[111] The OSA-18 questionnaire also contains a global rating of QoL on a visual analogue scale (VAS QoL) of 0 to 10 points.

OSA-18 Quality of Life Survey
Evaluation of Sleep-Disordered Breathing

Instructions. For each question below, please circle the number that best describes how often each symptom or problem has occurred during the past *4 weeks* (or since the last survey if sooner). Thank you.

	None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
SLEEP DISTURBANCE							
During the past *4 weeks*, how often has your child had…							
…loud snoring?	1	2	3	4	5	6	7
…breath holding spells or pauses in breathing at night?	1	2	3	4	5	6	7
…choking or gasping sounds while asleep?	1	2	3	4	5	6	7
…restless sleep or frequent awakenings from sleep?	1	2	3	4	5	6	7
PHYSICAL SUFFERING							
During the past *4 weeks*, how often has your child had…							
…mouth breathing because of nasal obstruction?	1	2	3	4	5	6	7
…frequent colds or upper respiratory infections?	1	2	3	4	5	6	7
…nasal discharge or runny nose?	1	2	3	4	5	6	7
…difficulty in swallowing foods?	1	2	3	4	5	6	7
EMOTIONAL DISTRESS							
During the past *4 weeks*, how often has your child had…							
…mood swings or temper tantrums?	1	2	3	4	5	6	7
…aggressive or hyperactive behavior?	1	2	3	4	5	6	7
…discipline problems?	1	2	3	4	5	6	7
DAYTIME PROBLEMS							
During the past *4 weeks*, how often has your child had…							
…excessive daytime drowsiness or sleepiness?	1	2	3	4	5	6	7
…poor attention span or concentration?	1	2	3	4	5	6	7
…difficulty getting out of bed in the morning?	1	2	3	4	5	6	7
CAREGIVER CONCERNS							
During the past *4 weeks*, how often have the above problems…							
…caused you to worry about your child's general health?	1	2	3	4	5	6	7
…created concern that your child is not getting enough air?	1	2	3	4	5	6	7
…interfered with your ability to perform daily activities?	1	2	3	4	5	6	7
…made you frustrated?	1	2	3	4	5	6	7

OVERALL, HOW WOULD YOU RATE YOUR CHILD'S QUALITY OF LIFE AS A RESULT OF THE ABOVE PROBLEMS?
(Circle one number)

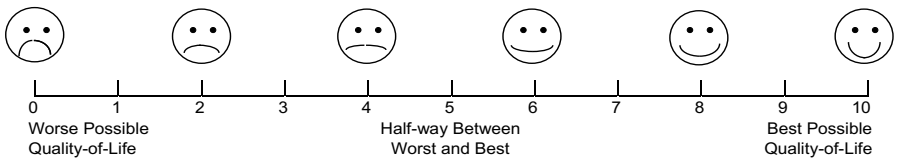


Figure 3 The OSA-18 questionnaire.

2.2.5 Treatment

2.2.5.1 Adenotonsillectomy and adenopharyngoplasty

Surgery is the primary treatment for pediatric OSA, and adenotonsillectomy (ATE), removal of the tonsils and adenoid, is considered the first choice of treatment[72,112]. ATE has been shown

to have a positive effect on respiratory sleep parameters, QoL, and patient behavior and has also resulted in improved healthcare costs[113,114]. Even so, residual OSA is reported to occur in 13% to 75% of children after surgery[112,115–118]. Risk factors for persistent OSA are severe OSA, obesity, and genetic, neurological, and craniofacial disorders[115,116,119–121].

To improve the surgical outcome, alternative methods to ATE have been developed to reduce the obstruction of the upper airway. The soft palate and pharyngeal walls are anatomical factors involved in the obstruction of the upper airway[122,123], and a closure of the tonsillar pillars after ATE is believed to enlarge the upper airway. In 2004, Guilleminault et al.[124] described that a modified adenotonsillectomy with closure of the tonsillar pillars, called adenopharyngoplasty (APP) (Figure 4), resulted in a 100% success rate. This was followed by a (RCT) in 2012 by Friedman et al.[125] between APP (n = 19) and ATE (n = 25). While the results from that study were in favor of APP, no significant group differences were observed, and the authors reported that the study was underpowered due to a high dropout rate (27%). Further, a non-randomized prospective controlled study by Chiu et al.[126] in 2013 showed that APP (n = 12) was significantly more effective than ATE (n = 12), with a reduction in apnea-hypopnea index (AHI) of 80% compared to 43%. These studies indicate that APP might be a more effective surgical method than ATE, but the overall evidence is weak. In this thesis, APP was evaluated in **Papers II and III**.

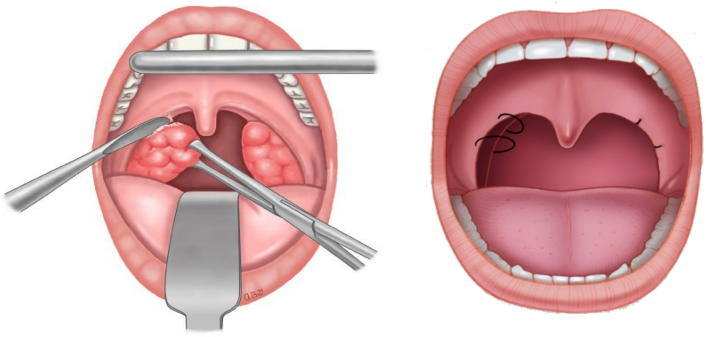


Figure 4 Left: Adenotonsillectomy (ATE): Removal of tonsils with cold steel technique. **Right:** Adenopharyngoplasty (APP): Closure of the tonsillar pillars after tonsillectomy, with two sutures on each side including fibers of the palatopharyngeus muscle. Reprinted with permission. © (2018). AMA. All rights reserved.

2.2.5.2 Watchful waiting

Not all children receive surgery, and, in accordance with some guidelines, children with mild OSA are not recommended ATE[95,127]. Through studies and clinical experience, it is known that children with less severe forms of OSA may get better without treatment. For example, a large randomized controlled trial known as the Childhood Adenotonsillectomy Trial (CHAT)[113] compared ATE with no treatment in 464 children with OSA. The children were between five and nine years of age, had primarily mild to moderate OSA, and the median obstructive apnea-

hypopnea index (OAHI) was less than 5 in both groups at baseline. The CHAT study reported that 46% of the group without treatment achieved normal PSG parameters (defined as OAHI < 2) at follow-up, compared to 79% in the group that received ATE. While the difference between the groups was significant, there seems to be a non-negligible spontaneous improvement in the group without treatment. Although ATE is one of the most common surgical procedures, there are no RCTs in children between two and four years of age that confirm the benefit of surgery compared to no treatment. This study has been requested[128] and was evaluated in **Paper IV**.

2.2.5.3 Other treatment methods

Alternative treatments for OSA in children include partial tonsillectomy, CPAP, and anti-inflammatory agents, such as intranasal steroids and leukotriene antagonists[72,129–131]. Partial tonsillectomy, also called tonsillotomy, is becoming more frequent in Sweden and has shown good treatment results[129,132]. Children seem to return faster to normal activity after tonsillotomy compared to tonsillectomy; nevertheless, the long-term effect and need for repeated surgery is still uncertain[133]. Children with non-severe OSA who receive intranasal steroids and leukotriene antagonists have shown improvement in their PSG parameters as well as their QoL[134–136]. CPAP is not a common treatment in Sweden for children with OSA, but it can be an option for children with persistent OSA after surgery or when surgery is not recommended (e.g. obesity and craniofacial disorders)[72]. However, as with adults, pediatric patients struggle with poor treatment adherence to CPAP[137].

3 MATERIALS AND METHODS

3.1 OVERVIEW OF STUDY DESIGNS

All papers were based on RCTs conducted at the Department of Otorhinolaryngology, Karolinska University Hospital, Stockholm, Sweden. An overview the papers is provided in Table 1.

Table 1 Overview of the papers included in this thesis.

Paper	Study design	Population	Intervention	Comparison	Outcome	Time
I.	RCT	Adults, BMI < 36, moderate to severe OSA	UPPP	No treatment	Blood pressure	6 and 24 months
II.	RCT	Children, 2-4 years, severe OSA	APP	ATE	Respiratory sleep parameters (PSG) and Quality of Life (OSA-18)	6 months
III.	RCT	Children, 2-4 years, severe OSA	APP	ATE	Postoperative morbidity (e.g. pain, bleeding, infection, satisfaction, swallowing, and speech)	6 months
IV.	RCT	Children, 2-4 years, mild to moderate OSA	ATE	No treatment	Respiratory sleep parameters (PSG) and Quality of Life (OSA-18)	6 months

Abbreviations: ATE, adenotonsillectomy; APP, adenopharyngoplasty; RCT, randomized controlled trial; BMI, body mass index; OSA, obstructive sleep apnea; UPPP, uvulopalatopharyngoplasty; PSG, polysomnography.

3.2 PAPER I – BLOOD PRESSURE AFTER MODIFIED UVULOPALATOPHARYNGOPLASTY

3.2.1 Design and study population

This study utilized data from a previous single-center RCT, called Sleep apnea Karolinska UPPP (SKUP^3)[45], that compared adult patients with OSA who received modified UPPP to a control group. The primary study was designed to evaluate respiratory sleep parameters using PSG.

All patients that were referred for UPPP were possible candidates for the study, and the following inclusion criteria were used: over 18 years of age; AHI ≥ 15 events/h of sleep; ESS score ≥ 8; expressed daytime sleepiness three times a week or more; BMI < 36 kg/m^2; Friedman stage I or II[50]; having failed treatment with MRD and CPAP; and no use of MRD nor CPAP three months before the first PSG. The exclusion criteria were: serious cardiopulmonary, psychiatric, or neurological disease; an American Society of Anesthesiologists classification of >3; did not want to perform surgery; insufficient knowledge of Swedish; nightshift worker; being potentially dangerous in traffic; severe nasal congestion; previous tonsillectomy; and Friedman stage III[50]. Those who experienced severely aggravated OSA symptoms during the study were also excluded.

Ultimately, a total of 65 patients were included in this study (Figure 5) and the primary follow-up was after six months. The control group received surgery after the initial six months and had an additional postoperative follow-up after six months. All patients had a follow-up after 24 months. Each follow-up included an overnight PSG, and the patient's blood pressure was measured manually the following morning at 6:00 am, directly after awakening, and while the patients were lying on their backs.

The PSG scorers and the nurses, who measured the blood pressure, were blinded for treatment allocation.

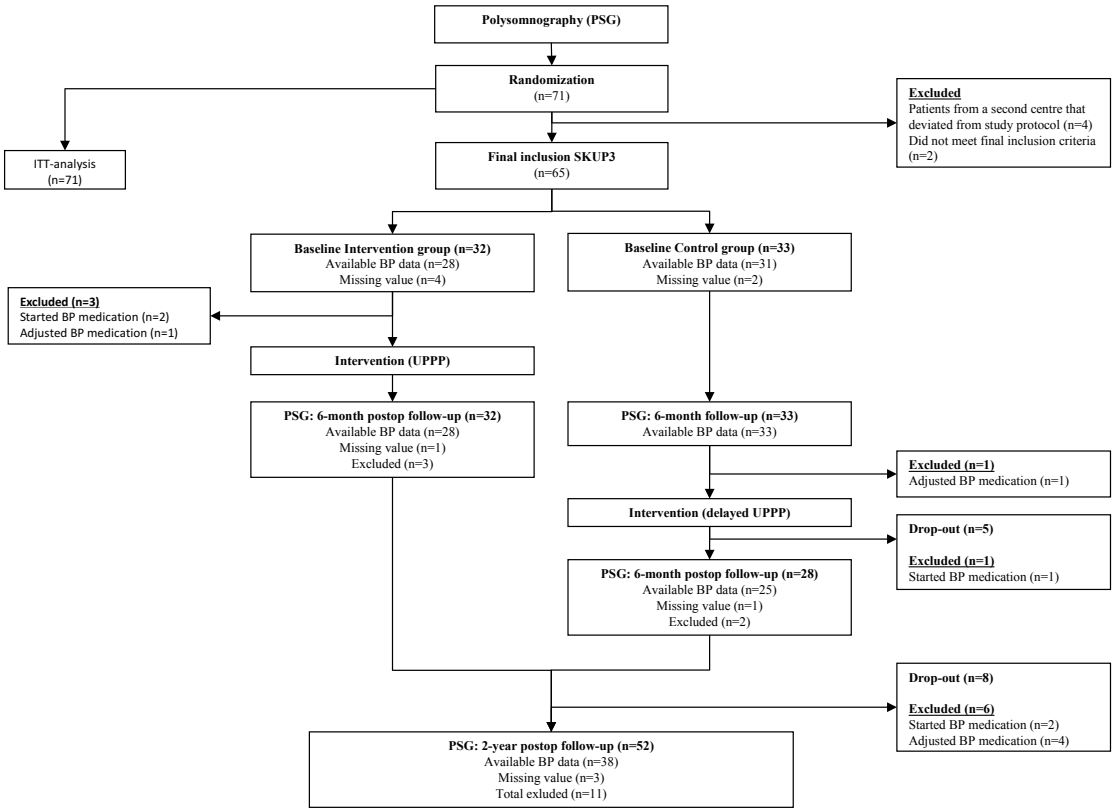


Figure 5 Flowchart **Paper I**. Abbreviations: BP, blood pressure; ITT, intention to treat; UPPP, uvulopalatopharyngoplasty; PSG, polysomnography.

