Upper Airway Surgery in Obstructive Sleep Apnoea -
descriptive, observational and randomised controlled studies

Nanna Browaldh
"Uppvaknandet är ett fallskärmsöpp från drömmen."

Tomas Tranströmer
ABSTRACT

Obstructive sleep apnoea syndrome (OSAS) is a general health problem which causes daytime sleepiness, impaired quality of life and increased morbidity and mortality. A narrow upper airway anatomy is a common cause of OSAS, and tracheostomy was the initial surgical treatment for OSAS. During the 1980s and 1990s uvulopalatopharyngoplasty (UPPP) was the predominant treatment before continuous positive airway pressure (CPAP) and mandibular retaining devices (MRDs) became available in Sweden. The degree of evidence for the efficacy of surgical treatments, especially UPPP, has been very low so far. The results have also varied, depending on the selection of patients and the surgical method. Therefore, randomised controlled trials (RCTs) and long-term follow-up studies in this field have been called for. This thesis evaluates the long-term findings after UPPP in unselected patients, as well as tracheostomy and UPPP (modified, conservative technique) as treatments in selected OSAS patients who have failed other non-surgical treatments and therefore risk remaining untreated.

In Paper 1, a retrospective cohort study of 10 severe and obese OSAS patients, the tolerability of custom-made tracheostomy tubes, nocturnal respiration and excessive daytime sleepiness (EDS) symptoms were evaluated. Eight tolerated the tube for more than 6 months. The oxygen desaturation index (ODI₄) decreased from 81 (range 55–126) to 13 (1–87) and EDS measured with the Epworth Sleepiness Scale (ESS) was reduced from a median of 18 (8–23) to 5 (0–7). Tracheostomy served as a link to other OSAS treatments.

Paper 2 was a 15-year follow-up of 50 OSAS patients after UPPP. In all, 13 patients had died; 26 patients underwent polygraphy recordings. The median ODI₄ had decreased from 26.5 (range 4–82) to 8.5 (0–60) (p < 0.01), a mean reduction of 52%. Sixty-five per cent of patients satisfied the success criteria. One third were objectively categorised as non-snorers. The median BMI was unchanged. The questionnaires were answered by 32 of 37 patients; 88% reported improved or cured EDS and 78% were satisfied. The median ESS score 15 years after UPPP surgery was 6 (0–19). Pharyngeal disturbance ratings were low. The standardised mortality rate did not differ from that of the general Swedish population.

Paper 3 was a prospective RCT called Sleep apnoea Karolinska UPPP (SKUP³), with two parallel arms and stratification by Friedman stage and BMI. Sixty-five consecutively included patients with moderate to severe OSAS, BMI < 36 kg/m², ESS ≥ 8, Friedman stage I or II. Sixty-five patients were randomised to intervention (UPPP) or control (expectancy and UPPP after a delay of six months). The mean AHI measured by polysomnography in the intervention group had
significantly decreased by 60%, from 53.3 (sd 19.7) to 21.1 (16.7). In the control group, the mean AHI decreased by 11%, from 52.6 (21.7) to 46.8 (22.8), a significant difference between the groups. The mean time in the supine position and BMI were unchanged in both groups. Subgroup analyses of Friedman stage, BMI group and tonsil size all showed significant reductions of AHI in the intervention group, compared to controls. There were no severe complications after surgery.

In Paper 4 the same SKUP³ subjects were evaluated concerning changes in the ESS and the quality of life, as well as in vigilance tests. The mean ESS in the intervention group decreased significantly from 12.5 (sd 3.2) to 6.8 (3.9), but there was a non-significant change in the control group. Significant differences between groups in favour of UPPP involved changes in the ESS, several SF-36 domains (general health, vitality and social functioning), as well as in sleep latency. Changes in the ESS correlated significantly with changes in vitality, social functioning and sleep latency, as well as with changes in the AHI, nadir O₂ and the arousal index.

In summary, tracheostomy may constitute an alternative treatment in obese patients with severe OSAS. The improvements in nocturnal respiration and daytime sleepiness after UPPP appeared to remain stable after 15 years. UPPP may also have a protective role against mortality. The SKUP³ showed that modified UPPP significantly improved respiratory parameters, daytime sleepiness and the quality of life, compared to controls. Since upper airway surgery appears to be effective and safe, it should be offered to selected OSAS patients.
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LIST OF PUBLICATIONS

This thesis is based on the following papers:

1. **Nanna Browaldh**, Agneta Markström, Danielle Friberg
   Elective tracheostomy is an alternative treatment in patients with severe obstructive sleep apnoea syndrome and CPAP failure

2. **Nanna Browaldh**, Danielle Friberg, Eva Svanborg, Pia Nerfeldt
   15-year efficacy of uvulopalatopharyngoplasty based on objective and subjective data

   SKUP³ randomised controlled trial: polysomnographic results after uvulopalatopharyngoplasty in selected patients with obstructive sleep apnoea.

4. **Nanna Browaldh**, Johan Bring, Danielle Friberg
   Uvulopalatopharyngoplasty reduces daytime sleepiness and improves the quality of life and vigilance in obstructive sleep apnoea syndrome: SKUP³, a randomised controlled trial
   Submitted.

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<thead>
<tr>
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<tr>
<td>AASM</td>
<td>American Academy of Sleep Medicine</td>
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<tr>
<td>AHI</td>
<td>Apnoea-hypopnoea index</td>
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<td>ASA</td>
<td>American Society of Anesthesiologists</td>
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<tr>
<td>BiPAP</td>
<td>Bi-level pressure device</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>BNSQ</td>
<td>Basic Nordic Sleep Questionnaire</td>
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<tr>
<td>BP</td>
<td>Bodily pain</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>CPAP</td>
<td>Continuous positive airway pressure</td>
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<td>dB</td>
<td>decibel</td>
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<td>DISE</td>
<td>Drug-induced sleep endoscopy</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<td>EDS</td>
<td>Excessive daytime sleepiness</td>
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<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<td>EMG</td>
<td>Electromyogram</td>
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<tr>
<td>EOG</td>
<td>Electro-oculogram</td>
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<tr>
<td>ESS</td>
<td>Epworth Sleepiness Scale</td>
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<td>FOSQ</td>
<td>Functional outcomes of sleep questionnaire</td>
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<td>GH</td>
<td>General health</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
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<tr>
<td>ITT</td>
<td>Intention-to- treat</td>
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<tr>
<td>LAUP</td>
<td>Laser-assisted uvulopalatoplasty</td>
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<td>LUPP</td>
<td>Laser uvulopalatoplasty</td>
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<tr>
<td>MCS</td>
<td>Mental component summary</td>
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<tr>
<td>MH</td>
<td>Mental health</td>
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<tr>
<td>MRD</td>
<td>Mandibular retaining device</td>
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<td>MSLT</td>
<td>Multiple sleep latency test</td>
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<td>MWT</td>
<td>Maintenance of wakefulness test</td>
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<tr>
<td>MWU</td>
<td>Mann-Whitney U</td>
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<tr>
<td>NRC</td>
<td>National Respiration Centre</td>
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<td>ODI</td>
<td>Oxygen desaturation index</td>
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<td>OHS</td>
<td>Obesity hypoventilation syndrome</td>
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<tr>
<td>ORL</td>
<td>Oto-rhino-laryngology</td>
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<td>OSA</td>
<td>Obstructive sleep apnoea</td>
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<td>OSAS</td>
<td>Obstructive sleep apnoea syndrome</td>
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<td>OSLER</td>
<td>Oxford sleep resistance</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>PCS</td>
<td>Physical component summary</td>
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<tr>
<td>PG</td>
<td>Polygraphy</td>
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<td>PF</td>
<td>Physical functioning</td>
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<td>PSG</td>
<td>Polysomnography</td>
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<td>QoL</td>
<td>Quality of life</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<td>RDI</td>
<td>Respiratory disturbance index</td>
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<tr>
<td>RE</td>
<td>Role emotional</td>
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<td>REM</td>
<td>Rapid eye movement</td>
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<td>RERA</td>
<td>Respiratory effort-related arousal</td>
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<td>RP</td>
<td>Role physical</td>
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<tr>
<td>SBU</td>
<td>Swedish Council on Technology Assessment in Health Care</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>SDB</td>
<td>Sleep disordered breathing</td>
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<td>SF</td>
<td>Social functioning</td>
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<td>SF-36</td>
<td>Short form-36</td>
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<tr>
<td>SIR</td>
<td>Standardized incidence ratio</td>
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<td>SKUP³</td>
<td>Sleep Apnoea Karolinska UPPP</td>
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<td>SMR</td>
<td>Standardised mortality ratio</td>
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<tr>
<td>SRC</td>
<td>Spearman’s rank correlation</td>
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<tr>
<td>TST</td>
<td>Total sleep time</td>
</tr>
<tr>
<td>UPP</td>
<td>Uvulopalatoplasty</td>
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<tr>
<td>UPPP</td>
<td>Uvulopalatopharyngoplasty</td>
</tr>
<tr>
<td>VT</td>
<td>Vitality</td>
</tr>
<tr>
<td>WMP</td>
<td>Wilcoxon matched-pairs</td>
</tr>
<tr>
<td>WSR</td>
<td>Wilcoxon signed-rank (same as WMP)</td>
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INTRODUCTION

Summarised introduction to the present studies

Obstructive sleep apnoea syndrome (OSAS) is a common disease, with a prevalence of 2% in females and 4% in males.1 The syndrome is defined by repetitive upper airway obstruction during sleep, which reduces the airflow during inspiration, despite a continued respiratory effort. These obstructive hypopnoeas and/or apnoeas result in fragmented sleep, frequent awakenings, and even oxygen desaturation. The quality of life is affected with an increased risk of poor sleep quality, excessive daytime sleepiness (EDS) and an increased risk for traffic accidents.2 This also leads to an augmented risk of developing cardiovascular diseases, stroke and death.3-5

Patients with OSAS can be treated in several alternative ways: especially continuous positive airway pressure (CPAP) or a mandibular retaining device (MRD), and more seldom surgically; mainly uvulopalatopharyngoplasty (UPPP) or, in very severe cases, tracheostomy. The treatment of OSAS in adults is a challenge since the compliance with non-surgical treatments like CPAP device and MRD is approximately 56–68% after 4–5 years,6,7 and therefore many patients risk remaining untreated. These patients could be offered surgery. Although UPPP was the predominant treatment for OSAS before CPAP was generally available, there is a lack of randomised controlled trials (RCTs). Furthermore, the efficacy of UPPP in OSAS treatment has been questioned, also in the long-term perspective. The Swedish Council on Technology Assessment in Health Care (SBU) report on OSAS from 20078 and the Cochrane report on OSAS surgery from 20059 draw the conclusion that more studies on surgical treatment for OSAS need to be done. As for all surgical interventions, the possibility of making blinded studies is difficult and therefore the evidence for efficacy is limited. However, the reports from SBU and Cochrane have been a wake-up call for the Oto-Rhino-Laryngology (ORL)-specialty and an inspiration for this thesis, as they have called attention to the insufficient scientific evidence concerning the efficacy of upper airway surgery in OSAS treatment. Furthermore, they have highlighted the difficulties connected with evaluating efficacy, side-effects and complication rates when different outcomes, surgical techniques and multilevel procedures have been used.

The overall aim of this thesis was to evaluate upper airway surgery, with short and long-term follow-up times in OSAS patients, using descriptive, observational and randomised controlled studies.
Clinical background of OSAS

SDB, OSA, OSAS and OHS
Sleep disordered breathing (SDB) includes a wide range of sleep-related breathing disorders, snoring and mouth breathing, OSAS. The mechanism is characterised by sleep-induced muscle relaxation, leading to partial or complete upper airway obstruction despite continuous or increased breathing efforts. The sleep pattern is fragmented, mainly due to the arousals as a result of the obstructive breathing. As a consequence, symptoms of daytime sleepiness often follow, and the condition is then defined as OSAS. Obstructive sleep apnoea (OSA) is the laboratory diagnosis after sleep recording without paying attention to the patients’ daytime symptoms. The narrow pharyngeal airway predisposes to snoring, increased respiratory resistance and obstructive episodes of sleep apnoea, but OSA and OSAS are not only to be regarded as a local abnormality of the respiratory track, but also more of a systemic illness, discussed further below. The term SDB also includes central sleep apnoea syndromes, characterised by disturbances in the respiratory effort, without obstructive mechanisms. See figures 1 and 2 for a sleep registration in a healthy person and a person with OSA.

Obesity hypoventilation syndrome (OHS) has clinical features such as obesity, daytime hypoventilation and SDB in the absence of an alternative neuromuscular, mechanical or metabolic explanation for hypoventilation. The syndrome was initially termed the Pickwickian syndrome. Studies have reported a prevalence of OHS between 10 and 20% in obese patients with OSA and the prevalence of OHS is higher in the subgroup of patients with OSA combined with extreme obesity. The mechanisms that lead to hypoventilation and hypercapnia in OHS are most likely multifactorial and include the presence of SDB and a blunted central response to hypercapnia and hypoxia. Most patients with OHS have underlying upper airway obstruction and a symptomatology with daytime sleepiness similar to that reported in OSAS.

Prevalence
The prevalence of OSAS varies across different definitions and different study populations, but it is assumed to be 4% in males and 2% in females also in Sweden, which is similar to the figures in the USA during the 1990s. The prevalence of OSA without daytime symptoms was 17–26% in males and 9–28% in females in previous studies from abroad. Surprisingly, the prevalence of OSA in Swedish females from Uppsala County was shown to be very high (50%) in a recent epidemiological study. Obesity, older age and hypertension were risk factors. The prevalence of OSA, as well as the severity of the disease according to the apnoea-hypopnoea index (AHI), seems to increase with age in both males
Figure 1. Normal polygraphy.

Figure 2. Polygraphy in a patient with obstructive sleep apnoea. Note the repetitive obstructive apnoeas causing severe oxygen desaturations.
and females, although males have a higher prevalence of OSA.\textsuperscript{1,16} The gender differences for the prevalence rates are further discussed under pathophysiology and risk factors below.

**Incidence and progression**
The incidence of OSA is also described as being higher in males than in females. The Sleep Heart Health Study concluded that the incidence for at least moderate OSA with AHI > 15 was 11\% in males and 5\% in females over a period of 5 years.\textsuperscript{19} Several studies concluded that weight gain was a critical factor in the progression of the disease.\textsuperscript{19,20} Additional factors for the progression of OSA in adults may be pharyngeal neuromuscular impairment due to mechanical trauma and related inflammation in the pharyngeal upper airways as a consequence of the vibration and stretching related to snoring.\textsuperscript{21,22}

**Pathophysiology and risk factors**
During sleep the muscular tone naturally decreases. All mechanisms or factors that have the capability to aggravate the increased upper airway lumen resistance during sleep add to the risk of airway collapse. The main risk factors for OSA are decreased patency of the upper airway for obstructive reasons, obesity and male gender.\textsuperscript{1,23,24} Further important risk factors for OSA are advanced age, a family history of OSA, alcohol, smoking\textsuperscript{25} and reflux.\textsuperscript{26}

**Age**
The prevalence of OSA increases with age.\textsuperscript{16-18} Among several different age-dependent factors, Malhotra et al.\textsuperscript{27} found an age-dependent decrease in the response to negative pressure, an increased deposition of parapharyngeal fat, a lengthening of the soft palate and change of the shape of the bones surrounding the pharynx. All these findings could predispose to an upper airway collapse during sleep.

**Gender**
A higher prevalence of OSAS with a ratio of 2 to 3:1 for males compared to females in general population has been reported,\textsuperscript{28} but the differences between the genders seem to decrease with age.\textsuperscript{29} Many different reasons for the higher prevalence of OSAS in males have been discussed. White et al. reported that despite the larger upper airway dimensions in males, the breathing resistance is relatively higher.\textsuperscript{30} Furthermore, Schwab et al. suggest that gender differences may be dependent on a higher resting tone of pharyngeal dilatators in females, different fat distributions and other anatomical factors.\textsuperscript{31} There are also studies that suggest that female hormones could be protective.\textsuperscript{29,32}
Other possible explanations for the higher clinical male ratio may be differences in occupational, environmental and health risk factors between genders. In sleep clinic populations, the male predominance is higher than in general population-based samples, as reported by Lindberg et al. Hypothetically, females could present with different symptoms of OSA from males, or the symptoms are misdiagnosed with other illnesses, for example, depression. Although in a study by Young et al., significant differences between reported symptoms in males and females were not seen.

