Pharyngeal surgery and epidemiology in sleep apnea

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ABSTRACT

Obstructive sleep apnea syndrome (OSAS) occurs frequently among adults and children. The first-line treatments in adults are continuous positive airway pressure (CPAP) or mandibular retaining devices (MRDs), but the long-term efficacy is only around 60%. Uvulopalatopharyngoplasty (UPPP) has been criticized for lack of efficacy and a high degree of complications. In children the first-line treatment is adenotonsillectomy.

This thesis evaluates two major aspects of OSAS: firstly, UPPP in adult OSAS patients with failing CPAP and MRD treatment regarding efficacy, safety, satisfaction and side effects in Papers I and II. Secondly, the relationship between sleep disordered breathing (SDB) in children and adolescents, defined as first hospital diagnoses of OSAS, tonsillar and adenotonsillar hypertrophy (ATH), and parental diagnoses of OSAS, occupation and family socioeconomic status (SES) in Papers III and IV.

In Paper I, we measured changes in numbers of oxygen desaturations 4% (ODI4) with home based sleep apnea registrations and daytime sleepiness with validated questionnaires (Epworth sleepiness scale, ESS), as well as complication and satisfaction rate, before and 1 year after UPPP in 158 patients. There was a significant decrease in the ODI4 from median 23 (range 6-100) to 8 (range 0-60). The criteria of success (50% reduction and ODI<20), was 64% and UPPP reduced the nightly respiratory disturbances to a mean of 60 %. The ESS value decreased significantly from median 12 (range 0-21) to 6 (0-22). Four of 158 patients (2.5%) had serious postoperative complications, 88% of the patients were satisfied and there was no mortality.

In Paper II, a pilot study without previous power calculation, 47 of the patients in Paper I answered a questionnaire before and one year after UPPP, as well as 15 non-snoring controls. The median score of the patients was unchanged from 5 (range 0–17) to 5 (0–19), compared to 1 (0–3) for controls.

In Paper III we estimated the standardized incidence ratio (SIR) of hospitalization, 1997–2007, for OSAS and SDB caused by ATH in children (aged 0–18 years) with a parent affected by OSAS and compared this risk with that of children with OSAS and SDB without a parent affected by OSAS. We used the MigMed2 database which includes the Swedish Hospital Discharge Register. After accounting for SES, age, and geographic region, the SIRs of OSAS in boys and girls with a parent affected by OSAS were 3.09 (95% CI 1.83–4.90) and 4.46 (95% CI 2.68–6.98), respectively. The SIRs of ATH in boys and girls with a parent affected by OSAS were 1.82 (95% CI 1.54–2.14) and 1.56 (95% CI 1.30–1.87), respectively.
In Paper IV we analyzed the odds ratio (OR) in individuals aged 0–18 years, 1997–2007, for first hospital diagnoses of OSAS and ATH by family SES and parental occupation. The MigMed2 database was linked to the Swedish census. There were a total of 34,933 children with a first hospital diagnosis of OSAS and ATH. The ORs were increased in individuals with low family SES, defined as family income and maternal education. Increased ORs were found among 14 maternal and 13 paternal occupational groups. Decreased ORs were found for 10 paternal occupational groups. In paper III and IV there was no data available for individual risk factors and confounders such as BMI or passive smoking.

In summary, UPPP reduced the nightly respiratory disturbances to a mean of 60%, halved the daytime sleepiness, did not change the median scores of pharyngeal disturbances, and may be a safe alternative in selected OSAS patients. Swedish children with a parent affected by OSAS had a significantly higher risk of hospitalization for OSAS and SDB defined as ATH. Children with a low family SES and in some occupational groups were associated with an increased OR for hospitalization for OSAS and SDB.
LIST OF PUBLICATIONS

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

I. **Lundkvist K**, Januszkiewicz A, Friberg D.

II. **Lundkvist K**, Friberg D
    Pharyngeal disturbances in OSAS patients before and 1 year after UPPP. Acta Oto-Laryngologica, 2010; 130: 1399–1405.

III. **Lundkvist K**, Sundquist K, Li X, Friberg D

IV. **Lundkvist K**, Sundquist K, Li X, Friberg D

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<th>Description</th>
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<tr>
<td>ATH</td>
<td>Adenotonsillar and tonsillar hypertrophy</td>
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<td>AHI</td>
<td>Apnea hypopnea index</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<td>CPAP</td>
<td>Continuous positive airway pressure</td>
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<td>EDS</td>
<td>Excessive daytime sleepiness</td>
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<td>ESS</td>
<td>Epworth sleepiness scale</td>
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<td>GER</td>
<td>Gastroesophageal reflux</td>
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<td>LPR</td>
<td>Laryngopharyngeal reflux</td>
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<tr>
<td>MRD</td>
<td>Mandibular retaining device</td>
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<tr>
<td>ODI</td>
<td>Oxygen desaturation index</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<td>OSA</td>
<td>Obstructive sleep apnea</td>
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<td>OSAS</td>
<td>Obstructive sleep apnea syndrome</td>
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<td>PG</td>
<td>Polygraphy</td>
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<td>PSG</td>
<td>Polysomnography</td>
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<td>SDB</td>
<td>Sleep disordered breathing</td>
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<td>SES</td>
<td>Socioeconomic status</td>
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<td>SIR</td>
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INTRODUCTION

SDB, OSA and OSAS

This thesis was based on studies on sleep disordered breathing (SDB) and obstructive sleep apnea syndrome (OSAS). The first two investigations were prospective studies of OSAS patients with failing CPAP and MRD treatment who underwent uvulopalatopharyngeal (UPPP) surgery. The last two investigations were epidemiological studies on OSAS patients, both children and adults.

SDB is a broad concept with a spectrum of symptoms; the milder forms comprise primary snoring and mouth breathing and the more severe forms have symptoms similar to the more strict defined entity, OSAS. The syndrome is characterized by prolonged partial upper airway obstruction, intermittent complete or partial obstruction, or both prolonged and intermittent obstruction that disrupts normal ventilation during sleep or normal sleep patterns, or both.\(^1,2\) The intermittent obstruction of the pharynx during sleep causes apneas and arousals, which result in impaired sleep quality and often daytime sleepiness.\(^3\) OSA is the laboratory diagnosis after sleep recording without paying attention to the patients’ daytime symptoms.

Finally, SDB also includes patients with central apneas who make no breathing efforts, such as, for example, patients with heart failure and Cheyne-Stokes breathing.

Diagnosis of OSAS in adults

A nocturnal sleep investigation using polysomnography (PSG) is the golden standard for quantifying respiratory disturbances. PSG devices record EEG, EOG, and EMG together with respiration and are classified as Type I monitors. Portable monitors are classified as either Type II, which records all of the same information as PSG, or Type III. The latter is called a polygraphy (PG) or sleep apnea recording device, which records respiration, but does not differentiate between whether the patient is asleep or awake. A PG includes a minimum of two airflow channels (two airflow channels or one airflow and one effort channel), ECG and oxygen desaturation. Type IV fails to meet the criteria for Type III monitors, but usually record more than two bioparameters.

Since in-laboratory PSG is costly, resource-intensive, and potentially inconvenient for the patient, the simplified ambulant PG is widely used in many parts of the world, including Sweden.

See Figure 1 for an example of a PG device.
This ambulatory polygraphy device was used to diagnose the OSAS patients in Papers I and II.

Different parameters are used: the apnea-hypopnea index (AHI), the apnea index (AI), and the oxygen desaturation index (ODI).

**Definitions**

**AHI**, the total number of complete cessations (apnea) and partial obstructions (hypopnea) of breathing occurring per hour of sleep. These pauses in breathing must last for 10 seconds and are associated with a decrease in oxygenation of the blood. In general, the AHI can be used to classify the severity of disease.

**AI**, the number of apnea events per hour.

**ODI**, the average number of oxygen desaturations 4% or more below the baseline level per hour of sleep.

Based on recordings of the airflow with oronasal cannulas and the respiratory drive with respiratory belts, the episodes of sleep apnea are classified as obstructive, central or mixed. During an episode of obstructive apnea, there is virtually a complete cessation of airflow; at the most, there is only 10% of the flow of the baseline amplitude, which continues for a minimum duration of 10 seconds. The diagnostic criteria for OSAS are, according to the American Academy of Sleep Medicine:\footnote{1}

A patient must fulfill criterion A or B, plus criterion C.

A. Excessive daytime sleepiness (EDS) 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 awakening from sleep
   - unrefreshing sleep
   - impaired concentration; and/or

C. Overnight monitoring demonstrates five or more obstructed breathing events per hour during sleep. These events may include any combination of obstructive apneas/hypopneas or respiratory effort-related arousals. See Figures 2 and 3 for a PG in a healthy person and a person with OSA.
The degree of OSA is based on the following laboratory sleep recording criteria according to the level of obstructive breathing events:

1. Mild: 5–15 events
2. Moderate: 15–30 events
3. Severe: more than 30 events per hour

In addition to laboratory criteria, the severity of OSAS has another component: Severity of daytime sleepiness.

The most frequently used screening questionnaire in clinical practice is the Epworth sleepiness scale (ESS). This questionnaire has been translated into Swedish and validated for Sweden and was used in Papers I and II. However, the ESS is a poor instrument to screen for OSAS, as there are patients with moderate to severe OSAS who may score low rates. In clinical practice, the ESS is more useful when evaluating the effect of treatment on EDS; the same patient fills out the questionnaire repeatedly.

**Figure 2.**

Normal Polygraphy
Background OSAS in adults

Prevalence

OSAS is a common disease with a prevalence of 4% among men and 2% among women. The prevalence of SDB (defined as AHI ≥ 5 and without daytime somnolence) is 9–28% among women and 17–26% for men. The classic daytime manifestation in OSAS is excessive daytime sleepiness (EDS), but other symptoms, such as unrefreshing sleep, poor concentration, and fatigue are frequently reported.

Despite its high prevalence, OSAS often goes undetected. For example, in the general population, according to an American investigation, the Wisconsin Sleep Cohort Study, 82% of men and 93% of women with moderate to severe OSA had not been clinically diagnosed. The prevalence of OSAS is most common in the age group between 40 and 65 years, and men have a higher prevalence of sleep apnea than women in all age groups, with the highest prevalence between 40 and 49 years. Women have the highest prevalence between 50 and 60 years of age. The severity of OSAS increases with age in both men and women, but men have a consistently higher AHI for each age group. According to a recent epidemiologic study, there is a linear correlation between AHI and women’s age, in both obese and non-obese women. In men, the effect of age on AHI is different: their BMI interacted in such a way that in obese men, the AHI increased from age 20–40 years but remained stable thereafter.
The incidence of OSA has been much less studied than the prevalence. A longitudinal cohort study in the US communities assessed the incidence rate on two occasions, which were 5 years apart. Over the 5-year period, the overall incidence of moderate to severe OSA, defined by an AHI > 15, was 11% in men and 5% in women. Weight change was a critical factor for the progression of the disease.

**Risk Factors**

**Obesity**

Obesity is the strongest risk factor for OSAS in adults, and around 60 to 90% of the patients are obese. The definition of overweight is a body mass index (BMI) > 25 kg/m² and the definition of obesity is a BMI > 30 kg/m². It has been shown that a 1-SD increase in BMI is associated with a fourfold increased risk for the prevalence of sleep apnea, and a 10% weight gain was associated with a 6-fold increase in the OSA risk. Conversely, a 10% weight loss was associated with a 26% decrease in AHI. Similarly, SDB has been reported to occur in 50–77% of obese patients. Tishler et al. noted in their Cleveland Family Study that age, gender, BMI, and waist hip ratio were significant predictors of AHI, but that the waist/hip ratio reduced the odds ratio for gender by about 35%, suggesting that some of the association between gender and SDB is mediated by fat distribution. OSAS patients have more fat in the lateral pharyngeal walls than non-OSAS patients with a similar BMI. Further studies have shown that neck circumference in men and BMI in women were the strongest predictors of OSA. The type of body fat distribution seen in obese and overweight SDB patients has led to hypotheses that a large neck girth and a high-range waist-to-hip circumference are stronger predictors of SDB than BMI.

Leptin is a hormone which tends to reduce appetite. It is an adipocytokine studied in association with SDB. Leptin levels are higher in obese individuals, suggesting that leptin resistance exists in obesity. Additionally, SDB is associated with higher leptin levels than would be expected based on BMI alone.

**Gender**

The male-to-female ratio in OSA patient populations is 8:1, but in undiagnosed OSA from population studies, the ratio is 2:1. This finding indicates that women with OSA are less likely to be evaluated and diagnosed. The gender difference seems to diminish in elderly people. A possible protective role of female hormones could partly explain this difference. Bixler and co-workers studied the relationship between menopause and OSA and, after adjusting for several potential cofactors, determined that in comparison to premenopausal women, postmenopausal women on hormonal replacement therapy (HRT) were not at increased risk of OSA, but postmenopausal women not on HRT had an almost four-fold risk. However, when controlling for age and BMI, this group difference was less significant.
Other factors of importance for the gender difference might be anatomical, higher resting tone of pharyngeal dilators in women and differential fat distribution (lateral pharyngeal fat pads).20

Another postulated explanation for the higher clinical male ratio may be a result of the fact that women do not show the classical symptoms, and thus may be under diagnosed. However, according to a study by Young,21 women did not report symptoms that differed significantly from those of men and snoring was the most sensitive and strongest predictor of OSA.

A further hypothesis is that women presenting with daytime sleepiness may be misdiagnosed with depression or other illnesses. This may also be a result of the fact that women are more reluctant than men to complain of snoring, a symptom some think is masculine and most think “unladylike”. Another theory is that men have more severe OSA and thus are more likely to be diagnosed by their primary care physician.

Anatomy

OSA is characterized by narrowing at one or more sites along the upper airway: retropalatal, retroglossal, or hypopharyngeal obstructions.