3.2.2 Intervention

The surgical method was a modification of the UPPP originally described by Fujita et al.[42]. There were only minor resections of the uvula and soft palate, including tonsillectomy, and the surgery was performed with the cold steel technique (Figure 6).

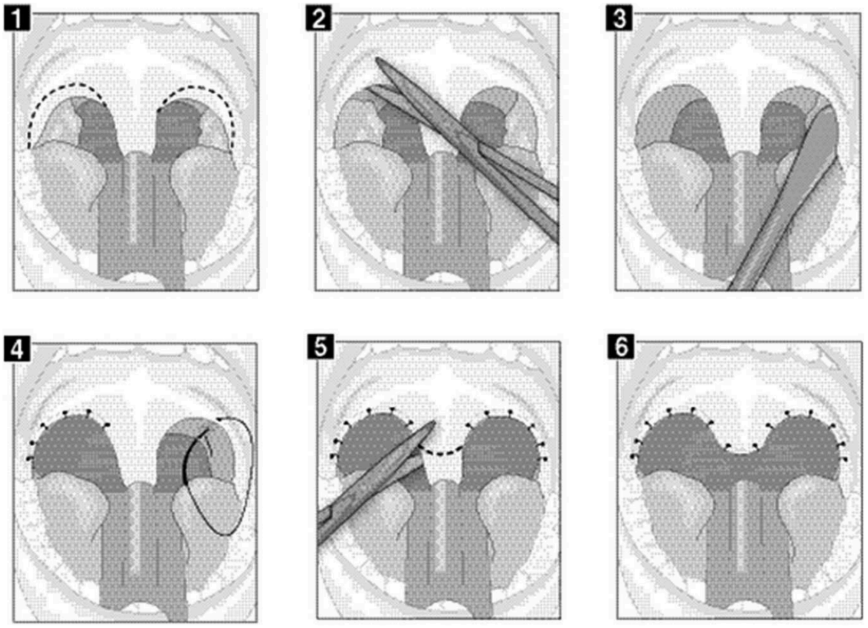


Figure 6 Modified uvulopalatopharyngoplasty. (1) Marked excision line laterally to the uvula. (2) Excision of the anterior tonsillar pillar 2–3 mm and the mucosa between the pillars. (3) Tonsillectomy with cold steel. (4) Suturing of the soft palatal mucosa. Single sutures lift up the posterior pillar and the palatopharyngeal muscle to the anterior pillar. (5) Amputation of the uvula leaving approximately 1 cm. (6) Final result. Reprinted with permission. © (2013). BMJ. All rights reserved.

3.2.3 Outcome measures

The UPPP and control group patients' systolic and diastolic blood pressures were compared between the baseline and at the initial six-month follow-up. Additionally, after the control group received delayed surgery, blood pressure was evaluated for all operated patients after six and 24 months. Correlation tests were also performed in order to compare the blood pressure with respiratory sleep parameters (e.g. AHI, ODI and oxygen saturation nadir).

3.2.4 Statistical analyses

The blood pressure is presented as mean with either standard deviation (SD) or 95% confidence interval (CI). Paired and unpaired t-tests were used to analyze blood pressure changes within and between the groups. Pearson's correlation test was used to determine the relationship between blood pressure and respiratory sleep parameters. All available blood pressure data were

included in the analyses, but blood pressure values that may have been affected by changes in antihypertensive treatment were excluded from the primary analysis.

An intention-to-treat (ITT) sensitivity analysis was performed to compare the surgery and control groups at the six-month follow-up. Missing values and values that might have been affected by changes in antihypertensives were imputed as no change from baseline, same as follow-up, or, if both values were missing, the mean value for the group at baseline. A sensitivity analysis was also performed for all operated patients. Values that may have been affected by changes in antihypertensives were imputed as a "worst case scenario" with a value of 250/150. This sensitivity analysis was analyzed with the Wilcoxon signed rank test, a non-parametric test.

3.3 PAPERS II and III – ADENOTONSILLECTOMY VS. ADENOPHARYNGOPLASTY

3.3.1 Design and study population

This study was a blinded RCT with two parallel arms comparing APP and ATE in children who were two to four years of age, otherwise healthy, and had severe OSA. All children referred for OSA to the Otorhinolaryngology department at Karolinska University Hospital, Stockholm were offered a PSG. Children who completed the PSG were possible candidates for the study and they were offered participation if they met the inclusion criteria (≥ 2 to < 5 years of age; history or symptoms of OSA; severe OSA, defined as an OAHI ≥ 10; tonsil hypertrophy 2–4 according to Brodsky[138]; and caregivers with sufficient knowledge of Swedish) and exclusion criteria (presence of craniofacial abnormality, cardiopulmonary disease, chromosomal abnormality, previous adenotonsillar surgery, neuromuscular disease, or bleeding disorder). Final inclusion was determined on the day of operation.

A study population of at least 44 children was recommended, but a total of 83 children were included in order to compensate for limitations in the power analysis and dropouts. The power analysis (α level of 0.05 and 90% power) was based on a reduction of 75% in OAHI after ATE[113,116] and that a further decrease of 10% after APP would be of clinical value.

The randomization was performed on the day of operation with sealed envelopes, which were stratified into two strata (OAHI <30 or OAHI ≥30). The surgeons received sealed envelopes with the surgery type and did not meet the children or the caregivers after the operation. The caregivers, patients, researchers, and PSG scorer were blinded to surgical method.

Both groups had a follow-up six months after surgery, during which they were assessed with a new PSG. At both baseline and the follow-up, the caregivers answered the OSA-18 questionnaire. Furthermore, a logbook was used to evaluate the patient's postoperative pain, and an additional questionnaire regarding postoperative morbidity was answered at the follow-up. The flow of participants is illustrated in Figure 7.

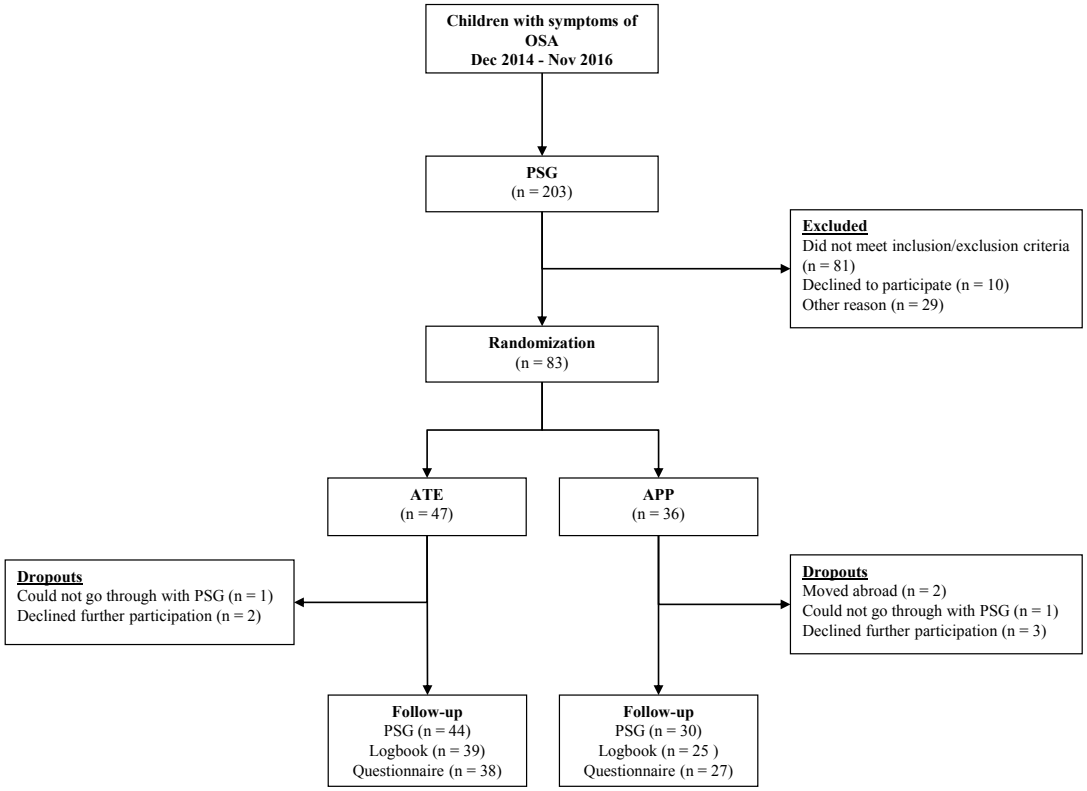


Figure 7 Flowchart **Paper II and III**. Abbreviations: ATE, adenotonsillectomy; APP, adenopharyngoplasty; OSA, obstructive sleep apnea; PSG, polysomnography.

3.3.2 Intervention

All children were operated on with the cold steel technique. The tonsils were removed by blunt extracapsular dissection, and the adenoid was removed with a ring knife. The children in the APP group also had their tonsillar pillars lateralized and closed. This was performed with two inverted sutures, Monocryl 4/0 (Ethicon, USA), on each side, including fibers of the palatopharyngeus muscle (see Figure 4). All children received locally administrated bupivacaine perioperatively, and perioperative hemostasis was obtained with compression and bipolar diathermia. Perioperative blood loss was registered by the surgeon. All children were prescribed analgesics (paracetamol and ibuprofen) according to a standardized schedule. No antibiotics were given peri- or postoperatively.

3.3.3 Outcome measures

3.3.3.1 Paper II

The primary outcome was to compare how the OAHI changed after surgery for the children who underwent ATE versus APP at the six-month follow-up. Other outcomes included comparing for changes in other PSG variables: central AHI, rapid eye movement AHI, ODI (using

the ≥ 3% desaturation criteria), RDI, mean oxygen saturation, lowest oxygen saturation level, total sleep time, and sleep efficiency. The level of postoperative OAHI (< 1, < 2, < 5, and < 10) was analyzed to evaluate the success of surgery. Subgroup analyses were performed for children with obesity (BMI z-score ≥ 1.67) and for different levels of preoperative OAHI (≥ 20 and ≥ 30).

Furthermore, the data from the OSA-18 questionnaire were used to analyze differences between the groups for postoperative changes in total symptom score, sleep disturbance index, and general health related QoL. The need for repeated surgery because of residual OSA and postoperative complications, such as infection and readmission due to bleeding, was also evaluated.

3.3.3.2 Paper III

All patients received a logbook to record pain level, analgesics given, and food intake for the first 10 days after surgery. Pain was assessed three times per day by both the children and the caregivers. The children used a standardized self-reporting scale (0–10) called the Faces Pain Scale – Revised (FPS-R) (Figure 8). This scale consists of six different faces, is validated for children from four years of age, and is recommended by the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials[139–141]. The caregivers assessed the pain from 1–10 by using a visual analogue scale (VAS). The food intake was registered by the caregivers as amount (less than normal, normal, or more than normal) and texture (liquid, soft, or normal). Also, the patient's weight in kilograms was registered, using the same scale, on the first and tenth day after surgery.