**Upper airway anatomy in OSAS patients**

Snoring and apnoeas are signs of upper airway obstruction. The main obstructive sites in OSA are retropalatal, retroglossal and hypopharyngeal or a combination of several sites. The negative intraluminal pressure generated during inspiration and the Bernoulli principle result in a suction force, especially around these main narrow anatomical sites. All anatomical factors that contribute to the upper airway narrowing during sleep may increase the risk of collapse. Macroglossia, excessive mucosa in the posterior pharyngeal walls, large tonsils, and elongation of the uvulopalatal region, nasal obstruction and deformity or disproportion of the facial skeleton are all possible structural upper airway narrowing factors. Among OSA patients, palatal tonsil hypertrophy amounts to only about 6%, as reported in one study by Dahlqvist et al. The study comprised of 801 snoring males and females referred for evaluation of sleep apnoea. It showed that large tonsils, a high tongue and a wide uvula in males and large tonsils and mandibular retrognathia in females were found to be independent factors associated with an AHI > 15. The authors concluded that these anatomical findings were unreliable for predicting OSA among snorers being investigated for suspected sleep apnoea. Another study on the anatomical associations connected with OSA investigated 420 patients who had been referred to a sleep clinic because of anatomical abnormalities of the oropharynx. After adjusting for the body mass index (BMI) and neck circumference, only enlarged tonsils and lateral narrowing of the pharyngeal walls were found to be significant, but not an enlarged uvula, a low-lying soft palate, retrognathia or overbite. Furthermore, a study showed that significant predictors of OSA in non-obese females were a low soft palate, retrognathia and a uvula touching the posterior wall in the supine position.

**Overweight**

Overweight is one of the main single risk factors for SDB. Forty per cent of obese males have OSAS and 70% of OSAS patients are obese. There are also studies that report that changes in AHI are related to changes in weight: a 10% weight gain in patients with SDB increases AHI by 32% and, conversely, that a 10% weight loss is associated with a 26% decrease in the AHI. Ciscar et al. noted in their study that OSAS patients have more fat in the lateral pharyngeal
walls than non-OSAS patients with similar BMIs. Patients with extreme obesity also risk developing OHS.

There are discussions as to whether OSAS is an anatomical disorder or not. Obesity may affect the anatomy, including the upper airway anatomy, but it could also play a role through its metabolic activity, just as in the metabolic syndrome. In the article by Vgontzas et al., the authors concluded that obesity may contribute to the pathogenesis of sleep apnoea, sleepiness and the associated cardiovascular co-morbidities.

**Heredity**

Heredity has also been suggested to predispose to OSAS. In a study of 2350 OSAS patients from Iceland, the risk ratio for a first-degree relative of a patient with OSAS was 2.0. An epidemiological study from our group showed an increased risk in adult siblings of having a hospital diagnosis of OSAS (standardised incidence ratio, SIR, 3.3). Apart from heredity, the result may be influenced by increased awareness in OSAS families. Another study from our group concluded that there was familial clustering of SDB among parents and their children.

**Smoking, alcohol and reflux**

Mechanisms contributing to the airway collapse are inflammation and oedema of the pharyngeal mucosa caused by smoking, alcohol consumption or gastroesophageal reflux.

Several studies have reported that current smoking is associated with an increased risk of OSA. The Wisconsin Sleep Cohort Study showed a 4.4 times increased risk of moderate to severe OSA in smokers compared to non-smokers.

Alcohol decreases muscle tone and increase the AHI and hypoxaemia in otherwise normal men. The prevalence of alcohol abuse did not differ from that of approximately 10% in the general population in Sweden according to a study from our group.

**Snore-induced mechanical damage and local neuropathy**

To prevent the upper airway from collapse during sleep, several nerves and muscles are activated. The vibrations from snoring may cause local nerve lesions that gradually lead to a collapse of the pharyngeal upper airway. Furthermore, several studies from our group indicate an impaired pharynx dilatation reflex owing to nerve lesions, abnormal pharyngeal muscles and inflammation. The degree of muscular as well as sensory neuropathy in the upper airway correlated with the degree of OSA.
Supine sleep
In general, the frequency and severity of apnoea increase in the supine position owing to the force of gravity that predisposes the tongue and mandible to falling backwards. Fifty-six per cent of patients with OSA have position-dependent OSA (defined as a difference of 50% or more in AHI for supine and non-supine positions), as reported by Oksenberg et al.52 Furthermore, young, thin patients with mild to moderate OSA were more likely to have position-dependent OSA than older, obese patients with severe OSA. In a recently published study by Sunnergren et al., it was found that more than 50% of the studied population of 265 subjects had position-dependent OSA, suggesting that variations in supine time between nights can cause large AHI variations.53 This can influence the night-to-night variability described under Diagnosis of OSAS below.

Morbitidy and mortality
OSAS is a risk factor for cardiovascular disease, including hypertension and stroke, but also for the metabolic syndrome, diabetes, gastro-oesophageal reflux and pharyngeal disturbances.3, 26, 39, 54-56 Furthermore, the risk for traffic accidents is also increased in OSAS.2 The evidence is particularly well-documented and strong for cardiovascular disease, three major mechanisms having been described.57 Primarily, the arousals following apneas and hypopneas lead to sympathetic nervous system over-activity and increased levels of catecholamines. Secondly, the balance of partial pressures of blood oxygen and carbon dioxide induced by the obstructive breathing events is disturbed. Finally, there is an increase in the negative intrathoracic pressure caused by the continuous breathing against the occluded airway. The pathogenesis of cardiovascular disease in OSAS is probably multifactorial, thus it also includes endothelial dysfunction, abnormal coagulation, increased inflammation activity and metabolic dysregulation.58

Hypertension
The prevalence of OSA is about 30–83% among patients with hypertension.57 In the Wisconsin Sleep Cohort Study, Peppard et al. reported a dose-response relationship between the severity of SDB at baseline and hypertension at the four-year follow-up. The odds ratio for development of hypertension in patients with an AHI >15 was 2.9, compared to patients with AHI = 0, independently of known confounding factors.56 In patients with resistant hypertension, OSA is particularly common.59

Cardiovascular disease and stroke
A large observational study by Marin et al. showed that the incidence of fatal and non-fat...
coronary insufficiency requiring an invasive intervention) in untreated patients with severe OSA was significantly three times higher than in a matched control group from the general population. Furthermore, CPAP treatment significantly reduced the cardiovascular risk.

The prevalence of OSA is reported to be 11–37% in patients with congestive heart failure and 43–72% in patients with stroke, and stroke can both precede and follow the stroke event. The Wisconsin Sleep Cohort found that an AHI > 20 led to an odds ratio of 4.3 for the risk of stroke, compared to an AHI < 5 during the 4-year follow-up.

**Diabetes and the metabolic syndrome**

Punjabi et al. reported that OSA is a risk factor for developing glucose intolerance, insulin resistance and type 2 diabetes. In the Swedish community-based cohort of 141 males without diabetes at baseline studied by Lindberg et al., it was found that an ODI > 5 at baseline was a predictor of developing diabetes, with an odds ratio of 4.4 after adjustment for known confounders. Both the prevalence and incidence of diabetes increased with increased levels of SDB at baseline, but they may be confounded by obesity.

**Gastro-oesophageal reflux and pharyngeal disturbances**

Gastro-oesophageal reflux has been reported to be higher in OSAS patients than in the normal population. Different mechanisms may be repeated increases in negative intrathoracic pressure or transient lower oesophageal sphincter relaxation. A longitudinal population-based study by Emilsson et al., showed that persistent symptoms of nocturnal gastro-oesophageal reflux significantly contributed to the development of respiratory symptoms (odds ratio, 3.0). Treatment with proton pump inhibitors has also significantly decreased the level of AHI in OSA patients with gastro-oesophageal reflux, as shown by Friedman et al.

Our group has previously evaluated the results from UPPP patients both pre- and postoperatively and demonstrated no increased rating of pharyngeal discomfort postoperatively, with a median value of 5. However, in a non-snoring age-, BMI- and gender- matched control group, the median value was only 1. This difference indicates a certain amount of discomfort already before surgery among the OSAS patients, possibly owing to the vibrational trauma and obstructive tension of the pharyngeal tissue.

**Traffic accidents**

There is a 3 to 7-fold increased risk for traffic accidents in OSAS patients, compared to normal subjects, already at AHI > 5. Although sleepiness is a common
risk for traffic accidents, several studies found that the association between OSA and traffic accidents is not dependent on sleepiness. In a study by Haraldsson et al., the risk for single-car accidents returned to normal after treatment with UPPP.

**Mortality**

OSAS is associated with an increased mortality rate. The Wisconsin Sleep Cohort Study with a follow-up period of 18 years showed an association between both all-cause mortality (hazard ratio, HR, 3.0) and cardiovascular-related mortality (HR, 5.2) in OSA patients after adjusting for potential confounders. Similar results were shown in a study by Marshall et al., which reported an increased risk of all-cause mortality (HR, 6.24) in patients with moderate to severe OSA in a 14-year follow-up. Marin et al. demonstrated in a 10-year follow-up that in patients with an AHI > 30, the increased risk for cardiovascular death was 2.87. Furthermore, simple snorers and OSAS patients under CPAP treatment showed similar morbidity and mortality rates to those in the general population. A Swedish population-based study showed that there was an increased mortality rate of 2.7 in men < 60 years of age with both snoring and EDS compared to men without snoring or EDS, adjusted for age. There are also studies reporting declining mortality rates in elderly men with moderate to severe sleep apnoea and that older patients with mild and moderate OSA had a lower mortality rate than the matched population.

**Symptoms of OSAS**

Many different symptoms are connected with OSAS, and in the following segments, EDS and the quality of life (QoL) will be discussed. Many different causative factors could have an impact on EDS and QoL; for example, age, physiological and psychological diseases, depression, family situation and sleeping habits. Also depression, obesity and the metabolic syndrome have been suggested to be major factors associated with EDS. A clinical examination including various questionnaires is often used to exclude other reasons for EDS. The answers to the question concerning which factors may cause the symptoms in OSAS are probably multidimensional.

**Daytime sleepiness**

The cardinal symptoms of OSAS are EDS and/or fatigue, which may affect daily activities and QoL. Patients who are referred to a sleep clinic for evaluation of OSAS often describe symptoms of EDS, a lack of energy and/or a sense of unrefreshing sleep. The Wisconsin Sleep Cohort Study reported that 23% of females and 16% of males with an AHI > 5 reported sleepiness at least two days a
week. In subjects without SDB, the corresponding figures were 10% and 3%, respectively.\textsuperscript{1} The occurrence of EDS in patients with OSAS has been ascribed to nocturnal hypoxaemia, sleep fragmentation, or both.\textsuperscript{72} The Sleep Heart Health Study reported significant associations between EDS (measured on the Epworth sleepiness scale, ESS), snoring and the respiratory disturbance index (RDI), respectively.\textsuperscript{73, 74} Furthermore, Goncalves et al. showed that ESS scores correlated significantly with the arousal index and the AHI and negatively with the nadir of oxygen saturation.\textsuperscript{75}

There is, however, often a discrepancy between objective signs and symptoms related to OSAS. Weaver et al. investigated whether polysomnography indexes were associated with EDS (measured with the ESS) and QoL (measured with the Short-form 36, SF-36, and the Functional Outcomes of Sleep Questionnaire, FOSQ) in mild to moderate OSAS patients.\textsuperscript{76} The patients were randomised to either surgical treatment with radiofrequency tongue and palate reduction or sham surgery. The authors concluded that there was a poor correlation between polysomnography (PSG) indexes and associated sleepiness, QoL or reaction time, measured both at baseline and as changes in the outcome. Roure et al. investigated patients with an AHI > 5 (measured with PSG) with (ESS > 10) or without (ESS < 10) symptoms of EDS.\textsuperscript{72} There were differences between groups regarding several parameters. For example, total sleep time, sleep efficiency, the AHI and the arousal index were all significantly higher and the nadir of oxygen saturation was significantly lower in the group with EDS symptoms. The authors concluded that although patients with EDS showed worse respiratory and sleep disturbances, sleep apnoea and sleep disruption are not the primary determinants of EDS in all patients. Furthermore, Vgontzas et al.,\textsuperscript{12} suggested that inflammatory cytokines are mediators of EDS and that sleep apnoea and sleepiness may be a manifestation of the metabolic syndrome.

Quality of Life
Both the Wisconsin Sleep Cohort Study and the Sleep Heart Health Study have shown associations between the SF-36 and the degree of OSA, and the results from the SF-36 were comparable to those for patients with other chronic diseases.\textsuperscript{77, 78} Patients with OSA also had an impaired QoL compared to an age- and gender-matched control group.\textsuperscript{79} The PSG parameter arousal index is also found to correlate significantly with several subscales of the SF-36.\textsuperscript{75} The SBU-report concluded that there was an improvement in the vitality domain of the SF-36 after CPAP treatment, but only a few studies were available and the scientific evidence was insufficient.\textsuperscript{8}
Diagnosis of OSAS

The evaluation of OSAS is multidimensional. The individual view concerning the quality of sleep is highly subjective and it is often described as undisturbed and restorative. Based on the laboratory and clinical perspective, it can be measured with polygraphic or polysomnographic recordings, and the evaluation of EDS will also be described in more detail below. There are disadvantages with all types of tests and therefore it is important to keep in mind that questionnaire are sensitive to recall bias, motivation, degree of education, and fatigue, as well as personality. Objective tests are often more expensive and complicated and have poor availability. Furthermore, correlations between different evaluations of OSAS are not necessarily concordant, and this also applies to the perspective of daily life. The definitions of both OSA and OSAS have changed over the years and a new version of the guidelines for classifications appeared in 2013. In the following, the guidelines for OSAS from 1999 (used in this thesis) and for OSA, adult from 2005 will be described in detail (Box 1 and 2). Furthermore, the revised criteria for scoring hypopnoeas from 2007 will be described.

Evaluation of sleep

The diagnostic criteria for OSAS according to the American Academy of Sleep Medicine (AASM) 1999 are presented in box 1 below.

**Box 1. Definition of obstructive sleep apnoea syndrome suggested by American Academy of Sleep Medicine in 1999 (AASM 1999)**

The individual must fulfill criterion A or B, as well as criterion C.

A. Excessive daytime sleepiness that is not better explained by other factors.

B. Two or more of the following that are not better explained by other factors:
   – choking or gasping during sleep
   – recurrent awakenings during sleep
   – unrefreshing sleep
   – daytime fatigue
   – impaired concentration.

C. Overnight monitoring demonstrating five or more obstructive breathing events per hour during sleep. These events may include any combination of obstructive apnoeas/hypopnoeas or respiratory effort-related arousals.
The severity of OSAS has two components: severity of daytime sleepiness and severity of laboratory sleep recording according to the level of obstructive breathing events:

1. Mild: 5–14.9 events/hour
2. Moderate: 15–29.9 events/hour
3. Severe: > 30 events/hour

The rating of severity for the syndrome should be based on the most severe component.

**Box 2. International Classification of Sleep Disorders. Diagnostic criteria for obstructive sleep apnoea 2005 (AASM 2005)**

A, B and D or C and D satisfy the criteria:

**A.** At least one of the following applies:
  i) The patient complains of unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue or insomnia,
  ii) The patient wakes with breath holding, gasping, or choking,
  iii) The bed partner reports loud snoring, breathing interruptions, or both during the patient’s sleep.

**B.** Polysomnographic recordings shows the following:
  i) Five or more scoreable respiratory events (i.e., apnoeas, hypopnoeas, or respiratory effort related arousals, RERAs) per hour of sleep.
  ii) Evidence of respiratory effort during all or a portion of each respiratory event (in the case of a RERA, this is best seen with the use of esophageal manometry).

**OR**

**C.** Polysomnographic recording shows the following:
  i) Fifteen or more scoreable respiratory events (i.e., apnoeas, hypopnoeas, or RERAs) per hour of sleep.
  ii) Evidence of a respiratory effort during all or a portion of each respiratory event (in the case of a RERA, this is best seen with the use of esophageal manometry).

**D.** The disorder is not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder.
Definition of parameters according to AASM 2007:

The AHI is the total number of ≥90% decreases in airflow compared to baseline (apnoea) and partial obstructions (hypopnoea) of breathing occurring per hour of sleep. The event must last for at least 10 seconds and is associated with a decrease in oxygenation of the blood. In general, the AHI is used to classify the severity of disease.

**Hypopnoea** Criteria A (used at polygraphy, PG, in Paper 2)
- ≥30% flow limitation at the nasal cannula and
- ≥4% desaturation or an arousal

**Hypopnoea** Criteria B (used at PSG in Papers 3 and 4)
- ≥50% flow limitation at the nasal cannula and
- ≥3% desaturation or an arousal

**Respiratory effort-related arousal** (RERA) (used at PSG in Papers 3 and 4)
- <30% flow limitation at the nasal cannula and
- arousal

**Respiratory disturbance index** (RDI): AHI plus RERA index (events per sleep hour).

**Oxygen desaturation index** (ODI) is the average number of oxygen desaturations per hour of sleep. The desaturations can be measured at different levels compared to baseline. ODI 4% (ODI₄) is used in Papers 1 and 2, and ODI 3% (ODI₃) in Papers 3 and 4.

**Diagnostic levels**
A nocturnal sleep investigation using PSG is the golden standard for determining respiratory events. This recording includes an electroencephalogram (EEG), an electro-oculogram (EOG), an electromyogram (EMG), an electrocardiogram (ECG), airflow, respiratory effort, oxygen saturation and body position. The PSG can be done in a sleep laboratory (level 1), as in Papers 3 and 4, or at home when the heart rate might substitute for ECG (level 2).

