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Nasal obstruction – impact on insomnia symptoms and sleep- disordered breathing

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Abstract

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Background: Nasal obstruction is very common in the general population, but the role of nasal obstruction in sleep quality is not clear. Nasal obstruction is also prevalent in patients with obstructive sleep apnoea (OSA) and may contribute to poor adherence to continuous positive airway pressure (CPAP) treatment.

Aims: To investigate the impact of subjective nasal obstruction, as a single symptom or as part of chronic rhinosinusitis (CRS), in both objective and subjective sleep quality, in three different population based cohorts. Another aim was to investigate the usefulness of the Sinonasal Outcome Test-22 (SNOT-22) and peak nasal inspiratory flow (PNIF) in the treatment of OSA patients.

Methods and results: In paper I (the SHE-study), a community-based sample of 400 women were investigated with polysomnography and questions on sleep quality, daytime- and nasal symptoms. Women with nasal obstruction at night (n=30) had significantly higher prevalence of several night time symptoms and excessive daytime sleepiness (EDS), but the polysomnography was normal.

In paper II (the GA²LEN study, n= 26, 647) and paper III (RHINE II and RHINE III studies, n= 5, 145) questionnaires on sleep quality, daytime- and nasal symptoms were used, and CRS was defined according to the epidemiological diagnostic criteria of the European Position Paper of Rhinosinusitis and Nasal Polyps (EPOS). In paper II, sleep problems were highly prevalent in CRS, and there was a dose-response relationship between the disease severity of CRS and sleep problems. The addition of persistent allergic rhinitis to CRS further increased the risk of sleep problems.

In paper III, 2.7% of individuals without nasal symptoms at baseline had developed CRS at follow-up 10 years later. Strong associations between incident CRS and impaired sleep quality and EDS were found. Three insomnia symptoms at baseline increased the risk for CRS at follow-up.

In paper IV, 197 OSA patients initiating CPAP treatment were investigated before starting CPAP and at the follow-up 3-4 weeks later. SNOT-22 scores were generally high among all OSA patients indicating a large sinonasal disease burden, and improved among those with CPAP adherence ≥ 4 hours/night. A low PNIF value increased the risk for poor CPAP adherence.

Conclusions: Subjective nasal obstruction at night impairs subjective sleep quality in women, but does not affect objective sleep quality. CRS impairs subjective sleep quality, and insomnia symptoms may be a risk factor for CRS. SNOT-22 and PNIF may be useful tools in the treatment of OSA patients.

Keywords: Chronic rhinosinusitis, CRS, nasal obstruction, sleep, sleep apnoea.

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To Martin, Lovisa and Linnéa

*Sömnen är ett helt förunderligt
phaenomenon*

*...så nyttig är den för oss men-
niskjor, ja den aldra angenäm-
aste i naturen, ty utom den få wi
ingen nytta af mat eller dricka,
ingen styrkja, utom den hjelpa
medicamenter intet.*

Carolus Linnaeus 1756

List of Papers

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

- I Bengtsson C, Jonsson L, Holmström M, Svensson M, Theorell-Haglöw J, Lindberg E. (2015) Impact of nasal obstruction on sleep quality: a community-based study of women. *European Archives of Otorhinolaryngology*, 272(1):97-103.
- II Bengtsson C, Lindberg E, Jonsson L, Holmström M, Sundbom F, Hedner J, Malinovschi A, Middelveld R, Forsberg B, Janson C. (2017) Chronic rhinosinusitis impairs sleep quality: Results of the GA²LEN study. *Sleep*, 1;40(1).
- III Bengtsson C, Jonsson L, Holmström M, Hellgren J, Franklin K, Gislason T, Holm M, Johannessen A, Jögi R, Schlünssen V, Janson C, Lindberg E. (2019) Incident chronic rhinosinusitis is associated with impaired sleep quality: Results of the RHINE study. *Journal of Clinical Sleep Medicine*, 15;15(6):899-905.
- IV Bengtsson C, Jonsson L, Theorell-Haglöw J, Holmström M, Janson C, Lindberg E. Sinonasal outcome test -22 and peak nasal inspiratory flow – valuable tools in obstructive sleep apnoea. Submitted.

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Abbreviations

AASM	American Academy of Sleep Medicine
ACTH	Adrenocorticotrophic hormone
AHI	Apnoea-hypopnoea index
AR	Allergic rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
BBB	Blood-brain barrier
BMI	Body mass index
BNSQ	Basic Nordic Sleep Questionnaire
CI	Confidence interval
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CRS	Chronic rhinosinusitis
CT	Computed tomography
DIS	Difficulties inducing sleep
DMS	Difficulties maintaining sleep
DSM-V	The Diagnostic and Statistical Manual of Mental Disorders, 5 th edition
ECG	Electrocardiogram
EDS	Excessive daytime sleepiness
EEG	Electroencephalography
EMA	Early morning awakening
EMG	Electromyography
EOG	Electrooculography
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
ESS	Epworth sleepiness scale
FESS	Functional endoscopic sinus surgery
GABA	Gamma-aminobutyric acid
GA ² LEN	Global Allergy and Asthma European Network of Excellence
HAD	Hospital anxiety and depression
HPA	Hypothalamic-pituitary-adrenal
HSAT	Home sleep apnoea test
IAR	Intermittent allergic rhinitis
ICSD-3	The International Classification of Sleep Disorders, 3 rd edition
Ig E	Immunoglobulin E
IL-1	Interleukin-1
IL-1 β	Interleukin-1 beta
ISI	Insomnia severity index

NANIR	Non-allergic non-infectious rhinitis
nGER	Gastroesophageal reflux at night
NO	Nitric oxide
NON	Nasal obstruction at night
NREM	Non-rapid eye movement
ODI	Oxygen desaturation index
OR	Odds ratio
OSA	Obstructive sleep apnoea
OSAS	Obstructive sleep apnoea syndrome
PEF	Peak expiratory flow
PER	Persistent allergic rhinitis
PG	Polygraphy
PNIF	Peak nasal inspiratory flow
PNO	Persistent nasal obstruction
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
REM	Rapid eye movement
RERA	Respiratory effort-related arousal
RHINE	Respiratory Health in Northern Europe
RLS	Restless legs syndrome
SCN	Suprachiasmatic nucleus
SD	Standard deviation
SDB	Sleep-disordered breathing
SHE	Sleep and Health in women
SNOT-20	Sinonasal outcome test-20
SNOT-22	Sinonasal outcome test-22
SRS	Sleep regulating substance
TNF- α	Tumour necrosis factor alfa
UPPP	Uvulopalatopharyngoplasty
VLPO	Ventrolateral preoptic nucleus

Introduction

Sleep is of fundamental importance and is a prerequisite for maintaining good health and well-being. On average, humans spend one-third of their lives sleeping, but being asleep is a delicate state and numerous factors can cause sleep disruption (1). One such factor is nasal obstruction, which is a prevalent symptom in humans. Although previously investigated in numerous ways, the role of nasal obstruction in sleep disturbances is not clear. In this thesis, this subject will be further explored.

The Nose

Normal physiology of the sinonasal cavities

Providing the mouth is closed, the negative intrathoracic pressure created by an inspiration causes an airstream through both nostrils. The alar cartilages prevent alar collapse and enable the air to pass through the nasal valves, which are the narrowest passages of the nasal airway (2). The inspired air then reaches the two nasal cavities, which are separated by the nasal septum and constitute the beginning of the airway. The sinuses are connected to the nasal cavities by ostiae and constitute one entity, the sinonasal cavities. Inside the nasal cavities, the air flow will be laminar and pass through the middle meatus, but also turbulent, due to the effect of the inferior, medial and superior nasal turbinates, which are attached to the lateral walls of each nasal cavity (3) (Figure 1).

The inside of the sinonasal cavities is lined with a mucus membrane, which has a pseudostratified, columnar, ciliated epithelium (4). The mucus membrane has a high blood flow and is well innervated (5). Arteries, arterioles and arteriovenous anastomoses and capacitance vessels, consisting of veins and cavernous sinusoids, are controlled by the autonomic nervous system. The sympathetic and parasympathetic nervous systems control the regional blood flow, which determine the degree of swelling of the mucosa and consequently nasal patency (5). Sympathetic stimulation, as seen in exercise and by the use of sympathomimetic medications, causes vasoconstriction of the capacitance vessels and a decrease in nasal airflow resistance and vice versa (6, 7).

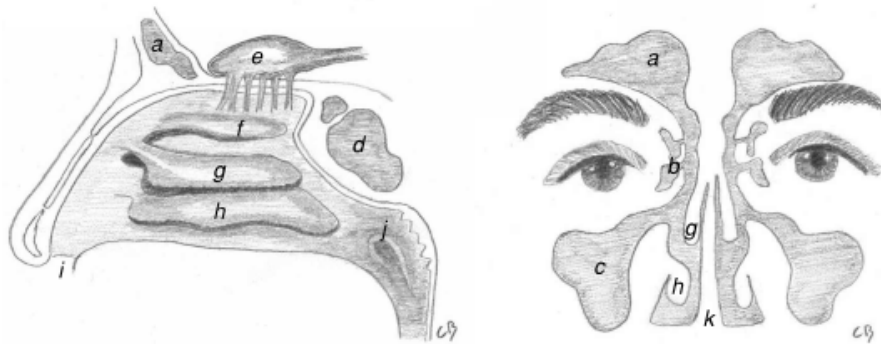


Figure 1. Lateral and coronal view of the nose and sinuses, a) frontal sinus, b) ethmoidal sinuses, c) maxillary sinus, d) sphenoidal sinus, e) olfactory bulb, f) superior turbinate, g) middle turbinate, h) inferior turbinate, i) nostril, j) epipharynx, k) nasal septum

One main function of the nose is air-conditioning. The high blood flow and ample innervation enables the nose to warm up, cool and humidify the air we breathe, always keeping it at a perfect temperature (8). In less than a second, the nose warms up the ambient air to $+34^{\circ}\text{C}$ as it reaches the epipharynx. On expiration, the air returning from the lungs will be warmer than the nasal cavity, condensation will occur, and the mucus membrane will be kept moist (9).

Another function of the nose is the immune system and clearance of mucus (10). Inhaled antigens that attach to the mucus membrane will be taken care of by local enzymes, proteases and immunoglobulins, which will trigger an appropriate immune system response. In addition, the mucosa of the paranasal sinuses produce nitric oxide (NO), which will be inhaled and transported to the lungs, where it will improve oxygen exchange and contribute with a bacteriostatic effect (10). The cilia of the mucus membrane transport the mucus secretion in a specific pattern towards the epipharynx, keeping the nose clean as the mucus will eventually be swallowed.

A further function of the nose is olfaction. The olfactory receptor neurons, which originate from the olfactory nerve, are situated cranially in the nasal cavities on both sides of the septum (11). The turbulent air flow causes the inspired air, carrying the odour molecules, to reach the olfactory receptors and enable odour detection (3, 11). By sniffing, the turbulence will increase and olfaction improves (12). The number of smells humans can remember is debatable. However, it is established that the olfactory function, i.e. thresh-

olds for identifying different odours, decreases with age, more than the ability to discriminate and identify odours (13).

Normal physiologic variations of the nasal mucosa

The nasal cycle is defined as a spontaneous and reciprocal congestion and decongestion of the nasal venous sinusoids, without change in the total nasal airflow (10). It can be detected in 70–90% of humans (14). Swelling of the septum, the inferior and middle turbinates, and the sinuses has been demonstrated with magnetic resonance imaging (15). The duration of the nasal cycle varies in different reports, from one to ten hours, whereas the shift from one side to another happens within minutes (10). Mucociliary clearance is enhanced by 2.5 times on the decongested side (16), which may play a role in the respiratory immune system (17). The exact role of the nasal cycle is not clear, however.

A recumbent position causes an increase in nasal resistance (18), which may be relevant during night time. A recumbent lateral position will induce pressure on the lateral thoracic wall, and cause reduced nasal patency on the ipsilateral side of the nose, and increased nasal patency on the contralateral side (19, 20). Exercise will result in a reduction of nasal resistance and improve nasal airflow (21).

Conditions that cause nasal obstruction

There are many different conditions that cause nasal obstruction. Two main categories can be identified: mucosal diseases and structural abnormalities, which sometimes co-exist. The symptom of nasal obstruction can also be referred to as nasal blockage, nasal congestion and nasal stuffiness, which all have slightly different meanings. In line with papers I–IV, the term nasal obstruction will mainly be used in the following text to describe both subjective and objective nasal obstruction, independent of cause.

Allergic rhinitis

Allergic rhinitis (AR) is an inflammatory disease in the nasal mucosa, triggered by inspired allergens. The inflammatory response in the nasal mucosa includes an immediate immunoglobulin E (Ig E) mediated mast cell response with the release of antihistamines, and a late phase response characterised by recruitment of numerous inflammatory cells (22). The cardinal symptom of AR is nasal obstruction (23). Other symptoms from the nose include rhinorrhea, pruritus and sneezing. Ocular symptoms (24) and the oral allergy syndrome caused by cross reactions between fresh fruits, vegetables and pollen

(25) are also prevalent in AR. The diagnosis is made by medical history and a physical examination in combination with a skin prick test or a blood sample of Ig E antibodies to airborne antigens (26).

AR affects approximately 500 million people worldwide (26). In an epidemiological study in Europe, using the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, the prevalence of allergic rhinitis was found to be approximately 23%, and nasal obstruction was reported by 59% of patients with a clinical diagnosis of AR (27). In a population based study in Sweden in 2011, the prevalence of self-reported AR was 28%, with self-reported chronic nasal symptoms among 37% of AR sufferers (28). AR and asthma are strongly associated, and AR increases the risk of asthma (29). AR has a large negative impact on quality of life, work- and school performance and sleep quality (30, 31). Consequently, allergic rhinitis causes a substantial economic burden for the individual and society (32, 33).

Chronic Rhinosinusitis

Chronic rhinosinusitis (CRS) is a chronic, inflammatory disease of the sinonasal mucosa with or without nasal polyps. CRS includes a heterogeneous group of different conditions, which manifest similar symptoms. The etiology and pathophysiology of CRS is complex and not entirely clear. CRS is described as a multifactorial disease caused by an imbalance in the host-environment interaction. Current theories of causation include fungal infection, biofilm, bacterial super antigens, smoking, anatomical factors and different immunological hypotheses (34). Diagnosis is made by medical history and a clinical examination and/or computed tomography (CT) scan.

Epidemiological data on CRS in Europe was unavailable until 2011 when the first multi-centre study was published. The main symptom was nasal obstruction, reported by 83.7% of participants (35). The prevalence of nasal discharge was 63.6%, followed by facial pressure or pain, 64.7%, and lack or loss of smell, 48.5%. The estimated prevalence of CRS in the study was on average 10.9%, with differences between European countries, ranging from 6.9% to 27.1% (35). In the sub-analysis of the four different study centres in Sweden, the prevalence of CRS ranged between 8.1–9.6%. Epidemiological studies of CRS in the US, Canada and Korea report prevalence numbers ranging between 1–15.9% (36-39).

Studies using patient related outcome measures have found that CRS has negative impact on quality of life (40-42). Associated risk factors for CRS are smoking, depression, female gender and age (35, 43). The impact on sleep quality has been less investigated, although research in this field has increased during recent years. The socioeconomic costs of the disease are vast for both the individual and society (34).

Other causes of nasal obstruction

Non-allergic non-infectious rhinitis (NANIR) is a group of conditions in which there are no signs of clinical infection or systemic signs of allergic inflammation (44). There is no uniform definition or international consensus on diagnostic criteria of NANIR; consequently, there is a lack of epidemiological data. In a Swedish population-based study, however, approximately 20% of adults suffered from rhinitis and nasal symptoms that were not related to allergic or infectious disease (45). NANIR can be divided into subgroups, depending on etiology.

Drug-induced rhinitis is dominated by nasal obstruction. Prolonged use of local decongestants may cause rhinitis medicamentosa, which is characterised by the development of a tolerance and rebound effect of the nasal mucosa. Systemically given drugs that may cause rhinitis include non-steroid inflammatory drugs, beta-blockers, sedatives, antidepressants and oral contraceptives and sildenafil (46).

