

Paediatric sleep-disordered breathing

- diagnostics and treatment

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ABSTRACT

Sleep-disordered breathing (SDB) in children causes multiple health problems and diminished quality of life. It is usually caused by tonsil and adenoid hypertrophy and is traditionally treated with adenotonsillar surgery. The aims of the first paper were to examine the prevalence of SDB in Swedish children and the extent to which these children attract the attention of the health-care system. Further aims of the thesis were to examine different aspects of diagnostics and treatment, such as the quality and usefulness of at-home respiratory polygraphy, the health-economic aspects of tonsil surgery and the effect of nasal steroid treatment on symptoms and health-related quality of life in children with SDB.

Methods/Results: **Paper I** is a population-based, cross-sectional study in which 1,320 randomly selected Swedish children, aged 0-11, received questionnaires regarding symptoms of SDB in the previous month, health-care contacts and general health; 4.8% of the children had frequent SDB symptoms. Of these children, only 31% had been in contact with the health-care system due to their SDB symptoms. **Paper II:** A retrospective register study was conducted on all children aged 1-11 years that had tonsil surgery due to upper airway obstruction in 2011 and were included in the National Tonsil Surgery Register in Sweden (NTSRS), n=4,534. The mean duration of analgesic treatment was 4.6 days and the mean number of days with temporary parental benefits from the Social Insurance Agency was 2.9 days. The indirect costs were 61% higher after tonsillectomy than after tonsillotomy, due to a shorter recovery time after tonsillotomy. **Paper III** is a randomised, placebo-controlled study that comprised 60 children with SDB, aged 4-10 years. They were treated with budesonide or placebo nasal spray for six weeks. The improvement in health-related quality of life, measured by the OSA-18 total score, was significantly greater in the budesonide group than in the placebo group. The VAS scores for quality of life, as well as snoring, apneas and nasal obstruction, improved after budesonide treatment. In **Paper IV**, the quality of the at-home respiratory polygraphies performed on the children in Paper III was analysed and found to be poor, most often due to a missing nasal airflow signal. In an analysis of 17 polygraphies of good quality, the interrater correlation between two independent scorers was moderately good, but, when the nasal airflow signal was excluded and the scores for respiratory events were based on RIP flow, the correlation was negatively affected.

Conclusions: Many children with SDB do not get an appropriate evaluation and treatment. The costs for parental absenteeism after tonsillotomy are lower than after tonsillectomy. Nasal steroid treatment is effective in children with mild to moderate SDB. The quality and reliability of at-home respiratory polygraphy in children with SDB is questionable and needs further evaluation.

Keywords: Sleep-disordered breathing, children, tonsillectomy, tonsillotomy, absenteeism, intranasal steroid treatment, respiratory polygraphy, RIP flow

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LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Gudnadottir G, Ehnhage A, Bende M, Andersson M, Cervin A, Cardell L O, Hellgren J.
Healthcare provider contact for children with symptoms of sleep-disordered breathing: a population survey.
The Journal of Laryngology & Otology, 2016
Mar;130(3):296-301
- II. Gudnadottir G, Ragnarson Tennvall G, Stalfors J, Hellgren J.
Indirect costs related to caregivers' absence from work after paediatric tonsil surgery.
European Archives of Otorhinolaryngology, 2017, Jun;
274(6): 2629-2636
- III. Gudnadottir G, Ellegård E, Hellgren J.
Intranasal budesonide and quality of life in pediatric sleep-disordered breathing – a randomized, controlled trial.
Otolaryngology – Head and Neck Surgery, 2017, Nov. *Epub ahead of print*
- IV. Gudnadottir G, Hafsten L, Redfors S, Ellegård E, Hellgren J.
Respiratory polygraphy in children with sleep-disordered breathing.
Manuscript

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ABBREVIATIONS

AAO-HNS	American Association of Otolaryngology – Head and neck surgery
AAP	American Academy of Pediatrics
AASM	American Association of Sleep Medicine
AHI	Apnea-hypopnea index
BMI	Body mass index
CI	Confidence interval
CO ₂	Carbon dioxide
CPAP	Continuous positive airway pressure
EEG	Electroencephalography
ERS	European Respiratory Society
HRQoL	Health-related quality of life
NTSRS	National Tonsil Surgery Register in Sweden
OSAS	Obstructive sleep apnea syndrome
PSG	Polysomnography
RDI	Respiratory disturbance index
REM	Rapid eye movement
RERA	Respiratory effort related arousal
RIP	Respiratory inductance plethysmography
RP	Respiratory polygraphy
SD	Standard deviation
SDB	Sleep-disordered breathing

SpO ₂	Oxygen saturation measured by pulse oximetry
TE	Tonsillectomy
TSS	Total symptom score
TT	Tonsillotomy
VAS	Visual analogue scale

1 BACKGROUND

1.1 Paediatric sleep-disordered breathing

Sleep-disordered breathing (SDB) is a common condition in children, characterised by a broad spectrum of symptoms, from partial upper airway obstruction, with primary snoring, to severe obstructive sleep apnea syndrome (OSAS), with sleep severely disrupted by periods of respiratory obstruction and hypopnea. Children on all levels of this spectrum risk developing various health and behavioural problems and often have reduced quality of life.¹ Reaching an accurate diagnosis and deciding on the proper treatment is one of the most common management challenges for otolaryngologists. There has been increasing research interest in this condition over the past twenty years, but many questions regarding the optimal way to diagnose and treat SDB in the most clinically effective and cost-effective way still remain unanswered.

1.1.1 Aetiology

Obstructive SDB is characterised by reduced or absent airflow during sleep, due to the obstruction of the upper airway, but with continued respiratory effort. This can cause arousals and disruptions of the normal sleep pattern. The term “SDB” also encompasses central hypoventilation where the respiratory effort is missing due to rare conditions affecting central neurological respiratory control during sleep.² Central causes of SDB will not be discussed further in this thesis and the term “SDB” will refer solely to obstructive SDB.

The causes of SDB are primarily obstructive anatomic or hypotonic/dynamic in nature, although there is a significant overlap between the two. Obstructive SDB in children is most often caused by hypertrophy of the tonsils and/or the adenoids.³ This causes narrowing of the upper airway and can promote airway collapse during sleep, with resulting hypoventilation. Craniofacial syndromes and other alterations to the normal facial anatomy and narrowing of the upper airway may also be underlying reasons for obstructive breathing during sleep. Hypotonia of the upper airways, mainly seen in neuromuscular disorders and in children below one year of age, predisposes to the collapse of the airway.⁴

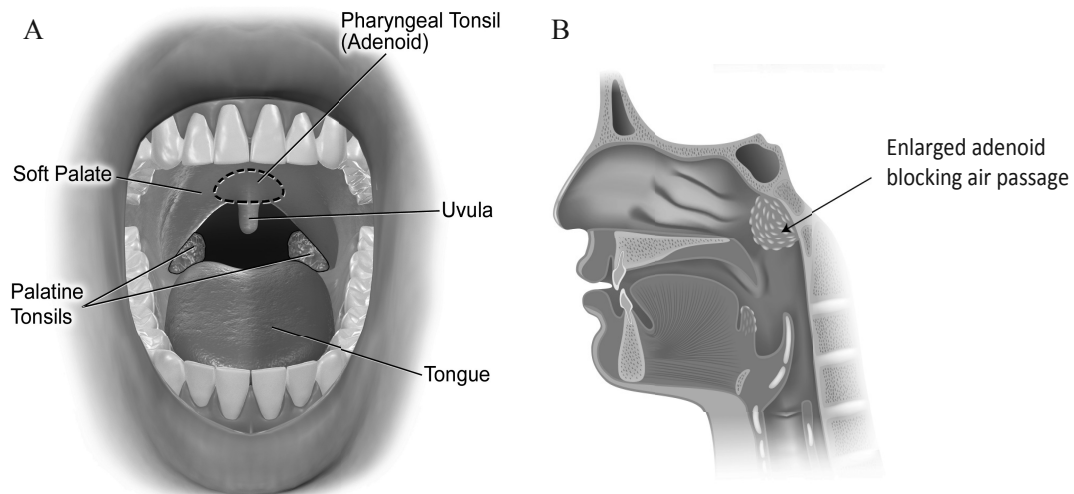


Figure 1. A. Normal anatomy of the throat. (Source: Blausen Medical Gallery)⁵
B. Enlarged adenoid blocking air passage. (Source: Dreamstime.com, with permission)

Children have higher arousal thresholds than adults, leading to fewer apnea-related arousals, and the sleep architecture is less disturbed in children with OSA than in adults.² Contrary to adults, apneas and hypopneas in children are most common during REM sleep, suggesting a loss of upper airway neuromuscular activity in children with OSA, although the mechanism is incompletely understood.^{6,7}

Studies have shown increased levels of inflammatory biomarkers such as CRP, leukotrienes and various cytokines, both systemically and locally in the tonsils and adenoids in children with SDB. It is, however, still unclear whether this inflammatory response is a cause or a consequence of the condition.⁸

1.1.2 Epidemiology and risk factors

The prevalence of SDB is estimated at 4% to 11%, based on various constellations of parent-reported symptoms in questionnaire studies.⁹ The prevalence of OSA, diagnosed by polysomnography (PSG) is 1-4%.⁹ The diagnosis of OSA is predominantly based on the apnea hypopnea index (AHI), but, at present, there is no international consensus regarding AHI cut-

off values when grading the severity of OSA. In research, an AHI or respiratory distress index (RDI) of 1-5 is most often used to identify children with OSA.⁹

The peak prevalence of SDB is in the age group of two to eight years when the tonsils and adenoids are largest in relation to the airway.² As the child grows, the airway widens and the adenoid and tonsil growth recedes.¹⁰ Follow-up studies have shown that OSA tends to resolve naturally during the transition to adolescence^{11,12} and the prevalence of snoring also decreases with age.

Multiple studies have found a higher prevalence of SDB in boys than in girls, but the reasons for this are unclear. The difference is more pronounced in children over 13 years of age, but it is also evident in the majority of studies of prepubertal children.⁹ There is also evidence that children with a lower socioeconomic status and racial/ethnic minorities, such as African-American or Hispanic children in the USA, display an increased prevalence of SDB.^{13,14} However, the prevalence of SDB in different countries and therefore different ethnic groups does not appear to show significant variations.⁹

Overweight and obese children run a higher risk of developing SDB,¹⁵⁻¹⁷ but the clinical picture more closely resembles that of adult OSA, in that it is less dependent on adenotonsillar hypertrophy and, instead, fat deposits in the pharyngeal structures play a greater role.¹⁸ This is reflected by the fact that obese children benefit less from adenotonsillectomy than children of normal weight.¹⁹ There is a well-established association between asthma and SDB, but it is yet not known whether the relationship is causal.²⁰ There also appears to be an association between SDB and allergic rhinitis, but the methodological quality of the studies performed thus far has been low.²¹ Children with allergic rhinitis are more likely to have adenoid hypertrophy.²² These two conditions have similar symptoms and may easily be confused in young children. Gastroesophageal reflux also appears to be associated with SDB in children. A good medical control of asthma, allergic rhinitis and gastroesophageal reflux leads to improvements in SDB symptoms and AHI.²³ Preterm birth entails an increased risk of developing SDB in the following years.²⁴ Different craniofacial syndromes that cause narrowing of the airways, including cleft lip/palate,²⁵ Pierre Robin²⁶ and Treacher-Collins syndrome²⁷ and neuromuscular disorders, are a risk factor for SDB.²⁸ Children with Down syndrome have a high prevalence of SDB and OSAS, which is related to their unique upper airway anatomic features, as well as an increased risk of obesity, hypothyroidism, gastroesophageal reflux disease and generalised hypotonia.²⁹