A full PSG measures both sleep and breathing parameters. The advantages of PSG compared to PG are mainly that PSG measures the arousals caused by obstructive events and the exact time of sleep, which enables a more exact calculation of the respiratory and sleep events. PSG is resource-demanding and costly and therefore the simplified ambulant PG (level 3) is widely used. The device should record ventilation (at least two channels of respiratory effort or airflow...
and one respiratory effort channel). ECG or heart rate and oxygen saturation should also be recorded. The PG used in Papers 1 and 2 included nasal respiratory airflow, respiratory effort belts (thorax and abdomen), ECG and oxygen desaturation. The same equipment was used in Paper 2 after 15 years as in the previous follow-ups after 6 months and 2 and 4 years. See figures 3 and 4 for examples of PG and PSG.

The disadvantage with PG is that the total sleep time risk can be estimated to be longer than the actual true sleep time. This means there is a risk of diluting the AHI, which will actually be lower than the true AHI. Furthermore, since PG lacks EEG, EOG and EMG, arousals and sleep stages cannot be measured. This risk of a lower rate of both hypopnoeas and RERA events and sleep fragmentation is not truly evaluated. To enhance the estimation of sleep time in PG, the subjects in a study by Santos-Silva et al. were told to record when they went to sleep, wake-up time and wake-up periods of more than 15 minutes. This study showed strong correlations between AHI recorded with both PG and PSG. Additionally, a study by Franklin and Svanborg reported that the correlation between PSG-recorded sleep time and subjective sleep time is adequate, even though the individual differences are large. In a clinical study from our group, patients with 'normal' PGs and symptoms of tiredness and/or sleepiness, as well as snoring, underwent PSG, and 90% had at least a mild degree of OSAS. In the clinical situation, it is therefore important to offer PSG to patients with EDS and snoring when PG is 'normal', as PG cannot exclude OSAS. See figure 5 for an example of PSG recording.
Night-to-night variability and sleeping position
The night-to-night variability between recordings may vary for different reasons: for example, sleeping position, intake of alcohol, but also getting used to the equipment. One way to enhance the diagnostic precision is to perform recordings on at least two consecutive nights. Bittencourt et al. showed in a study with 20 subjects that there was no significant difference between the mean AHI on four recorded nights, but a substantial individual variability, and 50% of the subjects showed a change in the degree of OSA severity from the first night to the following nights. Conversely, a review published by the SBU concluded that the AHI shows good agreement between two nights of PSG. Also Mendelson et al. found that one night of PSG should generally be sufficient and, in 50 patients with suspected OSA, the correlation of the AHI between nights was high (r = 0.86).

Figure 5. Polysomnographic recording of a patient with obstructive sleep apnoea. An obstructive apnoea is marked with a rectangle, followed by an arousal shown in EMG of the chin and EEG channels, arrows.

Subjective evaluation of daytime sleepiness
EDS can be evaluated in several different ways, including both subjective and objective measurements. ESS is the most frequently used subjective sleepiness assessment test for OSAS. The version of the ESS used was translated into Swedish upon request by the Swedish Society for Sleep Research and Sleep Medicine. It has been back-translated into English and approved by M.W. Johns.
The ESS is a self-administered eight-item questionnaire pertaining to the propensity to fall asleep in different situations in daily life. The questionnaire evaluates the situation during the past two weeks and the items are presented in scales of 0–24. The interpretation of the scale results varies among studies, but in some studies an ESS score of 8–10 is called mild sleepiness, 11–15 moderate sleepiness, 16–20 severe sleepiness and 21–24 excessive sleepiness.

The advantages of the ESS are that it is designed to reflect the patient’s subjective symptoms, and it is inexpensive and easy to administer. It is useful individually when evaluating the effect of treatment on EDS. However, a study by Nguyen et al. found that when the ESS questionnaire was administered twice with a few months’ interval, 23% had a difference of at least 5 scale points. Results from the Sleep Heart Health Study showed that ESS ratings correlated positively with the AHI, but patients with the worst apnoeas had a mean ESS score of 9, compared to normal subjects with a mean score of 7. Yaremchuk et al. studied the relationship of the ESS and the AHI and found that the only significant predictor of the change in the ESS was the initial ESS score and that the AHI was not related to the change in the ESS. Another weakness of the ESS is the risk of recall bias. Furthermore, a small, but reproducible differential item functioning (a subject’s response to the item is affected by other aspects than that which the test is intended to assess) for age has been described.

Another questionnaire for evaluating EDS is the Basic Nordic Sleep Questionnaire (BNSQ), which consists of 21 main questions about sleep, stressing how many occasions per week something has occurred during the past three months. The BNSQ was developed to create a standardised questionnaire for Nordic countries. The Karolinska Sleepiness Scale and the FOSQ are also frequently used in sleep studies.

Objective evaluation of daytime sleepiness

The objective tests of EDS are often time- and facility-demanding and are therefore difficult to use in clinical practice. The Multiple Sleep Latency Test (MSLT) measures the ability to fall asleep and consists of a 20-minute test, which is repeated four to five times with two-hour intervals. The Maintenance of Wakefulness Test (MWT) measures the ability to stay awake during 40 minutes and is repeated four times a day. Both tests record sleep latency with EEG, EOG and EMG.

The Oxford sleep resistance (OSLER) test is an objective sleepiness test suitable for OSAS patients. It has been shown to distinguish normal sleep subjects from OSAS patients as well as the traditional test, the MWT. The OSLER test is performed in a dark room, isolated from external noise. The original test is...
performed 4 x 40 minutes during one day and the patient is asked to remain awake and press a switch in response to a small illuminated light, lit every three seconds. When the patient fails to respond for 21 seconds, the test is ended, and it is understood that the patient is asleep. The standard analytical purpose of the OSLER test is to determine sleep latency, measured as the delay before seven consecutive flashes without a response. The test is less expensive and easier to use, although it does not involve EEG. A modified OSLER test was used in Paper 4. The associations between objective and subjective measurements of EDS are not always coherent.99

Evaluation of Quality of Life

The health survey SF-36 covers 8 domains of health-related quality of life measurements (HRQoL) for evaluation of the last four weeks. The domains are: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). Scores from each subscale range from 0 to 100, and a higher score indicates a better HRQoL.100 The SF-36 also includes the Mental Component Summary (MCS) and the Physical Component Summary (PCS). These summary scores replicate the results from the eight domains of the SF-36. The Swedish version of the SF-36 has been translated from English and validated for the Swedish population.101, 102 The SF-36 questionnaire was used in Paper 4.

Determination of the level of upper airway obstruction

Friedman stage

In 2002 Friedman et al. found in a non-randomized study that their staging system (Figure 6) based on palate position, tonsil size and the BMI predicted a positive treatment effect of UPPP.103, 104 The authors demonstrated a success rate (defined as RDI reduced by at least 50% and a postoperative RDI of 20 or less) of as high as 80% for patients with Friedman stage I and 38% for Friedman stage II. Furthermore, an additional tongue base reduction was recommended in patients with high tongue position. Patients with Friedman stage III, or stage IV (BMI > 40), were not recommended to undergo surgery.

Flexible nasal endoscopy of the upper airways

The upper airway anatomy and potential sites of obstruction may be evaluated by flexible nasal endoscopy. An additional examination is drug-induced sleep endoscopy (DISE), but it is costly and time-consuming.
In a recent study by Ravesloot et al., 100 patients eligible for sleep surgery or MRD underwent PSG and DISE to investigate the distribution of sites and patterns of obstruction. Eighty-three per cent of the patients had palatal obstruction, 56% had tongue base obstruction, 38% had epiglottis obstruction and 7% oropharyngeal obstruction. In 76 patients, a multilevel obstruction was visualised. The authors concluded that the AHI was significantly higher in patients with a multilevel obstruction, and a complete collapse or a tongue base collapse was associated with higher AHI values. A tongue base collapse or epiglottal collapse was associated with supine-positional OSA.

In a retrospective study by Koutsourelakis et al., 49 OSA patients underwent DISE, upper airway surgery (palatal surgery and/or radiofrequency ablation of the tongue base, and/or hyoid suspension), followed by PSG. Forty-seven per cent of the patients were responders, with a success criterion of a postoperative AHI of < 10 events/hour and at least a 50% decrease from the baseline AHI. Twenty-two out of 23 (96%) of the successes had a complete (16 of 23) or partial (6 of 23) anterior-posterior collapse of the velum. Complete circumferential collapse at the velum or complete anterior-posterior collapses at the tongue base were the only independent predictors of upper airway surgery failure. Further studies showing that DISE really improves the surgical results are needed before DISE will be used in our clinical practice.
Treatment of OSAS

Weight reduction and positional therapy
Weight reduction is a highly effective treatment for OSAS. In an RCT of 63 moderate to severe OSAS patients, the intervention consisted of a very low-energy diet for seven weeks. In the intervention group, the AHI was reduced by 67% compared to baseline, but it was unchanged in the control group. A cohort study from our group showed a significant decrease in respiration measured with the ODI from 42 to 23, as well as daytime sleepiness measured as an ESS score from 9 to 5 after a two-year weight reduction programme. In addition, significant improvements in the SF-36 domains physical functioning and vitality were seen in the per protocol analysis. Since many patients have residual OSA, a weight reduction programme may be regarded as an adjacent treatment rather than a cure.

Bariatric surgery has also been shown to be an effective treatment for OSAS and has been associated with a decrease in sleep respiratory parameters, as well as daytime sleepiness in 100 consecutive obese OSAS patients.

Another treatment option is positional therapy, which is aimed at maintaining the patient in a preferred position at sleep. There are several different devices, and most of them prevent the patient from sleeping in a supine position. In a study by Jokic et al., positional treatment was compared to CPAP in 13 patients with position-dependent OSA. CPAP was more effective in lowering the AHI, but no differences were found between therapies concerning sleep architecture, ESS, sleep latency (MWT) and QoL measures.

CPAP
CPAP treatment for OSA was introduced in 1981 by Sullivan and it is the golden standard for the treatment of OSA and when fully utilised, it has been proven to be very effective for treating upper airway obstruction. The CPAP machine delivers a positive airway pressure through a mask to the oropharynx, thereby functioning as a splint that keeps the airway open. A meta-analysis of 10 different studies concluded that the mean AHI was decreased from 32 at baseline to 5 during treatment. Studies have shown that CPAP therapy is effective for reducing all-cause mortality, as well as the risk of fatal and non-fatal cardiovascular events. A meta-analysis of 18 different studies reported that the mean ESS decreased from 12.4 to 8.1 during treatment. The largest included study with 114 patients showed a mean ESS score of 9.2 for the CPAP group, compared to 10.2 for placebo, and compared to 10.7 at baseline for all the groups together.
In an RCT that compared therapeutic with subtherapeutic CPAP in OSAS patients, the ESS was decreased significantly from a median of 15.5 to 7.0 on therapeutic CPAP, and from 15.0 to 13.0 on subtherapeutic CPAP. Also the results from the SF-36 domains RP, RE, MH, VT and vigilance measured by the MWT showed significant differences between groups. Furthermore, Pichel et al. reported that patients treated with CPAP for 6 months significantly improved the SF-36 vitality dimension, and after 18 months there were additional improvements in PF, RP, SF, VT and GH. Unfortunately, long-term follow-ups are rare, but the median compliance rate is approximately 50–68% after 1–4 years. Furthermore, studies show that approximately 46–83% of patients are non-adherent to CPAP treatment for more than 4 hours a night.

Mandibular retaining device
MRD is the second most usual treatment for OSAS, especially for patients with mild to moderate OSA, who prefer an oral appliance to CPAP or do not respond/adhere to CPAP. The device is generally custom-made by dentists. The SBU reported in a meta-analysis of 8 studies that the mean AHI was reduced from 24 at baseline to 12 during MRD treatment. Furthermore, it was reported that in six RCTs including patients treated with an active MRD, the ESS decreased from a mean of 11.4 to 9.0. Again, the study by Barnes is the largest study included in this report and showed the same mean ESS value of 9.2 for the MRD as for CPAP, compared to 10.2 for placebo. Furthermore, no improvement of objective sleepiness measured with MWT for CPAP or MRD was seen compared to placebo, and the QoL (measured with the SF-36 and the FOSQ) improved to a similar degree with both treatments. The compliance rate for MRD treatment is moderate, i.e., about 56% after 5 years. Patients with a mild OSAS are more likely to continue treatment than patients with a severe OSAS.

Uvulopalatopharyngoplasty and other palatal surgery
Up to now, there is no ultimate treatment option for OSAS patients who do not accept or adhere to the non-surgical alternatives. For patients with a clearly defined anatomic airway obstruction and prior non-invasive treatment failures, surgical treatment may be an option.

The Cochrane report for OSAS surgery from 2005 and the Nordic meta-analysis from 2007 both concluded that there is insufficient evidence for the effectiveness of surgical intervention for OSA. According to the AASM clinical guidelines for OSA in adults, UPPP is not a reliable treatment for reducing the AHI, and therefore CPAP and MRDs should be offered to the patient before UPPP. The fact that blinded studies for surgical interventions are challenging may also be taken into account.
Surgical technique
UPPP was first described by Fujita in 1981, the same year as CPAP was introduced. Since UPPP started, it has dominated the surgical treatment of OSAS. UPPP includes tonsillectomy and a reduction of the soft palate and uvula, and suturing of the tonsillar pillars. Over the years, the surgical techniques have been modified to lesser resection of the soft palate and uvula. The removal techniques include a conventional scalpel and/or scissors. Laser-assisted procedures for the palate are seldom used nowadays in Sweden because of the postoperative pain and side-effects. The technique used in Paper 2 and in a previous study by Lundkvist et al. was a conservative UPPP with cold steel (Figure 9 on page 45), meaning a more careful reduction of the soft palate than the technique described by Fujita. This technique was initiated at Söder Hospital in Stockholm by Associate Professor Britt Nordlander during the 1980s, and has been used since then in our group. However, when the SBU report sounded the alarm about all the side-effects after UPPP, our research group decided to further modify the procedure to be used in Sleep Apnoea Karolinska UPPP (SKUP), Paper 3 and 4, as well as in the clinical routine (Figure 10 on page 45). From 2007, only minor resections of the soft palate and uvula have been performed (Figure 7).

![Figure 7. A pharynx before and 7 months after modified UPPP ad modum Karolinska. The arrows point at the lumen used for breathing](image)

Respiratory parameters
The definition of success and efficacy for UPPP varies among studies, but the most frequently used definition of success is an at least 50% reduction of the AHI and/or an AHI ≤ 20. Many authors also present success rates according to an AHI ≤ 5 or ≤ 10. In a meta-analysis by Caples et al., the ratio of means was used. This is a relative measure of effect that describes the extent to which the mean postoperative AHI has changed compared to the mean AHI at baseline. The authors showed a 33% reduction of the AHI after UPPP according to 15 UPPP studies.
The patients in Paper 2 were first evaluated at 6 months, 2 and 4 years postoperatively, by Larsson et al. regarding daytime sleepiness and sleep apnoea with PG recordings.\textsuperscript{125, 126} They showed significant decreases in the mean $\text{ODI}_4$ and 50\% of the patients were regarded as successes (defined as $\text{ODI}_4$ reduced by at least 50\% and postoperative $\text{ODI}_4 < 20$). Obesity and severe degrees of OSAS were found to be negative predictors.\textsuperscript{126} Boot et al. followed 58 OSAS patients for an average median of 34 months.\textsuperscript{127} Sixty-three per cent were improved regarding snoring and 38\% regarding excessive daytime sleepiness. Thirty-eight out of the 58 included patients (66\%) had respiratory sleep recordings at follow-up. Ten out of 38 (26\%) were classified as successes ($\text{ODI}_4$ reduced by at least 50\% and postoperative $\text{ODI}_4 < 20$). In the study by Lundkvist et al. of 158 patients treated with UPPP, the success rate was 64\% (defined as $\text{ODI}_4$ reduced by at least 50\% and postoperative $\text{ODI}_4 < 20$).\textsuperscript{122} The preoperative BMI did not correlate with the success rate and no significant difference between the groups with large or small tonsils was found.

\textit{Subjective parameters}

Yaremchuk et al. reported that the mean ESS score was reduced by 5.6 after upper airway surgery including UPPP.\textsuperscript{91} This ESS result is similar to those from a study by Lundkvist et al., in which the ESS score decreased significantly from a median of 12 to 6.\textsuperscript{122} Eighty-eight per cent of the patients were satisfied after UPPP.\textsuperscript{122}

Walker-Engström et al. investigated the quality of life (measured with the MSE-P questionnaire) after UPPP and MRD, respectively, in a prospective one-year-follow up.\textsuperscript{128} The authors concluded that the mean values for the three dimensions vitality, contentment and sleep improved significantly one year after the intervention in both groups. Furthermore, UPPP patients showed a significantly higher level of contentment compared to MRD patients, despite the fact that the MRD group improved their nocturnal respiration significantly more.\textsuperscript{129}

\textit{Complications in connection with OSAS surgery}

Kezirian et al. investigated the complication rate from medical records retrospectively for 3130 patients who had undergone UPPP or other surgical procedures for OSAS.\textsuperscript{130} They demonstrated a 1.5\% incidence of serious complications (mainly respiratory). A high AHI, a high BMI, medical co-morbidity and concurrent retrolingual surgical procedures were especially associated with an elevated risk of complications. Performance of several surgical procedures simultaneously was not recommended.\textsuperscript{131} The SBU reported a high complication rate and concluded that pharyngeal surgery was associated with several adverse effects: for example peri- and postoperative bleeding, respiratory compromise, and difficulties in swallowing in 28\% of the patients after UPPP.\textsuperscript{8} Franklin et al.
investigated the complication rate in Sweden between 1997 and 2004 and concluded that UPPP compared to tonsillectomy did not lead to increased peri-operative complications. In the study by Lundkvist et al., a safety programme was used as the clinical routine and 2.5% had serious postoperative complications.