Factors such as macroglossia and excessive mucosa in the posterior pharyngeal walls can cause a narrowing of the upper airway during inspiration and sleep. Tonsil size is another factor of importance, but it is not a common condition among OSA patents; the frequency is around 6%.22 Furthermore, craniofacial abnormalities, such as mandibular and maxillar retro- or micrognathia, increase the prevalence of OSAS, as well as such abnormalities as Down’s syndrome, Treacher Collins and Pierre-Robin syndrome, which are overrepresented in patients with OSA.23,24

Nasal congestion at night, whether due to allergic rhinitis, acute upper respiratory tract infection, or anatomy, has been linked to snoring and OSA in both experimental and epidemiological studies.19 However, the success rate for nasal surgery is below 20% in the treatment of OSA and there are no studies reporting statistically significant AHI changes or improved oxygen saturation after surgery.25 On the other hand, studies have reported that nasal surgery can improve CPAP compliance in selected patients.26

The frequency and the severity of apneas are generally increased in a supine position due to repositioning of the mandible and the tongue. An average of 56% of patients with OSA have position-dependent OSA, commonly defined as a difference of 50% or more in apnea index between supine and non-supine positions.27

Smoking and Alcohol

Smoking is a possible risk factor for OSA, but few studies on this topic have been reported.

In epidemiological studies, current smoking has been associated with a higher prevalence of snoring and OSA.28 For
example, in the Wisconsin Sleep Cohort Study, current smokers had a 4.4 times increased risk of moderate to worse OSA than individuals who had never smoked.29

Upper airway inflammation and overnight withdrawal from nicotine have been hypothesized to contribute to the effect of tobacco consumption on OSA.29,30

Regular intake of alcohol can transform a snoring person into a patient with OSA.31 Alcohol consumption before bedtime has also been shown to increase the number and duration of hypopnea and apnea events.32,33

One of the mechanisms has been hypothesized to be the result of alcohol-induced oropharyngeal muscle hypotonia.34 The prevalence of alcohol abuse has been investigated by our group; the prevalence did not differ from that of approximately 10% in the general population.35

Natural History and Progression of OSAS

The natural history of OSA is still uncertain, and it may be a progressive disease. The etiology of the progression in adults is probably an increased upper airway resistance due to weight gain and/or dysfunction of the reflexogenic dilatation during inspiration and sleep. The latter may be explained by a pharyngeal nerve lesion with damaged pharyngeal muscles and mucosa caused by the trauma of snoring, i.e., vibration and stretching.36,37

Enlarged tonsils and adenoids during childhood may cause abnormal growth patterns of the lower face and jaw (adenoidal face) and predispose to OSA later in life. Surgical correction of these anatomic defects can reduce the AHI and symptoms of OSA.38

A study by Anuntaseree et al. showed that 5 of 7 children studied with mild OSA at the initial survey had significant disease progression.39 According to a Chinese study of 56 children 6–13 years old with mild OSA, 29% had worsened OSA at the follow-up. Factors predicting progression were a greater increase of waist circumference, large tonsils, and a higher prevalence of snoring.40 A European study by Urschitz et al. has demonstrated that low-level maternal education, household smoking and loud snoring were predictors of persistent snoring in children.41

Co-morbid Conditions

Cardiovascular Disease and Diabetes

There is considerable evidence available to support an independent association between OSAS and cardiovascular disease.

Hypertension

OSA prevalence is high in patients with hypertension and a causal role of OSA in hypertension has been suggested.42 In a longitudinal population study, persons with moderate or worse OSA had 3 ti-
omes the adjusted odds ratio for developing hypertension, compared with persons without OSA. OSA is particularly common in patients with resistant hypertension.43

The association between AHI and hypertension has been evaluated in a large cohort study.44 The authors found a dose response association between SDB at base-line and the presence of hypertension four years later, independently of known confounding factors.

Cardiovascular Disease and Stroke
Marin et al.45 found an association between OSA and non-fatal and fatal cardiovascular disease (myocardial infarction, stroke, acute coronary insufficiency requiring an invasive intervention). In this study only participants with an AHI ≥ 30 events per/hr and who were not treated with CPAP were at a statistically significant increased risk.

A review by Young et al. reports studies of patients with congestive heart failure, in whom the prevalence of OSA ranged from 11% to 37%.42

OSA is also highly prevalent in patients with stroke (43–72%)42 and it can both precede and follow the stroke event.46

Diabetes
OSA is considered to be a risk factor for developing glucose intolerance and insulin resistance as well as type-2 diabetes.

The correlates of OSA, including excess body weight and hypertension, overlap with those of diabetes mellitus, and reports that OSA is associated with insulin resistance and other factors related to the metabolic syndrome are increasing.47

There are studies suggesting an association between type-2 diabetes and a higher AHI. According to a study by Botros et al., AHI ≥ 8 events/hr was significantly associated with diabetes after a mean of 2.7 years in an analysis controlling for BMI.48 According to other studies, there is a suggestion that the association may be confounded by obesity, as measured by waist girth.49

A recent Swedish community-based cohort study analyzed the influence of SDB on glucose metabolism after more than 10 years. 141 men without diabetes were investigated at baseline. At the follow-up, 23 men had diabetes. An ODI of > 5 was the predictor of developing diabetes (OR 4.4, after adjusting for BMI, delta BMI, hypertension, and CPAP use) The authors concluded that SDB was independently related to the development of insulin resistance, and thereby the risk of manifest diabetes.50

Motor Vehicle Accidents
Untreated OSAS is also linked to motor vehicle accidents. Data have indicated a three to seven-fold increased risk for OSAS patients compared to normal subjects.51

Gastroesophageal Reflux and Pharyngeal Disturbances
Gastroesophageal reflux (GER) is a common condition characterized by such symptoms as heart burn and acid
regurgitation. An approximate prevalence of 10-20% has been reported. GER has been shown to be significantly higher in OSAS patients than in the normal population.\textsuperscript{53}

GER may be a particular problem for patients with OSA, as they exhibit an increase in both daytime GER symptoms and events, as well as an increase in nocturnal GER (nGER) symptoms and events, compared to individuals without OSA. The risk is independent of other risk factors including age, BMI, and gender, and this suggests a casual relationship. The prevalence of nGER decreases substantially in patients with OSA following CPAP treatment, and treatment of GER has a significant impact on the AHI index, snoring and daytime sleepiness.\textsuperscript{54-56}

Many theories have attempted to explain what causes nGER in OSA patients, from a repeated increase in negative intrathoracic pressure to transient lower esophageal sphincter relaxation.\textsuperscript{57}

Laryngopharyngeal reflux (LPR) is a part of the GER disease syndrome. The prevalence of LPR in OSAS patients is unknown. LPR signifies that GER continues to the laryngopharynx, oral cavity, etc. The disorder is characterized by hoarseness, cough, excessive throat clearing, excessive mucus, sore throat, globus sensation, and dysphagia.\textsuperscript{58,59}

In 2002 the Reflux Symptom Index (RSI) Questionnaire was published, which is designed to measure the severity of laryngeal symptoms,\textsuperscript{60} and in 2010 a Swedish group published a study concerning the Pharyngeal Reflux Symptom Questionnaire (PRSQ), which has been translated into Swedish.\textsuperscript{61} At the time for the initiation of Study and Paper II, there was no validated questionnaire concerning LPR or pharyngeal reflux symptoms.

The number of questions in the PRSQ is 17, and with regard to similarities to the local questionnaire used in Paper II, the PRSQ contains questions concerning difficulties swallowing, phlegm in the throat, and lumps in the throat. The PSQR contains a Likert scale, which was also used in our local questionnaire.

Studies have been made on the pharyngeal mucosa in OSAS patients. A study by Jobin et al. found that the vibration sensation threshold and two-point discrimination were significantly impaired in OSA patients, compared to controls. The authors suggest that there is an oropharyngeal sensory impairment in the mucosa of OSA patients.\textsuperscript{62} Similar results were found earlier by Kimoff; they showed an improvement in the vibration threshold in the upper airway after CPAP treatment.\textsuperscript{63}

Studies have also been conducted on swallowing function in OSA patients and patients with habitual snoring which suggest impaired function in patients with OSA.\textsuperscript{64,65}

There is also evidence that the mechanisms of the impaired swallowing function might be a neurogenic inflammation.\textsuperscript{36,37}
Mortality

OSAS is associated with an increased mortality rate, but there are diverging results in different studies. Marshall et al. found that moderate to severe OSA was associated with a greater risk of all-cause mortality, hazard ratio (HR) 6.24, compared to non-OSA. This was adjusted for age, BMI, gender mean arterial blood pressure, total cholesterol, high-density lipoprotein cholesterol, diabetes, and medically diagnosed angina in those free from heart attack or stroke at baseline. The same study showed that mild OSA was not a risk factor for high mortality.

Young et al. found in the Wisconsin Sleep Cohort that the all-cause mortality risk, adjusted for age, sex, BMI and other factors, increased with OSA severity. The adjusted HR for all-cause mortality with severe OSA versus no OSA was 3.0. After exclusion of participants on CPAP treatment, the adjusted HR rose to 3.8 and the adjusted HR for cardiovascular mortality was 5.2.

According to an earlier study by Marin et al., there was an association of cardiovascular mortality among individuals with an AHI of >30 events/hr. The same study found that patients with a lower AHI, or those treated with CPAP, did not have an increased risk of cardiovascular death. Punjabi et al. found an interaction between AHI and both age and sex and that the association between AHI and death was seen only in men up to the age of 70. In older men (>79 years) and in women, no significant association was found.

In a recently published study, snoring in patients without OSAS and with a BMI less than 30 was also associated with increased all-cause mortality.

Treatment

Weight Loss and Other Treatments

The treatments for weight loss in this population are the same as for the general population, and weight loss remains a highly effective strategy for treating OSAS. According to a study on our group of 33 obese patients on a 2-year weight reduction program, there was a significant decrease in BMI from 40 to 35, in ODI from 42 to 23 and an ESS reduction from 9 to 5. In a randomized control trial, a very low energy diet has been shown to improve obstructive sleep apnea in obese men, with the greatest effect in patients with severe disease. According to a review, two controlled studies, investigators have demonstrated that a 10–15% reduction of body weight leads to an approximately 50% reduction of sleep apnea severity (AHI) in moderately obese male patients. In recent years bariatric surgical procedures have been used increasingly for the treatment of severe obesity. These procedures lead to an approximately 60% loss of excess body weight in the first 12 to 18 months after surgery and there are studies that have documented dramatic improvement in the vast majority of patients after surgery regarding AHI and sleep apnea resolution.

Positional therapy involves the use of
devices that maintain the patient in a preferred position during sleep. Most prevent the patient from sleeping in a supine position, which in many patients exacerbates airway obstruction. Studies made on this area are predominantly conducted as case series on a comparably small number of patients. Positional therapy (PT) has produced significant results, and a great deal could be gained in treating patients with positional therapy. However, long-term compliance with positional therapy remains an issue and there is room for both technical improvement of the devices and for further research.27

CPAP
CPAP was first described by Sullivan in 1981, and it is the standard first-line therapy for most patients diagnosed with OSA throughout the world.72 The CPAP machine relieves the obstruction by counteracting airway narrowing by the delivery of compressed air to the oropharynx, thereby keeping it open with increased air pressure. CPAP relieves such symptoms as daytime sleepiness and mounting data suggest that CPAP therapy may favorably impact cardiovascular outcomes such as hypertension.73 There is also evidence of decreased mortality after successful CPAP treatment of patients with OSAS.45

The evidence suggests that the use of CPAP for longer than 6 hours decreases sleepiness, improves daily functioning, and restores memory to normal levels. When adherence to CPAP therapy is defined as use longer than 4 hours a night, 46–83% of patients with OSA have been reported as being non-adherent to treatment.74 Unfortunately, long-term follow-ups are rare, but the median compliance rate with CPAP is rather low, i.e. 50% after 1–3 years.75 There are many reasons why patients do not comply with CPAP therapy, e.g. discomfort with the mask, nasal congestion, poor mask fit, claustrophobia, costs for the patients, and psychological effects of a never-ending treatment.

MRD
Mandibular appliances, i.e. a mandibular advancement device or mandibular retaining devices (MRDs), generally fitted by a dentist, are the second most common treatment of OSAS. The American Academy of Sleep Medicine (AASM) recommends oral appliances for patients with mild to moderate OSA who prefer an oral appliance to CPAP or do not respond to or fail at CPAP.76 The reduction of AHI is less successful compared to CPAP and there are studies suggesting a compliance rate of 56% after 5 years.77

On the other hand, the compliance rate in MRD studies is based solely on questionnaires, since it is not possible to perform objective measurements. As in CPAP treatment, there are various reasons why the patients quit or do not comply with MRD requirements: for example, tenderness in the jaws, triggering of the gag reflex, costs for the patients, and psychological effects of a never-ending treatment.

Both CPAP and MRD are life-long treatments and studies on the compliance rate after more than five years are lack-
ing, and the rate probably decreases further with time. Moreover, there are no follow-up studies of patients having tried both CPAP and MRD.

Up to now there is no ultimate alternative treatment to OSAS patients who are failing at non-surgical alternatives. Weight reduction is often difficult to achieve and maintain. Treatment of nasal obstruction, changes in lifestyle, avoidance of alcohol, hypnotics and the supine position may be helpful but they all lack an evidence-based evaluation.

Surgery
For patients with clearly defined anatomic airway obstruction or prior treatment failures with non-invasive techniques, oropharyngeal surgery may be an option. The specific surgery used depends on the patient’s anatomy and the location and cause of the airway obstruction. As for all surgical interventions, the possibility of making blinded studies is limited and therefore the evidence of efficacy is also limited.

According to a paper recently published by AASM, concerning clinical guidelines for the evaluation, management and long-term care of OSA in adults: surgical procedures may be regarded as a secondary treatment for OSA, when CPAP therapy is inadequate or as a secondary therapy when there has been an inadequate treatment outcome with MRD.78

A few systematic reviews of surgical treatments of OSA have been published. For example, in the Cochrane report the authors concluded that there are now a small number of trials assessing different techniques using inactive and active control treatments. The studies assembled do not provide evidence supporting the use of surgery since, overall, no significant benefit has been demonstrated.79

In 2007 a Nordic meta-analysis came to the same conclusion that there is insufficient evidence for the effectiveness of any surgical intervention for OSA.80 Therefore, at least in Scandinavia, the number of surgically treated patients has declined over the past few years.