Hormonal rhinitis is another subgroup of NANIR, dominated by pregnancy rhinitis which has an incidence of 22%. It may occur any time during pregnancy, and smoking is a risk factor (47). Symptoms will disappear after delivery. Hypothyroidism and acromegaly are other rare causes of hormonal rhinitis (26).

Occupational rhinitis is a further subgroup of NANIR. It is defined by inflammation of the nasal mucosa caused by exposure to irritants at the workplace. It typically occurs during working hours and improves during leave, although there is a risk for adaptation to symptoms (48).

In about 50% of NANIR, no clear aetiology can be identified behind the condition. This large subgroup is referred to as idiopathic rhinitis, previously named vasomotor rhinitis (44), and it is characterised by nasal hyper reactivity to non-specific stimuli (49). Rare diseases that may affect the nasal mucosa include granulomatosis with polyangiitis, sarcoidosis and cystic fibrosis (26).

Tobacco smoking

Smoking may cause nasal obstruction. It is associated with inflammation of the nasal mucosa and squamous cell metaplasia (50). Objective nasal measurements can be altered in smokers, according to a large cross-sectional study (51). Smokers were found to have lower nasal minimal cross-sectional areas, lower nasal cavity volumes and lower peak nasal inspiratory flow (PNIF) scores compared with controls. A lower decongestive capacity due to a less compliant nasal mucosa was also found in smokers compared with non-smokers. In the same cohort, smokers were more likely to report severe upper airway complaints, including nasal obstruction compared with non-smokers (52). Smoking has also been found to impair mucociliary clearance

(53). Moreover, cigarette smoking has also been associated with insomnia-like sleep disturbances, both objectively and subjectively (54, 55).

Anatomic and structural causes for nasal obstruction

Anatomic causes for nasal obstruction include septal deviation, turbinate hypertrophy and nasal valve collapse. In a recent study of 1,900 patients with moderate to severe sinonasal complaints, the prevalence of nasal valve collapse was 67%, of septal deviation 76% and of inferior turbinate hypertrophy 72% (56). Prevalence rates of these anatomical variations are not available in the general population.

Unusual structural causes are benign and malignant tumours of the nasal cavity (57) and rare congenital disorders such as choanal atresia. These anatomic and structural abnormalities may co-exist with mucosal conditions mentioned previously.

Classification and assessment of nasal obstruction

It is challenging to classify and assess nasal obstruction for research purposes. Since nasal obstruction is a sensation and subjective experience, it is often analysed using questionnaires and scales. Objective nasal obstruction can be analysed using different methods of measurement of the dimensions of the nasal cavities and of the airflow. The correlation between the subjective feeling of nasal obstruction and objective nasal measurements is uncertain, despite extensive research in this field. One suggested explanation for the discrepancies between subjective and objective measurements is that it is primarily the nasal valve that determines nasal resistances, and the feeling of nasal obstruction can instead be related to mucosal swelling in other areas of the nose, such as the ethmoid (58). Another explanation is the lack of use of validated questionnaires in many studies. According to a meta-analysis of 16 different studies, it was concluded that if a sensation of nasal obstruction was present, it was more likely to correlate with objective tests than in the absence of symptoms. There also seemed to be greater likelihood of a correlation between unilateral symptoms and unilateral objective measurements, than between bilateral symptoms and bilateral objective measurements (59). In a large cross-sectional study, highly significant associations were found between the subjective sensation of nasal obstruction and corresponding measures for nasal cavity volume, area and airflow (60).

The conflicting evidence in this field of research underlines the importance of using internationally, standardised definitions and classifications of nasal disease, validated questionnaires and scales, and standardised objective methods of nasal measurement. It is a prerequisite for uniformity and comparison of research results. A description of the different methods used

to define subjective and objective nasal obstruction in papers I–IV is presented below.

Allergic rhinitis and its Impact on Asthma (ARIA)

ARIA is a recognised consensus document that classifies AR into two categories: intermittent allergic rhinitis (IAR) and persistent allergic rhinitis (PER) (26). The presence of symptoms such as nasal obstruction, rhinorrhea, nasal pruritus, sneezing and possible conjunctivitis determines the classification.

IAR is defined by the presence of symptoms less than 4 days/week or less than 4 consecutive weeks. PER is defined when symptoms are present more than 4 days per week and more than 4 consecutive weeks.

Disease severity is defined as mild and moderate-severe. Mild encompasses presence of symptoms but no effect on sleep or daytime performance. Moderate-severe encompasses troublesome symptoms of various degrees with impaired sleep and daytime performance.

Few studies have validated the ARIA definition of IAR and PER. In a large epidemiological study, however, it was found that the previous definitions of seasonal allergic rhinitis and perennial allergic rhinitis cannot be used interchangeably with the new classification of IAR and PER (61). It seems as if PER is a distinct group, characterised by a more severe form of disease.

European Position Paper on Rhinosinusitis and Nasal polyps (EPOS)

According to the European Position Paper on Rhinosinusitis and Nasal polyps (EPOS), CRS is defined by two or more symptoms, one of which has to be nasal obstruction or nasal discharge, \pm facial pain/pressure, \pm reduction or loss of smell (34). There also has to be either endoscopic signs of nasal polyps, and/or nasal secretion, and/or oedema in the middle meatus, or CT scans with mucosal changes in the osteomeatal complex and/or sinuses. The symptoms must be present for at least 3 months without complete resolution. For research purposes, the epidemiological definition excludes endoscopic examination and CT scans. This CRS definition has been found to have a reasonable reproducibility and correlation with endoscopic findings and should be sufficiently reliable for use in epidemiological surveys (35, 62).

Sinonasal outcome test-22 (SNOT-22)

The most versatile disease specific, health related, quality of life instrument developed for use in CRS is the validated sinonasal outcome test-22 (SNOT-22) (63). It encompasses 22 questions on patient reported sinonasal complaints, physical problems, functional limitations and emotional consequences. It is sub-categorised into four domains: 'rhinologic' (seven questions), 'ear/facial' (five questions), 'sleep' (four questions) and 'psychologic' (six questions), which improve the precision when interpreting the data (64). The total score ranges from 0–110 points, with a low score indicating better quality of life. The minimal clinically important difference is 8.9 points (63).

According to a recent original and review study, the SNOT-22 score among healthy individuals without sinonasal disease was 11 ± 9.4 (65). SNOT-22 is a modified version of the SNOT-20, which did not include questions on nasal obstruction and loss of sense of taste and smell (66).

Questions on nasal symptoms, SHE-study

Questionnaires can be used to assess subjective symptoms of disease and should preferably be validated in order to improve specificity and sensitivity rates. The questions on nasal obstruction in the Sleep and Health in women (SHE) study questionnaire (paper I) were used to identify three subgroups: persistent nasal obstruction (PNO), hay fever and nasal obstruction at night (NON). The questions used were not validated initially, but the sensitivity and specificity were calculated during the study using objective nasal measurements, which had been performed on a subset of participants in a previous study (67).

Peak nasal inspiratory flow (PNIF)

Peak nasal inspiratory flow (PNIF) is a portable tool with which to measure nasal airflow (litres/minute, range 0–400) (58) (Figure 2). It should be performed after acclimatisation to indoor temperature, in a sitting or standing position (68). At the end of a full expiration, inhalation is performed as quickly and forcefully as possible through the nose. The mouth must be closed, and the mask should be pressed firmly over the face. The highest PNIF value of three satisfactory inspirations should be used since PNIF values improve with practice (69).

There are several factors that influence the PNIF value. Female gender and increasing age are associated with lower PNIF values (69), whereas height seems to affect the results in some studies but not in others (58). In one study of 100 healthy volunteers, a low peak expiratory flow (PEF) was predictive of a low PNIF (70). Hence, the low PNIF value may indicate a lower respiratory tract function or weak thoracic musculature, rather than

nasal obstruction. As a measure of lung function, however, PEF shows moderate correlations (0.6–0.7) with other measures of airflow limitation, such as forced expiratory volume in 1 second (71). PNIF has been used in a wide range of studies and has proven to be reliable and with a high reproducibility (58, 72-74). Technical shortcomings may, however, influence the results (75).



Figure 2. PNIF measurement

Other objective measurements of the nasal cavity may also be used for clinical and research purposes. Rhinomanometry measures the change in pressure and flow during normal respiration, and acoustic rhinometry measures the cross sectional area and volume of the nasal cavity through acoustic reflections (59). Neither method was used in papers I–IV; however, they deserve mentioning due to their extensive use in both clinical practice and research.

Sleep

Sleep regulation and normal sleep physiology

The neurobiology behind sleep and wakefulness is very complex. An intricate neural network in the brainstem, midbrain, hypothalamus and thalamus which extends to the cerebral cortex forms the basis of this system. In wakefulness, excitatory neurons, in the ascending reticular arousal system, arouse the thalamus and the cerebral cortex. In sleep, these excitatory neurons are inhibited by gamma-aminobutyric acid (GABA) neurons in the ventrolateral preoptic nucleus (VLPO). A mutual inhibition between these two systems enables the relatively sharp transition between sleep and wakefulness, described as the “flip-flop” switch. This switch is stabilised by orexin neurons in the hypothalamus, which are active during wakefulness (76).

Sleep regulation, i.e. the sleep-wake cycle, is considered to be an interaction between two processes, the circadian process (process C) and the homeostatic process (process S) (77). The circadian process is controlled by the neurons in the suprachiasmatic nucleus (SCN) in the hypothalamus, the brain's master clock. The SCN works in a 24-hour cycle. It is kept in synchrony with the external day-night cycle by light inputs from the retina and other exogenous factors during the day, and by melatonin secretion from the pineal gland during the dark cycle (76).

The homeostatic process (process S) is defined as an increase in sleep pressure, starting from the moment of awakening and continuing until the moment of sleep. The longer the time awake, the more sleep pressure is accumulated in the brain, and the longer it takes to dissipate it in sleep (78).

The mechanisms generating the sleep homeostasis are not completely known, but theories include the effect of neural energy metabolism and related adenosine and nitric oxide levels, the synaptic homeostasis hypothesis and the effect of immune system components, such as tumour necrosis factor alfa (TNF- α) and interleukin-1 β (IL-1 β) (78). These theories are closely linked to the physiological purpose of sleep, which is not known. A recent discovery, which links to the purpose of sleep, is the glymphatic system (79). It functions mainly during sleep, is largely disengaged during wakefulness and it clears the brain of neurotoxic waste products produced during wakefulness.

Sleep is analysed by electroencephalography (EEG), electrooculography (EOG) and electromyography (EMG) and staged into rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep, with stages N1, N2 and N3 (80). The progression from N1 to N3 typically occurs in succession order from light to deep sleep, with an accompanying increasing arousal threshold. Arousals are caused by both intrinsic and extrinsic stimuli and can disturb the progression of sleep stages any time. Normal sleep consists of 4–6 repetitive cycles of sleep of 90–120 minutes. Each cycle starts with NREM sleep and ends with REM sleep. In a young healthy adult, NREM sleep makes up about 75% of the whole night and dominates in the beginning of the night. Stage N2 makes up about 50% of the night's sleep, whereas REM sleep episodes make up about 20% of the night, and are short in the beginning of the night and longer and more frequent in the second sleep half. With advancing age, the proportion of deep sleep (N3) decreases and sleep fragmentation increases (1, 81).

Normal sleep duration ranges between 6 to 9 hours per night. U-shaped associations have been found between sleep duration and all-cause mortality and cardiovascular disease, with the lowest risk for a sleep duration of approximately 7 hours (82).

NREM sleep is characterised physiologically by slow, regular breathing, low blood pressure and pulse, and a sinking body temperature. REM sleep is characterised by the opposite, with irregular breathing and surges in cardiac-bound sympathetic and parasympathetic activity. Vivid, visual dreams occur during REM sleep. Muscle atonia prevails, except for the diaphragm and eye muscles, so that dreams are not acted out (1, 81).

Sleep disorders

Sleep disorders are common in the general population. The International Classification of Sleep Disorders, Third Edition (ICSD-3), classifies sleep disorders into seven main categories (83). The first and second categories are insomnia and sleep related breathing disorders, or sleep-disordered breathing (SDB), including obstructive sleep apnoea (OSA), which are the two most common sleep disorders and will be further discussed below.

The third category is central disorders of hypersomnolence, which include the rare disorders narcolepsy and idiopathic hypersomnia. The estimated prevalence of narcolepsy in Europe is 0.047% (84). The fourth category describes circadian rhythm sleep-wake disorders. The most common type is delayed sleep-wake phase disorder with a prevalence of 4% among Swedish adolescents (85). The fifth category is parasomnias, which are classified into NREM-related and REM-related parasomnias. NREM-related parasomnias include confusional arousals, sleep walking, sleep terrors and sleep related eating disorder with a prevalence of 1 to 4%. REM-related parasomnias in-

clude REM sleep behaviour disorder, isolated sleep paralysis and nightmare disorder with a prevalence of approximately 0.5%, with higher frequencies among patients with neurodegenerative disease, narcolepsy, or those taking antidepressant medications (86). The sixth category defines sleep-related movement disorders including Willis Ekbom disease/restless legs syndrome (RLS), which has a prevalence of 5–15% among Caucasians. It increases with age and is more prevalent among women. Periodic limb movements occur in 80% of patients with RLS and may aggravate the insomnia and sleep fragmentation caused by RLS (87). The seventh category defines other sleep-related symptoms or events that do not meet the standard definition of a sleep disorder.

Sleep-disordered breathing (SDB)

Obstructive sleep apnoea – definition and diagnosis

The official definitions of OSA and the related obstructive respiratory events of the upper airway have varied through the years, with consequences for prevalence rates, study results, scoring of sleep recordings and treatment of OSA. The current recommended definition of OSA, according to the American Academy of Sleep medicine (AASM), is the presence of at least five obstructive respiratory events (apnoeas, hypopnoeas or respiratory effort-related arousals) per hour of sleep, in combination with associated sleep related symptoms or medical disorders or as the presence of 15 or more obstructive respiratory events per hour of sleep in the absence of associated symptoms and disorders (83).

The golden standard method to diagnose OSA is with a polysomnographic (PSG) recording (see below). The definition of an apnoea is a reduction in airflow of $\geq 90\%$ compared with baseline for ≥ 10 seconds. An hypopnoea should be scored when there is a reduction in airflow of $\geq 30\%$ compared with baseline for ≥ 10 seconds in association with either $\geq 3\%$ arterial oxygen desaturation or an arousal (80). The severity of OSA is based on the number of apnoeas and hypopnoeas per hour of sleep, the apnoea-hypopnoea index (AHI), and is generally classified into three categories: light ($\text{AHI} \geq 5\text{--}14.9$), moderate ($15\text{--}29.9$) and severe ($\text{AHI} \geq 30$) OSA. In the Nordic countries and Europe, polygraphy (PG) or home sleep apnoea testing (HSAT) (see below) is generally used to investigate the presence of OSA. Due to inconsistencies regarding the guidelines for scoring between countries, Swedish national guidelines for scoring PG and PSG are available (88).

Risk factors and symptoms of obstructive sleep apnoea

Risk factors for OSA include obesity and other conditions that contribute to the narrowing of the upper airway, such as enlarged tonsils, macroglossia and retrognathia (89). Male gender, age and alcohol are also known risk factors for OSA (90). Typical symptoms of OSA include snoring, witnessed apnoeas, disturbed sleep, insomnia symptoms, awakenings due to choking at night, sweating, nocturia, dry mouth on awakening, morning headache, decreased libido, irritability, decreased concentration, memory loss, fatigue and excessive daytime sleepiness (EDS) (89). The latter was previously a pre-requisite for the diagnosis of obstructive sleep apnoea syndrome (OSAS), which included OSA and EDS, but has been replaced by OSA as defined above.

EDS is a symptom characterised by persistent sleepiness during the day-time despite an adequate time spent in bed during the night (91). It is also accompanied by impaired performance or neurocognitive function. EDS is considered an important symptom of OSA despite its poor correlation with objective sleep variables and low prevalence in OSA patients (92-94). The combination of severe OSA and EDS has been associated with increased risk for hypertension and increased mortality (95, 96). One possible explanation for EDS in OSA is the repetitive obstructive respiratory events that cause sleep fragmentation. This causal link is supported by the improvement in EDS by continuous positive airway pressure (CPAP) treatment (97). A vast number of other different medical, psychiatric and neurologic disorders besides OSA can cause sleep fragmentation and EDS, however, but insufficient sleep due to poor sleep hygiene or social factors is the most common cause. Consequently, the prevalence of EDS is difficult to estimate (91).

