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PREVALENCE OF UPPER AIRWAY SYMPTOMS AND ASPECTS ON TREATMENT OF NASAL POLYPOSIS

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Cover photo by Petter Olsson. Nasal polyp in left nasal cavity.

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En näsa
kan fräsa,
har två hål
och föder en ål.

Näsans lukt
känner frukt.

Madeleine Olsson, 7 år

ABSTRACT

Background: Non-allergic rhinitis is a disease that is often trivialised, leading to inadequate management and unnecessary costs. One of the most common types of severe non-allergic nasal inflammation is nasal polyposis. Nasal polyposis is associated with asthma. The aims of this thesis were to estimate the prevalence of self-reported non-allergic nasal symptoms and explore relations of these symptoms to age and sense of smell (I), to study the effects of functional endoscopic sinus surgery (FESS) and fluticasone propionate nasal drops (FPND) 400 µg twice daily on lower airway and nasal parameters in patients with nasal polyposis and asthma (IV), to investigate the health impact of nasal polyposis with asthma and to study effects of FESS, as well as addition of FPND, on health related quality of life (HRQoL) in this patient group (V), to study the efficacy of mometasone furoate nasal spray (MFNS) 200 µg once daily in reducing relapse of nasal polyps in subjects with nasal polyposis who underwent FESS (II) and, to study the effect of FESS on sense of smell and olfactory thresholds in patients with nasal polyposis (III).

Methods: A questionnaire to a random sample of 15,000 individuals, 19-80 years (I). A randomised, double-blind, placebo-controlled study. 68 patients, ≥18 years, with nasal polyposis and asthma were randomised to FPND or placebo for 4 weeks prior to, and 5 weeks after FESS. For an additional 7 weeks all patients received FPND. Assessments pre- and post-FESS included; asthma symptoms, PEFR, FEV_1, nasal symptoms, PNIF, olfactory thresholds, SF-36 (IV and V). A randomised, double-blind, placebo-controlled, multi-centre study. 162 patients, ≥18 years, with nasal polyposis were randomised to MFNS or placebo approximately 2 weeks after FESS until relapse of nasal polyps or for a maximum of 6 months. Nasal polyps were scored on a 4-point scale for each nasal cavity (II). A study of 160 patients who had undergone FESS. Olfactory thresholds and sense of smell were measured pre-FESS and 2 weeks after surgery (III).

Results: The prevalence of self-reported non-allergic nasal symptoms was 19.3 % (95% CI 18.4-20.2) and did not change with age. In that group the prevalence of reduced sense of smell was 25.6% (95% CI 23.3-28.0) (I). Asthma symptoms decreased after FESS in both FPND and placebo groups 5 weeks after FESS (p=0.007), and PEFR was increased in the placebo group (p=0.010). All nasal symptoms decreased and PNIF and olfactory thresholds improved in both groups after FESS (p=0.015 – 0.001). There were no significant differences between the two groups (IV). At baseline HRQoL was decreased in both Physical Component Summary, PCS, (p=0.049) and Mental Component Summary, MCS, (p<0.001), as well as in 6 out of 8 domains compared with the reference population. FESS improved PCS (p=0.027) and MCS (p=0.021) as well as 5 out of 8 SF-36 domains after 5 weeks. We found additional benefit of FPND on 3 domains (V). Time to relapse was >175 days in the MFNS group and 125 days in the placebo group (ITT, p=0.049) (II). Olfactory threshold increased from 0 pre-FESS to 3.0 (p<0.001) 2 weeks post-FESS. Sense of smell score decreased from 3.0 pre FESS to 1.7 (p<0.001) post-FESS, i.e. improvement (III).

Conclusions: Self-reported non-allergic rhinitis symptoms are highly prevalent independent of age, and reduced sense of smell is a common complaint (I). FESS, but not addition of FPND, improved asthma symptoms as well as olfaction and PEFR in patients with nasal polyposis and asthma (IV). HRQoL is impaired in patients with nasal polyposis and concomitant asthma. FESS seems to have benefits on HRQoL in these patients and FPND can be added to improve, and also to reach population levels of, HRQoL at 5 weeks post-FESS (V). Post-FESS use of MFNS 200µg once daily increases time to relapse of polyps in patients with nasal polyposis (II). There are indications of a positive effect of FESS on olfaction in nasal polyposis (III).