**Side-effects after pharyngeal surgery in OSAS**

Persistent adverse effects have been reported in 14-62% of the patients after UPPP, for example difficulties in swallowing, globus sensation, voice changes and persistent dryness of the throat. Levring-Jäghagen et al. investigated patients with OSAS using videoradiography and found subclinical pharyngeal swallowing dysfunction after pharyngeal surgery. However, a study from our group comprising 58 OSAS patients treated with a conservative, modified UPPP showed that the median score for pharyngeal disturbances measured by a questionnaire one year after UPPP was unchanged compared to the preoperative score. The OSAS patients had significantly higher scores for pharyngeal disturbances before surgery than non-snoring controls.

**Mortality in connection with UPPP: per-operative and long-term**

Kezirian et al. reported a per-operative mortality of 0.2% after UPPP or other surgical procedures for OSAS. Franklin et al. also investigated the mortality rate in Sweden between 1997 and 2004 and concluded that no mortality at all was found after UPPP. In a large Swedish study by Lysdahl et al., 400 non-obese heavy snorers were studied. Among these patients, 256 had OSAS. The patients had undergone UPPP or laser uvulopalatoplasty (LUPP) and were compared with a matched control group of patients who had nasal surgery. The authors concluded that there was no increased mortality and that palatal surgery may have a protective role. Weaver et al. investigated the mortality in a retrospective study of OSAS patients treated with UPPP or CPAP. When the data were adjusted for age, gender, year of initiation of treatment and co-morbidities, the mortality for UPPP was lower than for CPAP. However, the lack on data on the use of CPAP and AHI values are possible explanations for why the CPAP patients may have had more severe OSAS.

**Long-term follow-up**

Few studies have investigated UPPP in the long-term perspective. A long-term study on 34 patients by Janson et al. used the success criteria of an at least 50% reduction of the AHI and AHI < 10 and found that 12 of 25 (48%) were responders 4–8 years after UPPP surgery. A success factor in the study was a low preoperative AHI.

In a long-term follow-up by Värendh et al., 186 patients underwent pharyngeal surgery between 1985 and 1991, and were evaluated 19 to 25 years after surgery.
with questionnaires, but without sleep recordings. The surgical technique was performed as described by Fujita, and cold steel was used in all cases, but 11 patients where laser surgery was performed. About 50% of the patients were satisfied with the operation and one third had CPAP at the follow-up. A large proportion of the patients also reported side-effects.

Previous RCT
The only known previous RCT of UPPP compared to expectancy is a study by Lojander et al., in which 18 patients were randomised to UPPP (5 of them had an additional mandibular osteotomy) and 14 to expectancy. After one year the ODI changed significantly from 45 events/h sleep to 14 events/h sleep in the intervention group, compared to 34 events/h sleep to 23 events/h sleep in the control group, but the difference between the groups was not significant. The results may be explained by the small study sample.

Comparing compliance with treatment
The compliance for UPPP is 100%, but the efficacy has been questioned. In contrast, the efficacy of MRD and especially CPAP treatment when used properly is clear, but they are limited by their fairly low compliance. In a four-year follow-up of a randomised trial of MRD and UPPP, Walker-Engström et al. concluded that the MRD group showed a significantly higher success rate regarding the AHI compared to the UPPP group, i.e., 72% compared to 35%, but that the effectiveness of the MRD was invalidated by a compliance rate of only 62%. However, Weaver applied an intention-to-treat (ITT) analysis to the data from the Walker-Engström study. The purpose was to include all the drop-outs in the MRD group, as treatment adherence is not an issue with surgical therapy. When evaluating the laboratory success rates for MRDs, it was found to be 54% compared to 49% for UPPP in the ITT analysis, i.e., no significant difference. Additionally, Weaver argued that the sleep recording values obtained while patients wore the MRD during the sleep recording night should be corrected for the actual usage in everyday life in order to measure the full effectiveness of the treatment.

Tracheostomy
Tracheostomy is an upper airway bypass procedure and was first introduced as treatment for patients with the most severe apnoea syndrome. Today it is only recommended when other treatment alternatives do not exist. In many cases, these patients are obese.
Success rate
Tracheostomy is highly effective, as shown by Guilleminault et al. in a one-year follow-up study of 50 tracheostomised OSAS patients, with a success rate of 100% (apnoea index < 5).\textsuperscript{141} In this study, also the central apnoeas were reduced and daytime sleepiness was improved. In contradiction, there are studies that report that although the obstructive events decreased after tracheostomy, some patients had an increased number of central apnoeas.\textsuperscript{142, 143} Tracheostomy can also improve the subjective quality of life.\textsuperscript{144}

Long-term follow-up
In a retrospective study by Thatcher et al. of 79 OSA patients who had undergone tracheostomy between 1979 and 1999, it was concluded that the procedure was 100% effective in terms of nocturnal respiratory disturbances and well tolerated in these severe OSA patients after a mean follow-up time of 8 years.\textsuperscript{145}

Complications and adverse events
As an elective treatment, tracheostomy is a procedure for which the patient can be prepared, but the immediate postoperative risks are respiration-related ones, haemorrhage and infections. The long-term adverse effects are stoma granulation, excessive mucotic secretion, respiratory tract colonisation and recurrent infections.\textsuperscript{141} Tracheostomy may also have an impact on daily life and social activities. However, it has also been shown that tracheostomy in patients with other diseases does not lead to a reduced QoL.\textsuperscript{146}

Mortality
In a study by Partinen and colleagues, patients with severe OSAS who had a tracheostomy or weight reduction were investigated.\textsuperscript{147} At the five-year-follow-up the mortality was 0 of 71 patients in the tracheostomy group and 14 of 127 in the weight reduction group. Compared to CPAP, tracheostomy did not result in a higher mortality in an 8-year follow-up study by He et al.\textsuperscript{148} In the retrospective study by Thatcher et al. described above 14 deaths were identified.\textsuperscript{145} Five deaths were cardiopulmonary-related, four were from cancer, two were from postoperative complications of unrelated surgery and one was from aspiration. Tracheostomy-related mortality included one postoperative myocardial infarction and one tracheal-innominate fistula.

Other upper airway surgical techniques for treating OSAS
Woodson et al. investigated coblation of the soft palate in an RCT. There were no significant differences in the AHI between the intervention and the control groups.\textsuperscript{149}
LAUP is a laser-assisted modification of the conventional uvulopalatoplasty (UPP, without tonsillectomy). It involves bilateral vertical incisions directly along both sides of the uvula and laser ablation thereof. A meta-analysis of LAUP showed an AHI reduction of 32%, comparable to 33% in UPPP, but LAUP has not been approved for OSA treatment according to the AASM because of insufficient evidence of efficacy.

Solely tonsillectomy as OSAS treatment in adults has been shown to be effective in a study of seven patients, five of whom underwent tonsillectomy. In another study of nine OSAS patients by Verse et al., the success rate was 80% in patients with severe OSA (defined as a decrease in the postoperative AHI $\geq 50\%$ and a postoperative AHI $< 20$).

There are numerous other surgical procedures for treating OSAS: for example, maxillomandibular advancement, genioglossus advancement and rapid maxillary expansion, which will not be further discussed in this thesis.

**HYPOTHESES AND AIMS**

Hypothetical questions for the four papers were:

1. Is elective tracheostomy a tolerable and efficient treatment in selected OSAS patients?
2. Is UPPP an efficient and safe treatment in OSAS patients in the long-term perspective?
3. Are the respiratory events during sleep significantly reduced in selected patients with OSAS treated with UPPP compared to expectancy for six months?
4. Are the subjective and objective parameters of EDS and quality of life significantly improved and correlated in selected OSAS patients treated with UPPP compared to expectancy for six months?

The overall aim of this thesis was to evaluate subjective and objective outcomes of upper airway surgery in OSAS patients.

The specific aims for the four papers were:

1. To describe the tolerability of elective tracheostomy using custom-made tubes, as well as the effects on daytime sleepiness and nocturnal respiration in obese patients with severe OSAS.
2. To investigate the efficacy of UPPP treatment after 15 years, objectively with sleep apnoea recordings and subjectively with questionnaires regarding satisfaction, daytime sleepiness, pharyngeal side effects and snoring. Also, to compare the mortality rate in patients operated upon with that in the normal population.
3. To evaluate nocturnal respiration using polysomnography in moderate-to-severe OSAS patients after UPPP compared to the six-month expectancy (delayed surgery) in an RCT (SKUP3).
4. To compare UPPP treatment with expectancy (RCT SKUP3), according to changes in EDS measured with questionnaires and vigilance tests, as well as the quality of life, and, furthermore, to perform correlation tests of changes in outcomes, also using respiratory parameters.

SUBJECTS AND METHODS

SUBJECTS

PAPER 1
This was a retrospective *descriptive* study of tracheostomised patients with OSAS who attended the Department of ORL at the Karolinska University Hospital Huddinge between 2002 and 2007. Inclusion criteria were (1) acceptance of elective tracheostomy, (2) failure of or not accepting treatment with CPAP or a bi-level pressure device (BiPAP), (3) a score of > 10 on the ESS or severe morning drowsiness and (4) a high ODI4 score, indicating a severe degree of OSAS. Ten patients, all males, met the inclusion criteria. Seven of these male patients had hypertension, five had suffered from stroke or myocardial infarction and four had diabetes mellitus. The only patient with an ESS < 10, complained about a marked morning drowsiness, in combination with insulin-resistant diabetes mellitus. Table 1 shows the baseline characteristics of the patients included in the study.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age in years</th>
<th>BMI</th>
<th>ESS before</th>
<th>ESS after</th>
<th>ODI before</th>
<th>ODI after</th>
<th>Time to first follow up sleep registration (months)</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>45</td>
<td>13</td>
<td>6</td>
<td>73</td>
<td>70</td>
<td>1</td>
<td>Decannulated after 3 months, CPAP</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>45</td>
<td>17</td>
<td>0</td>
<td>55</td>
<td>13</td>
<td>4</td>
<td>Decannulated after 5 months, CPAP</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>37</td>
<td>20</td>
<td>5</td>
<td>91</td>
<td>1</td>
<td>2</td>
<td>UPPP, decannulated after 26 months</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>35</td>
<td>22</td>
<td>6</td>
<td>99</td>
<td>14</td>
<td>3</td>
<td>UPPP, decannulated after 23 months, CPAP</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>50</td>
<td>19</td>
<td>3</td>
<td>85</td>
<td>87</td>
<td>23</td>
<td>Tube since February 2003</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>33</td>
<td>8</td>
<td>7</td>
<td>126</td>
<td>24</td>
<td>4</td>
<td>Tube since February 2006</td>
</tr>
<tr>
<td>7</td>
<td>77</td>
<td>37</td>
<td>37</td>
<td></td>
<td>61</td>
<td></td>
<td>4</td>
<td>Tube 60 months, until death</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>33</td>
<td>18</td>
<td>2</td>
<td>60</td>
<td>4</td>
<td>6</td>
<td>Tube since June 2002</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>42</td>
<td>23</td>
<td>0</td>
<td>77</td>
<td>3.5</td>
<td>3</td>
<td>Tube since May 2003</td>
</tr>
<tr>
<td>10</td>
<td>43</td>
<td>31</td>
<td>11</td>
<td>7</td>
<td>100</td>
<td>2.5</td>
<td>6</td>
<td>Tube since April 2007</td>
</tr>
</tbody>
</table>

Table 1. Baseline characteristics of the 10 patients studied

Median 53.5 36 18 5 81 13 4
PAPER 2
This was a non-randomised observational study of 50 unselected consecutive patients with habitual snoring and subjective symptoms of OSAS (48 males and 2 females) who underwent UPPP between 1985 and 1988 at the Department of ORL at Söder Hospital in Stockholm. The patients had previously been evaluated at 6 months and 2 and 4 years postoperatively regarding EDS using a local questionnaire and renewed sleep apnoea recordings. The present study was the long-term follow-up of the same cohort.

The median age at inclusion was 49 years (range 38–71), BMI was 30 (20–43) and the median ODI₄ was 26.5 (4–82). Among the 50 patients, 8 had no EDS, 11 mild, 21 moderate and 10 severe EDS at baseline according to responses to a question as to what degree they experienced subjective EDS. One patient with moderate EDS had a baseline ODI₄ value of only 4. However, as the patient had undergone all previous follow-ups, he was also included in this study.

PAPERS 3 AND 4
This was a randomised controlled study, RCT. At the start it was a two–centre study (see below), but soon thereafter it became a single-centre RCT of 65 OSAS patients (59 men and 6 women) referred consecutively to the ORL Department of the Karolinska University Hospital at Huddinge, Stockholm, Sweden, from June 2007 to May 2011 for possible UPPP. All patients had undergone screening ambulatory PG prior to the first visit to a physician. Examinations by an ORL physician included nasoscopy, flexible fibre endoscopy of the upper airways and staging of tonsil size (scale 0–4), as well as tongue position (scale 1–4), leading to the Friedman staging system.

The patients underwent a first full-night in-lab PSG. The morning after, they filled in questionnaires and underwent a vigilance test (modified Osler). If the study criteria were still satisfied, they were included in the study by randomisation.

The inclusion criteria were: (1) males and females > 18 years of age, (2) AHI ≥ 15 events/h sleep (from PSG), (3) ESS score ≥ 8, (4) excessive daytime sleepiness three times a week or more, a single selected question from the BNSQ, (5) BMI < 36 kg/m², (6) Friedman stage I or II and (7) failure of CPAP and MRD treatments and no use of these treatments during the last three months. Patients with Friedman stage I and BMI < 30 kg/m² did not have to have failed CPAP/ MRD treatment before inclusion.

The exclusion criteria were: (1) serious psychiatric, cardiopulmonary or neurological disease or an American Society of Anesthesiologists (ASA) classification > 3, (2) patients negative to surgery, (3) insufficient knowledge of Swedish, (4)
nightshift workers, (5) patients who could be dangerous in traffic, (6) severe nasal congestion (could be included after local treatment), (7) previous tonsillectomy, (8) Friedman stage III and (9) severe clinical worsening of the OSAS during the study. For baseline characteristics see table 2.

There were six women in the study, and only three patients with Friedman stage I and a BMI < 30 kg/m² who had not failed CPAP and MRD treatment before inclusion. At PSG 1, eight patients had a moderate OSAS with an AHI of 15 to 29.9 events/h sleep, and 57 patients had a severe OSAS with an AHI ≥ 30 events/h sleep. Sixteen of 32 patients had Friedman stage I and 18 of 32 had tonsillar hypertrophy (sizes 3 and 4) in the intervention group. Corresponding figures for the control group were 13 of 33 and 17 of 33.

To increase the external validity, a two-centre study was initially developed: the ORL outpatient clinics at Karolinska University Hospital, sites Huddinge and Solna. At the start of this study, these sites were two separate clinics but, during the study, were fused into one, and all OSAS patients were allocated to site Huddinge. Subsequently, there were only a total of four patients included from the Solna site. As all four deviated from the study protocol for different reasons and because of the low statistical power at this centre, we were urged by the statisticians to exclude these patients, as well as the centre itself. Accordingly, all participants in this study were recruited from site Huddinge as a single-centre study.