1.1.3 Symptoms and morbidity

Snoring, disturbed sleep, nocturnal sweating and abnormal sleeping positions are frequent night-time symptoms reported by the parents of children with SDB.³⁰ Daytime symptoms include daytime fatigue, aggressiveness, hyperactivity and inattention.³⁰ Neurocognitive or behavioural problems and learning disabilities have been clearly linked to SDB, both primary snoring and OSA.³¹⁻³⁴ Possible causes of these comorbidities are intermittent hypoxemia, sleep fragmentation and local or systemic inflammation.⁸

The growth retardation frequently seen in children with SDB is caused by multiple factors. SDB interrupts slow-wave sleep, when growth hormone is mainly secreted, causing reduced serum levels. Dysphagia, due to large tonsils and adenoids, and increased energy expenditure during the night also play a role. After tonsillectomy, the children show significantly increased growth and increased levels of growth hormones.³⁵

Chronic mouth-breathing due to nasal obstruction during critical growth periods affects the growth of the facial skeleton, causing retrusion of the mandible and a disproportionate increase in anterior lower vertical face height, giving affected children a distinct appearance, as well as malocclusion.^{36,37}

Nocturnal enuresis is associated with SDB and, in a systematic review, one third of children with SDB had nocturnal enuresis.³⁸ The pathophysiology is probably complex. Obstructive nocturnal breathing causes increased intra-abdominal pressure and changes in systemic blood pressure that induce natriuresis and polyuria by altering levels of antidiuretic hormone and atrial and brain natriuretic peptides.³⁹

Negative effects on the cardiovascular system that are seen in SDB include hypertension, increased pulmonary artery pressure and cor pulmonale.⁴⁰⁻⁴² Arousal from sleep and hypoxemia resulting from apneas and hypopneas are accompanied by sympathetic nervous system activation, peripheral vasoconstriction and intermittent blood pressure elevation.⁴²

1.2 Diagnosis of sleep-disordered breathing

1.2.1 History and clinical examination

The detection and diagnosis of SDB in children is important in order to ensure that affected children receive the appropriate treatment to minimise the risk of comorbidities and improve their quality of life. Historically, awareness of paediatric SDB has been low, among both parents⁴³ and health-care professionals.⁴⁴

The majority of cases of paediatric SDB are diagnosed by a clinical examination and history.⁴⁵ However, research shows that the predictive value of these methods in diagnosing OSA is low.⁴⁶ The clinical examination includes grading tonsil and adenoid size. The Brodsky grading scale is used to evaluate tonsil size (*Fig 2*).⁴⁷ The size of the tonsils according to Brodsky has not been shown to correlate well with baseline OSA severity.^{48,49} However, when magnetic resonance images are used to measure tonsil size, the correlation is better.⁵⁰ This method is only used for research purposes due to high costs and inconvenience to the patient. Tonsil and adenoid size may be difficult to assess accurately in the clinical setting, especially in the youngest children who do not co-operate well. Adenoid size can be evaluated with a transnasal endoscope and it is usually expressed as the percentage of choanal occlusion or by using different grading systems.^{51,52}

Grade	Proportion of tonsil in oropharynx
1+	Tonsils occupying less than 25% of oropharynx
2+	Tonsils occupying 25-50% of oropharynx
3+	Tonsils occupying 50-75% of oropharynx
4+	Tonsils occupying >75% of oropharynx

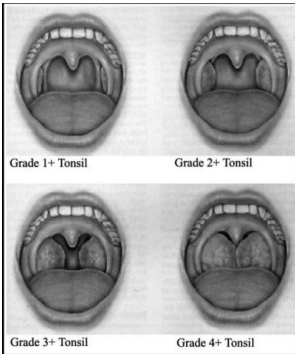


Figure 2. Grading of tonsil hypertrophy according to Brodsky.⁴⁷

1.2.2 Polysomnography

Polysomnography (PSG) is regarded as the gold standard in diagnosing OSA in children.⁵³ It is a non-invasive procedure, recording several physiological measurements, such as the sleep stage and respiratory functions.

According to guidelines from the American Academy of Pediatrics (AAP) and the American Academy of Sleep Medicine (AASM), PSG should be performed in all children with suspected OSA.⁴⁶ In clinical practice, this is rarely the case, as PSG is expensive, resource demanding and rarely readily available. In fact, fewer than 10% of children with suspected OSA undergo PSG prior to any decision on tonsil surgery, according to figures from the USA and Great Britain.^{45,54} The American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) recommends that PSG should be performed prior to deciding on tonsil surgery in children with special medical conditions such as obesity, Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, or mucopolysaccharidoses and, moreover, when the need for surgery is uncertain or when there is discordance between tonsillar size on physical examination and the reported severity of sleep-disordered breathing.⁵⁴

PSG is usually performed in a hospital setting, although some research has been conducted on the feasibility of unattended PSG in the patient's home.⁵⁵⁻⁵⁷ The standard PSG includes the following recordings: electroencephalogram (EEG), electromyogram (EMG), electrocardiogram (ECG), electro-oculogram (EOG), oronasal airflow, oxygen saturation (SpO₂), respiratory movements (respiratory inductance plethysmography (RIP) belts around the thorax and abdomen), transcutaneous or end-tidal carbon dioxide (CO₂), body position and video and sound recordings.

EEG provides reliable information on the child's sleep time. It is necessary in order to score sleep stages (Stages I-IV and REM) and arousals. Children have higher arousal thresholds than adults and many respiratory events in children are not linked to arousals.⁵⁸

Airflow monitoring

Airflow monitoring is performed with a nasal pressure transducer via a cannula and/or an oronasal thermistor. The oronasal thermistor detects the temperature difference between inspired and expired air. Airflow measurements via a nasal cannula connected to a pressure transducer have been shown to be more effective than the thermistor in detecting hypopneas.⁵⁹ This provides a signal proportional to the square of the flow. A square root

transformation of the signal provides a more accurate estimate of the flow, usually giving a slightly lower AHI.⁶⁰

However, the fact that many children with SDB are mouth-breathers makes the nasal airflow an unreliable signal.² The AASM recommends the use of an oronasal thermistor primarily for the detection of apneas and the nasal cannula pressure transducer for the detection of hypopneas. When one of these recommended sensors does not function or is not reliable for these purposes, the other one may be used as an alternative sensor. RIP sum or RIP flow are also possible alternative sensors when the recommended sensors fail.⁶¹

Respiratory inductance plethysmography

Respiratory inductance plethysmography (RIP) is the most commonly used method to measure respiratory effort in sleep studies. An oscillating electrical current travels through a wire inside belts placed around the patient's chest and abdomen. The electrical current generates a magnetic field that is modified by movement due to breathing.⁶² Belts with piezo-electric sensors have also been used for this purpose, but RIP is the preferred method.⁶³

The RIP sum is the summation of the abdominal and thoracic signals, providing a semi-quantitative measurement of tidal volume. The RIP flow is the time derivative of the RIP sum and excursions of the signal are an estimate of airflow.⁶¹ An uncalibrated RIP signal may result in flow traces where apnea- and hypopnea-like traces are produced artificially due to the modulation. A calibrated RIP signal should bypass this problem, although more research is needed to confirm this. Oesophageal manometry is the gold standard in measuring respiratory effort. The validation of RIP against oesophageal manometry reveals good sensitivity and specificity and acceptable intra- and interobserver variability.⁶³

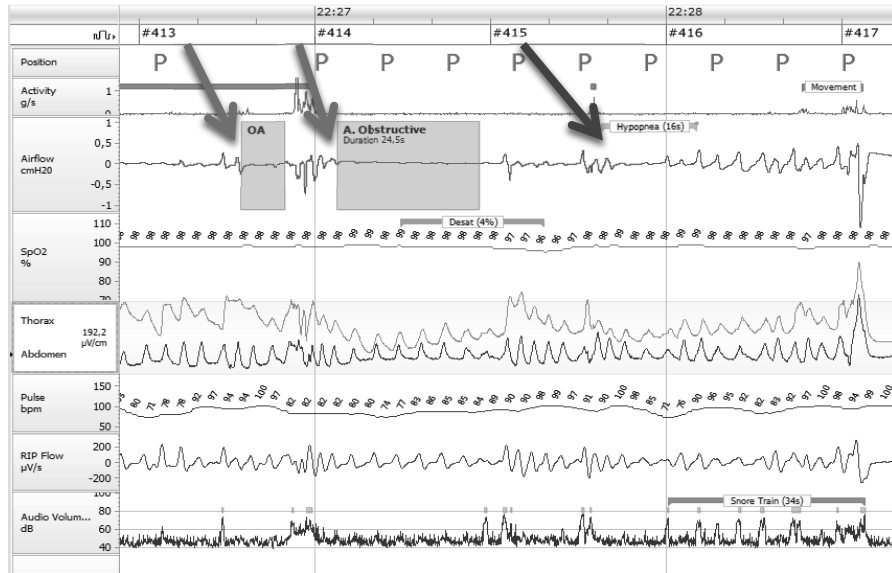


Figure 3. Respiratory polygraphy recording with examples of two obstructive apneas (Red arrows) and a hypopnea (blue arrow) The leads shown are, from the top; body position, movements (activity), airflow, SpO₂, thoracic and abdominal movements, pulse, RIP Flow and audio recording of snoring sounds.



Figure 4. Girl with the Nox T3 portable sleep monitor for respiratory polygraphy. Photo: Louise Hafsten.

Scoring PSG

The scoring of PSG in children is done in accordance with the AASM manual as shown below.^{60,61}

Obstructive apnea	Drop in airflow amplitude of $\geq 90\%$ from baseline for at least two respiratory cycles, with continued inspiratory efforts during the period of absent airflow.
Central apnea	Drop in airflow amplitude of $\geq 90\%$ from baseline without inspiratory effort, either with a duration of at least 20 seconds or a duration of at least two breaths and associated with an arousal and/or a 3% oxygen desaturation.
Mixed apnea	Drop in airflow amplitude of at $\geq 90\%$ from baseline for at least two respiratory cycles with the absence of inspiratory effort during one portion of the event and the presence of inspiratory effort during another portion, regardless of which portion came first.
Hypopnea	Drop in airflow amplitude of $\geq 30\%$ from baseline, for a duration of at least two breaths, associated with an arousal and/or a 3% oxygen desaturation.

AHI is the number of apneas and hypopneas per hour of sleep time. The results may also be presented as a respiratory disturbance index (RDI) that includes the AHI, as well as all respiratory effort-related arousals (RERA) per hour of sleep time. RERAs are arousals that disturb sleep without fulfilling the criteria for apneas or hypopneas.

There is no international consensus regarding the limits of severity of OSA in children, but an AHI of 1-5 is generally regarded as mild OSA, whereas an AHI of > 10 is severe.^{2,53,64} These limits are considerably lower than in adults, where an AHI of 5-15 is regarded as mild OSA and an AHI of > 30 is severe.

1.2.3 Respiratory polygraphy

Respiratory polygraphy (RP) sleep studies include a more limited number of channels than a PSG, usually four to seven. Possible leads include a nasal cannula pressure transducer for measurements of respiratory flow, thoracic and abdominal calibrated RIP bands for measuring respiratory effort, SpO₂ via pulse oximetry, body position, actigraphy and audio recording. In an RP, it is not possible to score sleep stage or arousals, as there is no EEG channel.