The data retrieved from the logbook were evaluated according to seven different pain-related outcomes: (1) first day when the child was pain free (FPS-R = 0); (2) first day when the child had FPS-R < 6; (3) first day when the caregiver estimated the child to be free of pain (VAS = 1); (4) first day when the caregiver estimated the child to have VAS ≤ 5; (5) first day without analgesics; (6) first day with normal diet (defined as normal texture in combination with normal or more than normal amount); and (7) mean weight change.

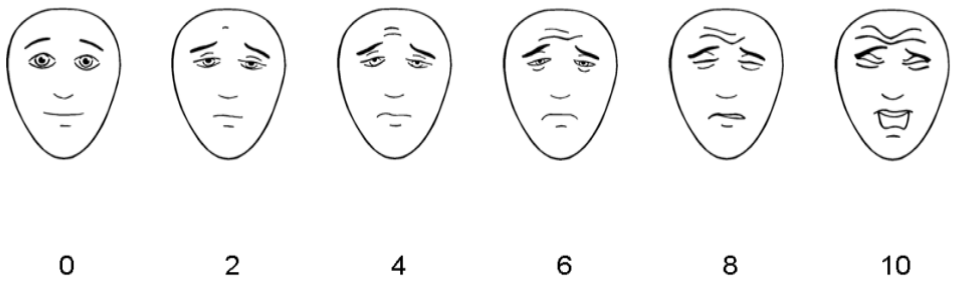


Figure 8 Faces Pain Scale-Revised (FPS-R). https ://www.iasp-pain. org/fpsr. Copyright © 2001, International Association for the Study of Pain®. Reproduced with permission.

Postoperative bleeding and infection were assessed by evaluating clinical records and a questionnaire at the six-month follow-up. Only bleeding that required surgical treatment or readmission was defined as postoperative bleeding. Perioperative blood loss was also evaluated.

Further, the caregivers answered a questionnaire at the six-month postoperative follow-up regarding global satisfaction with treatment (yes or no), patient's speech (improved, unchanged, worse, or much worse) and patient's swallowing (improved, unchanged, worse, or much worse). Swallowing and speech data were dichotomized to impaired (worse or much worse) and not impaired (improved or unchanged).

3.3.4 Statistical analyses

3.3.4.1 Paper II

The primary analysis was per protocol, but an ITT analysis was also performed regarding the primary outcome of change in OAHI. Missing values were imputed by the last observation carried forward method. The PSG variables were continuous data, and parametric statistical tests, including paired and unpaired t-tests, were used to analyze differences within and between the groups. The results are given as the mean (SD) or as the mean (95% CI). The test of proportion was used to compare different levels of surgery success.

The OSA-18 questionnaire consisted of ordinal data and was analyzed with non-parametric tests, including the Wilcoxon signed-rank test within groups and the Mann–Whitney U-test between groups. The results are given as the median (interquartile range) or as the median (95% CI).

All data were analyzed with Stata 15 (StataCorp, USA).

3.3.4.2 Paper III

The analysis was per protocol. The pain-related outcomes are reported as the median (interquartile range). The group differences were analyzed with log-rank tests (nonparametric) and illustrated with Kaplan-Meier plots. The mean weight in kg and mean perioperative blood loss in ml are reported with SD or 95% CI and were analyzed with independent t-tests (parametric). Postoperative bleeding, infection, global satisfaction with treatment, impaired speech, and impaired swallowing are reported as number (n) and percent (%) and were analyzed with Fisher's exact test (nonparametric).

All data were analyzed with Stata 15 (StataCorp, USA).

3.4 PAPER IV – ADENOTONSILLECTOMY VS. WATCHFUL WAITING

3.4.1 Design and study population

This study was an RCT with two parallel arms comparing ATE with watchful waiting in children, two to four years of age, with mild to moderate OSA. The recruitment process was the same as in **Papers II and III** (see chapter 3.3.1), and the inclusion/exclusion criteria were also the same, except from an OAHI of ≥ 2 and < 10 (mild OSA, OAHI ≥ 2 and < 5; moderate OSA, OAHI ≥ 5 and < 10). Both groups had a PSG and answered the OSA-18 questionnaire at baseline and at the follow-up after six months. The PSG scorer was blinded to treatment allocation. The flow of participants is illustrated in Figure 9.

The power analysis was calculated with an α level of 0.05 and 80% power. A difference of 2 (2.5 SD) in OAHI change was used as the minimal clinically important difference between the groups. This generated required a study population of 52 children, but a total of 60 children were included in this study to compensate for dropouts and limitations in the power analysis.

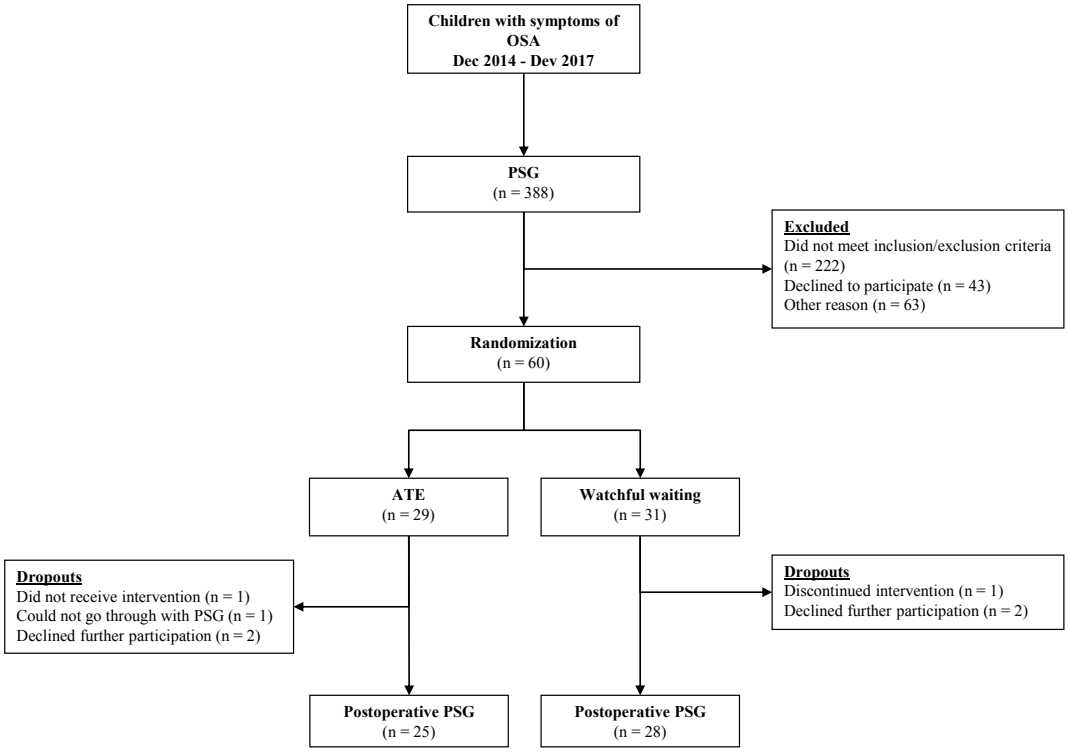


Figure 9 Flowchart **Paper IV**. Abbreviations: ATE, adenotonsillectomy; OSA, obstructive sleep apnea; PSG, polysomnography.

3.4.2 Intervention

The patient's tonsils were removed by blunt extracapsular dissection, and the adenoid was removed with coblation or a ring knife.

3.4.3 Outcome measures

The primary outcome was the difference in mean OAHI score change. Secondary outcomes were changes in other PSG variables, the OSA-18 questionnaire, the need for surgery because of residual OSA, and postoperative complications, such as infection and readmission due to bleeding.

3.4.4 Statistical analyses

The primary analysis was per protocol, but an ITT sensitivity analysis was also performed for the primary outcome of change in OAHI score. Missing values were imputed by multiple imputation. The statistical inference was performed by comparing effect sizes and 95% CI.

The PSG variables were continuous data, and the results are given as the mean (SD) or as the mean (95% CI). Standardized effect sizes were calculated with the use of Cohen's d, relating the magnitude of group difference to the standard deviation, and may be interpreted as follows: small, more than 0.20 to 0.49; medium, 0.50 to 0.79; and large, 0.80 or more.

The OSA-18 questionnaire consisted of ordinal data and the results are given as the median (interquartile range), the median (95% CI, which is given with the Hodges–Lehmann estimator), as well as a standardized effect size, Cohen's d.

Univariate associations were tested using logistic regression models to find factors that could predict an OAHI ≥ 2 and a total OSA-18 score ≥ 60 at follow-up. Variables that were considered predictive ($p < 0.05$) in the univariate analysis were included in a forward stepwise logistic multiple regression model.

4 RESULTS

4.1 PAPER I – BLOOD PRESSURE AFTER MODIFIED UVULOPALATO-PHARYNGOPLASTY

A total of 71 patients were initially randomized for this study, but six patients deviated from the study protocol and were excluded. The remaining 65 patients were randomized to either UPPP (n = 32) or the control group (n = 33). The baseline characteristics were similar in both groups, and six patients had no documented blood pressure values at baseline (Table 2).

Table 2 Baseline characteristics

Parameter	n	Intervention group	n	Control group	p
Age (years)	32	41.7 (11.4)	33	42.9 (11.8)	0.662
Sex (number and % of women)	32	4 (12.5%)	33	2 (6.1%)	0.370
Body mass index (kg/m^2)	32	28.2 (2.9)	33	27.7 (3.3)	0.519
Apnea-Hypopnea Index (events/h sleep)	32	53.3 (19.7)	33	52.6 (21.7)	0.901
Oxygen desaturation index (events/h sleep)	32	44.6 (23.5)	33	41.1 (22.2)	0.541
Nadir O_2 (%)	32	79.9 (5.3)	33	81.0 (6.6)	0.449
Epworth Sleepiness Scale	32	12.5 (3.2)	33	12.9 (3.1)	0.631
Systolic blood pressure (mmHg)	28	132.0 (15.9)	31	131.3 (16.5)	0.867
Diastolic blood pressure (mmHg)	28	82.5 (10.9)	31	82.7 (10.9)	0.942

Data are mean (SD), except for sex.

At the six-month follow-up, the mean blood pressure had decreased in the UPPP group but not in the control group, and there were significant differences between the groups (SBP −9.4 mmHg; 95% CI, −17.9 to −0.8; and DBP −6.4 mmHg; 95% CI, −12.8 to −0.04) (Table 3). In the sensitivity analysis, the UPPP group also had lower blood pressure values at the six-month follow-up, but the difference between the groups was not significant (SBP −5.3 mmHg; 95% CI, −13.6 to 2.7; and DBP −4.1 mmHg; 95% CI, −9.8 to 1.7).

As mentioned, the mean (SD) blood pressure was unchanged in the control group at the six-month follow-up. However, after the delayed surgery the blood pressure also decreased in the control group (n = 25/33), and the decrease in systolic blood pressure was significant (SBP −3.7 [8.8] mmHg, $p < 0.05$; and DBP −2.1 [6.9] mmHg, $p = 0.14$) (Figure 10).

When analyzing all operated patients, there were significant decreases in both SBP and DBP after six months (n = 49, 75%) and 24 months (n = 35, 54%) (Table 4). Also, there were no change in mean BMI. However, 11 of the 65 operated patients were excluded due to changes in their antihypertensive treatment and the significant decrease in blood pressure was lost in

the sensitivity analysis. Further, there were significant correlations between the blood pressure and all the respiratory sleep parameters at the six-month follow-up.

Table 3 Changes in blood pressure in the intervention and control group.

	Intervention group			**Control group**			**Group difference**	
	Baseline (n=28)	**Follow-up** (n=28)	**p** (n=24)	**Baseline** (n=31)	**Follow-up** (n=33)	**p** (n=31)	**Difference at follow-up** (95% CI)	**p** (n=61)
SBP (mmHg)	132.0 (15.9)	121.8 (15.2)	**0.011**	131.3 (16.5)	131.2 (17.7)	0.793	-9.4 (-17.9, -0.8)	**0.032**
DBP (mmHg)	82.5 (10.9)	76.4 (12.6)	0.117	82.7 (10.9)	82.8 (12.2)	0.601	-6.4 (-12.8, -0.04)	**0.049**

Data presented as mean (SD) or mean (95% CI). Group difference compared at the 6-month follow-up. P values from paired and unpaired t-tests. Significant differences ($p<0.05$) are shown in bold type. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; n, number of patients.