Table 2. Baseline characteristics in each group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41.5 (11.5)</td>
<td>42.9 (11.7)</td>
</tr>
<tr>
<td>Body mass index (BMI) (kg/m²)</td>
<td>28.2 (2.9)</td>
<td>27.7 (3.3)</td>
</tr>
<tr>
<td>Tonsil size</td>
<td>2.5 (0.8)</td>
<td>2.3 (0.9)</td>
</tr>
<tr>
<td>Friedman stage</td>
<td>1.5 (0.5)</td>
<td>1.6 (0.5)</td>
</tr>
<tr>
<td>Apnea Hypopnea Index (AHI) events/h sleep</td>
<td>53.3 (19.7)</td>
<td>52.6 (21.7)</td>
</tr>
<tr>
<td>Oxygen desaturation index (events/h sleep)</td>
<td>44.6 (23.5)</td>
<td>41.1 (22.2)</td>
</tr>
<tr>
<td>Nadir of oxygen saturation (%)</td>
<td>79.9 (5.3)</td>
<td>81.0 (6.6)</td>
</tr>
<tr>
<td>Arousal index (events/h sleep)</td>
<td>64.0 (16.2)</td>
<td>60.3 (22.7)</td>
</tr>
<tr>
<td>Epworth Sleepiness scale (ESS)</td>
<td>12.5 (3.2)</td>
<td>12.9 (3.1)</td>
</tr>
<tr>
<td>SF-36 physical functioning (PF)</td>
<td>83.7 (19.2)</td>
<td>87.0 (18.4)</td>
</tr>
<tr>
<td>SF-36 role physical (PR)</td>
<td>69.5 (36.3)</td>
<td>75.8 (39.3)</td>
</tr>
<tr>
<td>SF-36 bodily pain (BP)</td>
<td>78.3 (27.1)</td>
<td>80.9 (23.0)</td>
</tr>
<tr>
<td>SF-36 general health (GH)</td>
<td>61.3 (24.1)</td>
<td>59.8 (23.9)</td>
</tr>
<tr>
<td>SF-36 vitality (VT)</td>
<td>42.8 (22.0)</td>
<td>42.3 (21.9)</td>
</tr>
<tr>
<td>SF-36 social functioning (SF)</td>
<td>74.2 (23.3)</td>
<td>77.3 (22.4)</td>
</tr>
<tr>
<td>SF-36 role emotional (RE)</td>
<td>77.1 (36.6)</td>
<td>81.8 (34.5)</td>
</tr>
<tr>
<td>SF-36 mental health (MH)</td>
<td>71.8 (19.3)</td>
<td>66.1 (18.8)</td>
</tr>
<tr>
<td>SF-36 physical component summary (PCS)</td>
<td>47.3 (8.6)</td>
<td>49.2 (8.9)</td>
</tr>
<tr>
<td>SF-36 mental component summary (MCS)</td>
<td>42.5 (10.7)</td>
<td>41.2 (10.1)</td>
</tr>
<tr>
<td>Sleep latency (minutes)</td>
<td>30.7 (11.1)</td>
<td>33.6 (9.0)</td>
</tr>
</tbody>
</table>

The above data are the mean (sd). n = number of patients
METHODS

PAPER 1

Outcomes
The primary outcome was tolerability of the custom-made tube for more than six months. Other outcomes were changes in the ESS and the ODI₄.

Custom-made cannula
The National Respiration Centre (NRC) was started in 1982 and is classified by the Swedish National Board of Health and Welfare as a national referral clinic for patients with chronic respiratory disorders. The clinic has a unique team of doctors specialised in ORL and anaesthesia and nurses and technicians. The NRC manufactures custom-made tubes and provides careful preoperative information, as well as postoperative support, for each patient. The tubes were exclusively designed at the NRC for each patient with regard to material, thickness, length, curvature, position of the window, quality of stoma, the need for an inner tube, ability for speech and the patient’s requests. All patients with a tube underwent monthly follow-ups of their stoma at the NRC. Figure 8.

Epworth Sleepiness Scale
The ESS questionnaire was distributed during the medical consultations at the clinic and in connection with the sleep recordings.

Sleep apnoea recordings
Ambulatory polygraphy recordings were made with the use of the Embletta (Medcare Flaga, Reykjavik, Iceland) and the MicroDigitrapper (Synectics Medical, Stockholm, Sweden). The ODI₄ was determined. The AHI measured by the thermistor, and in some patients also oro-nasal flowmetry, was not considered to be a consistently reliable measure of the airflow at this time and was therefore excluded. All recordings were interpreted by specialists in neurophysiology.
PAPER 2

Outcomes
The primary outcome was changes in ODI₄. Other outcomes were the evaluation of questionnaires concerning EDS, satisfaction and pharyngeal symptoms and subjective and objective evaluations of snoring, as well as the mortality rate.

Surgical method of conservative uvulopalatopharyngoplasty
The patients underwent conservative UPPP, including tonsillectomy, using a cold-steel technique. The mucosa from the anterior soft palate and anterior tonsil pillar was reduced by approximately 2–3 mm, and in the upper lateral corner by 3–4 mm. The mucosa between the anterior and posterior pillars was removed. The posterior tonsil pillar was preserved. The uvula was cut to a width and length of approximately 1 cm. An extracapsular tonsillectomy was performed with a sharp elevator. The posterior pillar was lifted up laterally and sewn up to the anterior pillar with separate inverted sutures. In the upper lateral corners, two or three sutures also included fibres from the palatopharyngeal muscle. Finally, the soft palate and the uvula were sutured. (Figure 9)

Figure 9.
Schematic picture of conservative UPPP used in Paper 2.

Figure 10.
Schematic picture of modified UPPP used in Papers 3 and 4.
Sleep apnoea recordings and laboratory criteria for success

Ambulatory sleep apnoea recordings, using the same equipment and approach as at baseline and at the previous follow-ups, were used. Patients who had additive treatment (CPAP or MRD) did not use it during the night of the sleep recording. From the PG recordings, the ODI_4 was measured, and also sound (decibel, dB) measurements were performed using the digitised Apnolog system (C-A Tegner Inc., Stockholm, Sweden). Sleeping time was estimated manually from the movement recording by one of the investigators, who was blinded to the patient’s subjective symptoms.

The percentage of the estimated total sleep time (TST) during which respiratory sounds exceeded 40 dB was calculated, and if the time was above 40%, the patient was objectively classified as a snorer.

The success criteria for recordings were ODI_4 < 20 and a reduction of at least 50% compared with baseline, as well as no more than 10 desaturations below 90% during 6 hours of sleep.

Questionnaires

(A) A locally developed questionnaire concerning satisfaction, EDS and subjective snoring. The questions were: 'Are you satisfied with the UPPP surgery?' (Yes/No), ‘Do you regret the UPPP surgery?’ (Yes/No), ‘Would you recommend UPPP surgery to others?’ (Yes/No/Do not know), ’Do you snore?’ (Never/Sometimes/ Often/Always) and ’How would you estimate your daytime sleepiness compared to before UPPP surgery?’ (Cured/Better/Unchanged).

(B) A questionnaire concerning pharyngeal symptoms such as vivid, queasy feelings, globus sensation and trouble with swallowing (for details, see Lundkvist et al.55) The 10 questions were answered on a four-point Likert scale in the order none, mild, moderate, severe, with a maximum symptom score of 30. This questionnaire had not been validated, but four of the questions have been used in a previous study by Levring-Jäghagen.66 This questionnaire had not been used previously on this cohort of OSAS patients.

(C) ESS^{88} was used only at this 15-year follow-up.

Drop-out and subgroup analyses

Drop-outs were defined as patients not answering the 15-year questionnaires. Further subgroups were ‘living’ or ‘deceased’, as well as those who made sleep apnoea recordings or did not.
PAPERS 3 AND 4

Outcomes
Paper 3: The primary outcome was changes in the AHI measured by PSG. Other outcomes were changes in other respiratory and sleep parameters.

Paper 4: Changes in the ESS questionnaire. Other outcomes were changes in the SF-36 questionnaire and changes in sleep latency from a vigilance test measurement using a modified OSLER test. Further outcomes were from correlation tests for changes in subjective and objective data.

Another outcome was changes in the BNSQ ‘excessively sleepy’ question, but this result was considered to be excessive and was not reported in Paper 4, but it is in this thesis.

Intervention
Patients were randomised to receive either UPPP within one month or no treatment at all for seven months. After the second evaluation with PSG, the patients in the control group also underwent UPPP. All patients were instructed to maintain their weight, to avoid new medicines and were restricted from other OSAS treatments during the study.

Surgical method of modified uvulopalatopharyngoplasty
All patients underwent UPPP under general anaesthesia using a nasal tube at the ORL Department of Karolinska University Hospital, site Huddinge. Local anaesthesia was administered before the surgery. The surgical procedure was carried out using the cold-steel technique and included tonsillectomy. On the advice of Associate Professor Per Olle Haraldsson the procedure had been slightly modified since a previous study from our group to minimise the risk of side-effects. In this study the excisions of the soft palatal mucosa were performed only laterally to the uvula, which was only reduced (modified UPPP) (Figure 10). A total of eight different surgeons, all ORL specialists, performed the UPPPs.

Safety
All the patients who underwent UPPP were included in our safety programme, described earlier by our group and directly after extubation they were transferred to the postoperative care unit for 6–24 hours of observation, depending on the severity of their condition. Additionally, all patients received perioperative penicillin prophylaxis, and postoperatively for three days. Two modifications of the safety programme were made before this study: perioperative cortisone and peri- and postoperative tranexamic acid were given for five days.
Polysonomography
Respiratory and sleep parameters were measured at baseline and six months after intervention or expectancy by an in-lab, full-night PSG, using the same Embla technology (Flaga Medical; Reykjavik, Iceland). Measurements were interpreted manually by a single blinded scorer. The patients were awakened at 6 a.m. due to the fact that the sleep laboratory located in a day-care unit. Sixteen channels were recorded: EEG (sensors C3-A2, O1-A2, O2-A1, C4-A1), EOG (left and right), EMG chin and tibialis (left and right), oronasal thermistor and flowmetry, transcutaneous oxygen saturation, respiratory movements (abdomen and thorax), snoring, ECG, pulse and body position. Parameters were defined according to AASM 2007 using criteria B for the hypopnoea. The patients were also informed that, before PSG nights, they should not have travelled abroad through more than two time zones during the last three weeks or consumed theine or caffeine during the afternoon and evening before PSG.

Sample size
The sample size was chosen to obtain 90% power with an α level of 5% and resulted in a total of 64 patients. The sample size calculation was based on the night-to-night variability of the ODI values in patients with OSAS and also on findings from one of our previous studies on patients with OSAS undergoing UPPP.

Randomisation
Stratified randomisation within four strata was used. Group A: Friedman stage I and BMI < 30 kg/m²; B: Friedman stage II and BMI < 30 kg/m²; C: Friedman stage I and BMI 30–35.9 kg/m²; D: Friedman stage II and BMI 30–35.9 kg/m². Sixty-five randomised patients followed the study protocol and fulfilled all criteria; see Figure 11. Altogether, 71 patients were randomised. After randomisation, the researchers discovered that two patients did not meet all the inclusion criteria and they were therefore excluded. Four patients were also excluded owing to deviation from the study protocol.

Epworth sleepiness scale
The ESS questionnaire was distributed in connection with the PSG recordings.

Health Survey SF-36
The health survey SF-36 questionnaire was distributed in connection with the PSG recordings.
Vigilance test
A modified OSLER test was performed. The patients performed the test once (instead of four times), directly after the in-lab PSG night. At study start the first seven patients performed the vigilance test in a different room from the one used later in the study. The research nurse who assisted the patients in the vigilance test was blinded to the patient group. The patients were not allowed to consume caffeine, theine or alcohol before the vigilance test (modified OSLER).

Basic Nordic Sleep Questionnaire
In the RCT study, we selected a single question (in the following called ‘Excessively sleepy’) from the BNSQ\textsuperscript{93}: Question no. 9, with the score 1 to 5; see below.

Do you feel excessively sleepy during the daytime?
1. Never or less than once per month
2. Less than once per week
3. On 1-2 days per week
4. On 3-5 days per week
5. Daily or almost daily
STATISTICAL ANALYSES

PAPER 1
No statistical analysis was performed owing to the small number of subjects.

PAPER 2
Wilcoxon matched-pairs (WMP) tests were used to compare the results before and after surgery and Mann-Whitney U (MWU) tests for unpaired tests of drop-out and subgroup analyses. Correlation analyses were performed using Spearman’s rank correlation (SRC) tests. The software programme Statistica 6.0 was used.

Standardised mortality ratio (SMR) calculations: the cohort was followed from the date of surgery up to the date of death or 31 December 2008, whichever occurred first. The expected mortality in the patient group was estimated by splitting the person-years of follow-up according to the attained age in 5-year age bands and calendar years, and multiplying these by the corresponding sex-specific mortality rate in the general population. The overall and circulatory disease-specific mortality rates were obtained from the Swedish Cause of Death Register. The SMR was calculated by dividing the observed number of deaths by the expected number. The 95% confidence interval (CI) for the SMR was calculated assuming that the observed number of deaths follow a Poisson distribution.

PAPER 3
Changes within groups were calculated by subtracting the outcomes from PSG 1 from those from PSG 2, presented as the mean and standard deviation (sd). Changes between groups were presented as the mean and 95% CI. Since the sample size was over 30, parametric statistical analyses were used, and we also checked the distribution. Paired t-tests were used to compare the differences between PSG 1 and PSG 2 in each group, and unpaired t-tests were used to compare the changes between the two groups. All 65 participants were analysed in the per protocol analysis.

There were no drop-outs, and the sensitivity analysis with ITT was performed with the 65 patients together with the six excluded patients. Missing values for these patients were imputed by using their baseline values + 1. Also for analyses of different subgroups, t-tests were used due to the normal distribution. All statistical calculations were performed using Statistica 10.0.

PAPER 4
Changes within groups were calculated by subtracting the outcomes at the first
recording in connection with PSG 1 from those in PSG 2. Because of the nature of the questionnaire parameters and the skewed distribution of the vigilance, non-parametric statistical analyses were chosen: p values from the Wilcoxon signed-rank (WSR) test for within-group comparisons and p values from independent samples between group comparisons, MWU tests. For correlations between changes in ESS, SF-36, vigilance and PSG parameters, a non-parametric SRC test was used.

For ESS scores, a sensitivity analysis with ITT was performed including the six excluded patients. Missing values were imputed by using the baseline values +0.5. Non-parametric tests were used, as above. Paired and unpaired t tests were also performed to investigate whether the results changed with parametric statistical methods.

A Kaplan-Meier analysis was performed for all patients who had vigilance data at the follow-up. The vigilance test (time to fall asleep) was completed six months after intervention compared to no treatment. Patients who remained awake for 40 minutes were censored. The difference between intervention and control was tested using the log-rank test. The Kaplan-Meier analysis is not reported in Paper 4, but in this thesis.

All statistical calculations were performed using Statistica 10.0 or R ver. 2.15.

ETHICAL PERMISSION

All participants in all studies gave their informed consent. Studies 1 and 2 were approved by the Swedish Local Ethics Committee. Studies 3 and 4 were first rejected by the Swedish Regional Ethics Committee and, after an appeal, approved by the Central Ethics Committee.

RESULTS

TRACHEOSTOMY (PAPER 1)

Results
Eight of 10 patients tolerated the tube more than six months. Two patients insisted on decannulation due to respiratory problems during sleep, severe cough and infections. Thereafter, they were treated with CPAP again. Two additional patients were decannulated; they underwent UPPP one year after tracheostomy.
and were thereafter successfully decannulated with normalised ODI₄ values. One of these two patients had a dramatically reduced weight and required no additional treatment. The other one had high ODI₄ values one year after UPPP and was therefore treated with CPAP again.

One patient with persistently high ODI₄ values despite the tube was offered invasive CPAP (CPAP connected to the tube). One patient had to use a ventilator during the first months after tracheostomy because of hypercapnoea. Neither his daytime sleepiness nor his ODI₄ was normalised and he was therefore offered an invasive CPAP. However, he experienced the tube to be highly beneficial, with less severe morning drowsiness, and was not motivated to use an invasive CPAP. One of the patients died of cancer while still having his tube and therefore did not undergo the evaluation with postoperative sleep recordings and questionnaires. Three patients were complete responders and were still using their tubes with no additional treatment, and with normalised values for the daytime sleepiness score, as well as for the ODI₄. (Figure 12)

The ESS score was reduced from a median of 18 (range 8–23) to 5 (0–7) and the ODI₄ values from 81 (55–126) to 13 (1–87). (Table 1)

Severe cough, sputum infections and stoma granuloma were seen in all patients. None of the patients had serious postoperative bleeding or any other serious complication. There was no mortality associated with the tracheostomy.

Figure 12. Flow diagram for the 10 patients studied.
UPPP 15-YEAR FOLLOW-UP (PAPER 2)

Results
The median follow-up time was 189 months (15.75 years) (range 183–219 months). At follow-up 13 patients had died. Twenty-six of the 37 living patients underwent postoperative sleep apnoea recordings. In the per protocol analysis, the median ODI$_4$ had significantly decreased from 26.5 (range 4–82) to 8.5 (range 0–60), $p < 0.01$, figure 13. The mean ODI$_4$ was reduced from 31.8 to 15.4, a reduction of 52%. Seventeen out of 26 (65%) of the patients fulfilled the success criteria. Thirteen of these 17 patients were also classified as successes at the four-year follow-up. With a stricter success criteria (50% reduction and ODI$_4$ < 10) 14 of 26 patients (54%) were successes at the 15-year follow-up.

With regard to objective snoring, 9 of 26 patients (35%) were categorised as non-snorers and for subjective snoring 13 of 32 (40%) rated ’never’ or ’sometimes’. There was no correlation between subjective and objective snoring. However, a significant correlation between the ODI$_4$ and the percentage of objective snoring during the estimated total sleep time was found: $p < 0.05$.

The median BMI was unchanged between baseline, 30 (20–43) kg/m$^2$, and 15 years, 30 (22–42) kg/m$^2$.

Figure 13. Box-plots showing the oxygen desaturation index 4% (ODI$_4$) values in the 26 patients who underwent sleep recordings, at baseline and different follow-ups at 6 months and 2, 4 and 15 years. Note the significant difference between baseline and 15 years in ODI$_4$, ** $P < 0.01$ (Wilcoxon-matched pair tests).
The questionnaires were answered by 32 of the 37 living patients (86%). In the per protocol analysis, twenty-five of 32 patients (78%) were satisfied with the surgery, but four regretted it. Twenty-three of 32 patients (72%) stated that they would recommend the surgery to another person. The results for EDS over the 15 years are presented in Figure 14. At the follow-up, the median ESS value was 6 (range 0–19) and the median pharyngeal disturbances value was 3 (range 0–10).