RP can be performed in hospital settings, but it is more commonly performed at the patient's home. The benefits of at-home sleep studies are that they are less expensive and that the children may be less stressed and sleep better in their usual home environment. The negative aspects are that the equipment is set up by the parents, who are not as experienced as trained personnel, and the child is not as closely supervised during the night. If leads fall off, they are not replaced and there is more uncertainty regarding actual sleep time.

In adults, at-home RP has been shown to be a cost-effective and reliable substitute for PSG.⁶⁵ The few studies of the technical feasibility of at-home RP in children have shown conflicting results, with the rate of technically successful studies varying from 29-100%.^{55,66} Studies in which trained staff set up the equipment⁶⁷⁻⁶⁹ generally have higher success rates than those in which the caregivers handle the set-up.^{66,70} There are no official guidelines for scoring paediatric RP; it is scored by the same rules as PSG with some modifications because arousals cannot be scored. A few studies designed to compare the diagnostic reliability of home RP with in-lab PSG indicate that the sensitivity and specificity of home RP appear to be reasonably good, especially in children with moderate to severe OSA,⁵⁵ but other studies have not been able to show equally good reliability.^{66,71} Tan et al. found that there was a tendency towards underscoring AHI when EEG, EOG and EMG channels were deleted from the original unscored PSG recordings to transform them into RP.⁷¹

1.2.4 Nocturnal oximetry

Nocturnal oximetry has been proposed as a screening tool for OSA in symptomatic children. Low costs and easy availability make it an attractive option when PSG is not available. Studies have shown that nocturnal oximetry has high sensitivity in detecting OSA, but the specificity is limited.⁷² Recently developed neural network-based automated analyses of nocturnal oximetry recordings appear, however, to be able to provide a relatively accurate identification of OSA severity among children with SDB symptoms, making it an interesting alternative to PSG and RP.⁷³

1.2.5 Questionnaires

Symptom-based questionnaires

There are a multitude of questionnaires that are primarily designed for the diagnosis, screening or assessment of SDB or OSA based on symptoms.⁷⁴ Two of the more well-known and widely used questionnaires are the Brouillette score⁷⁵ and the Pediatric Sleep Questionnaire (PSQ).⁷⁶ The Brouillette score is calculated from the caregivers' answers to questions regarding their children's snoring, apneas and breathing difficulties during sleep.⁷⁵ The PSQ is a questionnaire with 57 items regarding the child's sleep that range from sleep onset difficulty, insomnia, restless legs syndrome, snoring, excessive daytime sleepiness, parasomnias and daytime behavioural symptoms of hyperactivity and inattention.⁷⁶

Health-related quality of life questionnaires

Quality of life is a broad term that has been described as “a broad ranging concept, incorporating in a complex way individuals' physical health, psychological state, level of independence, social relationships, personal beliefs, and their relationship to salient features of the environment”.⁷⁷ There is no clear consensus on how to measure health-related quality of life (HRQoL). It was introduced to emphasise life domains directly related to a person's health and within the influence of the health-care system. The core domains are the physical, mental and social aspects, but disease-specific instruments may include various other domains.⁷⁸ One problem when measuring HRQoL in young children is that it usually relies on the parents' perception of their children's problems. Assessments of the parent-child agreement on HRQoL assessments have shown conflicting results,⁷⁸ but children under 10 years of age are generally considered to be unable consistently to rate their own health.⁷⁴

Studies of paediatric sleep-disordered breathing have used both generic HRQoL instruments, such as the Child Health Questionnaire (CHQ-PF28) and the Pediatric Quality of Life Inventory (Peds-QL) that measure general quality of life, as well as disease-specific HRQoL instruments like the OSA-18 and Obstructive Sleep Disorders-6 (OSD-6), where the OSA-18 is the one most commonly used to evaluate the effect of surgical treatment on HRQoL.^{74,79}

OSA-18

The OSA-18, used in this thesis is an 18-item questionnaire, was developed by Franco et al.⁸⁰ It has been widely used for comparing HRQoL before and after tonsil surgery in children with SDB. It has been shown to have good

test-retest reliability, construct validity and internal consistency⁸⁰ and the Swedish version has also been validated.⁸¹ The test-retest validity has been shown to be excellent, as it is responsive to change after tonsil surgery.^{82,83} It correlates well with the results of the OSD-6, another validated HRQoL instrument for children with SDB.⁸² Although Franco et al. found a significant correlation between the OSA-18 and the RDI, according to a nap PSG⁸⁰, the sensitivity and positive predictive value when comparing OSA-18 scores with PSG results have, however, been shown to be low in subsequent studies.^{84,85} The OSA-18 is further described in the methods section of this thesis.

1.2.6 Video recordings

Home video recordings are a valuable tool for screening for paediatric sleep apnea. They appear to have high sensitivity (94%) when compared with PSG, but the specificity is lower (68%).⁸⁶ Further studies are needed, as well as algorithms, to evaluate the recordings.

1.2.7 Other diagnostic methods

There is an on-going search for appropriate diagnostic biomarkers to aid in the diagnosis of SDB. They are mainly aimed at markers associated with the systemic inflammation associated with OSA, but none of these biomarkers is yet in use in clinical practice.⁸⁷ Drug-induced sleep endoscopy has been used to identify the area of obstruction when the tonsils are not the obvious cause of obstructive breathing.⁸⁷ Measurements of peripheral arterial tone have been shown to correlate well with PSG AHI in adults,⁸⁸ but it needs further testing in children to assess its usefulness.⁸⁹

1.3 Treatment for sleep-disordered breathing

1.3.1 Surgical treatment

Tonsil surgery is one of the most commonly performed surgical procedures in children. In the USA, more than 500,000 adenotonsillectomies are performed annually in children⁹⁰ and almost 7,000 tonsil surgeries are performed with or without concomitant adenoidectomy in children under 12 years of age in Sweden each year, 87% of them due to obstructive breathing during sleep.⁹¹

Tonsillectomy

A tonsillectomy (TE) is the complete surgical removal of the tonsils. It is often performed in combination with an adenoidectomy. There are, however, no available, well-designed studies comparing the efficacy of isolated adenoidectomy or tonsillectomy with adenotonsillectomy in children with SDB.⁹² Adenotonsillectomy has been shown to be effective in improving the symptoms, behaviour, quality of life and AHI in children with SDB.⁹³⁻⁹⁶ A meta-analysis of 51 studies with 3,413 subjects revealed a mean decrease in AHI of 12.4 events/hour after tonsillectomy, but only 51% of the subjects had an AHI of < 1 postoperatively and 81% had an AHI of < 5. Severe OSA and obesity were risk factors for residual disease after surgery.⁹⁷

An AHI of >5 episodes/hour has been used as an indication for tonsillectomy, irrespective of the presence of morbidity, but lower cut-off values have also been applied.⁹² If there is a clinical suspicion of obstructive SDB and if polysomnography is not available, surgery is considered when an alternative diagnostic method indicates OSAS or if there is SDB-associated morbidity, such as dysphagia, growth failure, cardiovascular complications or reduced quality of life. This approach is proposed in recent guidelines from the European Respiratory Society (ERS) Task Force on the diagnosis and management of obstructive sleep-disordered breathing in childhood.⁹²

In Sweden, 74% of paediatric tonsil surgeries are performed in day surgery.⁹⁸ However, certain patient groups have higher risks of respiratory complications, such as pulmonary oedema, hypoxemia and bronchospasm, and they should be therefore be admitted for postoperative surveillance according to AAP and AAO-HNS guidelines.^{46,54} The high-risk factors include age < 3 years, severe OSA (AHI >10, oxygen saturation nadir <80% or both), obesity or comorbidities. Non-respiratory complications include

dehydration (4.5%), bleeding (2.3%) and fever (0.5%).⁹⁹ Mortality rates are very low.¹⁰⁰

Tonsillotomy

A tonsillotomy (TT) is the partial excision of excessive tonsil tissue, leaving some tonsil tissue and the lateral tonsil capsule intact. It can also be referred to as subtotal, intracapsular or partial tonsillectomy. Various methods, including Coblation, radiofrequency and CO₂ laser, have been used for this procedure. In Sweden, TT has become the most common surgical treatment for children with SDB.¹⁰¹ There is strong evidence that pain is less severe after TT than TE and the recovery time is shorter.¹⁰² The risk of postoperative bleeding is also significantly lower.¹⁰³ TT has been shown to be as effective as TE in terms of improving symptoms, quality of life and PSG results.¹⁰⁴⁻¹⁰⁶ TT does, however, carry a higher risk of subsequent secondary surgery due to infections or tonsillar regrowth.^{102,107}

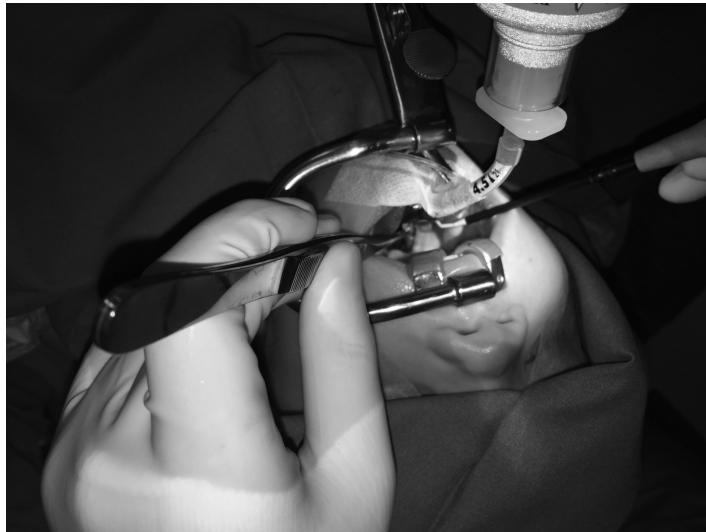


Figure 5. Radiofrequency tonsillotomy. Photo: Gunnhildur Gudnadottir.

1.3.2 Medical treatment

Nasal steroids

Nasal steroids have been used for many years in the treatment of allergic rhinitis in children and are known to be a safe treatment with minimal side-effects.¹⁰⁸ In the last few years, interest in using nasal steroids as a treatment for SDB in children has been increasing. According to guidelines from the ERS task force on the diagnosis and management of obstructive SDB in childhood, nasal steroids are now recommended as a first step in the treatment of SDB in children.⁹² Research has shown that nasal steroid treatment reduces the size of the adenoids.¹⁰⁹ Possible explanations for this include the direct reduction of adenoid size by the lympholytic action of steroids on adenoidal tissue, the anti-inflammatory effects of steroids or a reduction in the significance of the adenoids as a reservoir for infection.¹¹⁰ There is also evidence that nasal steroids improve the symptoms of snoring, apneas and nasal obstruction.^{109,111} Two randomised trials have been conducted on nasal steroid treatment in children with OSA. In a placebo-controlled, randomised trial by Kheirandish-Gozaal comprising 62 children with mild OSA, there was an improvement in symptoms and PSG results after six weeks' treatment with budesonide. A normalisation of sleep measurements was observed in 54 per cent of treated children and it was sustained at eight weeks after the discontinuation of treatment.¹¹² Brouillette et al. also found an improvement in AHI and symptoms after six weeks' treatment with fluticasone in a trial comprising 25 children.¹¹³ The optimal length of treatment has not yet been established. No previous randomised trials have examined the effect of nasal steroids on HRQoL as the primary outcome in children with SDB.