Table 4 Blood pressure and body mass index for all operated patients at the 6-month and 24-month postoperative follow-ups.

	Preop (n=61/65)	**6 months postop** (n=53/65)	**24 months postop** (n=38/65)	**Preop compared to 6 months postop** (p) (n=49)	**Preop compared to 24 months postop** (p) (n=35)
SBP (mmHg)	131.6 (16.8)	122.6 (14.3)	118.7 (15.9)	**0.001**	**< 0.0001**
DBP (mmHg)	82.7 (11.5)	77.5 (11.3)	76.6 (11.1)	**0.030**	**0.012**
BMI (kg/m^2)	28.1 (3.4)	27.9 (3.3)	28.0 (3.4)	0.884	0.534

Data are presented as mean (SD). P values from paired t-tests. Significant differences ($p<0.05$) are shown in bold type. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; n, number of patients.

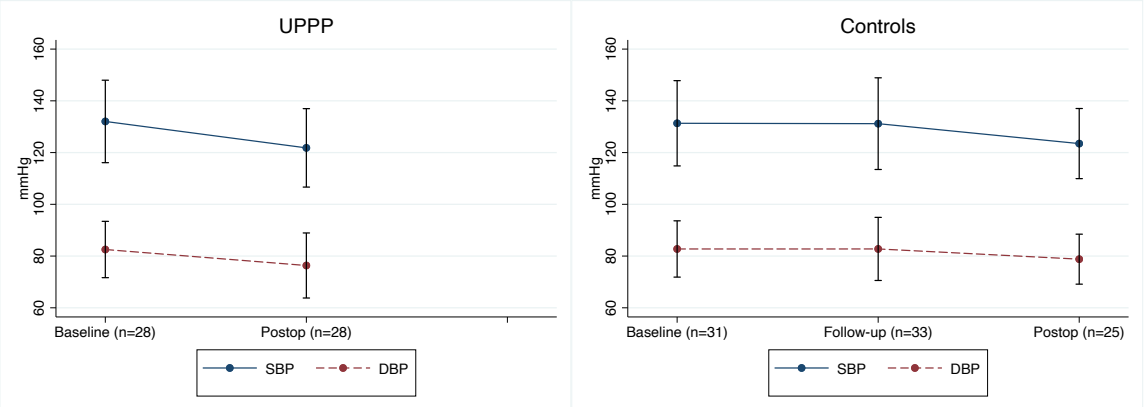


Figure 10 Blood pressure results for the UPPP and control group. Abbreviations: BL, baseline; 6m, six months; SBP, systolic blood pressure; DBP, diastolic blood pressure; UPPP, uvulopalatopharyngoplasty; n, number of patients.

4.2 PAPER II – ADENOTONSILLECTOMY VS. ADENOPHARYNGOPLASTY

A total of 83 children were randomly assigned to either APP (n = 36) or ATE (n = 47), and the groups were similar at baseline (Table 5). Four children in the ATE group and three children in the APP group were obese (BMI z-score ≥ 1.67). Of the 83 children, 44 (94%) in the ATE group completed the follow-up compared to 30 (83%) in the APP group.

Table 5 Baseline characteristics.

Parameter	**ATE** (n = 47)	**APP** (n = 36)
Age at intervention, mean (SD), months	36.3 (9.7)	37.0 (8.7)
Sex, No. (%)		
Male	26 (55)	23 (64)
Female	21 (45)	13 (36)
Length, mean (SD), cm	93.2 (6.6)	93.5 (6.6)
Weight, mean (SD), kg	14.2 (2.6)	14.1 (2.8)
BMI z-score, mean (SD)	−0.08 (1.46)	−0.20 (1.52)
Tonsil size[a], median (IQR)	4 (3–4)	3.5 (3–4)
Adenoid size[a], median (IQR)	3 (3–4)	3 (2–4)
OAHI, mean (SD), events/hour of sleep	23.7 (11.5)	23.8 (11.5)

Abbreviations: OAHI, Obstructive Apnea-Hypopnea Index; ATE, adenotonsillectomy; APP, adenopharyngoplasty.
[a] Data are expressed as the median (interquartile range). Tonsil size scored according to Brodsky. Adenoid size scored according to occlusion (%) of the epipharynx: 1 = 0–25%, 2 = 25–50%, 3 = 50–75%, and 4 = 75–100%.

All children had improved their OAHI scores at the follow-up, but one child in the ATE group still had severe OSA (OAHI = 27) at the follow-up compared to none in the APP group (Figure 11). The ATE group had a mean decrease of 21.1 (88%; 95% CI 17.7 to 24.5), and the APP group had a mean decrease of 21.7 (91%; 95% CI 17.2 to 26.3). There was no significant difference between the groups (0.7; 95% CI −4.8 to 6.1). Moreover, the difference between the groups was also not significant in the ITT analysis (−1.6; 95% CI −7.3 to 4.0).

Furthermore, statistical analyses found that there were no differences in other respiratory sleep parameters, success rates at different levels of postoperative OAHI, subgroup analyses for different preoperative OAHI and BMI z-scores, or OSA-18 scores (Tables 6 and 7). One patient in each group was readmitted due to postoperative bleeding, but no other complications were seen.

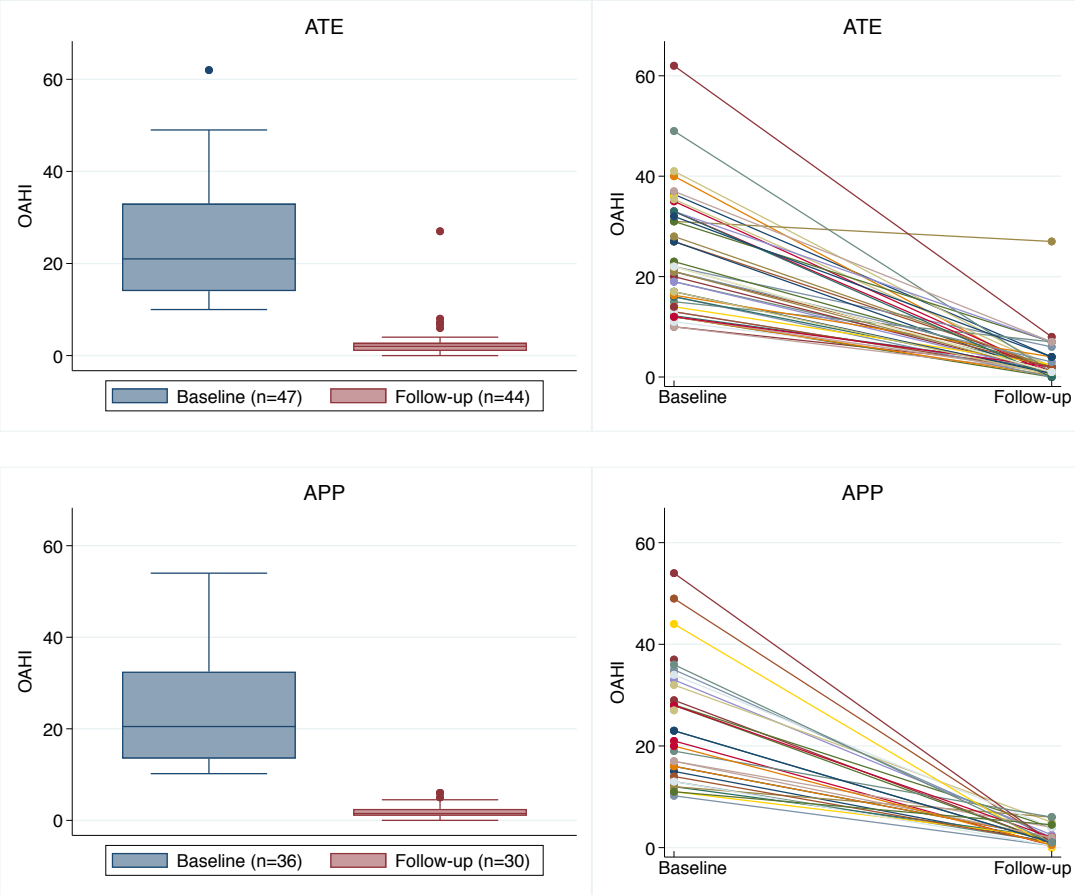


Figure 11 Boxplots and line graphs for the ATE and APP group. **Boxplots:** Boxes include the median and the first to third quartile. Whiskers are within the 1.5 interquartile range, and circles are outliers. **Line graphs:** Lines connecting individual pre- and postoperative OAHI scores. Abbreviations: ATE, adenotonsillectomy; APP, adenopharyngoplasty; OAHI, obstructive apnea-hypopnea index.

Table 6 Success rate at different postoperative OAHI levels.

OAHI Follow-up	**ATE** (n = 44)	**APP** (n = 30)	p
< 1	20% (9)	17% (5)	0.68
< 2	48% (21)	50% (15)	0.85
< 5	84% (37)	90% (27)	0.47
< 10	98% (43)	100% (30)	0.41

Rate of success, %, at a given postoperative OAHI level. The number of patients (n) is given within parentheses. Statistical analysis with the test of proportions. Abbreviations: ATE, adenotonsillectomy; APP, adenopharyngoplasty; OAHI, obstructive apnea-hypopnea index.

Table 7 Polysomnography and OSA-18 results from baseline and the six-month postoperative follow-up.

Parameters	n	**ATE** Baseline	**ATE** Follow-up	p	n	**APP** Baseline	**APP** Follow-up	p	Difference in change between the groups (95% CI)	p
PSG[a]										
OAHI	44	23.8 (11.5)	2.8 (4.3)	**< 0.001**	30	23.8 (11.8)	2.1 (1.7)	**< 0.001**	0.7 (−4.8 to 6.1)	0.81
Central AHI	42	2.7 (3.1)	2.0 (1.9)	0.17	30	2.9 (6.0)	1.9 (2.3)	0.36	0.3 (−1.7 to 2.4)	0.74
REM AHI	40	51.1 (28.2)	6.5 (8.9)	**< 0.001**	29	42.5 (28.1)	4.1 (3.5)	**< 0.001**	−6.2 (−20.1 to 7.6)	0.37
ODI	42	17.2 (11.0)	3.2 (2.8)	**< 0.001**	30	16.0 (12.7)	2.7 (2.2)	**< 0.001**	−0.8 (−6.3 to 4.8)	0.78
RDI	42	24.1 (11.5)	3.0 (4.5)	**< 0.001**	29	23.8 (11.7)	2.1 (1.7)	**< 0.001**	0.6 (−5.0 to 6.3)	0.82
Mean Sat O_2, %	42	96.6 (0.8)	97.0 (0.8)	**0.01**	30	96.7 (0.9)	97 (0.7)	0.20	0.2 (−0.4 to 0.7)	0.51
Nadir O_2, %	41	83.4 (6.8)	89.4 (4.3)	**< 0.001**	29	83.6 (8.2)	88.3 (4.5)	**0.002**	1.3 (−2.4 to 5.0)	0.49
Total Sleep Time, min	41	454 (38)	457 (33)	0.60	29	460 (41)	458 (37)	0.77	5.7 (−14.6 to 25.9)	0.58
Sleep Efficiency, %	41	93 (6)	95 (4)	0.14	29	93 (5)	92 (6)	0.38	3.2 (−0.7 to 7.1)	0.11
OSA-18[b]										
Total Symptom Score	40	63 (49–78)	28.5 (26–39.5)	**< 0.001**	29	67 (57–78)	30 (26–42)	**< 0.001**	−0.5 (−13 to 12)	0.64
Sleep Disturbance Index	40	18.5 (16–23.5)	5 (4–6.5)	**< 0.001**	29	18 (16–23)	6 (4–8)	**< 0.001**	−2 (−6 to 2)	0.28
HRQoL	39	7 (4–8)	9 (8–10)	**< 0.001**	27	7 (4–8)	9 (8–10)	**< 0.001**	0 (−1 to 1)	0.91

Abbreviations: PSG, polysomnography; ATE, adenotonsillectomy; APP, adenopharyngoplasty; OAHI, obstructive apnea-hypopnea index; REM AHI, rapid eye movement apnea-hypopnea index; ODI, oxygen desaturation index; RDI, respiratory distress index; Mean Sat O_2, mean oxygen saturation; Nadir O_2, oxygen saturation nadir; HRQoL, health-related quality of life; n, number of patients. Significant differences are marked in bold ($p < 0.05$).

