Impaired nasal patency and sleep disturbances - prevalence, quality of life, and treatment

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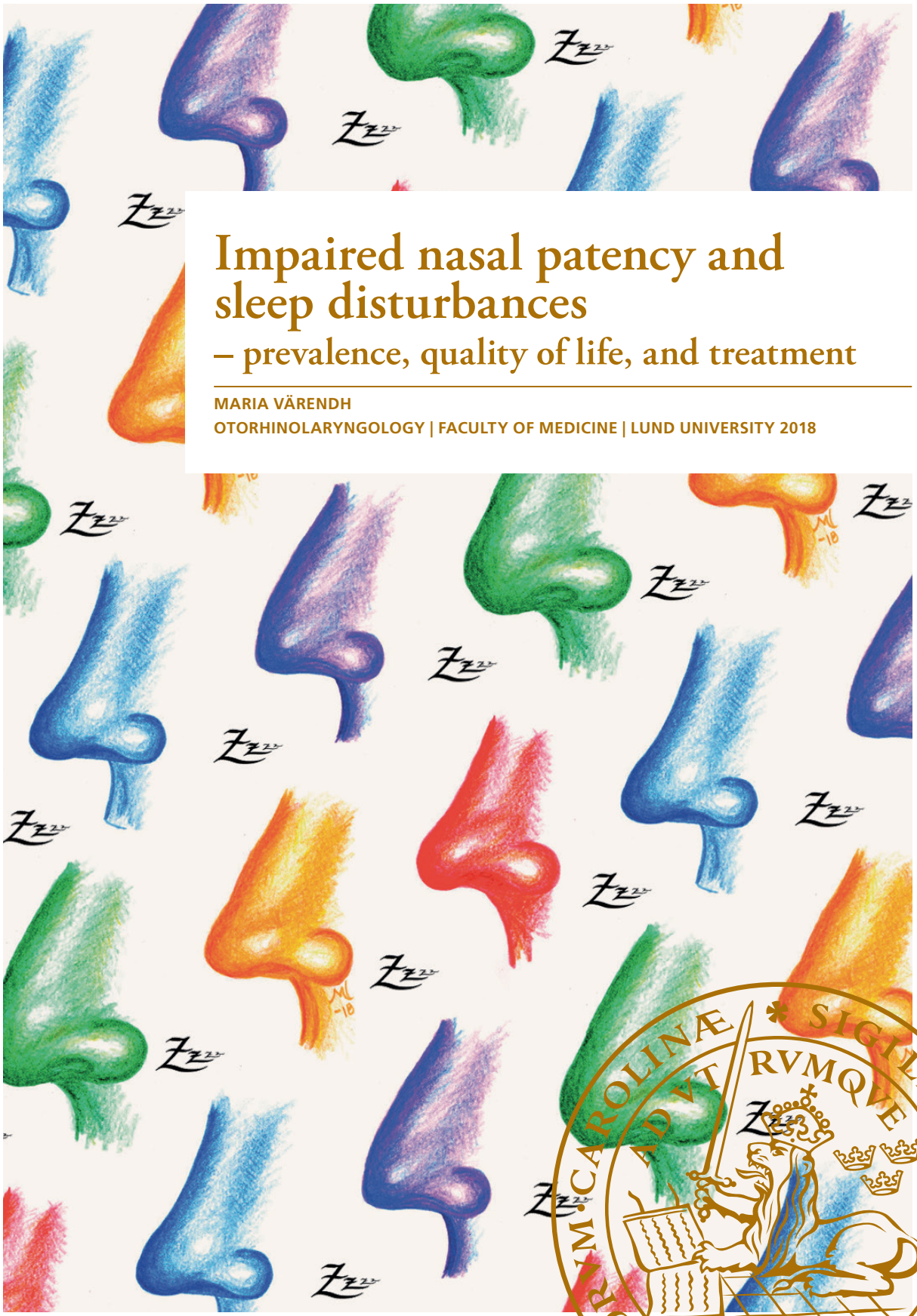

Impaired nasal patency and sleep disturbances

– prevalence, quality of life, and treatment

MARIA VÄRENDH
OTORHINOLARYNGOLOGY | FACULTY OF MEDICINE | LUND UNIVERSITY 2018

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Maria Värendh

LUND UNIVERSITY

DOCTORAL DISSERTATION

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Supervisor Morgan Andersson, Co supervisor Harald Hrubos-Strøm

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Impaired nasal patency and sleep disturbances - prevalence, quality of life, and treatment

Abstract

Background: The main objective was to investigate impaired nasal patency and sleep disturbances with respect to prevalence of nasal obstruction in OSA patients and patients with severe nasal obstruction, and the consequences concerning sleep quality, quality of life, and effect of treatment.

Materials and methods: The first study investigated the effect of UPPP (Uvulopalatopharyngoplasty) in OSA patients and snorers, 19-25 years post surgery with questionnaires (n = 129) (I). The second study investigated 42 patients pre- and post endsocopic surgery for nasal polyposis with questionnaires and spirometry (II). In the third and fourth study a cohort of 810 OSA patients were evaluated before and two years after the initiation of PAP treatment (III and IV). The methods used were home sleep apnoea testing at baseline and at both baseline and follow up acoustic rhinometry and questionnaires.

Results: At follow up for UPPP, 51 % of the patients were satisfied with previous surgery. Side-effects were reported in 38% of the patients. An additional finding was that 32% of the patients had subjective nasal obstruction (I). In study II, the nasal disease specific quality of life improved (SNOT-22 median score (IQR), 51.5 (37) vs. 26.5 (15), $p < 0.001$) and daytime sleepiness decreased after surgery (ESS (7,5(6) to 6.0(5), $p < 0.05$). Dissatisfaction with sleep was a problem for 32% preoperatively compared to 16% after surgery ($p < 0.001$). The Berlin questionnaire investigated the risk for OSA, showing that 13 of the patients went from risk to non-OSA-risk after surgery. In study III the prevalence of subjective nocturnal nasal obstruction (≥ 3 times/week) in OSA patients was 35% prior to PAP initiation. The patients with subjective nocturnal nasal obstruction had smaller minimum cross-sectional area within the smallest nasal valve ($p = 0.013$), reported more daytime sleepiness (mean ± SD) (ESS score 12.5 ± 4.9 vs. 10.8 ± 5.0, $p < 0.001$) and mental quality of life was lower (SF-12 score 46.4 ± 11.4 vs. 49.8 ± 10.5, $p < 0.001$) compared to OSA patients without nocturnal nasal obstruction. In study IV, two years after the initiation of PAP treatment the proportion of patients in the total study sample reporting subjective nocturnal nasal obstruction decreased (baseline: 35% vs. follow up: 24%, $p < 0.001$). Small interior nasal dimensions increased ($p < 0.001$) independent of adherence to treatment. Having small nasal volume at baseline was a determinant for becoming a non user of positive airway pressure treatment ($p = 0.002$).

Conclusions: Impaired nasal patency in OSA patients is frequent, and influences sleep quality, and quality of life, which is improved two years after initiating positive airway treatment. Patients with severe nasal obstruction have impaired sleep quality which is improved by surgery.

Key words Apnoea, nasal obstruction, nasal congestion, OSA, PAP, questionnaire, quality of life, rhinometry, and sleep.

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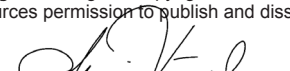
Signature  Date 2018-04-13

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Till Henrik, Klemens, Hannes och Oda.

Table of contents

List of papers

The thesis is based on the following papers and they will be referred to in the text by their roman numbers and a keyword.

I. (UPPP) **Värendh M**, Berg S, Andersson M. (2012) Long-term follow-up of patients operated with Uvulopalatopharyngoplasty from 1985 to 1991. *Respir Med. 106*(12), 1788-93.

II. (Polyposis) **Värendh M,** Johannisson A, Hrubos-Strøm H, Andersson M. (2017) Sleep quality improves with endoscopic sinus surgery in patients with chronic rhinosinusitis and nasal polyposis. *Rhinology. 55*(1), 45-52.

III. (OSA symptoms) (2017) Värendh M, Andersson M, Björnsdóttir E, Hrubos-Strøm H, Johannisson A, Arnardóttir ES, Gíslason Þ, Júlíusson S. (2017) Nocturnal nasal obstruction is frequent and reduces sleep quality in patients with obstructive sleep apnoea. *J Sleep Res.* Nov 6. doi: 10.1111/jsr.12631. [Epub ahead of print]

IV. (OSA treatment) **Värendh M**, Andersson M, Björnsdóttir E, Arnardóttir ES, Gíslason Þ, Pack A, Hrubos-Strøm H, Johannisson A, Júlíusson S. Nasal obstruction improves after two years of PAP treatment in patients with obstructive sleep apnoea. *Submitted*

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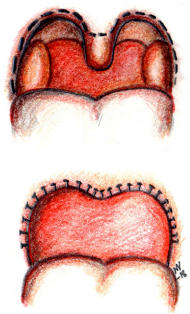
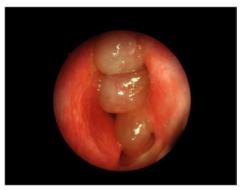
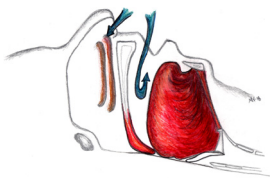
Thesis at a glance

Study number (Keyword)	Objective, to investigate	Methods	Results	Conclusions
I (UPPP) 	Satisfaction of previous UPPP surgery 19-25 years post op.	Retrospective. Questionnaire and patient files.	50% satisfaction with previous surgery. No difference in PAP users and non users 19-25 years post op. Additional finding: Nasal obstruction: 32%.	One third of the patients experienced nasal obstruction.
II (Polyposis) 	How major nasal pathology influence sleep quality.	Prospective. Questionnaire and spirometry. Pre- and post-op.	ESS reduced from: median (IQR) 7.5 (6) to 6.0 (5), $p < 0.05$. 13 patients went from risk for OSA to non risk in questionnaire.	Polyposis patients had reduced sleep quality, which improved after surgery.
III (OSA symptoms) 	Nasal patency in patients with OSA prior to PAP start.	Cross-sectional. Acoustic rhinometry, home sleep apnoea testing, questionnaire, and patient files.	Patients with nocturnal nasal obstruction (35%) vs. no obstruction: mean ± SD, ESS 12.5 ± 4.9 vs. 10.8 ± 5.0, $p < 0.001$. MCA-min smaller 0.42 ± 0.17 vs. 0.45 ± 0.16 cm^2, $p < 0.05$.	Nocturnal nasal obstruction is frequent in OSA and those patients had more daytime sleepiness and one smaller minimal cross section area.
IV (OSA treatment)  With courtesy Olle Johansson.	Nasal patency in patients with OSA 2 years after start of PAP.	Prospective cohort. Acoustic rhinometry, home sleep apnoea testing, questionnaire, and patient files.	Nocturnal nasal obstruction reduced: baseline 35% vs. follow up: 24%, $p < 0.001$. Small nasal dimensions increased ($p < 0.001$). Small nasal volume at baseline OR: 2.22, CI 95% 1.35 -3.67, for becoming a non user of PAP.	Nocturnal nasal obstruction decreased two years after PAP. Small nasal dimensions increased. Small nasal volume at baseline = negative predictor for PAP adherence.

Preface

Research starts with curiosity. In my first problem- basedlearning group the tutor was professor Øystein Fodstad, head of the Tumor Biology department, Radiumhospitalet, Oslo, Norway. I asked him about his research and he ended up offering me a summer job in his research laboratory. I was overwhelmed when I found myself in research discussions combining theory, methods, and further directions for the experiments. During the discussion everything stopped, and people joined the dialogue, which could go on for hours! I had never experienced a place where thinking, improving, exploring, and reflecting could get so much space.

This fascination with the research process, through merging of ideas, was further fed when I had the privilege to spend time in the lab of professor Robin L. Anderson, who at the time was working at the Peter MacCallum Cancer institute (Melbourne, Australia). I learned the new methods of the day, which included a foundation for the understanding of basic cell biology, genetics, as well as other areas. As a medical student it was a stimulating experience; the process of diving into the fine details, stepping back to see things in overview, and then diving into the details yet again. We had very stimulating discussions in the lab and I was encouraged by my supervisor professor Robin L. Anderson to do a PhD.

Performing research forms one part of the education required to become an ear, nose and throat (ENT) specialist. I asked around at the clinic for a project with the possibility of being able to finish within a reasonable time period, and with the potential to publish a scientific article. An additional criteria was a supervisor who was easy to cooperate with, and therefore it was an easy decision to start the UPPP project associate professor Morgan Andersson suggested. We share curiosity, a fascination over research, enjoy challenges, and laugh often which made a solid foundation. This is where this thesis begins.

Abbreviations

AHI	Apnoea-hypopnea index
AR	Acoustic rhinometry
BMI	Body mass index
CT	Computerized tomography
ESS	Epworth sleepiness scale
Diff MCA-min	Difference between non-decongested and congested Minimal cross-sectional area within one nasal valve (investigated with AR)
Diff TMCA	Difference between non-decongested and congested Total minimal cross-section area in the nose, left and right nasal valve combined (investigated with AR)
Diff TVOL	Difference between non-decongested and congested Total volume of left and right nasal volume combined (investigated with AR)
ISAC	The Icelandic Sleep Apnea Cohort
MCA	Minimal cross-sectional area within one nasal valve, before nasal decongestant spray (investigated with AR)
MCA-min	Minimal cross-sectional area within the smaller nasal valve (either left or right), before nasal decongestant spray (investigated with AR)
OSA	Obstructive sleep apnoea
PAP	Positive airway pressure
SF-12	The 12-Item Short Form Health Survey (SF-12) a smaller version of the SF-36v2 Health Survey
TMCA	Total minimal cross-section area in the nose, left and right nasal valve combined, before nasal decongestant spray (investigated with AR)
TVOL	Total volume of left and right nasal volume combined before nasal decongestant spray (investigated with AR)
UPPP	Uvulopalatopharyngoplasty
vs.	Versus

Definition suggestions

Congested, blocked, stuffy, or obstructed nose are terms often used for difficulties breathing through the nose. In general use they denote a similar meaning with different levels of severity. The words could be symptoms of health problems, such as upper respiratory tract infections, allergy, or other issues. Below follow the different terms presented as used in the thesis and an interpretation on how the terms are used in the medical literature.

Nasal patency

- The ability of the nasal cavity to stay open. "Patens, open a state of being open or exposed." (The free dictionary by Farlex, medical(a).)

Nasal obstruction

- Not defined as subjective or objective. Not defined as mucosal swelling or structural.
  Interference with the free passage of air through either side of the nose from any cause. Causes of obstruction include enlarged *conchae inferior* or *conchae media,* swelling of the mucus membrane (nasal congestion), nasal polyposis, nasopharyngeal carcinoma, or foreign bodies. (The free dictionary by Farlex, medical (b).)

Nasal congestion

- In general communication this term is used in a subjective perspective, which is not recommended in medical literature where it has an objective meaning. During congestion the nasal mucosa is thicker due to vasodilation of the capacitance vessels in the cavernous tissues of mainly the concha inferior and concha media. Congestion does not give any information about anatomical structures. Problems can however occur if a patient has a bone or cartilage structure partly blocking the airway and then nasal congestion in addition give symptoms for the patient.
- "Difficulty in nasal breathing, due to an increased vascular thickness of nasal mucosa." (The free dictionary by Farlex, medical (c).)

Nasal blockage

- This term has possibly the same meaning as nasal obstruction. Not as frequently used in medical scientific literature defined as subjective or objective.

Nasal stuffiness

- Subjective. Not as common in scientific literature as in popularized literature. Would be used when the nose is lightly blocked. "A sensation of difficulty in nasal breathing, and/or associated with increased nasal airway resistance. " (The free dictionary by Farlex, medical (d).)

Rhinitis

- Rhino- means of the nose (greek), thus the term rhinitis denotes an inflammatory process in the nasal mucosa. The symptoms of rhinitis often involve sneezing, nasal congestion, nasal discharge, and possibly postnasal dripping.

Sleep quality

- A subjective parameter, which has been investigated with questionnaires in this thesis. Impaired sleep quality includes insomnia and snoring. Sleep related symptoms like day-time sleepiness, waking up with a dry mouth, and waking up with headache are also here included in sleep quality.

Sleep disturbances

- In this thesis used as impaired sleep quality, see above.

Apnoea

- The word apnoea has its origin from the from the Greek word *ápnoia*, with the meaning "want of breath". The American English spelling is apnea and the British English spelling is apnoea. In this thesis the British English spelling is used unless in names where the American spelling is used as in the source referred to. Apnoea is defined by a cessation, or near cessation, of respiratory airflow lasting for at least 10 seconds (Madani & Madani, 2007; K.J. Lee, 2012). Apnoea is more frequent in oral breathing than in nasal breathing (Fitzpatrick, et al., 2003)(b).

Obstructive sleep apnoea (OSA) versus Obstructive sleep apnoea syndrome (OSAS)

- The diagnosis of OSA is defined in the International Classification of Sleep Disorders – Third Edition (ICSD-3) (Sateia, 2014). OSA is the term used in this thesis. In this thesis, only adults are included. OSAS, obstructive sleep apnoea syndrome includes daytime sleepiness.

PAP

- Continuous positive airway pressure (CPAP) produces a constant flow of air into the patient. Some patients experience difficulty to breath out against the airflow. Nowadays, auto-adjusting PAP (Positive airway pressure) is used as well as BiPAP (BiLevel positive airway pressure). All these versions are called PAP, positive airway pressure since they all induce positive pressure during inspiration.

Compliance vs. adherence

- These days compliance has a paternalistic connotation, such that if the doctors tell the patients to use a treatment, the patient should use it (Aronson, 2007). The word adhere originates from the Latin word *adherer*, with the meaning "remain constant, to cling to, or to keep close". It is a more modern approach to medical treatment with an agreement between doctor and patient when selecting the treatment for the patient to use. The word *adhere* is used in this thesis.

Objectives

Main original objective

To investigate the association between nasal obstruction and obstructive sleep apnoea (OSA), and effects of treatment for these associations in patients with obstructed upper airway and sleep apnoea.

Main objective as developed during the progression of the project

To investigate impaired nasal patency and sleep disturbances with respect to prevalence of nasal obstruction in OSA patients and patients with severe nasal obstruction, and the consequences concerning sleep quality, quality of life, and effect of treatment.

Objectives for each study

- Study I (UPPP): to investigate satisfaction with UPPP surgery performed 19 to 25 years previously.
- Study II (Polyposis): to investigate the prevalence of sleep disturbances in patients with nasal polyposis pre- and post-surgery.
- Study III (OSA): to investigate the prevalence of subjective and objective nasal obstruction in OSA patients when untreated, and to assess if nasal obstruction was associated with sleep related symptom and quality of life compared to patients without nasal obstruction.
- Study IV (PAP): to examine long-term effects of PAP treatment on subjective nasal obstruction and objectively measured nasal dimensions, and to study whether subjective and objective nasal obstruction at baseline influenced PAP adherence.

Hypothesis

Main hypothesis

We hypothesized that nasal obstruction in OSA patients was frequent, and that nasal obstruction would have a negative impact on quality of sleep and quality of life. We further hypothesized that nasal obstruction was *induced* by PAP (Positive airway pressure) and nasal obstruction would have a negative impact on PAP adherence. Finally, that severe nasal obstruction was associated with sleep disturbances.

Hypothesis for each study

- Study I: Patients were unsatisfied with previous UPPP surgery.
- Study II: Nasal obstruction in nasal polyposis induced sleep disturbances, and sleep quality improved after surgery.
- Study III: Nasal obstruction in OSA patient was frequent, and nasal obstruction gave sleep disturbances, but did not impact on quality of life.
- Study IV: Positive airway pressure treatment induced nasal obstruction and reduced nasal cavity dimensions due to mucosal swelling. Subjective and objective nasal obstruction at baseline would negatively affect positive airway pressure adherence.

Background

General background impaired nasal patency

How is the nose valuable in human breathing? What is the role of the nose while sleeping?

George Catlin (1796-1872) was a lawyer in the city of Philadelphia, USA, and started a research study in 1832. He conducted a systematic study on 150 tribes of Native American in the upper Missouri river (Catlin, 1861). The findings of his thesis showed an interesting relationship between good health and well-functioning nasal breathing, observing that "There is no animal in nature except Man, that sleeps with the mouth open." He concluded that persons should close their mouth and breathe through the nose in order to improve their health and wellbeing.

The nose and the nasal airways are important for olfaction, filtering and humidifying the air. The interior parts of the nose are also essential for heat exchange, and for protecting the lungs against inhaled toxic agents. The ciliary system, as well as the sneeze reflex is likewise important for protecting the lungs from particles entering the airways via the nostrils.

Anatomy with relevance for impaired nasal patency

The external nose consists of two pyramidal bones supporting on a midline structure, the septum, which split the cavity in two nasal spaces (left and right) sagittally (Petrén, 1969; Pevernagie et al., 2005). The three elevations inside the lateral walls are *concha inferior* (also called inferior turbinate), *concha media* (figure 1), and *concha superior*. The olfactory region is localized cranially of *concha superior* and the septum. The rest of the nasal cavity is known as the respiratory region (Mygind, 1978). The nares, or the nostrils, are the frontal openings while the openings towards the back of the nose are called the choanae. The nasal vestibules are immediately posterior of the nares. The *limen nasi,* or the nasal valve, is the narrowest area and it is limited by the lower edge of the *cartilage nasi lateralis, cartilage septi nasi,* and the head of the *concha inferior*. The nasal valve is the communication area between the aperture of the nose and the nasal fossa.

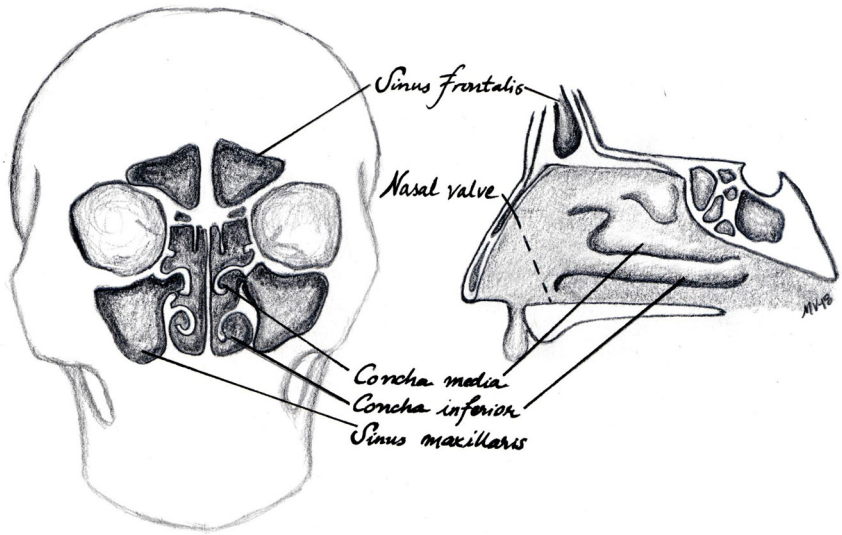


Figure 1.
A coronal schematic illustration showing the bone structures of the internal nose with the two cochae and sinus cavities. In the sagittal plane the lateral wall of the right nasal cavity is visualised. Concha superior is illustrated cranially of concha media. The nasal valve is also shown. There is a mucosa covering the concha and the rest of the nasal cavity and the sinuses. The mucosa can vary in thickness.

The mucosa

In the respiratory region of the nasal cavity, the mucosa is an epithelium on a basement membrane and the submucosa is called *lamina propria* (Mygind, 1978). The respiratory epithelium (ciliated columnar pseudostratified) is constructed of mainly ciliated columnar cells, non-ciliated columnar cells, goblet cells, and basal cells. There are cavernous sinusoids connecting capillaries and venules in the nasal mucosa, which can vasoconstrict by smooth musculature. The nasal mucosal circulation is complex and adaptable (Widdicombe, 1997). During a vasodilation of sinusoids expansion of the mucosa occurs and since the nose is enclosed in bone the airway become reduced. The venous sinusoid system is under autonomic nerve system control (Arbour & Kern, 1975; Eccles, 1996).

Physiology of the nose

When inhaling through the nose the air becomes humidified, as well as being filtered and heated. It is important that the airflow becomes turbulent for this process to occur. The delicate construction of the nose with *conchae* is well designed for creating turbulence, such that if the ambient air temperature is 22°C it is warmed up by passing through the nasal cavities to reach 32°C in epipharynx (Rouadi et al., 1999). In order to produce the perfect air conditioning effect, nasal resistance is important,

such that the nose contributes with two thirds of the total resistance of the respiratory system (Ferris et al., 1964). The different parts of the nasal cavity contributing to the nasal resistance are the *concha inferior*, the nasal septum, nasal vestibule, the nasal valve, and the turbinated nasal passages (Busse & Holgate, 2000). The *Concha inferior* has the largest impact on the airflow. The nasal vestibule and the nasal valve are kept open during inspiration by the stability of the *alar cartilages,* as well as the muscles *m. dilator naris* and parts of *m. nasalis* (Bloching, 2007). The swell body is located in the nasal valve area, on the septum anteriorly to the middle turbinate and is around 2.5 cm from the nasal floor (Costa et al., 2010). It has a large proportion of venous sinusoids and is suggested to influence the nasal airflow.

The nasal cycle is a phenomenon with spontaneous variations in the level of congestion of the nasal mucosa with corresponding fluctuations in the nasal resistance (Ogle et al., 2012). The sinusoid periodic vasomotoric activity with constriction and dilation in the nasal mucosa contribute to the spontaneous variations, which occur in irregular time frames (Arbour & Kern, 1975; Eccles, 1996). Although the congestion can alternate between left and right side, the two nasal cavities also have a cycle independent of the other nasal cavity.

Why breath through the nose during sleep?

Healthy adults prefer to inhale and exhale through the nose and the oral fraction of breathing during sleep has been demonstrated to be as small as 4% in healthy subjects (Fitzpatrick et al., 2003)(a). There are sensitive negative pressure reflex receptors in the nose, which stimulates upper airway dilator activity in *m. genioglossus* (Horner et al., (Pierce et al., 2007; Burger et al., 1993). Ventilation of the lungs is larger during nasal breathing compared to oral breathing during sleep (McNicholas et al., 1993). In supine, while sleeping, there is a high resistance in the upper airway. When awake there is a high effort in breathing through the nose (Butler, 1960) however during sleep oral breathing shows 2.5 times higher resistance compared to nasal breathing (Fitzpatrick et al., 2003)(b).

Pathophysiology of impaired nasal patency

In nasal congestion, and possibly nasal obstruction, there is a reduction in internal nasal dimensions, which may cause an increased resistance of airflow (Santos et al., 2006). There are different contributing factors causing nasal congestion, such as rhinitis, hypocapnia, cold air, alcohol, as well as pregnancy (Pevernagie et al., 2005).

There are several reasons for the nose to be obstructed (Valero et al., 2018). The unilateral reasons include septal deviation, unilateral chronic rhinosinusitis, *antrochoanal* polyp, tumours (benign or malignant), or *concha bullosa*. Bilateral explanations for reduced nasal patency include rhinitis of different ethiology (allergic,

pregnancy, medication, common cold), chronic rhinosinusitis with or without nasal polyposis (CRSwNP and CRSsNP) (Fokkens et al., 2012), benign or malignant tumours, systemic diseases, turbinate hypertrophy, nasal valve insufficiency, empty nose syndrome, as well as drug induced nasal obstruction (Georgalas, 2011).

Nasal obstruction can also be differentiated with respect to structural vs. mucosal problems. Either way nasal obstruction induces a shift from nasal to oral breathing with the consequence that the negative pressure reflex is not stimulated with an increased risk of collapsed airways and apnoea. (Fitzpatrick et al., 2003 (a); Fitzpatrick et al., 2003; (b); Meurice 1996).

When a person is lying down in supine the nose is more congested (Nakajima et al., 2015; Rundcrantz, 2009). There are numerous reasons why this could be the case. There is a reflex, the corporo-nasal reflex, which is induced by sympathetic activity when a person is lying down and there is pressure on shoulder girdle, lateral thorax, and lateral pelvis. The contralateral nasal cavity compared to the side which the person is lying on, will decongest and the lower side becomes congested. A decreased blood volume in the mucosa of the less congested nose is caused by an upright position, physical activity, hypercapnia, adrenergic drugs, and atrophic rhinitis (for review see Pevernagie et al., 2005).

Cortisol, in its endogenous form is produced by the adrenal gland. The levels of cortisol decrease to the lowest level, nadir, at midnight, then begin to rise two-three hours later and reach maximum at 9 am, for details see review by Buckley & Schatzberg (2005). When the cortisol levels are low the inflammatory cytokines increase and so does the nasal obstruction. The mechanism has been suggested to be of importance in allergic rhinitis (Landstra et al., 2002). Cytokines related to allergic nasal rhinitis has been shown to correlate with sleep disturbances (Krouse et al., 2002).