UPPP
The most common surgery for OSAS is uvulopalatopharyngoplasty (UPPP), first described by Fujita in 1981.81 UPPP includes a tonsillectomy as well as a reduction of the soft palate and uvula. This procedure enlarges the retropalatal airway through trimming and reorienting of the posterior and anterior pillars and reduction of the uvula. Removal techniques used in UPPP include conventional scalpel or laser-assisted procedures.

There have been several modifications of the original description of UPPP: for example, submucosal UPPP, the Fairbanks technique,82 UPPP with preservation of the uvula,83 and transpalatal advancement pharyngoplasty.84 The technique used in Studies I and II is a conservative UPPP with cold steel as described on page 31.
Success rate
One of the problems when comparing studies concerning airway surgery is the definition of success and efficacy; many studies have variable success criteria. The most frequently used definition of success is a 50% reduction of AHI and/or AHI ≤ 20, but there are authors proposing to redefine success to an AHI of ≤ 5 or ≤ 10. Caples used a relative measure of effect, the ratio of means (ROM), which describes the extent to which the mean postoperative AHI has changed compared to the mean AHI before surgery.

Several meta-analyses have, however, reported success rates for OSA between 30% and 60%. According to a recently published meta-analysis of 15 UPPP studies, there was a 33% reduction of AHI. An older meta-analysis concluded that UPPP is, at best, effective in treating less than 50% of patients with OSAS. Patients who achieved a favorable response to UPPP tended to have a less severe OSA.

In a randomized controlled trial by Ljander et al., 18 patients were randomized to UPPP (and 5 of these had an additional mandibular osteotomy) and 14 to expectancy (CPAP). The follow-up time was one year. The authors evaluated the patients’ excessive daytime sleepiness, and the results showed a statistically significant difference between the groups in favor of surgery. The ODI decreased from 45 to 14 (39%) in the UPPP group, compared to 34 to 23 (62%) in the expectancy group. The difference between the groups was insignificant, probably because of the small sample size of 32 patients.

In a Swedish study by Wilhelmsson et al., UPPP was compared with MRD. There was a significant difference in favor of MRD therapy compared with surgical treatment alone at one- and four-year follow-ups regarding the AHI. The success rate (defined as at least a 50% reduction of AHI) for the MRD group was 95%, which was significantly higher than the 70% success rate in the UPPP group. Quality of life was measured with a questionnaire (MSE-P-VAS) and no significant differences were reported between surgery and MRD for vitality and sleep, but there was a significant difference in favor of surgery for contentment. In the 4-year follow-up, the MRD group showed a significantly higher success rate regarding AHI, i.e. 81% compared with 53%, but the compliance for the MRD-treated group was only 62%. However, Weaver performed an intention-to-treat analysis with inclusion of the drop-outs in the MRD group and showed that the laboratory success rate for MRD was 54% compared to 49% in the UPPP group, i.e. a non-significant difference.

UPPP is effective in eliminating snoring and it is generally more effective in reducing apneas than hypopneas and is most effective in patients with primarily oropharyngeal obstruction.

In 2002 Friedman et al. proposed a method of classification of preoperative tonsil size, tongue-palate position, and BMI that could be used for redefining
the prediction of success for subgroups of patients who undergo UPPP.92,93 They demonstrated a success rate (defined as RDI reduced by at least 50% and a postoperative RDI of 20 or less) of 80% for subjects with large tonsils and low tongue position, compared to 38% in patients with small tonsils and low tongue position or large tonsils and high tongue position. They recommended addition of tongue base reduction using a radio-frequency technique when their staging system indicates a high tongue position. Patients with small tonsils and high tongue position and/or BMI over 40 were not recommended to undergo surgery.

Most studies on the efficacy of UPPP are not prospective; nor do they indicate long-term follow-up; the typical follow-up time has been only 3 to 12 months. Studies with longer follow-ups have shown variable success. A study by Janson et al. followed the patients 4–8 years after UPPP. A positive response to treatment was defined as at least a 50% reduction in AHI and a postoperative AHI of less than 10. They found a success rate of about 50%. A success factor in the study was lower preoperative AHI.94 Another Swedish study followed 50 men with OSAS up to 4 years after UPPP found no increased mortality in a 5- to 9-year follow-up of 400 consecutive, on average, non-obese snorers, 256 of whom had OSAS. The UPPP patients were compared to 744 controls (median age 43) who underwent nasal surgery during the same period and to a matched general control population. The authors concluded that their results might indicate a positive survival effect of surgery.97

Another Swedish study followed 50 patients for 15 years after UPPP. It found a mean reduction of ODI of 52% and a success rate (ODI < 20 and 50% reduction) of 65%. The standardized mortality rate did not differ from that of the general Swedish population,98 also suggesting a protective effect of surgery.

**UPPP complications and adverse events**

Another reason for the controversial of surgery for the treatment of snoring and OSA is studies that have reported adverse events and a high complication rate, including mortality.79,85
Kezirian et al. made a large study of complications in 2004. They investigated the medical records of 3130 patients who had undergone different surgical procedures for OSAS, mostly UPPP. They showed a 1.5% incidence of serious complications (mostly ventilator complications) and an intraoperative mortality of 0.2%. On analyzing the risk factors for surgery, a high BMI, a high AHI, medical comorbidity and concurrent retrolingual procedures were associated with an elevated risk of complications.

In a review of four papers, Franklin et al. reported life-threatening side effects and death after UPPP. However, the authors found that lower complication rates were reported in more recent publications.

With regard to peri- and postoperative bleeding after UPPP, it may be relevant to compare this condition with bleeding after tonsillectomy. In a recent study comparing tonsillectomy and UPPP in Sweden, the author did not find any mortality or increased complication rate after UPPP compared to tonsillectomy.

According to a review, persistent side effects occurred in a mean of 58% (range 42–62). Swallowing difficulties were listed, including nasal regurgitation, voice changes, and taste and smell disturbances, as well as globus sensation. Levring-Jäghagen et al. have shown in videoradiographic studies that OSAS patients had subclinical pharyngeal swallowing dysfunction after UPPP and UPP (without tonsillectomy).

This was a retrospective study and no videoradiography or questionnaires were used before surgery. The same author conducted another study with a prospective design and 7 of 42 patients reported preoperative dysphagia. Pharyngeal swallow dysfunction was demonstrated in 6 of these 7 patients with preoperative dysphagia and in 18 of 35 patients without dysphagia. Ten of the 35 patients without preoperative dysphagia developed dysphagia after UPPP.

**Other Surgical Techniques**

Laser-assisted uvulopalatoplasty (LAUP) is a procedure involving placing bilateral vertical incisions directly along both sides of the uvula, followed by laser ablation of the uvula. LAUP has not been approved by the American Academy of Sleep Medicine for treating OSA because it has no proven efficacy in treating daytime sleepiness and changing the AHI.

Maxillomandibular advancement (MMA) involves simultaneous advancement of the maxilla and mandible by means of sagittal split osteotomies. It effectuates enlargement of the retrolingual airway and some advancement of the retropalatal airway. A meta-analysis has shown a high success rate in treating OSA, and MMA maintains its efficacy in long-term follow-ups. In Sweden it is not a common procedure for treating OSA. Solely tonsillectomy can be effective in selected OSAS patients.

There are numerous other surgical procedures for treating OSAS used worldwide to modify the skeletal or soft tis-
sue structures in the upper airway, such as midline glossectomy, radiofrequency ablation of the tongue, nasal procedures, pillar implants, genioglossus advancement, hyoid myotomy and suspension, mandibular (or maxillary) distraction osteogenesis, maxillomandibular expansion, and rapid maxillar expansion.107

Tracheostomy can be characterized as an upper airway bypass procedure, and it has been shown to be a single intervention for treating OSA. Many studies have reported a nearly complete resolution of nocturnal and daytime symptoms.107 A study from our group showed that the patients may still have nocturnal desaturations after the tracheostomy, but with relieved symptoms.108 This operation could be considered when there are no other options; it may be life-saving, but it is associated with several problems including patient’s dissatisfaction and different kinds of wound problems.

**In summary:** All treatments performed on OSAS patients have consequences. Health-related quality-of-life measurements have shown better results in patients with post-UPPP side effects, compared with CPAP users (independently of compliance) with side effects.109 Unfortunately, there is no treatment with 100% compliance, a 100% success rate and without side effects.

### Background OSAS in children

#### Prevalence

The prevalence of OSA in children according to PSG is 1–3 %; however, according to parent-reported symptoms and the wider definition SDB, the prevalence might be as high as 11%. The highest frequency of OSA or SDB occurs among the smaller children aged 2–6 years.110 The gender ratio is equal, but in studies including adolescents, the male ratio may be higher.111

#### Symptoms

Snoring occurs in almost all children with SDB, and it is the main reason why many parents seek medical advice. However, children with severe OSA may manifest the condition without clear snoring because of prolonged breathing pauses. Restless sleep and persistent body movements are frequently observed in children with SDB, as well as odd sleep positions. Other symptoms in younger children are frequent arousals, nocturnal sweating, mouth breathing, dry mouth, failure to thrive, nasal congestion, a hyperextended neck, noisy breathing, sleep terrors, enuresis, drooling, and morning headache. In the older children there are symptoms of frequent arousals, nocturnal sweating, mouth breathing, dry mouth, nasal congestion, sleep walking, daytime sleepiness, difficulty waking up in the morning, crossbite, malocclusion, and hypertension.112,113

Daytime symptoms in older children include hyperactivity, irritability, poor social skills, decreased attention and memory and impaired school performances.114
Diagnoses in Children
A sleep history screening for snoring should be part of routine healthcare visits. In children, OSAS is unusual in the absence of habitual snoring. However, histories and physical examinations are poor predictors of OSA in children. Most studies have shown that such screening techniques as video-taping or nocturnal pulse oximetry may be helpful if the results are positive, but they have low predictive value if the results are negative. There are also different questionnaires for scoring symptoms, but so far the sensitivity and specificity of these questionnaires are poor.

The golden standard method of diagnosing OSA in children is polysomnography. It is agreed that an AHI > 1 is abnormal in pediatric patients, and studies have shown that healthy children have an AHI of 0. The International Classification of Sleep Disorders 2nd Edition (ICSD 2) defines apneas as a secession of airflow over two or more respiratory cycles. A specific time in seconds is not applicable in children since normal respiration varies from 12 to 60 breaths per minute, depending on age. The definition of hypopnea is more variable across sleep centers; however, most agree that a reduction in airflow of at least 30% is required, with or without an arousal and/or oxygen desaturation of 3 to 4%.

Unfortunately, there is limited access to pediatric PSG laboratories worldwide, and the diagnosis is therefore mostly clinical, also in Scandinavia.

Risk Factors and Comorbidity
In younger children, the most common risk factor for SDB and OSAS is adenotonsillar hypertrophy (ATH). However, several studies have failed to show a strong correlation between upper airway adenotonsillar size and OSA. In older children, obesity is a strong risk factor. Dayyat et al. suggested a phenotypic division of the SDB affecting the youngest children, which is characterized by hyperactivity, aggressive behavior, and failure to thrive (Type I). SDB affecting the older children resembles OSAS in adults and is characterized by overweight, obesity, and daytime somnolence (Type II).

SDB may also be associated with craniofacial abnormalities and neuromuscular impairment. The complications of pediatric SDB, regardless of disease severity, have been shown to be similar in several studies: daytime neurobehavioral problems, impaired school performance, and hypertension.

In recent years there has been growing evidence of autonomic alterations in children with OSA: for example, increased arterial blood pressure, severity-dependent elevations in catecholamine levels, and heart rate variability, all of which respond to treatment. Thus OSA may also elicit metabolic and cardiovascular morbidities in children. As in adults, there is also evidence of systemic inflammation.
Heredity and Familial Association

Several studies have demonstrated an increased risk of OSA in families of patients with OSA. For example, Redline reported that habitual snoring, daytime sleepiness, snorting, and gasping or apneas were reported two to four times more frequently among the first-degree relatives of patients with OSAS than among controls. These findings were independent of familial similarities in BMI, smoking, and alcohol consumption, as well as age or gender. Having one relative with OSA increases one’s risk of apnea by 50% and the risk steadily increases with additional affected relatives. Heredity might be an explanation for the increased familial risk, as indicated by studies on adults and children. Additionally, twin studies have shown a higher concordance for snoring between monozygotic twins than between dizygotic ones.

Previous epidemiologic studies from Sweden and our group have indicated that OSAS in adults and also OSAS and SDB in children display familial clustering.

In summary, it has been estimated that 40% of the variance in the AHI may be explained by familial factors and the genetics of OSA is probably multifactorial.

Ethnicity and Socioeconomic Status

Ethnicity and socioeconomic disparities are prevalent among children with SDB. According to recent meta-analyses, Afro-American children are the minority population addressed most frequently, and besides being at increased risk for SDB, they have an earlier onset and a greater likelihood of persistent SDB after surgery. These findings were independent of SES. The same review showed an increased prevalence of SDB in children with a lower SES. Spilsbury et al. have performed a cross-sectional analysis of children aged 8 to 11 years living in a neighborhood with a severe socioeconomic disadvantage. They found a significant association with OSA and low SES after adjusting for the effect of previously established risk factors, i.e. premature birth, obesity, and African ethnicity. A more recent Canadian study, including 436 children aged 2–8 years, concluded that those with OSA were more likely to reside in disadvantaged neighborhoods.

However, the role of family environmental factors, such as parental occupation and family SES, in SDB has not been fully investigated in children and adolescents. A study from our group found that SES and occupation had a minor effect on the adult population’s likelihood of hospitalization for OSA. Some oc-
ocupational studies have, however, found increased risks of adult OSA in occupations involving exposure to organic solvents, although other studies have not demonstrated any association between occupation and adult OSAS. There is therefore a need for more knowledge about parental occupational exposures and pediatric OSAS.