Prevalence of obstructive sleep apnoea

The prevalence of OSA in epidemiologic studies has increased steadily through the years. Methodological differences, varying scoring criteria and the obesity epidemic are considered important factors for this development. According to a review of eleven epidemiological studies between 1993 and 2013, the prevalence of OSA defined at an AHI ≥ 5 was a mean of 22% (range, 9–37%) in men and 17% (range, 4–50%) in women (90). OSA syndrome, defined as apnoea-hypopnoea index ≥ 5 and EDS, occurred in 6% (range, 3–18%) of men and in 4% (range, 1–17%) of women. In a Swiss population-based study of 2,121 individuals (the HypnoLaus cohort), who performed a PSG, the prevalence of moderate-to-severe OSA (≥ 15 events per h) was 23.4% in women and 49.7% in men (98). In these epidemiological studies, OSA is associated with cardiovascular disease such as hypertension, coronary artery disease, stroke and the metabolic syndrome, including diabetes and depression.

The high prevalence rates, the differences in clinical presentation, symptomatology and compliance with treatment for OSA patients demonstrate the complex pathophysiology behind the condition. OSA truly is a multifaceted disease, and there is a need for an individual risk assessment for associated diseases and an individualised treatment. Recent research in this field has therefore focused on identifying different phenotypes of OSA, where combinations of anatomic, physiological and subjective variables in OSA patients have been analysed (99-101).

Treatment of obstructive sleep apnoea

The primary treatment for OSA worldwide is nasal continuous positive airway pressure (CPAP). It reverses the repetitive upper airway obstruction, normalises sleep architecture and reduces associated symptoms and diseases, as well as reduces automobile accidents (102). Despite the efficacy of CPAP in reversing sleep apnoea, in studies using the cut-off point of at least 4 hours per night to define adherence, 29 to 83% of patients were non-adherent (103). Many predictors for CPAP adherence have been explored, but few have been identified. Nonetheless, important factors for CPAP adherence include the patient's knowledge of OSA and assessment and awareness of symptoms, referral source, bedpartner's involvement, exposure to and perception of CPAP treatment, psychological traits and claustrophobic tendencies (103).

In addition, nasal obstruction seems to play an important role in initial acceptance and adherence to CPAP. Studies of internal nasal dimensions by acoustic rhinometry and of nasal resistance by anterior rhinomanometry report that smaller nasal dimensions and high nasal resistance predict low CPAP adherence (104-106). Those reports are supported by the finding that nasal surgery of the septum and the inferior turbinates enable CPAP adherence in CPAP-refractory OSA patients with increased nasal resistance (107). Studies of long-term use of CPAP therapy have found improvement of both subjective and objective nasal obstruction, whereas short-term CPAP use (2 hours) causes subjective and objective reduction of nasal patency (106, 108, 109).

Other treatments for OSA include weight loss, mandibular advancement device and positional therapy. Surgery is also a treatment option for OSA. Although uvulopalatopharyngoplasty (UPPP) surgery has been found to cause long-term negative side-effects (110), a recent long-term follow-up study of modified UPPP found improvements in both AHI and daytime sleepiness (111). Tonsillectomy has been found to be an effective treatment of OSA in adults with a body mass index (BMI) below 32 kg/m² and large tonsils (Friedman size 3 and 4) (112).

Snoring and respiratory effort-related arousal

Snoring is a sound generated by vibrations of the soft and relaxed tissues in the oropharynx/pharynx during sleep. There is no international standardised method with which to perform objective measurements of snoring, nor a consensus regarding the analysis of sound recordings. Consequently, reports on the prevalence of snoring vary to a large extent.

According to epidemiological studies, the prevalence of self-reported snoring in women varies between 6.7% and 19.4% (113-115), and in men between 14.6% and 20.4% (113, 116). In those studies, self-reported snoring in both men and women was associated with obesity and was age-dependent, with peak prevalence between the ages of 50 and 60. Furthermore, self-reported snoring was associated with hypertonia and smoking in both genders and EDS in women. In the HypnoLaus cohort, PSG was used to investigate the objective prevalence of snoring, which was 44% in women and 66% in men (98).

Respiratory effort-related arousal (RERA) is considered an intermediate form of SDB in between snoring and sleep apnoea. It is defined by repetitive respiratory events lasting at least 10 seconds with a drop in inspiratory flow, increased respiratory effort and brief change in sleep state or arousal without concomitant oxygen desaturation (117). The first study on the prevalence of RERA in an unselected general population was performed on the HypnoLaus cohort. Less than 1% exhibited RERA as the predominant SDB, and ≥ 5 events per hour were found in 3.8% of the population (118). No associations between RERAs and EDS, hypertonia and the metabolic syndrome were found in that study in contrast to earlier studies in this field. The authors suggest that the low prevalence rates and lack of clinical associations may be due to their use of the most recent AASM hypopnoea definition which includes arousals, as opposed to previous, older AASM definitions of a hypopnoea, which did not include arousals.

Insomnia

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) and ICSD-3 define the criteria for the diagnosis of insomnia as a disorder similarly (83, 119). Insomnia as a disorder is defined by sleep disturbances at night, such as difficulties inducing sleep (DIS), difficulties maintaining sleep (DMS) and early morning awakenings (EMA), combined with related impaired daytime functioning such as EDS. The sleep problem has to occur at least 3 nights a week for a period of 3 months and is not better explained by another sleep disorder, mental disorder, or the direct physiological effects of a substance or medical condition.

According to epidemiological data from 10 different European countries, the prevalence of insomnia as a disorder varies between 5.8%–19% (120). In the Nordic countries of Finland and Norway, the prevalence has been estimated to 11.7% and 15.5%, respectively. In Sweden, a population based study, based on telephone interviews with 1,128 individuals in 2014, found that approximately 10.5% of the population had insomnia as a disorder, with a prevalence of 7.1% in men and 13.6% in women. The highest prevalence of insomnia disorder was 21.6% among women aged 40–49 years (121). The prevalence of insomnia symptoms (DIS and/or DMS) in the same study was 24.6%, with a higher prevalence reported by women than by men, 29.3% versus 19.4%.

In the general population, insomnia symptoms (DIS, DMS and EMA) are common with an average prevalence of about 30% according to international studies (122). Although data is limited on the natural history of insomnia, a Canadian study found insomnia to be a persistent condition, with a 1-year persistence of 74.2% and a 3-year persistence of 45.9% (123).

Risk factors for insomnia are female gender and old age (124). Co-morbid conditions associated with an increased risk for insomnia are multiple chronic medical conditions, chronic pain, and other primary sleep disorders including OSA. Substance abuse and shift work also increase the risk for insomnia (120, 124). The most common comorbidities associated with insomnia, however, are various psychiatric disorders, such as depression and anxiety disorders, with a co-occurrence with insomnia of 40% (122). There is a strong association between insomnia and depression, and insomnia is a risk factor for depression. Indeed, persistent insomnia has been found to increase the risk for developing a major depressive illness within a one-year period with a risk factor of at least 4. Also, insomnia symptoms are present in over 80% of subjects with a major depressive illness (122). Insomnia is also a risk factor for cardiovascular disease and diabetes mellitus type II (120).

Subjective assessment of sleep

There are numerous questionnaires with which to investigate different sleep disorders, sleep disturbances and consequences thereof. Only two, the Epworth Sleepiness Scale (ESS) and The Basic Nordic Sleep Questionnaire (BNSQ), have been used in this thesis, and those will be discussed below.

There are two questionnaires of great importance used internationally that also must be recognised, one of which is the Pittsburgh Sleep Quality Index (PSQI) (125). It can be used to assess subjective sleep during the previous month. Not only does it cover sleep quality but also other aspects such as sleep latency, sleep efficiency, sleep duration, daytime function and sleep medication. The second questionnaire widely used is the Insomnia Severity Index (ISI) to assess insomnia and which is also useful to follow-up the med-

ical treatment of the condition (126). It encompasses 5 questions, 7 items in total, regarding sleep quality, consequences for daytime functioning and assessments of how bothersome the sleep problems are to the individual and how obvious they are to others.

Epworth Sleepiness Scale (ESS)

The ESS is a well-known, validated questionnaire, evaluating the subjective risk of dozing off in eight different daytime situations (127). The ESS score (the sum of 8 item scores, 0–3) can range from 0 to 24 where a higher score indicates a higher degree of daytime sleepiness. A score of ≥ 10 points is often used as a cut off value for EDS in studies, whereas a value of > 10 is used clinically (128).

The ESS scale is considered an important measure of daytime sleepiness in clinical sleep medicine and has been used extensively in a wide variety of studies. Reports on the association between the ESS score and objective sleep variables demonstrate conflicting results. This is often the case, however, when evaluating a subjective state such as sleepiness, which is difficult to define with exact measurements (93, 94, 129). A recent study found poor test-retest reliability of the ESS scale, underlining the risk for misinterpretation of results (130).

Basic Nordic sleep questionnaire (BNSQ)

The BNSQ is a widely used sleep quality tool, which estimates subjective sleep problems and daytime symptoms according to their prevalence (131). It consists of 27 different items in 21 questions. In papers II and III, the questions on snoring, difficulties inducing sleep (DIS), difficulties maintaining sleep (DMS), early morning awakening (EMA) and excessive daytime sleepiness (EDS) were used to assess sleep quality. The response options of the BNSQ are never or almost never, less than once a week, once or twice a week, 3–5 nights/days per week and almost every day or night. A response of 3–5 nights/days per week or almost every day or night is usually considered pathological in epidemiological studies. Although widely used, the BNSQ has not been validated with objective sleep measurements.

Objective assessment of sleep

Polysomnography

Objective measurement of sleep and wake is ideally performed using polysomnography (PSG). It is used to understand normal and abnormal sleep patterns, to diagnose and exclude sleep disorders clinically and for research purposes. PSG includes recordings of electroencephalogram (EEG), electrooculogram (EOG), electrocardiogram (ECG), electromyogram (EMG) (chin muscles and m. tibialis anterior), (oro-) nasal airflow and snoring, oxygen saturation, respiratory movements (abdominal and thoracic respiratory effort bands) and body position during sleep. It can be performed in a sleep laboratory or as an ambulatory investigation. Sometimes, transcutaneous carbon dioxide measurements and video- and sound recordings are used in the sleep laboratory. All data from the PSG are scored manually and analysed according to international guidelines (80).

Polygraphy

Polygraphy (PG) or home sleep apnoea test (HSAT) is a less comprehensive method than PSG. It is mainly an analysis of the breathing pattern during sleep used to diagnose OSA. It is an ambulatory device most often used for one night in an in-home setting. It includes measurements of nasal airflow and snoring, oxygen saturation, pulse and respiratory movements and body position (80). PG is less sensitive than PSG, since it produces an estimate of respiratory events based on monitoring time, whereas PSG identifies the apnoea-hypopnoea index (AHI) based on actual sleep time. A PG recording is also unable to detect hypopnoeas that are only associated with cortical arousals. Due to these limitations, a PG recording may underestimate the severity of OSA (132). This is also why the Swedish sleep apnoea registry has introduced a 3% oxygen desaturation limit in the hypopnoea definition, instead of 4%. The difference in AHI between PSG and PG will then be reduced (88).

Other objective methods of importance when investigating sleep disturbances and sleepiness include the Multiple Sleep Latency Test, the Maintenance of Wakefulness Test, different vigilance tests and actigraphy. Although not an objective measurement, the sleep diary is a valuable tool in diagnosing sleep disturbances.

Nasal obstruction and sleep

Numerous studies have identified associations between nasal obstruction and sleep impairment. However, the studies differ greatly in design, number of subjects included and methodology, which makes it difficult to make comparisons and draw conclusions on the role of nasal obstruction *per se* in relation to sleep quality. The majority of investigations have been performed on subjects with allergic rhinitis and CRS, diseases where nasal obstruction is the major symptom. Nasal obstruction and its role in SDB have also been investigated, with inconclusive results. These three perspectives on nasal obstruction and sleep quality will be discussed separately below.

Nasal obstruction, allergic rhinitis and sleep

According to epidemiologic data, there is a strong association between allergic rhinitis and impaired sleep quality (Table 1). Two population-based studies from Europe, using validated questionnaires on allergic rhinitis and sleep quality, reported strong associations between the disease severity of allergic rhinitis and sleep impairment (31, 133). Furthermore, in a large cross-sectional study in Sweden, Iceland and Belgium, allergic rhinitis was found to be independently associated with DIS, daytime tiredness and daytime sleepiness (134). In an early report from the Wisconsin Sleep Cohort Study, which included both questionnaires and PSG, self-reported nasal obstruction at night due to allergy was associated with snoring (OR 1.5) and SDB with an AHI > 15 (OR 1.8) (135). In addition, strong associations were found for chronic night-time symptoms of rhinitis and snoring, EDS and chronic non-restorative sleep. Also, a cross-sectional, follow-up study of the same cohort after 5 years confirmed that nocturnal nasal congestion was strongly and independently associated with snoring frequency. The adjusted odds ratios for habitual snoring with severe nasal congestion, as opposed to none was 3.0 (95% CI, 2.2–4.0). Patients with significant sleep-disordered breathing (i.e. AHI > 5/h) were excluded from analysis (136).

Studies of treatment of allergic rhinitis with intranasal corticosteroids reported an improvement in subjective sleep quality and daytime somnolence, which were strongly correlated with a reduction in subjective nasal obstruction (137).

Table 1. *Epidemiological studies on nasal obstruction and sleep quality*

Author	Year	Study design	Study group	Methods	Results
Colas et al. ³¹	2012	Population-based	AR (n=2,275)	TSS, RQLQ, PSQI	AR disease severity had a strong relationship with sleep impairment. Nasal obstruction contributed to poor sleep quality.
Leger et al. ¹³³	2006	Population-based	AR (n=591)	SDQ, ESS, symptom score	AR impaired all dimensions of sleep. Disease severity of AR correlated with the degree of sleep impairment.
Young et al. ¹³⁵	1997	Population-based	Survey subjects (n=4,297) Objective testing subjects (n=911)	Questionnaire, PSG	AR and nasal obstruction were associated with snoring, EDS and SDB.
Janson et al. ¹³⁴	1996	Observational cross-sectional	Random population of the ECRHS (n=2,661)	SPT, methacholine challenge, questionnaire	AR was independently associated with DIS (OR 2.0) and daytime sleepiness (OR 1.3).

AR – allergic rhinitis, DIS – difficulties inducing sleep, ECRHS – European Community Respiratory Health Survey, EDS – Excessive daytime sleepiness, ESS – Epworth Sleepiness Scale, PSG – polysomnography, PSQI – Pittsburgh Sleep Quality Index, RQLQ – Rhinoconjunctivitis Quality of Life Questionnaire, SDB – sleep-disordered breathing, SDQ – Sleep Disorders Questionnaire, SPT – skin-prick test, TSS – total symptom score

Objective measurements of sleep quality in allergic rhinitis reveal mixed results. One study using actigraphy found increased sleep fragmentation and reduced sleep quality in subjects with PER (138). Studies using PSG to investigate sleep quality in IAR and PER compared with healthy controls found no or modest changes without clinical relevance in PSG parameters (139, 140). Similarly, no differences were found in PSG parameters among patients with symptoms of SDB and PER, compared with a matched control group without any nasal inflammation (141). On the other hand, there are reports with opposite results. In the early 1980s, both an increased number of microarousals and more frequent and longer apnoeas were reported in subjects with allergic rhinitis (142, 143). Also, quite recently, in OSA patients with allergic rhinitis, treatment with intranasal corticosteroid improved the oxygen saturation level and the supine AHI score compared with OSA patients without allergic rhinitis receiving the same treatment (144).

Nasal obstruction, CRS and sleep

Few studies have investigated sleep quality in CRS. In recent years, however, the body of literature in this field of research has increased. Prior to the publication of paper II, there was no population-based study investigating sleep quality in CRS, although there were studies using other methodologies as presented in Table 2.