Objective and subjective nasal obstruction

Whether there is a relation between subjective nasal obstruction and objective measures of nasal obstruction has been debated for a number of years. André et al. (2009) conducted a systematic review and found a correlation in 19 studies but no correlation in the remaining 11studies (no RCT). Thus, it is not possible to conclude either way due to divergence of the results. André et al. observed that the likelihood of finding a correlation when each nasal valve is evaluated separately.

Treatment of impaired nasal patency

The pharmacotherapy of congestional or inflammatory nasal conditions often relies on the use of intranasal steroids, sometimes in combination with oral steroids. Over

the counter (OTC) products like nasal decongestants are often used. The surgical treatments of reduced nasal patency are used according to the indications. The surgical procedures can involve, for instance, septoplasty, turbinectomy, and endoscopic surgery, which sometimes includes polypectomy with a microdebrider.

Nasal polyposis

Chronic rhinosinusitis has been defined in the European Position Paper on Rhinosinusitis with and without nasal polyposis (EPOS2012)(Fokkens et al., 2012) where rhinosinusitis in adults is defined as:

Inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):

- ± facial pain/pressure
- ± reduction or loss of smell

and either endoscopic signs of:

- nasal polyps, and/or
- mucopurulent discharge primarily from middle meatus

and/or

- oedema/mucosal obstruction primarily in middle meatusand/or

CT changes:

- mucosal changes within the ostiomeatal complex and/or sinuses."
- This definition unfortunately does not discriminate between Chronic Rhinosinuitis with and without nasal polyposis very well. These two diagnoses frequently differ in terms of symptoms, pathophysiology and treatment. In this thesis the term nasal polyposis is used instead of Chronic rhinosinusitis with nasal polyps.

Prevalence

In a Swedish population-based study the prevalence of nasal polyposis in the general population was demonstrated to be 2.7% (Johansson, et al., 2003). A French study found a similar prevalence of 2.1% (Klossek et al., 2005). A recent study reported a higher prevalence of nasal polyposis (8.8%) in textile workers compared to a control group (Veloso-Teles et al, 2018).

Anatomy/Patophysiology

Nasal polyposis is a manifestation of a chronic inflammation in the nasal mucosa. A polyp is macroscopically an elongated process with slim or broader base, often originating from the meatus into the nasal cavity (Larsen & Tos, 1995) (figure 2). Nasal polyps are microscopically characterised by a high number of eosinophils, fibroblasts, H2-like lymphocytes, goblet cells, and mast cells (Bachert et al., 2001)

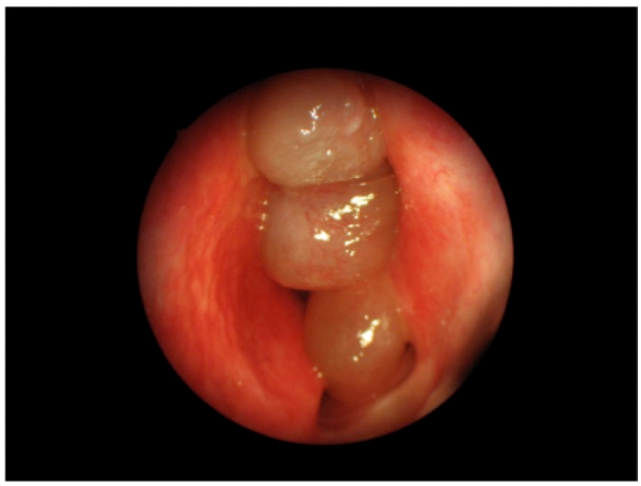


Figure 2.
Nasal polyposis in the left nasal cavity. Photo: Morgan Andersson.

Symptoms

Nasal obstruction is the most common symptom in nasal polyposis patients also experience sneezing, rhinorrea, sweating, and reduced, or loss of, olfactory function (Rudmik & Smith, 2012), and thus the disease has an impact on quality of life (Leynaert et al., 2000).

In addition, it is common that patients with nasal polyposis also have asthma, intolerance to acetylsalicylic acid, and other non-steroidal anti-inflammatory drugs (NSAID) The combination is termed Samter's triad.

Treatment

The first line of treatment of nasal polyposis is an intranasal steroid. When the condition become more troublesome, and severe, oral steroids can sometimes be given for a shorter period of time. Local treatment with nasal steroids has been shown to reduce the size of the polyps, but when the medical treatment is insufficient, surgery is necessary (Tuncer et al., 2003). Currently, the surgical procedure is often performed using an endoscopic technique. Oral corticosteroids and surgery improve

the nasal symptoms and the quality of life (Alobid et al., 2008) and the surgery may also improve olfactory function (Haxel et al., 2017). Regrowth of polyps after endoscopic surgery is common (Dalziel et al., 2006), and repeated surgery is often necessary in several patients while topical corticosteroid treatment have to be continued postoperatively, often lifelong. New treatments with monoclonal antibodies for nasal polyposis are under development and may serve as an important tool for treatment of nasal polyposis in the future (Tsetsos et al., 2018).

In this thesis nasal polyposis is the main focus in study II to investigate impaired nasal patency and the consequences in terms of sleep quality.

General background sleep disturbances

Sleep is an essential process for all mammals, but we do not know for certain why we sleep or why we sleep in the way that we do. The evolution from using a sleeping nest up in the trees to sleeping on the ground is speculated to be an important step towards the process of deeper sleep. Deeper sleep with relatively short durance, 7-8 hours, is thought to have improved memory for motor skills and improved cognitive function essential for the human development (Samson & Nunn, 2015).

The more recent discovery of the glymphatic system in the central nervous system, which corresponds to the lymphatic system in the body, could help to explain the need for sleep in vertebrates. This intriguing system, rinses the brain parenchyma, helping to remove potentially toxic waste products, which accumulate during awake time. The glymphatic is specifically active during sleep (Iliff et al., 2012; Xie et al., 2013).

Sleep also seems to be of importance for the immune system, along with many other functions. Patients with ≤ 7 hours of sleep has been shown to have a threefold increased probability of developing a cold compared to those with ≥ 8 hours of sleep (Cohen et al., 2009).

Evolutionary medicine and modern research might in the future provide us with a more in depth understanding on why we sleep, though the knowledge is not here yet.

Sleep disturbances and consequences of poor sleep quality

Sleep fragmentation, experimentally induced in healthy subjects, is associated with increased daytime sleepiness, impaired cognitive function, as well as having an impact on mood (Martin et al., 1996). Sleep deprivation results in similar effects to those seen in sleep fragmentation in terms of daytime sleepiness (Patrick & Gilbert, 1896), and total sleep deprivation has been shown to be fatal.

Snoring

Snoring is a sound derived from different parts of the upper airways during sleep. It is more frequent when the person is lying in supine position. Nocturnal nasal obstruction is an independent risk factor of snoring (Young et al., 2001). The prevalence of snoring is reported to be 20-40%, at least in developed countries like Poland and Australia (Bearpark et al., 1995; Jennum & Sjøl, 1993; Zielinski et al., 1999).

Obstructive sleep apnoea (OSA)

Pathophysiology of OSA

Obstructive cessation of breath during sleep was first described, and polygraphically studied, in 1966 by Gastaut et al. (1966). A patient with OSA has repeated cessations of airflow through the upper airways during sleep, despite muscular respiratory effort. The pathophysiology of OSA remains unclear, but there are two main hypotheses as to what the underlying mechanisms are.

The traditional way of explaining apnoea has been a mechanical obstruction, partial or total, at different levels of the oropharyngeal airway (Morrison et al., 1993), refer also to figure 3. The obstructive sites are formed by the soft palate, or the base of the tongue (Katsantonis et al., 1993). The *M. genioglossus,* and *m. tensor palatine* are dilating the airway but show lower activity during sleep (Sauerland et al., 1981; Morrison et al., 1993). Obesity and craniofacial dysmorphology are additional factors known to limit the airway.

Another approach to explain the pathophysiology is neuromuscular. Patel et al. (2018) conducted a systematic review of a possible neuromuscular pathophysiology of OSA. They reported histology observations of diffuse inflammatory changes and muscular changes consistent with neuropathy.

Symptoms

Due to sleep arousals, deoxygenation, and frequent apnoea many patients with OSA experience fragmentized sleep. This results in both nocturnal and daytime symptoms symptoms other than the above-mentioned insomnia and daytime sleepiness are sweating (Arnardottir et al., 2013), impaired cognitive function, morning headache, snoring, nocturia, bruxism, and nocturnal gastroesophagal reflux (Kryger et al., 2005). OSA is also a risk factor associated with difficulties in tracheal intubation and in-mask ventilation (Leong et al., 2017).

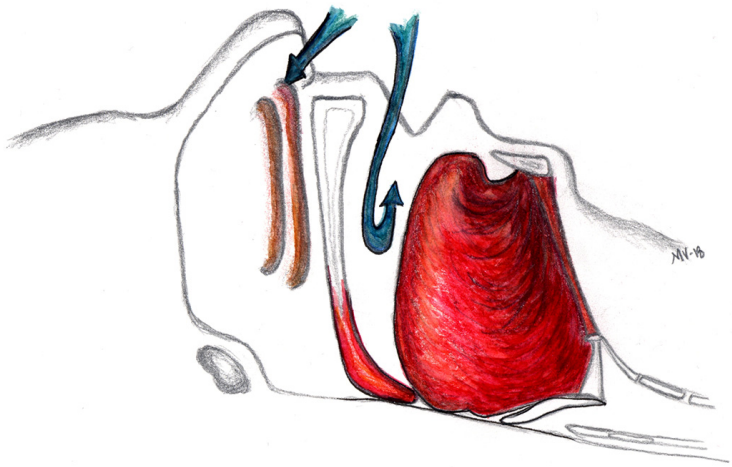


Figure 3.
Schematic drawing illustrating an apnoea with total obstruction of the airway with the soft palate and base of tongue. In this case impaired nasal patency as well.

Prevalence

OSA was previously thought to be a rare disease. A rising prevalence has been reported in the recent years, and some of the factors explain that can be attributed to increasing rates of obesity, changes in diagnostic tools used, as well as changed definitions of disease severity (Franklin & Lindberg, 2015). Rising awareness of OSA can possibly also increase prevalence numbers. Knowledge on the diagnosis is rising in developed countries, however, in developing countries the knowledge, and awareness, of the condition among doctors is still insufficient (Hussain et al., 2003).

The prevalence has been reported to be 17% among men between 50 to 70 years old (Peppard et al., 2013) but daytime sleepiness was part of the diagnose (i.e. OSAS) in that study. A recent review demonstrated prevalence numbers in all ages, of Apnoea-hypopnea index (AHI) ≥5 (also including mild OSA) ranging between 9 and 38%. When using an AHI ≥ 15 (moderate to severe OSA) the prevalence in a general adult population ranged between 6 to 17%, and reaching as high as 49% in middle aged patients (Senaratna et al., 2017). Reported prevalence numbers diverge but OSA can now be considered a common disease.

Risk factors

The primary factors influencing OSA prevalence are age, male gender, and higher body mass index (BMI) (Senaratna et al., 2017) as well as craniofacial dysmorphism (Kryger et al., 2005).

Diagnosis

Polysomnography has been considered the golden standard when diagnosing the patients with OSA (Chesson et al., 2002) however, home sleep apnoea testing is normally sufficient for diagnosing OSA (Arnardóttir et al., 2016; Berry et al., 2015). The process involves measuring airflow in the nasal cannula, the respiratory effort is measured by a thorax band and abdominal bands, and oximetry is tested on the finger, and while snoring is typically recorded, see figure 4.

Figure 4.
The placements for the different measuring signals, nose canula, thorax band, abdominal band, oximetry, and snoring by microphone. With permission of person in picture (MA).

AHI is an index of the numbers of apnoeas and hypopnoeas (reduced airflow), which results in an arousal or a desaturation per hour of sleep. This measure is used as the main outcome in OSA. AHI is used to define severity; mild sleep apnoea AHI 5–14, moderate 15–30, and severe >30 respiratory events/h sleep (Osman et al., 2018).

AHI is an index number of apnoeas and hypopnoeas (reduced airflow) per hour of sleep. Both apnoeas and hypopnoeas often result in an arousal or a desaturation. Apnoeas can however, be scored without arousals or desaturations but hypopneas need the additional events to be scored as a hypopnoea. AHI is used as the main outcome in OSA. AHI is used to define OSA severity, which is generally considered; mild sleep apnoea AHI 5–14.9, moderate 15–30, and severe ≥30 respiratory events/h sleep (Osman et al., 2018).

The scoring criteria from 2007 were updated in 2012 in AASM Manual for the Scoring of Sleep and Associated Events. An apnoea is scored when the flow signal

drops by ≥90%. Hypopnoea is scored when there is a drop in the peak signal excursion by ≥30% or an alternative sensor (≥10 sec) in combination with either ≥3% arterial oxygen desaturation or an arousal, see example in figure 6. This can be compared to a normal registration shown in figure 5.

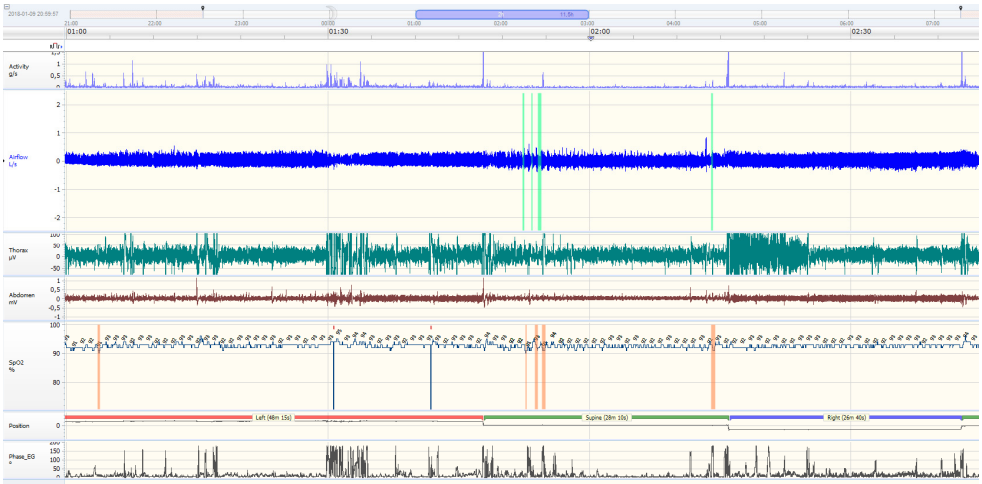


Figure 5.
Normal home sleep apnoea testing registration result. Labels shown from top activity, airflow, thorax band, abdominal band, oxymetry, position, and phase (a combination of abdominal and thoraxband).

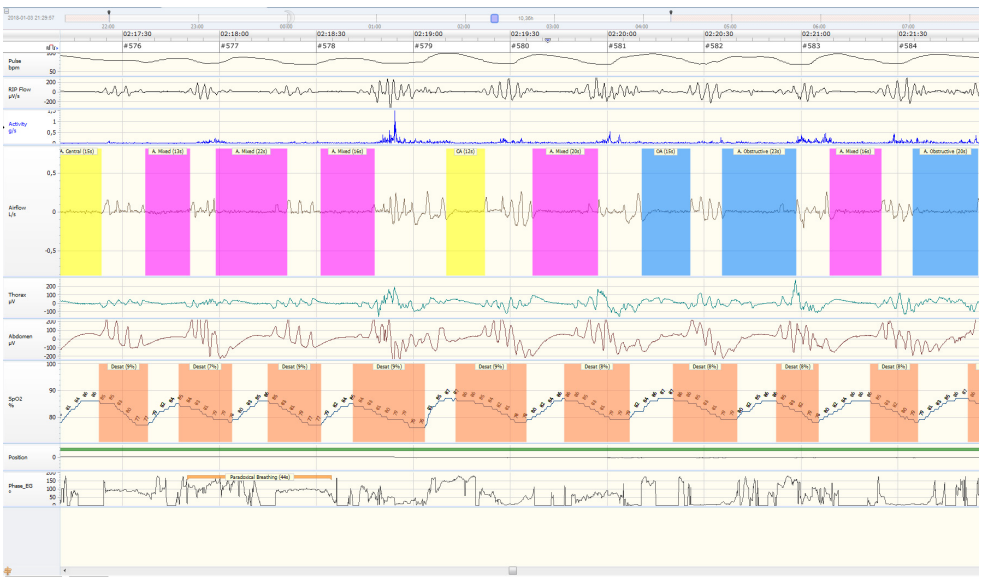


Figure 6.
Home sleep apnoea testing registatrion result showing disturbed sleep in OSA patient with obstructive apnoeas, central and mixed apnoeas, as well as desaturations. For labels, see picture text figure 5.

There is an on-going debate on how to diagnose OSA and criticism has been raised against the use of AHI. Measuring outcome with AHI has limitations. For example, a patient with a low a low number of long AHI events will have substantial desaturation despite a low AHI score (Muraja-Murro et al., 2012).

Comorbidity

In OSA there is an increased risk of cardiovascular diseases hypertension, stroke, atrial fibrillation, and heart failure (Ayas et al., 2016). The risks are thought to be a result of changes in endothelial dysfunction, systemic inflammation, and also oxidative stress. PAP has a small, but significant, effect on blood pressure, however, it remains unclear if PAP prevents cardiovascular events. The common coexistence of OSA and obesity also complicates studies aiming to assess the individual effects of OSA on other comorbidities, often also impacted by the presence of obesity (Arnardóttir et al, 2009 review).

Treatment

Positive airway Pressure (PAP)

PAP is a treatment with an airflow providing the patient with air through a mask. Sullivan et al. (1981), first described treating OSA patients with PAP in 1981. PAP is an effective treatment to reduce OSA severity (Gay et al., 2006) and also to improve daytime sleepiness, and improving quality of life in OSA patients (Epstein, et al., 2009). Gelardi et al. (2012) found that OSA patients who used PAP had a reduction in inflammatory cells.

The original mask was the full-face mask with a continuous airflow. Several adjustments and improvements have been made to make the PAP treatment more convenient to use. The following are examples of mask alternatives for PAP; nasal masks, nasal pillows, under-nose nasal-mask, oral masks, and full-face masks (BaHammam et al., 2017), see figure 7. Heated humidification has also been used to an increasing extent in recent years. Nasal side effects are reduced with heated humidification, however, quality of life of the patients does not seems to be improved (Ruhle, et al., 2011).

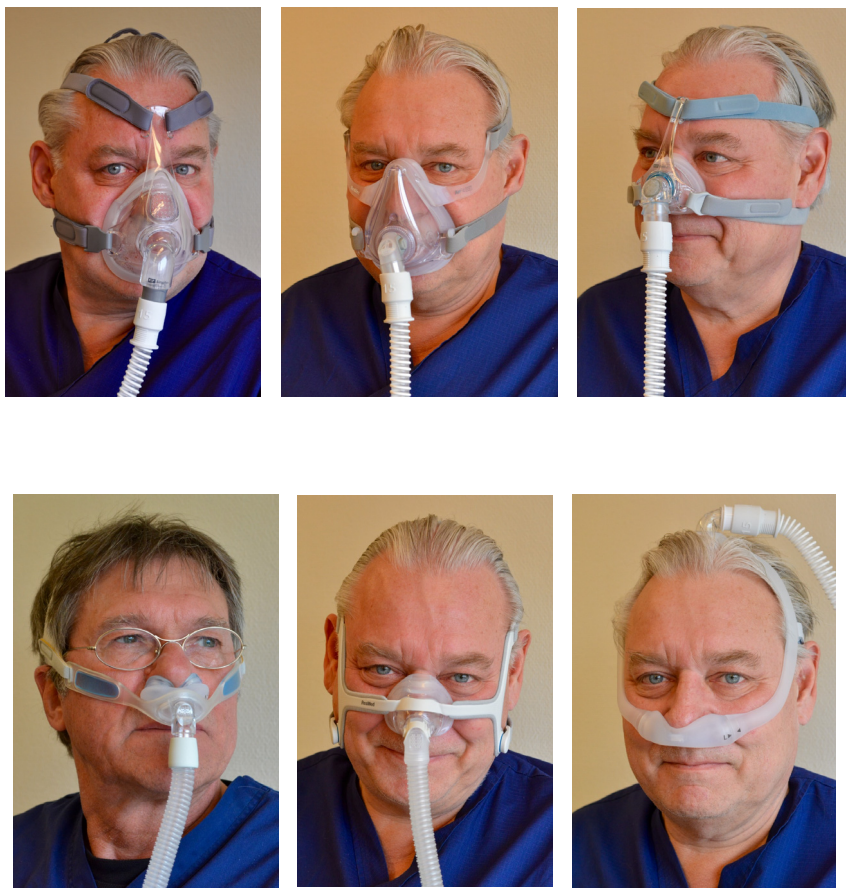


Figure 7
The pictures are showing alternatives of PAP masks. From left top, two fullface masks, and top right a nasal mask. Bottom left is a mask with nasal pillows, another nasal mask, and an under-nose nasal-mask. With permission of persons in pictures (SB)(OJ).

Adherence to PAP

Adherence to PAP in patients with OSA show levels around 50-68% after 2.5-5 years of treatment (McArdle et al., 1999) (Grote et al., 2000). Many factors influence the rates of adherence. Several factors have been shown to have a positive impact on adherence, including higher AHI, more daytime sleepiness, and anticipated symptomatic benefit (for review see (Kakkar & Berry, 2007; Engleman & Wild, 2003). Different factors have been associated with negative adherence such as lack of daytime sleepiness, previous UPPP, lack of perceived symptomatic benefit, side effects of PAP, insomnia and claustrophobia. There are conflicting results as to whether heated humidification can improve adherence (for review see Kakkar & Berry, 2007). Mouth leak, where air leaks out of the mouth when nasal PAP is used, can cause an increased nasal resistance, which can be improved with heated humidifier (Richards, et al., 1996).

An interesting finding is that also non-PAP users report small reductions in OSA symptoms (Pien et al., 2018). It has been speculated whether this is due to regression to the mean, or if the patients had benefit of other treatments. This finding emphasises the need for control groups in PAP studies as some of the benefits of PAP treatment may be overstated without the comparison of a non-PAP group.

Different ways of approaching/describing OSA

One way to classify a disease is to separate it into phenotypes. The phenotypes of OSA have been described in different ways and are debated. The first way was originally described by Eckert et al. (2013) as an *anatomical compromised narrow or collapsible upper airway* or *insufficient pharyngeal dilator muscle activity during sleep, low arousal threshold to airway narrowing during sleep,* and *high loop gain meaning unstable control of breathing* (Osman et al., 2018).

Another way of defining into phenotypes is perform cluster analysis. This attempts to group individuals within a study sample to be as similar to the other the individuals in the same cluster as possible and to be as unlike persons in the other cluster groups as possible. The following phenotypic clusters have been described: The disturbed sleep group, the minimally symptomatic group, and the excessive daytime sleepiness group (Sleepy) (Ye et al., 2014). The minimally symptomatic group showed the largest probability of having comorbid hypertension and cardiovascular disease. The same research group has recently published that the sleepy group showed the highest adherence compared to the other groups, and furthermore the largest improvement with respect to daytime sleepiness, as well as drowsiness, when driving (Pien et al., 2018). Saaresranta et al. (2016) found in a large European study (n = 6555) similar phenotypes and they also found that patients with insomnia had more psychiatric disease than the other groups.

Uvulopalatopharyngoplasty (UPPP)

The Japanese doctor Ikematsu performed the first UPPP surgery on an elderly woman with pronounced snoring. The woman returned one week later with a large smile telling her doctor that her snoring was gone (Ikematsu, 1964; Ikematsu, 1988). Ikematsu devoted his life to the study of snoring and to the development of surgery to reduce it. The UPPP surgery did not become widely used until in 1984 when Fujita published his paper on UPPP as a treatment for OSA (Fujita, 1984). The originally technique using cold knife steel performing tonsillectomy, uvula removement, reduction of the soft palate, and adapting the anterior tonsil pillar to the posterior tonsil pillar. Variations of the original surgery are performed as an alternative treatment when PAP is found insufficient (Browaldh et al., 2013) and resulted in a reduction in AHI by 60% has been demonstrated. A recent review found that Laser assisted UPP (palatoplasty) can worsen AHI, which was the case in 44% of the patients (Camacho et al., 2017). An improvement in AHI was seen in 32% of the patients. LAUP may result in the destruction of the reflexogenic dilatation of the pharyngeal airway mediated by pharyngeal afferent nerve fibres.

Mandibular Advancement Device (MAD)

A review by Marklund et al. (2012) found that MAD reduced 28-80% of the respiratory disturbances while and PAP reduced frequencies with 74-94%. MAD is recommended in mild to moderate OSA although and the treatment needs to be followed up and adjusted according to the result of the treatment. PAP is more efficient in reducing AHI (Schwartz et al., 2017) but not with respect of improving sleep quality. The adherence rates are higher in MAD when comparing with PAP. There are no differences in daytime sleepiness, quality of life, and cognitive function between PAP and MAD and it suggested that the reason is lower rates of adherence in PAP.

Alternative treatments

Even though PAP, MAD, and upper airway surgery dominate the treatments in use for OSA there is a long list of other treatments. These include positional treatment (Chan, 2008), tracheostomy, weight reduction, and nerve stimulation of *N.* hypoglossus (Certal et al., 2015).

Insomnia and OSA

Insomnia is defined by difficulties in falling asleep or maintaining sleep with the consequences of daytime fatigue (Buysse, 2013). The prevalence of insomnia is around 10-20% in the general population. Insomnia can be divided into initial insomnia defined by difficulties initiating sleep, middle insomnia with difficulties maintaining sleep, and finally late insomnia when the patient wakes up early and struggles to get back to sleep again (Björnsdóttir et al., 2012). Insomnia therapy

consists of cognitive, behavioural, and pharmacological treatment (Buysse, 2013). OSA patients have been reported to have insomnia in 40% of the cases, with middle insomnia being the most prevalent subtype (Benetó, et al., 2009). OSA patients with insomnia experience more daytime sleepiness and lower quality of life than patients without insomnia (Björnsdóttir et al., 2012).

Daytime sleepiness

Excessive daytime sleepiness is defined as an impaired ability to maintain wakefulness during hours of being awake, which results in the individual falling asleep involuntarily (Monderer et al., 2017). Sleepiness should not be mistaken for being the same as fatigue or lacking energy. In this thesis the term *excessive* is not used, but *daytime sleepiness* is. At what point the limit is for when the daytime sleepiness becomes excessive is unclear in the literature. Ways to investigate daytime sleepiness can be to objectively measure the patient using polysomnography to investigate if the reason for the sleepiness might be OSA. Another objective test is multiple sleep latency test which investigates the sleepiness after planned sleep deprivation. Daytime sleepiness is however, most frequently investigated with the questionnaire Epworth sleepiness scale (ESS) (Johns, 1991).

Specific background impaired nasal patency and sleep disturbances

A relation between impaired nasal patency and poor quality of sleep has been known since the time of Hippocrates (Freind & Frewin, 1717), when it was observed ”that nasal polyposis was associated with restless sleep“.

Prevalence

Prevalence of subjective nasal obstruction in OSA patients prior to intervention

The prevalence of impaired nasal obstruction in OSA patients has been insufficiently studied. There has been little effort to distinguish between symptoms prior to start of treatment, and from the side-effect from PAP treatment. In previous studies during the 1990´s, the patients that had been on PAP treatment for variable length of times where investigated, with questionnaires. Hoffstein et al. (1992), found a prevalence of nasal side effects in 44% of the patients. However, it was, not possible to conclude if the nasal problems were symptoms, or side-effects of the treatment.

Other studies conducted during the same time period indicate that nasal problems were observed during PAP treatment in 25-64% of patients (Brander et al., 1999; Engleman et al., 1996; Hoffstein et al., 1992; Pépin et al., 1995; Waldhorn et al., 1990), and compromised nasal patency was most frequent (Kribbs et al., 1993).

Kreivi et al. (2012) investigated upper airway symptoms in snorers and OSA patients (n = 524, 72% with OSA) with questionnaires on nasal symptoms prior to treatment. They found that more than 50% of the patients experienced nasal “stuffiness” (to quote the authors) and dryness of nose prior to start of PAP.

Modern PAP treatment, with heated humidification has been reported to reduce subjective nasal obstruction. Kreivi et al. (2010) showed a decrease in the proportion of patients reporting nasal stuffiness after using PAP for two months.

In summary, nasal obstruction in OSA patients can be either a symptom prior to treatment, but also a side effect of PAP treatment. The prevalence of nocturnal nasal obstruction as a symptom prior to treatment in OSA patients has not previously been investigated in a large group of patients.

Prevalence of objective nasal obstruction in OSA patients prior to intervention

It has been demonstrated that OSA patients have smaller internal nasal minimal cross section areas compared to non-OSA patients (Banabilh et al., 2010). The authors, however, did not find any differences in internal nasal volume. This observation is supported in a study by Liu et al. (2006), who found that OSA patients with high respiratory disturbance index (RDI) had smaller minimal cross-sectional area. RDI, in addition to AHI, is also includes respiratory-effort related arousals (RERAs). Lofaso et al. (2000) found that nasal resistance, investigated with rhinomanometry, to be an independent risk factor for OSA in a cross-sectional study of 541 snorers with suspected OSA.