**Treatment**

The most common treatment of SDB in children and adolescents is adenotonsillectomy. Follow-ups of surgically treated children with SDB show significant improvement in sleep, behavior, cognition, and quality of life. However, a significant proportion of children have residual OSAS post-operatively. The efficacy of pediatric adenotonsillectomy for snoring is high according to parent-reported questionnaires. The cure rate for OSA in children, as determined by an AHI < 5 events per hour postoperatively, varies between 78% and 100%. Particularly older children (> 7 years of age), children with severe OSAS disease, and children with underlying medical conditions such as obesity, craniofacial abnormalities, and neuromuscular deficits may have residual OSAS after surgical treatment.

When there is residual SDB after adenotonsillectomy, other factors should be evaluated to determine the next course of action. CPAP can be used as the second-line treatment. There are studies on the efficacy of CPAP in children which show significant improvement in neurobehavioral function, even in developmentally delayed children.

For children with a high arched palate, rapid maxillary expansion has been shown to improve the AHI.
AIMS

There were mainly two overall aims of this thesis; Firstly, to evaluate UPPP in adult OSAS patients with failing CPAP and MRD treatment regarding efficacy, safety, satisfaction, and side effects. Secondly, to investigate the relationship between pediatric OSAS/SDB and parental OSAS, occupation, and family SES.

The specific aims of the four papers were:

**Paper I**
To evaluate the efficacy and safety one year after UPPP in 158 OSAS patients after failed CPAP and MRD treatment by measuring changes in the number of oxygen desaturations and excessive daytime sleepiness, as well as complication and the satisfaction rate.

**Paper II**
To investigate the pharyngeal disturbances before and one year after UPPP in OSAS patients, and to compare the responses to a questionnaire comprising non-snoring healthy controls.

**Paper III**
To estimate the standardized incidence ratios for first hospital diagnoses during 1997–2007 of OSAS/SDB caused by ATH in children (aged 0–18 years) with a parent affected by OSAS, and to compare this risk with that of children with OSAS/SDB without a parent affected by OSAS.

**Paper IV**
To analyze the odds ratio in individuals aged 0–18 years in 1997–2007 for first hospital diagnoses of OSAS/SDB caused by ATH in Sweden by family SES and parental occupation.
METHODS AND STUDY POPULATIONS

Study Populations

Paper I
A non-randomized prospective intervention study (2002–2006) of 158 patients, 139 men and 19 women, with OSAS (ODI 23, range 6–100; ESS 12, 0–21), median age 45 years (20–75), median body mass index (BMI) 29 kg/m² (20–48) with failing CPAP and MRD treatment who underwent UPPP. The one-year follow-up comprised ambulatory sleep apnea recordings and questionnaires concerning the Epworth sleepiness scale (ESS) and satisfaction rate. Hospital records concerning complications were analyzed.

Inclusion criteria were ODI > 5 and or AHI > 9, as well as daytime symptoms of OSAS. The patients should have failed or not accepted CPAP and MRD treatment. For characteristics of the patients before surgery, see Table I.

Exclusion criteria were a negative attitude to surgical treatment, severe heart, pulmonary, psychiatric or neurological disease, American Society of Anesthesiologists (ASA) class > 3, and coagulopathy.

Paper II
A prospective intervention study conducted in 2002–2004. The first 50 men and 8 women in Study I, median age 46 (25–75), median BMI 28 kg/m² (20–38) and median preoperative oxygen desaturation index (ODI) 16 (7–100), answered a questionnaire before and one year after UPPP. The same questionnaire was answered by 15 age-, gender- and BMI-matched non-snoring controls. For characteristics of the patients and controls before surgery, see Table II.

<table>
<thead>
<tr>
<th>Table I. Characteristics of patients before surgery</th>
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</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>All</strong></td>
</tr>
<tr>
<td><strong>Male</strong></td>
</tr>
<tr>
<td><strong>Female</strong></td>
</tr>
<tr>
<td><strong>Drop-outs</strong></td>
</tr>
<tr>
<td><strong>Number of subjects</strong></td>
</tr>
<tr>
<td>158</td>
</tr>
<tr>
<td>139</td>
</tr>
<tr>
<td>19</td>
</tr>
<tr>
<td>38</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td>45 (20–75)</td>
</tr>
<tr>
<td>43 (20–75)</td>
</tr>
<tr>
<td>49 (31–71)</td>
</tr>
<tr>
<td>38.5(20-62)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
</tr>
<tr>
<td>29 (20–48)</td>
</tr>
<tr>
<td>29 (22–48)</td>
</tr>
<tr>
<td>29 (20–39)</td>
</tr>
<tr>
<td>29 (22–42)</td>
</tr>
<tr>
<td><strong>ODI4</strong></td>
</tr>
<tr>
<td>23 (6–100)</td>
</tr>
<tr>
<td>24 (6-100)</td>
</tr>
<tr>
<td>15 (8-77)</td>
</tr>
<tr>
<td>25.5 (7-85)</td>
</tr>
<tr>
<td><strong>ESS</strong></td>
</tr>
<tr>
<td>12 (0-21)</td>
</tr>
<tr>
<td>12 (0-21)</td>
</tr>
<tr>
<td>14 (4-19)</td>
</tr>
<tr>
<td>11.5 (1-21)</td>
</tr>
<tr>
<td><strong>Tonsil size (1-4)</strong></td>
</tr>
<tr>
<td>2 (1-4)</td>
</tr>
<tr>
<td>2 (1-4)</td>
</tr>
<tr>
<td>2 (1-4)</td>
</tr>
<tr>
<td>3 (1-4)</td>
</tr>
</tbody>
</table>

Values are presented as the median and range. BMI, body mass index; ODI4, oxygen desaturation index ≥ 4%; ESS, Epworth sleepiness scale.
Papers III and IV

A national research database was used to obtain data on all children aged 0-18 in Sweden between 1997-2007 (> 3 million individuals). These children were linked to the Hospital Discharge Register (ICD-10) to identify all first hospital admissions for (1) OSAS (G 47.3) and/or SDB defined as (2) hypertrophy of tonsils, J 35.1, and (3) hypertrophy of adenoids and tonsils, J 35.3. Children with a first hospital diagnosis of snoring (R 06.5) or adenoid hypertrophy (J 35.2) or a primary diagnosis of upper airway infection or tonsillitis (chronic tonsillitis, J 35.0) were excluded. The ICD-10 code for OSAS (G47.3) was also used in the parents.

In Study III individuals were categorized as having or not having a parent affected by OSAS. Children with OSAS and/or adenotonsillar hypertrophy (ATH) without a parent affected by OSAS served as the reference group. The Multigeneration Register, were children and parents are linked, was used to obtain the family data.

In study IV the research database was also linked to Swedish census data.

Methods: Papers I and II

Before surgery all patients underwent an upper airway examination with grading of tonsil size on a scale of 1–4 (4 being the maximum) similar to that used by Friedman et al.93 None of the patients had previously undergone tonsillectomy. Hypertrophied tonsils, defined as tonsil size 3 and 4, were found in 38% of the patients in Paper I and in 26% in Paper II.

Drop-outs

Paper I

Thirty-eight of 158 patients (24%) did not turn up for a second sleep apnea recording and were defined as drop-outs.

Table II. Characteristics of patients before surgery

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All</th>
<th>Male (m)</th>
<th>Female (f)</th>
<th>Drop-outs</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>58</td>
<td>50</td>
<td>8</td>
<td>11 (9m/2f)</td>
<td>15 (12m/3f)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46 (25-75)</td>
<td>45 (25-75)</td>
<td>47 (31-70)</td>
<td>42 (30-58)</td>
<td>43 (18-58)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>28 (20-38)</td>
<td>28 (22-35)</td>
<td>27 (20-38)</td>
<td>27 (23-35)</td>
<td>27 (22-31)</td>
</tr>
<tr>
<td>Total score for pharyngeal disturbances</td>
<td>5 (0-17)</td>
<td>5 (0-17)</td>
<td>7 (1-14)</td>
<td>5 (0-11)</td>
<td>1 (0-3)</td>
</tr>
<tr>
<td>ESS</td>
<td>12 (1-21)</td>
<td>12 (1-21)</td>
<td>9 (4-19)</td>
<td>13 (2-21)</td>
<td></td>
</tr>
<tr>
<td>ODI4</td>
<td>16 (7-100)</td>
<td>16 (7-100)</td>
<td>14 (10-70)</td>
<td>15 (7-100)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as the median and range. BMI = body mass index, ODI4= oxygen desaturation index > 4%.
They were all men and were significantly younger (p < 0.035, two-sample t test) with significantly larger tonsils (p < 0.038, Pearson’s chi-squared test) than the patients who completed the study. There were no differences concerning ODI, ESS, or BMI.

**Paper II**

Drop-outs were defined as OSAS patients who had not filled out the postoperative questionnaire on pharyngeal disturbances, and they were 11, 19% (Table II). There were no significant differences in age, BMI, score for pharyngeal disturbances, tonsil size, ESS or ODI when comparing the drop-out group with the patients who completed the study (Mann-Whitney U test).

**Safety Program and Anesthesiologic Aspects**

A safety program very similar to the one in the report of the AASM Clinical Practice Review Committee,141 is routinely used at our clinic. The surgery was performed under general anesthesia. It was induced with rapid sequence induction. Remifentanil infusions and sevoflurane were used to maintain the anesthesia. All patients were extubated immediately after surgery. Thereafter, they were transferred to the postoperative care unit for careful monitoring of vital signs for between 6 and 24 h. All patients received oxygen and/or CPAP if needed. Bensylpenicillin was given as infection prophylaxis. The patients had the opportunity to stay a second night on a ward, but if the course was uncomplicated, they went home the day after surgery.

**Surgical Procedure (Figure 4)**

No concurrent surgery, for example, of the nose or tongue, was performed. Different ear, nose and throat surgeons (12 in Study I and 11 in Study II) performed a conservative UPPP with tonsillectomy, using a modified method of Fujita et al.81 with cold-steel instruments comprising a scalpel and scissors (see Figure 4). Local anesthesia was used (bupivacaine, 5 mg/ml). 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. Extracapsular tonsillectomy was carried out with a sharp elevator. Hemostasis was achieved using bipolar diathermy. The posterior pillar was lifted up laterally and sewn up to the anterior pillar with separate inverted sutures (4/0 Monocryl). In the upper lateral corners, two or three sutures also included fibers from the palatopharyngeal muscle. Finally, suturing of the soft palate and uvula was performed. If the patients had profuse bleeding or pharyngeal edema postoperatively, desmopressin and tranexamic acid or cortisone was injected intravenously.

**Follow-up**

All patients were followed up at a visit to the surgeon 2–3 months after surgery and with a letter containing a questionnaire 1 year after surgery. Furthermore, they were referred to the Department of Clinical Neurophysiology for ambulatory sleep apnea recordings, before
Figure 4. Schematic picture of UPPP used in Papers I and II

Figure 5. A pharynx before UPPP

Figure 6. A pharynx 3 months after UPPP
and approximately 1 year after surgery. Patients with a severe degree of OSAS were offered the opportunity to undergo recordings within 6 months, in order to identify those with failed surgery and offer them additional treatment. One of the authors, K.L. conducted telephone interviews with some of those who had not returned the questionnaire.

See Figures 5 and 6 for a picture of a pharynx before and three months after UPPP.

Sleep Apnea Recordings and Laboratory Criteria of Success
All ambulatory recordings were performed with Embletta (Medcare Flaga, Reykjavik, Iceland). The ODI of 4% (ODI4) was measured. The AHI measured by the thermistor or nasal flow was not considered to be a consistently reliable measure of the air flow at this time and was therefore excluded. All recordings were interpreted by specialists in neurophysiology from the same laboratory department. The patients were categorized into responders or non-responders according to two laboratory criteria of success.

The first criterion of success was a >50% reduction and ODI < 20; the second criterion was a reduction in ODI >50% and ODI values < 10. After the publication of Paper I we also calculated a reduction in ODI >50% and ODI values < 5 and the ratio of mean ODI change by dividing the changes in mean ODI by the mean ODI before surgery.

Questionnaires

Paper I
All patients answered the ESS questionnaire, which consists of eight questions concerning their likelihood of falling asleep in a variety of frequently encountered situations. An extra question was added: Are you satisfied with the operation? The question was to be answered with ‘yes’ or ‘no’.

Paper II
Ten questions were about the degree of pharyngeal disturbances. Four of the questions (numbers 6, 8, 9, and 10) have been used previously by others.

Questions concerning pharyngeal disturbances:
1. Do you have vivid queasy feelings in your throat, for example, when you brush your teeth?
2. Do you have a globus sensation in your throat, for example, at dry swallowing?
3. Do you have problems with excessive mucus secretion in your throat?
4. Do you have problems with a swollen throat in the morning?
5. Do you have problems with a feeling of scraping in your throat?
6. Do you have any trouble with swallowing when drinking, for example, water?
7. Do you have any trouble with swallowing when eating solid food?
8. Do you get drinks or food behind or into your nose when swallowing?
9. Does food or drink go down into the trachea so that you have to cough when you swallow?
10. Do you have to concentrate on swallowing to avoid problems?
Questions in Swedish:

1. Har du livliga kräkrefluexer i svalget, t.ex. vid tandborstning?
2. Har du ”klumpkänsla” i halsen, t.ex vid torrsväljning?
3. Har du problem med kraftig slembildning i halsen?
4. Har du problem med att ”svullna till” i halsen på morgonen?
5. Har du problem med skavningskänsla i halsen?
6. Har du några besvär med att svälja när du dricker t.ex vatten?
7. Har du några besvär med att svälja när du äter fast föda?
8. Får du dryck eller mat bakom eller upp i näsan när du sväljer?
9. Får du mat eller dryck i luftstrupen så att du får hosta vid sväljning?
10. Måste du tänka på hur du sväljer för att det ska gå bra (koncentrera dig)?