Altogether, eight patients had complementary treatment at the 15-year follow-up (CPAP, MRD or mandibular surgery). Five of these eight (62%) were still satisfied with UPPP, and also rated themselves as being better concerning EDS. Their median 15-year ODI₄ value was 19 (8–39). Among the patients without any complementary treatment (n = 24), the corresponding values were 20 (83%) satisfied and 23 (96%) had EDS improvement and their median 15-year ODI₄ value was 5.5 (0–60).

In the mortality analysis we had a prolonged observation period of, in total, 18.2 years up to 31 December 2008, thus approximately 3 years extra observation time. We noted 18 deaths during a total of 908 person-years of follow-up. The expected number of deaths, assuming that this cohort had the same mortality as the general population, was calculated to be 13.6, corresponding to an SMR of

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**Figure 14.** The rating of changes in excessive daytime sleepiness (EDS) among the included patients at evaluations after 6 months (m) as well as after 2, 4, and 15 years (y) after UPPP surgery for OSAS.
1.32 (95% CI, 0.78–2.09). Thus, no significantly elevated mortality compared to the general population could be observed. Ten of the deaths were due to circulatory diseases, yielding a cause-specific SMR of 1.72 (95% CI, 0.83–3.17).

Because of the high drop-out rate for both questionnaires and sleep recordings, subgroup analyses were performed for the baseline values. Concerning the questionnaires there were no significant differences in baseline values for age, BMI, ODI4, or nadir SaO2. However, the patients who dropped out were in median 9 years older than those who filled in the questionnaires. The subgroup analyses of the postoperative ODI4 values at 6 months, 2, 4 and 15 years between living and deceased subjects, as well as between those who performed sleep recordings and those who did not, showed small and non-significant differences.

**SKUP3 RCT POLYSOMNOGRAPHIC RESULTS (PAPER 3)**

**Results**
All 65 patients, 32 in the intervention group and 33 in the control group, completed the trial. The median period between PSG 1 at baseline and PSG 2 at follow up was 7.2 months (range 4.8–14.6) for the intervention group and 6.7 months (range 4.8–8.5) for the control group.

The mean AHI in the intervention group had significantly decreased (p < 0.001) by 60%, from a mean (sd) of 53.3 (19.7) to 21.1 (16.7) (Figure 15). In the control group, the mean AHI decreased non-significantly, by 11%, from 52.6 (21.7) to 46.8 (22.8), with a significant difference between the groups, p < 0.001. Similar results in favour of the intervention group were found in other respiratory parameters, as well as the arousal index, but not for other sleep parameters; see Table 3. The mean reduction of ODI3 after UPPP was 69%.

The success rate for AHI (defined as ≤ 20 and a reduction of ≥ 50%) in the intervention group was 19 of 32 (59%) and for the control group 2 of 33 (6%). The success rates for ODI3 and RDI (≤ 20 and a reduction of ≥ 50%) in the intervention group were 21 of 32 (66%) and 15 of 32 (47%), respectively. In the control group, the success rates for the ODI3 and RDI were 3 of 33 (9%) and 1 of 33 (3%), respectively. Fifteen of 32 patients in the intervention group were cured or had mild disease according to the AHI at PSG 2, compared to 1 of 33 in the control group (Figure 16).

Furthermore, analyses of the subgroups showed that, independently of the BMI group, tonsil size or Friedman stage, the differences in AHI reduction were significant in favour of the intervention group, except for tongue position 3 (Table 4).
Table 3. Values in (m) and polyomamic hematins in polyomamphatic (vol%) and mean difference between groups

<table>
<thead>
<tr>
<th>Group</th>
<th>d</th>
<th>Mean (sd)</th>
<th>d</th>
<th>Mean (sd)</th>
<th>d</th>
<th>Mean (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.00</td>
<td>(0.00)</td>
<td>0.00</td>
<td>(0.00)</td>
<td>0.00</td>
<td>(0.00)</td>
</tr>
<tr>
<td>2</td>
<td>0.00</td>
<td>(0.00)</td>
<td>0.00</td>
<td>(0.00)</td>
<td>0.00</td>
<td>(0.00)</td>
</tr>
<tr>
<td>3</td>
<td>0.00</td>
<td>(0.00)</td>
<td>0.00</td>
<td>(0.00)</td>
<td>0.00</td>
<td>(0.00)</td>
</tr>
</tbody>
</table>

Note: All values are mean ± standard deviation (SD).
The percentage of sleep time in the supine position was elevated from a mean of 39% to 45% (6%) in the intervention group but was unchanged in the control group at PSG 2, compared to baseline. The BMI remained stable in both groups: no change in the intervention group and an increase of 0.4 kg/m² in the control group.

The ITT analysis, in which all parameters in Table 3 were calculated for the 71 randomised patients, did not change the results compared to the per protocol analysis with 65 patients.

In total, six of 32 patients had non-serious complications. Four had prolonged duration of pain treated with various analgesics, and two patients had...
postoperative bleeding and were treated medically. One had a night of observation in hospital three days after surgery. There were no serious complications or mortality. No patient was excluded owing to serious clinical impairment.

**SKUP³ RCT DAYTIME SLEEPINESS AND QUALITY OF LIFE (PAPER 4)**

**Results**

All 65 participants completed all ESS questionnaires, and the results were analysed in the available data analysis (*per protocol*). The median ESS had significantly decreased from 12 (range 8–21) to 6 (2–16) (*p* < 0.001) in the intervention group, with a mean reduction of 5.7 (sd 3.9). The corresponding change for the control group was non-significant, from a median of 13 (8–18) to 12 (5–21), a significant difference between the groups (*p* < 0.001) (Figure 17, Table 5).

The SF-36 questionnaires were completed by 65 participants. Three patients failed to respond to one, two or three domains, respectively. In the intervention group, all domains showed improvements, and they were statistically significant for RP, GH, VT, SF and MH, as well as MCS and PCS. Changes in the control group were non-significant, and significant changes between the two groups were seen in GH, VT, SF, MCS and PCS (Table 5).

In the vigilance tests, only 48 of 65 patients had complete data (baseline and follow-up), with a drop-out rate of 26%. However, 57 patients had complete follow-up data, with a drop-out rate of 12%. In the available data analysis, the median sleep latency in the intervention group was significantly changed from 38.4 min (range 11–40) to 40 min (16–40), (*p* = 0.013), a median difference of

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**Table 4.** Mean apnoea-hypopnoea index (AHI) at polysomnography (PSG) 1 and PSG 2 in different subgroups and mean difference between groups

<table>
<thead>
<tr>
<th>Intervention group n=32</th>
<th>Control group n=33</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSG 1</td>
</tr>
<tr>
<td>BMI &lt;30</td>
<td>23</td>
</tr>
<tr>
<td>BMI ≥30</td>
<td>9</td>
</tr>
<tr>
<td>Tonsil size 1–2</td>
<td>14</td>
</tr>
<tr>
<td>Tonsil size 3–4</td>
<td>18</td>
</tr>
<tr>
<td>Tongue position 1</td>
<td>9</td>
</tr>
<tr>
<td>Tongue position 2</td>
<td>20</td>
</tr>
<tr>
<td>Tongue position 3</td>
<td>3</td>
</tr>
<tr>
<td>Friedman stage I</td>
<td>16</td>
</tr>
<tr>
<td>Friedman stage II</td>
<td>16</td>
</tr>
</tbody>
</table>

Data are mean (SD) for within-group comparisons and mean (95% confidence interval) for between-group comparisons.

*p* values from comparisons of dependent samples within groups and from independent samples between groups (*t*-tests).

Significant differences (*p*<0.05) are shown in bold type. BMI, body mass index; n, number of patients in each group.
**Figure 17.** Results for Epworth Sleepiness Scale (A) and ‘excessively sleepy’ question (B) for the intervention and the control group, respectively. Boxes represent the median and 25% and 75% values, whiskers the non-outlier range and dots the outliers. P-values represent the changes within groups, WSR test.

### A.
Box plots and lines showing the Epworth Sleepiness Scale (ESS) on two different polysomnography occasions (before and after) in the intervention group (grey) and the control group (white), respectively.

### B.
Box plots and lines showing the ‘excessively sleepy’ question on two different polysomnography occasions (before and after) in the intervention group (n=31)(grey) and the control group (n=32)(white), respectively.

### Table 5. Results from PSG 1 and 2 in each group, also within and between groups comparisons in the available data analysis

<table>
<thead>
<tr>
<th></th>
<th>Intervention group</th>
<th></th>
<th></th>
<th>Control group</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td></td>
<td>p-value</td>
<td>n</td>
<td></td>
<td>p-value</td>
</tr>
<tr>
<td>ESS</td>
<td>32</td>
<td>12.5 (3.2)</td>
<td>&lt;0.001</td>
<td>33</td>
<td>12.9 (3.1)</td>
<td>12.5 (3.9)</td>
</tr>
<tr>
<td>SF-36 PF</td>
<td>32</td>
<td>83.7 (19.2)</td>
<td>0.094</td>
<td>33</td>
<td>87.0 (18.4)</td>
<td>87.4 (16.7)</td>
</tr>
<tr>
<td>SF-36 RP</td>
<td>31</td>
<td>68.5 (36.5)</td>
<td>0.633</td>
<td>33</td>
<td>75.8 (39.3)</td>
<td>81.1 (31.9)</td>
</tr>
<tr>
<td>SF-36 BP</td>
<td>31</td>
<td>78.3 (27.1)</td>
<td>0.009</td>
<td>32</td>
<td>80.9 (23.0)</td>
<td>80.6 (25.9)</td>
</tr>
<tr>
<td>SF-36 GH</td>
<td>32</td>
<td>61.3 (24.1)</td>
<td>0.001</td>
<td>32</td>
<td>59.0 (23.7)</td>
<td>58.0 (25.6)</td>
</tr>
<tr>
<td>SF-36 VT</td>
<td>32</td>
<td>42.8 (22.0)</td>
<td>&lt;0.001</td>
<td>32</td>
<td>41.4 (21.7)</td>
<td>42.8 (24.3)</td>
</tr>
<tr>
<td>SF-36 SF</td>
<td>32</td>
<td>74.2 (23.8)</td>
<td>0.405</td>
<td>33</td>
<td>77.3 (22.2)</td>
<td>69.7 (29.8)</td>
</tr>
<tr>
<td>SF-36 RE</td>
<td>31</td>
<td>76.3 (36.7)</td>
<td>0.059</td>
<td>33</td>
<td>81.8 (34.5)</td>
<td>89.9 (27.0)</td>
</tr>
<tr>
<td>SF-36 MH</td>
<td>31</td>
<td>71.8 (19.3)</td>
<td>0.009</td>
<td>32</td>
<td>65.4 (18.6)</td>
<td>70.4 (19.7)</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>31</td>
<td>47.8 (8.3)</td>
<td>0.009</td>
<td>31</td>
<td>49.0 (9.0)</td>
<td>48.3 (9.1)</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>31</td>
<td>41.1 (10.8)</td>
<td>0.001</td>
<td>31</td>
<td>41.0 (10.2)</td>
<td>42.7 (11.5)</td>
</tr>
<tr>
<td>Sleep latency (minutes)</td>
<td>22</td>
<td>31.7 (10.8)</td>
<td>0.033</td>
<td>26</td>
<td>35.0 (8.0)</td>
<td>32.8 (10.9)</td>
</tr>
</tbody>
</table>

Data are the mean (sd) and p-values from the Wilcoxon signed-rank test for within-group comparisons. P-values from independent samples between-group comparisons, Mann-Whitney U tests. Significant differences, p < 0.05, are marked in bold. n = number of patients.
1.6 min and a mean change of 7 (12.4) min. Before intervention, 9 out of 22 (41%) patients passed the vigilance test, but, at follow-up, 20 of 22 patients (91%) passed the 40-minute test. In the control group, the median sleep latency remained unchanged with 40 min (15.5–40) at baseline and 40 min (3.65–40) at the follow-up. In the control group, 16 of 26 (62%) of the patients passed the vigilance test at baseline and 15 of 26 (58%) at the follow-up. The difference in sleep latency between the two groups was significant: p = 0.011.

The Kaplan-Meier analysis of the sleep latency from vigilance tests with data at the follow-up for 27 patients in the intervention group and 30 in the control group showed a significant difference between the two groups: log-rank test, p = 0.0182; see Figure 18.

For the correlation analysis, the mean changes (sd) for all 65 patients between follow-up and baseline data were used. The parameters for nocturnal respiration from PSG were as follows: AHI, -18.8 (24.9), nadir of oxygen saturation, 3.1 (6.2) and arousal index, -16.2 (23.1).

There were significant correlations between changes in ESS and changes in the AHI (Figure 19), nadir of oxygen saturation, arousal index, the SF-36 domains SF, VT and MCS, and sleep latency (Table 6). In addition, there were significant correlations...
Figure 19. Correlation between changes in Epworth sleepiness scale (ESS) and in apnoea-hypopnoea index (AHI), n=65. P=0.001, Spearman’s rank correlation (SRC test), R=0.389. Transparent dots for intervention group and filled dots for control group.

Table 6. Correlations between changes in ESS, nocturnal respiration, sleep latency and SF-36, respectively, in available data analysis

|                      | Change in ESS | Change in SF-36 PF | Change in SF-36 BP | Change in SF-36 GH | Change in SF-36 VT | Change in SF-36 SF | Change in SF-36 RE | Change in SF-36 MH | Change in SF-36 PCS | Change in SF-36 MCS | Change in sleep latency |
|----------------------|---------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|-----------------------|------------------------|
| Change in AHI        | 1             | -0.09              | -0.11              | 0.07               | -0.17              | -0.56 ***          | -0.50 ***          | 0.19               | -0.04              | -0.12              | -0.30 *               | 0.47 ***              |
| Change in AHI (%)    | -0.33 **      | -0.07              | 0.14               | 0.00               | 0.30 *             | 0.24               | 0.27 *             | -0.01              | 0.12               | 0.13               | 0.16                  | 0.23                  |
| Change in arousal index | 0.36 **      | -0.11              | -0.09              | 0.05               | -0.23              | -0.24              | -0.24              | -0.03              | -0.06              | -0.14              | -0.31 *               |                      |
| Change in sleep latency (n=48) | 0.47 *** | 0.07               | 0.20               | 0.23               | 0.27               | 0.38 **            | 0.41 **            | -0.33 *            | -0.33 *            | 0.31 *               | 0.03                  | 1                     |

Spearman’s rank correlation test was used. R values are presented. Significant correlations (p < 0.05) are shown in bold.

* P < 0.05, ** P < 0.01, *** P < 0.001. n = number of patients
correlations between changes in ESS, VT and SF and sleep latency, respectively. Reversely, there was a significant negative correlation between RE and sleep latency, $R = -0.33$, $p = 0.024$; Table 6.

Sixty-three patients responded to the ’excessively sleepy’ question and were in the available data analysis, with 1 drop-out in each group. The median value had decreased from 5 (4–5) to 3 (1–5) in the intervention group ($p < 0.001$) and had changed non-significantly in the control group from a median of 5 (4–5) to 5 (2–5), also with a significant difference between the two groups ($p < 0.001$), see Figure 17.

The ITT analysis for all 71 randomised patients for the ESS did not change the results compared to the per protocol analysis comprising 65 patients. $t$-tests showed no significant differences compared to the non-parametric results presented in Table 5.

**DISCUSSION**

OSAS is a general health problem that causes daytime sleepiness, an impaired quality of life and increased morbidity and mortality. Since there are many patients who do not accept or adhere to treatments with CPAP and/or MRD, there is a need for effective alternative surgical treatments.

**Tracheostomy**

In Paper 1 the major finding was that in selected patients with severe OSAS and obesity, tracheostomy may be an alternative treatment. Furthermore, tracheostomy was tolerable in the majority of patients. The patients in this study received a custom-made tube and careful information, support and regular follow-ups, which may have influenced the results. However, in studies where individualised tubes were not made, similar tolerability has been reported.¹⁴¹, ¹⁴³, ¹⁴⁵

All patients improved their daytime sleepiness measured with the ESS questionnaire. One explanation for this reduction of sleepiness might be fewer deep desaturations and a decreased time of oxygen tension lower than 90% after tracheostomy, which could be observed in three of these patients. However, there are many other studies showing divergent results between objective and subjective outcomes.⁷⁶

Previous studies have shown that tracheostomy is effective in terms of nocturnal breathing and mortality.¹⁴¹, ¹⁴⁷ The finding that the ODI$_4$ was not normalised in five patients despite the tracheostomy by-pass may be explained by the fact
that they were still obese. They might have had an undiagnosed OHS, which can co-exist in patients with OSAS. Unfortunately, blood-gas samples were not obtained in these patients. Some obstructive apnoeas may have changed into central apnoeas instead, as also found by Haapaniemi et al. The patients with persistently high ODI\textsubscript{4} values did not accept invasive CPAP (ventilator attached to the tube) treatment, which may reflect lower motivation for additional treatment because of improved daytime symptoms. This highlights the need for postoperative follow-up recordings, including blood gas samples and also evaluations of the need for assisted ventilation.