The internal anatomical nasal dimensions in OSA patients have never, to our knowledge, been previously studied in a large study sample prior to the initiation of PAP.

Quality of sleep/Sleep disturbances

Sleep disturbances in severe nasal obstruction

The early studies of nasal obstruction and its impact on sleep were performed by total artificial intranasal occlusion, which they found a significant increase in apnoeas and arousals (Suratt et al., 1981; Zwillich et al., 2015). Patients in an epidemiological study with nasal polyposis had a two-fold risk of suffering from disturbed sleep compared to healthy controls (Serrano et al., 2005).

One of the symptoms in rhinitis is nasal obstruction but the burden of disease includes nasal congestion with swelling of the mucosa, runny nose, and post-nasal drip. This should be kept in mind when evaluating the relation between rhinitis and sleep. In addition, it is well known that allergic rhinitis has an influence on sleep quality (Lavie et al., 1981; Sundbom et al., 2013).

The same matter is present when evaluating results from studies on chronic rhino sinusitis. The diagnose Chronic rhino sinusitis often involves nasal obstruction (Soler, et al., 2008). The symptoms associated with chronic rinosinusitis also have a poor relation to objective measurements (Stewart & Smith, 2005), which should be kept in mind when evaluating studies relying only on subjective parameters. Alt et al. (2013) found that 75% of chronic rhino sinusitis patients reported poor sleep quality. In addition, patients with poor sleep quality reported lower scores in disease-specific QoL questionnaires compared to those who reported good sleep quality. Depression and female gender were independent risk factors for poor sleep quality in CRS.

Reduced sleep quality is common in patients with inflammatory illnesses of the upper airway, and it can have several reasons like nasal obstruction, nasal secretion, sneezing,

circadian issues in inflammatory diseases, and cytokines with impact on sleep quality. Sleep quality is however not well studied in patients with non-allergic impaired nasal patency.

Insomnia, daytime sleepiness, and subjective self-reported sleep quality including risk for OSA

The relation between nasal obstruction and sleep disturbances in other diseases than OSA, has been investigated in a few studies. Patients with rhinitis reported more daytime sleepiness and non-restorative sleep than patients who seldom had symptoms (Young et al., 1997). In women, nocturnal nasal obstruction was an independent predictor of difficulties of falling asleep due to nasal obstruction, snoring, waking up hastily gasping for breath, waking up unrested, and daytime sleepiness (Bengtsson et al., 2015). The same group conducted an epidemiological cross-sectional study investigating self-reported symptoms related to chronic rhinosinusitis and nasal obstruction in relation to insomnia and daytime sleepiness (Bengtsson et al., 2017). They found a high prevalence of sleep related problems (early, middle, and late insomnia), excessive daytime sleepiness and found that the degree of CRS symptoms affected the extent of sleep related problems. However, we found, no studies investigating OSA patients with nasal obstruction in relation to aspects of disturbed sleep like insomnia and daytime sleepiness.

Quality of life

Nasal obstruction influences a patients quality of life (Hellgren, 2007) and untreated OSA patients have a decreased quality of life compared to controls (Björnsdóttir et al., 2015; Yang et al., 2000). The combination of nasal obstruction and OSA has to our knowledge not been studied in terms of quality of life and it is not known whether the combination further compromise the quality of life of the patients.

Treatment

There are different treatments that can influence the relation between nasal obstruction and sleep disturbances. Below are the treatments relevant for the current thesis listed.

UPPP

Welinder et al. (1997) performed a prospective study investigating the effect of UPPP surgery on nasal objective and subjective symptoms with rhinomanometry and questionnaires before and after UPPP. They found that 15% of subjects reported less subjective nasal stuffiness and that 63% had a reduction in nasal resistance.

Endoscopic Sinus surgery for nasal polyposis

Sleep quality in patients with nasal polyposis has not been studied thoroughly. In CRS without nasal polyposis very few studies on sleep has previously been undertaken. Alt & Smith (2013) found that patients with chronic rhinosinusitis had previously been investigated mainly with disease specific questionnaires concerning sleep, and there was a need to investigate patients with questionnaires developed specifically for sleep evaluation.

PAP

Short follow up studies investigating internal nasal dimensions in PAP users showed a decrease measured with acoustic rhinometry after one month of PAP use (İriz et al., 2017). After three months of PAP the internal nasal area returned to baseline values. A different study found immediate subjective and objective nasal obstruction after two hours of PAP use in healthy subjects (Balsalobre et al., 2017). According to Li et al. (2005), the number of PAP users was lower in patients with smaller nasal minimal cross section area after three months of PAP.

Materials and methods

Study designs

Study I (UPPP), was a retrospective questionnaire study. Study II (Polyposis) was a prospective cohort study with a three-month follow up period. Study III (OSA symptoms) was a cross sectional study with subjective and objective measurements. Study IV (OSA treatment) was a prospective cohort study with a two-year follow-up.

Study subjects

In all of the studies the study subjects were patients who planned for, underwent, or previously had undergone different investigations and treatments at the department of Otorhinolaryngology, Lund and Malmö, Skåne University Hospital, Sweden, as well as Landspitali, Reykjavik, Iceland. A healthy control group was recruited among persons in the surroundings of the authors for study II (Polyposis).

Study I (UPPP): The patients were located through the planning file (written on paper) of the local operating theatre. A questionnaire was sent by mail to all patients that underwent UPPP surgery in Lund, Sweden, between August 1985 and May 1991.

Study II (Polyposis): Patients with severe nasal polyposis (n = 45) with grade 2-3 polyposis according to the Lildholdt scale (Lildholdt et al., 1997; Johansson et al., 2000) who were offered surgery in Malmö or Lund, Sweden, were included. The inclusion period was between September 2013 and April 2014. Timeframe from baseline and follow up was in median 23 weeks (9 - 44 weeks). Healthy persons (n = 37) filled out the same questionnaire three months apart during the same period as the study was completed. That was done in order to see if there was a consistency in the questions over the three months.

Study III and IV (OSA symptoms and treatment): The Icelandic Sleep Apnea Cohort (ISAC) is a major research project on OSA with several different research focus areas. All patients in Iceland who were diagnosed with OSA were referred to the Department of Respiratory Medicine and Sleep at Landspitali – The National

University Hospital (LSH) of Iceland, for PAP treatment. All patients referred between September 2005 and December 2009 were asked to participate in the study.

Measurements

Home sleep apnoea testing

In study I (UPPP) one sleep apnoea testing was performed before and patients were investigated with a follow-up about three months after surgery. These recordings were performed at Department of Clinical Neurophysiology, Lund University Hospital, Sweden. The sleep registrations differed in methods compared to the methods used these days and multiple methods were used at that time. The recordings were often done in daytime after a full night of sleep deprivation. The patient arrived at the clinic in the morning and the recording was usually completed with polysomnographic registration. Occasionally the multiple sleep latency test (MSLT) was employed, a method used primarily to diagnose narcolepsy. Some patients underwent full night polysomnography. The selection of the patients for surgery at that time did not just depend entirely on the AHI but rather it was a decision of the doctor with support of the available measurements and complaints from the patients.

In study III (OSA symptoms) and IV (OSA treatment) patients underwent a home sleep apnoea testing at baseline with an Embletta portable monitor, an Embla 12 channel system (EMBLA™; Flaga Inc., Reykjavik, Iceland) or a T3 device (Nox Medical, Reykjavik, Iceland). Both systems record the same channels. The examinations were nasal airflow, oxygen desaturation, pulse, body position, activity by accelerometer, and also chest and abdominal movements by respiratory inductive plethysmograph. A centralized scoring laboratory using the Somnologica Studio (EmblaTM) software re-evaluated all sleep studies. For a sleep study to be evaluated more than 4 hours of a scorable oxygen saturation (SaO2) signal was required. The AHI was defined by the mean number of apnoea and hypopnea per hour of recording (time in upright position was excluded). An apnoea was characterized as ≥ 80% decrease in air flow for a time period of ≥ 10 sec. Hypopnea was defined as ≥ 30% decrease in the nasal flow with ≥ 4% oxygen desaturation or ≥ 50% decrease in flow for ≥ 10 sec with a prompt increase in flow at the end of the episode. The oxygen desaturation index (ODI) was determined as the number of temporal drops in oxygen saturation ≥ 4% per hour of recording. For more in depth details, see Arnardóttir et al. (2012) and Björnsdóttir et al. (2012).

Acoustic rhinometry

The process of Acoustic rhinometry relies on sending an acoustic signal into the nostrils, propagating further into the nasal cavity. The physical principle that the technique is built upon can be visualised by a sound wave sent into a cylindrical tube. The sound wave is reflected by impedance changes, which are caused by changes in the dimensions of the tube. When an acoustic signal is sent into the nose (called an incident sound wave) it is reflected (then called a reflected sound wave) (MeitY, 2018) by parts of the internal nose like the concha inferior. The incident acoustic signal is then compared to the reflected signal and the information is used to determine the cross-section area (Clement et al., 2005; Hilberg & Pedersen, 2000). In conclusion the method provides an anatomical characterization of the measurements from the nasal cavity.

The rhinometer used in study III and IV (OSA symptoms and treatment) was a single-impulse rhinometer (RhinoScanTM SRE2000, Rhinometrics, Assens, Denmark). Examinations were performed with patients in an upright sitting position, see figure 8 and 9. The variables examined in the project was: total minimal cross-sectional area (TMCA, cm^2) in both nasal valves added together (figure 10), minimal cross-sectional area within the smaller nasal valve (either left or right) (MCA-min, cm^2), total volume of left and right nasal cavity added together (TVOL, cm^3), and the difference between MCA before and after nasal decongestive spray (MCA-diff, cm^2),. The examinations were used when measuring from the nostril and at the maximum 8 cm into the nose. Further into the nose the method is more uncertain since limitations in the airway can be hidden behind a more prominent structure closer to the nostril. Three examinations per nasal cavity were performed and then a decongestive spray, oxymethazoline (0.5 mg/ml) was given with two puffs into each nostril. The next examinations were performed after 15 minutes with three measurements on each side. The mean value for each nasal cavity was calculated before and after nasal decongestive spray.

Figure 8.
Visualising how the acoustic rhinometry was performed with nose piece sealing the nostril. Photo: Sigurður Júlíusson.

Figure 9.
The acoustic rhinometry equipment shown with the nosepiece in pink or blue. Two different sizes were used depending on the size of the nose. Photo: Sigurður Júlíusson.

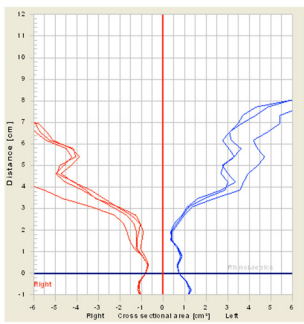


Figure 10.
In the result graph the strait blue line is symbolizing the nostril where the measurement begins. The red straight line is visualising the nasal septum. Lines showing measurement on the right nasal cavity have the colour red and the left nasal cavity measurements are blue.

Polyp size evaluation

In study II (Polyposis) the Lildholdt scale was used to quantify to what extent patients have nasal polyposis (Lildholdt et al., 1997; Johansson et al., 2000). The degree of nasal polyposis is quantified in relation to fixed landmarks as follows: 0–3, where 0: no polyposis, 1: mild polyposis (small polyps not reaching the upper edge of the inferior turbinate), 2: moderate polyposis (polyps reaching below the upper and but not below the lower edges of the inferior turbinate), and 3: severe polyposis (extensive polyps reaching the lower edge of the inferior turbinate or below). In study II (Polyposis) patients with grade 2 and 3 were included.

Lund-Mackay scoring system

Computerized tomography (CT) scans were used to assess polyp size assessments in all patients prior to surgery according to the Lund-Mackay scoring system with a scale 0-2 (Lund, 1997). (0: no abnormality; 1: partial opacification; 2: total opacification.) The sinus systems were as follows: maxillary, anterior ethmoids, posterior ethmoids, sphenoid, and frontal. The scoring of the ostiomeatal complex was 0: not obstructed or 2: obstructed. Total possible scores were 0-24.

Spirometry

In study II (Polyposis) patients were examined with spirometry to ensure that if an improvement of the sleep quality occurred it was not because of an improvement in the asthma of the patients. An electronic spirometer was used for spirometry assessment in a standing position (Micro lab 3300, Micromedial Ltd, Rochester, England). Patients were told to inhale air and exhale as hard as they could. Patients then inhaled a bronchodilator, Oxis® (Formoterol® 4.5 µg, AstraZeneca AB) and 15 minutes later a second measurement was conducted in the same way. FEV1 (per cent of the expected value of forced expired volume in one second) was used for analysis. Patients reporting a diagnosis of asthma/COPD from a MD and were on asthma/COPD medication were classified as suffering from asthma/COPD.

Questionnaires

Disease specific Qol questionnaire: SNOT-22

The sino-nasal outcome test SNOT-22 item version is a validated disease specific quality of life questionnaire on symptoms related to chronic rhinosinusitis with or without nasal polyposis. The SNOT-20 was developed by (Piccirillo et al., 2002). Browne et al. (2006) added two questions about taste and smell and removed the

importance rating, naming the new instrument SNOT-22. The Swedish version of the SNOT-22 was validated by Sahlstrand-Johnson et al., (2011) . Healthy subjects report in SNOT-22 a score from 0-7 (Yeolekar et al., 2013). The total score can range between 1-110. The questionnaire has been shown to provide a high-quality Patient related outcome measure (PROM) to assess chronic rhino sinusitis patients to assess patients with chronic rhino sinusitis (CRS) (Rudmik et al., 2015). The questionnaire has been used to evaluate outcome in polypectomy in patients with chronic rhino sinusitis with nasal polyposis (Browne et al., 2006).

Subjective nasal obstruction

When evaluating subjective nasal obstruction in study II (Polyposis) it was not defined weather the patient had daytime or night-time nasal obstruction and the only alternatives for this item was yes/no. In study III (OSA symptoms) and IV (OSA treatment) subjective nocturnal nasal obstruction was evaluated with the question: 'Is your nose congested at night?'. The response categories were alternatives on a frequency scale from 1 to 5: 1 = never or very seldom, 2 = less than once a week, 3 = once to twice a week, 4 = 3–5 times a week, and 5 = every night or almost every night of the week. Patients reporting a score of 4 or 5 were defined as having nocturnal nasal obstruction.

Generic quality of life questionnaire

The Medical Outcome Study´s Short Form Survey, SF-36, is a questionnaire measuring health related quality of life (McHorney et al., 1993; Ware & Sherbourne, 1992). SF-12 was developed from SF-36 as a more condensed version and it has been validated to express equivalent results (Ware et al., 1996). In study III and IV (OSA symptoms and OSA treatment) the SF-12 was used to evaluate the health-related quality of life before and two years after initiating PAP treatment. The scores were illustrating either physical or mental health. Compromised ability to move a table or walk up several flights of stairs where examples of reduced physical health. Impaired mental health was for example feeling depressed or anxious, and if those feelings limited daily life of the patient. The scoring scale was 0-100 and a score of 100 considered the best health related quality of life.

Questionnaire in study I (UPPP)

The questionnaire in study I (UPPP) study was questionnaire specific with questions from the validated ESS included. The questionnaire investigated satisfaction with previous surgery, present symptoms which were considered side effects by the patient, whether the patients would have chosen to undergo the surgery with the information available at present when filling out the form, subjective assessment of snoring, apnoea, daytime sleepiness, use of PAP, and comorbidity.

Sleep questionnaires

The Sleep Apnea Genetics International Consortium (SAGIC, 2018) is an international collaboration with several sleep research departments around the world. The consortium has developed a set of questionnaires investigating sleep. There are general questions as well as the Epworth Sleepiness Scale (ESS) (Johns, 1991), the Basic Nordic Sleep Questionnaire (BNSQ) (Partinen & Gislason, 1995), the questionnaire (BQ) (Netzer et al., 1999), and the Multivariable Apnea Prediction (MAP) index (Maislin et al., 1995). The SAGIC version includes minor adjustments in, as described when the questionnaire is described in the following text. The set of questionnaires was translated according to guidelines (Wild et al., 2005) by a professional interpreter into Swedish and re-translated into English by another professional interpreter. Questions about former surgery were included in study II (Polyps) from study I (UPPP).

Epworth sleepiness scale (ESS)

The ESS is a validated and widely used questionnaire to measure daytime sleepiness (Johns, 1991). The questions focus on probability of falling asleep on a scale from 0 to 3 for eight different situations common in life in industrialised countries (maximum score 24). A score between 0 and 10 is considered normal for healthy subjects, scores 11-15 are recognized as mild to moderate daytime sleepiness, and scores higher than 15 indicate severe daytime sleepiness. When testing healthy subject, without snoring, they have an average score of 6-7 (Hrubos-Strøm et al., 2011; Johns, 1991). In study III (OSA symptoms) and IV (OSA treatment) an ESS score of ≥ 10 was considered excessive daytime sleepiness (Björnsdóttir et al., 2012).

Basic Nordic Sleep Questionnaire (BNSQ)

The BNSQ investigate different aspect of sleep quality and consequences of poor sleep quality. Questions focus on for example insomnia, number of awakenings per night, and naps per day (Partinen & Gislason, 1995). In study III and IV (OSA symptoms and OSA treatment) the following questions were used: *"I have difficulties falling asleep at night* "(Initial insomnia), *"I wake up often during the night"* (Middle insomnia), and *"I wake up early and find it difficult to fall back asleep"* (Late insomnia). Three times per week or more often was the frequency required for a patient to be defined as having insomnia. The SAGIC version of BNSQ also contains a question on being tired when using a computer; and an additional "*Don't know"* alternative has been added to all categorical items. The other categories are *"Never", "Rarely: less than once a week"*, *"Frequently: 3-4 times a week"* and *"Always: 5-7 times a week"*. In study II (Polyposis) we also calculated BNSQ-symptoms as a sum.

The Berlin questionnaire

The Berlin questionnaire (Netzer et al., 1999) is a screening questionnaire used to identify patients at high risk of OSA. The index result is the following 0: no risk of OSA or 1: risk of OSA. A healthy non-snorer will not be at risk for OSA. The questionnaire includes 11 questions in three different categories: snoring and apnoea during sleep; daytime sleepiness; and comorbidity with high blood pressure. Patients were considered to be at high risk for OSA if two or more categories had a positive result. The SAGIC version of the Berlin questionnaire has also added "don't know" to all questions with alternatives "yes" and "no". Moreover, the item "Do you have high blood pressure?" has been adjusted to "Did you ever get a diagnosis of hypertension from a doctor?" If yes, the categories are: "Are you on anti-hypertensive medication at the moment? No/Yes".

Multivariable Apnea Prediction index (MAP)

In study II (Polyposis) the MAP index was used (Maislin et al., 1995). The index predicts OSA risk using both demographic data and subjective apnoea symptoms. Information on gender, age, height, and weight are incorporated with questions on nocturnal breathing (snoring and apnoea) to produce a MAP index of 0: low risk or 1: high risk.

Treatment

UPPP surgery

During 1985-1991 UPPP was performed at the hospital in Lund as previously described by Fujita et al. (1984). Patients were investigated by a doctor specialized in Phoniatry to evaluate the soft palate in order to plan the surgery, so it should not interfere with *m. pharyngopalatinus*. The technique used was cold knife steel in all patients except eleven patients where the surgeons used laser surgery. The surgery procedure included tonsillectomy, removing the entire uvula, and then the soft palate was reduced. The final step was stitching the anterior and posterior tonsil pillars together. A total of fifteen different ENT surgeons performed the surgeries.

Positive Airway pressure treatment (PAP)

The Sleep Department at Landspitali University hospital in Reykjavik is the only site in Iceland prescribing PAP treatment. All patients from the entire country of Iceland who are prescribed treatment receive the PAP from the Sleep Department. In ISAC (study III (OSA symptoms) and IV (OSA treatment)) the patients received initially an

auto-adjusting PAP or continuous PAP device (ResMed, San Diego, California, USA). In case of problems with treatment effectiveness the treatment was changed to bi-level PAP or adaptive servo ventilation. Inadequate treatment efficacy was defined AHI ≥ 15 events per hour during treatment with PAP. Patients had different masks and humidifiers available to choose from. From 2009 all PAP devices were delivered with in-line heated humidifiers.

PAP adherence was read from memory cards in the ResMed S8 devices (ResMed, San Diego, CA, US) from the previous 4 weeks of usage if available. This was not possible in older devices and then self-reported data was used based on three multiple-choice questions concerning average PAP usage. The questions were: "*Do you use a CPAP machine for sleep apnoea?" "How many nights per week do you usually use a CPAP machine?"* and *"For how much of the night (sleeping time) do you usually use CPAP?* "

The sensitivity was 98.6% with self-reported results and when differentiating full users and partial users the specificity was 45.1% (Arnardóttir et al., 2013; Björnsdóttir et al., 2013). Full PAP usage was considered the mean use of ≥ 20 days and ≥ 4 h day^{-1} for the past four weeks of machine derived data or ≥ 5 nights·$week^{-1}$ for ≥ 60% of the night by questionnaire. Partial user did not fulfil the criteria for full usage. Patients returning their devices <365 days after start of treatment were defined as early quitters and late quitters returned their PAP 365 - 729 days after first receiving the device (Eysteinsdóttir et al., 2017).

Nasal surgery

In study II (Polyposis) patients had general anaesthesia when they underwent endoscopic sinus surgery in day-care settings following standard procedure at our clinic. Microdebrider was used during the surgery. The surgeries were completed by five experienced ENT surgeons and the majority was performed by one surgeon (MA). The surgeons administered the written consent, were well informed about the study and informed the patients. Nasal packing was used postoperatively (1-3 days) and nasal washings with saline were recommended for a restricted time. Oral corticosteroid treatment was prescribed postoperatively up to maximum three weeks in accordance with the EPOS guidelines (Fokkens et al., 2012) All the patients continued the prescribed local corticosteroids throughout the study. The medical treatment of the patients was not changed between baseline and follow-up.

In study II and IV (OSA symptom and treatment) patient files were utilised to derive data on nasal surgery including septoplasty, turbinectomy, and endoscopic surgery (Fokkens et al., 2012).

Inclusion/exclusion criteria

In study I (UPPP) the inclusion criteria were having undergone UPPP surgery between August 1985 and May 1991.

In study II (Polyposis) the inclusion criteria were being over 18 years of age; nasal polyposis surgery planned; having capability to understand written information in Swedish; and able to independently answer written questionnaires. Pregnancy was an exclusion criterion.

The only inclusion criteria used in study III (OSA symptoms) and IV (OSA treatment) was being prescribed PAP treatment in Iceland between September 2005 and December 2009 (Arnardóttir et al., 2103).

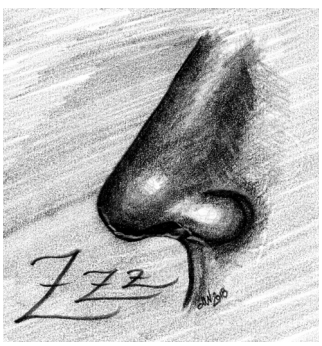
Statistical analysis

In study I (UPPP), nominal data are presented as frequencies and percentages without decimals. Ordinal and quantitative data were presented by mean and min-max. Other ways of presenting nominal data were in median and interquartile range (IQR) (study II (Polyposis)) or as mean and standard deviation (mean ± SD study III (OSA symptoms) and IV (OSA treatment)). Non-parametric statistics were used to compare the different groups. The chi-squared test was used in comparisons between nominal data in independent groups. Fisher's exact test was used when the expected values were insufficient for a chi-squared test. Mann–Whitney U-test was used in two independent group comparisons of ordinal and quantitative data and Wilcoxon signed rank test was used when calculating paired group differences for 2 groups. Kruskal-Wallis test was performed for >2 independent group comparison. Post-hoc tests were then calculated with the Mann–Whitney U-test between two groups at the time. Spearman's rank correlation (rs) was used when measuring associations. In the binominal Logistic Regression analysis, the Enter method was used, i.e. all predictors in the model were included in the calculations. Imputations were used in study II (Polyposis). Missing data in any ordinal variable were replaced with the median data value given by each subgroup; the polyposis and the controls. The imputations were used when presenting and comparing group data. When presenting data regarding change of risk over time, the Berlin questionnaire and the MAP Index were computed as instructed by the manufacturers. For the other questionnaires, the variables were presented one by one or/and summarized to scores.

The statistical software used was PAST.10 in study I (UPPP) and SPSS 22.0 and 23.0 in the other studies. A two-sided p-value <0.05 was considered significant.

Ethical considerations

Approval by the regional ethical committee at Lund University was granted for study I (UPPP), Dnr 2010/519 and for study II (Polyposis), Dnr 2013/491. The National Bioethics Committee of Iceland, the Data Protection Authority of Iceland and the Institutional Review Board of the University of Pennsylvania approved study III (OSA symptoms) and IV (OSA treatment). All patients, in all four studies, signed a written informed consent.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Results

The study cohorts

Study I (UPPP) included 186 consecutive patients who had undergone UPPP surgery in Lund, Sweden, between August 1985 and May 1991. Updated information was possible to retrieve in 179 patients through the national ID register, seven patients were not possible to localise, and 35 patients were deceased. The response rate was 88% and the final study sample consisted of 129 patients.

Patients with severe nasal polyposis, who were offered surgery in Malmö and Lund, Sweden, between September 2013 and April 2014, were asked to participate in study II (Polyposis)(n = 45). One patient decided not to undergo surgery and two patients had their surgery delayed and could therefore not be included. The final study population included 42 patients.

Among the patients asked for participation, over 90% of the subjects (n = 822) agreed to participate in study III (OSA symptoms) and IV (OSA treatment). All but nine patients initiated PAP treatment. At follow-up (study IV (OSA treatment)) seven patients were deceased, 13 had moved over-seas, and 61 patients declined to participate in the follow-up, see adjusted figure 11. Due to economical shortage of the study the patients underwent acoustic rhinometry only if the follow-up was performed prior the 1st of September 2008. In total, 419 patients were examined with acoustic rhinometry at follow up corresponding to 78% of the patients who had follow up before 1st of September 2008. Patients who did not answer the question about nocturnal nasal obstruction at follow up where excluded from the study (n = 3).

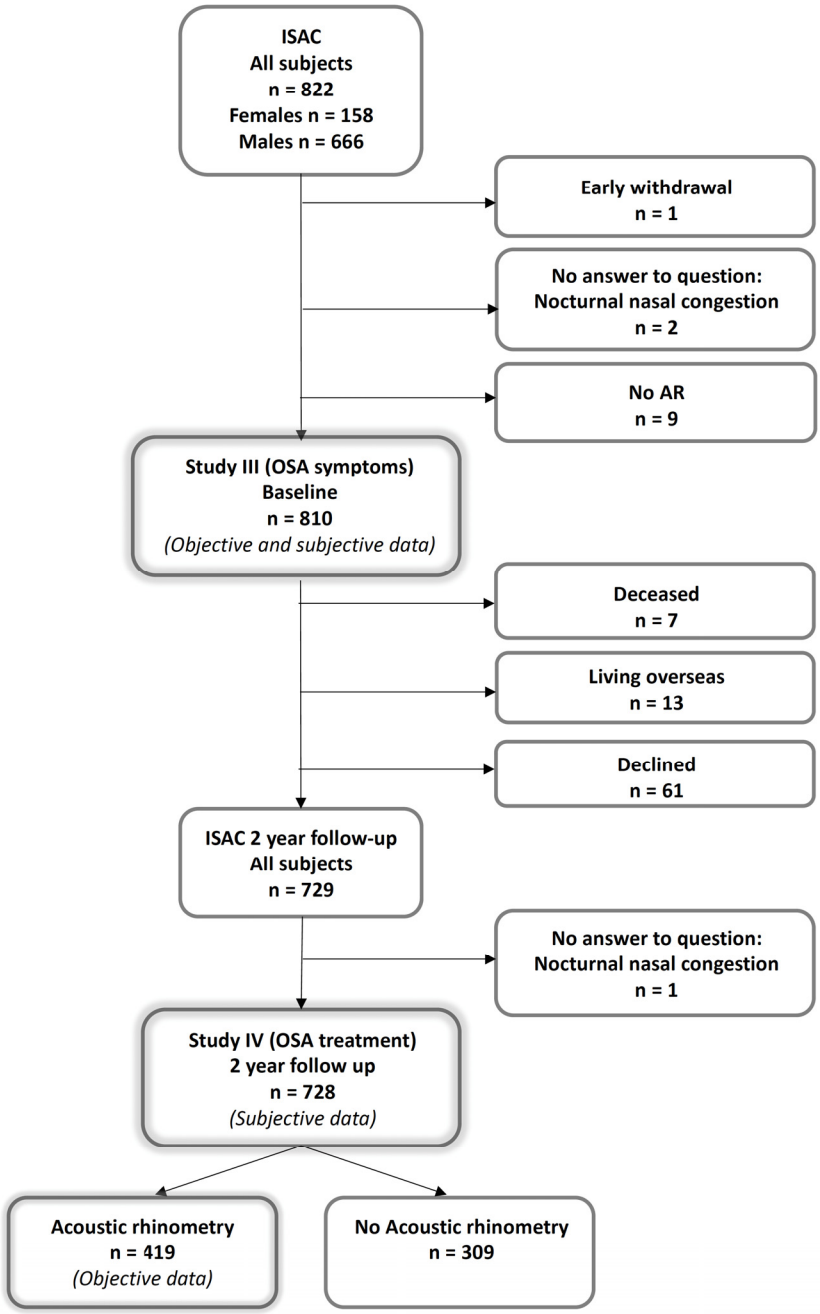

Figure 11
Outline of the study sample in study III (OSA symptoms), the upper part of the figure, and study IV (OSA treatment). For study IV only baseline values for the n = 728 and n = 419 respectively, are presented.