In a case-control study from France, CRS patients with nasal polyps were found to have a two-fold higher risk of suffering from sleep disturbance compared with controls, and snoring was reported by 50.5% of patients with nasal polyps (145). In a cross-sectional analysis of a multi-centre study in North America, 75% of patients with CRS reported poor sleep quality (146). Furthermore, in a cohort study based on the same CRS population, but analysing patients who voluntarily elected endoscopic surgery as treatment modality, 72% reported poor sleep quality at baseline and improved sleep after surgery (147). Similarly, 53 patients with CRS, but without nasal polyposis, were found to have poor sleep quality prior to surgical intervention with improved scores post-surgery (148). Indeed, most studies on CRS and sleep quality is interventional and have been performed on patients before and after functional endoscopic sinus surgery (FESS). The results are consistent, with improved subjective sleep quality post-surgery (149-151). Studies on CRS and objective sleep quality using PSG are scarce. The few studies that have included PSG pre- and post-surgery report no or minor changes in AHI and other PSG parameters (152, 153).

Table 2. *Studies measuring sleep quality in CRS.*

Author	Year	Study design	Study group	Methods	Results
Serrano et al. ¹⁴⁵	2005	Case control	212 CRS patients with nasal polypsis, 502 controls	A validated sleep quality questionnaire with 4 domains related to sleep	The OR (95% CI) of sleep disturbance in CRS patients was 2.25 (1.54-3.29) compared with healthy controls
Alt et al. ¹⁴⁶	2013	Cross-sectional	268 patients with CRS	PSQI	75% of patients reported poor sleep quality with PSQI scores > 5. Mean \pm SD PSQI score was 9.4 (4.4).
Alt et al. ¹⁴⁷	2014	Cohort	301 patients with CRS	PSQI	72 % of patients reported poor sleep quality with PSQI scores > 5. Mean \pm SD PSQI score was 9.4 (4.6).
Rotenberg et al. ¹⁴⁸	2015	Cohort	53 patients with CRS, without nasal polypsis	PSQI ESS	Mean \pm SD PSQI score was 10.9 \pm 2.8 Mean \pm SD ESS score was 14.7 \pm 3.1

CRS – Chronic rhinosinusitis, ESS – Epworth Sleepiness Scale, PSQI – Pittsburgh Sleep Quality Index

Only a few studies have evaluated CRS and its association to OSA, with inconsistent results. The prevalence of self-reported physician-diagnosed OSA was 15% among 405 patients with medically refractory CRS (154), as opposed to 64.7% of 139 CRS patients, when OSA was diagnosed with PSG (155). In a retrospective, population-based study in Taiwan, the adjusted hazard ratio of subsequent CRS for patients with OSA was 3.18 (95% CI, 2.27–4.45), compared to those without OSA, regardless of gender (156).

Nasal obstruction and sleep-disordered breathing

The number of population-based studies on nasal obstruction and SDB is limited, but associations between nasal obstruction and snoring and OSA have been reported (135, 136). However, the pathophysiological mechanisms behind this link are not clear, but theories include the Starling resistor model, the unstable oral airway, the nasal ventilatory reflex and the role of NO (157). According to these theories, increased nasal resistance will cause a negative oropharyngeal pressure and suction force. A higher fraction of oral breathing will cause an unstable airway. Furthermore, a reduced stimulation of the nasal ventilatory reflex will cause a reduction in muscle tone in the oropharynx, as well as a reduction in respiratory rate and minute ventilation. A reduction in nasal flow will also generate a lower concentration of pulmonary NO with reduced ventilation-perfusion ratio as a consequence (157).

In healthy individuals, without nasal obstruction and sleep apnoea, nasal breathing dominates both during wakefulness and during sleep, regardless of sleep stage and position (158). The oral fraction of inhaled air accounts for only 7% during wakefulness and 4% during sleep. Furthermore, upper airway resistance is increased 2.5 times when breathing orally compared with nasally during sleep, with an associated increase in AHI and shorter total sleep time (159). When comparing OSA patients and simple snorers without nasal obstruction, OSA patients were found to spend more time breathing orally and oro-nasally compared with simple snorers (160). Also, AHI was found to be a determinant of time spent breathing orally and oro-nasally. Consistent results were reported from studies performed in the 1980s, in which nasal obstruction was induced experimentally in healthy subjects, with findings of increased arousals and AHI, altered sleep architecture with decreased deep sleep and more frequent sleep stage changes (161-163). Subjective complaints such as dry mouth, frequent awakenings and restlessness were also reported.

The above-mentioned theories and results suggest a plausible link between nasal obstruction and OSA. Indeed, a large clinical study of 541 unselected, consecutive snorers found nasal obstruction to be an independent, but small, risk factor for OSA, along with BMI, male gender and cephalometric

parameters, which also were contributing factors to the AHI (164). On the other hand, there are several reports that have not found a correlation between the degree of nasal obstruction and OSA severity/AHI (165-167) (Table 3). For example, in a study of 683 patients referred for investigation of snoring and possible sleep apnoea, no significant difference in AHI and snoring indices were found among three nasal resistance groups (normal, high unilateral and high bilateral). Furthermore, there was no significant difference in the frequency of patients with different severities of AHI and snoring among the three groups (166). Importantly, in these studies, nasal resistance was measured in the awake, sitting position, which may have influenced the results. When body position was taken into consideration, similar study results have been achieved, however, with no association between the degree of nasal obstruction and AHI and snoring severity (168). Nevertheless, in one study a correlation was found between total nasal resistance measured in a supine position and AHI and ODI in non-obese patients (169).

Most studies on nasal obstruction and OSA have focused on AHI as an outcome measure. Studies on sleep architecture and analysis of arousals in the context of nasal obstruction and sleep disturbances, including OSA, are scarce. This was stated in a systematic review of 11 different studies of the influence of nasal obstruction on OSA and other polysomnography indices associated with respiratory events (170). Only four of the 11 studies meeting the inclusion criteria had analysed arousals before and after successful medical or surgical treatment of nasal obstruction. Of these, one study using nasal decongestant as treatment modality reported reduced number of arousals, and only a modest reduction of AHI and no change in subjective outcome score (171). The other three studies, in which surgical treatment had been performed, did not find a reduction in arousal index or AHI, but in two of them snoring and ESS improved (152, 172, 173).

In summary, results of studies on the association between nasal obstruction (independent of cause) and sleep quality are inconsistent. One possible explanation for this is the wide variety of different study methodologies, study subjects, sample sizes, outcome measures, etc. Collectively, current knowledge indicates that nasal obstruction plays an important, albeit not decisive, role in sleep quality. It contributes to worse subjective sleep quality, which is improved by medical and surgical treatment in most studies. Nasal obstruction also seems to be a contributing factor to snoring, but has a limited effect on other objective sleep variables measured with PSG. The lack of improvements in objective sleep parameters despite adequate treatment of nasal obstruction in interventional studies supports this notion, including the fact that most studies have failed to establish a linear relationship between the degree of nasal obstruction and OSA severity.

Table 3. *Studies of nasal resistance and OSA.*

Author	Year	Study design	Study groups	Methods	Results and conclusions
Blakley et al. ¹⁶⁵	1987	Case control	53 OSA patients 37 controls	NR measured with anterior rhinomanometry in an upright position, PSG	No correlation between NR and AHI. NR is not a major factor in severe OSA.
Miljeteig et al. ¹⁶⁶	1992	Cohort	683 snorers, divided into 3 NR groups: normal, high unilateral, high bilateral	NR measured with plethysmographic recordings in an upright position, PSG	No difference in sleep and snoring variables among the three NR groups. NR has little effect on snoring and OSA severity.
Atkins et al. ¹⁶⁷	1994	Case control	70 apnoeic snorers 71 non-apnoeic snorers	NR measured with anterior rhinomanometry in an upright position, PSG	NR did not differ in the two groups. No correlation between NR and AHI. NR is not a significant risk factor in the development or severity of OSA.
Lofaso et al. ¹⁶⁴	2000	2-year prospective cohort	541 snorers	NR measured with posterior rhinomanometry, in an upright position, PSG, cephalometry	NR was higher in snorers with an AHI > 15. NR is an independent, small risk factor for OSA.

De Vito et al. ¹⁶⁸	2001	Cohort	36 OSA patients, 3 groups of NR severity identified	NR measured with anterior and positional rhinomanometry, PSG	No difference in OSA severity between normal NR and pathological NR. NR is not a risk factor for OSA severity.
Virkkula et al. ¹⁶⁹	2003	Case control	41 snorers, apnoeic and non-apnoeic, 19 controls	NR measured with anterior rhinomanometry and NV with acoustic rhinometry in an upright, supine and upright position after decongestion, PSG	Supine NV correlated with AHI in all patients. Supine NR correlated with AHI in non-obese patients. No correlation between upright NR and AHI. NR may influence OSA severity.

AHI – apnoea-hypopnoea index, NO – nasal obstruction, NR – nasal resistance, NV – nasal volume, OSA – obstructive sleep apnoea, PSG – polysomnography

Sleep, nasal obstruction and inflammatory cytokines

Treatments of nasal obstruction in AR and CRS have been found to reduce the inflammatory status of the nasal mucosa and improve subjective sleep quality (137, 174). These findings have suggested a role for immune modulating mediators, such as cytokines, in sleep regulation of these diseases and as a contributing factor to the sickness behaviour seen in these patient groups (175). The bidirectional communication between the immune system and sleep is the basis for this theory. It is a very sophisticated interaction, which not only requires further research to be completely elucidated, but which is far too complex to be fully described in the scope of this introduction. Hence, selected points of interest will be presented below.

There are many different cytokines, but the two pro-inflammatory cytokines, IL-1 and TNF- α , are the best studied cytokines in the context of sleep regulation. This is because of their definition as sleep regulating substances (SRS) (176). As such, they are involved in the homeostatic regulation of sleep. By definition, a SRS should increase sleep amount, whereas inhibiting the biological action or production should result in a decrease of spontaneous sleep, and the daily cyclic variations in the synthesis of the SRS should follow sleep-wake behaviour (1). SRS (IL-1 and TNF- α) are produced peripherally as a response to inflammation and infection and can communicate via juxtacrine, autocrine and paracrine signalling pathways with the CNS. Five main pathways have been identified through which SRS stimulate sleep: 1) stimulation or alteration of afferent transmission (e.g. through the vagus) with consequential signalling to the brain, 2) transport across the blood brain barrier (BBB) through the circumventricular organs, 3) altering the level or activity of another substance that signals the brain, 4) altering the blood-brain barrier and 5) direct passage across the BBB (175).

IL-1 and TNF- α play a critical role in the regulation of NREM sleep, and have been found to promote NREM sleep under both physiological and inflammatory conditions (176). A theory of an adaptive sleep response to immune activity has been put forward recently (1). It means that the doses of environmental stimuli (i.e. food intake, stress), commensal gut bacteria and pathogens (virus, bacteria) determine the effect on NREM and REM sleep. According to this theory, a subtle immune activation, causing low levels of IL-1 and TNF- α , may be involved in the homeostatic regulation of NREM sleep that in turn may serve to restore immune homeostasis. A severe immune activation, causing high levels of IL-1 and TNF- α , seems to disrupt both NREM and REM sleep and is often accompanied by sleep fragmentation, feelings of non-restorative sleep and daytime fatigue. A moderate immune activation during an infection may enhance NREM sleep and reduce

REM sleep, which in turn may support host defence and immunological memory formation (1).

The role of other inflammatory cytokines in sleep regulation is less well studied than that of IL-1 and TNF- α . Although they do not meet the criteria of SRS, pro-inflammatory cytokines (i.e. interferon- γ , IL-2, IL-6, IL-15, IL-18) seem to promote NREM sleep, whereas anti-inflammatory cytokines (i.e. IL-4, IL-10, IL-13) appear to reduce NREM sleep (1). One must remember, however, that most studies in this field have been performed in animals and need further confirmation in human studies. Also, there are several other factors of importance in sleep regulation besides cytokines, including hormones of the hypothalamic-pituitary-adrenal (HPA) and the somatotrophic axes; neurotransmitters such as acetylcholine, serotonin, norepinephrine, histamine and dopamine; neuropeptides such as orexin; the nucleoside adenosine and the hormone melatonin (1).

There is ample evidence that sleep-deprivation enhances the levels of IL-1 and TNF- α , leading to a wide range of symptoms of sleep loss such as sleepiness, fatigue, sensitivity to pain, depression, impaired cognition, memory and performance (176). These symptoms can also be induced by injections of exogenous IL-1 and TNF- α and in some cases blocked if the cytokines are inhibited. Further, elevated levels of IL-1 and TNF- α have been found in chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease (1). These diseases are not only associated with sleep disturbances, but also with the above-mentioned symptoms, often referred to as symptoms of sickness behaviour. The same pattern with poor sleep quality and sickness behaviour is found in AR and CRS, also inflammatory disorders.

There is a paucity of studies, however, that have addressed the pathophysiological mechanisms responsible for sleep disturbances in CRS and AR. It may be due to the difficulty in interpreting sleep and immune system markers, since they would also be affected by comorbid conditions (i.e. depression, pain, obesity). Another challenge in such studies would be to interpret the associations between sleep and immune system markers in light of disease intensity and duration (1). Available studies in this field have reported elevated levels of several pro-inflammatory cytokines in the nasal mucosa of CRS patients, including IL-1 β and TNF- α (175, 177). Anti-inflammatory treatment with systemic steroids significantly reduced those levels and corresponding inflammation. Increased gene expression of the anti-inflammatory cytokines IL-4 and IL-13 in the nasal mucosa of CRS patients were associated with some aspects of sleep dysfunction (178). When interpreting those results, the limited number of 20 patients, who all had received prednisone treatment before mucosal collection, has to be taken into consideration. In patients with AR, increased levels of serum IL-1 were found compared with non-allergic controls (179). The serum IL-1 level was related to increased

latency to sleep onset and REM, as well as decreased time in REM according to PSG recordings.

It is not known what happens with sleep regulation and the levels of TNF- α and IL-1 after treatment of nasal obstruction in CRS and AR. However, it is known that the subjective sleep quality improves as well as quality of life measures, indicating a reduction in sickness behaviour (137, 149-151). Whether this is caused by a reduction in nasal obstruction, or of the local inflammation of the nasal mucosa (i.e. lower TNF- α and IL-1 levels as a result of intra-nasal cortisone treatment and FESS) is not known. In addition, the mechanisms by which cytokines signal the CNS to cause sickness behaviour and poor sleep quality in patients with CRS and AR are unknown.

Although the traditional view of the cause-effect relationship is that an inflammatory response causes poor sleep quality, the opposite relationship also has to be considered in this context. Epidemiological data on asthma, also an inflammatory disorder of the upper airway, have linked insomnia symptoms to an increased risk of developing asthma (180, 181). Experimental studies have found associations between sleep deprivation and increased secretion of pro-inflammatory cytokines (182, 183). Hence, the underlying pathophysiology may be that insomnia symptoms contribute to a state of inflammation. Furthermore, sleep deprivation, as seen in chronic insomnia, has been associated with a state of hyperarousal, with an activation of the HPA axis and the sympathetic nervous system, resulting in increased levels of cortisol and adrenocorticotrophic hormone (ACTH) in insomniacs compared with controls (184). Such prolonged stress may cause glucocorticoid receptor resistance, which results in failure to down-regulate the inflammatory response, thereby increasing the risk of inflammatory disorders (185).

In summary, chronic inflammatory diseases have been associated with increased levels of the SRS TNF- α and IL-1. These diseases have also been associated with sleep disturbances and sickness behaviour, which can be induced by TNF- α and IL-1. Although poorly investigated in AR and CRS, increased levels of inflammatory cytokines, such as TNF- α and IL-1, have been suggested to contribute to the poor sleep quality and sickness behaviour seen in these patient groups. Whether elevated levels of cytokines caused by the chronic inflammation contribute to sleep disruption and sickness behaviour, or vice versa, remains to be elucidated. Further investigations into this field are necessary to understand the complex and bidirectional communication between the immune system and sleep regulation.

Rationale

The role of nasal obstruction in sleep quality is not clear. Additional research is needed to better understand this relationship.

Only a few population-based studies on nasal obstruction and sleep quality have been performed. No gender specific studies have been performed in this field. Further studies exploring the relationship between subjective nasal obstruction, and both subjective and objective sleep quality, are needed.