The questions were answered on a four-point Likert scale:
1. Never 0 p (Swedish Aldrig)
2. Sometimes 1 p (Swedish Ibland)
3. Often 2 p (Swedish Ofta)
4. Always 3 p (Swedish Alltid)

The maximum symptom score was 30 p.

Complications

Paper I

The medical complications in connection with the surgery and type of reoperations caused by complications were recorded and classified for each patient. Severe bleeding or pharyngeal edema leading to reintubation were classified and shown as a serious complication. Less severe complications were not shown.

Statistics, Papers I and II

Comparisons were made between unpaired groups using the Mann-Whitney U (MWU) test, Pearson’s chi-squared test, or the t test. The Wilcoxon signed rank (WSR) or the Wilcoxon matched pair (WMP) test for paired groups, and the Spearman rank correlation (SRC) for correlation tests between variables were used. Missing values for drop-outs were imputed by using their baseline values +1. Logistic regression analyses were used to identify factors predicting success. The first criterion of success, > 50% reduction and ODI < 20, was used in these analyses. A p value < 0.05 was considered significant.

Methods Papers III and IV

MigMed Research Database

Data used in this study were retrieved from the MigMed2 Database located at the Center for Primary Health Care Research, Lund University, Sweden. MigMed is a single comprehensive database that has been constructed using several national Swedish data registers, including, but not limited to, the Population Register, the Multigeneration Register, and the Swedish Hospital Discharge Register. Information from the various registers in the database was linked at the individual level via the national 10-digit civic registration number assigned to each person in Sweden for his/her lifetime. Prior to inclusion in the MigMed database, civic registration numbers were replaced by serial numbers to ensure the anonymity of each individual. Since the database contains information from the Multigeneration Register, it is possible to link more than 7.6 mil-
lion index persons (persons born in or after 1932 and registered in Sweden any time since 1961) with their biological parents, children, and siblings.

During the study period 1997–2007, a total of 3 050 263 children and adolescents (1 567 656 boys and 1 482 607 girls) were included in the studies.

**Outcome Variables**
Since SDB has no specific diagnostic code, hospitalized children with such symptoms and suspected OSAS are most often coded for adenotonsillar or tonsillar hypertrophy (ATH) instead. Such children are normally referred to an otorhinolaryngological clinic by a primary healthcare or hospital physician. They are mainly admitted to hospital wards for surgical removal of ATH tissue or, less frequently, for sleep studies. Between 1997 and 2007, approximately 80% of adenotonsillectomies due to SDB were performed in hospitals according to the Swedish National Quality Register for tonsil surgery (A.C. Hessén Soderman, personal communication).

**Explanatory variables**

*Gender:* Male and female children were included in the studies.

*Family income* was divided into four categories based on the income level recorded by the taxation authorities. Family income information was provided by Statistics Sweden and was defined as the family income during the year of childbirth divided by the number of people in the mother’s family. The income parameter also considered the ages of individuals in the family and used a weighted system whereby small children were given lower weights than adolescents and adults.

**Geographic region of residence** was broken down into (1) large cities (cities with a population of more than 200,000, i.e., Stockholm, Gothenburg, and Malmö), (2) Southern Sweden, and (3) Northern Sweden.

**Paper III**
Explanatory variables included gender, age at first hospital diagnosis of OSAS and/or ATH, socioeconomic status (SES) (defined as family income), geographic region of residence (i.e., in most cases, geographic region of hospitalization), and family income. The geographic region was included as an explanatory variable to adjust for possible differences between the geographic regions in Sweden with regard to hospital admissions for the different outcome variables.

**Paper IV**
Period of birth was divided into 10-year groups from 1979 through 2007. We used two variables to define familial SES, i.e., family income and maternal education.
Family income was categorized into four groups as in paper III: low, low-middle, high-middle, and high.

Educational attainment was divided into three groups: compulsory school or less (≤ 9 years), vocational high school or some theoretical high school (10–11 years), or theoretical high school and/or college (≥ 12 years). The mother’s educational level was used.

The geographic region of residence was included as an individual variable to adjust for possible differences between geographic regions in Sweden regarding hospital admissions. The mother’s geographic region of residence was used as a proxy for the family’s region of residence.

Family History of a First Hospital Diagnosis of OSAS
Offspring were divided into two groups: with or without a parental history of a first hospital diagnosis of OSAS.

Parental occupation was used as a proxy for occupational exposure. This variable has also been used in numerous previous studies. Information on parental occupations was obtained from the 1990 Swedish census. It includes nationwide, individual level occupational categories that are consistent with the International Standard Classification of Occupations (ISCO). The census includes 99.2% complete information on occupations for the entire population of Sweden. Census information was coded using a national Swedish adaptation of the Nordic Occupational Classification (NYK). Since some occupational groups in the census included too few individuals to conduct a meaningful statistical analysis, we combined the occupational groups in the NYK into 51 large occupational categories. These 51 categories were defined by previous researchers on the basis of occupational similarities and have been used in multiple previous studies. A list of the NYK codes included in each of the 51 categories has been described previously.

Statistical Analyses
Paper III
Using the individual-level data in the MigMed2 database, the entire pediatric population of Sweden was sorted into families based on a shared mother and father. The database was then used to determine the presence or absence of a primary hospital diagnosis of pediatric OSAS and/or ATH in each individual aged ≥ 18 years during the follow-up period. Next, the children were categorized as having or not having a parent affected by OSAS. Children with a diagnosis of OSAS and/or ATH but without a parent affected by OSAS constituted the reference group. The individual serial numbers described in the section on the MigMed2 research database were used to ensure that individuals with hospital diagnoses of pediatric OSAS and/or ATH only appeared once in the dataset (i.e. for their first hospital diagnosis during the study period). Person-years were calculated from the start of follow-up on January 1, 1997, to hospitalization for OSAS and/or ATH; death; emigration; or the end of the study on Decem-
November 31, 2007. Age-specific incidence rates (defined as first hospitalization rates during the study period) were calculated for the entire follow-up period. The results are shown as standardized incidence ratios (SIRs) with 95% confidence intervals (CIs). SIRs were calculated as the ratio of the observed number to the expected number of cases. The expected number of cases was calculated for age-, gender-, period-, region- and socioeconomic-status-specific standard incidence rates derived from children without a parent affected by OSAS. The test statistic \( \chi^2 \) was used to calculate the probability (p value) of the SIR between boys and girls. Interaction was tested between the age of the child and a parental history of OSAS.

**Paper IV**

Using logistic regression analysis, we estimated the odds of hospitalization for pediatric OSAS or SDB defined as ATH by family income, region of residence, educational attainment, family history of OSAS, and parental occupation. The reference groups were: period of birth 1979–1988, female gender, highest family income, large cities, highest educational attainment, and no family history of OSAS (OR, 1.0). For parental occupation the reference group consisted of all women or all men in the parental population. All estimates were adjusted for period of birth (in 10-year periods). The estimates of OSAS and or SDB by occupational status were also adjusted for family income, region of residence, educational attainment, and family history of OSAS. There were no gender differences in the outcomes for family SES or parental occupation; the results are therefore given for females and males together. We used SAS version 9.2 for the statistical analyses.

**Ethical permission**

All four studies were approved by the local ethics committee and participants in Studies I and II gave their informed consent.

**RESULTS**

**Paper I**

**Results**

*Objective Results*

120 of 158 patients underwent a second sleep apnea recording at a median of 12 months (range 2–34) after surgery which showed a significant decrease in ODI from a median of 23 (range 6–100) to 8 (0–60) \( (p < 0.001, \text{WSR test}) \) (Figure 7). The mean ODI before surgery was 27.2 and the mean ODI after surgery was 10.8. The mean difference was 16.4 and the mean reduction in the ODI was 60%. The intention-to-treat analysis for all 158 patients also showed a significant decrease in the ODI \( (p < 0.001, \text{WSR test}) \). With the use of the first criterion of success (\( > 50\% \) reduction and \( \text{ODI} < 20 \)), the success rate for the group of 120 patients was 64%. With the use of the second criterion (\( 50\% \) reduction and \( \text{ODI} < 10 \)), the success rate was 54% for the group of 120 patients. The third criterion (\( 50\% \) reduction and \( \text{ODI} < 5 \)) was 32% and these patients can be considered cured.
Figure 7. 120 patients had sleep apnea recordings approximately one year after UPPP and there was a significant decrease in the oxygen desaturation index (ODI) from a median of 23 (6–100) to 8 (0–60), p < 0.001 (WSR).

Figure 8. 107 patients evaluated their sleepiness before and one year after UPPP and there was a significant decrease in the Epworth Sleepiness scale score from a median of 12 (0–21) to 6 (0–22), p < 0.001 (WSR).
The median BMI for 117 patients was unchanged after surgery. Preoperative tonsil size, BMI and ESS did not correlate significantly with changes in ODI or ESS, respectively (SRC test). There was a significant correlation between the preoperative ODI and changes in the ODI (p < 0.001, SRC test). Success factors were female gender (p = 0.023, log reg) and young age (p = 0.044, log reg). There was an indication that a low preoperative ODI (p = 0.07, log reg) was also a success factor, but not large tonsils, low BMI or surgeon.

**Subjective Results**

Responses to the ESS questionnaire were obtained before and after surgery from 107 of the 158 patients. Their median values showed a significant decrease in the ESS score from a median of 12 (range 0–21) to 6 (range 0–22) (p < 0.001, WSR test) (Figure 8). In the intention-to-treat analysis the ESS decreased significantly for all 158 patients (p < 0.001, WSR test). The question concerning satisfaction was answered by 104 patients, 92 of which (88%) were satisfied with the surgery.

**Postoperative Complications**

Four of the 158 patients (2.5%) had serious complications at the postoperative care unit and were reintubated. Two of them had profuse bleeding from the tonsillectomy site. The bleeding did not stop after medical treatments but did after reoperation. Two patients had substantial pharyngeal edema. One of them was directly tracheotomized for safety reasons. After two weeks he was decannulated without complications; he was still satisfied with the surgery one year after the procedure. The other patient was successfully treated with steroids and extubated the day after surgery. None of these four had any known risk factor, i.e. high BMI, high ODI or advanced age. None received a blood transfusion. All complications were taken care of immediately and no patient has suffered from sequels caused by these complications. There was no mortality.

**Paper II**

Forty-seven of the 58 OSAS patients answered the questionnaire both preoperatively and one year postoperatively, giving a drop-out rate of 19%. There was no change between pre- and postoperative symptom scores, a median of 5.0 (range 0–17) and 5.0 (0–19), respectively. The intention-to-treat analyses of the 58 patients showed the same results: medians of 5.0 (range 0–17) and 5.0 (0–19).

Preoperatively, 38 of 58 patients (66%) and, postoperatively, 31 of 47 (66%) had a total score higher than 3 of a maximum of 30. In contrast, none of the controls had a total score above 3.

**Separate Questions Asked by Patients**

*Before and After surgery (The range of the scores varied between 0 and 3.)*

The scores of the 47 patients showed significant decreases between pre- and postoperative scores for questions Nos. 2 and 4 (Figures 9 and 10).

**Patients before Surgery Compared to Controls** (The range of the scores varied between 0 and 30.)
“Do you have a ‘globus sensation’ in your throat, for example, at dry swallowing?” The question was answered on a four-point ranking scale: never, sometimes, often, and always. The figure shows the percentage of the answers for each group. Comparisons was made between the patients preoperatively (n = 47) and the controls (n = 15), p = 0.0009 (Mann-Whitney U test). Comparisons was made between the patients preoperatively (n = 47) and postoperatively (n = 47), p = 0.02 (Wilcoxon matched pair test).

“Do you have problems with a swollen throat in the morning?” The question was answered on a four-point ranking scale: none, sometimes, often, and always. The figure shows the percentage of the answers for each group. Comparisons was made between the patients preoperatively (n = 46) and the controls (n = 15), p = 0.024 (Mann-Whitney U test). Comparisons was made between patients preoperatively (n = 46) and postoperatively (n = 46), p = 0.003 (Wilcoxon matched pair test).
The 58 patients had a significantly higher median score of 5 (range 0–17), compared to the 15 controls, with a median score of 1 (range 0–3), p < 0.001, MWU test.

IV. Separate Questions Asked by Patients Compared to controls (The range of the scores varied between 0 and 3.)

There were significant differences between patients and controls for question No. 2 (Figure 9), question No. 3, question No. 4 (Figure 10) and Question No. 5.

Satisfaction with the Surgical Procedure
Fifty-seven of the 58 patients answered the question about satisfaction and 52 (91%) answered yes and 5 (9%) answered no.

Results from the Sleep Recordings
Fifty patients had both pre- and postoperative sleep apnea recordings. Their ODI was significantly reduced from a median of 16 (7–70) to a median ODI of 7.0 (0–60), p < 0.0001 (WMPT).

Correlations between Pharyngeal Disturbances and Other Outcomes
Significant (p < 0.05) positive correlations were found between changes in scores for pharyngeal disturbances and age (r = 0.38) and postoperative scores (r = 0.43), and significant negative correlations were found between changes in scores for pharyngeal disturbances and satisfaction (r = -0.35) and the pre-operative score (r = -0.33), (SRC).

Further significant correlations were found between pre- and postoperative scores for pharyngeal disturbances, p<0.05, r=0.63, SRC.

There were no significant correlations between scores for changes in pharyngeal disturbances and preoperative ODI, BMI, or for changes in ODI. Only seven women responded to the questionnaire pre- and postoperatively, making statistical calculations of gender differences inappropriate. The median BMI values were unchanged.

Paper III

Results
Descriptive characteristics of the study population and their parents
In total, 34 933 children with OSAS and/or ATH and 23 413 parents with OSAS were identified during the study period (Table III). Among the diagnosed children, 5.7% had a first hospital diagnosis of OSAS. The majority of the children were aged 4–7 years and 54.1% were boys. The most usual age at diagnosis among the parents was 50–59 years. Pediatric OSAS and/or ATH were most usual in families with low and low-middle income: 42.5% and 34.9%, respectively.