[a]PSG data are expressed as mean (SD) and are analyzed with parametric tests (paired and unpaired t-tests).

[b]OSA-18 scores and HRQL are expressed as median (interquartile range) and are analyzed with non-parametric tests (Wilcoxon signed-rank test and Mann–Whitney U-test).

4.3 PAPER III – POSTOPERATIVE MORBIDITY AFTER ADENOTONSILLECTOMY VS. ADENOPHARYNGOPLASTY

A total of 64 out of 83 (77%) patients returned the logbook; 39 (83%) of these patients were in the ATE group, and 25 (69%) were in the APP group. Sixty-five (78%) patients answered the questionnaire regarding bleeding, infection, satisfaction with treatment, speech, and swallowing; in this subset were 38 (81%) patients from the ATE group and 27 (75%) patients from the APP group. Data regarding postoperative infection and peri- and postoperative bleeding were obtained for all children through medical records.

Table 8 Pain-related outcomes for adenotonsillectomy versus adenopharyngoplasty.

Parameter	n	**ATE**	n	**APP**	p
First day when child estimates pain = 0 (FPS-R)	33	7 (6–10)	22	9 (7 to >10)	**0.018**
First day when child estimates pain < 6 (FPS-R)	32	2 (1–7)	22	4 (1–10)	0.117
First day when caregiver estimates pain = 1 (VAS)	39	7 (6–10)	25	8 (7–10)	0.548
First day when caregiver estimates pain ≤ 5 (VAS)	38	3 (1–7)	25	3 (1–7)	0.657
First day without analgesics	39	9 (8–10)	25	8 (8–10)	0.798
First day with return to normal diet	39	7 (6–9)	25	8 (7 to >10)	0.111
Weight change (kg)	35	0.0 (0.6)	22	0.1 (0.5)	0.273

Abbreviations: ATE, adenotonsillectomy; APP, adenopharyngoplasty; FPS-R, Faces Pain Scale – Revised; VAS, visual analogue scale; kg, kilograms; n, number of patients.

Data are expressed as median, with interquartile range, and the groups are compared with log-rank tests, except for weight change. The weight change is expressed as mean, with standard deviations, and the groups are compared with an independent t-test.

Statistical analysis determined that there was a significant difference regarding the first day that the children graded themselves as pain free (FPS-R = 0). Median day (interquartile range) was 7 (6 to 10) in the ATE group, compared with 9 (7 to > 10) in the APP group (p = 0.018). There were no significant differences in mean weight change (−0.2 kg; 95% CI −0.5 to 0.1) or in any other pain-related outcomes (Table 8) (Figure 12).

Additionally, there were no significant differences regarding other outcomes of bleeding, infection, satisfaction with treatment, speech, and swallowing. However, three children in the APP group reported worse speech compared to none in the ATE group (p = 0.067) (Table 9).

Table 9 Bleeding and other postoperative outcomes for adenotonsillectomy versus adenopharyngoplasty.

Parameter	n	**ATE**	n	**APP**	p[a]
Perioperative bleeding, ml (SD)	47	34 (17)	36	37 (21)	0.5075
Postoperative bleeding, n (%)	47	1 (2)	36	1 (3)	1.000
Postoperative infection, n (%)	47	0 (0)	36	1 (3)	0.434
Impaired swallowing, n (%)	36	1 (3)	24	0 (0)	1.000
Impaired speech, n (%)	38	0 (0)	27	3 (11)	0.067

Abbreviations: ATE, adenotonsillectomy; APP, adenopharyngoplasty; n, number; SD, standard deviation; ml, milliliter.
[a] The groups were compared with Fisher's exact test; however, the mean perioperative bleeding (ml) was analyzed with an independent t-test.

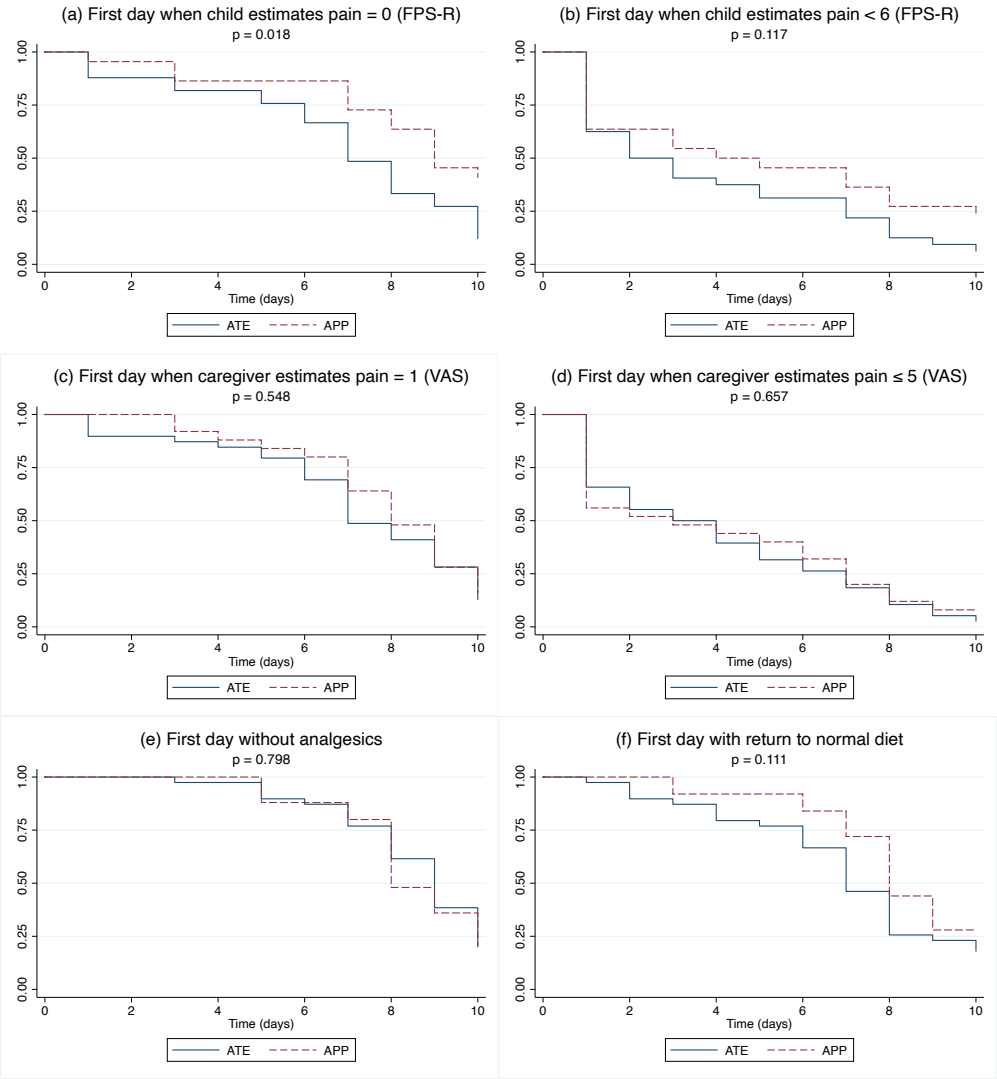


Figure 12 a–f Kaplan-Meier plots for six pain-related outcomes in both groups. P-values for group comparison with log-rank tests. ATE, adenotonsillectomy; and APP, adenopharyngoplasty.

4.4 PAPER IV – ADENOTONSILLECTOMY VS. WATCHFUL WAITING

A total of 60 children were randomly assigned to either ATE (n = 29) or watchful waiting (n = 31), and 53 of the children (88%) completed the study; 25 (86%) in the ATE group and 28 (90%) in the watchful waiting group. The groups were similar at baseline (Table 10). One child in the ATE group and three in the watchful waiting group were obese (BMI z-score ≥ 1.67).

Table 10 Baseline characteristics

Parameter	ATE (n = 29)	Watchful waiting (n = 31)
Age at first PSG, mean (SD), months	39 (8)	37 (11)
Sex, No. (%)		
Male	15 (52)	19 (61)
Female	14 (48)	12 (39)
BMI z-score, mean (SD)	0.2 (1.4)[a]	0.2 (1.1)
Tonsil size[b], median (IQR)	3 (3–3)	3 (2–3)
OAHI, mean (SD), events/hour of sleep	4.9 (1.9)	5.0 (2.2)
OSA severity, n (%)[c]		
Mild OSA	15 (52)	16 (52)
Moderate OSA	14 (48)	15 (48)
Total OSA-18 score, median (IQR)[d]	59 (49–74)	58.5 (48–69)
< 60, n (%)	14 (50)	17 (57)
60 to 80, n (%)	10 (36)	10 (33)
> 80, n (%)	4 (14)	3 (10)

Abbreviations: ATE, adenotonsillectomy; OAHI, Obstructive Apnea-Hypopnea Index; OSA, obstructive sleep apnea.
[a] One missing value in the ATE group (n = 28).
[b] Tonsil size scored according to Brodsky (scored according to occlusion (%) of the oropharynx: 1, 0–25%; 2, 26–50%; 3, 51–75%; and 4, 76–100%).
[c] Mild OSA, OAHI ≥ 2 and < 5; Moderate OSA, OAHI ≥ 5 and < 10.
[d] One missing value in each group; ATE group = 28 and watchful waiting group = 30.

Both groups showed a statistically significant reduction in mean OAHI score at the follow-up in the per protocol analysis. The ATE group had a mean OAHI score decrease of −2.9 (95% CI −4.0 to −1.9; Cohen's d = −1.14), the watchful waiting group had a mean decrease of −1.9 (95% CI −3.0 to −0.9; Cohen's d = −0.71). The difference between the groups was small and not statistically significant (−1.0; 95% CI −2.4 to 0.5; Cohen's d = −0.37). The result was similarly non-significant in the ITT analysis (−1.0; 95% CI −2.3 to 0.3; Cohen's d = −0.38; n = 60). Further, there were no or small differences between the groups in other PSG variables (Table 11), and ATE had slightly better success rates, but the difference was not statistically significant (Table 12).

Table 11 Polysomnography, OSA-18, and VAS QoL results from baseline to follow-up.