Prevalence

The high prevalence in study I (UPPP) of subjective nasal obstruction (32%) initiated our interest in impaired nasal patency and sleep. It was not specified as day or night-time.

In the ISAC study I (OSA symptoms) the prevalence of subjective nocturnal nasal obstruction in OSA patients (≥ 3 times per week) was 35% prior to PAP initiation. Nocturnal nasal obstruction once per week or more often was found in 65% of the OSA patients.

Sleep disturbance/sleep quality

In study I (UPPP) 37% of the patients reported waking up with a dry mouth. It is a common symptom in OSA patients and was not given any further attention in the published article.

In the project of study II (Polyposis), at baseline prior to surgery the patients reported daytime sleepiness (ESS, median (IQR) 7.5(6)) and 36% of the patients were unsatisfied or very dissatisfied with current sleep pattern. The Berlin questionnaire investigated the risk for OSA and 13 patients were at risk prior to endoscopic sinus surgery. The questionnaire MAP demonstrated similar results.

The patients with subjective nocturnal nasal obstruction in study III (OSA symptoms) had smaller minimum cross-sectional area within the smallest nasal valve (0.42 ± 0.17 vs. 0.45 ± 0.16 cm^2, $p = 0.013$), had more late insomnia and reported more daytime sleepiness (ESS score 12.5 ± 4.9 vs. 10.8 ± 5.0, $p < 0.001$), see figure 12 and 13. This was compared to patients without nocturnal nasal obstruction.

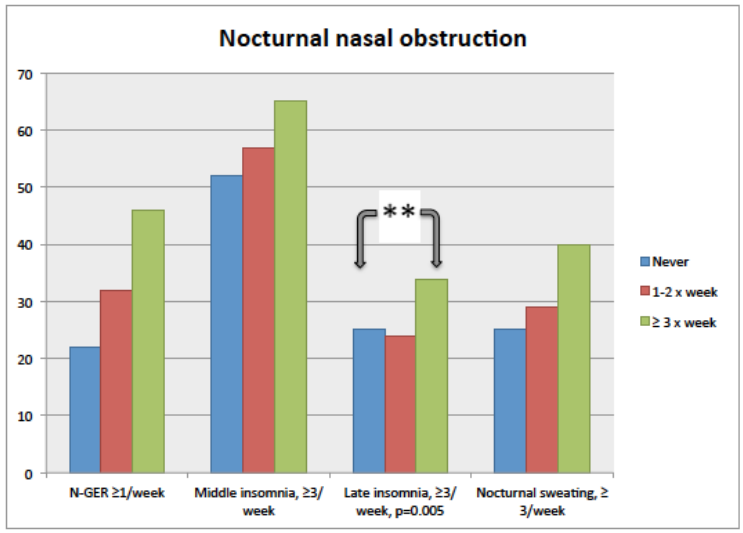

Figure 12.
At baseline in study III (OSA symptoms). Patients with nocturnal nasal congestion were more likely to report late insomnia when comparing to patients without any nocturnal nasal obstruction. Y-axis demonstrate per cent (%) of patients within the different groups with the different symptoms. ** Significance comparing the groups of patients without and with nocturnal nasal obstruction ≥3/week.

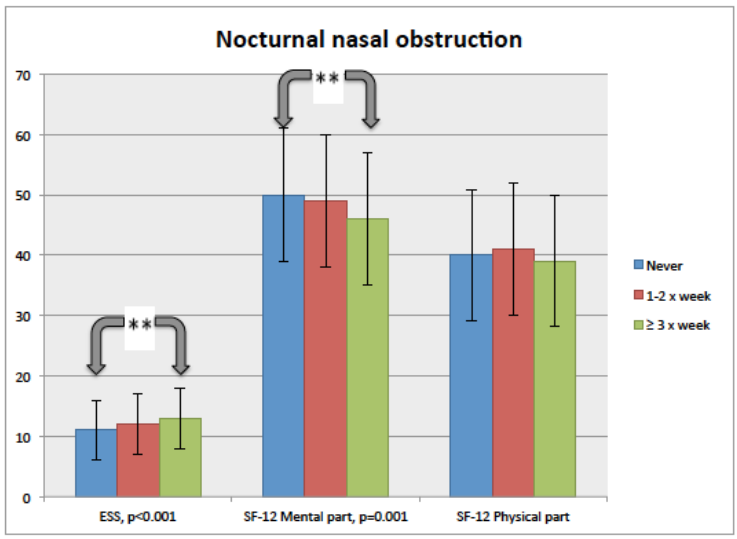

Figure 13
At baseline in study III (OSA symptoms) . Patients with nocturnal nasal congestion were more likely to experience daytime sleepiness and lower mental quality of life when comparing to patients without any nocturnal nasal obstruction. Y- axis demonstrate score. ** Significance comparing the groups of patients without and with nocturnal nasal obstruction ≥3/week.

Also, two years after initiating PAP treatment a larger proportion of patients with nocturnal nasal obstruction at follow-up had symptoms of poor sleep quality like nocturnal sweating, and insomnia independent of occurrence of symptoms at baseline (p-values < 0.02), see table 1.

Table 1
Study IV (OSA treatment). Patients with nocturnal nasal obstruction at follow up had more nocturnal sweating, insomnia, and worse physical quality of life compared to patients without nocturnal nasal obstruction at baseline.

Nocturnal Nasal Obstruction (n = 728)					
	Never (n = 418)	**Only at baseline (n = 134)**	**Only at 2 year follow-up (n = 52)**	**Both at baseline and at 2 year follow-up (n = 124)**	**p-value for group difference**
Underwent nasal surgery during the study	12%	25%	10%	15%	**0.01**
Nocturnal sweating, ≥ 3x week, 2 year	13%	14%	62%	25%	**0.007**
Nocturnal gastroesophageal reflux, ≥ 1x week 2 year	5%	14%	8%	15%	**0.002**
Daytime sleepiness (ESS), 2 year	8.4 ± 4.6	8.6 ± 4.7	9.7 ± 4.2	8.8 ± 4.9	0.17
Initial insomnia, ≥ 3x week, 2 year follow-up	9%	16%	10%	18%	**0.01**
Middle insomnia, ≥ 3x week, 2 year	29%	39%	57%	44%	**0.001**
Late insomnia, ≥ 3x week, 2 year	18%	31%	35%	30%	**<0.001**
SF-12 Mental part, 2 year	51.7 ± 9.9	50.2 ± 10.8	49.1 ± 10.0	50.2 ± 10.5	0.16
SF-12 Physical part, 2 year	43.4 ± 11.3	44.2 ± 10.7	42.4 ± 11.9	39.9 ± 11.4	**0.01**
Number of days on PAP	595 ± 241	593 ± 235.3	592 ± 223	573 ± 251	0.10
Hours of PAP use, last 28 days before 2 year (n=203, missing 215) Objective data	6.17 ± 2.22	6.49 ± 1.67	5.47 ± 2.42	6.60 ± 1.88	0.10
Late quitter (n =17)	2%	2%	4%	3%	0.41
Early quitters (n = 131)	18%	19%	15%	23%	
Partial users (n = 199)	14%	8%	23%	15%	
Full users (n = 480)	66%	71%	58%	63%	

ESS, Epstein Sleepiness scale. SF-12, The 12 Item Short Form Health Survey (SF-12) a smaller version of the SF-36v2 Health Survey, measuring quality of life. Significance in **bold**. Mean values shown as mean ± SD and p-values. Chi squared test when comparing proportions of groups here in %. Kruskall-Wallis Anova when comparing ordinal data. Posthoc test (Mann-Whitney U): Subgroup analysis comparing the groups SF-12 Physical part, 2 year, only baseline with both baseline and follow-up, p-value 0.18.

Quality of life

In study III (OSA symptoms) patients with nocturnal nasal obstruction reported lower mental quality of life compared to patients without nasal obstruction (46.4 ± 11.4 vs. 49.8 ± 10.5, $p < 0.001$), see figure 13.

In study IV (OSA treatment) patients with nocturnal nasal obstruction at follow-up were more likely to have reduced physical quality of life independent of symptoms at baseline (p-values < 0.02), see table 1.

Treatment

There was a major improvement in nasal symptoms after surgery evaluated with the questionnaire, SNOT-22, (median (IQR)): (51.5 (37) 26.5 (15) -18.0 (27), $p < 0.001$) (study II (Polyposis)). Nocturnal nasal obstruction was found in 75% of the patients prior to surgery and in 33% after surgery. There was an increase in the proportion of patients satisfied with current sleep pattern (pre- vs. post-surgery) (40% vs. 79%) post-surgery ($p < 0.001$). There was also a decrease in daytime sleepiness with total ESS scores from score 7,5(6) to 6.0(5), $p < 0.05$). The proportion of patients with excessive daytime sleepiness (score >10) was 36%. A smaller proportion of patients reported dry mouth after waking up in the morning at follow up ($p < 0.001$) post surgery compared to prior to surgery. The risk of OSA, investigated with questionnaire and MAP, was reduced from risk to no risk in 31% of the patients. One patient went from no risk to risk in Berlin questionnaire. The question: "Lack of good night´s sleep" was scored as a major problem in 32% compared to 16% after surgery ($p < 0.001$).

There was no improvement in lung capacity after surgery FEV1%: (median (IQR)): 94 (26) vs. 90 (24.2), $p = 0.322$. No difference in nasal obstruction was seen (SNOT-22, $p = 0.94$), daytime sleepiness (ESS, $p = 1$), or symptoms of poor sleep quality (BNSQ, $p = 0.654$) between asthmatics and non-asthmatics prior to or after surgery. In summary, the improvement in sleep quality was not an improvement of lung function.

In study I (UPPP) the current situation for the patients who had undergone UPPP 19-25 years earlier was investigated concerning satisfaction, side effects, daytime sleepiness, and PAP use. In the entire study sample 51% of the patients were satisfied with the result of the previous surgery and the same per cent would have chosen to undergo the surgery again with the information available 19-25 years post-surgery. The side effects experienced by the patients at follow-up are in figure 14. Daytime

sleepiness was investigated with questions derived from ESS and 9% reported falling asleep while reading.

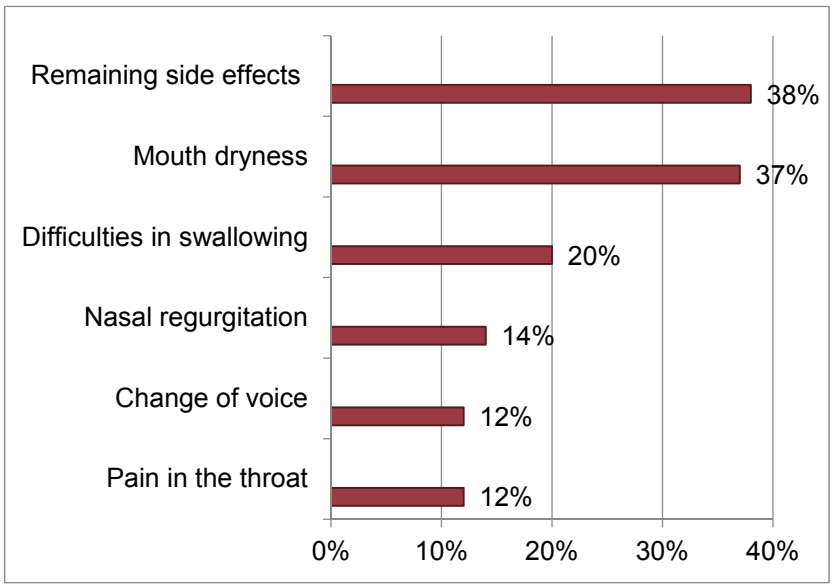

Figure 14
Study I (UPPP). It was common with symptoms considered as side-effects from previous UPPP surgery 19-25 years post-surgery.

Seventeen per cent of the PAP users reported satisfaction with the previous surgery while non-PAP users reported a satisfaction rate of 67%. Subjective nasal obstruction was reported with the same frequency in PAP users and non-PAP users (32%).

Subjective nasal obstruction

In study IV (OSA treatment), two years after the initiation of PAP treatment the proportion of patients in the total study sample, reporting subjective nocturnal nasal obstruction was decreased (baseline: 35% vs. follow up: 24%, $p < 0.001$).

Objective nasal obstruction

Measured with acoustic rhinometry all nasal dimensions increased on average after two years in mean (table 2). There was however no change in the reactivity of the nasal mucosa. The increase in interior nasal dimensions was not due to decongestion of the nasal mucosa. There was no difference in the reduction in nasal dimensions between PAP full users, partial users, early quitters, and late quitters (table 3).

Table 2:
Study IV (OSA treatment). Objective nasal dimensions (n = 419) improved two years after initiation PAP. The nasal mucosa reactivity did not change.

Objective nasal dimensions (n = 419)			
	Baseline	**2 year follow-up**	**p-value for group difference**
TMCA Total minimal cross-section area in the nose, left and right nostril combined before nasal decongestant spray, (cm^2)	1.06 ± 0.31	1.16 ± 0.33	**< 0.001**
TMCA Total minimal cross-section area in the nose, left and right nostril combined after decongestant spray, (cm^2)	1.24 ± 0.33	1.35 ± 0.32	**< 0.001**
MCA-min smallest nasal valve of right and left, before decongestant spray, (cm^2)	0.43 ± 0.16	0.48 ± 0.17	**< 0.001**
MCA-min smallest nasal valve of right and left after decongestant spray, (cm^2)	0.53 ± 0.17	0.58 ± 0.17	**< 0.001**
TVOL Total volume of left and right nasal volume combined before nasal decongestant spray, (cm^3)	4.10 ± 0.82	4.37 ± 0.88	**< 0.001**
TVOL, Total volume of left and right nasal volume combined mean after decongestant spray, (cm^3)	4.30 ± 0.84	4.61 ± 0.87	**< 0.001**
Diff TMCA difference between after and before decongestant spray, (cm^2), reactivity of the nasal mucosa	0.19 ± 0.21	0.20 ± 0.24	0.61
Diff MCA-min, smallest nasal valve of right and left, difference between after and before decongestant spray, (cm^2), reactivity of the nasal mucosa	0.10 ± 0.12	0.10 ± 0.13	0.31
Diff TVOL difference between after and before decongestant spray, (cm^3), reactivity of the nasal mucosa	0.20 ± 0.34	0.24 ± 0.41	0.37
Significance in **bold**. Numbers given as mean ± SD if not specified and p-values when comparing mean values were calculated with Wilcoxon signed rank test. Nominal data in independent groups shown with %. The chi-squared test was used for comparisons between nominal data.			

Table 3:
Study IV (OSA treatment). There was no difference in PAP users compared to the partial users, early, and late quitters in terms of objective measurements of nasal dimensions.

PAP use and nasal dimensions					
	PAP full users n = 480 with AR: **n = 264**	**PAP partial users n = 99** with AR: **n = 52**	**Early quitter n = 131** with AR **n = 95**	**Late quitter n = 17** with AR **n = 5**	**p-value for group difference**
Baseline TMCA, Total minimal cross-section area in the nose, left and right nasal cavity combined before decongestant spray (cm^2)	1.00 ± 0.31	1.00 ± 0.31	0.95 ± 0.30	0.92 ± 0.28	0.41
Baseline TVOL, Total volume of left and right nasal volume combined before nasal decongestant spray(cm^2)	3.96 ± 0.81	3.98 ± 0.81	3.82 ± 0.88	3.58 ± 0.54	0.21
Baseline MCA-min, minimal cross-sectional area within the smallest cavity of either left or right before decongestant spray, (cm^2)	0.40 ± 0.16	0.40 ± 0.16	0.38 ± 0.15	0.38 ± 0.14	0.57
Diff. between 2 year and baseline TMCA, before decongestant spray (cm^2)	0.17 ± 0.31	0.21 ± 0.64	0.16 ± 0.30	0.42 ± 0.19	0.07
Diff. between 2 year and baseline TVOL, before decongestant spray (cm^3)	0.45 ± 0.31	0.47 ± 0.45	0.46 ± 0.69	1.15 ± 0.76	0.73
Diff. between 2 year and baseline MCA-min, before decongestant spray (cm^2)	0.09 ± 0.17	0.10 ± 0.15	0.08 ± 0.16	0.15 ± 0.04	0.08

PAP: Positive Airway pressure. PAP users: ≥ 730 days of paying for and having the equipment. PAP early quitters: < 365 days, delivering the equipment before the end of 1 year of use, late quitter > 364 days of PAP use and < 730 days of PAP use. Mean values shown as mean ± SD and p-values. When comparing mean values in multiple groups Kruskall- Wallins test was used. The Chi square test was used for comparisons between dichotomized nominal data in independent groups (here shown in %).

We divided the study sample in quartiles depending on the total minimal cross section area. Patients with the smallest total minimal cross section area at baseline had an increase in dimensions at follow-up ($p < 0.001$) while patients with the largest total minimum cross section area had no changes in dimensions ($p = 0.65$) (figure 15). The effect was independent of adherence to treatment.

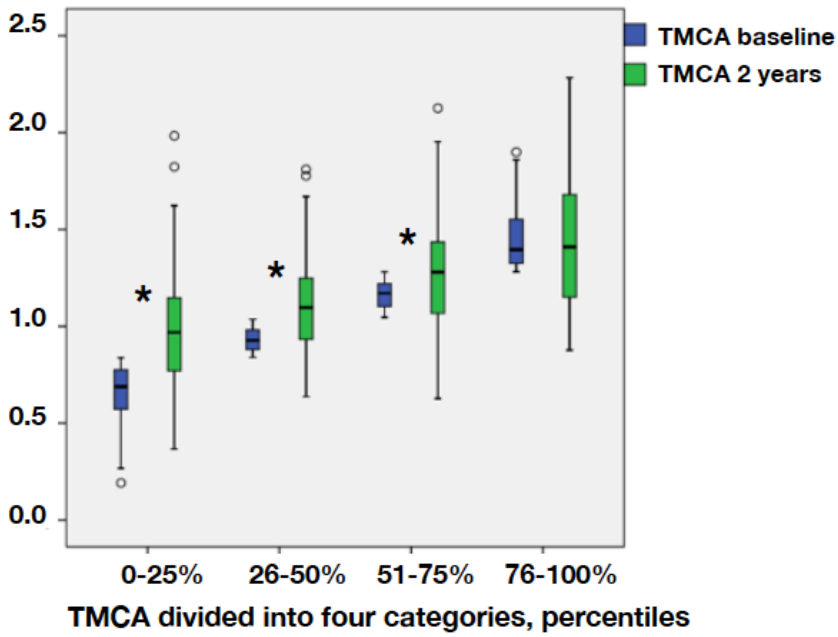

Figure 15.
Study IV (OSA treatment). Patients with small total minimal cross section area had an increase in total minimal cross section area (cm^2) (y-axis) two years after PAP start.

Relation to PAP use

There was a decrease after two years in the proportion of patients with subjective nocturnal nasal obstruction between baseline and follow up in full users ($p < 0.001$) and also early quitters ($p = 0.005$) (figure 16).

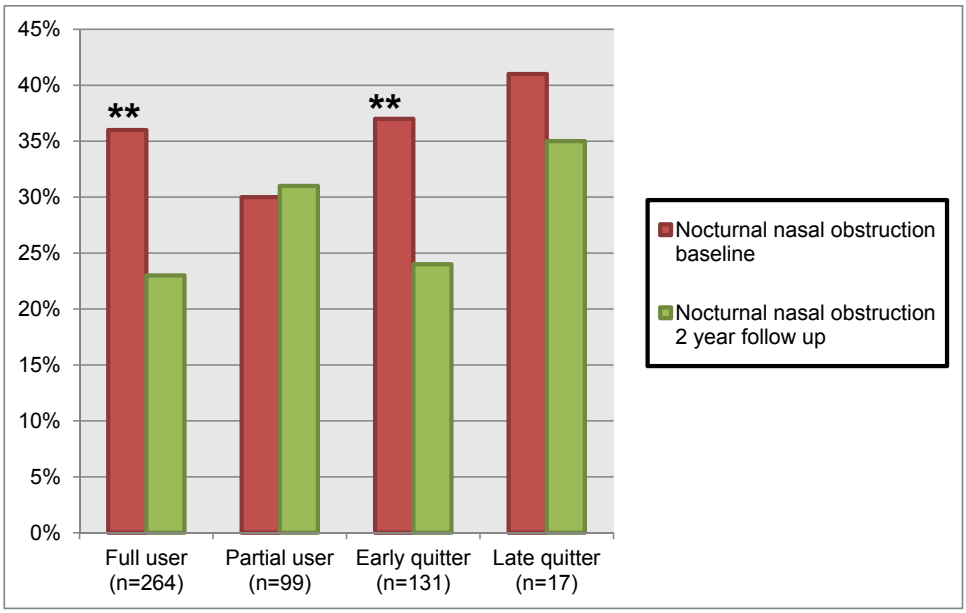

Figure 16:
Study IV (OSA treatment). The proportion of patients reporting subjective nasal obstruction (≥ 3x week), at baseline compared to follow up. There was a significant ($p \leq 0.01$) decrease in the proportion of patients with nocturnal nasal obstruction in full users and early quitters. There was no significant difference between the groups at baseline ($p = 0.67$) or at follow up ($p = 0.20$). The early quitters had used their equipment less than one year. The late quitters had used their treatment more than one year and less than two years.

There was no significant difference in reported nocturnal nasal obstruction between full users, partial users, early quitters, and late quitters baseline ($p = 0.67$) or at follow up ($p = 0.20$), (table 4).

Table 4:
Study IV (OSA treatment). Nocturnal nasal obstruction was not different at baseline or at follow up in the different groups of PAP use.

Nocturnal nasal obstruction and PAP use					
	PAP full users n = 359 with AR: **n = 200**	**PAP partial users n = 101** with AR: **n = 53**	**Early quitter n = 265** with AR **n = 157**	**Late quitter n =18**	**p-value for group difference**
Nocturnal nasal obstruction, ≥ 3x week, at baseline, %	37%	32%	34%	39%	0.67
Nocturnal nasal obstruction, ≥ 3x week, at 2 year, %	21%	32%	26%	33%	0.20
Independent groups shown with %, and when comparing nominal data the Chi square test was used.					

Small nasal volume at baseline was a determinant for becoming a non-user of positive airway pressure treatment (Odds ratio 2.22, Confidence Interval 95% 1.35 - 3.67, p = 0.002). However, having subjective nocturnal nasal obstruction at baseline could not predict being a quitter during the first two years of use, see table 5.

Table 5:
Study IV (OSA treatment). Prediction of PAP non-use (early and late quitters) depending on subjective and objective nasal obstruction at baseline was found in patients with the smallest nasal volumes.

Prediction of PAP non-use (early and late quitters)				
	Unadjusted odds ratio (95% CI)	**p-value for group difference**	**Adjusted odds ratio (95% CI)**	**p-value for group difference**
Nocturnal nasal obstruction at baseline, ≥ 3x week	1.11 (0.79-1.57)	0.55	1.18 (0.80-1.74)	0.42
TMCA percentiles at baseline, comparing the smallest quartile with the largest	1.80 (1.11-2.93)	**0.02**	0.35 (0.07-1.83)	0.22
TVOL, percentiles at baseline, comparing the smallest quartile with the largest	2.22 (1.35-3.67)	**0.002**	3.31 (1.07-0.26)	**0.04**
MCA-min, percentiles at baseline, comparing the smallest quartile with the largest	1.80 (1.08-3.00)	**0.02**	2.01 (0.48-8.47)	0.34
CI: confidence interval. MCA-min: Minimal cross-sectional area within the smallest nostril of either left or right before decongestant spray. TMCA: Total minimal cross-section area in the nose, left and right nostril combined before nasal decongestant spray. TVOL: Total volume of left and right nasal volume combined before nasal decongestant spray. Included in this analysis: auto-adjusting PAP, continuous PAP device and adaptive servo ventilation. Significance in **bold**. Multiple regression analysis was used. Odds ratio adjusted for age, BMI, and AHI at baseline.				

Relation between subjective and objective nasal obstruction

In study III (OSA symptoms), the minimum cross-sectional area within the smaller nasal valve prior to decongestive spray was smaller in the patients with subjective nocturnal nasal obstruction (0.42 ± 0.17 vs. 0.45 ± 0.16 cm^2, p = 0.013).

The study sample was separated in to the groups improved subjective nocturnal nasal obstruction, no change, and worse nocturnal nasal obstruction comparing from baseline with follow-up. There was no relation between these concerning changes in objective total minimal cross section area (correlation coefficient -0.02 (p = 0.66) (p = 0.98). In the subgroup analysis in patients with worse nocturnal nasal obstruction there was also an increase in nasal dimensions after the two years (table 6).

There was no significant relation between the size of polyps (CT assessment/Lund-Mackay) and Asthma/COPD vs. non-Asthma/COPD: (17.5 vs. 13.5, p = 0.058) (study II (Polyposis)).

Table 6:
Study IV (OSA treatment). When comparing patients who experienced an improvement in nocturnal nasal obstruction compared to acquired nocturnal nasal obstruction at follow up. Both groups had the same improvements in nasal dimensions.

Improved vs. aquired nocturnal nasal obstruction with respect to nasal dimension			
	Improved in nocturnal nasal obstruction (n = 134)	**Increased nocturnal nasal obstruction (n = 52)**	**p-value for group difference**
Diff. between 2 year and baseline TMCA, before decongestant spray, (cm2)	0.18 ± 0.30	0.20 ± 0.32	0.9
Diff. between 2 year and baseline TVOL, before decongestant spray, (cm3)	0.44 ± 0.69	0.58 ± 0.59	0.3
Diff. between 2 year and baseline MCA-min, before decongestant spray, (cm2)	0.09 ± 0.16	0.09 ± 0.19	0.4
Diff: difference, MCA-min: Minimal cross-sectional area within the smallest nostril of either left or right before decongestant spray, TMCA: Total minimal cross-section area in the nose, left and right nostril combined before nasal decongestant spray, TVOL: Total volume of left and right nasal volume combined before nasal decongestant spray Numbers given as mean ± SD if not specified and p-values when comparing mean values was calculated with Wilcoxon signed rank test. Improved in nocturnal nasal congestion: nasal congestion at baseline and not congestion at follow up. Acquired nocturnal nasal obstruction: nasal congestion at follow up but not at baseline.			

Nasal surgery

Patients with previous nasal surgery had in study III (OSA symptoms) more subjective nasal obstruction than patients without previous surgery (47% vs. 34% p = 0.02). There was no relation between AHI and previous nasal surgery (40.7 ± 16.2 vs. 45.3 ± 21.1, p = 0.12). Previous nasal surgery had no impact on objective acoustic rhinometry measures (p = 0.84 – 0.99).

Discussion

The studies in this thesis were retrospective, cross sectional, or prospective cohort studies. The overall findings in these studies are that nasal obstruction is frequent in OSA patients and has an impact on sleep quality, quality of life, and that nasal obstruction improved two years after initiating positive airway pressure treatment. Most importantly, PAP treatment does not induce long-term nasal obstruction in the majority of the patients. Sleep quality in patients with nasal polyposis is compromised and improves by surgery of the nasal polyps.

Prevalence of nasal obstruction in sleep

Our findings

We found a frequency of subjective nasal obstruction in OSA patients of 32-35% (study I (UPPP) and study III (OSA symptoms)).

Others have shown

Our results are in agreement with other studies. Brander et al., (1999) conducted a prospective cohort study in OSA patients before and after 6 months of PAP treatment. They found that many of the patients had nasal symptoms before starting the treatment. Nasal blockage (authors choice of word used) was found in 45% and rhinorrhoea in 37% of the patients. This is a fairly high number when comparing with the general population in Sweden where nasal obstruction prevalence of 15% has been reported (Eriksson et al., 2011). Another study by Gelardi et al., (2012) including a rather low number of subjects found that 47% of the OSA patients reported nasal obstruction prior to treatment. A recent retrospective questionnaire study by Lam et al. (2017) investigating OSA patients with and without PAP found nasal obstruction in 68% of the patients. Severe nasal obstruction was found in 36% of these OSA patients. It is however not possible to conclude from the study by Lam et al. if nasal obstruction was a symptom prior to treatment or a side effect from PAP treatment.