Leukotriene-receptor antagonists

It has been suggested that leukotriene-receptor antagonists reduce adenotonsillar hypertrophy through their anti-inflammatory effect. Two randomised trials on 12 and 16 weeks' treatment with oral montelukast, in children with OSA, have shown improvements in AHI, symptoms and adenoid size.^{114,115} Combined treatment with oral montelukast and intranasal budesonide has also been shown to improve and/or normalise respiratory and sleep disturbances in children with residual SDB after adenotonsillectomy.¹¹⁶

1.3.3 CPAP

Continuous positive airway pressure (CPAP) is a form of positive airway pressure ventilator, which applies mild air pressure on a continuous basis to keep the airways open. In children with OSA, it can be an alternative

treatment for children with residual OSA after tonsillar surgery or when the main cause of the upper airway obstruction is not adenotonsillar hypertrophy, in obese children and children with craniofacial abnormalities, for example. It is usually well tolerated and highly effective.⁴⁶ However, poor adherence to treatment is a common problem.^{117,118} Potential problems and side-effects include technical problems with mask fitting and leakage, nasal congestion, rhinorrhea or bleeding, skin irritation or midface hypoplasia.^{118,119}

1.3.4 Orthodontic treatment

Rapid maxillary expansion is an orthodontic treatment that may be indicated in children with OSA and clinical signs of malocclusion, a high, narrow palate associated with deep bite, retrusive bite or crossbite. It improves SDB symptoms, quality of life and AHI in patients with this combination of problems.^{120,121}

1.3.5 Tracheostomy

Tracheostomy is regarded as the most definitive treatment for patients with refractory OSA. In children, this form of treatment is very rarely necessary. Children who require a tracheostomy for severe OSA usually suffer from either craniofacial abnormality or a serious neuromuscular comorbidity resulting in hypotonia.¹²²

1.4 Health economics

Health-care resources are limited and, as the cost of health care continues to rise, it is important to examine not only the medical outcome of treatments but also whether they are cost effective. In this complex evaluation, it is important to take account of the medical benefits and improvements in quality of life that patients stand to gain from surgery and weigh them up against medical issues such as complications, pain and discomfort, as well as economic costs. The costs can be divided into *direct* and *indirect costs*.

Direct costs

Direct costs are costs related to the actual disease or treatment, such as the cost of surgery, anaesthesia, inpatient and outpatient care and drug costs. The direct costs of tonsil surgery are likely to vary considerably between health-care systems and countries and are influenced by market competition and the ability to implement correct pricing in complex hospital economies.^{123,124}

Indirect costs

Indirect costs are the costs that arise due to the patients' or caregivers' absence from work, or absenteeism, because of the actual condition or treatment. According to the *human capital approach*, the value of time lost from work due to a child's illness is directly related to the expected earnings during that period, which means that one day of lost productivity is equal to one day of salary plus social costs.¹²⁵ The indirect costs due to caregiving in relation to SDB and after surgery have not been studied before.

2 AIMS

The overall aim of this thesis is to add knowledge to the field of sleep-disordered breathing in children in order to improve the diagnostics and treatment of this common and potentially serious disorder.

Paper I

- To examine the prevalence of SDB symptoms in Swedish children
- To determine the extent to which children with frequent SDB symptoms attract the attention of the health-care system for their symptoms

Paper II

- To investigate the number of missed working days and resulting indirect costs due to caregivers' absenteeism after their children's tonsil surgery
- To compare the indirect costs associated with tonsillectomy and tonsillotomy

Paper III

- To examine the effect of nasal steroid treatment on the symptoms and HRQoL of children with sleep-disordered breathing

Paper IV

- To evaluate the quality of at-home respiratory polygraphy in children with SDB and the reasons for failed sleep studies
- To investigate the interrater reliability of respiratory polygraphy
- To examine the reliability of RIP flow as a substitute for nasal pressure airflow in detecting respiratory events during sleep

3 PATIENTS AND METHODS

3.1 Subjects and study design

Paper I is a population-based, cross-sectional study, comprising 1,320 children aged 0-11 years, randomly selected from the Statens Personadressregister (SPAR) national database, which includes all Swedish residents at any given time. The children were selected from different parts of the country to represent the demographic distribution in Sweden. The caregivers received two questionnaires, the OSA-18 and an additional questionnaire constructed for the actual study. The children that scored six or seven points (“most of the time” or “all of the time”) on at least one of the first three items on the OSA-18, snoring, apneas or choking sounds, were classified as having frequent SDB symptoms. The second questionnaire contained the following question regarding health-care contacts.

Have you been in contact with a health-care provider due to your child’s sleep-related breathing problems and/or snoring?

The possible response options were “yes” and “no”. The second questionnaire also included questions on allergic rhinitis, asthma, pseudocroup, respiratory syncytial virus infections, enuresis or night sweats, or if daytime sleepiness had been reported by the day-care centre. The caregivers were also asked about previous tonsillectomy or adenoidectomy, otitis media or tympanostomy tube insertion.

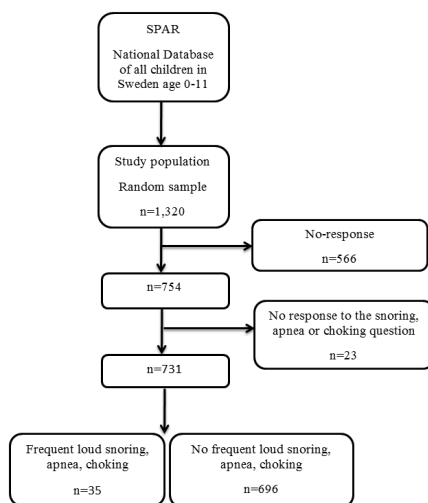


Figure 6. Patient selection in Paper I. SDB symptoms defined as loud snoring and/or apnea and/or choking sounds during sleep either most or all of the time during the previous month.

Paper II is a retrospective register study of all children aged 1-11 years that underwent tonsil surgery due to upper airway obstruction in 2011 and were included in the National Tonsil Surgery Register in Sweden (NTSRS), n=4,534. The reported number of days the child required analgesic treatment, according to the answers to a questionnaire sent out by the NTSRS 30 days after surgery, were used as a proxy for the minimum numbers of days the child needed to stay at home after surgery. Data were also retrieved from the Social Insurance Agency (Försäkringskassan) on how many days the caregivers received temporary parental benefits in the month following surgery. This information was used to calculate the indirect costs due to caregivers' absenteeism after tonsillectomy vs tonsillotomy, using the human capital method.¹²⁶ The calculations of the indirect costs were based on information from Statistics Sweden regarding the average salaries for men and women in Sweden,¹²⁷ and from the National Institute of Economic Research regarding the average number of working days in Sweden per year.¹²⁸ *Figure 7* shows the selection of the study population in Paper II.

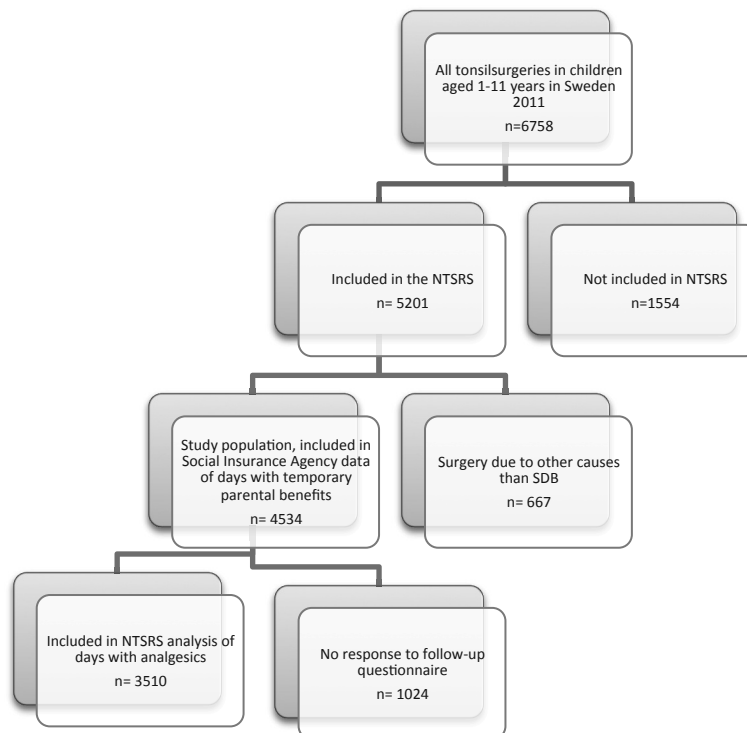


Figure 7.
The selection of the study population in Paper II

Paper III is a randomised, placebo-controlled trial that comprised 60 children, aged 4-10 years, with SDB symptoms for at least three months. The exclusion criteria were as follows: guardian not able to read and write Swedish; an acute respiratory infection at inclusion; the use of nasal or systemic corticosteroids or antibiotics within four weeks prior to enrolment; a history of previous tonsil or adenoid surgery; craniofacial, neuromuscular, or genetic disorders; severe SDB symptoms requiring urgent surgery or unwillingness to participate in a randomised study. All the participants underwent a medical examination prior to inclusion. Tonsil size was evaluated using the Brodsky classification and adenoid size was examined via fiberoscopy, recording the percentage occlusion of the choana. A Phadiatop allergy test was conducted at inclusion. The caregivers completed the OSA-18, as well as a questionnaire on general health. An at-home respiratory polygraphy was performed the following night with a Nox T3 portable home sleep monitor (Nox Medical®, Reykjavík, Iceland). The children were randomly assigned to the treatment groups, receiving six weeks' treatment with either budesonide nasal spray (Rhinocort Aqua® 64 µg/ml), or placebo nasal spray, one dose in each nostril twice daily. During the treatment period, the caregivers completed a weekly questionnaire on symptoms and possible side-effects. After treatment, the medical examination was repeated, as well as the OSA-18 and the respiratory polygraphy.

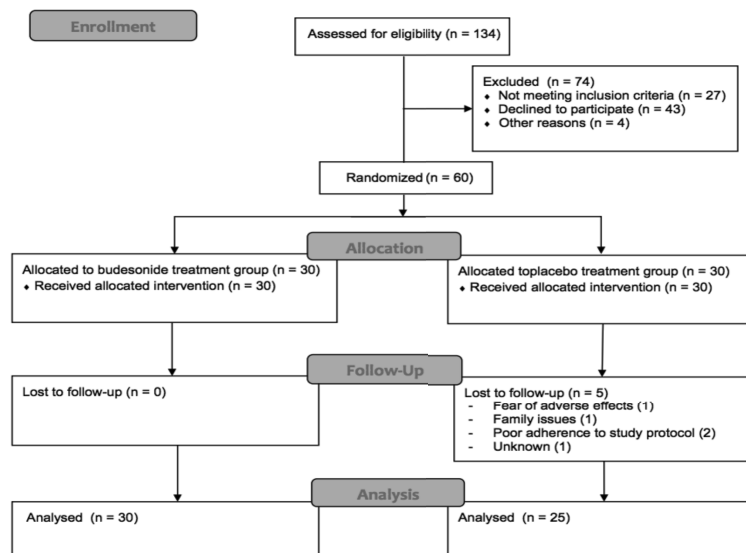


Figure 8. Patient flow in Paper III.

Paper VI is a prospective study, using the 113 respiratory polygraphies that were performed as part of Paper III. The number of failed studies and reasons for failure were examined. Seventeen technically successful polygraphies were selected for a pilot study comparing the mean AHI for the included RPs, scored by two experienced scorers with nasal flow and without nasal airflow, in which case the scoring of respiratory events relied primarily on the RIP flow.