EPOS 2012 stated a paucity of accurate epidemiological data on CRS, and a need for large-scale, epidemiological studies in Europe to analyse the prevalence and incidence of CRS. In addition, sleep quality in CRS has not been investigated with sleep quality instruments in epidemiological studies.

Sinonasal complaints are prevalent among OSA patients, but have been sparsely investigated using sinonasal health-related quality of life instruments, such as SNOT-22. In OSA patients, treatment with CPAP is often terminated due to nasal obstruction. To improve CPAP adherence rates, it would be desirable to have a tool that was able to identify patients with nasal obstruction who may be at risk of low adherence. Initial CPAP treatment could then be personalised and optimised, with improved adherence as a result.

Aims

- I To analyse the impact of self-reported nasal obstruction at night in women, on subjective sleep quality and daytime symptoms, and on objective sleep variables measured with PSG.
- II To analyse the prevalence of sleep problems and excessive daytime sleepiness in subjects with CRS, as assessed by the EPOS epidemiological diagnostic criteria, and to determine whether the disease severity of CRS affects subjective sleep quality.
- III To analyse if incident CRS, as assessed by the EPOS epidemiological diagnostic criteria, is associated with impairments of subjective sleep quality and excessive daytime sleepiness, and to study if insomnia symptoms constitute an increased risk for the development of CRS.
- IV To analyse the sinonasal health in obstructive sleep apnoea patients using the SNOT-22, and to analyse if the SNOT-22 is influenced by the level of CPAP adherence. To investigate if PNIF can predict adherence to CPAP.

Methods

Study populations

Paper I

A cross-sectional, community-based study

‘Sleep and health in women’ (SHE) is a community based study in Uppsala, Sweden. A postal questionnaire was sent to 10,000 randomly selected women aged ≥ 20 years in 2000. The response rate was 71.6%, and 7,051 women were included. Of those, 400 women aged 20–70 years were included in paper I. They underwent a home PSG recording overnight and completed an additional questionnaire. An oversampling of habitual snorers was made to obtain a wider range of SDB in the study population.

Paper II

A national, cross-sectional, population-based study

The Global Allergy and Asthma European Network of Excellence (GA²LEN) consists of 22 centres in Europe. In 2008, the Swedish GA²LEN survey was conducted to collect information on asthma, allergy and upper airway disease among adult Europeans. It was sent to 45,000 randomly selected subjects aged 16–75 years in the four cities of Umeå, Uppsala, Stockholm and Gothenburg. After three reminders, the response rate was 59.2%, equivalent to 26,647 subjects.

Paper III

An international, multi-centre, population-based prospective study

The Respiratory Health in Northern Europe (RHINE) study is an ongoing population-based study that has been conducted in five Northern European countries since the early 1990s (186). Paper III is based on data from the two follow-up stages, RHINE II and RHINE III, which were conducted in 1999–2001 and 2010–2012, respectively. Randomly selected men and women born in 1945–1973 were sent almost identical postal questionnaires to collect baseline (RHINE II) and follow-up data (RHINE III). After two reminders,

the response rate for RHINE II was 75%, equivalent to 16,106 subjects, and for RHINE III 53%, equivalent to 11,441 subjects. To be able to analyse those who developed CRS, a subgroup of 5,145 subjects was identified among those who had responded to both questionnaires. These subjects had no nasal symptoms at baseline. The data on this subgroup were analysed at baseline and follow-up.

Paper IV

A clinical, prospective cohort study

The study was conducted at the Centre of Sleep and Breathing at Uppsala University Hospital in 2014–2015. Patients aged 18 to 80 years, diagnosed with OSA and prescribed CPAP treatment, were consecutively recruited to the study in connection with the initiation of CPAP treatment. The cohort of 197 patients was subsequently divided into two groups, based on adherence to CPAP. An average use of CPAP treatment of ≥ 4 hours/night was regarded as adherent, while < 4 hours/night was non-adherent.

Definitions and questionnaires

Nasal obstruction was defined by questionnaire data in all four studies; moreover, in paper IV, it was also investigated objectively with PNIF.

In paper I, the participants were classified into three subgroups: persistent nasal obstruction (PNO), hay fever and nasal obstruction at night (NON). To be defined as having PNO, the participants had to answer yes to the question ‘Have you ever suffered from nasal symptoms such as nasal obstruction, rhinorrhoea and/or sneezing without having a current cold?’ They also had to confirm the symptom ‘nasal obstruction’ when asked ‘What nasal symptoms do you suffer from?’ and had to answer ‘daily/several times a week’ to the question ‘How often have you had nasal symptoms during the last 12 months?’ Participants answering ‘yes’ to the question ‘Do you suffer from hay fever or any other nasal allergy?’ were defined as having hay fever. The question ‘Do you suffer from nasal congestion at night?’ had five alternative answers of ‘never’, ‘rarely’, ‘sometimes’, ‘often’ and ‘very often’. Participants answering ‘often’ and ‘very often’ were defined as having NON.

To investigate the extent to which NON affected the other two subgroups and related symptoms, two more subgroups were defined, PNO-NON and hay fever-NON, where all NON subjects were excluded from the total population and the subgroups.

In papers II, III and IV, nasal obstruction was defined as part of the CRS definition according to the EPOS epidemiological criteria with a minimal duration of 3 months (34). In paper II, disease severity of CRS was defined

by categorising the subjects into five groups according to the number of CRS symptoms they confirmed (0-4). The symptoms were added without any specific order. PER was defined according to the ARIA definition in paper II (26). In paper IV, the sinonasal domain of the SNOT-22 was also analysed (63).

Sleep quality and daytime symptoms were defined using questionnaire data in all four studies. In paper I, questions on several different aspects of sleep quality, including snoring and daytime symptoms were considered positive if they occurred 'often' or 'very often' or were rated 'severe' and 'very severe'. The BNSQ was used in papers II and III to define DIS, DMS, EMA and EDS at least 3–5 times/week (131). In paper III, insomnia was defined as either of DIS, DMS or EMA in combination with EDS at least 3–5 times/week. Snoring was defined as 'having loud and disturbing snoring' at least 3–5 times/week in papers II and III (187). In Paper IV, the sleep domain of the SNOT-22 was also analysed.

To investigate daytime sleepiness, the ESS was used in papers I and IV (127). A score ≥ 10 was considered to indicate excessive daytime sleepiness. To evaluate anxiety and depression, the Hospital Anxiety and Depression (HAD) scale was used in papers I and IV (188). The HAD scale is a validated 42-point self-assessment scale consisting of 14 questions, seven on anxiety and seven on depression. A score of ≥ 8 in either category was considered to indicate possible disease.

In papers I and IV, sleep quality was also investigated objectively with PSG and PG, respectively. For an overview of the methods used to define and assess nasal obstruction, sleep quality and daytime symptoms, see Table 4.

Table 4. *Methods used to define and assess nasal obstruction, sleep quality and daytime symptoms in the four papers included in the thesis.*

	Paper I	Paper II	Paper III	Paper IV
Nasal obstruction	SHE questionnaire	EPOS ARIA	EPOS	EPOS SNOT-22 PNIF
Sleep quality	SHE questionnaire PSG	BNSQ (DIS, DMS, EMA, snoring)	BNSQ (DIS, DMS, EMA, snoring)	SNOT-22 PG
Daytime symptoms	SHE questionnaire ESS HAD scale	BNSQ (EDS)	BNSQ (EDS)	ESS HAD scale

ARIA – Allergic Rhinitis and its Impact on Asthma, BNSQ – Basic Nordic Sleep Questionnaire, EMA – early morning awakening, DIS – difficulties inducing sleep, DMS – difficulties maintaining sleep, EPOS – European Position Paper on Rhinosinusitis and Nasal Polyps, ESS – Epworth Sleepiness Scale, HAD – Hospital Anxiety and Depression, PG – Polygraphy, PNIF – Peak Nasal Inspiratory Flow, PSG – Polysomnography, SHE – Sleep and Health in women study, SNOT-22 – Sinonasal Outcome test 22

The four study questionnaires also included questions on:

SHE: airway diseases, allergies, nasal surgery, hormonal treatment, tobacco use, physical activity, cardiometabolic disease and current medication.

GA²LEN: upper and lower respiratory disease, age, gender, height, weight, tobacco use, sleep medication, eczema, environmental and workplace exposure, education level, physical activity and cardiovascular co-morbidity.

Combined RHINE questionnaires: upper and lower respiratory diseases, age, gender, height, weight, smoking habits, co-morbidities, diet, environmental and workplace exposure. Questions on menstrual cycle and sleep medication were only asked in the baseline questionnaire, whereas education level, marital status, heredity of disease, physical activity and OSA were only asked in the follow-up questionnaire.

Paper IV: nasal symptoms and nasal allergies, nasal medication and smoking. Baseline information on comorbidities was collected from the medical records associated with the sleep apnoea investigation. A questionnaire on symptoms related to CPAP treatment was used at follow-up.

BMI was calculated based on self-reported height and weight in papers II and III, whereas it was measured and calculated in conjunction with PSG and PG in papers I and IV.

Peak nasal inspiratory flow (PNIF)

In paper IV, PNIF was measured at baseline and at follow-up, with a standard peak nasal inspiratory flow meter, range 0–370 litres/minute. After having become acclimatised to the indoor room temperature for ≥ 30 minutes, all the patients were tested in a sitting position. At the end of a full expiration, the patients were instructed to inhale as quickly and forcefully as they could through the nose, with the mouth closed and with the mask firmly over the face. Three satisfactory inspirations were obtained, and the highest PNIF value was used in the statistical analyses.

Peak expiratory flow (PEF)

As part of the clinical sleep apnoea investigation in paper IV, patients also performed peak expiratory flow (PEF), to measure lower respiratory tract function. This was performed in a sitting or standing position two or three times with a standard range peak flow meter. The highest value was used in the statistical analyses.

Polysomnography

The participants in paper I underwent a complete, ambulatory PSG recording (Embla, Flaga hf, Iceland) during one night, in their own homes or at the patient hotel in close proximity to the hospital. Sleep was scored manually in 30-second epochs (189). An obstructive apnoea was defined as the complete cessation of the oronasal airflow for at least 10 seconds with continuing thoracic and abdominal movements. An obstructive hypopnoea was defined as a decrease in the oronasal airflow of at least 50% compared with baseline for at least 10 seconds, accompanied by a desaturation of 3% or an arousal, and with continuing thoracic and abdominal movements. An apnoea-hypopnoea index (AHI) was calculated as the average number of apnoeas and hypopnoeas per hour of sleep, while the oxygen desaturation index (ODI 4%) was calculated in a similar manner based on desaturations of $\geq 4\%$. Total sleep time (TST), sleep latency (SL), sleep efficiency, number of awakenings (at least 30 seconds), percentage of sleep time spent in sleep stages 1 and 2 and 3 and 4, percentage of sleep time spent in REM sleep, percentage of sleep time spent in a supine position, percentage of sleep time spent snoring, number of transitions and saturation minimum were collected from the polysomnographic data (Somnologica, Version 2.0, Flaga hf).

Polygraphy

The patients in paper IV underwent a diagnostic, ambulatory PG recording (Nox T3, Nox Medical, Iceland) during one night in their own homes. It included measurements of saturation and pulse by pulse oximetry, respiratory movements by thoracic and abdominal belts and nasal airflow and snoring by a nasal thermistor. An apnoea was defined as a $> 90\%$ reduction in nasal airflow lasting ≥ 10 seconds. A hypopnoea was defined as a 30–90% reduction in nasal airflow lasting ≥ 10 seconds with a desaturation of $\geq 4\%$ measured by pulse oximetry. The AHI was divided into four categories based on generally applied clinical thresholds: 0 to < 5 , 5–14.9, 15–29.9 and ≥ 30 events/hr. The oxygen desaturation index ODI was defined as the number of desaturations per hour of $\geq 4\%$, as measured by pulse oximetry.

Statistical methods

All statistical analyses were performed using STATA 10.1 (paper I) and STATA 12.1 (papers II–IV) (Stata Corp, TX, USA).

For categorical variables, the differences between groups were calculated using the χ^2 test. For continuous variables, the differences between two groups were calculated using the unpaired t test. Frequency variables were presented as n (%) and continuous data as mean \pm SD.

Simple logistic regression analysis (paper I) and multiple logistic regression analysis (papers I–IV) were used to examine possible associations between dichotomous dependent variables and independent, explanatory variables. Results were presented as odds ratios (OR) and 95% confidence intervals (95% CI) or adjusted OR and 95% CI.

Multiple linear regression analysis was used to examine possible associations between dependent variables and independent, continuous variables (paper I, data not shown).

Confounders used in the regression models were selected based on existing literature and on the results of previous studies in this field.

Sensitivity and specificity were calculated for the questions used to identify subjective nasal obstruction in the three subgroups in paper I. The calculations were based on objective nasal measurements that had previously been investigated on 132 of the 400 participants. Objective nasal obstruction was defined as a PNIF < 100 l/min or a septal deviation.

Simple mean imputation was used for missing data when calculating the sum of SNOT-22 (paper IV). It was applied when at least 50% of the items were completed, and means that the value of the missing data was replaced by the mean of the values of the completed item.

P-values of < 0.05 were considered significant.

Ethics

All studies were approved by the Regional ethical review board in Uppsala, Sweden, (Dnr 01/238 (I), Dnr 2008/014 (II), Dnr 1998/495 and Dnr 2010/068 (III) and Dnr 2014/189 (IV)). Informed written consent was obtained from all participants in the studies.

Results

Paper I

Of the 400 women, 46 were defined as having PNO, 88 as having hay fever and 30 as having NON. The overlap between the groups is presented in Figure 3.

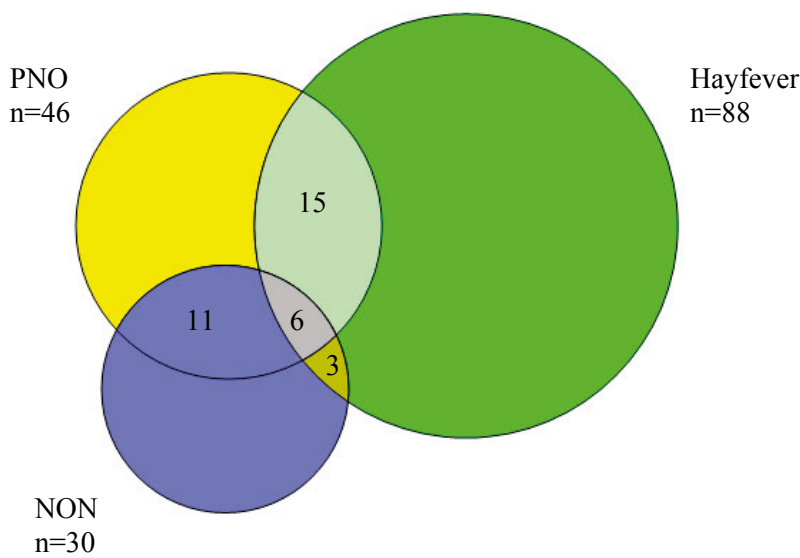


Figure 3. Number of participants in the three different subgroups and overlap between groups.

There were no significant differences for any of the groups when comparing BMI, age and $HAD \geq 8$ with the total population. Current smoking was more common in the NON subgroup compared with the other subgroups and the total population. The prevalence of physician-diagnosed asthma and use of asthma medication was high in all subgroups, although the asthma prevalence in the NON subgroup did not differ statistically from the remainder.

Of the 12 different sleep problems and daytime symptoms analysed for the three subgroups, three symptoms were significantly more common in all subgroups compared with the total population: ‘Difficulties inducing sleep

due to nasal obstruction', 'Waking up hastily gasping for breath' and 'Daytime nasal obstruction'. In the NON subgroup, 9 out of 12 symptoms had significantly higher prevalence rates compared with the total population and the other subgroups. Higher prevalence rates were also found for 'Sweating at night' and 'Dry mouth on awakening' in the PNO subgroup, and for 'Excessive daytime sleepiness' and 'Difficulties with memory' in the hay fever subgroup.

Significant associations were found between the NON subgroup and the 9 symptoms with high prevalence after adjustment for confounders. The PNO and hay fever subgroups were associated with 5 and 3 symptoms, respectively (Table 5).