To summarize

Nasal obstruction is common in OSA patients with a probable prevalence of more than 30%.

Sleep disturbances/Sleep quality

Our findings

Quality of sleep was slightly reduced in OSA patients with nocturnal nasal obstruction and those patients had more daytime sleepiness and insomnia compared to OSA patients without nasal obstruction.

Sleep quality in patients with nasal polyposis was impaired and improved by surgery.

Others have shown

One study was found investigating the relationship between impaired nasal patency in OSA patients and sleep disturbances like daytime sleepiness and insomnia. The study by Lam et al. (2017), involved 172 OSA patients, with and without PAP, found that daytime sleepiness was moderately correlated to nasal obstruction.

More studies, however, have investigated the relationship between chronic rhinosinusitis with and without nasal polyposis and sleep disturbances. Jiang et al., (2016) showed that 38% of the patients with nasal polyposis reported daytime sleepiness. A moderate correlation between daytime sleepiness and disease specific quality of life was found, and that OSA is frequent in patients with rhino sinusitis with and without nasal polyposis. Thirty-five per cent of the patients had an AHI of more than 15%.

Most studies focus on chronic rhinosinusitis without nasal polyposis, which found that the majority of patients (around 75%) with chronic rhinosinusitis without nasal polyposis had impaired sleep quality measured with the questionnaire PSQI (Pittsburgh Sleep Quality Index) (Alt & Smith, 2013; Alt et al., 2014). A small study by Thomas et al., (2016) showed that all chronic rhinosinusitis patients had nasal obstruction and a high score on PSQI (impaired quality of sleep), but no correlation between nasal obstruction and sleep disturbances could be found. Moreover, symptoms related to chronic rhinosinusitis has been reported to impact the degree of sleep related problems (insomnia and excessive daytime sleepiness) (Bengtsson et al., 2017).

To summarize

OSA paients with nasal obstruction have more daytime sleepiness and insomnia compared to OSA patients without nasal obstruction. Few other studies have investigated sleep in patients with chronic rhinosinusitis with and without nasal polyposis, but these studies also indicate compromised sleep quality.

Quality of life

Our findings

We found a reduced quality of life in OSA patients with nocturnal nasal obstruction compared to OSA patients without nasal obstruction (in study III (OSA symptoms)).

Others have shown

OSA patients have impaired quality of life compared to the general population (Björnsdóttir et al., 2015). No other study investigating the influence of nasal obstruction on quality of life in OSA patients have been found.

However, disease specific quality of life questionnaires in OSA patients have been used. When OSA patients are compared with a control group of healthy persons, the OSA patients report more nasal obstruction and lower disease specific quality of life (SNOT-20) (Moxness et al., 2017).

Quality of life has also been studied in patients with nasal polyposis. Not surprisingly, patients with nasal polyposis have impaired quality of life (SF-36) to a larger extent than patients with perennial allergic rhinitis (Radenne et al., 1999).

To summarize

The consequences for OSA patients with nasal obstruction regarding quality of life have not been investigated thoroughly. Our results indicate that patients with nasal obstruction have lower quality of life than OSA patients without nasal obstruction.

Treatment

Our findings

In study II (Polyposis) sleep quality in terms of daytime sleepiness, consequences of sleep disturbances, and nasal patency improved after endoscopic sinus surgery. A large number of patients were at risk for OSA, which reduced after surgery.

Concerning PAP treatment (study IV (OSA treatment)) in OSA, we showed that subjective nasal obstruction improved after two years of PAP treatment. Objectively, especially patients with small total minimal cross section area at baseline increased at follow up. Patients with small nasal volumes at baseline were at risk for becoming a non-user of PAP. Small interior nasal dimensions increased ($p < 0.001$) independent of adherence to treatment.

Others have shown

In general, a large number of studies have demonstrated that quality of life is improved after sinus surgery, reviewed by (Soler et al., 2018). Few studies have specifically evaluated sleep disturbances in nasal polyposis patients pre- and postoperatively. Tosun et al., (2009) conducted a cohort study, where patients with nasal polyposis were examined with nasal endoscopy, acoustic rhinometry, ESS, and polysomnography prior to surgery and 3 months postoperatively. They found an improvement in minimal cross section area, nasal resistance, daytime sleepiness, and subjective snoring, but no improvement in AHI.

Endoscopic sinus surgery decreased daytime sleepiness in patients with chronic rhinosinusitis without nasal polyposis in a study by Rotenberg & Pang (2015). In this study, more daytime sleepiness was found compared to our study, but also a similar improvement. In contrast to our study, the nasal scores did not change significantly.

(Rassi et al., 2016) used questions in SNOT-22 to evaluate sleep disturbances in a wide variety of nasal diseases and found that surgery of different kinds improved the sleep quality.

PAP

The effects of PAP on the nose may differ with respect to the immediate effects, and the long-time outcomes. An acute effect of decreased nasal volumes and an increase of subjective nasal symptoms after two hours of PAP use in non-OSA subjects, was reported by Balsalobre et al., (2017). After six hours of PAP use in healthy persons Willing et al., (2007) showed a reduction in nasal resistance measured with rhinomanometry compared with the control condition. Rhinomanometry, however, measures nasal resistance and not the internal nasal anatomy like in our study, where AR was used. After six hours with PAP no change in subjective nasal obstruction was found in healthy subjects. A finding which, like our study, also supports, the idea that the objective measurements of nasal obstruction, and subjective assessments, can disagree.

The influence of internal nasal dimensions on PAP adherence in OSA has been investigated in a few small studies with different time frames. After three months of PAP use So et al. (2009) showed that the PAP adherent group had larger minimal

cross section area both in the nasal cavities combined and in the smallest of left or right cavity. After 18 months of PAP use smaller minimal cross section areas were found in non-PAP users (Morris et al., 2006). This study relied on self-reported use of PAP. Tárrega et al. (2003) retrospectively studied a cohort with nasal questionnaire symptoms. They found that 46 % of patients reported subjective nasal symptoms after 15 days of PAP, and after 3 months 37% reported nasal symptoms and after one year only 26% reported nasal symptoms. In contrast another study found no differences in objective or subjective nasal obstruction between users and non-users of PAP (Haddad et al., 2015)

A few studies have investigated whether nasal obstruction in OSA patients can predict if patients adhere to PAP. Sugiura et al. (2007) investigated if OSA patients accepted PAP initially at the time of trying out the equipment. Factors predicting non-acceptance of PAP were high AHI and high nasal resistance. On the other hand, Haddad et al. (2013) found that subjective nasal obstruction at baseline could not predict PAP adherence 6 months later, but smaller nasal volumes in supine position and lowest score of nasal symptoms was predictive of more hours of PAP use.

When an organ like the nose is not used it becomes less functional. In a long term follow up after laryngectomy it was found that patients who did not inhale or exhale at all through the nose had smaller minimal cross section areas (Ozgursoy & Dursun, 2007).

To summarize

It is suggested that PAP treatment induces an initial swelling of the mucosa in the first month of use with subjective symptoms. After approximately three months of PAP use the nasal mucosa becomes adjusted and the mucosal congestion improves. Maybe a mechanical enlargement of the upper airway can occur as well during this time.

A hypothesis for further studies can be; a reduced use of the nasal cavity in OSA patients induces nasal congestion which improves during treatment when the patient starts using the nose also during the night.

Relation between subjective and objective nasal obstruction

Our findings

In study III (OSA symptoms) patients with nocturnal nasal obstruction were more likely to have one small minimal cross section area. In study IV (OSA treatment) however no relation between subjective and objective nasal obstruction was found.

Others have shown

It is still unclear if there is a relation between subjective and objective nasal obstruction (André et al., 2009) but evaluating each nasal cavity separately increases the likelihood of finding a correlation. Vidigal et al. (2013) conducted a comparison between OSA patients and healthy controls to evaluate different methods to investigate the nasal dimensions (Haddad et al., 2013). They found no difference in AR value compared to control group, but OSA patients did indeed have more nasal symptoms than the control group.

To summarize

The findings in the literature harmonise with our findings of a relation between the smallest minimal cross section area and patients experiencing nocturnal nasal obstruction (André et al., 2009). On the other hand, the difference in subjective and objective nasal obstruction and prediction of adherence to PAP use suggest that subjective and objective nasal obstruction can be different issues which then may need separate approach to treatment.

Strengths and limitations

In study I (UPPP), the results were strengthened by the long follow up data (19-25 years), as well asthe high (age of responding patients. (It is worth mentioning as a curiosa that one case of oropharyngeal cancer was found due to that study.) One limitation of the study is that it was not planned when performing the surgery, but instead relied upon a cross sectional study. The sleep recordings were of variable quality at the time of the study, and unfortunately it was not possible to follow up recordings.

A strong feature of study II (Polyposis) was that the patients were well diagnosed with respect to the nasal polyposis, with clinical examination as well as CT scans and spirometry.

The main limitation of this study was the low number of patients, and the open design. Sham surgery is sometimes done in studies and could have been an alternative in a single blinded study design. However, there is a major risk of a selection bias in such a study, because a large number of patients would probably not agree to undergo the study under conditions.

The major strength of study III and IV (OSA symptoms and treatment) is the large and well described study sample and the most important limitation is the lack of a control group. In study IV the lack of difference in subjective nocturnal nasal obstruction between early quitters and full users at the two years follow up make it challenging to attribute the effect to PAP treatment. There are different aspects to consider concerning this result. It could be argued that the acoustic rhinometry equipment was unstable and that the results are coincidental. The machine was however calibrated every morning, and the acoustic rhinometry results show consistency in minimal cross-sectional area and volume. It could also be argued that the allergic season could have an influence. However, the Icelandic temperatures are relatively stable throughout the year and the pollen season is short, occurring mostly during July, when no measurements were performed. Another aspect is the circadian rhythms of the nasal mucosa, which could hamper the interpretation of the results. Nevertheless, the patients had the acoustic rhinometry measurements performed randomly during morning or afternoon at baseline and follow-up, suggesting in is unlikely to play a role. However, it is not possible to exclude totally.

Very recently an improvement in OSA symptoms in non-PAP users has also been shown in other studies (Pien et al., 2018). It will be very interesting to to see what unfolds with respect to further studies regarding the natural progress is in the disease OSA.

The major strength is that it has never before been published a paper with such a large subjective and objective investigated group of OSA patients at baseline.

Conclusions

Main conclusion

Nasal obstruction in OSA patients is frequent and it influences sleep quality, quality of life, and is improved two years after initiating positive airway pressure treatment. Patients with severe impaired nasal patency experienced sleep disturbances which improved with surgery.

Additional conclusions

Prevalence of nasal obstruction in sleep disturbances

The thesis suggests that nasal obstruction in OSA patients is frequent with prevalence numbers over 30%.

Sleep disturbances/Sleep quality and quality of life

Patients with severely impaired nasal patency had sleep disturbances with the consequences of daytime sleepiness and risk for OSA.

Patients with OSA and nocturnal nasal obstruction had disturbed sleep in the sense of more daytime sleepiness and insomnia. These patients also had a lower quality of life compared to OSA patient without nocturnal nasal obstruction.

Treatment

Subjective and objective nasal obstruction improved two years after initiating PAP and small nasal volume at baseline was a negative predictor for PAP treatment adherence. Most importantly, PAP treatment did not induce objective nasal obstruction and the majority (93%) did not experience PAP treatment to induce or worsen nocturnal nasal obstruction.

Future prospects

Working with a question generates more questions. The pathophysiology in OSA is fascinating, and numerous questions have arisen during the process of the research in this thesis. These are interesting questions like what is the role of the nose in the development of OSA? Is the early switch from nocturnal nasal breathing to oral breathing important (Rappai et al., 2003)? Is it possible to stop the switch by early intervention? If so, what would the appropriate interventions be? Does the nose become more congested if no airflow passes through the nasal cavity in severe OSA? Can nasal patency be more important for the development of OSA in some patients than in others?

Optimal treatment is crucial for OSA patients since the consequences for the patients are severe. What happens if patients are selected prior to the start of OSA? If patients have only subjective nasal obstruction, then what happens if patients adhere to the treatment prescribed? Does nasal obstruction improve after MAD, or other treatments? Will OSA in the future consist of several diagnoses with individualized treatments?

It would be fascinating to investigate further how the natural progression of impaired nasal patency occurs in OSA. Each question generates more questions: Is nasal obstruction a true symptom of OSA? Is there an improvement in nasal symptoms over years as a natural progression of OSA? Do other symptoms as well improve over the years with OSA? Is there a peak in symptoms during middle age followed by a decrease?

Being able to answer these, and other questions, will improve the treatment for sleep impaired patients, as well as patients with severe nasal obstruction. It is of major importance that future research progresses as clinical cooperation between rhinologists, pulmonary doctors, and sleep physicians (in those countries where they exist), as well as many other specialists.

From the clinical side impaired nasal patency requires attention from all specialists working with sleep disturbances, and that doctors meeting with their patients with nasal obstruction should also focus on sleep disturbances.

Populärvetenskaplig sammanfattning

Bakgrund och material samt metoder

Allvarlig eller nästintill total nästäppa drabbar patienter med olika sjukdomstillstånd i sin näsa. Subjektiv nästäppa är en upplevelse hos patienten som kan undersökas genom frågeformulär. Objektiv nästäppa mäter man genom att undersöka näsan med tekniska hjälpmedel. I denna avhandling har en ljudvågsundersökning gjorts som speglar näsans inre mått (akustisk rinometri). Ett av de sjukdomstillstånd i näsan som kan påverka patienters livskvalitet i stor utsträckning är polypsjukdom. Vid näspolyper kan dessa efter hand utfylla alla bihålor och hela näsan om de får växa utan någon behandling. En vanlig behandling är kortison som man sprayar i näsan och en annan är kirurgisk behandling. Nästäppa i samband med allergisk sjukdom är en känd riskfaktor för dålig sömnkvalitet. Däremot är det outforskat om polyper i näsan påverkar sömnen och vad som händer med sömnen när man genomgått en operation av näspolyperna. Detta var bakgrunden till att delarbete II gjordes.

Under sömn kan luftvägen stängas igen genom att underkäken faller bakåt, nedåt och då blockeras luftvägen helt eller delvis genom att tungan och den mjuka gommen ligger an mot den bakre väggen i svalget. Bröstkorgens muskler fortsätter att jobba för att få in luft i den sovande personen. Det är vanligt att friska personer har något enstaka andningsuppehåll varje natt. Om man har upprepade andningsuppehåll (så kallade apnéer) som varar mer än 10 sekunder kallas detta för obstruktiv sömnapné (OSA). Dessa patienter har ofta nedsatt livskvalitet, ökad risk för hjärtkärlsjukdom och en del patienter lider av svår dagtrötthet. Den vanligaste behandlingen är PAP (Positive airway pressure). Den mest kända undergruppen är CPAP (Continuous positive airway pressure) som ger ett konstant flöde av luft genom en mask över ansiktet in i patienten. Många varianter av PAP finns nu där luftflödet under utandningen anpassas efter patientens utandning och alla dessa andningsmaskiner går under benämningen PAP. Det finns också ett antal masker som antingen täcker bara näsan eller även munnen.

Patienter som både har andningsuppehåll under sömn och svårt att andas genom näsan är dåligt undersökta i den vetenskapliga litteraturen. OSA-patienter beskriver ibland nästäppa som orsak till sömnstörning. Om detta beror på objektivt försämrad näsandning eller subjektiv upplevelse var oklart innan projektet startades men är viktigt för förståelsen av sjukdomen och dess behandling. Det har funnits en klinisk

föreställning om att välfungerande näsandning är viktigt för att man skall använda sin PAP-behandling så mycket som krävs för att minska andningsuppehållen. Äldre studier antyder att PAP ger ökad nästäppa. Vårt projekt avsåg att bättre kartlägga den täppta näsans betydelse för OSA och sömn- och livskvalitet samt hur kirurgi och PAP kunde påverka detta. Om man i framtiden kan öka PAP-patienters behandlingsföljsamhet genom en utvidgad kunskap om näsans roll i OSA och behandling kan detta vara av stor vikt.

När projektet startades frågade vi oss vilken påverkan nästäppa har på sömnstörningar? Vår hypotes var att nedsatt näsandning har betydelse för sömnstörningar. Vi undrade också: Hur stor andel av patienterna med OSA har nästäppa och hur påverkas de av nästäppan? Hur mår patienter med sömnapné och snarkning som genomgick operation för andningsuppehåll och snarkningar (så kallad UPPP, Uvulopalatopharyngoplastik) 19 till 25 år efter operationen? Kan grav nästäppa i form av polypsjukdom i näsan ge sömnstörningar och påverka sömnkvaliteten? Vad händer med sömnen efter en operation av polyperna? Vad betyder näsandningen för patienter med sömnapné? Hur påverkar PAP näsan och hur förändras näsan subjektivt och objektivt efter två år av PAP-behandling?

Projektet består av fyra delar. I första studien studerades effekt av sömnapné-kirurgi (UPPP) efter 19–25 år hos 129 patienter (I). I andra delen undersöktes 42 patienter före och efter näspolypkirurgi (II). I tredje och fjärde arbetet studerades 810 OSA-patienter som genomgått nattlig aningsregistrering innan start av behandling, samt akustisk rinometri och frågeformulär före och 2 år efter start av PAP (III och IV).

Resultat

Vi fann i studie I och III att 32–35% av patienterna med OSA har besvärande nästäppa. Patienter med näspolyper led av försämrad sömnkvalitet vilken förbättrades av kirurgi (II). OSA patienter med nästäppa upplevde mer dagtrötthet, mer sömnsvårigheter (så kallad insomni) och nedsatt livskvalitet jämfört med patienter utan nästäppa. Efter två år med PAP behandling hade de små inre näs-areorna ökat i storlek och patienterna upplevde mindre nattlig nästäppa (III och IV). Patienter som hade små inre näsvolymer hade större sannolikhet att inte använda sin PAP i den utsträckning som krävs för att bli av med sina apnéer.

Konklusion

Avhandlingen visar att obstruerad näsandning är vanlig vid OSA och att svårighet att andas genom näsan påverkar sömn- och livskvaliteten. Vidare visar avhandlingen att patienter blir bättre både avseende subjektiv och objektiv nästäppa två år efter start av PAP behandling samt att liten näsvolym vid startpunkten för behandlingen kunde förutsäga en låg användandegrad av PAP-behandlingen. En konklusion som är användbar i sjukvården är att subjektiv nästäppa vid OSA kan förbättras om man

använder PAP och att patienter med objektiv nästäppa möjligtvis skall erbjudas kirurgisk behandling innan start med PAP. Vi kan konstatera att i motsats till vad de flesta inom sömnforskningen hittills trott så ger inte PAP behandling någon uttalad subjektiv eller objektiv nästäppa om patienterna fortsätter under en längre tid med behandlingen. Detta är viktig information till patienter som startar med PAP behandling pga. OSA.

"Think in the morning.
Act in the noon.
Eat in the evening.
Sleep in the night."

William Blake

Acknowledgement

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Appendix

Questionnaires

SAGIC including Berlin questionnaire, BNSQ, ESS, and MAP

Frågeformulär om sömn **Patientnummer……..**

Tack för att du tar dig tid att fylla i detta frågeformulär!

INSTRUKTIONER:

1. Om du är osäker på hur du ska svara på en eller flera frågor så lämnar du dem obesvarade.

2. Det går bra att fylla i frågeformuläret tillsammans med någon, t.ex. din partner, en släkting eller vän.

All information behandlas strikt konfidentiellt och kommer att användas för godkända forskningsändamål.

A. Frågor om sömnvanor (Omarbetad version av BNSQ)

Först några frågor om hur dags du oftast har gått och lagt dig och stigit upp den senaste månaden, både arbetsdagar och lediga dagar. Skriv tidpunkten (t.ex. 23.30) eller skriv ett X om tidpunkten varierar väldigt mycket mellan olika dagar.

1. Hur dags brukar du gå och lägga dig för att sova? Arbetsdagar..... Lediga dagar.....

2. Hur dags brukar du vakna efter vanlig sömn? Arbetsdagar.....Lediga dagar.....

3. Hur lång tid brukar det ta innan du somnar efter att du har släckt lampan? Timmar.....minuter.....

4. Hur många gånger brukar du vakna per natt? Aldrig eller mindre än 1 gång/natt 1–2 gånger/natt 3–5 gånger/natt Mer än 5 gånger/natt

5. Om du vaknar på natten, hur lång tid **sammanlagt** är du då vaken? Timmar.....minuter.....

6. Hur många timmars sömn sover du i genomsnitt/natt? Timmar.....minuter.....

7. Hur nöjd/missnöjd är du med ditt sömnmönster?

0 = mycket nöjd 1 2 3 4 = mycket missnöjd

8. Hur mycket sömn anser du att du behöver? Timmar ..... minuter.....

9. Hur dags vill du helst somna? Klockan .....

10. Hur dags vill du helst vakna? Klockan .....

11. Hur lätt är det för dig att vakna i tid för skola, arbete eller andra aktiviteter?

Lätt (jag vaknar av mig själv)

Måttligt (behöver väckarklocka för att vakna)

Svårt (jag är beroende av att någon annan väcker mig)

Mycket svårt (ibland vaknar jag inte trots att jag har väckarklocka eller någon som försöker väcka mig)

12. Hur ofta tar du en tupplur eller slumrar till?

..... Gång(er) / dag ..... gång(er)/ vecka ..... gång(er) / månad ..... gång(er) / år Aldrig

Om du tar tupplurar eller slumrar till:

a. Sammanlagt hur många timmar och/eller minuter sover du vanligtvis/dag? Timmar ..... minuter.....

B. Frågor om snarkning, andningsuppehåll och trötthet (Berlin questionnaire)

1. Snarkar du? Nej Ja Vet ej

Om du snarkar:

a. Dina snarkningar är Lite ljudligare än andetag Lika ljudlig som att prata Ljudligare än att prata Mycket ljudlig (kan höras i rummet intill) Vet ej

b. Hur ofta snarkar du? I stort sett varje natt 3–4 gånger i veckan 1–2 gånger i veckan 1–2 gånger i månaden Aldrig eller nästan aldrig Vet ej

c. Har din snarkning stört andra någon gång? Nej Ja Vet ej

d. Har någon annan märkt att du har slutat andas under sömnen? I stort sett varje natt 3–4 gånger i veckan 1–2 gånger i veckan 1–2 gånger i månaden Aldrig eller nästan aldrig Vet ej

2. Hur ofta känner du dig trött eller sömnig när du har sovit? I stort sett varje dag 3–4 gånger i veckan 1–2 gånger i veckan 1–2 gånger i månaden Aldrig eller nästan aldrig

3. Känner du dig trött, sömnig eller ur form under din vakna tid? I stort sett varje dag 3–4 gånger i veckan 1–2 gånger i veckan 1–2 gånger i månaden Aldrig eller nästan aldrig

4. Har du någonsin slumrat till eller somnat bakom ratten? Nej Ja

Om ja, Hur ofta händer det? I stort sett varje dag 3–4 gånger i veckan 1–2 gånger i veckan 1–2 gånger i månaden Aldrig eller nästan aldrig

5. Under den senaste månaden, hur många gånger per vecka har någon påpekat något av följande om dig *(kryssa bara i en ruta per fråga)*? (**MAP**)

		Aldrig	Sällan	Ibland	Ofta	Alltid	Vet ej
			Mindre än 1 gång i veckan	1–2 gånger i veckan	3–4 gånger i veckan	5–7 gånger i veckan	
a	Ljudliga snarkningar						
b	Snarkningar eller att du kippar efter andan						
c	Andningsuppehåll eller att du kämpar för att få luft						

C. Frågor om tidigare sömnundersökningar och behandling

1. Har du deltagit i någon sömnundersökning under en hel natt? Nej Ja, vilket år? .....

2. Har du någonsin blivit diagnostiserad med sömnapné i en sömnundersökning? Nej Ja

Om ja,

a. Har du genomgått kirurgi i svalget (dvs. tonsillektomi, laser eller liknande) pga. din sömnapné? Nej Ja

b. Är du idag nöjd med resultatet av snarkoperationen? Ja Nej

c. -om Nej, är det på grund av utebliven effekt? Ja Nej

d. -om Nej, är det på grund av kvarstående besvär? Ja Nej

e. -om Nej, berodde det på förhållanden vid själva operationen? Ja Nej

f. -Annan orsak till att Du inte är nöjd med resultatet av snarkoperationen, i så fall vad?

……

g. Om du haft den samlade erfarenheten av operation, biverkningar och effekt Du har idag då Du blev opererad, skulle Du då velat genomgå operationen? Ja Nej

h. Har du behandlats för sömnapné med något av följande? CPAP-maskin snarkskena (Mandibelframdragande tandställning) Annat

i. Behandlas du för närvarande för sömnapné med något av följande? CPAP-maskin snarkskena (Mandibelframdragande tandställning) Annat

Om ja,

j. Hur lång tid/natt använder du hjälpmedlet? Timmar.....minuter.....

D. Frågor om dagtrötthet (ESS)

1. **Den senaste månaden:** Hur troligt är det att du skulle slumra till eller somna i följande situationer, i motsats till att bara känna dig trött? Detta avser din normala livsstil den senaste tiden. Försök att fundera ut hur de olika situationerna skulle ha påverkat dig även om du inte har upplevt alla nyligen.

	Situation	Skulle aldrig slumra till	Liten risk att slumra till	Måttlig risk att slumra till	Stor risk att slumra till
a.	Sitta och läsa				
b.	Titta på TV				
c.	Sitta overksam bland andra människor (t.ex. på teater eller i möte)				
d.	Vara passagerare i en bil i en timme utan rast				
e.	Ligga ner och vila på eftermiddagen om det är möjligt				
f.	Sitta och prata med någon				
g.	Sitta still efter en lunch utan alkohol				
h.	Sitta i en bilkö som står stilla ett par minuter				

E. Frågor om symtom

Svara på följande frågor baserat på hur det har varit den senaste månaden.

		Aldrig	Sällan Mindre än en gång i veckan	Ibland 1–2 gånger i veckan	Ofta 3–4 gånger i veckan	Alltid 5–7 gånger i veckan	Vet ej
1.	Jag vaknar med huvudvärk						
2.	Jag är torr i munnen när jag vaknar						
3.	Jag vaknar pga. värmevallningar						
4.	Jag svettas mycket på natten						
5.	Jag kastar mig mycket av och an under natten						
6.	Jag svettas mycket på dagen						
7.	Jag får halsbränna i liggande ställning						
8.	Jag får halsbränna under dagen						
9.	Jag somnar ofrivilligt under dagen, t.ex. när jag tar en paus i arbetet						
10.	Jag känner mig mycket sömnig under dagen, t.ex. när jag sitter framför datorn						

N. Frågor om riskfaktorer och sjukdomar

1. Har du någonsin rökt cigaretter? Nej Ja (”nej” innebär mindre än 20 paket i hela livet eller mindre än 1 cigarett per dag i ett år)

Om ja,

b. Hur många cigaretter per dag har du i genomsnitt rökt under hela den tid som du har rökt?.....

2. Under en genomsnittlig vecka det senaste året, hur många dagar drack du en alkoholhaltig dryck?.....dagar/vecka

3. De dagar du drack alkohol, ungefär hur många standardglas (33cl starköl eller 1 glas vin) alkohol drack du?.....standardglas/dag

4. Har du någonsin fått diagnosen högt blodtryck av en läkare? Nej Ja Vet ej (questionnaire)

Om ja,

a. Tar du för närvarande blodtryckssänkande medicin? Nej Ja

5. Har du eller har haft luftvägssjukdom (astma, bronkit, KOL eller liknande)? Nej Ja Vet ej

6. Har du eller har haft hjärtsjukdom (infarkt, kärlkramp, hjärtsvikt)? Nej Ja Vet ej

7. Har du eller har haft blodpropp (cirkulationsrubbning i hjärnan)? Nej Ja Vet ej

8. Har du diabetes? Nej Ja Vet ej

9. Annan kronisk sjukdom?.....

10. Har du blivit opererad i din näsa? Nej Ja

a. om ja vilken operation?

11. Har du nattlig nästäppa? Nej Ja

12. Har du genomgått någon annan operation?

13. Har du pollenallergi? Nej Ja Vet ej

14. Annan allergi? …….

O. Bakgrundsinformation

1. Kön: Man Kvinna 2. Yrke:.....

3. Hur lever du? Ensam Med make/maka eller partner Med andra familjemedlemmar Annat

4. Har du fått hjälp av någon för att fylla i det här frågeformuläret? Nej Ja **Om ja,** av

Person jag delar sovrum med Person som bor i samma hus/lägenhet men i ett annat sovrum Person som bor på i annat hus, men som har observerat mig sova Person som bor på i annat hus, och som inte har observerat mig sova Stort tack för din medverkan!!