3.2 OSA-18

The OSA-18 HRQoL questionnaire was used in Papers I and III. It contains questions across five domains (sleep disturbance, physical symptoms, emotional distress, daytime function, caregiver concerns). Each item is scored in relation to its frequency from *never* to *all the time* on a 1-7 scale with a possible total symptom score, TSS, of 18 to 126. A total score of < 60 suggests a small impact on HRQoL, scores of 60-80 suggest a moderate impact and scores of > 80 suggest a large impact.⁸⁰ The OSA-18 also includes a direct global rating of the child's general HRQoL via a 10-point VAS (0=poorest, 10=best). Data from other evaluative surveys with seven-point response scales suggest that a mean change score per item of 0.5 indicates a trivial change, 0.5 to 0.9 indicates a small change, 1.0 to 1.4 indicates a moderate change and 1.5 indicates a large change.^{82,129}

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

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

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

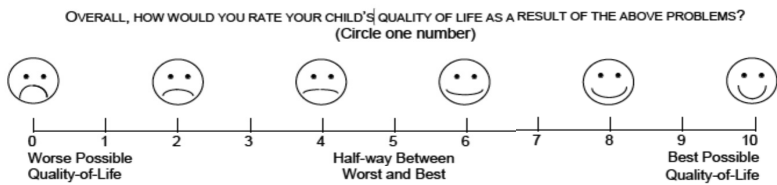


Figure 9. The OSA-18 questionnaire.

3.3 Statistics

Continuous variables are expressed as the mean \pm SD and categorical variables are expressed as percentages, unless otherwise stated. A two-sided p-value of < 0.05 was considered statistically significant. IBM SPSS Statistics version 21 and 22 and Microsoft Visual Basics were used to perform statistical analyses.

Paper I: The 23 respondents that did not answer the question about loud snoring, apnea or choking were not included in the analysis. Missing data for other items was scored as 1 (never). Fisher's permutation test was used to analyse between-group differences. The results were presented as odds ratios with 95% CI. Correlations were evaluated using Pitman's test.

Paper II: Descriptive analyses including frequencies, the mean, minimum and maximum, as well as a one-sample t-test with calculations of 95% confidence intervals (CI), were conducted.

Paper III: The power calculation was based on a previous open-label study that showed a mean improvement of seven points on the OSA-18 after four weeks' treatment with nasal steroids.¹³⁰ According to our power calculation, 30 patients were required in each treatment group to detect a change of at least seven points in the total OSA-18 score, with 80% power and an α -level of 5%. An intention-to-treat analysis was performed. Fisher's permutation test was used to compare primary and secondary outcomes between the two treatment groups. Cohen's d and a 95% CI were calculated for the difference in OSA-18 total score after treatment.

A multivariate, linear regression analysis was conducted to adjust for the difference in baseline OSA-18 total score. For the diary findings a linear regression coefficient was calculated to describe the trend over time, i.e. the slope of the regression line from week one to week six for each patient and each variable in the diary. The time point in weeks (1-6 weeks) is the independent variable and the variable in the diary at each time point is the dependent variable. The slope of the regression line from each individual contributes to the analysis of trend over time. Fisher's test for paired comparisons was used to test whether the trend over time (regression coefficient) differed from zero,

Paper IV: Fisher's test for paired comparisons was used for comparisons of differences between nominal variables. Fisher's exact test was used for comparisons of categorical data. The interclass correlation coefficient (ICC)

was calculated to assess agreement and Bland-Altman graphs were constructed. The significance levels were set at 5% and 95% confidence intervals (CI) were calculated. The levels of agreement using the ICCs of AHI were classified as follows: values less than 0.5 = poor reliability, values between 0.5 and 0.75 = moderate reliability, values between 0.75 and 0.9 = good reliability and values greater than 0.9 indicate excellent reliability.¹³¹

3.4 Ethical considerations

The studies were conducted in accordance with the Declaration of Helsinki and were approved by the Regional Ethics Committee at the University of Gothenburg (Dnr 594-10 (Paper I), 885-12 (Paper II) and 719-13 (Papers III and IV)). The study protocol for Papers III and IV was also approved by the Swedish Medical Products Agency (Läkemedelsverket) Dnr 5.1-2014-84538 and registered at the European Clinical Trials Database, EudraCT 2013-004620-10. All the legal guardians of the participants were carefully informed prior to giving their written consent to their child's participation in the study. The children were also given the opportunity to consent in writing, but this was not always possible due to their young age. The potential negative effects associated with participation were small compared with the possible benefit of receiving effective medical treatment, with minimal known side-effects, instead of surgery.

4 RESULTS

4.1 Paper I

The response rate was 57%, with 754 returned questionnaires. There were no statistically significant differences between responders and non-responders in terms of age, gender or place of residence.

Table 1 shows the demographics of the study population, divided into children with and without frequent SDB symptoms. In 4.8% of children, loud snoring, apneas and/or choking sounds were reported “most of the time” or “all of the time” during the previous month.

Table 1. Demographics of the study population in Paper I, divided into those with and without SDB symptoms most or all of the time.

	No SDB symptoms (n(%))	SDB symptoms (n(%))
Total	696 (95.2)	35 (4.8)
Age (years)		
- 0-2	185 (97.4)	5 (2.6)
- 3-5	186 (93.5)	13 (6.5)
- 6-8	170 (93.9)	11 (6.1)
- 9-11	155 (96.3)	6 (3.7)
Gender		
- Male	364 (94.5)	21 (5.5)
- Female	332 (96.0)	14 (4.0)
Place of residence		
- Rural area	104 (98.1)	2 (1.9)
- Medium-sized town	288 (94.7)	16 (5.3)
- Large city	304 (94.7)	17 (5.3)
BMI (kg/m ²) ^a	16.5 ± 2.1	15.5 ± 1.9
Prevalence of other conditions		
- Asthma	57 (8.2)	4 (11.4)
- Allergic rhinitis	32 (4.6)	4 (11.4)
- Tonsil surgery ^b	24 (3.4)	0 (0)
- Adenoid surgery ^b	24 (3.4)	3 (8.6)
- Otitis media	88 (12.6)	8 (22.8)
- Tympanostomy tubes	32 (4.6)	4 (11.4)
- Eczema	65 (9.4)	0 (0)
- Food allergies	89 (12.8)	3 (8.6)
- Passive smoking	54 (7.8)	3 (8.6)
- Other disease	63 (9.1)	6 (17.1)

^a Mean ± standard deviation. ^b Combinations possible. Total number who underwent surgery = 34

Snoring was the most common symptom of the three: 4.7% of children were frequent loud snorers, while 0.5% had frequent apneas and 0.4% had frequent choking sounds during sleep. The QoL VAS was significantly lower in the children with frequent SDB symptoms (7.4; 95% CI: 6.4-8.1) compared with the rest of the study population (9.10; 95% CI: 8.9-9.1). None of the children who had undergone previous tonsil surgery (TE or TT) was reported as having frequent SDB symptoms, while 11% of those who had undergone adenoidectomy still had frequent SDB symptoms.

Health-care contacts

Only 31% of the children with frequent SDB symptoms had been in contact with a health-care provider about these problems. When looking at the whole study material ($n=731$), divided into those who have sought health care due to SDB symptoms ($n=60$) and those who have not ($n=671$), the children who have had contact with the health-care system are more likely to have allergic rhinitis, otitis media, tympanostomy tube insertion or other disease than the rest of the population (*Table 2*).

Table 2. Prevalence of other conditions in those who have and have not been in contact with the health-care system due to SDB symptoms, $n=731$

	Health-care contacts due to SDB $n=60$ (% who have condition)	No health-care contacts due to SDB $n=671$ (% who have condition)	Odds ratio	95% CI	p-value
Asthma	16.7	8.5	2.2	1.0 – 4.6	0.05
Allergic rhinitis	15.7	4.7	3.8	1.7 – 8.8	0.002*
Otitis media	28.9	12.1	3.0	1.6 – 5.6	<0.001*
Tympanostomy tubes	18.9	3.9	5.8	2.6 – 12.8	<0.001*
Eczema	5.8	9.3	0.6	0.2 – 2.0	>0.30
Food allergies	17.3	12.7	1.4	0.7 – 3.1	>0.30
Other disease	26.9	8.1	4.2	2.1 – 8.2	<0.001*

4.2 Paper II

There were 4,534 tonsil surgeries due to upper airway obstruction in children aged 1-11 years reported to the NTSRS in 2011 (*Fig 7*). Data on temporary parental benefits were collected for all these patients. The 3,510 that answered the question on how many days the child required analgesics after surgery were included in the second analysis for comparison.

The mean duration of analgesic treatment was 4.6 days, with an indirect cost of EUR 747, and the mean number of days with temporary parental benefits was 2.9 days (EUR 667). The indirect costs related to TE and TE+A were 61% higher than those for TT and TT+A, measured as days with analgesics, as shown in *Table 3*. This is explained by a recovery time that was two days shorter after TT compared with TE. An adenoidectomy did not contribute any additional recovery time.

Table 3. Indirect costs due to the caregivers' absenteeism after their children's tonsil surgery.

Type of surgery	N	Days with analgesics ^a	95% CI	Indirect costs (EUR)	Days with temporary benefits ^b	95% CI	Indirect costs (EUR)
Tonsillectomy	273	6.2	5.50-6.80	1010	3.5	3.07-4.00	813
Adenotonsillectomy	1117	6.3	5.96-6.61	1031	3.5	3.24-3.71	799
Tonsillotomy	429	3.8	3.46-4.19	629	2.5	2.18-2.73	564
Tonsillotomy + adenoidectomy	2705	3.8	3.65-3.97	626	2.7	2.61-2.84	627
Total	4524	4.6	4.46-4.69	747	2.9	2.84-3.03	674

^aDays with analgesics are multiplied by 5/7 when calculating the cost, to eliminate weekends from the calculation. ^bThe reported number of days with temporary benefits, the actual working days that have been compensated for by the Social Insurance Agency. No calculations are therefore needed to exclude the weekends.

4.3 Paper III

Sixty patients were included, whereof five patients were lost to follow-up, all in the placebo group (*Figure 8*). There were no statistically significant differences between the two treatment groups except for the mean baseline OSA-18 total score that was higher in the budesonide group than in the placebo group (65.2 vs 54.8, $p=0.013$) (*Table 4*). The improvement in the OSA-18 total score was significantly larger in the budesonide group than in the placebo group (-19.5 vs -7.5, $p=0.0014$). There was a significantly larger improvement in the budesonide group regarding the OSA-18 domains of “sleep disturbance” and “caregivers’ concerns”, as well as in the VAS for overall quality of life. Adenoid size decreased by a mean of 9.8% (95% CI: -16.3, -3.4) in the budesonide group ($p=0.004$) but not in the placebo group (-4.1, (95% CI: -10.7, 2.6) $p=0.23$). Tonsil size remained unchanged in both treatment groups. When adjusting for the baseline OSA-18 total score in a multivariate regression analysis, the improvement in the OSA-18 total score was still larger in the budesonide group ($p=0.010$). Baseline tonsil size, adenoid size or BMI did not have a statistically significant effect on the size of the improvement in the OSA-18 total score, nor did allergic sensitisation. No serious adverse effects were linked to either treatment.

Table 4. Baseline values and mean differences after treatment with budesonide or placebo nasal spray twice daily for six weeks (budesonide 64 µg/ml). OSA-18 and VAS for quality of life. Results are presented as mean (95% CI).