	ATE				**Watchful waiting**				**Group difference**	
Parameters[a]	n	**Baseline**	Change at **follow-up** (95% CI)	Effect size[b]	n	**Baseline**	Change at **follow-up** (95% CI)	Effect size[b]	Difference in change (95% CI)	Effect size[b]
OAHI	25	4.8 (1.9)	-2.9 (-4.0 - 1.9)	-1.14	28	5.1 (2.2)	-1.9 (-3.0 to -0.9)	-0.71	-1.0 (-2.4 to 0.5)	-0.37
Central AHI	24	1.7 (1.6)	-0.5 (-1.2 to 0.3)	-0.26	25	2.1 (2.2)	-0.5 (-1.2 to 0.2)	-0.32	0.1 (-0.9 to 1.1)	0.03
$ODI_{3\%}$	25	3.0 (2.5)	-0.4 (-1.3 to 0.5)	-0.20	27	3.7 (2.6)	-1.0 (-1.9 to -0.1)	-0.44	0.5 (-0.7 to 1.7)	0.24
Mean Sat O_2, %	25	97.2 (1.0)	-0.3 (-0.7 to 0.1)	-0.31	27	97.0 (0.7)	-0.2 (-0.4 to 0.1)	-0.29	-0.1 (-0.6 to 0.3)	-0.16
Nadir O_2, %	24	89.6 (3.7)	0.2 (-1.7 to 2.0)	0.04	27	88.0 (5.5)	-0.1 (-3.2 to 3.0)	-0.01	0.2 (-3.4 to 3.9)	0.04
Sleep Efficiency, %	25	91.7 (5.9)	2.0 (-1.4 to 5.4)	0.24	26	93.6 (6.0)	0.1 (-3.7 to 3.9)	0.01	1.9 (-3.1 to 6.9)	0.22
Sleep stage 1, %[c]	25	1.7 (1.9)	-0.3 (-1.4 to 0.7)	-0.13	26	2.1 (2.2)	-1.1 (-2.1 to -0.1)	-0.43	-0.7 (-0.7 to 2.2)	0.30
Sleep stage 2, %[c]	25	23.4 (12.4)	1.6 (-3.7 to 6.9)	0.12	26	30.7 (12.5)	-7.1 (-14.1 to -0.1)	-0.13	8.7 (0.1 to 17.4)	0.57
Sleep stage 3-4, %[c]	25	56.9 (14.2)	0.0 (-6.5 to 6.6)	0.00	26	49.0 (14.3)	7.3 (-0.1 to 14.6)	0.40	-7.2 (-16.9 to 2.4)	-0.42
Sleep stage REM, %[c]	25	18.0 (5.5)	-1.3 (-4.2 to 1.6)	-0.19	26	18.1 (5.0)	1.0 (-1.2 to 3.1)	0.18	-2.3 (-5.8 to 1.2)	-0.37
Total OSA-18 Score	23	57 (48–74)	-23.5 (-31.5 to -15)	-1.24	26	56.5 (48–70)	-4.5 (-12 to 1.5)	-0.36	-17 (-24 to -10)	-0.97
Sleep Disturbance Score	23	15 (11–18)	-7 (-8.5 to -4.5)	-1.39	26	15 (12–16)	-0 .5(-2.5 to 1)	-0.13	-6 (-9 to -4)	-1.23
VAS QoL	24	6.5 (5–9)	1.5 (0.5 to 3)	0.72	24	7 (4.5 to 8.5)	0.5 (-0.5 to 2)	0.25	1 (0 to 2)	0.40

Abbreviations: ATE, adenotonsillectomy; OAHI, obstructive apnea-hypopnea index; $ODI_{3\%}$, oxygen desaturation index; Mean Sat O_2, mean oxygen saturation; Nadir O_2, oxygen saturation nadir; QoL, quality of life; VAS, visual analogue scale; CI, confidence interval; n, number of patients.

[a] Polysomnography data is expressed as mean (SD). OSA-18 scores and VAS QoL are expressed as median (interquartile range).

[b] Effect sizes were calculated with the use of Cohen's d, relating the magnitude of group difference to the standard deviation, and may be interpreted as follows: small, more than 0.20 to 0.49; medium, 0.50 to 0.79; and large, 0.80 or more.

[c] % of total sleep time.

Table 12 Success rate at different levels of OAHI at follow-up.

OAHI at follow-up	**ATE** (n = 25)	**Watchful waiting** (n = 28)	**Difference** (95% CI)
< 1	36 (9)	25 (7)	11 (−14 to 36)
< 2	60 (15)	50 (14)	10 (−17 to 37)
< 5	96 (24)	82 (23)	14 (−2 to 30)

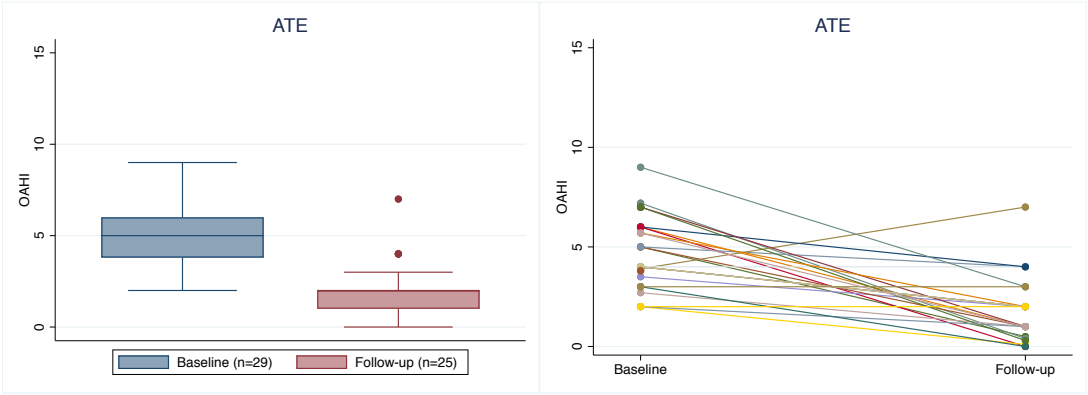
The results for each group are given as % (n). Abbreviations: ATE, adenotonsillectomy; OAHI, obstructive apnea-hypopnea index; and n, number of patients.
Z-test of two proportions was used when comparing different levels of success.

Two children in the ATE group had an increased OAHI score at the follow-up, compared to four in the watchful waiting group. Also, two children with moderate OSA in the watchful waiting group had developed severe OSA (Figure 13). At baseline, 11 children in the ATE group (mean OAHI score 6.5; SD 1.2) and 13 children in the watchful waiting group (mean OAHI score 7.1; SD 1.1) had moderate OSA. Subgroup analyses on children with moderate OSA showed a meaningful and statistically significant group difference with a mean OAHI score change of −3.1 (95% CI −5.7 to −0.5; Cohen's d = −1.00) in favor of ATE. On the other hand, for the subset of children with mild OSA, the difference in the OAHI score was 0.7 (95% CI −0.5 to 1.9; Cohen's d = 0.42), which was small and statistically non-significant.

There were large improvements in total OSA-18 score (−23.5; 95% CI −31.5 to −15; Cohen's d = −1.24) in the ATE group, but there were only small improvements in the watchful waiting group. The difference between the groups was large, clinically meaningful, and statistically significant (Table 11). Upon follow up, all 23 (100%) children in the ATE group had a total OSA-18 score of less than 60. In the watchful waiting group, 20 (76%) children had a total OSA-18 score of less than 60, five (19%) had a score between 60-80, and one (4%) had a score over 80.

In the watchful waiting group, 10 of 28 (36%) children received ATE after the follow-up due to persistent symptoms. Of these children, seven (70%) had moderate OSA at baseline, and two (20%) still had an OAHI score of 2 or more at the postoperative follow-up. One patient in the ATE group was readmitted due to postoperative bleeding, but no other complications were observed.

A



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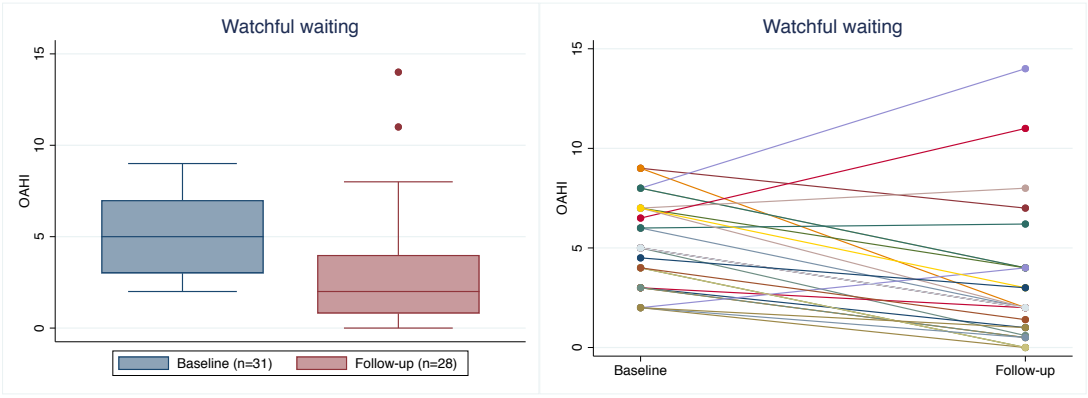

Figure 13 Boxplots and line graphs that illustrates the obstructive apnea-hypopnea index scores (OAHI) for adenotonsillectomy (ATE) (A) and watchful waiting (B) at baseline and follow-up. **Boxplots:** Boxes include the median and the first to third quartile. Whiskers are within the 1.5 interquartile range, and circles are outliers. **Line graphs:** Lines connecting individual OAHI scores.

5 DISCUSSION

5.1 RANDOMIZED CONTROLLED TRIAL

There are several different types of study designs, but RCTs are considered the best design for evaluating cause-effect relationships between a treatment and an outcome. While both researchers and study participants can affect the results through selection bias, the randomization process balances both known and unknown characteristics between study groups; this is not possible with other study designs. Additionally, if the randomization is successful, an RCT is the best way to remove the effect of regression to the mean. To further decrease bias, the participants and researchers, if possible, can be blinded for treatment allocation, as this prevents preconceived views to systematically bias the treatment assessment. Further, to prevent manipulation of the results, an RCT should have a pre-specified primary outcome and be registered in a clinical trials database.

Although RCTs are powerful tools for evaluating various treatment effects, there are limitations to their applicability. For instance, it may not be ethical to randomly select participants for a treatment that is believed to be inferior. RCTs are also not suitable for studies about rare diseases, for which it can be difficult to recruit participants. Finally, RCTs are time consuming and have high costs. Despite these limitations, there is a need for well-designed RCTs, when suitable, in order to improve the evidence-based treatment for OSA.

5.2 PAPER I – DOES SURGICAL TREATMENT FOR OBSTRUCTIVE SLEEP APNEA ALSO IMPROVE THE BLOOD PRESSURE?

Although UPPP was the primary treatment for adult OSA before the introduction of CPAP, the effect of UPPP on the patient's blood pressure is less understood. The effect of CPAP and MRDs on blood pressure has been widely studied, but the effect seems to be modest. Systematic reviews have only shown a decrease of 2.6 to 2.7 mmHg in SBP and 2.0 to 2.7 mmHg in DBP[61–63]. Other studies[142–144] have shown that sleep surgery may have a positive effect on blood pressure and other cardiovascular endpoints, but the evaluation of these relationships is difficult because there is no standard surgical procedure to treat OSA in adults. The overall evidence for improvement in cardiovascular endpoints after surgical treatment is weak, and, thus, there is a need for RCTs[66].

In an RCT that studied the effect of UPPP on blood pressure in adults with OSA (**Paper I**), we found that blood pressure significantly decreased six months after surgery; the SBP decreased by 9.4 mmHg, and the DBP decreased by 6.4 mmHg. The control group also experienced a significant decrease in blood pressure six months after surgery. Furthermore, there were significant correlations between respiratory sleep parameters and blood pressure, which further indicated a beneficial treatment effect. The decrease in blood pressure was still significant after two years. Weight loss, which is another important factor in treating adult OSA, did not seem to affect the result, as the mean BMI was unchanged.

The combined results from this study and the original SKUP[3] study[45] suggest that modified UPPP has a positive effect on respiratory sleep parameters, QoL, and blood pressure. This is important to address, as both OSA and hypertension are major health concerns and may be lifelong conditions, and other treatments, such as CPAP, MRDs, and antihypertensives, suffer from poor patient compliance[37–39,41,145]. If untreated, patients with OSA face a higher risk for cardiovascular mortality and other serious disorders[5]. Therefore, modified UPPP should be considered in selected cases where CPAP or MRDs fail.

5.2.1 Limitations

The results of this study must be interpreted with caution, as the sensitivity analyses showed neither significant differences between the groups nor improvements in all operated patients. There was a high risk for attrition bias related to the exclusion of patients with changes in antihypertensive treatment and a high proportion of missing values (46%) at the follow up after two years. Furthermore, this study was small and was not primarily designed to evaluate blood pressure; hypertension, antihypertensive treatment, and blood pressure were not part of any inclusion or exclusion criteria. However, there were no differences between the groups regarding these cardiovascular factors at baseline. The blood pressure measurement protocol in this study was also a limiting factor. While blood pressure was taken manually and only once in the morning after a PSG, a 24-hour ambulatory blood pressure would have been preferable, since blood pressure fluctuates over time. Additionally, smoking, exercise, and other comorbidities that can affect blood pressure were not controlled for during this study.

5.3 PAPERS II AND III – IS ADENOPHARYNGOPLASTY BETTER THAN ADENOTONSILLECTOMY?

Surgery is the primary treatment for OSA in children, as adenotonsillar hypertrophy is the major risk factor. ATE is the most common surgical procedure for OSA in children worldwide, although adenotonsillotomy is becoming more popular. However, residual OSA after surgery is not uncommon and more frequent in children with obesity, severe OSA, and genetic, craniofacial, and neurological disorders. Various surgical procedures have been investigated to improve the surgical outcome. For instance, APP is believed to reduce the obstruction of the upper airway by closure of the tonsillar pillars after ATE. Previous studies of APP have shown promising results regarding respiratory sleep parameters and QoL, but further research is needed[125,126]. Moreover, previous work has shown contradicting results regarding postoperative morbidity, such as pain and postoperative bleeding[125,146–148].