An additional finding in the present study was that tracheostomy served as a link to other treatments, for example, UPPP surgery, weight reduction or the use of CPAP again. The tracheostomy might improve the patients’ understanding of their OSAS disease, and therefore these patients may be better motivated for another attempt with non-surgical treatments. Some suitable patients could be offered other OSAS surgery, which should be performed while they still have their tubes in place to maintain a secure airway. Also in the study by Thatcher et al., it was found that a few of the 79 studied patients underwent decannulation because of switching to CPAP treatment, resolution of OSA after UPPP and weight loss.

Paper 1 has some limitations; the design was retrospective with a small number of patients, which made it difficult to draw general conclusions. Further PG and not PSG recordings were performed, and the nasal flowmetry or a thermistor was not considered reliable at the start of the study. Therefore, changes in the ODI\textsubscript{4} instead of the AHI were chosen as the outcome. In addition, follow-up data are missing for one patient who died of cancer. Finally, the fact that only custom-made tubes were used and the regular follow-ups at the NRC may have affected the results in a positive way.

The strengths of the study are that it reflects the difficult clinical situation for patients with severe OSAS who have had failed non-surgical treatments. We also consider it a strength that the study emphasises the need for a careful preoperative investigation of possible additional diseases and postoperative recordings, as well as an evaluation of the occurrence of hypercapnoea and the need for additional ventilator treatment.

**Uvulopalatopharyngoplasty**

Our main findings from the UPPP studies are that there was a significant difference in respiratory parameters, as well as daytime sleepiness, after UPPP compared to before surgery. The SKUP\textsuperscript{3} showed that these outcomes, as well as the quality of life, differed significantly in the intervention group, compared to
controls, in favour of the intervention group. Also, the ODI_{4} remain reasonably stable over time, as well as the symptoms of daytime sleepiness.

According to the 15-year follow-up after UPPP (Paper 2), the success rate according to the ODI_{4} was 17 out of 26 (65%) in the per protocol analysis. As reported earlier by Larsson et al., who had a higher number of follow-ups, the success rate was 30/50 (60%) after 6 months, 19/49 (39%) after 2 years and 24/48 (50%) after 4 years. In the SKUP^{3} (Paper 3), the success rate for the ODI_{3} was 66%. Furthermore, the mean AHI reduction in the intervention group was 60%, compared to 11% in the control group. Also patients with severe AHI values at baseline showed significant reductions of the respiratory parameters.

Our results can also be compared with those from a previous study by our group comprising 158 OSAS patients undergoing UPPP. The results showed a similar success rate (50% reduction and ODI_{4} < 20) of 64%, compared to the present study of 65% in the 15-year follow-up and 66% in the SKUP^{3}. Furthermore, a later analysis of the 158 patients in the study by Lundkvist et al. showed a mean reduction of the ODI_{4} of 60%, compared with mean reduction of ODI_{3} of 69% in the SKUP^{3}. Also, the mean AHI reduction of 60% after UPPP in the SKUP^{3} can be compared with those from other centres reported in a recently published meta-analysis of 15 cohort studies after UPPP with a wide range and a mean AHI reduction of 33%. Our success rates are better than those of most centres, which might be explained by the use of different surgical techniques and/or different selections of patients.

Although the respiratory parameters changed significantly in the SKUP^{3} study, surprisingly, we did not find any significant differences in the other sleep quality parameters, i.e., total sleep time, percentage of rapid eye movement (REM) and N3 stage sleep and sleep efficiency, between the two groups. A slight improvement in the percentage of deep and/or REM sleep would have been expected in the intervention group. However, the restricted sleep time, with wake-up at 6 a.m., may have influenced these results, especially in those who are used to sleeping longer in the mornings, a time when most of the REM normally occurs. Furthermore, the baseline values were mainly within the normal range, without the possibility of large-scale improvement. On the other hand, the mean total arousal index decreased in favour of the intervention group. Sleep fragmentation caused by arousals is considered to be a major factor in daytime symptoms.

The apnoea index decreased significantly, but the hypopnoea index was not reduced in the same marked way. Furthermore, there was a significant increase in the mean RERA index after UPPP, compared to the control group. These findings are in accord with a conclusion drawn in a review by Sher et al. and could be
explained by the hypothesis that UPPP only partially increases the airflow, thereby transforming an apnoea (90% flow reduction) to a hypopnoea (50% reduction) and a hypopnoea to an RERA (< 30% reduction).

When evaluating the excessive daytime sleepiness, the median ESS score after UPPP was 6 in the 15-year follow-up and, in the SKUP³ (Paper 4), the median ESS score was halved from 12 to 6 and the mean ESS deceased from 12.5 to 6.8 in the intervention group. These results are identical to those from the 1-year follow-up of 158 OSAS patients.¹²² The ESS results are also similar to those reported by Yaremchuk et al., where the mean ESS score was reduced by 5.6 after UPPP (in some patients including radiofrequency ablation of the tongue),⁹¹ compared to a mean reduction of 5.7 in this RCT. Our results are also comparable to those in a meta-analysis of CPAP or MRD treatments, where the mean ESS results decreased from 12.4 to 8.1 and 11.4 to 9.0, respectively.⁸ Also the ‘excessively sleepy’ question from the BNSQ showed a significant improvement in the UPPP group compared to the controls. It must also be remembered that the cut-off limit for inclusion in the present study was ESS ≥ 8 of a maximum of 24 and, for the ‘excessively sleepy’ score ≥ 4 of a maximum of 5. This may have influenced our results since it precluded a large improvement, especially for ‘excessively sleepy’. However, the cut-off limit for ESS in the SKUP³ was chosen to be in the lower interval of the cut-off for mild EDS.⁸⁸,¹⁵⁷ The 15-year follow-up (Paper 2) showed that 28 of 32 (88%) were ‘better’ or ‘cured’ concerning EDS, indicating both a stable EDS and ODI₄, although the large number of drop-outs after 15 years weaken the result.

Our vigilance test in the SKUP³ (Paper 4) was a modified Osler test, but it showed a significant mean improvement of 7 minutes in sleep latency after UPPP. This could be compared to the results from a meta-analysis including patients with severe OSAS which showed that CPAP therapy improved the mean sleep latency measured with the MWT significantly by only one minute, compared to placebo.¹⁵⁸ However, as there were only 22 of the 32 treated patients who underwent the test before and after UPPP, our results should be taken with caution. Because of the number of missing data for individual changes in the vigilance test, a Kaplan-Meier analysis for sleep latency at follow-up was performed. Also this test revealed significant differences between the two groups.

In order to understand EDS and other symptoms in OSAS, it is important to also look beyond the respiratory disturbances and consider the role of obesity and metabolic activity.¹²,⁷² Furthermore, there are many other different factors that could have an impact on daytime sleepiness and the QoL. This risk is especially pronounced in long-term follow-ups such as in Paper 2. However, the short follow-up time of six months in Papers 3 and 4 may minimise such
possible changes. Again, it cannot be excluded that the outcome in the self-reported questionnaires may be affected by the placebo effect of surgery and recall bias. However, the objective vigilance tests as well as PG and PSG, are less sensitive to placebo effects, and these investigations showed the same pattern as the questionnaires.

In Paper 2, there was a surprisingly high satisfaction rate of 78% and few regrets, considering the very long follow-up period, which may reflect the fact that the majority of the patients considered themselves improved in their symptoms. Subjectively, the majority had improved or cured EDS and were satisfied. Our results are well in line with those of another Swedish long-term follow-up study\(^\text{137}\) of 186 patients who had undergone UPPP, in which only 66 of 129 (51%) patients who had completed the questionnaire were satisfied with their treatment. As described by the authors, UPPP was performed according to Fujita.\(^\text{121}\) The cold knife technique was used in all but 11 patients, in whom the laser technique was performed. Also, a phoniatric investigation was performed prior to surgery to determine how much of the soft palate could be removed. The satisfaction rates of the patients did not differ between the surgical techniques in their study. The reasons for the different results from ours could be that they underwent a more radical surgical technique.

The results from Paper 2 concerning subjective snoring showed that 13 of 32 (40%) rated this as ‘never’ or ‘sometimes’. Regarding objective snoring from the PG recording, 9 of 26 patients (35%) were categorised as non-snorers at the follow-up. Furthermore, the results showed that the level of success for snoring was quite low, but this did not seem to influence the satisfaction rating. Also, even among the patients who had complementary treatment (CPAP, MRD or mandibular surgery), the majority were satisfied with the surgery.

Regarding the quality of life, compared to the general Swedish population, the patients in SKUP\(^3\) (Paper 4) had a lower subscale score on the SF-36, especially on RP, GH, VT and SF, but it increased to normal or less subnormal values for the present age group after UPPP.\(^\text{159}\) Many studies show significant adverse effects of sleep apnoea on the patients’ quality of life, but also that CPAP treatment improves the SF-36 scores, especially on RP, GH, VT and SF.\(^\text{114, 160, 161}\)

The SKUP\(^3\) study (Paper 4) showed significant correlations between changes in subjective and objective outcomes, also with nocturnal respiration. There were significant correlations between changes in ESS and the AHI and the nadir of oxygen saturation, as well as the arousal index, suggesting that the improved quality of sleep and respiration increase the self-reported EDS, and that the effect may be caused by UPPP. Also, the objective vigilance test showed signifi-
cant correlations between changes in ESS and sleep latency, as well as changes between the AHI and GH, VT and SF. This can be compared to the findings of Bennett et al., in which 51 patients with SDB were evaluated concerning the quality of life measured with the SF-36 before and after CPAP treatment. PSG was performed at baseline. Significant associations were found between AHI and arousals and change in the VT and PR. Furthermore, sleepiness measured with the ESS and OSLER correlated significantly with the pretreatment values of the SF-36 domain VT.

An inconsistent finding in our study was the negative significant correlation between changes in sleep latency and the SF-36 domain role emotion (RE). This may be explained by the fact that the three patients with the most impaired sleep latency had improvements in RE. On the other hand, the finding of few improvements in some aspects of the quality of life in the expectancy group is not unexpected, as all patients were part of a study and probably felt cared for. However, the findings that three SF-36 domains, GH, VT, and SF, all showed highly significant differences between groups in favour of UPPP, are important and consistent.

Significant correlations between the SF-36 and the degree of OSAS, as well as between the respiratory disturbance index and the ESS, have been demonstrated previously. To the best of our knowledge, the UPPP findings with correlations for changes in the PSG parameters, daytime sleepiness symptoms and quality of life, respectively, have not been reported previously in adults with OSAS.

The results concerning postoperative subjective pharyngeal symptoms in Paper 2 showed that the pharyngeal symptoms after UPPP are mild even in long-term aspects (median value of 3 of maximum 30). The results are comparable to the ones in the study by Lundkvist et al., in which the median score was 5 one year after UPPP. Jäghagen et al. have performed objective measurements (videoradiography) of the swallowing process before and after pharyngeal surgery, and preoperative pharyngeal swallowing dysfunction was not shown to predict the development of dysphagia after surgery. There have been reports of large percentages of dysphagia and globus sensation in UPPP patients, but the surgical techniques have changed over time, making the reports confusing. Often a mixture of different methods has been used and the reports are therefore difficult to interpret. However, at our centre, a similar conservative technique using cold steel with a one-stage procedure has been performed throughout the years and further modified in 2007 at the start of SKUP.

In the SKUP (Paper 3), 6 of 32 patients had non-serious complications, two of which (6%) were postoperative bleeding and were treated medically. The fact
that no patients had severe complications may be the result of our safety programme, which was supplemented with cortisone and tranexamic acid, compared to the previous study by Lundkvist et al. in 158 patients,\textsuperscript{122} with four (2.5\%) intraoperative complications, mostly bleedings after tonsillectomy. As only 32 patients so far have been evaluated concerning complications, the figures should be taken with caution, but further evaluation also of side-effects in all 65 patients is planned.

The mortality after UPPP was investigated in Paper 2. The SMR indicated no increased mortality in this heterogeneous OSAS population, compared to the general population in Sweden. Several studies have indicated an approximately 3–6 times increased mortality in untreated OSAS.\textsuperscript{3-5} One reason for the low mortality rates in Paper 2 could be the fact that several patients were treated with CPAP, MRD or had additional mandibular surgery. Another speculative reason could be a protective role of having moderate OSAS at more advanced ages, as suggested by Lavie et al.\textsuperscript{70} It must not be ignored that UPPP could have a protective effect, as described by other authors.\textsuperscript{134}

The efficacy of UPPP in OSAS treatment has been questioned because of the lack of randomised studies.\textsuperscript{9} Furthermore, there has also been a call for research in RCTs of surgery other than UPPP and UPP because of the fear of a high risk of long-term side-effects,\textsuperscript{163} as discussed above. The only previous RCT of UPPP compared to expectancy is a study by Lojander et al., described above.\textsuperscript{138} The ODI\textsubscript{4} changed significantly from 45 to 14 in the intervention group, compared to 34 to 23 in the control group, but the difference between the groups was not significant. The results may be explained by their small study sample. There are few other RCT studies on surgical intervention for OSAS. Woodson et al. conducted an RCT of blinded treatment in OSAS patients using a temperature-controlled radiofrequency and Steward et al. with palatal implants of the soft palate, both compared to sham-placebo.\textsuperscript{149, 164} None of these studies were able to show any significant improvement in the AHI compared to control as was shown in the present SKUP\textsuperscript{3}. The efficacy of UPPP compared to untreated controls in the present setting is hereby proven, even though further RCTs at other centres are needed.

UPPP includes tonsillectomy \textit{per definition} and has been a well-known surgical treatment for OSAS since it was first introduced in 1981.\textsuperscript{121} However, there are always difficulties when evaluating a two-stage treatment. In adults, studies evaluating tonsillectomy for OSAS are rare. One study of nine adult OSAS patients with large tonsils who underwent tonsillectomy showed an 80\% success rate.\textsuperscript{152} Adult OSAS patients with large tonsils are few in number, only 6\% according to one study.\textsuperscript{35} The majority have a soft palate and uvula which has been
traumatised and deranged after several years of snoring and vibrations, leading to bulky tissue which obstructs the airway during sleep. The results from the study by Lundkvist et al. for 158 OSAS patients undergoing UPPP showed that young age, but not tonsil size was a success factor.\textsuperscript{122} In our experience, tonsillectomy independently of tonsil size is important, as a part of UPPP in OSAS as it enables the lateralisation and suturing of the posterior tonsillar pillar, thus widening the airway space, which is supported by the results in Paper 3 and the study by Lundkvist et al.\textsuperscript{122} A meta-analysis of LAUP showed an AHI reduction of 32%, comparable to 33% in UPPP,\textsuperscript{124} indicating that the palatal resection also improves nocturnal respiration.

The results of our studies show that UPPP could be offered to selected patients: Friedman stage I or II and BMI < 36, who have failed non-surgical treatments and have no contra-indications to surgery. Patients with a BMI of up to 40 have undergone UPPP at our clinic, as also reported in our previous study,\textsuperscript{122} and in a study by Friedman,\textsuperscript{104} as salvage procedure and after careful preoperative information. To severe obese patients with Friedmans stage III, or stage IV (BMI>40), or with other severe co-morbidities, who have totally failed non-surgical treatment, tracheostomy should be offered instead. For younger patients with Friedman stage I and BMI < 36, UPPP may be an option as a first line treatment.

When discussing the efficacy of different treatment options for OSAS, it is of importance to consider the compliance in everyday life. Devices are only effective while they are used. CPAP treatment is often considered to be compliant when patients use CPAP ≥ 4 hours/night as an average over all nights observed. However, this may hide insufficient reductions of the AHI. When comparing non-optimal use of optimal CPAP therapy with the continuous effect (100% compliance) of often not optimal UPPP surgery, it would be more appropriate to compare the AHI according to a mean AHI over the night, also for CPAP. According to a study by Ravesloot et al.,\textsuperscript{165} the episodes without effective treatment indicate that patients with moderate OSAS reduce the AHI only by 33–48% when using CPAP 4 hours per night and those with severe OSA reduce their AHI by 42%.

There has also been a worry as to whether UPPP influences future use of CPAP.\textsuperscript{166} The surgical method used at the start in the 1980s and 1990s was more radical than it is today. The patients in the present studies had only minor resections of the soft palate and uvula, i.e., a modified UPPP. A small Chinese study compared the classical UPPP with a modified UPPP and noted that all the problems with CPAP titrations occurred in the group of classical UPPP patients.\textsuperscript{167} Based on our studies and clinical experience, patients who fail surgical treatment could return to CPAP or MRD and comply.
In all studies, especially in long-term follow-up studies as in Paper 2, there is always a risk of other changes: for example, in lifestyle or other treatments that may influence the results. In Paper 2 the median BMI did not change over the years, which might be explained by our clinical practice of informing all patients of the importance of a stable weight. Also in Papers 3 and 4, the mean BMI and mean time in the supine position were stable in both groups, and thus probably did not affect the results.