Measure	Budesonide Group		Placebo Group		P Value ^b
	Baseline Value	Mean Difference After Treatment	Baseline Value	Mean Difference After Treatment	
OSA-18	65.2 (58.8 to 71.7)	-19.5 (-24.6 to -14.4)	54.8 (50.1 to 59.5)	-7.5 (-12.5 to -2.5)	.0014 ^c
Sleep disturbance	16.7 (14.7 to 18.6)	-6.5 (-8.4 to -4.6)	15.0 (13.2 to 16.8)	-2.0 (-4.0 to 0.0)	.0020 ^c
Physical symptoms	14.7 (13.0 to 16.4)	-3.9 (-5.6 to -2.3)	11.9 (10.3 to 13.5)	-2.0 (-4.1 to 0.1)	.17
Emotional distress	10.3 (8.4 to 12.2)	-2.0 (-3.7 to -0.4)	8.8 (7.1 to 10.4)	-1.0 (-2.8 to 0.9)	.44
Daytime function	10.3 (8.4 to 12.2)	-2.2 (-3.6 to -0.8)	8.7 (7.5 to 10.0)	-1.8 (-2.8 to -0.6)	.71
Caregivers' concerns	13.3 (11.2 to 15.3)	-4.8 (-6.7 to -2.9)	10.4 (8.7 to 12.1)	-0.8 (-2.8 to 1.3)	.0057 ^c
VAS	6.4 (5.6 to 7.2)	1.4 (0.8 to 1.9)	7.1 (6.4 to 7.7)	-0.6 (-1.3 to 0.1)	<.001 ^c

4.4 Paper IV

In all, 46% (n=52) of the 113 included sleep studies were defined as acceptable by Scorer 1. The requirement of three hours of valid data for an *acceptable* RP was not fulfilled for nasal airflow in 40%, for SpO₂ in 19% and in 11% both parameters were missing. Other technical issues, including misunderstanding instructions by the caregivers and malfunctioning batteries, occurred in 5% of the measurements. Seventeen RPs were included in the analysis with and without a nasal airflow signal. The mean AHI was higher in the RP scores where the nasal airflow signal was omitted, relying on RIP flow. This difference was more pronounced for S1 than for S2. Both scorers had a significantly higher hypopnea index ($p<0.05$) when scoring without nasal flow. There was moderate agreement between the two scorers, both when the nasal airflow signal was present (ICC=0.66) and absent (ICC=0.53). The agreement in AHI with and without a nasal airflow signal was poor for S1 (ICC=0.12). S2, on the other hand, had good agreement between AHI with and without the nasal flow signal (ICC=0.81) (*Fig 10*).

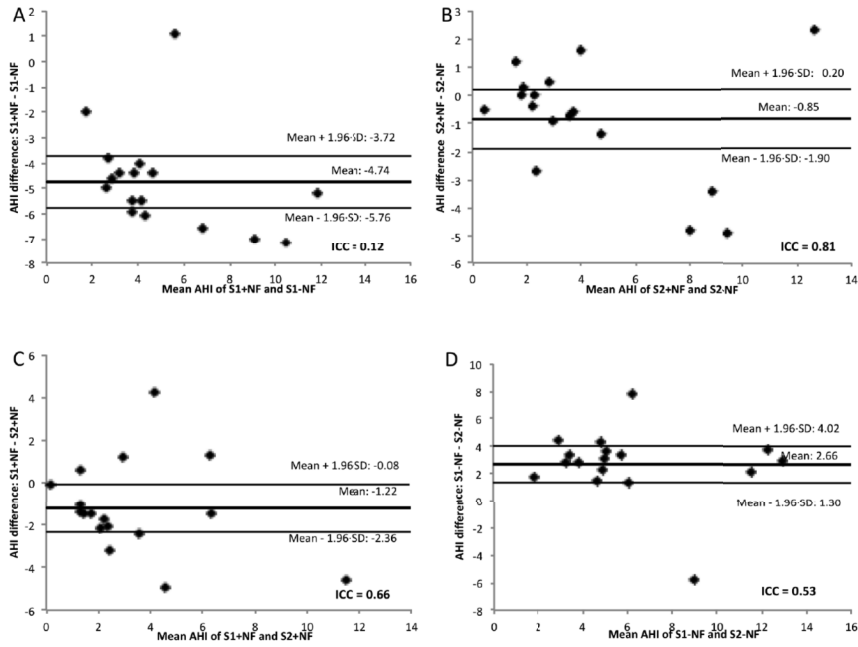


Figure 10. Bland-Altman plots showing the agreement in AHI between scores for RP with and without nasal flow and scored by different scorers. A. Scorer 1 with nasal flow vs without nasal flow. B. Scorer 2 with nasal flow vs without nasal flow. C. Scorer 1 with nasal flow vs Scorer 2 with nasal flow. D. Scorer 1 without nasal flow vs Scorer 2 without nasal flow. RP = respiratory polygraphy; AHI = apnea hypopnea index; ICC = intraclass correlation coefficient; S1+NF = Scorer 1 with nasal flow, S1-NF; Scorer 1 without nasal flow; S2+NF = Scorer 2 with nasal flow; S2-NF = Scorer 2 without nasal flow.

5 DISCUSSION

5.1 Diagnostics

Are children with SDB attracting the attention of the health-care system?

The main result of Paper 1 was that only 31% of children with frequent SDB symptoms (snoring, apneas or choking sounds) have sought medical care for these problems. Since frequent SDB problems were present in 4.6% of the children, it is safe to assume that there are many children in Sweden that do not receive the appropriate attention and treatment for these problems. These results are disturbing, as these are children running a high risk of having, or developing various comorbidities that may have a large negative impact on their quality of life. Not all these children will need treatment and some of them may only have had problems for a shorter period, as the questions related to the previous month. The majority of these children should, however, be offered a medical evaluation. The results are not entirely surprising. In a population-based poll study, Strocker et al. found that only one fifth of parents had knowledge of the comorbidities associated with OSA and fewer than 20% knew that paediatric OSA could be treated with adenotonsillectomy.⁴³

Children with allergic rhinitis, otitis media and tympanostomy tube insertion were more likely to have also been in contact with a health-care provider due to SDB symptoms than the general population. These patient groups run a higher risk of having SDB and this possibly leads to their treating physicians being more likely to enquire about these problems. These are also patients that are likely to have come into contact with otolaryngologists with knowledge of SDB. Studies from the USA have shown that general paediatricians are generally not well educated when it comes to paediatric sleep disorders¹³² and these problems are seldom addressed when children seek help for other problems or on visits when they are well.^{44,133} One study, conducted at two general paediatric clinics, examined the medical records of children seeking for other issues but who also had symptoms of sleep disorders. They found that sleep problems were only discussed on 15% of the visits, a diagnosis was made on only 2% and none mentioned any treatment.⁴⁴ This has not been studied in Sweden, but our results indicate an existing need to educate medical health practitioners on paediatric sleep disorders to be able to detect these problems, even in children seeking for other reasons. The

health care personnel must be able to counsel parents and to take the right steps towards a proper evaluation and treatment.

Diagnostic challenges of paediatric SDB

To date, there is no perfect method for diagnosing SDB and OSA in children and determining which children need treatment. PSG has traditionally been regarded as the gold standard in diagnosing OSA⁵³ with which other diagnostic methods are frequently compared. The ideal diagnostic method would, however, have to be less expensive and more readily available than PSG is today and there are still many unanswered questions regarding the usefulness of PSG in children with SDB. In fact, there are no prospective studies that confirm that routine preoperative PSG in otherwise healthy children improves the clinical outcome.¹³⁴

In a comprehensive evidence-based review of the validity and reliability of PSG in children, Wise et al. concluded that *“the gold standard for diagnosis of sleep related breathing disorders in children is not PSG alone, but rather the skillful integration of clinical and PSG findings by a knowledgeable sleep specialist”*.¹³⁴ PSG results do not correlate well with the history, clinical symptoms⁴⁶ or quality of life measurements^{84,85,135} in children with suspected SDB. This can be seen as a weakness of other methods in diagnosing OSA, but the clinical picture and quality of life are, of course, highly important aspects that cannot be ignored when determining the need for treatment. It is also possible that the PSG measurements used today are insufficient to detect subtle respiratory events in children that may be of clinical importance. When oesophageal pressure measurements are used, more respiratory effort-related arousals (RERA) are detected and the correlation with symptoms appears to improve.^{136,137} A less invasive method to measure these RERA is desirable and RIP is probably the closest non-invasive measurement we have.⁶³

An AHI of ≥ 5 an hour has been shown to be an independent risk factor for elevated blood pressure,¹³⁴ but there is a lack of high-quality evidence showing that the severity of PSG-verified OSA is in proportion to the severity of other comorbidities that are associated with SDB, such as enuresis,³⁸ failure to thrive,³⁵ neuro-cognitive deficiencies, behavioural problems and learning disabilities.^{31,32,34} In fact, children with primary snoring and OSA have similar cognitive and behavioural morbidity, both groups performing less well than children with no signs of SDB.³¹ PSG can provide valuable information in situations where the clinical picture is unclear or in patients where surgery is associated with a high risk due to other

medical conditions such as obesity, Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, or mucopolysaccharidoses.^{54,134} In the majority of cases with otherwise healthy children, however, the history and clinical examination is probably sufficient to make a treatment decision.⁵⁴ As yet, we do not have any perfect methods for diagnosing SDB and it is important to be aware of the problems and pitfalls associated with the methods in use today.

The quality of respiratory polygraphy

RP is an appealing option as a substitute for PSG, as it is less expensive and labour intensive. It has also been shown to give reliable results compared with PSG in adults.⁶⁵ Studies of the correlation between RP and PSG in children have shown more conflicting results.^{66,71}

Only 46% of the RPs in Papers III and IV were of acceptable quality, in spite of the fact that great efforts were made to instruct and inform the parents and children and to ensure high-quality readings. The most common problem was an absent nasal airflow signal, but there were also problems with the pulse oximeter falling off the finger during the night. The caregivers were asked to check on the children a few times during the night and replace dislodged leads, but everyone did not comply with these instructions. These problems will not be as frequent in an in-lab PSG with trained staff who set up the equipment and monitor the child during the night. These are issues that need to be resolved in order for RP to be a useful alternative to PSG.

Another problem with RP is that it does not include EEG as PSG does and it is impossible to score the sleep stages and to detect arousals. This may lead to an underscoring of hypopneas, as hypopneas with arousals but less than 3% desaturation will be missed.^{68,71} The total sleep time is also more accurate when determined by EEG rather than by sound recordings and the child's movements, as was done in Paper IV and this may affect the results.

The problems associated with measuring nasal airflow with a nasal cannula are well known in children with SDB, as many of them are mouth-breathers.² Studies show that a high proportion of RP and PSG have inadequate nasal airflow if measured by a nasal cannula.^{57,70,138} In the TuCASA study, 28% of the at-home PSG studies had less than two hours of scorable tracings from the nasal pressure transducer. This was done in a community sample, so it is to be expected that the results are even worse in a sample of children with SDB, where a larger proportion are mouth-breathers, as was the case in Paper

IV. This problem can be partly bypassed by also using an oro-nasal thermistor, but it is less efficient in detecting hypopneas than nasal pressure measurements via a nasal cannula. The signal from the thermistor is not proportional to flow and often overestimates flow as flow rates decrease.⁶⁰ In a study of high-quality at-home PSG from a community sample of 6-11 year olds, Budhiraja et al. found that the combination of a nasal pressure transducer via a cannula and a thermistor was more sensitive in detecting respiratory events than a thermistor alone.¹³⁸ The sensitivity of the thermistor alone in diagnosing severe OSA with an AHI of > 10 was only 50% when compared with the transducer-thermistor combination.¹³⁸ This was, however, a community sample and the results might be different in a sample of children with a clinical suspicion of SDB. Both the nasal cannula pressure transducer and the oro-nasal thermistor have important flaws, but, as there is a shortage of better options, the combination of the two is preferable to using one or the other. This is also the current recommendation of the AASM,⁶¹ but it is not the standard practice in paediatric sleep studies in Sweden where the oro-nasal thermistor is seldom used.