An RCT was developed to evaluate the efficacy of APP over ATE for otherwise healthy children with severe OSA. The findings of this study were reported in **Papers II and III**. In **Paper II** no significant differences were found regarding changes in the OAHI, other respiratory sleep parameters, or QoL. The APP group had a large reduction in mean OAHI of 91%, but the ATE

group had a reduction of 88%, and the difference between the groups was small. The non-significant difference between the groups could not be explained by an unexpectedly high reduction in OAHI after ATE, since the results for ATE are similar to those of other studies with comparable preoperative values[115,118]. Furthermore, previous studies that indicate that APP is more effective than ATE are not convincing. For instance, in the small prospective study from Chiu et al.[126] (n = 24), the groups were not randomized and not similar at baseline, which could explain the better effect after APP. Nevertheless, while Friedman et al.[125] (n = 60) conducted an RCT and have suggested there might be a difference between APP and ATE, their results were not statistically significant. This might be explained by a high dropout rate (27%), rendering the Friedman et al. study underpowered. Their study was also limited by the fact that only 25% of the children were evaluated with PSG.

In **Paper II** no differences in QoL, as measured with OSA-18, between the two groups were observed, while Friedman et al.[125] found a difference in QoL in favor of APP. However, the groups in the Friedman et al. study were already different at baseline, which likely explains the significant difference at follow-up.

Friedman et al.[125] could not show a statistically significant difference between the groups in postoperative pain, which was measured by return to normal diet and activity. While there are reports that covering the tonsillar fossa after ATE could affect the postoperative pain and the risk for postoperative bleeding, the results are not consistent[125,146–149]. In **Paper III**, postoperative morbidity, such as postoperative pain, bleeding, infection, satisfaction with treatment, and impaired speech and swallowing, was evaluated. The results regarding pain were slightly in favor of ATE, but the only statistically significant difference in outcome was for when the children scored themselves as pain free (FPS-R = 0). There were no significant differences in any other pain-related outcomes, such as pain reported by the caregivers, weight change, number of days with analgesics, or when the children returned to normal diet. However, the results from the FPS-R must be interpreted with caution, as the FPS-R is validated and recommended for children from four years of age[141], and 80% of the children who responded to the logbook were less than four years of age. Nevertheless, Borgström et al.[150] conducted an RCT comparing ATE with ATT that used the same methodology as in Paper III for a similar group of children. In the Borgström et al. study, children scored themselves as pain free eight days after ATE, which is similar to the seven days reported in **Paper III**. The combined results from all pain-related outcomes in **Paper III** were slightly in favor of ATE.

It is difficult to compare these pain-related outcomes with other studies due to differences in methodology. For instance, there is an extensive RCT by Matt et al.[146] (n = 763) in which the tonsillar pillars were closed after ATE on one side and left open on the other side, effectively making the pediatric patients their own controls. Matt et al. have reported that the children felt more pain after APP compared to ATE. The number of patients included is a strength of the study, but to evaluate two different methods in the same patient is difficult, especially in young children. The results in **Paper III** are more comparable with the results from two smaller studies with similar design, surgical techniques, and outcomes. Friedman et al.[125], as mentioned

earlier, did not report a difference between when the two groups returned to normal diet or activity, and an RCT by Fornazieri et al.(n = 132)[147] found neither a difference in return to normal diet nor in pain that was self-reported using a faces pain scale. Even so, **Paper III** suffers from a small sample size and no well-defined clinically important differences regarding the outcomes.

One patient in each group was readmitted due to postoperative bleeding, but the sample size was too small in order to draw any conclusions. Larger studies are contradictory on this matter. Matt et al.[146] showed no difference in postoperative bleeding, but a retrospective study by Senska et al.[148] (n = 2000) reported that the need for second surgery due to bleeding after APP was almost halved compared to after ATE. These differences may be explained by several factors, such as surgical technique and study design.

Swallowing and speech disorders after APP are not well documented but are well-reported in adults who have received UPPP[151]. While the sample size in **Paper III** was too small to yield conclusive results, three children reported impaired speech after APP compared to none after ATE. The difference was not statistically significant (p = 0.067), but probably of clinical interest, and should be studied further with validated methods.

In summary, the results from **Papers II and III** did not show any certain clinically important differences between APP and ATE regarding respiratory sleep parameters, postoperative morbidity, or QoL. However, APP is a more extended method and therefore ATE should still be considered as the primary treatment for otherwise healthy children with severe OSA.

5.3.1 Limitations

There are several limitations in **Papers II and III** that should be considered. First, there was a skewed distribution (n = 47 for ATE and n = 36 for APP), which probably can be explained by a logistical error – i.e. the sealed randomization envelopes were not taken in order from the stack. Even so, the groups were similar at baseline, and there were enough children in each group according to the power analysis. Although obesity is a risk factor for persistent OSA, the results are not generalizable for obese children because there were only a few obese patients included in this study. Furthermore, the power was probably not sufficient in order to show any statistically significant differences regarding postoperative morbidity. Also, the FPS-R is not validated for children below four years of age, and the questionnaire regarding speech and swallowing was not validated. However, these outcomes are generally difficult to study in young children, and these tools were used in the absence of other validated methods.

5.4 PAPER IV – SHOULD ALL CHILDREN WITH OBSTRUCTIVE SLEEP APNEA RECEIVE SURGERY?

Obstructive sleep apnea is a common disorder in children, and ATE is overall one of the most frequent surgical treatment methods in children. Previous reports have shown that ATE is effective at improving QoL and respiratory sleep parameters[128,152], but children can also improve without treatment. For instance, in CHAT[113], a large RCT (n = 464) by Marcus et al., ATE was compared to watchful waiting in children with mild to moderate OSA. The study was not designed to primarily study the effect of treatment on respiratory sleep parameters, but the results showed significant improvements in OAHI and QoL after ATE compared to after watchful waiting. Nevertheless, as many as 46% of the children in the watchful waiting group achieved normal sleep parameters (OAHI <2) by the follow-up, and children with a lower OAHI at baseline had a higher degree of normalization. These results suggest that watchful waiting could be an alternative for children with mild OSA. However, the children in the CHAT study were between five and nine years of age. The effect of watchful waiting in children between two and four years of age is still unknown according to a review by Cochrane[128], and there is a need for RCTs that evaluate the effect in these children. It is important to study children in this age group, as they have the highest prevalence of OSA and are the primary recipients of surgery. Thus, peri- and postoperative risks must be considered.

In **Paper IV**, ATE was compared to watchful waiting in children between two and four years of age. This study found significant improvements in mean OAHI score change within both groups, but the difference between the groups was small and not statistically significant (−1.0; 95% CI −2.4 to 0.5). A similar result (−0.98) was found in a recent RCT known as the Preschool Obstructive Sleep Apnea Tonsillectomy and Adenoidectomy (POSTA) study[153] (n = 190), which compared ATE with watchful waiting in children between three and five years of age with a baseline mean OAHI of 1.9. Although the difference in OAHI between the patient groups in POSTA was statistically significant, the study was designed to evaluate cognition rather than respiratory sleep parameters, and, therefore, the result may not reflect a clinically relevant difference. The statistical significance can probably be explained by a large study sample. However, it is difficult to define a clinically relevant group difference in OAHI scores, as there are no well-established and predetermined values. In the present study, which was designed to study changes in OAHI, a group difference of 2, which we believed would be of clinical value for this group of children, was defined as clinically relevant. Although the difference in mean OAHI between the groups was small (−1.0) and not significant, the result is not totally conclusive, as the confidence interval (95% CI −2.4 to 0.5) does not exclude a difference of 2 between the groups. However, children with moderate OSA seemed to have a larger and statistically significant improvement after ATE compared to after watchful waiting. As this is a subgroup analysis, the results should be interpreted with caution; nevertheless, the CHAT[113] study arrived at the same conclusion. Further and larger studies are needed to confirm these results.

Why some children improve without treatment is not well understood, but lower OAHI, smaller waist circumference, and absence of obesity may increase the chance of spontaneous

improvement.[154] This was partly confirmed in **Paper IV**, where a lower baseline OAHI was also found to be a predictor for OSA resolution (OAHI <2) after watchful waiting. However, other factors, such as wider airways due to growth, regression to the mean and night-to-night variability, should also be taken into consideration.

Although PSG is the gold standard method to diagnose OSA, there are no strong correlations between improvements in respiratory sleep parameters and changes in QoL[99–102]. Even mild OSA has been shown to have a large impact on QoL[155], which indicates that PSG is not perfect in measuring all aspects of OSA and might miss improvements that are important for children with OSA. QoL is a crucial health outcome measure, and, therefore, it is of importance to consider both PSG outcomes as well as QoL to properly treat children with OSA. This study found large improvements in OSA-18 scores after ATE, which is consistent with findings in other RCTs[99,129,156]. The difference between the groups was also large and relevant, in favor of ATE, and agrees with the result in CHAT[113].

To summarize, the combined results from **Paper IV** and other studies suggest that otherwise healthy children, two to four years of age, with moderate OSA should be recommended ATE. This supports the recommendations for OSA treatment in children from the European Respiratory Society[127]. However, children with mild OSA and low impact on QoL might benefit from a period of watchful waiting. Even so, larger studies are needed to confirm these results.

5.4.1 Limitations

This study has several limitations. First, it was a small study (n = 60). It primarily included otherwise healthy children, so the results are not applicable to children with obesity, comorbidities or severe OSA. Additionally, the study was not blinded for children and caregivers, so the differences in QoL may be explained by a surgical placebo effect. The choice to evaluate children with both mild and moderate OSA might be questioned, but this design was selected to enable comparison to the CHAT study. Furthermore, PSG is in general not used, and it is difficult to distinguish between mild and moderate OSA using only history and clinical examination.

6 CONCLUSIONS

The results from the studies included in this thesis suggested that:

Paper I Blood pressure decreased significantly six months after modified UPPP in a selected group of adult patients with moderate to severe OSA. The effect was maintained two years after surgery, but more uncertain due to a high proportion of missing values.

Paper II APP was not more effective than ATE at improving respiratory sleep parameters or QoL in otherwise healthy children with severe OSA.

Paper III ATE was slightly favored over APP regarding postoperative morbidity (e.g. pain, bleeding, infection, satisfaction with treatment, speech, and swallowing). The combined results from **Papers II and III** suggested that ATE should still be considered as the primary treatment for otherwise healthy children with severe OSA.

Paper IV Otherwise healthy children with moderate OSA did benefit from early ATE, and a period of watchful waiting could be an alternative for children with mild OSA and a low impact on QoL.

7 ETHICAL CONSIDERATIONS

In all scientific research, ethical considerations must be made regarding the autonomy, integrity, quality, as well as the risks and benefits of the research.

Autonomy was considered for the studies reported in **Papers II, II, and IV**, in which young children were patients. The children were not capable of making an informed decision of whether or not to participate in the study, and thus their autonomy was compromised. However, written informed consent was attained from the caregivers, who were believed to be generally good representatives of the children's interests. The children approached for the study received proper treatment regardless of whether they ultimately participated in the study or not. Additionally, no economic compensation was provided that could have caused caregivers to disregard the children's interests. In **Paper I** all participants were adult, and the patient's autonomy was not considered to be compromised. All adult patients provided an informed consent, received treatment regardless of study participation, and received no economic compensations.

A considerable amount of sensitive personal data were handled in these studies. To protect the integrity of all study participants, the data was handled unidentified. All personal information was kept in a locked and safe place that was inaccessible to unauthorized persons.

The quality of the research is another ethical aspect to take into consideration. Low quality research does not generate new or increased knowledge, wastes resources, and exposes study participants to unnecessary risks and time-consuming procedures. Although the studies described in this thesis did not have large sample sizes, they were of high quality for several reasons. Importantly, all studies were RCTs, which have a high scientific value and are unusual in surgical treatment studies. PSG was used, which is the gold standard method to diagnose and evaluate OSA. The study samples were based on power calculations and there were low dropout rates. The participants and caregivers were blinded if possible and the PSG scorers were blinded in all studies. Finally, the studies were requested.