There are several limitations in Paper 2: firstly, the lack of a randomised control group and, secondly, a 15-year recall bias. Thirdly, a relatively small number of patients were subjected to the 15-year follow-up sleep apnoea recording, and no ITT analysis was performed. However, the very long follow-up quite naturally explains that 11 patients did not show up and that 13 were deceased. Altogether, the subgroup analyses indicated quite homogeneous groups at baseline, as well as stable and equal postoperative results of the sleep recordings throughout the years for all subgroups. Fourthly, the sleep apnoea recordings have clear weaknesses compared with the technology of today, since the AHI parameter was not measured at the Neurophysiological Department that we referred our patients to. During the 1980s, the available measuring technique with thermistors was not considered reliable in ambulatory monitoring. However, it is possible that oxygen desaturations have a great impact on cardiovascular health.168 Fifthly, there was no wash-out period for the patients with CPAP and MRD. However, the subjective outcome did not show any major differences and the ODI4 was higher than in the group without complementary treatment, as was expected. Other studies have shown that the majority of apnoeas relapse already during the first night without CPAP.169 Sixthly, the questionnaires used for EDS, satisfaction, snoring and pharyngeal symptoms have not been validated. Finally, we consider it a weakness that according to baseline parameters, 8 patients had no EDS and 1 patient had an ODI4 value of 4. However, we cannot exclude the possibility that these patients suffered from other symptoms of OSAS.

The main limitations of Papers 3 and 4 are the missing data and drop-outs for the vigilance test in both groups, but also the fact that six patients were excluded after randomisation. On the other hand, these patients were allocated to separate groups, and sensitivity analyses were performed and did not affect the results. Furthermore, there is the short duration of only six months, but the researchers, as well as the Ethical Approval Committee, found it unethical to leave the patients in the control group untreated for a longer time. Also, the PSG was not performed on two following nights at each evaluation point. However, all patients had undergone ambulatory PG before the baseline in-lab PSG, which implies that the AHI limit of 15 or more for inclusion was valid. Another weakness in Paper 4 is that the MWT was not used. However, the MWT is resource and
time-demanding, and our patients did not receive any economic compensation for the time spent in the study, which explains a high drop-out rate, and also that we were only able to perform the vigilance test once per day (modified OSLER). Yet, another study showed that the four times repeated OSLER test during one day produces reproducible and stable results over time in OSAS patients. A further weakness is that the vigilance was performed in different rooms and was not evaluated with an error profile, which could have refined the assessment of the variations. It must be taken into account that the change in vigilance may be affected by the fact that the patients were censored at 40 minutes in the vigilance test. Altogether, the results from the vigilance tests must be interpreted with caution, although we cannot ignore the fact that our results are coherent.

The most important strength of Paper 2 is the very long-term follow-up, including sleep recordings. Furthermore, the majority of these patients have undergone four different follow-ups over the years, which enabled us to show consistency in the results from sleep recordings. Also, considering the time period, the drop-out rate for the subjective measurement was quite low. Finally, the Swedish social security number register makes it possible to follow the study population’s mortality rates and causes.

The major strength of Papers 3 and 4 is the randomised, controlled design, but also the investigation of the OSAS patients with in-laboratory PSG, the application of the ESS for subjective evaluation of daytime sleepiness and the use of an objective vigilance test, as well as the well-known SF-36 questionnaire. Furthermore, the PSG recordings were performed the night before the vigilance test, allowing assessment of the quality of sleep. Additionally, only a single person, blinded to patient grouping, interpreted all PSGs manually and there were no drop-outs for PSG data in the study. The most probable reason why no one dropped out is that we encouraged the surgery patients on several occasions to complete their follow-up. Another strength is that eight different surgeons performed the surgery, which means that the result is not dependent on a single surgeon. In addition, the correlation tests in Paper 4 showed statistical significance and that the results from subjective and objective symptoms of daytime sleepiness and from PSG are concordant. Furthermore, our main results in Paper 4 were verified by both parametric and non-parametric statistical methods and it was also verified that the ITT analyses in Papers 3 and 4 did not markedly change the results compared to the per protocol analyses.

There is considerable evidence for OSAS being an anatomical disorder; patients with OSAS have an enlargement of the upper airway soft tissue structures, are often obese with an increased neck size and fat deposition along the upper airway, and several studies have also demonstrated a family aggregation of
craniofacial morphology. But there are also numerous arguments for obesity and its metabolic activity in development of OSAS. OSAS is probably a syndrome with many different faces. Nevertheless, the different treatment options serve to increase upper airway dimensions by altering upper airway anatomy.

Management of the OSAS patient is challenging. In the clinic and daily handling of these patients, all treatment options, both non-surgical and surgical, should be regarded as a spectrum of possibilities. The options often supplement each other when customizing an often life-long treatment to each patient individually. Also, in patients failing upper airway surgery, additional treatments with MRD or CPAP appear to be feasible.

The efficacy of UPPP in OSAS treatment has been questioned, as well as its very existence, because of a fear of side-effects and a lack of high-quality studies. In summary, the studies in this thesis show that there is a place for surgical treatment options in OSAS and that modified UPPP can be both safe and effective compared to controls. Furthermore, the fact that a previous prospective cohort study of 158 OSAS patients at our centre, and the 15-year follow-up, showed very similar subjective and objective outcomes compared to this RCT, certainly strengthens the positive effect of modified UPPP. However, more RCTs at other centres are needed.
GENERAL APPLICATIONS

In Paper 1, there were only 10 patients over a time period of five years who had tracheostomy for severe OSAS, indicating a very small and selected group of patients who are offered this treatment option, which makes general application difficult. The patients had standard tracheostomy surgery according to our clinical routines, but the fact that only custom-made tubes were used may limit the generalisability.

The study population in Paper 2 was heterogeneous concerning the degrees of severity of OSAS, the level of daytime sleepiness, obesity and cardiovascular co-morbidity. This could partly be explained by the fact that UPPP was practically the only available treatment for OSAS at the time, and it was offered to all in whom there was no major contraindication for surgery. At study start, this heterogeneous patient group most probably reflected the OSAS population eligible for surgical treatment at that time.

Conversely, the general population of adult OSAS patients in Sweden today is not similar to the one in Papers 3 and 4. Firstly, the population in the SKUP3 was at least 10–15 years younger and the majority had a BMI of less than 30 kg/m², much lower than the general adult OSAS population, also compared with a population having CPAP treatment. Secondly, the SKUP3 does not address patients with Friedman stage III or OSAS patients with severe co-morbidity or a BMI ≥ 36 kg/m². Furthermore, the SKUP3 was a single-centre study, and more centres are needed to enhance the generalisability.

The patients in Papers 1, 3 and 4 had not succeeded in complying with other alternative and non-surgical treatments, and the alternative to tracheostomy or UPPP was no treatment at all. Additionally, for all four studies, there were only few women. Consequently, the results of the present studies do not address all OSAS patients seen in general clinical practice.

The general applicability in these four studies is, however, valid, as all studies reflect our daily clinical routines at the ORL department. Patients who fail or do not accept non-surgical treatments should be referred to ORL specialists for assessment for upper airway surgery.
CONCLUSIONS

1. Elective tracheostomy was a tolerable and effective treatment in terms of daytime symptoms in a majority of selected patients with severe OSAS and served as a link to other treatments. Not all patients showed improvement in nocturnal respiration, and therefore postoperative sleep recordings are needed.

2. UPPP was a stable and successful treatment after 15 years according to the reduction of nightly respiratory disturbances and daytime sleepiness symptoms, and no increased mortality was seen compared to the normal population.

3. The RCT showed a highly significant and clinically relevant difference in respiratory disturbances in favour of UPPP, compared to expectancy, in selected OSAS patients. Also patients with small tonsils may benefit from surgery.

4. The RCT showed a highly significant and clinically relevant reduction in daytime sleepiness and sleep latency, as well as improvement in the quality of life, in favour of UPPP, compared to expectancy in selected OSAS patients. Significant correlations between changes in subjective (questionnaires) and objective (vigilance and PSG data) outcomes were seen.
FUTURE PERSPECTIVES

This thesis has raised many new questions.

Tracheostomy is a seldom used treatment option in patients with OSAS and therefore large randomised studies are difficult to perform. However, it is desirable to have future studies on the effect of tracheostomy and also to include measurements of changes in the quality of life and changes in metabolic parameters, the occurrence of hypercapnoea and the need for additional ventilator treatment.

Even though there is increasing evidence concerning which patients we may be able to help or cure with UPPP, there are still many questions to be answered. Friedman’s staging system is helpful, but there are also more anatomical factors to take into account, for example, the constitution of the tonsillar pillars, uvula and the tongue base, as well as sites of collapse during sleep. It would be interesting to investigate whether further anatomical correlates will help to refine the assessment of which OSAS patients we should offer UPPP surgery or not. Also, more RCTs comparing tonsillectomy, UPP and UPPP are recommended to further clarify the question of which parts of the surgery, or if all parts, are necessary in all patients.

Today, UPPP and other upper airway surgery methods are used primarily in patients who have rejected CPAP and other non-surgical treatments. With the knowledge of OSAS being a disease that may aggravate over time, should UPPP surgery be offered to younger patients as an early intervention to prevent the progression? In that case, which factors should predict an early recommendation of UPPP? A further step would also be to investigate the upper airway structure, respiratory airflow and breathing control, and also to determine which level of the obstruction site is the most important. Simulations of the airflow could also help to predict which patients will be cured and improved by upper airway surgery. Future studies with a multidisciplinary approach to investigating these more sophisticated diagnostic methods are both challenging and tempting.

Another question is the gender factor. Is the success factor the same in females and males? Also, how important is BMI for surgical success? It would also be highly useful to evaluate how UPPP affects blood pressure and other metabolic parameters. Further research priorities are evaluations of respiratory parameters, side-effects, the risk of traffic accidents and mortality in the long-term perspective. Is the AHI a surrogate measurement for OSA? More studies to investigate correlations of objective and subjective parameters are also needed.

Finally, our hope is that this thesis can be the start of a continuous effort to elaborate national standardised procedures for upper airway surgery in OSAS patients.
OBSTRUKTIVT SÖMNNESPÅSEYNDROM (OSAS) HOS VUXNA ÄR EN FOLKSJUKDOM MED EN FÖREKOMST PÅ 4% HOS MÄN OCH 2% HOS KVINNOR. PATIENTerna HAR OFTA UTTALAD SNARKNING SAMT ANDNINGSUPPEHÅLL UNDER SÖMN OCH FÅR SYREBRIST OCH STÖRD SÖMNKVALITET P.G.A. TÄTA MIKROUPPVAKNANDE. DETTA LEDER TILL DAGSÖMNIGHET OCH HÖGRE UTSCÖNDNING AV STRESSHORMONER MED PÅFÖLLJANDE MEDICINSKA KOMPLIKATIONER, TILL EXEMPEL ÖKAD RISK FÖR HJÄRTKÄRLSJUKDOM, DIABETES, TRAFIKOLYCKOR OCH EN ÖKAD DÖDLIGHET. DEN STÖRSTA RISKFAKTORN FÖR OSAS ÄR FETMA. ANDRA ORSAKER ÄR AVVIKANDE ANATOMI I DE ÖVRE LUFTVÄGarna, EXEMPELVIS STORA HALSMANDLAR, STOR TUNGA, HÄNGANDE GOMSEGEL.

IDAG ÄR DEN VANLIGASTE BEHANDLINGEN FÖR OSAS EN ÖVERTRYCKS-MASK S.K. CPAP, SOM PATIENTEN HAR FRAMFRÖN ANSIKTET UNDER SÖMN. EN ALTERNATIV BEHANDLING ÄR EN UNDERKÄKSFRAMDRAGANDE BETTSSKENA, S.K. MRD. CIRKA HALFTEN AV PATIENTerna SOM ERBJUDS DESSA HJÄLPMEDEL ANVÄNDER DET INTE PÅ ETT OPTIMALT SÄTT, EXEMPELVIS P.G.A. BIVERKNINGAR ELLEP OTILLRÄCKLIG Effekt. Vidare har långtidsuppföljningar visat en följsamhet på endast ca 50-70% av dessa icke-kirurgiska behandlingar. DÄRFÖR har DET ALITID FUNNITS ETT BEHOV AV KIRURGI SOM ALTERNATIV EFTERSOM MÅNGA PATIENTER ANNAS RISKERAR ATT FÖRBLI OBEHANDLADE.

DEN FÖRSTA KÄNDA KIRURGISKA BEHANDLINGEN AV OSAS ÄR TRACHEOSTOMI, VILket INNEHÄR EN ALTERNATIV LUFTVÄG DIREKT IN I ÖVRE DELAN AV LUFTSTRUPEN OCH PÅ SÅ VIS UNDVIKS DE TRÅNGA PARTIerna I SVALGET. TRACHEOSTOMI ANVÄNDS IDAG SOM BEHANDLING FÖR OSAS ENSTAKLIGT I SÄRSKILT UTVALDA MYCKET SVÅRBEHANDLADE FALL, SOM T.EX. KRAFTIGT ÖVERVITIGA MED KOMPLOCERANDE SJUKDOMAR.

FRÅN BÖRJAN AV 80-TALET började OSAS-PATIENTER GENOMGÅ OPERATION MED SVALGKIRURGI, SÅ KALLAD UVULOPALATOPHARYNGOPLASTIK (UPPP), vilket innebär bortopererande av halsmandlar samt gomplastik. Metoderna, lyckandegraden samt biverkningsfrekvensen för denna operation har varierat genom åren. En nordisk SBU rapport om OSAS från 2007 kom fram till att det inte fanns tillräckligt med vetenskapligt stöd för om UPPP är effektivt som behandling av OSAS, då det saknades randomiserade kontrollerade studier (RCT), samt att det förelåg hög risk för svalg-biverkningar och komplikationer i samband med kirurgin. DÄRFÖR har Det varit delade meningar om UPPP har en plats som behandling av OSAS.

Denna avhandling studerar två kirurgiska behandlingsmetoder för OSAS; tracheostomi samt modifierad UPPP (skonsam kirurgisk teknik).

I DELARBETE 1 utvärderade vi 10 patienter med grav OSAS och övervikt samt symptom på dagsömnighet. Patienterna hade inte tolererat eller accepterat icke-kirurgisk behandling. Trachealkanylerna var individuellt utförmade. 8 av 10 patienter tolererade trachealkanylen mer än 6 månader. Vid uppföljningen hade alla patienter normaliserat sina dagsömnighetsvärden, men den uppföljande sömmer egningen visade att 5 patienter inte fick normalisering under sömn, trots trachealkanylen. Det är viktigt med noggrann uppföljning för att fånga upp de patienter som behöver tilläggsbehandling.
I DELARBETE 2 fortsatte vi utvärderingen av 50 patienter som opererats med UPPP pga OSAS 15 år tidigare. Vid denna långtidsuppföljning hade 13 patienter dött. Av resterande 37 levande patienter gjorde 26 stycken den uppföljande sömnregistereringen. Denna visade att antalet andningsstörningar för gruppen var uttalat förbättrade jämfört med före operationen, och fortsatt låga. 32 av de 37 patienterna svarade på enkäter vid uppföljningen. Resultaten visade att även den subjektiva dagsömnigheten upplevdes som låg och stabil, samt att 78% av patienterna som svarade på enkäten var nöjda med operationen. Dödligheten för de opererade patienterna var inte ökad jämfört med den ålders- och köns-matchade normalbefolkningen i Sverige, vilket kan tyda på att UPPP har en viss skyddande effekt.

DELARBETE 3 är en randomiserad kontrollerad studie (RCT) kallad SKUP³ där 32 patienter lottades till UPPP direkt (operationsgruppen) och 33 patienter till exspektans i 6 månader och fördröjd UPPP (kontrollgruppen). Patienter aktuella för studien hade alla BMI <36, samt stora halsmandlar, eller små halsmandlar i kombination med låg tungposition. För operationsgruppen var minskningen av antalet andningsstörningar per sömntimme 60%, och för kontrollgruppen 11%, en uttalad skillnad mellan grupperna. Övriga andningsparametrar följde samma mönster. Studien visade även att patienter som har små halsmandlar eller övervikt kan ha god behandlingseffekt av UPPP. Dessa fynd liknar dem från tidigare studier utförda av vår forskningsgrupp. Alla patienter kunde skrivas hem dagen efter operation. 6 av 32 opererade patienter fick lindriga komplikationer, vilka kunde behandlas med vanliga läkemedel.


Sammanfattningsvis kan tracheostomi användas i vissa särskilt komplicerade fall. Långtidsuppföljningen visade att UPPP-effekten kvarstod över tid, både avseende andningsstörningar samt dagsömnighet, och ingen ökad dödlighet påvisades. Modifierad UPPP visade sig vara effektiv både avseende förbättrad nattlig andning och dagsymtom, och ett alternativ för patienter med vissa anatomiska förutsättningar i svalget, där icke-kirurgisk behandling inte har fungerat. Vi rekommenderar att sådana patienter erbjuds bedömning av öron-näsa-hals-specialister för eventuell svalgkirurgi.
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