In total, 153 children (7.6%) diagnosed with OSAS were also diagnosed with ATH. None of the children had two parents affected by OSAS.

Gender- and Age-Specific Incidence Rate of Pediatric OSAS
In the entire population, 1167 boys and 841 girls aged 0–18 years were diagno-
| Table III. Total number of cases of obstructive sleep apnea syndrome (OSAS), hypertrophy of tonsils or hypertrophy of adenoids and tonsils in offspring (aged 0 to 18 yrs) and OSAS in parent |
|---------------------------------|-----------------|-----------------|
|                                 | Offspring No. % | Parent No. %    |
| **Total cases**                 |                 |                 |
| OSAS                            | 34,933 5.7      | 23,413          |
| Hypertrophy of tonsils or hypertrophy of adenoids and tonsils | 32,925 94.3 |                 |
| **Gender**                      |                 |                 |
| Male                            | 18,914 54.1     | 18,158 77.6     |
| Female                          | 16,019 45.9     | 5255 22.4       |
| **Age at diagnosis, offspring (yrs)** |           |                 |
| 0–3                             | 6812 19.5       |                 |
| 4–7                             | 17,423 49.9     |                 |
| 8–12                            | 6487 18.6       |                 |
| 13–18                           | 4211 12.1       |                 |
| **Age at diagnosis, parents (yrs)** |           |                 |
| < 40                            | 1950 8.3        |                 |
| 40–49                           | 4030 17.2       |                 |
| 50–59                           | 8102 34.6       |                 |
| 60–69                           | 6246 26.7       |                 |
| 70–79                           | 2707 11.6       |                 |
| >= 80                           | 378 1.6         |                 |
| **Period of diagnosis (yrs)**   |                 |                 |
| 1997–1999                       | 11,470 32.8     | 8594 36.7       |
| 2000–2002                       | 8993 25.7       | 6640 28.4       |
| 2003–2005                       | 8937 25.6       | 5155 22.0       |
| 2006–2007                       | 5533 15.8       | 3024 12.9       |
| **Region of residence**         |                 |                 |
| Large cities                    | 9756 27.9       | 8975 38.3       |
| Southern Sweden                 | 16,369 46.9     | 10147 43.3      |
| Northern Sweden                 | 8808 25.2       | 4291 18.3       |
| **Family income**               |                 |                 |
| Low income                      | 14,839 42.5     | 5361 22.9       |
| Low-middle income               | 12,208 34.9     | 6460 27.6       |
| High-middle income              | 5849 16.7       | 6114 26.1       |
| High income                     | 2037 5.8        | 5478 23.4       |
sed with OSAS during the study period. The hospitalization rate was 10.5 per 100 000 person-years for boys and 8.0 per 100 000 person-years for girls \((p < 0.001)\). The difference between the genders was significant. For children with a parent affected by OSAS, the incidence of OSAS was 26.1 per 100 000 person-years among boys and 29.4 per 100 000 person-years among girls. The difference between the genders was not significant.

**Gender- and Age-Specific Incidence Rate of Adenotonsillar or Tonsillar Hypertrophy**

In the entire population, 17 747 boys and 15 178 girls aged 0–18 years were diagnosed with ATH during the study period. The rate was 159.1 per 100 000 person-years among boys and 143.8 per 100 000 person-years among girls \((p < 0.001)\). The difference between the genders was significant. For children with a parent affected by OSAS, the incidence of ATH was 219.0 per 100 000 person-years among boys and 190.3 per 100 000 person-years among 242 girls. The difference between the genders was not significant.

Figure 11 shows the hospitalization rates for pediatric OSAS and ATH in children with and without a parent affected by OSAS. The highest hospitalization rate was observed among children aged < 8 years regardless of whether or not they had a parent affected by OSAS.

**SIRs of pediatric OSAS and adenotonsillar or tonsillar hypertrophy**

The overall SIR of OSAS among children with a parent affected by OSAS was 3.09 (95% CI 1.83–4.90) in boys (Table IV) and 4.46 (95% CI 2.68–6.98) in girls (Table V). The overall SIR in children with ATH among those with a parent affected by OSAS was 1.82 (95% CI 1.54–2.14) in boys and 1.56 (95% CI 1.30–1.87) in girls.
The hospitalization rates per 100,000 person years by age group for (A) OSAS (B) adenotonsillar and tonsillar hypertrophy (ATH) in children with and without a parent affected by OSAS.
### Table IV. Standardized incidence ratios (SIRs) and observed number of cases (n) of obstructive sleep apnea syndrome (OSAS) or hypertrophy of tonsils or hypertrophy of adenoids and tonsils in boys, by age group

<table>
<thead>
<tr>
<th>Age at diagnosis (yrs)</th>
<th>Father with OSAS</th>
<th>Mother with OSAS</th>
<th>Parent with OSAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>SIR</td>
<td>95% CI</td>
</tr>
<tr>
<td>0-3</td>
<td>28</td>
<td>2.04</td>
<td>1.36</td>
</tr>
<tr>
<td>4-7</td>
<td>79</td>
<td>2.10</td>
<td>1.67</td>
</tr>
<tr>
<td>8-12</td>
<td>17</td>
<td>1.08</td>
<td>0.63</td>
</tr>
<tr>
<td>13-18</td>
<td>27</td>
<td>2.47</td>
<td>1.62</td>
</tr>
<tr>
<td>All</td>
<td>151</td>
<td>1.94</td>
<td>1.64</td>
</tr>
<tr>
<td>OSAS</td>
<td>17</td>
<td>3.37</td>
<td>1.96</td>
</tr>
<tr>
<td>Hypertrophy of tonsils or hypertrophy of adenoids and tonsils</td>
<td>134</td>
<td>1.84</td>
<td>1.54</td>
</tr>
</tbody>
</table>

CI = confidence interval
Bold type: 95% CI does not include 1.00.

### Table V. Standardized incidence ratios (SIRs) and observed number of cases (n) of obstructive sleep apnea syndrome (OSAS) or hypertrophy of tonsils or hypertrophy of adenoids and tonsils in girls, by age group

<table>
<thead>
<tr>
<th>Age at diagnosis (yrs)</th>
<th>Father with OSAS</th>
<th>Mother with OSAS</th>
<th>Parent with OSAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>SIR</td>
<td>95% CI</td>
</tr>
<tr>
<td>0-3</td>
<td>15</td>
<td>1.72</td>
<td>0.96</td>
</tr>
<tr>
<td>4-7</td>
<td>59</td>
<td>2.07</td>
<td>1.58</td>
</tr>
<tr>
<td>8-12</td>
<td>22</td>
<td>1.27</td>
<td>0.79</td>
</tr>
<tr>
<td>13-18</td>
<td>27</td>
<td>1.42</td>
<td>0.94</td>
</tr>
<tr>
<td>All</td>
<td>123</td>
<td>1.68</td>
<td>1.39</td>
</tr>
<tr>
<td>OSAS</td>
<td>16</td>
<td>4.27</td>
<td>2.43</td>
</tr>
<tr>
<td>Hypertrophy of tonsils or hypertrophy of adenoids and tonsils</td>
<td>107</td>
<td>1.54</td>
<td>1.26</td>
</tr>
</tbody>
</table>

CI = confidence interval
Bold type: 95% CI does not include 1.00.
Paper IV

Results

Table VI shows the total population, number of cases, and the ORs of SDB for the listed variables. During the study period a total of 34,933 children had a first hospital diagnosis of SDB, in this paper defined as OSAS or ATH. The OR for SDB was significantly higher for boys. For family income, the ORs were significantly increased for children and adolescents in families with low, low-middle and high-middle incomes. Furthermore, compulsory school or less (≤ 9 years) and vocational high school and some theoretical high schools (10–11 years) had a significantly increased OR compared to the reference group (theoretical high school and/or college (≥ 12 years). In offspring with a family history of OSAS, the OR was also significantly increased. There were 153 children who had both a diagnoses of OSAS and ATH during the study period (data not shown in tables).

Table VII shows the OR and 95% confidence intervals for SDB by parental occupation, adjusted for the children’s gender, period of birth, family income, region of residence, maternal education, and family history of OSAS. For maternal occupations, significantly increased ORs were observed among 14 occupational groups, for example, assistant nurses, cooks and stewards, and home helpers. Among paternal occupations, significantly increased ORs were observed among 13 occupational groups, for example, drivers, smelter and foundry workers, woodworkers, and other construction workers. Significantly decreased ORs for SDB were found for the following 12 paternal, including technical, scientific research-related workers, and sales agents.

Furthermore, ORs and 95% confidence intervals for SDB in different age groups were calculated by maternal and paternal occupation. The calculations were adjusted for the children’s gender, period of birth, family income, region of residence, maternal education, and family history of OSAS. According to maternal occupation, the OR was significantly increased in all age groups for assistant nurses and drivers. In children aged 0–6 and 7–12 years, there were significantly increased ORs for the following maternal occupational groups: textile workers, electrical workers, and food manufacture workers. In children aged 0–6 and adolescents aged 13–18 years, there were significantly increased ORs for glass, ceramic and tile workers, packers, loaders, and warehouse workers, and home helpers. For children aged 0–6 years the ORs were also significantly increased among welders, woodworkers, public safety and security workers, and hairdressers. Decreased ORs were observed in the youngest age group for the maternal occupational group artistic occupations, and farmers.

For paternal occupations, the ORs were significantly increased for children aged 0–6 and 7–12 years for the following occupational groups: drivers, smelters and metalware workers, mechanics and iron metalware workers, welders, woodworkers, other construction workers, brick-
Table VI. Study population, number of cases and odds ratios (ORs) of sleep disordered breathing (SDB) defined as obstructive sleep apnea syndrome (OSAS), hypertrophy of tonsils, or hypertrophy of adenoids and tonsils

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total population</th>
<th>OSAS and hypertrophy of tonsils or hypertrophy of adenoids and tonsils</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3,050,263</td>
<td>34,933</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1,482,607</td>
<td>48.6</td>
</tr>
<tr>
<td>Male</td>
<td>1,567,656</td>
<td>51.4</td>
</tr>
<tr>
<td><strong>Period (birth year)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1979–1988</td>
<td>1,023,660</td>
<td>33.6</td>
</tr>
<tr>
<td>1989–1998</td>
<td>1,133,966</td>
<td>37.2</td>
</tr>
<tr>
<td>1999–2007</td>
<td>892,637</td>
<td>29.3</td>
</tr>
<tr>
<td><strong>Family income</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low income</td>
<td>1,161,333</td>
<td>38.1</td>
</tr>
<tr>
<td>Low-middle income</td>
<td>886,286</td>
<td>29.1</td>
</tr>
<tr>
<td>High-middle income</td>
<td>650,668</td>
<td>21.3</td>
</tr>
<tr>
<td>High income</td>
<td>351,976</td>
<td>11.5</td>
</tr>
<tr>
<td><strong>Region of residence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large cities</td>
<td>1,005,601</td>
<td>33.0</td>
</tr>
<tr>
<td>Southern Sweden</td>
<td>1,267,533</td>
<td>41.6</td>
</tr>
<tr>
<td>Northern Sweden</td>
<td>777,129</td>
<td>25.5</td>
</tr>
<tr>
<td><strong>Educational attainment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compulsory school or less</td>
<td>1,290,646</td>
<td>42.3</td>
</tr>
<tr>
<td>Vocational high school or some theoretical high schools (10–11 years)</td>
<td>904,727</td>
<td>29.7</td>
</tr>
<tr>
<td>Theoretical high school and/or college (≥12 years)</td>
<td>854,890</td>
<td>28.0</td>
</tr>
<tr>
<td><strong>Family history of sleep apnea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3,031,476</td>
<td>99.4</td>
</tr>
<tr>
<td>Yes</td>
<td>18,787</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odd ratio; CI, confidence interval.
Bold type: 95% CI does not include 1.00.
Table VII. Odds ratio and 95% confidence intervals for sleep disordered breathing (SDB) defined as obstructive sleep apnea syndrome (OSAS), hypertrophy of tonsils, or hypertrophy of adenoids and tonsils by parental occupation

<table>
<thead>
<tr>
<th>Occupation of parents</th>
<th>By mother’s occupation</th>
<th>By father’s occupation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>OR</td>
</tr>
<tr>
<td>Technical and scientific research-related workers</td>
<td>429</td>
<td>0.88</td>
</tr>
<tr>
<td>and physicians</td>
<td>30</td>
<td>1.03</td>
</tr>
<tr>
<td>Nurses</td>
<td>784</td>
<td>1.15</td>
</tr>
<tr>
<td>Assistant nurses</td>
<td>2810</td>
<td>1.32</td>
</tr>
<tr>
<td>Other health and medical workers</td>
<td>410</td>
<td>1.05</td>
</tr>
<tr>
<td>Teachers</td>
<td>1122</td>
<td>0.95</td>
</tr>
<tr>
<td>Religious, juridical and other social science-related workers</td>
<td>901</td>
<td>0.99</td>
</tr>
<tr>
<td>Artistic occupations</td>
<td>108</td>
<td>0.81</td>
</tr>
<tr>
<td>Journalists</td>
<td>47</td>
<td>0.81</td>
</tr>
<tr>
<td>Administrators and managers</td>
<td>171</td>
<td>0.81</td>
</tr>
<tr>
<td>Clerical workers</td>
<td>2799</td>
<td>1.08</td>
</tr>
<tr>
<td>Sales agents</td>
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<td>Shop managers and assistants</td>
<td>1197</td>
<td>1.17</td>
</tr>
<tr>
<td>Farmers</td>
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<td>Gardeners and related workers</td>
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<td>Fishermen, whalers, and sealers</td>
<td>-</td>
<td>37</td>
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<tr>
<td>Forestry workers</td>
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<td>250</td>
</tr>
<tr>
<td>Miners and quarry workers</td>
<td>-</td>
<td>76</td>
</tr>
<tr>
<td>Seamen</td>
<td>-</td>
<td>24</td>
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<tr>
<td>Transport workers</td>
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</tr>
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<td>Mechanics and iron and metalware workers</td>
<td>353</td>
<td>1.22</td>
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<tr>
<td>Plumbers</td>
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<td>286</td>
</tr>
<tr>
<td>Welders</td>
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<td>235</td>
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<tr>
<td>Other construction workers</td>
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</tr>
<tr>
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<tr>
<td>Public safety and security workers</td>
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<td>1.44</td>
</tr>
<tr>
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<tr>
<td>Waiters</td>
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<td>1.11</td>
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<tr>
<td>Building caretakers and cleaners</td>
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<tr>
<td>Chimney sweeps</td>
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<td>Hairdressers</td>
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<td>1.27</td>
</tr>
<tr>
<td>Launderers and dry cleaners</td>
<td>286</td>
<td>1.10</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odd ratio; CI, confidence interval. Analysis adjusted for children’s sex, period of birth, family income, region of residence, maternal educational attainment, and family history of sleep apnea. Bold type: 95% CI does not include 1.00.
layers, chemical process workers, food
manufacture workers, and engine and
motor operators. In the paternal occupa-
tional groups painters and wall-paper-
hangers, printers and related workers, be-
verage manufacture workers, and glass,
ceramic and tile workers significantly
increased ORs were observed in the age
group 0–6 years. A decreased OR was
observed in all age groups for the patern
occupational group, teacher. Among
the paternal occupational groups, techni
cal, scientific research-related workers
and physicians, religious, juridical, and
other social science-related workers, ad
ministrators and managers, farmers, and
building caretakers and cleaners, the
ORs of SDB for children aged 0–6 and
7–12 years were significantly decreased.
There were more cases of SDB, de
fined as OSAS or ATH, in children aged 0–6
years than among the older children for
both maternal and paternal occupational
groups.