When the NON subgroup was excluded, there were 29 women in the PNO-NON subgroup and 79 women in the hay fever-NON subgroup. After adjusting for confounders, only one symptom, 'Daytime nasal obstruction', was significantly associated with PNO-NON. Two symptoms were significantly related to hay fever-NON, 'Waking up hastily gasping for breath' and 'Daytime nasal obstruction'.

The specificity for identifying nasal obstruction with the questions used was 95%, 89% and 83% for NON, PNO and hay fever, respectively, while the corresponding sensitivity was 7%, 13% and 27%.

Apart from a slightly higher number of awakenings and a somewhat higher minimal saturation level during the night among women with hay fever, there were no other significant differences regarding the PSG variables in any of the three subgroups. When adjusting for confounders, no significant differences were found in any of the three subgroups regarding the measured sleep variables.

Table 5. Associations between sleep problems and related daytime symptoms and PNO, hay fever, NON.

Symptoms	PNO OR (95%CI)	PNO Adj OR (95%CI)	Hay fever OR (95%CI)	Hay fever Adj OR (95%CI)	NON OR (95%CI)	NON Adj OR (95%CI)
Difficulties inducing sleep due to nasal obstruction	9.5 (4.0-22.5)	10.4 (4.0-27.3)	2.5 (1.0-6.0)	2.0 (0.7-5.4)	80.7 (28.0-232.7)	89.5 (27.0-296.7)
Snoring	1.4 (0.8-2.7)	1.3 (0.6-2.6)	1.0 (0.6-1.6)	1.0 (0.6-1.7)	3.5 (1.6-8.1)	4.2 (1.7-10.2)
Sweating at night	2.2 (1.1-4.4)	2.3 (1.1-4.9)	1.5 (0.8-2.7)	1.6 (0.8-3.0)	3.1 (1.4-6.8)	2.6 (1.1-6.1)
Difficulties maintaining sleep	0.8 (0.3-1.7)	0.7 (0.3-1.5)	1.0 (0.5-1.7)	0.9 (0.5-1.7)	2.4 (1.1-5.2)	2.7 (1.2-6.2)
Waking up hastily gasping for breath	4.1 (1.3-12.6)	3.5 (1.1-11.3)	3.6 (1.2-10.4)	3.5 (1.1-11.0)	20.9 (6.7-65.4)	32.2 (8.7-119.1)
Early morning awakening	0.4 (0.2-1.3)	0.4 (0.1-1.2)	1.0 (0.5-1.9)	1.1 (0.5-2.2)	1.7 (0.7-4.1)	1.4 (0.5-3.8)
Dry mouth on awakening	2.1 (1.1-3.9)	1.9 (1.0-3.8)	1.5 (0.9-2.5)	1.4 (0.8-2.4)	7.0 (3.1-15.7)	7.7 (3.2-18.4)
Waking up unrefreshed	1.3 (0.7-2.5)	1.2 (0.6-2.4)	1.5 (0.9-2.5)	1.4 (0.8-2.5)	2.8 (1.3-5.9)	2.7 (1.2-6.0)
Excessive daytime sleepiness	0.8 (0.3-1.7)	0.7 (0.3-1.5)	1.8 (1.1-3.1)	1.6 (0.9-2.9)	2.7 (1.3-5.9)	2.6 (1.1-6.0)
Difficulties with memory	0.8 (0.3-2.2)	0.7 (0.3-1.9)	2.3 (1.2-4.4)	2.2 (1.1-4.5)	1.80 (0.7-4.6)	1.4 (0.5-3.9)
ESS \geq 10	0.6 (0.3-1.2)	0.6 (0.3-1.2)	1.2 (0.7-1.9)	1.2 (0.7-2.1)	1.2 (0.6-2.5)	1.1 (0.5-2.4)
Daytime nasal obstruction	16.2 (7.2-36.5)	23.6 (9.4-59.5)	2.7 (1.2-5.9)	3.0 (1.3-7.1)	12.3 (5.1-29.3)	12.2 (4.8-31.2)

Odds ratios (OR) calculated with logistic regression are presented with 95% confidence intervals (95% CI).

Adjusted odds ratios (Adj OR) calculated with multiple logistic regression are adjusted for age, current smoking, body mass index (BMI), physician-diagnosed asthma and pre-sented with 95% confidence intervals (95% CI).

PNO – Persistent Nasal Obstruction, NON – Nasal Obstruction at Night

Paper II

The total study population consisted of 26,647 subjects, of which 2,249 (8.4%) had CRS according to the study criteria. Subjects with CRS had a higher mean BMI and were slightly younger than those without CRS. Current smoking and the use of smokeless tobacco were more prevalent among CRS subjects. Both PER and asthma were substantially more common among subjects with CRS. The use of sleep medication was substantially higher among CRS subjects. An academic degree was less common among CRS subjects, and their physical activity level was generally lower. The analysed co-morbidities did not differ with respect to the CRS definition.

Nasal obstruction was the most common symptom (89.1%) among the CRS subjects, followed by nasal discharge (59.4%), facial pain (57.9%) and loss of smell (44.5%) (Figure 4).

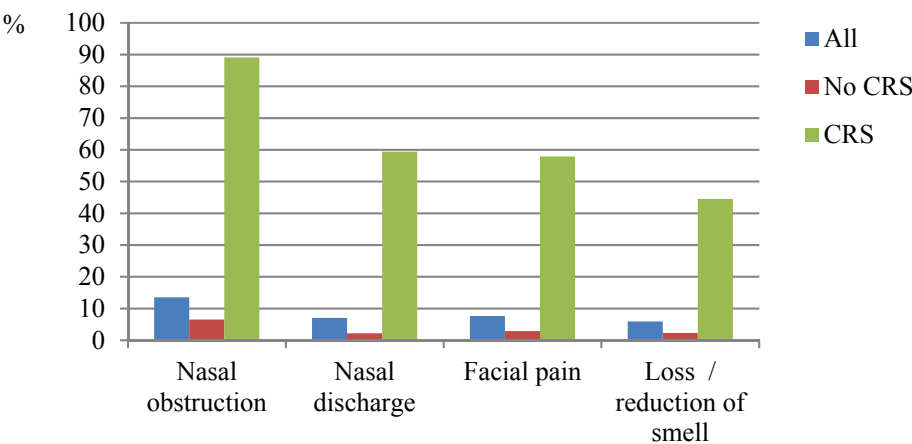


Figure 4. Prevalence of CRS symptoms in the total population and among subjects with and without CRS.

Analysed sleep problems and EDS were 50–90% more common among subjects with CRS (Figure 5).

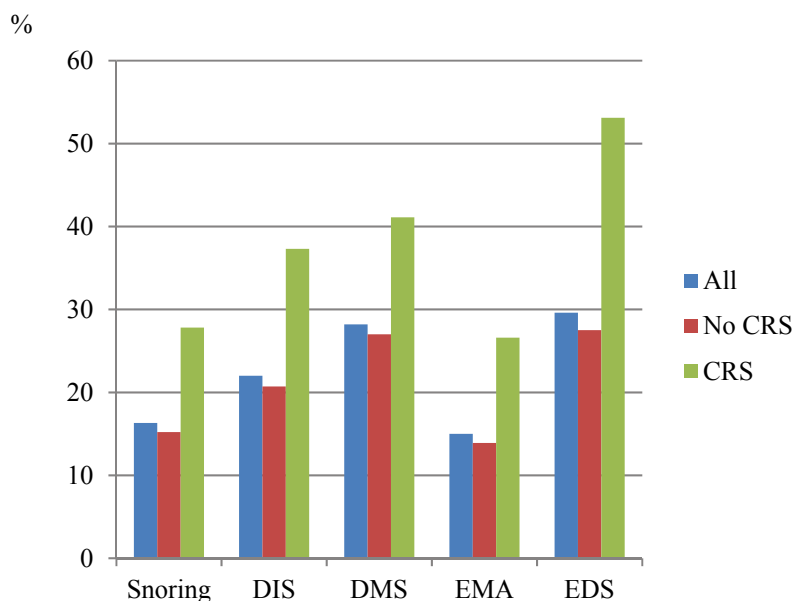


Figure 5. Prevalence of sleep problems and related daytime sleepiness in subjects with or without CRS.

As illustrated in Figure 6, there was a gradual increase in the prevalence of sleep problems and related daytime symptoms in parallel with an increase in the number of CRS symptoms.

After adjustment for possible confounders, significant associations were found between the number of CRS symptoms and the different sleep problems and related daytime symptoms. The highest odds ratio in each analysed category was seen when all four CRS symptoms were reported (Table 6).

The impact of PER on sleep problems and related daytime symptoms was analysed by categorising the subjects into four groups: a) no PER, no CRS (reference= 25,492), b) PER but no CRS (n= 1,949), c) CRS but no PER (n= 1,536) and d) both PER and CRS (n= 582). In this model, the strongest association with sleep problems was found among subjects suffering from both PER and CRS.

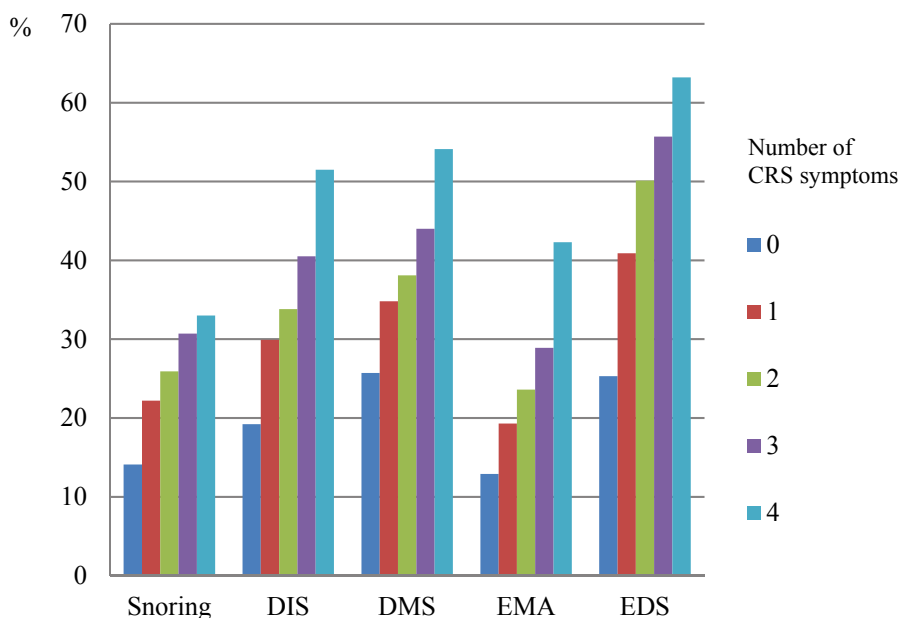


Figure 6. Prevalence of sleep problems in relation to the number of CRS symptoms.

Paper III

The total study population consisted of 5,145 subjects who did not report nasal symptoms at baseline. At the follow-up 10 years later, 141 subjects (2.7%) had developed CRS. The prevalence rates of the individual CRS symptoms at follow-up among subjects with and without CRS were: nasal obstruction 82.3% vs 2.0%, nasal discharge 72.3% vs 1.4%, facial pain/pressure 62.4% vs 1.7% and reduction/loss of smell 48.2% vs 1.7%. A cross-sectional analysis of the prevalence of CRS in the total study population (n= 11,441) was 6.8% at follow-up.

Subjects who developed CRS were slightly younger at baseline than those who did not develop CRS. They also had a larger weight gain at follow-up, but their BMI at follow-up did not differ compared with those who did not develop CRS. Current smoking was substantially more common among CRS subjects, as were asthma and gastroesophageal reflux at night (nGER). Current smoking had declined at follow-up, whereas asthma had increased from 4.3% to 17.0%. Neither hypertension, diabetes nor heart disease differed, with respect to the CRS definition, nor did educational level or gender.

Table 6. *Adjusted odds ratio (95% CI) * for the association between the number of chronic rhinosinusitis (CRS) symptoms and sleep problems and related daytime symptoms.*

No. of CRS Symptoms	Snoring	DIS	DMS	EMA	EDS
0	1.00	1.00	1.00	1.00	1.00
1	1.79 (1.61-2.00)	1.76 (1.60-1.93)	1.61 (1.47-1.75)	1.60 (1.43-1.78)	1.90 (1.75-2.07)
2	2.15 (1.85-2.49)	2.08 (1.83-2.37)	1.95 (1.72-2.21)	2.04 (1.76-2.37)	2.70 (2.39-3.04)
3	2.80 (2.28-3.45)	2.62 (2.16-3.16)	2.35 (1.96 -2.82)	2.48 (2.02-3.05)	3.33 (2.79-3.98)
4	3.13 (2.22-4.41)	3.98 (2.94-5.40)	3.44 (2.55-4.64)	4.71 (3.47-6.38)	4.56 (3.36-6.18)

*The odds ratios are adjusted for gender, BMI, age, smoking history, smokeless tobacco, asthma, diabetes, hypertension, COPD, physical activity level, centre and educational level. DIS – Difficulties inducing sleep, DMS – Difficulties maintaining sleep, EMA – Early morning awakening, EDS – Excessive daytime sleepiness

All analysed sleep problems and EDS were more prevalent among subjects who developed CRS compared with those who did not, both at baseline and follow-up (Figure 7). Although both groups had an increased prevalence of all symptoms at follow-up, the increase was much larger among subjects who had developed CRS.

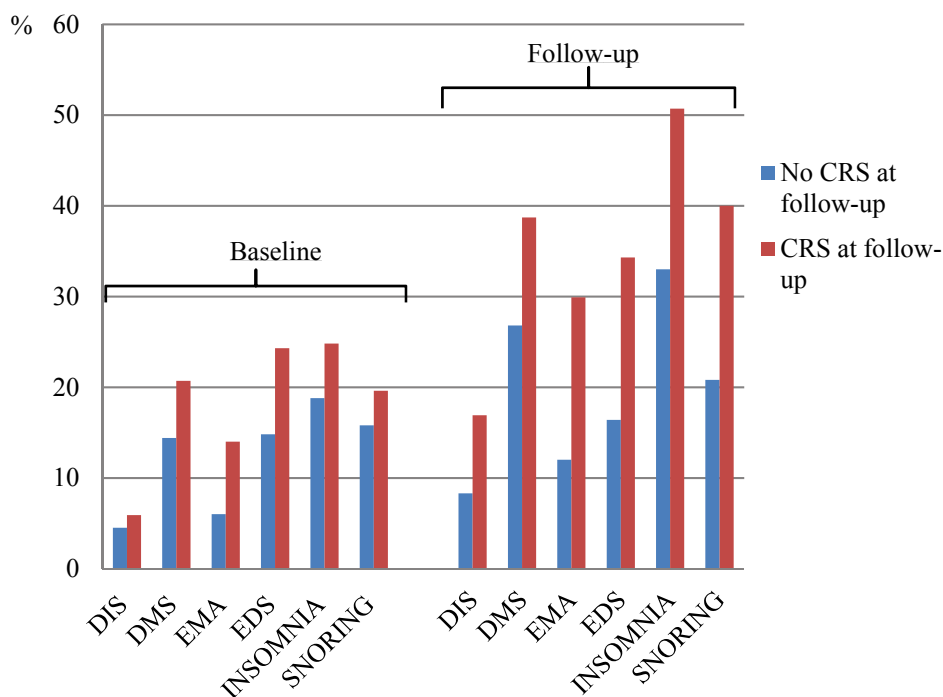


Figure 7. Prevalence of sleep problems and excessive daytime sleepiness (EDS) at baseline and follow-up in subjects with and without incident CRS during the 10-year study period.

In a cross-sectional analysis at follow-up, in which all subjects with the respective sleep problem (DIS, DMS, EMA, insomnia, snoring) and EDS at baseline were excluded, CRS was significantly associated with all the analysed sleep problems and EDS (adjusted OR range 2.07–3.31). Other significant associations were female gender, smoking, nGER and analysed comorbidities.

EMA and EDS were found to be risk factors for CRS with an adjusted OR of 3.06 and 1.79, respectively. Furthermore, two and three insomnia symptoms at baseline were associated with CRS at follow-up in the adjusted model (Table 7). Models including further adjustment for age, gender, BMI,

delta BMI, asthma at baseline, smoking at baseline, gastroesophageal reflux at baseline, cardiometabolic disease at baseline, centre and educational level at follow-up did not substantially change these results, nor did calculations excluding asthmatics.