Is RIP flow enough?

The results of Paper IV show that the correlations of RP scores with nasal airflow via a cannula, in combination with RIP flow versus only RIP flow, are scorer dependent. Scorer 1 showed a poor correlation between the two methods (ICC=0.12), while Scorer 2 showed a good correlation (ICC=0.81). This probably reflects the different scoring techniques of the different scorers and needs to be confirmed in studies with a larger number of individual scorers, preferably from multiple sites. The results would also have to be compared with in-lab PSG results, as we do not know which scorer is closer to the gold standard.

Since the nasal airflow signal is often poor and many home sleep studies do not include oronasal thermal flow sensors, it is reasonable to assume that, in clinical practice, RP scores are frequently based on RIP measurements. It is therefore important to know how reliable these measurements are. In adults, RIP has been shown to have good sensitivity and specificity compared with the gold standard, oesophageal manometry, in detecting respiratory effort-related arousals on PSG.^{139,140} Griffiths et al. reported comparable results from RIP and a nasal pressure cannula in detecting apneas and hypopneas in children.¹⁴¹ Their conclusion was that at least one of these methods, but preferably both, should be used. These were, however, in-lab PSG studies and the question is whether RIP flow can be used as an alternative when there is no EEG for detection of arousals. According to our results, this is questionable and there appears to be a risk of over-diagnosing OSA when

only using RIP. But this needs further examination in larger studies. Also, in Paper IV, the children had mild to moderate SDB and it is possible that the correlations would be better in children with severe sleep apnea

5.2 Treatment

Tonsillectomy vs tonsillotomy – the health-economic aspect

In Paper II, the indirect costs related to caregivers' absenteeism after their children's tonsil surgery were examined. The children stayed at home longer, at a higher indirect cost, after TE (6.2 days, 1,010 EUR) than TT (3.8 days, 629 EUR). This is in accordance with previous studies that have also shown that children have less pain and a faster recovery after TT than TE.^{142,143} The risk of postoperative bleeding is also significantly lower after TT than after TE, which leads to less absenteeism for the caregivers.

Absenteeism was evaluated by two different methods, firstly the parents' response to a question on how long analgesics were used after surgery, where this was used as a proxy for the time the child stayed at home, and, secondly, the number of days the caregivers received temporary parental benefits after surgery. Both methods have certain limitations that are discussed in the limitations section, but the fact that they both confirm that TT is associated with lower indirect costs increases the validity of the results.

Absenteeism was only examined for the first month after surgery. After a TT, there is a greater risk of regrowth of the tonsils, which may require additional surgery and additional absenteeism at a later point.^{102,107} Since a part of the tonsil is left in place, there is also a greater risk of tonsillitis compared with children that have had their entire tonsils removed in a TE.¹⁰² According to a literature review by Windfuhr et al., tonsillar regrowth and tonsillitis occur in < 6% of patients after tonsillotomy but only one third of these patients required secondary surgery.¹⁰² Both these factors may lead to increased total absenteeism and indirect costs and have to be examined further, but this is beyond the scope of the present study. Postoperative haemorrhage is more common after TE than tonsillotomy¹⁰⁵ and this may partly explain the higher absenteeism after tonsillectomy.

The indirect costs are, however, only a part of the total costs associated with SDB and tonsil surgery. In order to assess the total health-economic costs, it is necessary to look at multiple factors that have not been analysed in the present study. This includes the direct costs related to the surgery,

anaesthesia, inpatient and outpatient care and drug costs, but also the direct and indirect costs related to SDB.

Studies of the direct costs of tonsil surgery have shown a great variation in costs between different hospitals and there may even be considerable variation between surgeons at the same hospital.^{123,144} Factors that influence the direct costs include operating room costs, the cost of operating room supplies, anaesthesia costs, medication in hospital and pre- and postoperative care. The surgical technique is also an important factor. The Coblation¹⁴⁵ and radiofrequency¹⁴⁶ techniques are, for example, considerably more expensive than electrocautery, due to the high cost of disposables, despite a shorter time in the operating theatre. These methods are more frequently used in TT than TE and can thus lead to higher costs for TT. Day surgery is also less costly than inpatient surgery. According to the KPP (Kostnad per patient, cost per patient) database, administered by the Swedish Association of Local Authorities and Regions (SKL – Sveriges kommuner och landsting), tonsil surgery in day surgery costs EUR 1,000-1,500 and EUR 2,800-3,000 in inpatient care.

Children with SDB are known to have a higher health-care use than the rest of the population,¹⁴⁷ but it decreases considerably in the years after adenotonsillectomy.^{148,149} Tarasiuk et al. found that the decrease was mainly due to fewer upper respiratory infections after surgery.¹⁴⁹ If left untreated, SDB may cause significant morbidity and reductions in quality of life. In the light of this, the indirect costs associated with surgery seem reasonable, favouring TT when possible. However, further research is needed on the total costs and how they can be minimised.

Nasal steroid treatment for SDB

Paper III is the first randomised, placebo-controlled study of the effect of nasal steroids on paediatric SDB, where HRQoL is the primary outcome variable. The results show a moderate effect of a 19.5-point reduction in the OSA-18 total score in the treatment group and 7.5 in the placebo group. In the CHAT trial, where children were randomised to adenotonsillectomy or watchful waiting, the children had a mean baseline OSA-18 total score of 53.6, which is similar to that of the children in the present study. The improvement in the mean OSA-18 total score in the CHAT trial was 21.4 in the intervention group and 4.5 in the watchful waiting group, after seven months. These results are not, however, directly comparable, as not all the children in Paper III were surgical candidates. Other surgical trials, with more severely affected patients with higher baseline OSA-18 total scores, have shown a greater reduction in the OSA-18 total score after tonsil surgery.¹⁰⁴

Mean tonsil size, adenoid size, BMI or the OSA-18 total score at baseline did not predict the outcome of the treatment. A reduction in adenoid size of 10% was seen after budesonide treatment but not in the placebo group. Other studies have reported a similar or larger reduction in adenoid size.^{109,150} The tonsil size remained unchanged, which was to be expected, as the effects of nasal steroids are mainly local in the nose and epipharynx.

As nasal steroids have a well-documented effect on allergic rhinitis¹⁵¹ and children with allergic rhinitis run a greater risk of having SDB,²¹ it is possible to suspect that allergic children would respond better to nasal steroid treatment. However, neither the present study nor previous trials have been able to show such a correlation.^{116,152}

Nasal steroid treatment has previously been shown to improve AHI in children with mild to moderate SDB.^{112,113} Kheirandish-Gozal reported an improvement in the obstructive AHI from 3.7 at baseline to 1.3 after treatment. The AHI correlates poorly with the clinical symptoms and HRQoL, so it is important to include all these measurements in the evaluation to obtain a full picture of the treatment effect.

5.3 Limitations

Paper I

One major methodological problem in the research on SDB epidemiology in children is the lack of clear definitions of snoring and SDB. The OSA-18, used in Paper I, was not originally designed or validated for the screening of SDB⁸⁰ and so only the first three questions in the questionnaire, relating to SDB symptoms (snoring, apneas and choking sounds during sleep), were used to identify children with SDB. In lack of a validated Swedish screening questionnaire, this was considered to be an acceptable alternative. The question regarding health-care contacts was constructed specifically for this study and has not been validated. A PSG would have helped identify the children with OSA, but, the aim was to study the prevalence of SDB, not OSA specifically. The response rate of 57% was rather low. A low response rate has been an increasing problem in epidemiologic research and it may possibly cause selection bias. No internationally accepted cut-off for an acceptable response rate exists, and research has shown that studies with very low response rates may yield accurate results.¹⁵³ An analysis of the non-responders from the different strata did not reveal any significant differences compared with responders.

Paper II

The strength of register studies is easy access to an already existing large database with minimal selection bias and independently collected data. The main weakness is the inability of researchers to control and manage the quality of data gathering and necessary information may not be available.¹⁵⁴ A limitation when using the questionnaire from the NTSRS, was our inability to construct a direct question on absenteeism after surgery. Instead, a pre-existing question on how long the child used analgesics after surgery was used as a proxy for how long the child stayed at home. It is unlikely that the child returned to day-care or school earlier than that. It is, however, possible and perhaps even likely that children stay at home longer than analgesics are needed. There is a possibility of recall bias, as the questionnaire was answered a month after surgery. The absenteeism was also evaluated by gathering data on how many days the caregiver received temporary parental benefits, in the first month after surgery, from the Social Insurance Agency (Försäkringskassan). This may lead to an underestimation of the number of days children stay at home, as certain groups, such as students, parents on parental leave or those who are unemployed, are not included. Parties other than caregivers could also have been involved in the postoperative care of the child. The results from the two methods were, however, similar.

Other limitations include a possible selection bias, as only 77.5% of all performed tonsil surgeries were registered in the NTSRS.¹⁵⁵ There is no reason to believe that the patients not included in the NTSRS differ from the rest of the population in any important respects, as participation depends mainly on the clinics that report their performed tonsil surgeries, not the patients themselves. Confounding factors, such as socio-economic factors might influence both the response rate and the absenteeism. In the analysis of the temporary parental benefits, the entire population was included, which is an important strength. It is possible that the TE group differs from the TT group in that they have probably had more infections prior to surgery and this may affect the postoperative pain and recovery time.

The results relating to the number of days that the child stays at home should be generalisable, as they depend on the duration of analgesic treatment, which should be fairly universal, although local differences may exist in postoperative pain treatment. Differences in national reimbursement systems and family organisation in relation to working parents could, however, affect the final costs imposed on society in different countries.

Paper III

The two treatment groups in this randomized trial were equal in all the measured respects, except for the baseline OSA-18 total score that was higher in the budesonide group. This may have affected the results, as a higher baseline value leaves more room for improvement. However, the difference in OSA-18 improvement remained statistically significant between the treatment groups, even after correcting for this in a multivariate linear regression analysis. The OSA-18 is based on the caregivers' subjective reports. There may be personal and cultural variations in the way caregivers evaluate their children's symptoms and quality of life and the children may not agree with the caregivers' assessment. Few patients were lost to follow-up, but they all belonged to the placebo group. The caregivers of one patient did not offer any explanation of why they left the study, the other four left for personal reasons not related to the treatment. There were few overweight children in the study, which reflects the comparably low prevalence of obesity in Swedish children.¹⁵⁶ This may affect the generalisability, as obesity is a more prevalent problem in many other parts of the world and overweight and obese children do not respond as well to medical and surgical treatment.¹⁵⁷

Paper IV

The scorers were blinded to the identity of the children as well as the results from the previous scores. Their scoring was done according to their usual routines, so the results should correlate very well with the actual results in clinical practice. It is, however, possible that a more standardised approach, with clear guidelines on how to score the different sleep studies, would have resulted in a higher correlation. Moreover, to add strength to the results, a larger study with a larger number of scorers and sleep studies would be beneficial. Also, a comparison of the RP results with a full PSG would have been interesting.

6 CONCLUSIONS

- Paediatric sleep-disordered breathing is a common condition that is frequently ignored by caregivers. The majority of children with frequent SDB symptoms have not been in contact with the health-care system for these problems.
- The mean indirect costs due to the caregivers' absenteeism after tonsil surgery in children with SDB can be influenced by the choice of surgical technique, favouring tonsillotomy over tonsillectomy.
- Treatment with intranasal budesonide has a significantly better effect on health-related quality of life, adenoid size and symptoms in children with SDB than a placebo nasal spray.
- The quality of at-home respiratory polygraphy in children is often poor. The nasal airflow pressure is the signal most frequently missing. This limits the usefulness of at-home RP.
- The results of RP scoring are scorer dependent when the nasal airflow signal is missing and the scoring of respiratory events is based on RIP flow, limiting the reliability of this method.