DISCUSSION

Papers I and II

The most common surgical treatment in
Sweden and worldwide is UPPP, a met
hod that has been questioned because
of a lack of efficacy and a high level of
complications. The aims of Paper I and
II were therefore to evaluate pharyngeal
surgery in consecutive OSAS patients
failing CPAP and MRD treatment in
terms of conservative UPPP considering
efficacy, safety, and complications.

The major findings in Paper I were that
there was a significant and marked de
crease in nightly oxygen desaturations
as well as in daytime sleepiness one
year after surgery. The success rate, as
measured with sleep apnea recordings
and using different criteria, varied be
tween 64 and 32%, the mean reduction
in ODI was 60% and the satisfaction
rate was 88%. Therefore, we consider
both the objective and subjective results
to be surprisingly good in this group
of patients, who otherwise would have
probably been left untreated. Paper II
showed no changes in the median symp
tom scores between pre- and one-year
postoperative evaluations of subjective
pharyngeal disturbances in 47 OSAS
patients. Surprisingly, the preoperati
ve BMI did not correlate with success
concerning improvement of the nightly
oxygen desaturations. Our results differ
from those in an earlier study by Lars
son et al., but Friedman et al. have
shown results similar to ours concerning
patients with a BMI of up to 40. However,
they suggested that patients with
a BMI of over 40 should not undergo
UPPP. There were only two patients in
the present study with a BMI of over
40, both had enlarged tonsils; one was a
drop-out, the other a responder. In terms
of the ODI values, the study by Larsson
et al. showed that a low preoperative
ODI was a success factor. In Paper I the
there was a tendency for a low preoperative
ODI to correlate with success.

It was also surprising that no significant
differences were found in the success
rate between the groups of patients with
large (67%) and small tonsils (63%). This finding indicates that the effect of the surgery was a result of our UPPP with lateralization of tonsil pillars irrespective of tonsil size. Our results differ from those presented by Friedman et al.\textsuperscript{154} They found in a retrospective study of 134 OSAS patients that patients with hypertrophied tonsils in combination with a high palatal position had a considerably higher success rate of 80% compared to 8% for patients with small tonsils and a low palatal position. However, Friedman’s grading system had not been published at the start of our study. Therefore, we only estimated the tonsil size and our results therefore should not be compared with those of Friedman. Female gender correlated with success. However, it is difficult to draw any major conclusions from only 19 women who underwent surgery. Another success factor was younger age. This could be explained by the expression “heavy snorer’s disease”, which is a progressive local vibration-induced neuropathy of the pharynx.\textsuperscript{36,37}

Younger patients probably do not have the same amount of local neuropathy and/or inflammatory tissue as older ones, and therefore they may respond better to surgery.

According to Paper II dealing with pharyngeal disturbances, analyses of separate questions showed a significant decrease in the symptom score concerning “globus sensation” and “swollen” throat. All other questions, including nasal regurgitation, did not show any significant differences after surgery.

Correlation analyses showed that patients with high preoperative symptom scores for pharyngeal disturbances reduced their scores more than patients with low preoperative scores.

Furthermore, not surprisingly, satisfied patients had significantly less changes in the score for disturbances than nonsatisfied patients, and older patients had a significantly higher preoperative score than younger ones. The results differ from those of a recently published review that has evaluated surgery for snoring and OSA from 1989 and forward.\textsuperscript{101} The authors reported persistent side effects after surgery in a mean of 58% of such patients (range 42–62). However, they did not report preoperative symptoms, and many different surgical methods were included in the review. As described earlier, we have chosen to perform a conservative UPPP using cold steel, which may explain our results of unchanged median symptom scores one year after surgery. A possible explanation for the significant reduction of the specific disturbances “globus” and “swollen throat” in our OSAS patients could be the significantly reduced respiratory effort, indirectly measured using the ODI, which was halved. However, there was a wide range in the degree of symptoms both pre- and postoperatively, indicating a large inter-individual variability.

There was a significant difference in the median symptom score for pharyngeal disturbances on comparing OSAS patients with non-snoring controls. Furthermore, on analysing the score for
separate questions, there were significant differences between patients and controls regarding the questions concerning “globus sensation”, “excessive mucus secretion”, “swollen throat”, and “feeling of scraping”. The prevalence of dysphagia in OSAS patients is unknown and an interesting issue is the probable causes for the pharyngeal disturbances shown in our patients. There may be several: firstly, chronic vibrations of tissue due to snoring may cause neuronal damage,36, 37 and furthermore studies have shown a correlation with laryngeal sensory dysfunction and sleep apnea severity.155 Secondly, studies have assessed inflammation predominantly in the oropharyngeal tissues of OSAS subjects.156 Thirdly, there is a correlation between OSA and gastroesophageal and laryngopharyngeal reflux (LPR). Indirect symptoms of LPR were found in our patients before and, to a lesser degree, after surgery. Subsequently, several of these preoperative symptoms may have been caused by LPR and/or snoring trauma, which were decreased after surgery.

Both OSAS and obesity are known risk factors for surgery under general anesthesia.157 Thus, awareness of these risks is of great importance. Mortality may be avoided by careful postoperative observation and early treatment of complications. The rate of serious complications of bleeding and edema in the present study was 2.5%, and there was no mortality. However, the number of patients was relatively small. Our results can be compared with a previous report on more than 3000 patients showing a rate of serious nonfatal complications of 1.5% and a mortality rate of 0.2%.99 The authors concluded that concomitant tongue or nasal procedures are associated with increased risks of serious complications.100 Therefore, no other types of surgery than UPPP were performed in the present study.

Polysomnography (PSG) is the golden standard method for diagnosing OSA; however, in Papers I and II an ambulatory sleep apnea recording was used, and it has been validated against PSG.158 Since the apnea-hypopnea index was not considered to be a reliable parameter at the start of the study and the same recordings were used pre- and postoperatively, and also since the interpretations were done by the same specialist, we consider the results of changes in ODI to be valid.

Papers I and II have some limitations; the design was not a randomized controlled trial. There are still few such trials of UPPP because the procedure comprises removal of tissues and tonsils under general anesthesia, which is difficult to blind. There are also ethical aspects of having a group of untreated patients. In addition, surgery is often demanded by patients who have failed non-surgical treatments, as it is the only treatment involving a one-stage procedure.

Another limitation was that we did not objectively verify the pharyngeal disturbances in Paper II. Unfortunately, there are no such golden standard methods available. Another limitation is that the questionnaire used for pharyngeal distur-
bances has not been validated. However, there was no validated questionnaire in the Swedish language available for this patient group at the time of the study. Four of the questions have been used in previous studies, and all questions were considered to be clinically significant for this patient group. Additionally, there were no sleep apnea recordings of the non-snoring controls. However, they all had spouses who confirmed that they were non-snorers. A further limitation is that we did not perform a power analysis before including patients and controls in Paper II. The reason for this is that there had been no previous study to compare with, or to make the calculations from, so we consider our study to be a pilot study. The results surprised us, especially because of the small number of participants, as we did not expect to find unchanged median values before and after surgery nor the large difference between the controls and the patients.

We consider Papers I and II to have several strengths: it has a prospective design, our conservative method of UPPP is evaluated with a large number of patients undergoing postoperative sleep apnea recordings after one year, use of the validated Epworth sleepiness scale questionnaire, the safety program, and the selection of patients who have failed at or not accepted CPAP and MRD. Since the compliance with such devices is still inadequate, there is an obvious need for safe and efficient surgery to offer these patients. Most previous studies reporting postoperative dysphagia have usually been retrospective with the risk of “recall bias”. In our study this risk was avoided by having the patients fill out the questionnaire twice, directly before and one year after surgery. Furthermore, we had a control group of subjects’ age, gender- and BMI-matched with the OSAS patients who filled out the same questionnaire as the OSAS patients.

Finally, the general applicability is a strength, as the study reflects our daily clinical routines, including several different surgeons.

**Papers III and IV**

The main finding of Paper III was that the offspring of parents with OSAS had a substantially higher risk of hospitalization for pediatric OSAS and or SDB, defined as ATH, than offspring of parents without OSAS. The SIR was highest in the group with pediatric OSAS: 3.09 in sons and 4.46 in daughters. Additionally, a large number of children with ATH, one of the main etiologic factors for pediatric OSAS in young children, were included. The SIR was 1.82 in sons and 1.56 in daughters, i.e. lower than for OSAS, but still significantly increased. Paper III employs a novel approach to investigate familial aggregation: the use of hospital diagnoses and the investigation of individual correlations between pediatric OSAS/SDB and parental OSAS. The association between pediatric and parental OSAS/SDB is in accord with earlier studies, for example, one by Kalra et al., who found a significant association between children and parents with habitual snoring. Previous epidemiologic studies conducted in different adult populations have also
demonstrated familial aggregations of OSA.\textsuperscript{124,127} Heredity might be an explanation for the increased familial risk, as indicated by studies of adults and children.\textsuperscript{125}

Furthermore, ATH might be inherited, and the size of the tonsils and adenoids increases from birth to adolescence with the greatest increase during the first years of life.\textsuperscript{160} In a recent study by Khalyfa et al.,\textsuperscript{161} palatine tonsils in children were analyzed for gene expression in order to identify putative mechanistic pathways associated with tonsillar proliferation and hypertrophy in OSA. The authors found that phosphoserine phosphatase in tonsillar tissue played a role in hypertrophy in OSA children, but not in that from children with recurrent tonsillitis.

An additional genetic factor is facial growth and upper airway soft tissue (i.e., nasal obstruction). Bixler et al. have published data from the largest population-based sleep cohort, obtained from American children aged 5–12. The authors concluded that, besides excess weight, nasal abnormalities (and not tonsil size) were statistically significant predictors of SDB in this age group.\textsuperscript{162}

Paper IV constitutes the first large-scale study including children and adolescents aged 0-18 years and extending over 11 years to investigate the odds of SDB, defined as pediatric OSAS and/or SDB caused by ATH, in families with different family socioeconomic statuses, as well as in different maternal and paternal occupational groups. Only a few previous studies have examined the association between SDB and such socioeconomic factors as SES and neighborhood disadvantage,\textsuperscript{130,163} and, to the best of our knowledge, this was the first study that has considered maternal as well as paternal occupations in different age groups. The major findings were that Swedish children with low family income and low maternal education had raised ORs for hospitalization for SDB. A further finding was the increased ORs for several parental occupational groups and decreased ORs for 10 paternal occupational groups.

Previous studies from USA and Canada in different age groups have shown that residence in neighborhoods with socioeconomic disadvantages was significantly associated with OSAS, after adjusting for the effects of previously established risk factors and SDB symptoms.\textsuperscript{130,131,163}

According to education, a European study has shown that low-level maternal education was an independent risk factor for habitual snoring.\textsuperscript{41} It has been shown that childhood OSA may result in neurocognitive and attention deficits and daytime sleepiness.\textsuperscript{114} Untreated OSA may lead to poor school performances.\textsuperscript{164} Presumably, children with OSAS and poor school performance may have limited potential to advance educationally, socially, and economically.

Paper IV also showed significantly increased ORs for several parental occupational groups, and there may be several causes behind these findings. Ulfb erg
et al. have shown that snorers were more often occupationally exposed to organic solvents than non-snorers. The children in the present study might have been exposed by living in close proximity to an industrial environment or exposure to their parent’s clothing or hair and skin. Other studies have shown that passive smoking is associated with increased SDB and snoring in children. Exposure to irritants, such as environmental tobacco smoke, is often greater in neighborhoods with low SES. Chronic exposure to allergens and/or irritants has been shown to augment upper airway inflammation and increase nasal resistance. Exposure to irritants, poor indoor air quality and population density-related exposure to upper respiratory infections might predispose to airway infections and adenotonsillar hypertrophy and affect the immune response in the affected children. Chronic stress, which predisposes to sleep fragmentation, may also predispose to pediatric OSAS and may lie in the causal pathway as low SES could be considered as a chronic psychosocial stressor.

An interesting and novel finding in Paper IV is the decreased ORs for 10 paternal occupational groups, such as technical and science research-related workers and physicians, religious, juridical and other social science-related workers, and sales agents. Further studies are needed to examine why the paternal occupation has a greater importance than the maternal occupation; historically, the fathers’ income determined the families’ social class and neighborhood of residence. According to a recent study, the fathers’ occupational category had a significant association with biomarkers of inflammation and endothelial dysfunction.