SNOT-22

SINO-NASAL OUTCOME TEST (SNOT-22) Här är en lista över möjliga symptom, funktionsnedsättningar eller känslomässiga följder av dina näs- och bihålebesvär. Vi ber dig att skatta besvärsgraden enligt nedan:

Gradering av besvär

0 = inga besvär, 1 = minimala besvär, 2 = lindriga besvär, 3 = måttliga besvär, 4 = uttalade besvär, 5 = värsta tänkbara besvär

Hur mycket har du besvärats av vart och ett av följande problem från näsan/bihålorna under **de senaste två veckorna**? Ringa in ett alternativ för varje rad.

Besvär	Besvärsgrad					
Behov av att snyta näsan	0	1	2	3	4	5
Nysningar	0	1	2	3	4	5
Rinnande näsa	0	1	2	3	4	5
Nästäppa	0	1	2	3	4	5
Förlust av lukt eller smak	0	1	2	3	4	5
Hosta	0	1	2	3	4	5
Baksnuva (slem i halsen)	0	1	2	3	4	5
Tjock snuva	0	1	2	3	4	5
Lockkänsla i örat	0	1	2	3	4	5
Yrsel/ostadighet	0	1	2	3	4	5
Öronsmärta	0	1	2	3	4	5
Smärta/tryck i ansiktet	0	1	2	3	4	5
Svårt att somna	0	1	2	3	4	5
Vaknar på natten	0	1	2	3	4	5
Sover dåligt	0	1	2	3	4	5
Vaknar trött	0	1	2	3	4	5
Trötthet/orkeslöshet/bristande energi	0	1	2	3	4	5
Nedsatt prestationsförmåga	0	1	2	3	4	5
Minskad koncentrationsförmåga	0	1	2	3	4	5
Känsla av frustration, rastlöshet eller irritation	0	1	2	3	4	5
Ledsen/sorgsen	0	1	2	3	4	5
Besvärad/generad pga dina näs- bihålebesvär	0	1	2	3	4	5

Tack för att du har tagit dig tid att svara. Tveka inte att höra av dig om du tycker något är oklart.

Svensk version SNOT-22; Pernilla Sahlstrand Johnson, Lunds Universitet, Malmö

UPPP questionnaire

Frågeformulär: Undersökning av patienter som opererats mot snarkning och andningsuppehåll för drygt 20 år sedan

Tacksam om Du vill besvara nedanstående frågor och notera det som bäst stämmer överens med Ditt nuvarande tillstånd. Din nuvarande vikt:……. kg Din nuvarande längd: …….. cm Vad arbetar du med?

Rökning: Röker Du? Ja ☐ Nej ☐

Alkohol: Hur ofta dricker Du alkohol (en 33 cl flaska starköl eller motsvarande)?

En gång i månaden eller mindre (aldrig) ☐ 2-4 gånger i månaden ☐ 2-3 gånger i veckan ☐ 4 gånger i veckan eller mer ☐

Sätt en ring runt det siffervärde som Du tycker bäst passar med hur Du själv har det.

	Aldrig		Sällan		Ibland		Ofta		Alltid			Vet ej
Har Du svårt att somna?	0	1	2	3	4	5	6	7	8	9	10	
Snarkar Du högt och störande?	0	1	2	3	4	5	6	7	8	9	10	☐
Har Du andningsstopp i sömnen?	0	1	2	3	4	5	6	7	8	9	10	☐
Svettas Du nattetid?	0	1	2	3	4	5	6	7	8	9	10	
Kissar Du mer än en gång varje natt?	0	1	2	3	4	5	6	7	8	9	10	
Vaknar Du upp med torr mun?	0	1	2	3	4	5	6	7	8	9	10	
Vaknar Du med huvudvärk?	0	1	2	3	4	5	6	7	8	9	10	

Hur troligt är det att Du skulle slumra till eller somna i följande situationer, till skillnad från att bara känna dig trött? Det avser ditt vanliga levnadsätt på senaste tiden. Även om Du inte gjort allt detta nyligen, så försök att komma på hur det skulle ha påverkat dig. Använd följande skala för att välja den lämpligaste siffran för varje situation.

0=skulle aldrig somna 1=liten risk att slumra, 2=måttlig risk att slumra, 3=stor risk att somna

Situation	Risk att slumra
Sitter och läser	
Tittar på TV	
Sitter overksam på allmän plats (t ex teater eller möte)	
Som passagerare i en bil en timme utan paus	
Ligger ner och vilar på eftermiddagen om omständigheterna tillåter	
Sitter och pratar med någon	
Sitter stilla efter att ha ätit lunch (utan alkohol)	

När brukar du somna?..... Vakna?.....Arbetar oregelbundna tider?.....

Använder Du eller har Du blivit ordinerad en så kallad CPAP-maskin (apparat mot andningsuppehåll på nätterna)? Ja ☐ Nej ☐

Har du kvarstående besvär efter Din snarkoperation? Ja ☐ Nej ☐

Om Ja, har Du:

-Besvär med att mat ibland kommer upp i näsan vid födointag? Ja ☐ Nej ☐

-Besvär med smärtor i halsen/svalget? Ja ☐ Nej ☐

-Besvärande muntorrhet? Ja ☐ Nej ☐

-Lättare eller svårare sväljningsbesvär? Ja ☐ Nej ☐

-Förändring av talet? Ja ☐ Nej ☐

--Andra besvär, i så fall vad?.....

Är du idag nöjd med resultatet av snarkoperationen? Ja ☐ Nej ☐

-om Nej, är det på grund av utebliven effekt? Ja ☐ Nej ☐

-om Nej, är det på grund av kvarstående besvär? Ja ☐ Nej ☐

-om Nej, berodde det på förhållanden vid själva operationen? Ja ☐ Nej ☐

-Annan orsak till att Du inte är nöjd med resultatet av snarkoperationen, i så fall vad?

……

Har Du genomgått operationer efter snarkoperationen? Ja ☐ Nej ☐

om ja, vilka operationer?.....

Har du besvärande nästäppa på dagen eller natten? Ja ☐ Nej ☐

Har Du eller har haft luftvägssjukdom (astma, bronkit eller liknande)? Ja ☐ Nej ☐

Har du eller har Du haft någon hjärtsjukdom? Ja ☐ Nej ☐

-om ja, vilken/vilka (t ex kärlkramp, hjärtinfarkt)?.....

Har du Diabetes? Ja ☐ Nej ☐

Har Du eller har haft förhöjda blodfetter? Ja ☐ Nej ☐

Har Du eller har haft förhöjt blodtryck? Ja ☐ Nej ☐

Har Du haft blodpropp (cirkulationsrubbning) i huvudet? Ja ☐ Nej ☐

Har Du någon annan kronisk sjukdom, i så fall vilken?.....

Tar Du mediciner mot högt blodtryck (t ex Metoprolol, Enalapril, Seloken)? Ja ☐ Nej ☐

Tar Du mediciner mot kärlkramp (t ex Imdur, Nitroglycerin)? Ja ☐ Nej ☐

Tar Du mediciner mot förhöjda blodfetter (t ex Simvastatin)? Ja ☐ Nej ☐

Tar Du mediciner mot diabetes? Ja ☐ Nej ☐

Tar Du blodförtunnande mediciner (t ex Trombyl, Waran)? Ja ☐ Nej ☐

Tar Du några andra mediciner? Ja ☐ Nej ☐

om ja, i så fall vilka?.....

Om du haft den samlade erfarenheten av operation, biverkningar och effekt Du har idag då Du blev opererad, skulle Du då velat genomgå operationen? Ja ☐ Nej ☐

Stort tack för Din medverkan!

Paper I

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Long-term follow-up of patients operated with Uvulopalatopharyngoplasty from 1985 to 1991

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KEYWORDS
AHI;
CPAP;
Obstructive sleep apnoea (OSA);
Side effects;
Snoring

Summary
Objectives: Short-term outcome and side effects after Uvulopalatopharyngoplasty (UPPP) are well recognized. However, there is a lack of knowledge of the long-term outcome and side effects after this surgery. This study was completed to investigate the outcome and side effects 20 years after UPPP for snoring and obstructive sleep apnoea.
Methods: Medical records of patients who underwent UPPP surgery for sleep apnoea and snoring between 1985 and 1991 were investigated retrospectively. A specific questionnaire focusing on the present health profile, side effects of previous UPPP surgery and present sleeping patterns of patients was mailed out.
Results: UPPP patients, 186 (including 11 females) were identified. Of these, 35 (19%) had passed away and 7 (4%) were not located. 129 patients (mean: age 68 years, range 43–83) of the possible 144 patients answered the questionnaire (response rate 90%). At follow-up, 41 patients (32%) used continuous positive airway pressure (CPAP). 66 of the patients (52%) were satisfied with the result of the operation, but 61 (47%) were not satisfied. 49 patients (38%) reported persistent side effects (problems with nasal regurgitation 18 (14%), swallowing 26 (20%), changed voice 15 (12%), and pain in the oral cavity 15 (12%).
Conclusion: Almost 50% of patients operated with UPPP were not satisfied with the result of the operation after about 20 years, and one third used CPAP at follow-up. A large proportion of patients still experienced side effects, which, after this time, are likely to be permanent.

Introduction

Obstructive sleep apnoea (OSA) is a disease with a severe impact on quality of life for the individual, also leading to drowsiness that can cause traffic accidents.[1] Different treatments for OSA have been tested over previous decades but no cure is available. Current recommended treatments are a mandibular retaining device (MRD) or continuous

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positive airway pressure (CPAP), the latter being the treatment of choice for patients with severe OSA.[2] Adherence to CPAP as treatment for OSA is an issue with adherence rates ranging from 30 to 60%.[3]

Different surgical methods have been tried. Ikematsu[4,5] first developed Uvulopalatopharyngoplasty (UPPP) in 1952 as a treatment of snoring and Fujita et al.[6] made the surgical method popular worldwide in 1981. The adverse effects following this treatment include nasal regurgitation, voice changes, taste disturbances, globus sensation, velopharyngeal insufficiency, oral pain, difficulties in swallowing, smell disturbances and mouth dryness.[7] It is however not known whether these side effects are permanent, as discussed by Aurora et al.[8]

During the period that we have studied (1985–1991), UPPP at our hospital was performed as described by Fujita et al.[6] A phoniatric investigation was done prior to surgery to evaluate how much of the soft palate could be removed without damaging *m. pharyngopalatinus*. Cold knife was used in all but eleven patients where laser surgery was performed. The operation included conventional tonsillectomy, total removal of the uvula and reduction of the soft palate. Finally the anterior and posterior tonsil pillars were stitched together. Fifteen different ENT surgeons from the professor to the most junior resident performed the operations.

The aim of the present study was to investigate the current status of patients 19–25 years after UPPP surgery performed between 1985 and 1991. We focussed on patient satisfaction, their current health profile and side effects resulting from the previous UPPP. We also assessed if patients were present users of CPAP and reported snoring or sleep apnoea.

The study was approved by the Ethics Committee at the University of Lund (Dnr 2010/519).

Methods

Patients

The operating room listings from August 1985 to May 1991 at the ENT Department in Lund were reviewed manually. 186 consecutive patients who had UPPP surgery were included and records of 179 of them were retrieved through the national ID register (Fig. 1). The patients who were still alive and located received a study-designed questionnaire by mail. Pre- and postoperative data of the patients who agreed to participate were collected from the medical records. The questionnaires were mailed out a maximum of three times.

Questionnaires

The mailed out questionnaire focused on the following issues:

- Weight, height
- Satisfaction with the operation
- Present side effects
- Whether they would have chosen to take the operation with the information available today

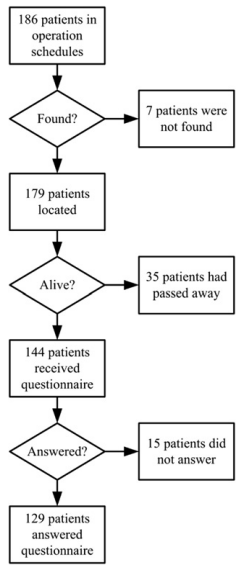


Figure 1 A schematic outline of how the patients were recruited. 129 Patients returned the questionnaires after two reminders.

- Subjective assessment of sleep pattern: snoring, apnoea, daytime drowsiness and use of CPAP
- Other diseases and medication

Sleep recordings

One sleep recording was completed before and a second recording about 3 months after surgery. These recordings were performed at dept. of clinical neurophysiology, Lund University Hospital. The recordings were often done in daytime after a full night of sleep deprivation. The patient arrived at the clinic in the morning and the recording was usually completed with polysomnographic registration. Occasionally the multiple sleep latency test (MSLT) was employed, a method used primarily to diagnose narcolepsy.[9] Some patients underwent full night polysomnography. In a number of patients one method of recording was used prior to surgery and another method was used after surgery.

Characteristics of the dropout group

Seven patients were not found in the National ID register and were not included. Another 35 patients had passed away and their medical records were not analysed. 15 patients did not answer the questionnaires despite two reminders. Pre- and postoperative data were not registered for any of these patients. Thus, in total, 129 of 186 patients were analysed.

Statistics

Values are given as mean ± sem. Non-parametric statistics were used to compare the different groups. The Wilcoxon signed rank (WSR) test for paired groups was used for the comparison of BMI (body mass index) at the time of surgery and at follow-up. A p-value < 0.05 was considered significant. The Chi-square test was used to analyse BMI and satisfaction. The patients were divided in two groups with respect to BMI (low BMI ≤ 29.9, and high BMI ≥ 30). Age was defined as low if it was less than 68 years (=mean age at follow-up) and high if over 68 years. The statistical program used was PAST.[10]

Results

Patient files

In total, 186 patients (including 11 females) were identified as having undergone UPPP during the period from 1985 to 1991 (Fig. 1). Seven could not be located and 35 patients had passed away. Hence, 129 out of 144 possible patients answered the questionnaires (response rate of 90%). Three patient records from the operation could not be found and three patients were not sleep registered prior to the operation. These patients answered the questionnaire and were included in the follow-up data. Mean BMI for the patients increased from 27.7 (range 19.6–41.2) at the time of operation to 29.5 (20.2–42.7) at follow-up ($p < 0.001$). The diagnoses of the patients are shown in Table 1.

Questionnaire

At follow-up, 41 patients (32%) were using CPAP and 88 patients (69%) were non-CPAP users. It was assumed that current CPAP users probably had a more pronounced OSA. Hence these patients were analysed as a separate group concerning satisfaction, self reported symptoms and if the patients would have chosen the operation over again.

Patient satisfaction with surgery is shown in Table 2. Sixty seven percent of the non-CPAP users were content with UPPP compared to 17% in CPAP users. Eleven patients were operated with laser. Six of these patients were satisfied and 5 were not (NS: chi-square test).

Table 1 Basic data of the patients (n: 129) at the time of surgery and at follow-up. Age and BMI are given as mean and range.

	At the time of surgery	2010
Age	47.4 years (19–70)	68.0 years (43–83)
BMI	27.7 (19.6–41.2)	29.5 (20.2–42.7)
Obstructive apnoea	99 (77%)	–
Central apnoea	5 (4%)	–
Mixed apnoea	14 (11%)	–
Snoring	11 (9%)	–
CPAP	0	41 (32%)

Table 2 Satisfaction with previous UPPP for all patients, separated into patients with and without CPAP.

Satisfied	All patients		CPAP users		Non-CPAP users	
Yes	66	51%	7	17%	59	67%
No	61	47%	34	83%	27	31%
No answer	2	2%	0	0%	2	2%
Total	129		41		88	

Factors putatively associated with contentment with UPPP surgery were investigated (BMI, side effects, snoring and age). In non-CPAP users there was no difference between those with low BMI (<29.9) and those with high BMI (>30) ($P = 0.9$: chi-square test).

As seen in Table 3 a larger proportion were satisfied with the operation when they did not experience any side effects. The largest group was those who were satisfied and had no side effects. In the non-CPAP users 20 (24%) reported lack of effect of surgery as reason for dissatisfaction.

Self reported symptoms in non-CPAP users were sleep apnoea in 11 patients (13%), snoring in 18 patients (20%) and 8 patients (9%) reported falling asleep while reading. Among the snorers 12 patients (55%) were satisfied with the results of the surgery. Eleven patients (13%) reported apnoea and of those, 46% were satisfied with the result. Nine patients reported both snoring and apnoea often or always. In total, 20 patients reported snoring and/or apnoea frequently or constantly. In the group that reported no snoring and no apnoea, 47 patients (69%) reported that they were satisfied with the result of surgery.

Among those without CPAP, we found that age at follow-up was not significantly related to satisfaction with UPPP (chi-square test).

As seen in Fig. 2, 49 (38%) of all patients reported side effects related to the operation (Fig. 2). Mouth dryness was reported by 37% of the patients, but since there can be multiple reasons for this symptom, the question was withdrawn from the analysis. Apart from mouth dryness, difficulty in swallowing was the most frequently reported side effect.

Patients were asked if they would have chosen the operation now with all the information about the operation they had at the time of follow-up (Figs. 3 and 4). As seen in Fig. 3, 53% of all patients would have chosen UPPP again. Answers to this question differed between CPAP users and non-CPAP users, where non-CPAP users were more likely to choose surgery again ($P < 0.0001$, chi-square test) (Fig. 4).

Table 3 Satisfaction and dissatisfaction in the group of non-CPAP users separated into those with and without remaining side effects.

Satisfied	No side effects		Remaining side effects		No answer	
Yes	33	38%	23	26%	2	2%
No	17	10%	10	11%	–	–
No answer	2	2%	–	–	–	–

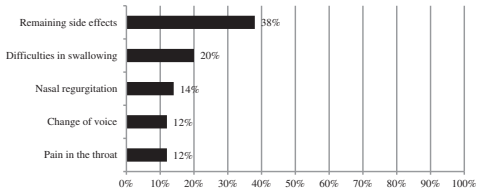


Figure 2 Reported side effects 19–25 years after UPPP surgery in percentage of all patients (*n*: 129). Remaining side effects include all patients who reported any kind of side effect (except mouth dryness which is excluded).

The entire group of patients reported 7 h and 35 min of sleep per night and the result was similar for the non-CPAP users and CPAP users (7 h 30 min). Nasal obstruction was reported equally by the non-CPAP and the CPAP users (both 32%).

In all of the patients, hypertension was reported by 56%, ischemic heart disease (35%), diabetes mellitus type II (23%), asthma/COPD (18%), and cerebrovascular insult (CVI) in 6% of the patients.

Discussion

The aim of this study was to investigate the long-term outcome and side effects of UPPP surgery in a cohort of patients who received the surgery at the ENT Department in Lund from June 1985 to September 1991. Of those who were still alive and could be retrieved from the national ID register a response rate of nearly 90% was achieved. This response rate is high compared to other mailed out questionnaires, where the response rates in general are about 60%.[11]

Patients seemed to be motivated to give their view of life after the operation. Many patients wrote extra notes in the margin. Some described unpleasant experiences around the operation and others described how the operation made them less tired. This kind of surgery is an important event in the lives of patients, as evidenced by their vivid memories after so many years.

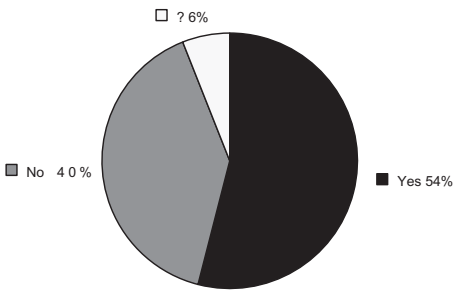
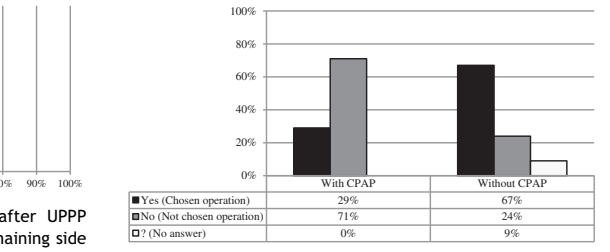


Figure 3 Response rate in percentage of all patients (*n*: 129) to the question: "Would you have chosen the operation with the information you have available today?"



	With CPAP	Without CPAP
Yes (Chosen operation)	29%	67%
No (Not chosen operation)	71%	24%
? (No answer)	0%	9%

Figure 4 Response rate in percentage of all 129 patients to the question: "Would you have chosen the operation with the information you have available today?" Separated into patients with and without CPAP.

It could be argued that a follow-up of surgery should have been planned when the UPPP-technique was introduced, but this was not the case. Therefore this study had to be done retrospectively. Moreover, the outcome of the surgery would have been easier to evaluate if the sleep recordings had been done in a standardised way before, after and at follow-up. Again, this was not the case. It is also difficult to assess if the patients would have received the same diagnosis with sleep recordings at follow-up in 2010. Due to shortage of resources it was not possible to do sleep recordings at follow-up.

UPPP has been debated for a number of years, and when the first patients in this study were subjected to the operation, the ENT surgeons were not aware that CPAP was a new treatment option for OSAS,[12] and therefore patients with snoring and OSA were all offered UPPP. Today, a majority of these patients would have been offered CPAP or the mandibular retaining device. In this study these patients had however not been prescribed CPAP. UPPP is currently only performed in selected patients when other treatments have failed.

It could be assumed that the patients in the present study who were not using CPAP suffered less from their OSA and almost 70% of them were satisfied with the result of the operation. Not surprisingly patients were also more likely to be satisfied with the result of surgery if they were not suffering from side effects. Almost 40% of the non-CPAP users were satisfied with the result of the operation and were not suffering from side effects. This is probably the group of patients who can benefit from UPPP but the challenge is to select them prior to surgery. BMI is sometimes used to help in the selection. There are diverging results on whether BMI influences the outcome of UPPP. Larsson et al.[13] showed that those with a lower BMI had better results in the lowering of AHI than those with a higher BMI. On the other hand, Lundkvist et al.[14] found no correlation between BMI and lowering of the apnoea/hyponoea index (AHI). In the present study we found no difference in satisfaction between patients with BMI <30 and the patients with BMI >30. Age was not related to satisfaction rate in this study and is not according to these data, helpful in the selection of candidates for UPPP. So far, factors to predict who will benefit from an operation are not recognized. Hence, it is difficult to select patients for this kind of surgery.

Obviously, patients with CPAP were less satisfied with the results of the operation. Almost 80% of the patients with CPAP would not undergo the operation again, compared to patients without CPAP where almost 70% would have chosen to take the operation again. It seems likely to assume that those with a more severe form of sleep apnoea were now using CPAP and then experienced a much better effect from that treatment than from the surgery.

Our results are in harmony with previous results, despite newer results from Browaldh et al.[15] who reported more satisfied patients at a shorter follow-up. In that study however, all patients who did not answer the question of satisfaction were excluded. We have included all patients and reported those who did not answer as well, which gives us a lower rate of satisfaction. Satisfaction with UPPP surgery varies in different studies. Röösli et al.[16] in 2006 reported a satisfaction rate of 73% with a median follow-up time of around six years and they found complications in 23% of patients. Pirsig and Verse[17] reviewed long-term satisfaction rates (up to three years after surgery) and they found that it varied between 31 and 74%.

There is a need for outcome analysis of different surgical methods. For instance a Meta analysis of several studies concerning septoplasty only 13 of more than 700 hundred fulfilled the criteria for eligibility.[18] For many surgical procedures we still don't know the long-term results. Bergler et al.[19] showed that in septoplasty after 12 months, 83% stated better nasal flow and 95% were willing to undergo the same operation again. This differs to a 10-year follow-up study after septoplasty where more than 40% were dissatisfied with the surgical result.[20] We think that these observations demonstrate that there is a difference in surgical outcome, when the evaluation is done quite close to the surgical procedure compared to an evaluation after a longer period of time. Tonsillectomy seems to have a high success rate and a high satisfaction rate and more than 90% of subjects are satisfied.[21] In general it is hard to assess which percentage of contentment after surgery that could be considered acceptable. Probably the doctor has a different view of success rate than the individual patient. Still, we consider that 50% contentment with surgery at long time follow-up is meagre and not very satisfying.

In our study, almost 40% of the patients still experienced side effects after 19–25 years. Hence, these adverse consequences from the operation could be considered permanent. Our result is in harmony with the results from other studies that have been reviewed by Franklin et al.[7] who found a similar percentage of side effects (42–62%) 5–7 years after surgery. Nowadays the operation is performed with less radical surgery and the uvula is never completely removed.[22] The reason for this change is probably due to the fact that the radical operation generated a high incidence of side effects, as shown here (compared to Lundkvist et al.[13]). Whether the previous more radical operation was more effective than the present less radical one is not known, since no studies have compared these methods.

This is probably the last chance to undertake a 20-year follow-up study of more than 100 patients operated in the 1980's. The majority of the patients were still alive and it seems less likely that it is possible to do a longer follow-up study.

Conclusion

In conclusion almost 50% of patients operated with UPPP were not satisfied with the result of the surgery. We have found that side effects after UPPP surgery are long lasting and permanent in a large proportion of patients. Many of the patients who underwent surgery now use CPAP.

Conflict of interest

None of the authors have any conflicts of interest.

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Paper II

Sleep quality improves with endoscopic sinus surgery in patients with chronic rhinosinusitis and nasal polyposis*

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Abstract

Background: Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP) is a chronic disease that has a major impact on generic and disease-specific quality of life. Little is known about the influence of CRSwNP on sleep and what effect surgery for CRSwNP has on sleep quality. The aim of the study was to investigate sleep quality in patients with CRSwNP before and after endoscopic surgery.

Methodology: Forty-two patients filled out four validated sleep questionnaires and one sino/nasal, disease specific quality of life questionnaire before surgery and three months later. A healthy control group filled out the same questionnaires at baseline and after three months.

Results: An impact on sleep patterns was found in all sleep questionnaires and surgery clearly improved the quality of sleep. The Sino-nasal outcome test sum score decreased from median 51,5 to 26,5. Epworth sleepiness scale showed a decline in score from score 7.5 to 6.0. Surgery also reduced the risk for obstructive sleep apnoea in 13 patients evaluated by the Berlin Questionnaire and Multivariable Apnea Prediction Index.

Conclusions: Patients with CRSwNP had impaired sleep quality, daytime sleepiness, nasal patency, and risk for sleep apnea, all of which improved after corrective surgery.

Key words: nasal mucosa, nasal surgical procedures, quality of life, respiratory tract diseases, sinusitis

Introduction

Chronic rhinosinusitis with nasal polyposis (CRSwNP) or without nasal polyposis (CRSsNP) are chronic diseases of poorly understood aetiology. These diseases are associated with other airway diseases and it has been well documented that the daily life of these patients is often severely impaired [(1)]. According to EPOS 2012 (European position paper on rhinosinusitis and nasal polyps 2012), a global evaluation of patients with CRSwNP should include symptom assessment, endoscopic examination, CT scan, and quality of life (QoL) evaluation. Several questionnaires have been developed for this purpose, including the Rhinosinusitis Disability Index (RDI) [(2)] and Sino-nasal Outcome Test (SNOT-22) [(3,4)]. However, RDI focuses mainly on daytime symptoms such as breathing through the nose. Nighttime symptoms and the consequences of a blocked nose and disturbed sleep have not been investigated thoroughly in this patient group [(5)]. Interestingly, even Hippocrates [(6)] observed that nasal polyposis was associated with restless sleep, but few studies today have focused on nighttime problems and associated daytime symptoms in patients with nasal polyposis. Hence, there is a lack of knowledge

Abbreviations: BNSQ (Basic Nordic Sleep Questionnaire), BQ (Berlin questionnaire), CRSwNP (Chronic rhinosinusitis with nasal polyps), CRSsNP (Chronic rhinosinusitis without nasal polyps), ESS (Epworth Sleepiness Scale), FESS (functional endoscopic sinus surgery), IQR (inter quartile range), MAP (Multivariable Apnea Prediction) Index, MD (median), OR (odds ratio), OSA (obstructive sleep apnoea), SAGIC (Sleep Apnea Genetics International Consortium), SDB (sleep disordered breathing), SNOT-22 (Sino-nasal outcome test-22), QoLQ (Quality of Life Questionnaire)

of how CRSwNP affects sleep, and any association between CRSwNP and sleep apnoea.
The gold standard for investigating patients who may suffer from sleep disordered breathing (SDB), including obstructive sleep apnoea (OSA), is polysomnography [7]. It is, however, an expensive and time consuming task to complete in patients. Sleep questionnaires are therefore often used to evaluate whether patients suffer from sleep related symptoms, are at risk of developing OSA, and/or suffer from daytime sleepiness, even if it is not as reliable as polysomnography. Thus, different sleep questionnaires have been used to select patients who are at risk of developing OSA, to detect sleep related QoL, and also to reveal sleep related symptoms.
It has been demonstrated that treatment of CRSwNP with topical steroids, oral steroids, and nasal surgery improves daytime quality of life [1]. Whether surgery also improves nighttime symptoms, patients' sleep quality, and daytime symptoms related to poor sleep, has not been thoroughly studied. The aims of this study were to determine if patients with CRSwNP suffered from reduced quality of sleep compared to a healthy population in terms of snoring, and indirect symptoms of sleep apnoea. A further aim was to investigate whether functional endoscopic sinus surgery (FESS) improved any of these symptoms in an unselected group of patients with CRSwNP.