7 FUTURE PERSPECTIVES

Although there has been increasing interest and research in the field of paediatric SDB in recent years, many questions still need to be explored. Many children with SDB symptoms do not receive appropriate evaluation and treatment. It is important to increase knowledge among both parents and health-care providers of the symptoms and risks involved with SDB in children.

One of the most important challenges is to develop the diagnostic methods further to be able to identify the children in need of treatment. PSG is usually regarded as the gold standard in diagnosing SDB in children, but it is costly and time and labour consuming. The search for simple diagnostic methods that are reliable and inexpensive has to continue. Also, prospective studies need to be conducted to determine whether performing a PSG, RP or using other diagnostic methods actually has a beneficial effect on the outcomes in children with SDB. Further examination of the usefulness of RIP flow in the interpretation of paediatric sleep studies is important, to ascertain whether RIP flow may be used as an alternative measure when nasal airflow is missing.

The optimal methods for treating SDB in children are those with maximum clinical benefits and minimal side-effects, but the health-economic aspect is also important. New surgical and medical methods need to be constantly evaluated to find the most effective treatments at the lowest costs. Moreover, it is important to consider the morbidity and the costs that untreated paediatric SDB impose on society in the form of increased health-care utilisation and indirect costs due to the caregivers' absenteeism when their children are ill.

Nasal steroids have been shown to be an effective treatment for SDB in children, but more research is needed to establish the appropriate doses, length of treatment and the children who benefit from the treatment. Furthermore, more long-term follow-up studies are needed in children that receive nasal steroid treatment.

SAMMANFATTNING PÅ SVENSKA

Sömnelaterade andningsstörningar är ett vanligt förekommande tillstånd hos barn. Det orsakas oftast av förstorade halsmandlar och körteln bakom näsan (adenoid) som förtränger luftvägarna vilket gör att barnen snarkar och får andningsuppehåll i sömnen. Andningsstörningar i sömnen orsakar, i sin tur, störd och fragmenterad sömn och kan leda till olika hälsoproblem som tillväxthämning, sömngångning, uppmärksamhets- och koncentrationssvårigheter och hjärtproblem. Många av dessa barn har en kraftigt nedsatt livskvalitet. Den vanligaste behandlingen idag är att man antingen opererar bort hela halsmandlarna (tonsillektomi) eller del av dem (tonsillotomi) samt körteln bakom näsan. Det är en effektiv behandling men operationen medför smärta och obehag, samt risk för komplikationer, främst blödningar. Diagnostik av sömnelaterade andningsstörningar hos barn baseras oftast på deras symptom och klinisk undersökning. Sömnregistreringar (polysomnografi, PSG) görs i valda fall men är kostsamma och endast tillgängliga på ett fåtal sjukhus i Sverige. Enklare varianter av sömnregistreringar (polygrafi) kan göras i hemmet men ger inte lika utförlig information. Dessa används i allt större utsträckning idag men det finns otillräcklig information om kvaliteten och användbarheten av denna metod hos barn.

Avhandlingens övergripande syfte är att tillföra kunskap rörande diagnostik och behandling av sömnelaterade andningsstörningar hos barn. I *delarbete 1* undersöktes hur stor andel av svenska barn i åldern 0-11 år som har symptom på sömnelaterade andningssvårigheter som snarkningar och andningsuppehåll. Enkäter skickades till 1320 slumpmässigt valda barn från olika delar av landet. Resultaten visade att 4.8% hade haft frekventa snarkningar och/eller andningsuppehåll den senaste månaden. Endast 31% av barnen med frekventa symptom hade någon gång sökt vård för dessa problem. Resultaten talar för att sömnelaterade andningsstörningar är ett vanligt problem som sällan uppmärksammas av föräldrar och vårdgivare. Det är viktigt att öka kännedom om tillståndet så att de barn som är i behov av behandling får den.

Delarbete 2 är en hälsoekonomisk studie baserad på 4537 barn som är opererade för sömnelaterade andningsstörningar och registrerade i nationella kvalitetsregistret för tonsilloperation. Data från Försäkringskassan avseende tillfällig föräldrapenning för vård av barn de första 30 dagarna efter operation användes för att räkna ut de indirekta kostnaderna på grund av föräldrarnas frånvaro från arbetet. De indirekta kostnaderna efter tonsilloperation var i genomsnitt 747 EUR. Kostnaderna efter tonsillektomi var 61% högre än efter

tonsillotomi vilket förklaras av att barn har mindre smärtor och hämtar sig snabbare efter tonsillotomi.

Delarbete 3 är en icke-sponsrad, randomiserad, placebo-kontrollerad studie på 60 barn i åldern 4-10 år. Sex veckors behandling med nasal kortison-spray (budesonid) har jämförts med placebo. Utvärdering av behandlingseffekten gjordes med OSA-18, ett sjukdomsspecifikt livskvalitetsformulär, bedömning av adenoid-och tonsillstorlek och polygrafi i hemmet före och efter behandling. Efter behandling med budesonid nässpray såg man en signifikant förbättring av livskvalitet, nästäppa, snarkningar, andningsuppehåll och adenoidstorlek jämfört med gruppen som fick placebo.

I **delarbete 4** gjordes en utvärdering av kvaliteten på de polygrafier som utfördes i hemmet i delarbete 3. Endast 46% av 113 polygrafier bedömdes vara av godkänd kvalitet och den vanligaste orsaken till icke godkänd mätning var bortfall av näsflödesmätning via den nasala luftflödeskatetern under sömn. Sjutton sömnregistreringar av god kvalitet tolkades av två oberoende experttolkare med och utan näsflödessignal. Vid tolkning utan näsflödessignal baserades räkning av andningsstörningar på andningsrörelser som mättes med band runt buk och bröstorg, dvs RIP-flow. Samstämmigheten av tolkningarna försämrades när näsflödessignalen var bortplockad vilket talar för att RIP-flow sannolikt ger otillräcklig information för diagnostik av sömnapné.

SAMANTEKT Á ÍSLENSKU

Algengt er að börn þjáist af öndunarröskunum í svefni (sleep-disordered breathing) sem einkennast af hrotum og órólegum svefni og 1-3% barna eru með kæfisvefn með öndunarhléum. Helsti orsakavaldurinn eru stækkaðir háls-eða nefkirtlar. Þessi börn geta þjáðst af ýmsum fylgikvillum svo sem vaxtarskerðingu, næturvætu, athyglisbresti, hegðunarvandamálum og hjarta- og æðasjúkdómum. Lífsgæði geta verið verulega skert. Hálskirtlataka og/eða nefkirtlataka er yfirleitt árangursrik meðferð en veldur talsverðum sársauka og hætta er á fylgikvillum svo sem blæðingum eftir aðgerð. Nú er orðið algengara að fjarlægja hluta af hálskirtlunum (tonsillotomia) frekar en að taka þá í heild sinni (tonsillektomia) og veldur það minni verkjum og blæðingarhættu. Við greiningu á öndunarröskunum í svefni er stundum stuðst við svefnrannsóknir, annars vegar polysomnografia sem er kostnaðarsöm rannsókn og ekki alls staðar aðgengileg og hins vegar polygrafia sem er einfaldari svefnrannsókn sem gerð er heima hjá sjúklingum og er því talsvert ódýrari. Polygrafia er orðin talsvert algeng rannsókn hjá börnum þar sem grunur er um kæfisvefn en lítið er um rannsóknir á gæðum og notagildi þessara rannsókna hjá börnum. Tilgangur þessa doktorsverkefnis er að bæta við þekkingu varðandi greiningu og meðferð barna með öndunarraskanir í svefni.

Í fyrstu rannsókninni var algengi öndunarraskana í svefni kannað hjá börnum á aldrinum 0-11 ára. Spurningalistar voru sendir til 1320 barna. Niðurstöðurnar sýndu að 4,8% barna hrjóta eða fá öndunarhlé í svefni “oft” eða “alltaf” á næturnar. Aðeins 31% þessara barna með tíð einkenni öndunarraskana höfðu fengið lækniþjónustu vegna þessara vandamála. Niðurstöðurnar benda til að stór hluti barna með öndunarraskanir í svefni fái ekki viðeigandi greiningu og meðferð. Mikilvægt er að auka fræðslu til foreldra og heilbrigðisstarfsfólks varðandi þessi mál.

Önnur rannsóknin var heilsuhagfræðirannsókn sem gerð var á 4537 börnum sem skráð voru í sænskan gagnabanka fyrir hálskirtlaaðgerðir (National Tonsil Surgery Register in Sweden) eftir að hafa gengist undir aðgerð á hálskirtlum vegna öndunarraskana í svefni. Fjarvera foreldra frá vinnu til að sinna barni sínu eftir aðgerð var rannsökuð á tvennan hátt. Annars vegar var gögnum safnað frá Försäkringskassan, sem greiðir bætur til foreldra vegna fjarveru frá vinnu vegna veikinda barna, og fjöldi fjarverudaga fyrstu 30 dagana eftir aðgerð var skráður. Hins vegar var fjöldi daga sem barnið fékk verkjalyf eftir aðgerð notaður sem óbeinn mælikvarði á fjarveru þar sem ólíklegt er að barn fari aftur í skóla eða dagvist á meðan það þarf enn á

verkjalyfjum að halda. Kostnaður vegna fjarveru foreldra eftir aðgerð barna þeirra var að meðaltali 747 EUR. Kostnaður vegna fjarveru foreldra var 61% hærri eftir tonsillektomiu en tonsillotomiu en það skýrist af minni verkjum og hraðari bata eftir tonsillotomiu.

Þriðja rannsóknin er tvíblind slembirannsókn á 60 börnum á aldrinum 4-10 ára, þar sem borin eru saman áhrif af meðferð með steranefúða (budesonide) og lyfleysu á einkenni og lífsgæði barna með öndunarraskanir í svefni. Heilsutengd lífsgæði voru metin með OSA-18 spurningalistanum fyrir lífsgæðamat. Einnig var stærð háls-og nefkirtla skoðuð og svefnrannsókn (polygrafia) gerð fyrir og eftir meðferð. Steranefúði hafði greinileg og tölfraðilega marktæk áhrif á lífsgæði, hrotur, öndunarhlé og nefkirtlastærð samanborið við lyfleysu.

Gæði polygrafianna voru svo skoðuð í fjórðu rannsókninni og kom þá í ljós að aðeins 46% af 113 polygrafíum sem gerðar voru reyndust uppfylla gæðakröfur. Algengasta ástæða fyrir misheppnaðri rannsókn var að nefloftflæði var ekki mælanlegt. Valdar voru 17 polygrafiur sem uppfylltu gæðakröfur og voru þær metnar af tveimur sérfræðingum með mikla reynslu á sviði svefnrannsókna. Þær voru metnar með og án nefloftflæðis. Þegar nefloftflæði var ekki til staðar byggði stigun stuðuls öndunarstopps/minnkaðrar öndunargetu (apnea-hypopnea index - AHI) á RIP-flow en það er útreiknað mat á öndunargetu byggt á mælingum á öndunarhreyfingum brjóstakassa og kviðar. Fylgni milli niðurstaðna úr mati sérfræðinganna tveggja var verri þegar nefloftflæði var ekki til staðar sem bendir til að RIP-flow gefi ekki nægjanlega áreiðanlegar niðurstöður við greiningu öndunarraskana í svefni hjá börnum.

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