Table 7. Odds ratios for chronic rhinosinusitis (CRS) at follow-up, depending on the number of insomnia symptoms at baseline.

Insomnia symptoms at baseline	CRS at follow-up Univariate	CRS at follow-up Adjusted Model
0	1.00	1.00
1	0.89 (0.52-1.55)	0.85 (0.48-1.50)
2	2.11 (1.12-4.00)	2.37 (1.24-4.51)
3	4.30 (1.68-11.06)	5.00 (1.93-12.99)

Adjusted Model – adjusted for age, gender, body mass index (BMI). Data presented as odds ratios and confidence intervals, 95%, OR (95% CI). Insomnia symptoms: difficulties inducing sleep (DIS), difficulties maintaining sleep (DMS), early morning awakening (EMA)

Paper IV

The total study population consisted of 197 patients, 60 females (30.5%) and 137 (69.5%) males, with a mean age of 57.7 years. Of the 197 patients, 113 were adherent CPAP users, while 84 were non-adherent users.

The mean BMI was 31.8. Smoking had a prevalence of 9.7%. The adherent and non-adherent groups were similar, in terms of these variables and the average number of days between the baseline and follow-up visits, with a mean \pm SD of 22.0 ± 20.4 and 26.9 ± 28.0 , respectively. Diabetes was more common among non-adherent CPAP users. The other analysed variables (asthma, allergic rhinitis, CRS, HAD scale, PEF, hypertonia, heart disease, nGER, headache, joint pain) did not differ between the two groups, nor did the use of nasal medication at baseline and at follow-up.

The mean ESS score in the total population at baseline was 10.5 ± 4.7 , with similar scores in the two groups. At follow-up, there was an improvement in the mean ESS score in both groups, which differed significantly from the baseline score. The largest improvement was in the adherent group, with an average reduction of 3.7 points.

The adherent and non-adherent CPAP users did not differ in terms of OSA severity. A total of 81.7% of the patients had moderate or severe OSA, equivalent to at least an AHI of > 15 .

Approximately 74% of patients used a nasal mask from the start of treatment (no difference between the adherent and non-adherent groups), and the remainder of the study groups were equipped with a full face mask or, in a few cases, both. At follow-up, 44.0% of the non-adherent users switched to a different mask model compared with 27.4% in the adherent group. Mask leakage was experienced by both groups, but the adherent group had a higher percentage of low mask leakage (< 5 litres/minute) than the non-adherent group, 63.7% vs 36.9%. High mask leakage (> 24 litres/minute) was also more common in the adherent group compared with the non-adherent group, 21.5% vs 10.6%. A humidifier was added to the CPAP treatment at follow-up in 46% of the patients in both groups.

Complete SNOT-22 data were available at both baseline and follow-up for 168 patients. The total SNOT-22 score at baseline in the total population was 36.1 ± 19.4 , and the scores were on the same level for the adherent and non-adherent groups. In addition, the subdomain scores did not differ between the two adherence groups (Table 8).

The adherent group had an improved and significantly lower total SNOT-22 score compared with the non-adherent group at follow-up. The sleep and psychologic domain scores improved the most for both groups, but the improvement was larger in the adherent group.

A PNIF value in the lowest quartile (< 100 l/min) at baseline was associated with a 2.24 risk of non-adherence. After adjusting for age, BMI, gender and smoking, the adjusted OR was 2.40 for non-adherence (Table 9).

The mean PNIF values at baseline for females and males in the adherent group were 130.0 ± 49.6 and 175.5 ± 68.3 litres/min, respectively. In the non-adherent group, the corresponding values were 134.4 ± 65.0 for females and 157.6 ± 77.2 for males. The delta PNIF did not differ significantly between the two groups, nor did PNIF at baseline when comparing smokers with non-smokers.

Table 8. Results of the sinonasal outcome test (SNOT-22) at baseline and follow-up. Data are presented as the mean \pm (SD).

	All (n=168)	Adherent ≥ 4 hours/night (n=100)	Non-adherent < 4 hours/night (n=68)	p
<i>Baseline</i>				
Total score	36.1 \pm 19.4	36.2 \pm 19.9	35.9 \pm 18.7	0.94
Rhino domain	9.6 \pm 6.9	9.4 \pm 6.9	9.9 \pm 6.9	0.60
Ear/facial domain	4.5 \pm 4.3	4.7 \pm 4.6	4.2 \pm 3.8	0.45
Sleep domain	10.2 \pm 5.4	10.4 \pm 5.4	9.8 \pm 5.3	0.53
Psychologic domain	11.8 \pm 7.2	11.7 \pm 7.1	12.0 \pm 7.5	0.84
<i>Follow-up</i>				
Total score	28.6 \pm 18.4	25.8 \pm 17.6	32.8 \pm 18.9	0.02
Rhino domain	10.1 \pm 7.2	9.7 \pm 7.0	10.6 \pm 7.5	0.45
Ear/facial domain	3.5 \pm 3.9	3.3 \pm 3.8	3.8 \pm 4.1	0.45
Sleep domain	6.9 \pm 5.00	5.9 \pm 4.8	8.4 \pm 4.9	0.002
Psychologic domain	8.2 \pm 7.0	6.9 \pm 6.5	10.1 \pm 7.2	0.003
Delta SNOT-22, total score	-7.5 \pm 14.9	-10.4 \pm 13.9	-3.2 \pm 15.4	0.002

Calculations include only those that answered the SNOT-22 at both baseline and follow-up.

Table 9. *Risk factors for low CPAP adherence in the total population.*

CPAP adherence < 4 hours/night (n=178)	OR	(95% CI)	p
PNIF <100 l/min, at baseline	2.40	1.16-5.00	0.02
Age	1.02	0.99-1.05	0.28
Gender (male)	0.72	0.36-1.44	0.36
BMI	1.04	0.99-1.11	0.14
Smoking	0.60	0.21-1.71	0.34

The results are presented as the OR (95% CI) after adjusting for all the variables in the table.

Calculations were made for all patients with complete data on the variables in the table.

CPAP – Continuous Positive Airway Pressure, PNIF – Peak Nasal Inspiratory Flow, l/min – litres/minute,
BMI – Body Mass Index

Discussion

The results of papers I–IV underline the importance of nasal obstruction in sleep dysfunction.

In paper I, it was primarily the NON subgroup which was associated with a negative impact on several subjective sleep problems and related daytime symptoms. The results support previous findings of associations between self-reported nasal obstruction at night and sleep disturbances and daytime sleepiness (135, 187).

In addition, the findings, particularly in the NON subgroup, are in accordance with several epidemiological studies and interventional studies using intranasal cortisone spray and actigraphy, showing that allergic rhinitis with related nasal obstruction is an independent risk factor for sleep disturbances and daytime sleepiness (133, 134, 137, 138). Furthermore, since there was no significant association between NON and hay fever, the results emphasise self-reported nasal obstruction at night, without related allergic rhinitis, as a key symptom in sleep medicine.

The questions used to define nasal obstruction in paper I were found to have a high specificity and a low sensitivity when they were analysed with the objective findings in a previous study (67). The low sensitivity may partly be explained by the technical shortcomings when performing PNIF and/or the weak correlation between objective nasal measures and the subjective feeling of nasal obstruction (59, 75).

In paper I, there were no significant differences between the three subgroups and the total population regarding any of the PSG variables, after adjusting for confounders. The results are in line with several studies indicating that nasal obstruction does not play a significant role in the pathogenesis of OSA (139, 166–168).

In papers II and III, nasal obstruction was the most common CRS symptom, with a prevalence of 89.1% and 82.3% among subjects classified as having CRS. In both studies, the prevalence of sleep problems and daytime symptoms was substantially higher among subjects with CRS compared with those without CRS and the total population. In addition, strong associations were found between the number of CRS symptoms (paper II) and incident CRS (paper III) and all sleep problems and EDS. By analysing subjects with both PER and CRS in paper II, an additional negative impact on sleep quality was found. The exclusion of subjects with the respective sleep problem or EDS at baseline in paper III is suggestive of a causal relationship between

CRS, with its associated nasal obstruction, and sleep disturbances. Collectively, these results underline the importance of nasal obstruction in sleep dysfunction. The results are also in line with several other studies, which have identified nasal obstruction as a contributory factor to both subjectively and objectively assessed sleep dysfunction (133, 134, 137, 145-148, 152, 172, 187). The association of nasal obstruction and sleep quality was limited however, when investigating 28 CRS patients in one study (190).

In paper IV, nasal obstruction was analysed as part of the SNOT-22 scores. The rhino domain score was 9.4 ± 6.8 , compared with 4.9 ± 1.0 in another study of 30 OSA patients diagnosed with polysomnography and without sinonasal disease, indicative of an increased sinonasal disease burden (191). In addition, 23.4% of the total study population in paper IV had symptoms of CRS, and the average SNOT-22 scores were equal to those of patients with CRS, with or without nasal polyposis, six and 12 months post-surgery (192).

In paper IV, nasal obstruction was also assessed objectively using PNIF. Among patients with a PNIF value of < 100 l/min, the odds ratio was 2.40 for non-adherence to CPAP. The association between a low PNIF value, indicating impaired nasal breathing, and low CPAP adherence is consistent with previous findings (104, 105, 107).

In paper II, there was a correlation between disease severity, defined as the number of reported CRS symptoms, and the degree of impairment of sleep quality. These findings are plausible considering that, in addition to nasal obstruction, facial pain had a prevalence of 57.9% among the CRS subjects. Disturbed sleep is one of the most widespread co-morbid conditions in chronic pain patients. As many as 50–77% of patients with orofacial pain and temporomandibular disorders report poor and reduced sleep quality (193). Although nasal secretion and olfactory function have been less studied as separate symptoms in relation to sleep disturbances, and mainly as co-morbid symptoms of AR and CRS, they have as such both been associated with poor sleep quality (133, 146). Furthermore, all four CRS symptoms, together with a cough, have been found to be predictors of an increased risk of sleep impairment in CRS (194).

An effect of the pro-inflammatory cytokines IL-1 β and TNF- α may have contributed to the high prevalence of sleep problems and EDS among subjects with CRS in papers II and III, including the clear impact of the disease severity of CRS on sleep quality in paper II. Elevated levels of both cytokines have been found in the nasal mucosa of CRS patients and of serum IL-1 in patients with AR (175, 177, 179). These cytokines are known SRS and have been associated with sleep disturbances, fatigue, pain, depression, impaired cognition and memory loss (177, 195). The mechanisms by which cytokines signal the CNS to cause sickness behaviour and poor sleep quality in patients with CRS and AR are unknown, however. It may be speculated that a gradual increase of the inflammation in the sinonasal mucosa (i.e. dis-

ease severity/number of CRS symptoms) causes a gradual increase of these SRS, with increasingly poor sleep quality as a consequence (1). The finding in paper II that the CRS subjects also suffering from PER experienced the poorest sleep quality of all subgroups, is in favour of such a theory.

In paper III, there was a higher prevalence of all sleep problems and EDS at baseline among those who developed CRS, compared with those who did not. Furthermore, EMA and EDS at baseline were associated with an increased risk of subsequent CRS. In addition, three insomnia symptoms at baseline were associated with a 5-fold increase in the risk of CRS.

It is difficult to discern why EMA and EDS are risk factors for CRS and not the other closely related sleep disturbances. They may represent symptoms of early stages of insomnia or another sleep disorder, which would explain the increase in prevalence of all sleep problems 10 years later. That, in turn, would support a theory of insomnia symptoms as a cause for CRS. These results are in accordance with a prospective study of asthma and sleep quality, in which insomnia symptoms were associated with an increased risk of developing asthma (180). Possible explanations for the observed associations include elevated levels of pro-inflammatory cytokines and stress hormones caused by sleep deprivation, which in turn increases the risk for subsequent inflammatory disease (182-185).

In paper IV, the average SNOT-22 score at baseline among all OSA patients was 36.1 ± 19.4 , with similar score levels in both the adherent and the non-adherent group. The scores were generally higher compared with the results of a recent original and review study in which the SNOT-22 score was 11 ± 9.4 among healthy individuals without sinonasal disease (65). As mentioned above, high scores in the rhino subdomain contributed to this result. The fact that the patients were diagnosed with OSA with a mean AHI of 32 most probably generated higher average scores in the other questionnaire domains as well. The improved scores in the sleep and psychological domains of the SNOT-22 and ESS score at follow-up among adherent CPAP users support this notion.

Cigarette smoking was an important confounder in papers I–III. It may cause inflammatory changes and disturb the function of the nasal mucosa, as well as cause subjective nasal obstruction (51, 52, 196). The prevalence of cigarette smoking was relatively high in the NON and CRS subgroups of papers I–III. In paper I, the prevalence was 40.0%; in paper II, 22.7%; in paper III, 38.6% at baseline and 25.5% at follow-up. Consequently, cigarette smoking most probably contributed to the symptom of nasal obstruction. Moreover, associations between cigarette smoking and CRS have been reported (35, 197). Furthermore, studies of smoking and nicotine on polysomnographic recordings reveal a negative effect on sleep quality (54, 55). Strong associations remained, however, between the NON and the CRS subgroups, and sleep problems and daytime symptoms after adjustment for smoking.

Asthma was another confounder of importance in papers I–III. Epidemiologic, pathophysiologic, and clinical evidence support the view of asthma and rhinitis (both allergic and non-allergic) as two aspects of one disease, the “united airway disease” (198). Indeed, asthma has been associated with AR, nasal obstruction, CRS and also sleep impairments (29, 187, 197, 199). The prevalence of asthma in the NON and CRS subgroups in papers I–III were relatively high, 25.0%, 18.7% and 17.0% at follow-up, respectively. No significant association was found between NON and physician-diagnosed asthma, however, and associations between NON and the related day- and night time symptoms remained after adjustment for asthma. Similarly, calculations in papers II and III included adjustments for asthma, and strong associations remained between CRS and sleep problems and EDS. In paper III, the association between insomnia symptoms at baseline and incident CRS at follow-up remained when asthmatics were excluded from the calculations. In summary, these results indicate a limited impact of asthma on the results of papers I–III.

Methodological considerations

The strength of paper I was the well characterised, community-based sample of 400 women, which rendered highly reliable gender-specific information. Furthermore, the study design included both subjective and objective sleep variables measured with PSG.

One limitation was that PSG was performed during one night only, increasing the risk of a first night effect (200). In addition, the oversampling of snorers may have influenced the results such that women with a higher BMI were overrepresented, which in turn may have increased the prevalence of subjective sleep problems, daytime symptoms and nasal obstruction (201). The main part of the study cohort was examined outside the pollen season which may have influenced the results of the hay fever subgroup. The results of paper I cannot directly be applied to men.

Papers II and III share several strengths, one of which is the large sample sizes on which they were based. A further strength of both studies was that the EPOS epidemiological diagnostic criteria were used to define CRS and also the use of the established BNSQ to analyse sleep. One additional advantage of paper III was the 10-yearlong study time frame, making it possible to investigate causal effects. Although both studies included men and women in urban areas, paper III also had an international perspective and was conducted in five different Nordic countries.

Papers II and III also share a few limitations. Firstly, OSA must be considered a confounding factor in both studies. In paper II, an attempt was made to estimate the prevalence of OSA, using snoring and EDS at least three times/week as a proxy for OSA. The prevalence was 6.2% in the total population and 15.5% among subjects with CRS. It is, therefore, likely that part of the subjectively reported insomnia symptoms in paper II reflect sleep fragmentation, secondary to a breathing disorder during sleep. In paper III, the prevalence of snoring and EDS increased substantially in subjects with CRS over ten years, which may indicate undiagnosed OSA. Calculations excluding CRS subjects with doctor diagnosed OSAS at follow-up (4.4%) did not change the results, however.

Secondly, the lack of information on depression, which is closely associated with CRS, sleep disturbances, daytime sleepiness, fatigue and use of sleep medication, is another drawback of papers II and III, and has to be considered when interpreting the results (43, 202, 203). Further information

on other psychiatric disorders, sleep disorders and on the duration of CRS, would also have added to the results.