Maternal factors during pregnancy may be affected by SES, and parental occupation may affect the risk of SDB during childhood. Studies have shown that preeclampsia, preterm birth, and very low birth weight are associated with childhood SDB. In a recent study Calhoun et al. showed a significant association between prenatal or perinatal distress and childhood SDB. Their study suggests an association between childhood SDB and prenatal exposure to several risk factors, for example, low SES. There is also an increased risk of preterm birth and small-for-gestational age in families with low income and among some occupational groups. The occupational groups with increased ORs for preterm birth and small-for-gestational age in these studies resemble the occupational groups with increased ORs for SDB in the present study. The results for some occupational groups, such as drivers, coincide with the results from a Swedish study conducted on adult OSAS, but other occupations differ. A further similarity between the studies is the regional differences. These differences can be explained by varying routines for hospitalizations and outpatient procedures in both diagnostic and therapeutic terms in different parts of Sweden.
Paper III and Paper IV showed a gender difference with a higher risk in sons than in daughters: a higher SIR in Paper III and a higher OR in Paper IV, and these findings are in accord with earlier studies when children aged 13 or older are included. Some have suggested that gender differences in SDB are more likely to emerge as children enter puberty, and a suggested explanation is hormonal and physiological changes.

Another factor that might affect the incidence of hospital diagnoses of OSAS and SDB is increased awareness among caregivers. If you are a snorer, have OSAS or have met relatives or patients with OSAS, you are more aware of the symptoms. This might be a possible explanation for the familial clustering in Paper III and increased awareness might also be a possible explanation for the high OR for the occupation as assistant nurses in Paper IV. Household crowding has been identified as a possible confounding factor in the association between low SES and SDB. Parents who live in smaller homes may be more likely to hear and recognize snoring or apnea than parents who sleep in separate rooms more fare away from the children.

Papers III and IV have limitations: firstly, the selection of hospital diagnoses of investigated patients. But according to the Swedish National Quality Register for tonsil surgery, approximately 80% of tonsil surgery for obstruction was performed at hospitals from 1997 to 2007. (A.C. Hessén Soderman, personal communication) Furthermore, the validity of the diagnoses in the children could not be confirmed. However, we used only primary diagnoses of OSAS and ATH from the Swedish Hospital Discharge Register, which means that the included patients were hospitalized because of their diagnoses, thus increasing the likelihood that the diagnoses are valid. Diagnosing adult OSAS by objective methods is obligatory in Sweden, and therefore the diagnosis is considered valid. The use of hospital data suggests that we may have also included adult patients with a more severe OSAS. Another possible limitation is that we did not include hospital diagnoses of adenoid hypertrophy or snoring. The reason for this is that these diagnoses probably represent a cohort with milder forms of SDB and the purpose of study III was to compare adult OSAS with pediatric OSAS. Up to now, in Paper IV, we have included 34 933 children and adolescents. We also performed an ancillary analysis and there were 12 590 children and adolescents with a primary diagnosis of snoring and 3 706 with a primary diagnosis of adenoid hypertrophy. Our intention was to evaluate if inclusion of these children with perhaps milder forms of SDB and in some cases only nasal congestion would change the outcomes. The results after including the children with diagnoses of snoring and adenoid hypertrophy (additionally 15 000 children) are similar as the results presented in Table VII on page 48.
According to Paper IV, the bias of not including patients treated on ambulatory wards is most likely present in all of the occupations compared, and is therefore probably of minor importance. However, the diagnostic and therapeutic traditions may vary in different parts of Sweden, which might be an explanation for the geographical differences in the present studies.

Furthermore, because of the large size of the study population, we have no data on individual risk factors for OSAS or physical examinations. An important factor that may have a causal relationship with SDB is overweight. In a study from 2002 and 2008 of 4-year-old children from the northern part of Sweden, the prevalence of overweight was approximately 15% among girls and 20% among boys. Other factors of importance, such as nutritional status in early life, passive smoking, early infections, tonsil size, and facial developmental factors were not eligible. Data on ethnicity are also lacking. In 2008 the Swedish population consisted of 14% immigrants (born outside Sweden). The majority were from Finland, Iraq, and the former Republic of Yugoslavia, and therefore we consider that most of the participants in the present study were Caucasians.

In Paper IV occupation was used as an approximation of occupational exposure. Information was not available on detailed job tasks or on potential exposure to harmful agents at or outside the workplace. Furthermore, some of the parents probably changed occupational category during the study period. Also, some parents may have been classified as students in the 1990 census and therefore were not included in this study. The errors according to this problem were, however, probably greater for those who gave birth later in the study period. A similar limitation in the dataset is that parents probably obtain more qualified and less exposed jobs with time. This misclassification of younger parents would probably result in an underestimation of risk for SDB in some occupations, although the magnitude is uncertain.

Despite these limitations, there are several strengths in the present studies. The study population included a well-defined open cohort, the entire population of Sweden under 19 years of age, linked to their parents. It was possible to track the records of every individual for the whole follow-up period because of the civic registration number assigned to each individual in Sweden. This ensured that there was no loss-to-follow-up. The data in the Swedish Hospital Discharge Register are also remarkably complete. In 2001 the main diagnosis was missing in 0.9% and the national civic registration number in 0.4% of hospitalizations. The quality of the multigenerational part of the MigMed database is also very high and it includes information about children, siblings, parents, and adoptions for index persons born in 1932 and onward and domiciled in Sweden any time between 1947 and 2007. We have also adjusted for geographic and
socioeconomic factors. The use of hospital register data eliminated recall bias, which is a potential problem with other study designs.

Furthermore, the 1990 data on occupational status used in Paper IV are remarkably complete (99.2%). The quality of data on occupational titles in the Sweden census data has been assessed and found to be reasonable. The proportion of concordant occupational titles was 72%. In terms of reliability, the coding showed that about 10% of occupations were misclassified. A further strength of the studies was the availability of family income for the year of birth.

CONCLUSION

- UPPP reduced the nightly respiratory disturbances to a mean of 60% and halved the daytime sleepiness and may be a safe alternative in OSAS patients who have failed or not accepted non-surgical treatment.

- UPPP did not change the median scores for pharyngeal disturbances according to a questionnaire for patients with OSAS after one year. OSAS patients had significantly higher median symptom scores for pharyngeal disturbances than non-snoring controls.

- Children with a parent affected by OSAS had a significantly higher risk of hospitalization for OSAS and SDB, defined as ATH.

- Swedish children with low SES, defined as low maternal education and low family income, have an increased OR for hospitalization for SDB, defined as OSAS and ATH. Furthermore, an increased OR for hospitalization for SDB was found in 14 maternal and 13 paternal occupational groups. A decreased OR was found in 10 paternal occupational groups.
FUTURE PERSPECTIVES

This thesis has raised many new questions. With regard to Paper I, there is a need for a randomized controlled trial evaluating the efficacy of UPPP with the highest level of evidence, and our group is at present actually doing such a study. The power analysis before the RCT is based on the ODI results in Paper I.

Even though there is an increasing body of evidence concerning which patients we have the opportunity to help or cure with UPPP, there are still questions left to answer. Friedman’s staging system for tongue position and tonsil size is helpful; however, there are more anatomical correlates to take into account, e.g. the constitution of the tonsillar pillars. A further question is the gender factor: Is the success factor the same in women as in men? Most participants in UPPP studies are men. Also, is the anatomical constitution the same in women as in men? How important is BMI for surgical success? Is it different in men and women and/or should we measure neck circumference or girdle and waist circumference before surgery?

With regard to Paper II, it would be interesting to make a polygraphy or, if possible, a PSG recording in both groups before inclusion in the study. The use of a validated questionnaire would increase the strength of the study. A further step would be performing an objective examination of the swallowing procedure in both groups. If this future study also shows a difference between controls and patients, why do the OSAS patients have more pharyngeal disturbances? Is it LPR?

Twenty-four-hour pH measurement and manometry of the esophagus could perhaps answer this question.

Papers III and IV and pediatric OSA raise even more questions. There is a familial clustering of OSAS both among siblings and among parents and children. We know that there are genetic mechanisms behind some of these findings. The shared environment perhaps has a key role. Can we cure OSAS in children and prevent the disease in adults? Does heavy snorer’s disease start in early childhood? Can we prevent the disease by preventive measures during early childhood? How important is SES and by which mechanisms does SES, parental education, and parental occupation affect the children? Is it primarily BMI, irritants in the air, or early infections that we can perhaps prevent in the future? Today we know that lymphadenoid tissue will proliferate especially in children exposed to environmental irritants. Viral respiratory infections during infancy are probably affecting the proliferative properties of upper airway lymphadenoid tissues. Additionally, the presence of allergic rhinitis and asthma has been implicated in the increased prevalence of ATH and OSA. In summary, we know that there are special groups of children that are at increased risk of developing OSAS, for example, children with low SES, children with a familial clustering of OSA, prematurely born children, obese children, children with neuromuscular diseases, and children with an anatomy that predisposes to OSAS. Awareness among caregivers and primary care physicians has an important role to play in identifying children at risk and offering early intervention and treatment.

Om CPAP och AAS inte fungerar kan patienterna remitteras för kirurgisk behandling. Den vanligaste är svalgkirurgi, så kallad Uvulopalatopharyngoplastik (UPPP) där bl.a. gomvalvet sys upp och halsmandlarna tas bort. UPPP har de sista åren i Sverige ifrågasatts och därmed använts allt mindre. Lyckandefrekvens har rapporterats till endast 30-50%, och hög andel biverkningar samt enstaka dödsfall har också redovisats.

Hos barn drabbas 1-3 procent av OSAS, men enligt enkätundersökningar har cirka 11 procent problem med snarkning och munandning. Barn med OSAS har ofta förutom snarkning och andningsuppehåll även uppmärksamhetsstörningar och försvagad skolresultat. De svårast sjuka barnen ökar inte i vikt som de ska. De vanligaste orsakerna är förstoring av tonsillerna och förstoring av körteln bakom näsan (adenoiden). Hos äldre barn har övervikt blivit en allt vanligare orsak.

Barn behandlas med ett kirurgiskt ingrepp där man tar bort eller minskar tonsillernas storlek och tar bort adenoiden. De får då diagnosen tonsill- och adenoidförstoring (ATH) eller OSAS. Denna avhandling utvärderar två huvudsakliga aspekter av OSAS, för det första; - UPPP hos vuxna patienter som misslyckats med behandling med CPAP och AAS (arbete I och II). Den andra aspekten är förhållandet mellan barn med diagnoserna OSAS och eller ATH, och deras föräldrar med och utan OSAS diagnos (arbete III). Dessutom barnens föräldrars yrke och socioekonomisk status (SES) (arbete IV)

I arbete I utvärderades effektivitet och säkerhet ett år efter UPPP hos 158 OSAS patienter, där behandling med CPAP och AAS misslyckats. Effektiviteten utvärderades med hemsömnregistreringar, där skillnaden mellan antalet andningsstörningar per sömntimme före och efter UPPP uppmättes. Dagtrötthet och patientnöjdhet ut-
värderades med ett frågeformulär. Resultatet av arbetet visade en tydlig minskning av antalet andningsstörningar per sömntimme. Lyckandefrekvensen beräknades vara 64 % och andningstörningarna minskade i medeltal med 60 %. Dagtrötthetsvärdet halverades och patientnöjdheten var 88 %. Fyra av 158 patienter drabbades av allvarliga komplikationer som blödning och svullnad, men vi fann inga dödsfall och inga kvarstående men av komplikationerna.

I arbete II fick 47 av patienterna i arbete I, svara på 10 frågor avseende besvär från svalget före och ett år efter operationen. Samma enkät besvarades också av 15 icke snarande kontrollpersoner. Resultatet visade att medianvärdet var samma före som efter operationen hos patienterna, och att kontrollpersonerna hade betydligt lägre medianvärde på frågeformuläret. Analys av frågorna var för sig visade en minskning av värdet före jämfört med efter operationen för frågorna “klumpkänsla i halsen” och “svullnadskänsla i halsen”.

Arbete III: med hjälp av en databas bestående av bland annat slutenvårdsregistret identifierades barn och ungdomar (0-18 år) som sjukhusvårdats för diagnoserna OSAS, och eller ATH under en 11-årsperiod. Därefter indelades barnen i två grupper utifrån slutenvårdsdiagnos OSAS hos föräldrarna. Referensgruppen bestod av barn och ungdomar med samma diagnoser, men utan föräldradiagnos OSAS. Resultatet visar att barn och ungdomar som har föräldrar med OSAS diagnos löper större risk att insjukna i OSAS/ATH.

I arbete IV användes samma databas som i arbete III som kopplades till folk och bo- stadsräkningen och vi undersökte samma slutenvårdsdiagnoser hos barn och ungdomar (0-18 år) som i arbete III (OSAS, ATH) under 11 år.

Resultatet visade att 34 933 barn hade dessa diagnoser och att risken att drabbas var förhöjd hos barn och ungdomar med låg familjeinkomst och låg utbildning hos modern. Hos 14 yrkesgrupper hos mamman och 13 yrkesgrupper hos pappan fann vi en ökad risk hos barn och ungdomar för att drabba av OSAS och ATH. Om exempelvis mamman arbetade som undersköterska eller motorfordonsförare, eller om pappan jobbade som motorfordonsförare, småttverk och gjuteri arbetare, mekanik och järn och metallarbetare och svetsare fann vi en ökad risk. Vi fann också en minskad risk hos barnen att drabbas av dessa sjukdomar inom 10 yrkesgrupper hos pappan, exempelvis; civilingenjörer, forskare, läkare, präster och jurister.

Sammanfattningsvis kan svalgkirurgi i form av UPPP vara en alternativ behandling för patienter som misslyckats med behandling av OSAS med AAS och CPAP. Barn och ungdomar som har föräldrar med OSAS löper större risk att få OSAS/ATH. Svenska barn och ungdomar med lågutbildad mamma och låg familjeinkomst, liksom barn till föräldrar inom vissa yrkesgrupper, löper större risk att drabba av OSAS och ATH.

Karin Lundkvist, 2012
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