Risks and benefits of the studies was also considered. Surgery always comes with risks, such as pain, bleeding, and infection. In **Paper IV,** some children with mild symptoms may have been unnecessarily exposed to surgical risks, but they would have been offered surgery regardless of study participation. In **Papers II and III**, the children received APP, which is not a standard treatment method and might be associated with higher risks, but previous studies have not shown any obvious negative side effects or complications. In **Paper I**, the adult patients were not exposed to any extra surgical risks, as they also would have been offered surgery regardless of study participation. Furthermore, one might argue that patients in the control groups in **Papers I and IV** experienced the risks associated with untreated OSA. However, the follow-up time was short, no children with severe OSA were affected, and both children and adults were offered surgery if their OSA symptoms clinically worsened during the follow-up period or if they still had OSA after the follow-up. Additionally, at the start of SKUP[3] in 2007, surgery for adult OSA was questioned. It was not obvious that adult patients should be offered surgery rather than be left untreated if they had failed treatment with CPAP and MRD. Thus,

despite the risks, we believe that the benefits of these studies exceeded the risks. We also believe that the results of these studies have increased the knowledge of surgical treatment of OSA, helped clinicians ensure that patients do not receive surgery unnecessarily, and helped patients with OSA to receive the correct surgical treatment.

All papers have been reviewed by an ethical board. The study in **Paper I** was approved by the Central Ethics Board (ref Ö21-2007), after first being rejected by the Swedish Regional Ethics Board, Stockholm (ref 2007/449-31/3). The studies in **Papers II, II, and IV** were approved by the Swedish Regional Ethics Board, Stockholm (ref 2014/1000-31/1).

8 FUTURE PERSPECTIVES

Sleep medicine research is performed all over the world to understand more about sleep and its important impact on our lives. However, increased knowledge leads to more questions and there are still a lot of questions to be answered in this vast research field.

OSA is a major health problem with increased risk for cardiovascular mortality, and there is a need for more studies that evaluate the effect on cardiovascular endpoints after surgery. Related to the research in **Paper I**, there is a need for larger RCTs that record the 24-hour ambulatory blood pressure and other surrogate markers, such as blood lipids and systemic inflammatory markers. Blood samples collected during SKUP[3] are being analyzed by our research team and will provide further knowledge about these surrogate markers.

Although APP was not shown to be a superior treatment option to ATE in **Papers II and III**, there are still questions to be answered. The results from **Papers II and III** are only generalizable to otherwise healthy children with severe OSA. Persistent OSA has been observed in some patients after ATE, and further studies in children with other risk factors, such as obesity and Down syndrome, would be of interest.

An important factor to consider is the discrepancy between PSG and subjective outcomes. In **Paper IV**, no differences were found in respiratory sleep parameters between the ATE and watchful waiting groups, but large differences in QoL were observed. Although PSG is gold standard, the correlation between respiratory sleep parameters, symptoms, behavior and QoL needs to be better understood to better define clinically relevant improvements in respiratory sleep parameters.

The results in **Paper IV** suggested that children with mild OSA could benefit from a period of watchful waiting. There are also studies indicating that anti-inflammatory drugs (e.g. intranasal steroids and leukotriene receptor antagonist) could improve both QoL and respiratory sleep parameters. Further studies with medical treatment would be of interest to confirm the efficacy and long-term results.

In general, there is a need for long-term follow-ups. Three- and ten-year follow-ups are planned for the patients who participated in the studies described in **Papers II, II, and IV**. Blood samples and tonsillar tissue from these pediatric patients have been saved. Hopefully, these samples can be analyzed to better understand the etiology of tonsillar growth and potentially lead to new and improved medical treatments.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Obstruktiv sömnapné (OSA) är vanligt hos både vuxna och barn. Tillståndet karaktäriseras av obstruktiva andningsuppehåll, vilket orsakas av trängsel i den övre luftvägen. Andningsuppehållen leder till upphackad sömn med störd sömnkvalitet och perioder med syrebrist. Hos vuxna kan detta exempelvis leda till uttalad dagtrötthet, högt blodtryck och ökad dödlighet i hjärt-kärlsjukdomar, medan det hos barn kan leda till påverkad tillväxt, inlärningssvårigheter och beteendestörningar.

Hos vuxna beror OSA främst på övervikt, men manligt kön, rökning och stigande ålder är också exempel på andra kända riskfaktorer. Förstahandsbehandlingen är CPAP (Continuous Positive Airway Pressure), men svalgkirurgi kan också vara ett alternativ i väl utvalda fall. Även om CPAP har visat sig vara effektivt för att behandla andningsuppehållen är effekten sparsam när det gäller att förbättra blodtrycket. Hur blodtrycket påverkas efter svalgkirurgi är dock mindre känt och detta utvärderades i **delarbete I**.

Hos barn orsakas främst trängseln i de övre luftvägarna av förstorade tonsiller (halsmandlar) och adenoid (körtel bakom näsan). Kirurgi är den primära behandlingen och traditionellt utförs adenotonsillektomi (ATE), vilket innebär att tonsillerna och adenoiden avlägsnas. Det är en beprövad metod med goda resultat, men en del barn har kvarvarande besvär. Övervikt och allvarlig OSA är exempel på riskfaktorer för kvarvarande OSA efter kirurgi. Det finns dock studier på barn som indikerar att adenopharyngoplastik (APP), vilket är en modifierad form av ATE där även de främre och bakre gombågarna sys ihop, förbättrar behandlingsresultaten. APP utvärderades i **delarbete II och III**. Utöver kirurgisk behandling har exspektans även varit klinisk rutin i lindriga fall, då det av klinisk erfarenhet och studier finns chans till spontan förbättring. Trots att det är vanligt att barn yngre än fem år opereras för OSA saknades randomiserade studier som bekräftar nyttan av operation för denna åldersgrupp. Detta utvärderades i **delarbete IV**.

Inom forskning finns det olika typer av studiedesign, men för att dra slutsatser om behandlingseffekt anses randomiserade kontrollerade studier (RCT) vara de med högst bevisvärde. Det övergripande målet med de fyra delarbetena i denna avhandling var att med hjälp av RCT utvärdera och utöka kunskapen om kirurgisk behandling av barn och vuxna med OSA.

Delarbete I var en RCT på vuxna, där effekten på blodtrycket utvärderades efter modifierad uvulopalatopharyngoplastik (UPPP), vilket är en form av svalgkirurgi. I denna studie lottades 65 patienter till antingen UPPP eller till en obehandlad kontrollgrupp. Blodtrycket mättes manuellt direkt på morgonen i samband med varje sömnundersökning. Resultatet visade att gruppen som opererats hade förbättrat sitt blodtryck jämfört med kontrollgruppen efter sex månader. Efter den första uppföljningen erhöll även kontrollgruppen UPPP och intressant nog förbättrades även kontrollgruppen efter att de erhållit kirurgi. Blodtrycket var fortsatt förbättrat två år efter operation för alla opererade patienter, men bortfallet var stort och resultatet måste tolkas med försiktighet.

Delarbete II och III var en RCT på 83 barn med grav OSA, i åldern två till fyra år. I denna studie lottades barnen till APP eller ATE, och följdes upp efter sex månader. De fick utföra polysomnografi (PSG), vilket är en sömnundersökning som anses vara den bästa metoden för att diagnosticera OSA, samt svara på olika frågeformulär. I **delarbete II** utvärderades resultaten från sömnundersökningen och OSA-18, ett livskvalitetsformulär. Båda grupperna förbättrades och APP visade sig inte vara mer effektivt än ATE gällande att minska andningsuppehållen eller förbättra livskvaliteten. I **delarbete III** utvärderades huruvida det fanns någon skillnad gällande smärta, infektion, blödning, tal- och sväljningssvårigheter samt nöjdhet efter operation. Detta bedömdes med hjälp av smärtdagbok, frågeformulär och journalanteckningar. Smärtdagboken fylldes i under tio dagar direkt efter operationen. Resultaten visade väldigt små skillnader mellan grupperna, men till fördel för ATE. De kombinerade resultaten från **delarbete II och III** visar att APP inte är mer fördelaktigt än den traditionella metoden ATE. Därmed bör ATE fortfarande betraktas som den primära behandlingen för annars friska barn med grav OSA.

Delarbete IV var en RCT på 60 barn i åldern två till fyra år med mild till måttlig OSA. De lottades till ATE eller ingen behandling, och utvärderades med polysomnografi och OSA-18. De följdes upp efter sex månader och resultaten visade på små skillnader, med avseende på sömnundersökningen. Däremot visade resultaten att barn med måttliga besvär från början hade en bättre effekt av kirurgi än de med milda besvär. Det var också stora skillnader i förbättrad livskvalitet mellan grupperna till förmån för ATE. Dessa resultat tyder på att barn med måttlig OSA bör erhålla ATE direkt, medan det kan vara en fördel att avvakta med behandling under en period hos barn med god livskvalitet och mild OSA.

10 ACKNOWLEDGEMENTS

I would like to thank my colleagues, patients, friends and family for making this doctoral thesis possible. In particular I would like to thank:

My supervisor and associate professor **Danielle Friberg**, for believing in me and for always being there. I don't know how you do it, but your energy seems bottomless. Also, thank you for your enthusiasm, generosity, and your ability to create memorable moments for me and the entire research team.

My friends and co-supervisors, **Pia Froissart-Nerfeldt** and **Nanna Browaldh**, for all the clever advice, kindness, and for always being positive. You are truly inspiring.

My friend and co-author **Anna Borgström**, for your kindness and clever thoughts. You really paved the way for me with your previous research.

My friend and co-author, **Joar Sundman**. This trip wouldn't have been the same without you. Thank you for always listening to me and giving me thoughtful advice about both work and life.

Johan Bring, co-author and statistical genius, for all the help with the statistics.

Anne-Charlotte Hessen Söderman, for all the help with the study participants.

Lars-Olaf Cardell, professor and Head of the Division of Oto-Rhino-Laryngology at the Department of CLINTEC, for creating an inspiring academic atmosphere.

Previous and present Heads of the Oto-Rhino-Laryngology Department, **Bo Tideholm**, **Sushma Nordemar**, **Alexander Ahlberg**, and Heads of the ENT residency program, **Karin Lundkvist** and **Rusana Bark**, for being encouraging and making it possible for me to do my research.

Agneta Wittlock, for all the help with the bureaucracy of Karolinska Institutet.

All present and former **colleagues** at Oto-Rhino-Laryngology Department. The immense knowledge, collegiality and friendship you have shown me as a resident and PhD student is admirable.

Jakob Enerdal, **Jacob Lien**, **Ann Abrahamsson**, **Gert Henriksson**, and **Magnus Starkhammar**. Without your help with recruiting and operating, these studies wouldn't have been possible.

Mats Holmström, Caroline Gahm and **Henrik Smeds**, for just being who you are, true inspirations in all aspects.

Carina Hedenström, **the staff at the sleep laboratory**, and polysomnographic technologist **Therese Murphy**. You have made my studies possible through your hard work with performing and interpreting the sleep studies in all children.

Secretaries **Ewa Hansson** and **Madeleine Roth Lundfeldt**, for all your professional help.

All friends and teachers from **the research school for doctoral students**. It's an excellent program that should be available for all clinical researchers. I want to especially thank **Robert Szulkin** for making statistics fun and easy to understand.

All my **friends**, you know who you are. Thank you for all the good times and for reminding me what really matters.

Johannes Asplund, for being by my side since day one at medical school. It feels good to know that I can always rely on you.

My **extended family in Finland**. Thank you for all the countless ours you have taken care of our children.

My mother and father, **Ing-Marie** and **Mats Fehrm**. Thank you for everything, a wonderful childhood, and for all the love and support you have given me.

Ida Bergman, my love and life companion. Thank you for your passionate view of life and your ability to make things happen. You have truly enriched my life and given me more than I could have dreamed of. I love you.

My children, **Rut** and **Iris**. You bring me happiness, love and pride. My love for you is bottomless. Your existence has really put everything into perspective. Thank you for reminding me every day what really matters.

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