Thirdly, selection bias also has to be considered in papers II and III, as the response rates were relatively low, 59.2% and 53% (follow-up), respectively. Non-response bias may cause an overestimation of symptom prevalence. In the GA²LEN cohort, selection bias was analysed by measuring the tendency of diseased subjects to respond earlier or later to the survey than that of non-diseased subjects (35). As there was no clear tendency for diseased subjects to respond faster or slower than non-diseased subjects within each centre, the authors suggest that prevalence estimates were less likely to be biased by differential response between the two groups.

In the RHINE cohort, selection bias was analysed by examining long-term participation and consequences of loss to follow-up. A lower baseline prevalence of several respiratory symptoms among long-term participants compared to all baseline participants was found. The prevalence rates of respiratory symptoms in paper III may therefore be underestimated. However, exposure-outcome associations were mainly unchanged by loss to follow-up, and the RHINE data were found to have high validity (186). The exclusion of subjects with nasal symptoms at baseline in paper III may have rendered a somewhat healthier cohort. This may have contributed to lower prevalence rates of incident CRS and the related sleep problems and EDS, thereby restricting the generalisability of the results to some extent.

A strength of paper IV was the inclusion of 197 consecutive OSA patients, who were examined in a regular clinical setting. In addition, OSA was diagnosed with a one-night ambulatory PG according to national guidelines. Validated questionnaires such as the SNOT-22 and ESS were used, and CRS was defined according to the EPOS diagnostic epidemiological criteria.

One limitation was the relatively short time before follow-up, which may have affected the results, since some patients may need a longer time to adjust to CPAP treatment. When evaluating SNOT-22 scores and PNIF values, it would have been desirable to have a control group.

Conclusions

- I Self-reported nasal obstruction at night in women has a significant negative effect on subjective sleep quality and daytime symptoms, but does not affect objective sleep variables measured by PSG.
- II Sleep problems and excessive daytime sleepiness are prevalent in CRS, as assessed by the EPOS epidemiological diagnostic criteria. The disease severity of CRS, defined as the number of CRS symptoms, correlates with impaired subjective sleep quality. The addition of persistent allergic rhinitis to CRS causes an additional negative effect on sleep quality.
- III Incident CRS, as assessed by the EPOS epidemiological diagnostic criteria, is associated with impaired subjective sleep quality and excessive daytime sleepiness. Insomnia symptoms may be a risk factor for the development of CRS.
- IV SNOT-22 is elevated in patients with OSA, indicating a large sinonasal disease burden. SNOT-22 improves with good CPAP adherence. A low PNIF value can predict poor CPAP adherence.

General discussion and future implications

The symptom of nasal obstruction is highly prevalent in the general population. It is the main symptom of CRS and AR, which affects millions of people worldwide. These diseases are associated with large negative socioeconomic consequences for the affected individuals and society (26, 34). In order to understand the full impact these diseases have on individuals' lives, it is also of great importance to analyse sleep quality.

The association between AR and poor sleep quality is well established according to epidemiological studies (31, 134). However, knowledge on the effect of self-reported nasal obstruction, as a single symptom, on sleep quality is limited. Furthermore, knowledge on sleep quality in CRS is still scarce, and it is only in the last decade that research on this topic has increased. Consequently, there is a need for further studies to elucidate the role of nasal obstruction in sleep quality. The results of the three epidemiological papers in this thesis (papers I–III) therefore contribute in an important way to this field of research by adding new knowledge.

Paper I is the first community-based study of women only in which sleep and nasal obstruction have been analysed with questionnaires in combination with PSG. It would be of interest to evaluate the obtained gender specific information for men, since female gender has been identified as a risk factor for both insomnia symptoms and for CRS, in which nasal obstruction is a cardinal symptom (35, 124). The Men in Uppsala Study of sleep, Apnoea and Cardiometabolic Health (MUSTACHE) is an ongoing study of men, who are matched by age and BMI to the participants in the SHE study, which will provide an opportunity to study possible gender differences.

Paper II is the first epidemiological study of CRS and sleep quality. The use of the EPOS epidemiological diagnostic criteria to define CRS is an advantage, as it will allow for results of future studies of CRS and sleep quality to be compared with those of paper II. Different definitions of nasal obstruction most likely contribute to the great disparities seen between studies of nasal obstruction and sleep quality. It is of great importance that future studies in this field use as uniform definitions as possible. Naturally, the use of standardised, preferably validated, sleep questionnaires is of equal importance. In papers II and III, the use of the BNSQ is an advantage, as it has been used in a wide range of studies, although it has not been formally validated with objective measurements. The results of paper II are new and highlight not only the high prevalence of sleep problems, EDS and nasal obstruc-

tion in CRS, but they also introduce the aspect of disease severity of CRS in regard to sleep quality. This finding raises several questions, one of which is causality. Due to the cross-sectional design of paper II, however, conclusions on causality cannot be drawn. Another question is the possible role of inflammation and the immune response.

These questions were addressed in paper III, which is the first epidemiological study of incident CRS and sleep quality. The results confirm those of paper II, with a high prevalence of sleep problems, EDS and nasal obstruction in CRS, and are also suggestive of a causal relationship between CRS and poor sleep quality. Paper III is also the first study to investigate possible associations between insomnia symptoms and the development of CRS. The results indicate that insomnia symptoms may be a risk factor for the development of CRS. Altogether, the findings of papers II and III suggest a possible role for inflammation, in terms of causality between CRS and sleep quality. Due to its complexity and bi-directionality, the immune response system needs to be further explored and investigated in order to bring clarity to the relationship between systemic inflammatory mediators and sleep disruption.

Nasal obstruction is also an important factor of causality in this context, considering its high prevalence in CRS. Future studies should include clinical evaluation of the nose and sinuses or CT scan, subjective and objective measurements of sleep quality and analyses of inflammatory pathways that can directly, or indirectly, cause sleep disruption. In these studies, it will also be of great importance to evaluate depression and other psychiatric conditions, since they are known risk factors for both CRS and sleep impairment (43, 122). Unfortunately, they were not evaluated in papers II and III. From an epidemiologic perspective, it would be of great interest to investigate the natural course of CRS regarding prevalence and incidence as well as possible long-term consequences of CRS on sleep quality. Naturally, the effect of insomnia symptoms on the development of CRS would also have to be investigated further. Similar studies on AR would also be of interest. The ongoing RHINE study offers a possibility to study this in its fourth stage, which is planned for 2020.

Paper IV is one of the first studies to use the SNOT-22 to evaluate sinonasal disease in OSA patients, and the first to analyse PNIF in relation to CPAP adherence. The results indicate a large sinonasal disease burden among OSA patients, and that a low PNIF value increases the risk for poor CPAP adherence. Confirmation of the results is needed and should include clinical assessments of the sinonasal status in OSA patients. Ideally, a future study should also include anterior rhinometry and CT scans and extend over a longer period of time, as there is a risk that CPAP adherence rates were underestimated due to the relatively short study timeframe. The DISCOVERY study (acronym for Diseases in patients in the Swedish CPAP-, oxygen- and ventilator registry) will make it possible to study OSA, CPAP adherence and sinonasal disease from a purely epidemiologic perspective too.

For the purpose of the study, a database is under construction, which will merge data from the two Swedish CPAP registries, Swedevox and SESAR, and multiple national healthcare registries. It is all made possible by the personal identity number of all Swedish citizens and presents a unique opportunity for further investigations.

Besides generating ideas for further research, the results of this thesis also generated a few clinical implications. Firstly, nasal obstruction should be investigated, and preferably treated, in women who are suffering from impaired sleep and daytime sleepiness, despite normal polysomnography. Secondly, the possibility of poor sleep quality in CRS patients should be considered and appropriate treatment for CRS initiated, not only to improve subjective sleep quality but also to prevent further possible inflammation. Thirdly, sinonasal symptoms, sleep quality and psychological issues are important variables to consider in the treatment of OSA patients. A low PNIF value should not exclude patients from initiating CPAP treatment but could be used as an incentive to treat nasal obstruction to optimise the treatment. Consequently, both the SNOT-22 and PNIF could be valuable tools in the evaluation of OSA patients and in the management of CPAP treatment. In summary, the symptom of nasal obstruction should raise the question of whether the patient also suffers from impaired sleep quality.

Sammanfattning på svenska

Nästäppa är ett mycket vanligt symtom i befolkningen. Det orsakas av avvikelser i nässlemhinnans funktion eller i näsans brosk- och benskett och ibland av en kombination av dessa faktorer. Flera olika sjukdomstillstånd har nästäppa som huvudsymtom. Två av dessa sjukdomstillstånd är allergisk rinit (hösnuva) och kronisk bihåleinflammation (CRS), som drabbar cirka 23 % respektive 11% av Europas vuxna befolkning.

Det är sedan tidigare forskningsresultat välkänt att dessa sjukdomstillstånd har stor negativ inverkan på drabbade individers livskvalitet. Dessutom bidrar de till stora, negativa ekonomiska konsekvenser för både individ och samhälle. Att allergisk rinit påverkar sömnkvalitet negativt är också känt sedan tidigare. Det är däremot inte helt klarlagt i befolkningsundersökningar, om självrapporterad nästäppa som ensamt symtom påverkar subjektiv och objektiv sömnkvalitet. Några studier på enbart kvinnor har inte tidigare utförts med denna frågeställning. Eventuella samband mellan CRS och sömnkvalitet är ofullständigt undersökt och det finns inga tidigare befolkningsundersökningar som har belyst denna frågeställning. Forskningen rörande CRS och sömnkvalitet är ett nytt fält och har ökat successivt det senaste årtiondet. Med tanke på den omfattande påverkan som CRS har på individers livskvalitet, är det också av stor vikt att undersöka huruvida sömnen påverkas eller inte.

Obstruktiv sömnapné (OSA) är ett annat vanligt sjukdomstillstånd, som drabbar cirka 6% av männen och cirka 4% av kvinnorna. Det finns dock undersökningar som visar betydligt högre förekomst, upp till 18% av männen och 17% av kvinnorna. Studier har visat att cirka en tredjedel av patienter med OSA rapporterar frekvent nästäppa innan behandling med continuous positive airway pressure (CPAP) påbörjas. Nästäppa är en bidragande orsak till dålig följsamhet och avbrytande av behandling. Det hade varit önskvärt med instrument som enkelt kunde identifiera OSA-patienter med nästäppa innan behandlingsstart, för att på så vis kunna individualisera och optimera behandlingen. Några sådana instrument finns inte i kliniskt bruk i dagsläget.

I detta avhandlingsarbete har förekomst av eventuella samband mellan självrapporterad nästäppa och sömnkvalitet studerats i tre olika delarbeten. I ett fjärde delarbete har följsamhet till behandling med CPAP studerats på OSA-patienter utifrån förekomst av näsbesvär.

I delarbete I studerades 400 kvinnor bosatta i Uppsala, som deltog i studien Sleep and Health in women (SHE). De genomgick en avancerad sömnregistrering (polysomnografi) under en natt i sina hem och besvarade frågor om sin hälsa. Tre grupper av olika besvär med nästäppa identifierades hos kvinnorna. Hörsnuva fanns hos 88 kvinnor, daglig nästäppa hos 46 kvinnor och nästäppa på natten hos 30 kvinnor. Förekomsten av subjektiva sömnbesvär och dagsömnighet var påtagligt större bland kvinnorna med nästäppa på natten jämfört med de andra två grupperna och hela populationen. Starka samband kunde bekräftas mellan nästäppa på natten och de subjektiva sömnbesvaren och dagsömnigheten. Däremot visade studien inga samband mellan nästäppa på natten och förändringar i objektivt mätt sömn.

I delarbete II studerades sambanden mellan CRS och sömnkvalitet hos 26 647 svenska individer som deltog i en stor befolkningsstudie utförd av Global Allergy and Asthma Network of Excellence (GA²LEN). CRS definierades enligt de epidemiologiska diagnoskriterierna i konsensusdokumentet European Position Paper on Rhinosinuitis and Nasal Polyps (EPOS). Sömnkvalitet mättes med frågeformuläret Basic Nordic Sleep Questionnaire (BNSQ). CRS förekom hos 8,4% av deltagarna. Bland dem var subjektiva sömnbesvär och dagsömnighet mycket vanligare jämfört med dem utan CRS och hela populationen. Det fanns starka samband mellan en ökande svårighetsgrad av CRS, definierat som antal CRS-symptom, och en ökande grad av sömnbesvär och dagsömnighet. Detta samband blev starkare när perenn allergisk rinit adderades som diagnos till CRS.

Delarbete III baserades på den stora, internationella befolkningsstudien Respiratory Health in Northern Europe (RHINE), i vilken 16 106 individer från fem olika Nordiska länder deltog. Även i denna studie användes EPOS-kriterierna för att definiera CRS och BNSQ för att utvärdera sömnkvalitet. Sambanden mellan nyinsjuknande i CRS och sömnbesvär och dagsömnighet studerades under en 10-årsperiod. Av de 5 145 individer som inte hade några näsbesvär vid studiens början hade cirka 2,7% insjuknat i CRS 10 år senare. Bland de som insjuknat i CRS var förekomsten av sömnbesvär och dagsömnighet betydligt högre jämfört med dem som inte hade insjuknat i CRS och hela populationen. Studien påvisade starka samband mellan nyinsjuknande i CRS och sömnbesvär och dagsömnighet efter justering för störfaktorer. Studien visade också att ett omvänt samband förelåg, nämligen att förekomst av sömnbesvär vid studiens början var en riskfaktor för att ha utvecklat CRS 10 år senare.

Delarbete IV baserades på 197 OSA-patienter som ordinerats CPAP-behandling vid Sömn- och andningscentrum, Akademiska Sjukhuset, Uppsala. Syftet var att undersöka förekomst av näsbesvär hos OSA-patienter och utvärdera om näsbesvär påverkade följsamhet till CPAP-behandling. Vid första utprovningstillfället av CPAP fick deltagarna genomföra peak nasal inspiratory flow (PNIF) mätningar, vilket är ett indirekt och objektivt mått på nästäppa. Dessutom fyllde de i frågeformuläret Sinonasal Outcome Test

22 (SNOT-22), som är utformat för patienter med CRS för att mäta besvärsggrad av sjukdomen utifrån de fyra domänerna näs- och bihålebesvär, öron/ansikts- besvär, sömnbesvär och psykologiska besvär. Både PNIF och SNOT-22 gjordes om i samband med första uppföljningen av CPAP-behandlingen. Resultaten visade att det förelåg ett samband mellan lågt värde på PNIF, talande för nästäppa, och ökad risk för dålig följsamhet till CPAP. Dessutom låg resultaten på SNOT-22 generellt högt bland samtliga OSA-patienter, talande för relativt utbredda besvär i denna patientgrupp relaterade till inte bara näsa och bihålor, men även de andra tre domänerna. En påtaglig förbättring av SNOT-22 resultaten kunde ses hos patienter med god följsamhet till CPAP-behandling, vilket i huvudsak berodde på förbättrade resultat avseende sömn och psykiskt välbefinnande.

Sammanfattningsvis har studierna i detta avhandlingsarbete visat att det finns starka samband mellan självrapporterad nästäppa, som enskilt symptom eller som del av CRS, och dålig subjektiv sömnkvalitet och dagsömnighet. Resultaten visar även att sömnproblem kan öka risken för att utveckla CRS över tid. Vidare var näs- och bihålebesvär, sömnbesvär och psykologiska besvär utbredda bland OSA-patienter. Lågt näsflöde kan hos denna patientgrupp bidra till sämre följsamhet till CPAP-behandling.

Ur ett kliniskt perspektiv innebär resultaten att nästäppa ska undersökas och med fördel behandlas hos kvinnor med en normal polysomnografi och som besväras av dålig sömnkvalitet och dagtrötthet. Patienter med CRS bör tillfrågas om sömnkvalitet och adekvat behandling för CRS initieras. Dels för att förbättra sömnkvaliteten, men även för att minska risken för ytterligare inflammation. SNOT-22 kan vara ett värdefullt redskap i behandlingen av OSA-patienter och för att utvärdera effekten av CPAP-behandling. Ett lågt PNIF-värde ska inte exkludera patienter från CPAP-behandling, men kan användas som ett incitament för att behandla nästäppa och på så vis optimera behandlingen. Slutligen, symptomet nästäppa ska väcka frågan om patienten också besväras av dålig sömnkvalitet.

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