Materials and methods

Study outline

This was an open prospective study with patients who were selected for endoscopic surgery due to nasal polyposis from September of 2013 to April of 2014 at the Department of Otorhinolaryngology, Skåne University Hospital, Sweden.

Subjects

45 patients (12 females and 33 males) participated. All patients suffered from severe nasal polyposis with grade 2-3 polyposis according to the Lildholdt scale and were offered surgery [8,9]. Lildholdt grade 2 (moderate polyposis) is recognized by "medium sized polyps reaching between the upper and lower edges of the inferior turbinate". Grade 3 (severe polyposis) is recognized by "large polyps reaching below the lower edge of the inferior turbinate". Preoperatively, patients were asked to answer four different validated sleep questionnaires and one sino/nasal QoL questionnaire. All patients underwent preoperative endoscopic nasal examination for polyp grading and spirometry, as well as a CT-scan. Approximately three months after sugery, patients were re-examined with the same questionnaires and a second spirometry was performed. All patients gave oral and written informed consent. Patients' files were retrieved to secure medication, smoking status, and co-morbidities (hypertension, asthma and allergies).
Inclusion criteria included: being over 18 years of age; surgery planned for nasal polyposis; being able to understand instructions and questions in Swedish; and able to fill out forms without major help. Patients were not included if pregnant.
The recruitment was consecutive and only a few patients were missed for inclusion due to clinicians forgetting to include them. An additional three patients were planned to participate in the study, but one dropped out due to an unwillingness to undergo surgery, and two were delayed for surgery and could therefore not be included during the study period. Median time between baseline and follow up was 23 weeks (9-44 weeks).
To assess reliability, 37 healthy subjects were prospectively asked to fill out the questionnaires three months apart during the same period as the study was completed.

Questionnaires

The sino-nasal outcome test SNOT-22 item version is a validated disease specific quality of life questionnaire focusing on symptoms related to CRS+/-NP. The SNOT-20 was developed by Piccirillo et al. [3]. In 2009, Hopkins et al. added two questions about taste and smell [4]. The Swedish version of the SNOT-22 was first validated in 2011 [10]. Healthy subjects report in SNOT-22 a total score between 0 and 8 [11, 12].

The Sleep Apnea Genetics International Consortium (SAGIC) (http://www.med.upenn.edu/sleepctr/SAGIC.shtml) has developed a set of sleep questionnaires including the Epworth Sleepiness Scale (ESS) [13], the Basic Nordic Sleep Questionnaire (BNSQ) [14], the Berlin Questionnaire (BQ) [15], and the Multivariable Apnea Prediction (MAP) index [16]. The SAGIC group has made minor changes in the sleep questionnaires, as described below. This set of questionnaires was translated by a professional interpreter into Swedish, double checked by a medical doctor and re-translated into English by another professional interpreter according to standardized guidelines [17]. Again a medical doctor revised it. Questions about former surgery were included from a previous study by the authors [18].
The ESS, that aims to measure daytime sleepiness, was developed by Murray Johns in 1991 [13]. Subjects are asked to rate their probability of falling asleep on a scale from 0 to 3 for eight different situations that are encountered during daily living (maximum score 24). A number from 0 to 10 is considered normal, scores from 11-15 are indicative of mild to moderate daytime sleepiness, whereas scores higher than 15 indicate severe daytime sleepiness. Healthy controls who do not snore tend to have an average score of 6-7 [13,19,20].

The BNSQ surveys perception of usual sleep quality, sleep latency, number of awakenings per night, naps per day and symptoms of poor quality of sleep in the past three months [14]. The SAGIC BNSQ version also contains an additional question about being tired in front of the computer; and an additional

"Don't know" alternative has been added to all categorical items. Other categories are "Never", "Rarely: less than once a week", "Frequently: 3-4 times a week and "Always: 5-7 times a week". We also calculated BNSQ-symptoms as a sum.

The BQ [15] is a screening tool used for the identification of patients who may be at high risk of OSA. The index gives either 0 for no risk of OSA or 1 for risk of OSA. Healthy non-snorers have 0 risk. The questionnaire consists of 11 questions separated into 3 categories: episodes of snoring and cessation of breathing while sleeping; daytime sleepiness; and incidence of high blood pressure. When two or more categories are classified as positive, the patient is considered to be at high risk for OSA. The SAGIC version of the BQ has also added a "don't know" category to all items with categories of "yes" and "no". Moreover, the question "Do you have high blood pressure?" has been changed to "Did you ever get a diagnosis of hypertension from a doctor?" If yes, the categories are: "Are you on anti-hypertensive medication at the moment? No/Yes".
The MAP index [16] predicts OSA risk using demographic data and self-reported apnoea symptoms. Three frequency questions as well as gender, age, height and weight are used to produce a MAP index between 0 (low risk) and 1 (high risk). The three questions determine the frequency at which the patient experienced loud snoring, snoring or gasping, cessation of breathing, or struggling for breath in the last month. Together, the questions produce a score referred to as index 1. A cut-off point of indication for a sleep registration has been suggested by Maislin to be 0.5 [16]. This value has been shown to have a sensitivity of 0.88 and a specificity of 0.55 and a positive predictive value of 0.75. Bjornsdottir [21] has chosen 0.75 for cut off in a clinical population since 0.5 is more appropriate for use in a general population. Accordingly, we chose 0.75 to separate the patients into low risk and high risk of OSA, since our patients have disease in their upper airways and are at risk of developing OSA. Twenty-two patients answered all three MAP questions before and after surgery and these patients were used for the results within. No imputations were used in MAP.

Measurements and equipment
An electronic spirometer was used for spirometry assessment in a standing position (Micro lab 3300, Micromedial Ltd, Rochester, England). Patients were told to take a deep breath and blow out as hard as they could. Then one inhalation of a bronchodilator, Oxis® (Formoterol® 4.5 µg, AstraZeneca AB) was given and 15 minutes later a second assessment was made in the same way. Percentage of the expected value of forced expired volume in one second was used for analysis (FEV1). Patients who reported a doctor diagnosis of asthma/COPD and were on asthma/COPD medication were classified as suffering from asthma/COPD.

Polyp size assessments
CT-scans were completed in all patients prior to surgery and the size of the polyps graded according to the Lund-Mackay scoring system [22].

Surgery
Patients underwent endoscopic sinus surgery under general anesthesia according to our clinical routine. All patients were operated with microdebrider in day-care settings using intravenous anesthesia. Five different well-established ENT surgeons completed the surgeries; but the majority were done by one surgeon (MA). The surgeons were well informed about the study and gave written consent. Postoperatively, nasal packing was used for one to three days and nasal washings with saline for a restricted time was recommended. Oral corticosteroid treatment was given for a limited time up to three weeks according to the EPOS guidelines [1]. All patients were pre- and postoperatively treated with local corticosteroids as a routine treatment for nasal polyposis. No extra oral corticosteroids except for the initial postoperative treatment were given, and no other pharmacotherapy was changed between the two assessments.

Approval by the regional ethical committee at Lund University was granted for this study (Dnr 2013/491).

Data analysis and statistical procedures
Data on nominal levels were presented as frequencies and percentages. No decimals were used for the percentages. The Chi-squared test was used in comparisons between nominal data. In case of insufficient number of expected count; Fisher's exact test was used. Ordinal data were presented as the median and interquartile range (IQR). All values are given as median unless otherwise stated. Differences between groups were calculated by means of Mann-Whitney U test. Wilcoxon's Signed Rank test was used for comparisons over time. Spearman's rank correlation (r_s) was used when measuring associations. The BQ and the MAP Index were computed according to the manufacturer's instructions. For the other instruments, the variables were presented one by one or/and summarized to scores. The actual number of observations is given as ratios, as the number of patients who have given a certain answer/total number, and as the percent of the number who provided an answer to that specific question.
The binary logistic regression was completed with the enter method, i.e. all predictors were included in the calculations. Imputations: Missing data in any ordinal variable were replaced with the median data value given by each subgroup; the polyposis and the controls. The imputations were used when presenting and comparing group data. When presenting data regarding change of risk over time in BQ and MAP, non-imputed individual data were used.

Table 1. Characteristics of the study population separated into Asthma/COPD (Chronic obstructive pulmonary disease) and Non-asthma/COPD groups, as well as healthy controls. Values are given as median, min-max and percentage of the whole study group. Lund-Mackay CT-staging evaluation smoking prevalence, OSA (Obstructive Sleep Apnoea), and hypertension are presented in numbers and proportions of patients. In the female group, asthma was more common (9/12: 75%) than in the male group (15/30: 50%). Other abbreviations used: BMI (Body Mass Index) and CT (computed tomography).

Subjects	Asthma/ COPD	Non-Asthma/COPD	Controls	All patients
	N = 24 (57%)	N = 18 (43%)	N = 38	N = 42
Female (Male)	9 (15)	3 (15)	22 (16)	12 (30)
Age (years)	51 (31-76)	50 (28-71)	40 (28-65)	50 (28-76)
BMI	26.0 (19-35)	27.0 (19-31)	-	26.2 (19-35)
Smoker	2	4	8	6 (14%)
OSA	1	1	1	2 (5%)
Hypertension	8	2	2	10 (24%)
Lund-Mackay	17.5 (6-24)	13.5 (8-24)	-	15.5 (6-24)

In all analyses, SPSS 22.0 was used. A two-sided p-value <0.05 was considered significant in all calculations. P-values (significant or not) are presented for all comparisons.

Results

Baseline data

Forty-two patients participated (12 females and 30 males). Their ages ranged between 28 to 76 years (median: 50 years). Ten patients suffered from pollen allergy and all ten also reported other allergies (house dust mite, animal dander). Another 4 patients reported allergies other than pollen and in total, 14 patients reported an allergy of any kind. There were 34 patients living in a household with at least one other person. Patients' characteristics are described in Table 1, showing that patients who had a diagnosis of asthma/COPD were quite similar to the non-asthma/COPD in terms of age and BMI. In both groups, one patient had a diagnosis of obstructive sleep apnoea. Asthma was more common in females (9/12: 75%) than in males (15/30: 50%). Patients with asthma and/or COPD had a tendency towards a more severe polyposis compared to the non-asthma/COPD patients according to the CT staging (17.5 vs. 13.5, p=0.058).

SNOT-22 questionnaire

Questionnaire derived pre- and postoperative sum scores are presented in Table 2. The SNOT-22 sum score declined from 51,5 to 26,5. Single item analyses showed that 38 out of a total of 42 patients (91%) suffered from major problems with blocked nose, rated 4 (severe) or 5 (as bad as it can be) prior to surgery, while just five patients reported major problems with blocked nose (12%) after surgery. Before surgery, 23/40 (55%) patients reported major problems with "nose blowing" (score 4-5). After surgery, 5/30 (12%) patients reported major problems with nose blowing (score 4-5).

Table 2. Pre- and post operative median and interquartile range for SNOT- 22 (Sino Nasal Outcome Test-22), BNSQ (Basic Nordic Sleep Questionnaire), and ESS (Epworth Sleepiness Scale). There was a significant improvement in SNOT, ESS, and BNSQ three months after surgery. Significant values in bold.

Questionnaire	Pre Op	Post op	Difference	p-value
	Med (IQR)	Med (IQR)	Med (IQR)	
SNOT-22	51.5 (37)	26.5 (15)	**-18.0** (27)	**< 0.001**
ESS	7.5 (6)	6.0 (5)	**-1.0** (4)	**0.048**
BNSQ	11.0 (8)	8.0 (8)	**-2.0** (4)	**0.001**

Patients who reported major problems with sneezing (score 4-5) had a 12.90 higher OR of reporting "Lack of a good night's sleep" when compared to patients without sneezing (C.I. 95% 2.02-70.03, p=0.006). Sneezing was reported as a major problem in 14/29 (48%) patients before surgery and just 5/29 (17%) after surgery.

The question: "Lack of good night´s sleep" was scored as a major problem in 10/31 (32%) compared to 5/31(16%) after surgery (p<0.001). When looking at patients aged over 60 compared to less than 60 years, the younger patients scored higher (11/30, 63%) compared to older patients (2/11, 18%) with respect to "Lack of good night´s sleep".

A large proportion of the patients (17/38, 45%) reported severe nasal symptoms prior to surgery ("Need to blow nose", "Nasal blockage", "Sneezing", and "Runny nose" (score 4-5 in all four)). There was no significant correlation between CT-stages and the total SNOT-22 score rs=0.033, p=0.863.

Sleep questionnaires

In Table 2, the total scores for ESS and BNSQ are depicted as well as SNOT-22, as mentioned earlier. Total ESS scores decreased from 7.5 pts. to 6.0 pts. (p<0.05) after surgery. Three patients scored over 15 before surgery, a score considered as excessive daytime sleepiness. Twelve patients scored over 10. Eleven patients (24%) scored 7 or 8. Regarding symptoms of poor sleep quality; BNSQ symptoms were calculated as a total sum and demonstrated a similar and clear decrease from 11.0 pts. to 8.0 pts.

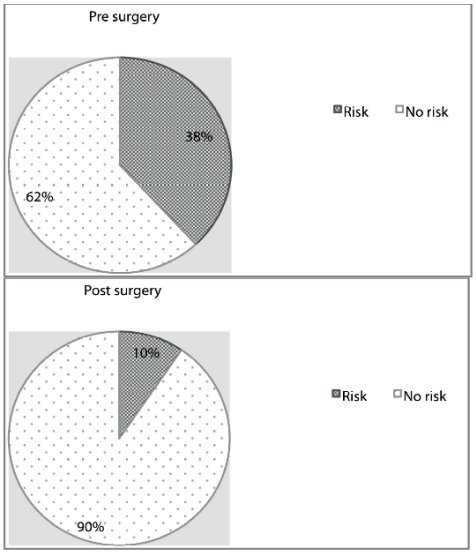

Figure 1. Results of the Berlin Questionnaire depicted in percentage of the whole patient group (n= 42). The risk changed in 13 patients from being at risk of obstructive sleep apnoea (OSA) to non-risk after surgery. One patient went from non-risk to OSA risk. Three patients who were at risk of developing OSA before surgery were still at risk after surgery.

Table 3. BNSQ (Basic Nordic Sleep Questionnaire), symptoms before (pre operative) and 3 months after (post operative) surgery (median and interquartile range). As seen, the individual responses improve after surgery. Significant values in bold.

BNSQ	Pre op	Post op	p-value
	Med (IQR)	Med (IQR)	
1) I wake up with a headache	1.0 (1.0)	1.0 (1.0)	0.224
2) I wake up with a dry mouth	3.0 (2.0)	1.0 (2.0)	**<0.0001**
3) I wake up because of hot flashes	0.0 (1.0)	0.0 (1.0)	**0.025**
4) I sweat/perspire excessively during the night	1.0 (2.0)	1.0 (1.0)	0.360
5) I toss, turn and thrash excessively during the night	2.0 (3.0)	2.0 (1.0)	0.374
6) I sweat/perspire excessively during the day	1.0 (4.0)	1.0 (1.0)	0.299
7) I get heartburn after lying down	0.0 (1.0)	0.0 (1.0)	1.00
8) I get heartburn during the day	0.0 (1.0)	1.0 (1.0)	0.273
9) I fall asleep involuntarily during the day e.g. when I take a break from my work	0.0 (0.0)	0.0 (0.0)	0.942
10) I feel very sleepy during the day. e.g. when I sit in front of the computer	1.0 (2.0)	1.0 (2.0)	0.073

(p<0.01) after surgery. Specific BNSQ items have been presented in Table 3. There was a significant decrease in symptoms of poor sleep quality in the item "I wake up with a dry mouth" from 1.52 to 1.0 (p< 0.001).

Other Sleep Questionnaires: Berlin Questionnaire and MAP

Using the BQ, subjects could be identified who are at risk of developing obstructive sleep apnoea (OSA). According to the BQ, surgery changed 13 of the patients from being at risk of OSA to a non-risk group after surgery, but one patient went from non-risk to OSA risk after surgery. Three patients who were at risk of developing OSA before surgery were still at risk after surgery (Figure 1). Of the 13 patients who moved from risk to non-risk after surgery, nine were snorers at baseline. All 13 patients were "tired, fatigued, or not up to par" 3-4 times per week or nearly every day before surgery. The question "Do you snore?" was answered "yes" by 26 (62%) before surgery and 15 (36%) after surgery (p=0.072).

MAP Index predicts OSA risk using demographic data and self-reported apnoea symptoms. The results are shown in Table 2. When using 0.75 as the cut off for being at risk, 13 patients went from risk to no risk after surgery. Four patients went from no-risk to risk after surgery.

Specific question

The question: " Do you suffer from a blocked nose at night?" was answered yes by 21/27 (75%) before surgery and by 8/24 (33%) after surgery.

To the general question: "How satisfied/unsatisfied are you with your current sleep? (0=very satisfied, to 4=very dissatisfied) 13/42 (36%) patients reported unsatisfied (score 3-4) with sleep before surgery, which improved to 3/34 (9%) after surgery. The number of patients who were satisfied with their sleep (score: 0 - 2) increased from 17/42 (40%) to 27/34 (79%) after surgery (p<0.001).

Comparison between the questionnaires

A relationship was noted between the answers in SNOT-22 and BNSQ (rs =0.659, p<0.001), as well as between SNOT-22 and ESS (rs =0.362, p=0.019).

Asthma

Twenty-nine patients were investigated by spirometry before and after surgery, but the rest could not be motivated or find the time to be investigated before and after surgery. However,

Table 4. Healthy control individuals answering the same questionnaires 3 months apart. Data presented in median and interquartile range. As seen there were no differences in the responses at baseline compared to three months later. SNOT-22 (Sino Nasal Outcome Test-22), ESS (Epworth Sleepiness Scale), and BNSQ (Basic Nordic Sleep Questionnaire) illustrated.

Questionnaire	Baseline	After 3 months	Difference	p-value
	Med (IQR)	Med (IQR)	Med (IQR)	
SNOT-22	5.5 (13.0)	8.0 (12.0)	0.5 (10.0)	0.08
ESS	5.0 (5.0)	5.0 (5.0)	0.0 (2.0)	0.786
BNSQ	3.0 (7.0)	3.0 (6.0)	0.0 (3.0)	0.775

surgery did not change FEV1%: 94 (IQR 26) vs. 90 (IQR 24.2) after surgery, p=322. This was true both for the asthmatic/COPD group at 86.7 (IQR 32) before and 75.4 (IQR 23) after surgery (p=0.455) and for the non-asthma/COPD group at 101 (IQR 21.3) before vs. 92 (IQR 20.8) after surgery (p=0.433).
There was no difference in SNOT-22 (p=0.94), ESS (p=1), or BNSQ (p=0.654) between asthmatics and non-asthmatics before or after surgery.

Healthy controls

Table 4 shows the questionnaire sum scores from 37 healthy volunteers. No significant differences in any of the answers could be found between the two occasions in SNOT-22 (p=0.08), ESS (p=0.786), BNSQ (p=0.775), and Berlin (no risk before (100%) and with one person scoring a risk after 3 months).

Discussion

In this prospective open study of an unselected group of patients suffering from CRSwNP, we found that a majority had reduced sleep quality compared to a healthy population, with associated night- and daytime symptoms. Endoscopic surgery improved these symptoms.

Our objective was to look into how patients with CRSwNP evaluated their quality of sleep and the consequences of poor quality sleep. We also assessed snoring and indirect symptoms of sleep apnoea, and whether functional endoscopic sinus surgery (FESS) improved any of these symptoms in an unselected group of patients undergoing surgery. Several questionnaires were used to evaluate sleep quality and associated daytime symptoms. The validated rhinological QoL questionnaire, SNOT-22, which also includes some sleep questions, found a clear relationship with some of the sleep questionnaires. In general, sleep questionnaires are useful tools for sleep categorization even though polysomnography is the golden standard for measurement of sleep apnoea. Questionnaires do of course not give an objective evaluation of patients' sleep, in contrast to polysomnography. However, a sleep registration was not possible to complete in the present study. All sleep questionnaires pointed in the same direction, namely that patients reported poor sleep before surgery and that surgery improved their sleep. By using the questionnaires on a healthy population during the same time of year, we demonstrated good test-retest reliability. A test-retest is one possible way to evaluate if similar results are reproduced under the same methodological conditions, but at different times [23].
SNOT-22 showed an improvement from being very abnormal to less abnormal. Before surgery, the patients suffered from major problems with nasal symptoms and reduced quality of life [11,12]. Patients in the present study reported a score of 26.5 after surgery, in contrast to healthy subjects who score 0-8 [10,11], a finding demonstrating that even though surgery improved quality of life, CRSwNP still has a major impact on daily life. However, the improvement in nasal scoring after surgery most likely remains of major importance to the patients.
With regard to the sleep questionnaires, we found a daytime sleepiness prior to surgery, as evaluated by ESS, which was similar to a normal value for a healthy person (6.6) [19]. Daytime sleepiness decreased with surgery from median score 7.5 to 6.0. Surgery has an impact on their level of tiredness. These patients are tired during the day at the same level reported by healthy people, but they are less tired after surgery than they were before. Healthy people score between 0 and 7 in ESS [13, 21]. Any improvement, within or from above normal score, is in any case of great value for the individual. Jiang et al. [24] found a high percentage of patients with CRSsNP having daytime sleepiness and they found a correlation between sleepiness and nasal blockage.
Since BNSQ-symptoms were calculated as a sum for the first time, there are no references for comparison, but there is an improvement compared to before surgery. When calculating the symptoms in BNSQ as a sum we get a score that gives a value for the consequences of poor sleep in the patients. The consequences of poor sleep are of great concern to patients and an improvement is most likely of great value for the individual patient.

The BQ gives a risk estimate of obstructive sleep apnoea. Interestingly, the BQ showed that a large proportion of the patients (38%) were actually at risk of developing sleep apnoea, but surgery reduced the risk for 13 patients. The MAP Index also provides an estimate of risk based on snoring and apnoea questions together with gender, age, height, and weight. The improvement in the MAP estimate was similar to the improvement in BQ risk. A large proportion of the patients demonstrated a risk for OSA prior to surgery, which was reduced by surgery. We found that the patients who improved were all tired or "not up to par" to a major extent during a normal week before surgery.

A correlation between nasal symptoms and sleep was observed. Patients who suffered from sneezing indicated a higher risk of waking up feeling tired.

Healthy people breathe through the nose to a major extent while sleeping [25]. It has been suggested that the negative pressure reflex is then stimulated by nasopharyngeal breathing, and through afferent nerves, stimulates the upper airway dilator muscle activity [26,27]. In the presence of nasal polyps, or other reasons for nasal congestion, the patients make a shift to oral breathing and the negative pressure reflex is not stimulated, which can result in an increased risk of collapsed airways leading to apnoea [28–30]. The nose seems to be an important factor for a good night's sleep. High nasal resistance could be considered as an important contributing factor in the pathogenesis of OSA in general. Any factor that produces nasal obstruction could lead to an increase in negative pressure in the upper airway. Factors that cause nasal obstruction, like nasal polyposis or hypertrophy of the inferior turbinate, have been associated with snoring and daytime sleepiness [31]. Some clinical studies have reported previously subjective and objective improvement of OSA after nasal surgery like rhinoplasty, septoplasty, turbinectomy, and polypectomy [32]. The patients in our study were clinically normal patients suffering from nasal polyposis. Hence, awareness of the risk for nasal polyposis patients to have or being at risk for obstructive sleep apnoea is highly warranted. Moreover, maybe surgery should be considered more often to reduce this risk.

Our finding of a high proportion of co-morbid asthma (57%) is in line with a previous study from Promsopa and colleagues [33] and we wanted to see whether FESS also improved lung function. If the asthma improved, it could have been a confounding factor also for the improvement of sleep related symptoms. The observation that the asthmatics in our study most likely had a more severe polyposis disease as assessed by CT scan, than the non-asthmatics, indicates support for a connection between asthma and nasal polyposis, as shown in earlier studies [34]. The observation that CT-stages did not correlate with patients' answers in SNOT-22 is in line with other types of studies looking at the relationship between objective findings comparing subjective data [35]. In contrast to other studies [1], although with some conflicting results [36], our patients with asthma did not improve their lung function as measured by spirometry three months after surgery. The number of patients who were investigated with spirometry was unfortunately low and the dropout may have caused a bias. It could be speculated that specific asthma questionnaires could have revealed improvements in this group or that any specific measurement of bronchial hyperactivity with bronchial provocations or measurements of exhaled nitric oxide would have been a better method to observe improvements in lung function after surgery. The objective of this study, however, was not to address the question of asthma improvements after endoscopic surgery.

Concerning allergies, the number of patients with any kind of allergy was low and the surgery was completed during the winter months rather than during the pollen season.

Strengths and limitations of the study

Although the number of patients in this study was fairly small, a clear reduction of sleep-associated symptoms was seen following surgery. It can be speculated that if a larger number of patients had been included, a larger impact on all symptoms might have been observed, but during the given timeline, it was not possible to recruit more patients. A selection bias is a problem when it comes to clinical studies, but all patients who were planned for surgery (except three excluded) also completed the whole procedure. Hence, the group of patients may well represent a fairly normal group of nasal polyposis patients. The study has an open design, which may hamper the results. A double blind placebo controlled randomised study would have been ideal, but for obvious reasons it is not possible to perform sham surgery. Questionnaires may have limits in how much they correlate with sleep registrations [20] and it is a limit of this study that a polysomnography was not completed. However, a sleep registration was not possible in the present study. The number of patients who were investigated with spirometry was unfortunately low and the dropout could have given a bias to the results.

In future studies it would be of great value if the shortfalls of this study concerning objective measurements could be improved to allow the possibility of discriminating between nasal patency before and after surgery.

Conclusion

In conclusion the study has demonstrated that patients with chronic rhinosinusitis with nasal polyposis have impaired sleep and that endoscopic sinus surgery can improve these sleep impairments. We propose that from a clinical point, it is important to address the sleep related symptoms of patients and be aware that those with polyposis are at risk of developing obstructive sleep apnoea syndrome. In general, surgery had a clear impact on nose symptoms, sleep symptoms, daytime drowsiness, and snoring scores.

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Authorship contribution

MV: Planned the study, organized the collection of data, performed statistical calculations and analysis, main writer of manuscript. AJ: Performed statistical calculations and analysis. HHS: Analysed results and wrote the manuscript. MA: planned and organized the study. Also took a major part in analysing results and writing the manuscript.

Conflict of interest

Authors declare no conflict of interest.

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Paper III

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Nocturnal nasal obstruction is frequent and reduces sleep quality in patients with obstructive sleep apnea

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SUMMARY

The prevalence and consequences of nasal obstruction in untreated obstructive sleep apnea patients are not known. The study objectives were to investigate the frequency of subjective and objective nasal obstruction in untreated sleep apnea patients and the associations with sleep and quality of life. Patients in the Icelandic Sleep Apnea Cohort were subjected to a type 3 sleep study, answered questionnaires and had their nasal dimensions measured by acoustic rhinometry. In total, 810 patients participated (including 153 females), aged 54.5 ± 10.6 years [mean ± standard deviation (SD)] with an apnea/hypopnea index 44.7 ± 20.7 h^{-1}. Nocturnal nasal obstruction (greater than or equal to three times per week) was reported by 35% of the patients. These patients had smaller nasal dimensions measured by the minimum cross-sectional area within the smaller nasal valve (0.42 ± 0.17 versus 0.45 ± 0.16 cm^2, $P = 0.013$), reported more daytime sleepiness (Epworth Sleepiness Scale score 12.5 ± 4.9 versus 10.8 ± 5.0; $P < 0.001$) and slightly lower mental quality of life than patients without nocturnal nasal obstruction. Nocturnal nasal obstruction is reported in one-third of the sleep apnea patients and they are more likely to suffer from daytime sleepiness and slightly reduced quality of life than other sleep apnea patients.

INTRODUCTION

Healthy people normally breathe through the nose during sleep, with only 0–4% of the sleeping time reported as oral breathing (Fitzpatrick *et al.*, 2003). Nasal obstruction is a problem reported by approximately 15% of the general population (Eriksson *et al.*, 2011), with decreased quality of life as consequence (Hellgren, 2007). Several structural problems may cause reduced nasal patency, including septal deviation, enlarged turbinates and nasal valve collapse. Moreover, inflammatory diseases of the nasal mucosa, such as allergic and non-allergic rhinitis, as well as chronic rhinosinutis with and without nasal polyposis, can cause nasal obstruction (Georgalas, 2011). We have reported recently that patients with nasal obstruction due to chronic rhinosinusitis with nasal polyps had impaired sleep quality that improved with surgery, and that the obstructive sleep apnea (OSA) risk was also decreased (Värendh *et al.*, 2017).

Obstructive sleep apnea is a common disease, affecting 25–50% of middle-aged people in the general population (Heinzer *et al.*, 2015). Using questionnaires, Hoffstein *et al.* (1992) asked patients for side effects during continuous positive airway pressure (CPAP) treatment and reported that nasal obstruction was a common issue. However, the degree of nasal symptoms before CPAP treatment was not reported, and the patients had been on CPAP for varying lengths of time. Krakow *et al.* (2016) studied non-allergic nasal obstruction retrospectively in patients referred to a sleep

investigation, but they did not specify differences in nasal obstruction between patients with and without OSA. Furthermore, they found more daytime sleepiness in patients with non-allergic nasal obstruction. No randomized controlled study has shown effect of nasal surgery on the apnea–hypopnea index (AHI) (Koutsourelakis *et al.*, 2008), but one meta-analysis showed a minor effect (Wu *et al.*, 2017). Two small meta-analyses by Ishii *et al.* (2015) and Li *et al.* (2011) concluded that nasal surgery in OSA patients with nasal obstruction leads to a decline in daytime sleepiness.

Several papers state that many OSA patients have nasal obstruction, but no well-defined, large studies have addressed the prevalence of subjective and objective nasal obstruction in these patients before initiating treatment. The pathophysiological role of the nose and the consequences of nasal obstruction for health-related quality of life in OSA are therefore not understood fully. Accordingly, the objectives of this study were to investigate the frequency of subjective and objective nasal obstruction in OSA patients while untreated, and to assess if nasal obstruction was associated with sleep-related symptoms and quality of life.

Our hypothesis was that subjective nocturnal nasal obstruction is common in OSA patients and is associated with objective narrowing of one nasal passage. Moreover, we hypothesized that nasal obstruction would influence insomnia and some other aspects of sleep quality or quality of life.

METHODS

Study design and study subjects

This is a cross-sectional study. The Icelandic Sleep Apnea Cohort (ISAC) is a project with the overall aim of studying the genetics of OSA. The project is performed in collaboration between the University of Iceland Reykjavik, Iceland and the University of Pennsylvania, USA. The major project is divided into many smaller studies, investigating different aspects of the OSA disease. Patients diagnosed with OSA who were referred to the Department of Respiratory Medicine and Sleep, Landspitali—The National University Hospital (LSH) of Iceland—for treatment with positive airway pressure (PAP) from September 2005 to December 2009 were invited to participate in the ISAC study. More than 90% of eligible and approached subjects (n = 822) agreed to participate and started PAP treatment following baseline assessment. Nine patients were excluded due to missing acoustic rhinometry (AR) data and one withdrew from the study (Fig. 1).

Furthermore, two patients were excluded, as they did not answer the question concerning nocturnal nasal obstruction. No other exclusion or inclusion criteria were used (Arnardottir *et al.*, 2013). The National Bioethics Committee of Iceland, the Data Protection Authority of Iceland and the Institutional Review Board of the University of Pennsylvania approved the ISAC study. All patients signed a written informed consent.

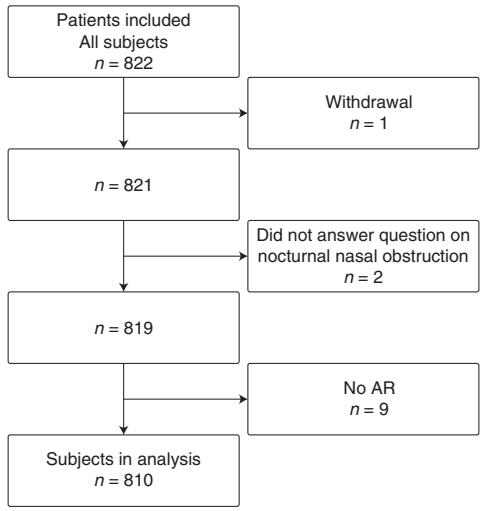

Figure 1. Outline of the patient sample.

Measurements and questionnaires

While untreated, the patients answered standardized questionnaires about their health and sleep. Nasal obstruction was evaluated with the question: 'Is your nose congested at night?'. The response categories were a frequency scale from 1 to 5: 1 = never or very seldom, 2 = less than once a week, 3 = once to twice a week, 4 = 3–5 times a week, and 5 = every night or almost every night of the week. A score of 4 or 5 was defined as nocturnal nasal obstruction. Patients completed the questionnaires the same day or, for some within the days before, were examined with Acoustic Rhinometry.

The Basic Nordic Sleep Questionnaire was used to evaluate sleep symptoms including insomnia symptoms (Partinen and Gislason, 1995). The following questions were asked: 'I have difficulties falling asleep at night' (initial insomnia), 'I wake up often during the night' (middle insomnia) and 'I wake up early and find it difficult to fall back asleep' (late insomnia). Symptoms of insomnia were considered present if reported three times per week or more often. All questions were based on the past month's experience. Nocturnal sweating was also considered present if reported three times per week or more often. Nocturnal gastroesophageal reflux was considered present if reported more than once per week (Emilsson *et al.*, 2012; Gislason *et al.*, 2002).

Daytime sleepiness was evaluated with the Epworth Sleepiness Scale (ESS), and an ESS score of $\geq$10 was considered excessive daytime sleepiness (Johns, 1991).

Health-related quality of life was examined with the Short Form Health Survey (SF-12) questionnaire (Ware *et al.*, 1996). Scores are divided into either physical or mental

health scores. Physical health is exemplified as moving a table or climbing several flights of stairs and if physical activities were limited due to compromised physical health. Concerning mental health, patients were asked if emotional issues such as feeling depressed or anxious have limited their daily activities. The scores range from 0 to 100 (score of 100 indicates the best health-related quality of life).

Patients were also asked if they were on nasal cortisone medication (yes/no).

Acoustic rhinometry

The AR technique works through an acoustic pulse sent into the nostrils. A single-impulse rhinometer (RhinoScan™ SRE2000; Rhinometrics, Assens, Denmark) was used. The method provides an anatomical description of the measurements of the nasal cavity. It compares the amplitude (representing the area) of sound waves that are reflected by the structures in the nasal cavity of an incident sound wave as a function of time (representative for the distance to the nasal cavity) (Clement and Gordts, 2005). Patients were examined sitting in an upright position.

The variables examined before nasal spray were: total minimal cross-sectional area in both nasal valves added together (TMCA, cm^2), minimal cross-sectional area within the smaller nasal valve (either left or right) (MCA-min, cm^2), total volume of left and right nasal cavity added together (TVOL, cm^3) and the difference between MCA before and after nasal decongestive spray (MCA-diff, cm^2). The decongestive spray, oxymethazoline (0.5 mg/ml) was given with two puffs in each nostril after the first AR. All AR measurements were re-evaluated on 2–6 of November 2015 by M.V. Three measurements were not of sufficient quality and were not used in calculations.

Sleep study

A type 3 sleep study was conducted with an Embletta portable monitor, an Embla 12 channel system (Embla™; Flaga Inc., Reykjavik, Iceland) or a T3 device (Nox Medical, Reykjavik, Iceland). All systems recorded the same channels. The sleep study included nasal airflow, oxygen desaturation, pulse, chest and abdominal movements by respiratory inductive plethysmography as well as body position and activity by accelerometer.

All sleep studies were re-read by a centralized scoring laboratory at the University of Pennsylvania using the Somnologica Studio (Embla™) software and were used for the analysis. More than 4 h of a scorable oxygen saturation (SaO_2) signal was needed for a sleep study to be scored. The AHI was defined as the mean number of apnea and hypopnea per hour of recording (upright time excluded). A hypopnea was classified as ≥30% decrease in the flow with ≥4% oxygen desaturation or ≥50% decrease in flow for ≥10 s, with a sudden increase in flow at the end of the event. The oxygen desaturation index (ODI) was defined as the number of transient drops in oxygen saturation ≥4% per hour of recording. OSA severity was defined as: severe OSA (AHI ≥ 30), moderate OSA (AHI 15–29.9) and mild OSA (AHI 5–14.9). See previous publications for further details (Arnardottir *et al.*, 2012).

Nasal surgery

Information on prior nasal surgery was derived from patient files, including septoplasty, turbinectomy and endoscopic surgery, sometimes with polypectomy.

Statistical analysis

Nominal data were presented as frequencies and percentages without decimals. In comparisons between nominal data in independent groups, the chi-squared test was used. Fisher's exact test was used when the expected values were insufficient for a chi-squared test. Ordinal and quantitative data were presented by mean and standard deviation (± SD). Independent group differences were calculated with the Mann–Whitney *U*-test for two groups and Kruskal–Wallis test for more than a two-group comparison. *Post-hoc* tests were calculated with the Mann–Whitney *U*-test between two groups when the Kruskal–Wallis test showed a significance of <0.05 for more than two-group comparisons. Multiple Logistic regression analyses were calculated with the Enter method; SPSS version 22.0 was used in all analyses. A two-sided *P*-value of <0.05 was considered significant in all calculations. All *P*-values, significant or not, are presented in the comparisons.

RESULTS

Study sample

The characteristics of the patients are shown in Table 1 (153 females and 657 males). The mean ± SD BMI was 33.5 ± 5.7 kg m^2. A large proportion of the patients (57%) was diagnosed with hypertension; 21% were current smokers and 27% were former smokers. Hypertension was more frequent in females ($P < 0.05$). Daytime sleepiness was common, and the overall mean score for ESS was 11.7 ± 5.0 (mean ± SD). Also, the SF-12 survey demonstrated a low mental and physical health-related quality of life. A larger proportion of the women reported nocturnal sweating, nocturnal gastric reflux and insomnia (both initial, middle and late) ($P < 0.05$).

A majority of the patients (73%) had severe OSA; 23% had moderate OSA and 3% had mild OSA.

Prevalence of subjective and objective nasal obstruction in OSA

Overall, 65% reported nasal obstruction during the night once per week or more often and 35% greater than or equal to

Table 1 Women had smaller nasal dimensions, more insomnia and a lower quality of life

Baseline characteristics, nasal dimensions and sleep quality (n = *810)*

	All n = *810*	*Female* n *(%)* *153 (19)*	*Male* n *(%)* *657 (81)*	P-*value for sex comparison*
Age (years)	54.5 ± 10.6	58.6 ± 9.0	53.6 ± 10.8	**<0.001**
Current smoker	21%	19%	22%	0.58
Body mass index (kg m^2)	33.5 ± 5.7	34.1 ± 6.3	33.3 ± 5.5	0.19
Weight (kg)	104.3 ± 19.2	93.0 ± 17.2	106.9 ± 18.7	**<0.001**
Hypertension	57%	67%	55%	**0.03**
Diabetes	11%	12%	11%	0.70
Coronary heart disease including coronary heart occlusion, heart failure or/and stroke	18%	10%	20%	**0.006**
Apnea–hypopnea index	44.8 ± 20.7	42.2 ± 20.0	45.4 ± 20.8	0.058
Oxygen desaturation index (4%)	35.5 ± 20.3	32.6 ± 20.5	36.2 ± 20.2	**0.008**
Nocturnal nasal obstruction ≥3 × week	35%	37%	35%	0.68
TMCA (cm^2)	1.06 ± 0.31	0.94 ± 0.28	1.08 ± 0.31	**<0.001**
MCA-min (cm^2)	0.43 ± 0.16	0.40 ± 0.15	0.44 ± 0.17	**0.02**
TVOL (cm^3)	4.10 ± 0.81	3.48 ± 0.65	4.25 ± 0.77	**<0.001**
Diff TMCA (cm^2)	0.19 ± 0.21	0.16 ± 0.20	0.20 ± 0.22	**0.02**
Diff MCA-min (cm^2)	0.10 ± 0.12	0.08 ± 0.11	0.11 ± 0.12	**0.03**
Diff TVOL (cm^3)	0.21 ± 0.34	0.22 ± 0.31	0.21 ± 0.35	0.30
Nocturnal gastroesophageal reflux ≥ 1 × week	14%	18%	13%	**0.006**
Initial insomnia, ≥3 × per week	16%	27%	13%	**<0.001**
Middle insomnia, ≥3 × per week	58%	62%	57%	**<0.001**
Late insomnia, ≥3 × per week	28%	33%	27%	**<0.001**
Nocturnal sweating ≥3 × per week	31%	33%	31%	**<0.001**
Daytime sleepiness (ESS)	11.7 ± 5.0	11.2 ± 5.2	11.8 ± 5.0	0.23
Mental quality of life (SF-12)	48.3 ± 10.9	46.8 ± 11.1	48.6 ± 10.8	**0.048**
Physical quality of life (SF-12)	40.2 ± 10.9	35.5 ± 10.9	41.3 ± 10.6	**<0.001**

ESS, Epworth sleepiness scale; Diff MCA-min, difference between MCA-min before and after nasal decongestant spray; Diff TMCA, difference between TMCA before and after nasal decongestant spray; Diff TVOL, difference between before and after nasal decongestant spray; MCA-min, minimal cross-sectional area within the smallest nostril of either left or right before decongestant spray; TMCA, total minimal cross-section area in the nose, left and right nostril combined before nasal decongestant spray; TVOL, total volume of left and right nasal volume combined before nasal decongestant spray

SF-12: The 12-Item Short Form Health Survey (SF-12), a smaller version of the SF-36 version 2 Health Survey.

MCA: minimal cross-sectional area within one nasal valve, before nasal decongestant spray; TVOL: total volume of left and right nasal volume combined before nasal decongestant spray.

Significance shown in bold type.

Numbers given as mean ± standard deviation if not specified, and *P*-values when comparing mean values calculated with Mann–Whitney *U*-test.

The chi-squared test was used for comparisons between nominal data in independent groups (here shown as %).

three times per week. No significant differences were seen in OSA severity, as measured by the AHI, between the three groups ($P = 0.57$) (Table 2).

Nasal cavity dimensions assessed by AR showed mean values of TMCA 1.06 ± 0.31, MCA-min 0.43 ± 0.16 and TVOL 4.10 ± 0.81. TMCA and TVOL were significantly smaller in female patients than in males ($P < 0.05$) but no sex differences were found in subjective nocturnal nasal obstruction; see Table 1.

Sleep-related symptom and nocturnal nasal obstruction

We divided the patients into three groups, depending on their subjective nocturnal nasal obstruction symptoms (Table 2). Women and men were distributed equally between the three groups ($P = 0.45$). There was a difference between the groups in MCA-min, assessed by AR, with the smallest mean value of 0.42 ± 0.17 cm^2 in the nocturnal nasal obstruction group compared to 0.45 ± 0.16 cm^2 in the group without any nocturnal nasal obstruction (*post-hoc* analysis between 'never nasal obstruction' and 'greater than or equal to three times per week', $P = 0.013$) (Table 2).

Late insomnia was reported by a larger proportion of the patients with nocturnal nasal obstruction more than three times per week compared to the group without (*post-hoc*: $P = 0.013$) (Fig. 2, *P*-value = 0.005 is calculated between all three groups); 65% of patients with nocturnal nasal obstruction greater than or equal to three times per week week have middle insomnia. Patients with nocturnal nasal obstruction also had more daytime sleepiness compared to patients

Table 2 Patients with frequent nocturnal nasal obstruction were slightly more likely to have one smaller nasal valve; no other significant differences were found between the groups

Nocturnal nasal obstruction (n = *810)*	*Never* n = *285*	*1–2 × per week* n = *240*	*≥3 × per week* n = *285*	P-*value*
Age (years)	55.4 ± 10.4	53.7 ± 10.3	54.1 ± 11.0	0.16
Current smoker	21%	27%	20%	0.85
Body mass index (kg m^2)	33.7 ± 5.8	33.1 ± 5.6	33.6 ± 5.6	0.30
Apnea–hypopnea index	43.5 ± 10.0	45.8 ± 20.5	45.2 ± 21.5	0.57
Oxygen desaturation index	34.3 ± 19.8	36.1 ± 20.0	36.3 ± 20.9	0.54
TMCA (cm^2)	1.11 ± 0.30	1.07 ± 0.30	1.03 ± 0.32	0.19
MCA-min (cm^2)	0.45 ± 0.16	0.44 ± 0.17	0.42 ± 0.17	**0.04***
TVOL (cm^3)	4.10 ± 0.83	4.13 ± 0.78	4.08 ± 0.81	0.78
Diff TMCA (cm^2)	0.17 ± 0.21	0.21 ± 0.19	0.20 ± 0.23	0.11

Diff MCA-min: difference between MCA-min before and after nasal decongestant spray; Diff TMCA: difference between TMCA before and after nasal decongestant spray
Diff TVOL: difference between before and after nasal decongestant spray; CA-min: minimal cross-sectional area within the smallest nostril of either left or right before decongestant spray
TMCA: total minimal cross-section area in the nose, left and right nostril combined before nasal de-obstruction spray; TVOL: total volume of left and right nasal volume combined before nasal decongestant spray. Significance shown in bold type.
Numbers given as mean ± standard deviation if not specified.
Independent group differences were calculated with Kruskal–Wallis test for >2-group comparison of mean values.
The chi-squared test was used for comparisons between nominal data in independent groups (here shown as %).
**P*-value for *post-hoc* test: 0.013 comparing the groups 'Never' and '≥ 3 × per week'.

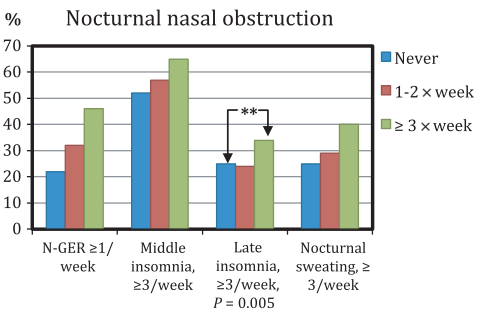

Figure 2. Patients with nocturnal nasal obstruction are more likely to have late insomnia and 65% of patients with nocturnal nasal obstruction greater than or equal to three times per week have middle insomnia. **Significance between the groups of patients without and with nocturnal nasal obstruction greater than or equal to three times per week. N-GER, nocturnal gastroesophageal reflux.

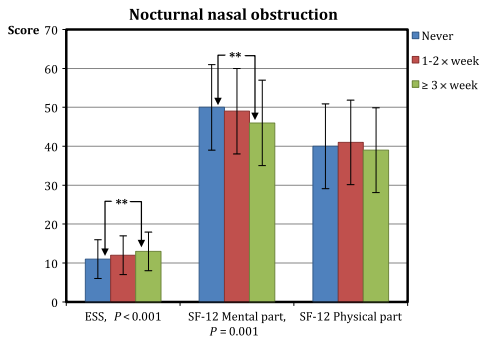

Figure 3. Patients with more nocturnal nasal obstruction have more daytime sleepiness and lower scores on quality of life, mental section. The figure describes nocturnal nasal obstruction and daytime sleepiness (ESS, Epworth Sleepiness Scale) and quality of life measured by SF-12. **Significant difference between the groups of patients without and with nocturnal nasal obstruction greater than or equal to three times per week.

without nocturnal nasal obstruction (ESS: 12.5 ± 4.9 versus 10.8 ± 5.0, *post-hoc* comparison, $P < 0.001$) (Fig. 3). Mental quality of life was reported lower in the group with nocturnal nasal obstruction compared to those without obstruction (46.4 ± 11.4 versus 49.8 ± 10.5, $P < 0.001$) (Fig. 3).

A multiple regression analysis was performed to predict subjective nocturnal nasal obstruction. The differences found in subjective nocturnal nasal obstruction remained significant after adjusting for sex, BMI, nocturnal gastroesophageal reflux and smoking.

Nasal surgery

A total of 86 patients had nasal surgery prior to PAP treatment and prior to being included in the study. Some patients underwent more than one kind of surgery and 18 patients underwent nasal surgery on two occasions. The different surgeries were: septal deviation surgery (61), turbinoplasty (37) and endoscopic sinus surgery and

Table 3 Former nasal surgery had no impact on AHI or nasal dimensions; a larger proportion of patients with previous nasal surgery were reporting nocturnal nasal obstruction

Former nasal surgery			
	Nasal surgery n *(%)* *86 (11)*	*No nasal surgery* n *(%)* *724 (89)*	P-*value*
Apnea–hypopnea index	40.7 ± 16.2	45.3 ± 21.1	0.12
TMCA (cm^2)	1.05 ± 0.30	1.05 ± 0.31	0.99
MCA-min (cm^2)	0.43 ± 0.16	0.43 ± 0.17	0.95
TVOL (cm^3)	4.06 ± 0.75	4.11 ± 0.81	0.84
Nocturnal nose obstruction	47%	34%	**0.02**

MCA-min: minimal cross-sectional area within the smallest nostril of either left or right before decongestant spray; TMCA: total minimal cross-section area in the nose, left and right nostril combined before nasal decongestant spray; TVOL: total volume of left and right nasal volume combined before nasal decongestant spray.
Significance shown in bold type.
Numbers given as mean ± standard deviation if not specified, and *P*-values when comparing mean values were calculated with the Mann–Whitney *U*-test.
The chi-squared test was used comparisons between nominal data in independent groups (here shown as %).

polypectomy (11). As a group, these patients reported significantly more frequent nasal obstruction compared to the others, despite surgery (47% versus 34%, respectively, $P = 0.02$), but no differences were found in OSA severity or measured nasal dimensions (Table 3).

Medication

Concerning medication with a possible impact on nasal obstruction, the following results were found: 37 patients used nasal steroids, 14 patients systemic steroids and six patients oral antihistamines. A total of 55 patients had one or more of these medications. However, there were no differences between the users of these drugs and non-users in terms of AHI ($P = 0.8$), TMCA ($P = 0.34$), MCA-min ($P = 0.77$) or TVOL ($P = 0.66$).

DISCUSSION

The present study demonstrates that the prevalence of reported nocturnal nasal obstruction was 35% in untreated OSA patients. Patients with nocturnal nasal obstruction were more likely to have one small nasal valve area (MCA-min). Moreover, OSA patients with nasal obstruction reported symptoms of late insomnia and daytime sleepiness slightly more often, and generally had a lower mental quality of life compared to OSA patients without nasal obstruction.

Prevalence of nocturnal nasal obstruction

The present study revealed a nocturnal nasal obstruction prevalence of almost 65% once per week or more often and 35% greater than or equal to three times in treatment-naive OSA patients. To our knowledge, the prevalence of nasal obstruction in OSA has not been described previously. A previous retrospective study reported a prevalence of non-allergic nasal obstruction of 45% in unselected sleepy patients (Krakow *et al*., 2016). The Wisconsin Sleep Cohort reported nasal obstruction to be a risk factor for apneas, hypopneas and habitual snoring (Young *et al*., 1997). However, they did not report a prevalence of nasal obstruction in patients with OSA.

Acoustic rhinometry

The minimal cross-section area within the smallest nasal valve of either left or right side, MCA-min, was the only parameter that was found to differ between OSA patients with and without nasal obstruction. In contrast to our results, Vidigal *et al.* (2013) used AR to study the nasal geometry in a small sample of OSA patients and a control group. They found more nasal symptoms in OSA patients compared to controls, but no difference in AR values. However, they did not investigate the smallest nasal valve compared to subjective obstruction.

There are at least two elements of nasal obstruction. The first is the structural part consisting of skeletal bone and cartilage and the second is the swollen mucosa causing congestion. The latter varies with the nasal cycle, the normal 'corporo-nasal' reflex, and possibly a separate airflow cycle within each nasal valve (Kahana-Zweig *et al*., 2016). These normal events could explain the influence of MCA-min on subjective nasal obstruction in the current study. If one side of the nose is obstructed structurally, subjective nasal obstruction will increase if subjects lie on their other side; the more open (lower) half of the nose that becomes congested, the more resistant (upper) half of the nose will not be patent (Pevernagie *et al*., 2005).

OSA severity between the groups

No differences were observed in OSA severity between the patients with and without nocturnal nasal obstruction. No other large study has, to our knowledge, investigated the relation between AHI and nocturnal nasal obstruction. There are conflicting results concerning OSA severity and impact of nasal surgery. Two previously mentioned meta-analyses by Ishii *et al.* (2015) and Li *et al.* (2011) included small, and only randomized and controlled, studies. These studies showed no improvement on OSA severity with nasal surgery. One small meta-analysis of Wu *et al.* (2017) showed an improvement of OSA severity with surgery.

Insomnia

Late insomnia was reported more often by patients with nocturnal obstruction compared to OSA patients without nasal obstruction ($P = 0.01$) despite similar OSA severity. This finding is in line with a previous study that reported more insomnia problems in patients with undifferentiated sleep problems and nasal obstruction than in patients without these problems. However, it was a retrospective questionnaire study, and the patients were not diagnosed with OSA (Krakow *et al.*, 2016). It is possible that nocturnal nasal obstruction has an influence on late insomnia in OSA patients.

Daytime sleepiness

Daytime sleepiness was found to be more slightly more pronounced in OSA patients with nocturnal nasal obstruction compared to patients without obstruction ($P < 0.001$). With a mean value of 12.5 ± 4.9, the sleepiness will most probably have an impact upon everyday life. Our results are therefore in agreement with previous studies showing that nasal obstruction has an impact upon daytime sleepiness (Ishii *et al.*, 2015; Li *et al.*, 2011; Värendh *et al.*, 2017).

Quality of life

Mental quality of life in patients with nasal obstruction was found to be slightly lower than in other OSA patients ($P < 0.001$) and lower compared to normal reference values for healthy adults (Hilberg, 2002). This matter has not, to our knowledge, been studied previously. A possible explanation for the decreased quality of life is that patients are influenced by their nasal obstruction, which is associated with more insomnia complaints and daytime sleepiness. Nocturnal nasal obstruction might increase the problems of insomnia and daytime sleepiness, which influences quality of life.

Medication

Using oral antihistamines, nasal or systemic corticosteroids did not have an impact upon nasal dimensions.

Strengths and limitations of the study

A major strength of this study is the large, well-defined clinical cohort of OSA patients in ISAC and that the nose is examined both subjectively and objectively.

Acoustic rhinometry is a valid technique provided that the limitations are understood (Arnardottir *et al.*, 2016; Clement and Gordts, 2005). The method describes anatomical structures, but does not give extensive information about nasal function. AR is conducted in an upright position during the daytime and therefore it is difficult to draw conclusions about nasal dimensions during sleep. However, an anatomical description of OSA patients prior to treatment is lacking in the literature, and is of interest and importance.

Sleep was recorded with a type 3 sleep study without electroenceophalography (EEG), and therefore it was not possible to study arousals. However, a type 3 sleep study is clinically acceptable for the diagnosis OSA (Berry *et al.*, 2015; Mols *et al.*, 2009). A limitation to the objective evaluation of insomnia in this study is that polysomnography was not used.

The nasal questions used were not validated and additional validated questionnaires, such as the Sino-Nasal Outcome Test (SNOT-22), would probably have provided a better evaluation of the patients' symptoms. Questionnaires have limitations, but subjective symptoms of patients are extremely valuable and important. It is difficult to obtain objective measurements in some issues in real-life circumstances, and the patient's complaint indicates what is affecting her/his quality of life.

A control group of healthy individuals would have been of major interest, but to gather such a large group of non-sleep-apnea patients of comparable age, sex and weight remains a future task.

Clinical implications

The findings in this study show that it is of great importance to increase the awareness of clinicians of the high incidence of nasal obstruction is OSA patients and how much it influences their daily life.

CONCLUSION

Nocturnal nasal obstruction was found in more than one-third of the OSA patients. Subjects with nocturnal nasal obstruction had, on average, one nasal valve with a smaller minimum cross-section area. Furthermore, measures of late insomnia, daytime sleepiness and mental quality of life were slightly worse compared to patients without nasal obstruction.

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AUTHOR CONTRIBUTIONS

MV took part in designing the calculations, in evaluating the results, performed statistical calculations and drafted the

paper. MA contributed to designing the calculations, took part in evaluating the results and reviewed the paper. EB contributed to designing the calculations, took part in evaluating the results and reviewed the manuscript. HH-S contributed to designing the calculations, took part in evaluating the results and reviewed the manuscript. AJ contributed to statistical analysis design and performed statistical calculations and analysis. ESA designed the study, contributed to designing the calculations, took part in evaluating the results and reviewed the manuscript. TG designed the study, contributed to designing the calculations, took part in evaluating the results and reviewed the manuscript. SJ designed the study, participated in data collection, contributed to designing the calculations and took part in evaluating the results. All authors participated in all revisions of the paper with co-authors.

CONFLICT OF INTERESTS

MV, MA, EB, AJ, TG and SJ: no conflicts of interest. HH-S received payments for lectures from the NOX, TAKEDA and RESmed companies outside the submitted work. ESA is part-time consultant for Nox Medical, Reykjavik, Iceland unrelated to this paper, outside the submitted work.

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Paper IV

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Impaired nasal patency and sleep disturbances

The overall findings in the thesis of Maria Värendh are that nasal obstruction is frequent in patients with Obstructive sleep apnoea, which subsequently impacts the patients sleep and life quality. The problems associated with nasal obstruction decline two years after initiating positive airway pressure treatment. Most importantly however, PAP treatment does not induce long term objective or subjective nasal obstruction. Sleep quality in nasal polyposis patients with severe nasal obstruction is compromised but improves with surgery.

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