Key Words: Non-allergic rhinitis symptoms, prevalence, randomised controlled trial, nasal polyposis, functional endoscopic sinus surgery, mometasone furoate nasal spray, fluticasone propionate nasal drops, olfaction, health related quality of life, SF-36.

LIST OF PUBLICATIONS

The present thesis is based on the following papers, which will be referred to by their Roman numerals (I-V):

I. OLSSON P, Berglind N, Bellander T, Stjärne P. Prevalence of Self-reported Allergic and Non-allergic Rhinitis Symptoms in Stockholm: Relation to Age, Gender, Olfactory Sense and Smoking. Acta Otolaryngologica 2003;123:75-80. www.informaworld.com/oto.

II. Stjärne P*, OLSSON P*, Ålenius M. Mometasone furoate prevents polyp relapse following endoscopic sinus surgery. Archives of Otolaryngology - Head & Neck Surgery, in press. **Both authors contributed equally to the manuscript*

III. OLSSON P, Stjärne P. Functional Endoscopic Sinus Surgery improves olfaction in nasal polyposis, a multi-center study. Manuscript.

IV. Ehnhage A, OLSSON P, Kölbeck K-G, Skedinger M, Dahlén B, Ålenius M, Stjärne P. Functional Endoscopic Sinus Surgery improved asthma symptoms as well as PEFR and olfaction in patients with nasal polyposis. Allergy, in press, DOI: 10.1111/j.1398-9995.2008.01870.x. www3.interscience.wiley.com/journal/118519659/home.

V. OLSSON P, Ehnhage A, Nordin S, Stjärne P. Quality of Life is Improved by FESS in Nasal Polyposis with Asthma. Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse event
ASA	Acetylsalicylic acid
BID	Twice daily *(Bis in die)*
CCCRC	Connecticut Chemosensory Clinical Research Center
CI	Confidence interval
ENT	Ear-, nose-, and throat
EP^{3}OS	European position paper on rhinosinusitis and nasal polyps
FESS	Functional endoscopic sinus surgery
FEV_1	Forced expiratory volume for 1 second
FPND	Fluticasone propionate nasal drops
FPANS	Fluticasone propionate aqueous nasal spray
HRQoL	Health related quality of life
ICS	Inhaled corticosteroids
ITT	Intention to treat
MFNS	Mometasone furoate nasal spray
MPA	Swedish Medical Products Agency (Läkemedelsverket)
NSAID	Non-steroidal anti-inflammatory drug
OCS	Oral corticosteroids
OR	Odds ratio
PEFR	Peak expiratory flow rate
PNIF	Peak nasal inspiratory flow
PP	Peak protocol
QD	Once daily (*Quaque die*)
QoL	Quality of life
SF-36	Short form 36 health survey
VAS	Visual analogue scale

1. INTRODUCTION

1.1 NON-ALLERGIC RHINITIS

According to the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline update 2008, allergic rhinitis is a symptomatic disorder of the nose induced after allergen exposure by an immunoglobulin E (IgE)-mediated inflammation of the membranes lining the nose [1] and was defined in 1929 by three cardinal symptoms: sneezing, nasal obstruction and mucous discharge [2]. In non-allergic rhinitis there is no similar consensus definition of the disease. Settipane and Charnock used the definition ”nasal diseases that are due to multiple etiologies, none of which involve an immunologic response modulated by IgE” , in a chapter of a recent textbook [3]. However, such a definition would also include e.g. infectious rhinitis, which would cause problems in classification.

1.1.1 Epidemiology

Data regarding the prevalence of non-allergic rhinitis are of substantial lesser quality and quantity than what has been published with regard to allergic rhinitis. However, non-allergic rhinitis appears to be very common with an estimated prevalence in Europe of 25% [4]. Three peer-reviewed published papers have helped to increase knowledge on its prevalence, although none of these makes an attempt to capture the frequency of coexisting allergic and non-allergic rhinitis, also described as mixed rhinitis, and they all have a selection bias towards allergic rhinitis patients [4-6] . A population-based questionnaire study of a random subsample of 1,469 persons in Sweden found the prevalence of non-allergic nasal complaints to be 21% [7]. Hellgren and co-workers report a prevalence of ”non-infectious rhinitis”, which comprises both allergic and non-allergic rhinitis symptoms, of 40% in another population based Swedish study of a random sample of 2,400 [8].

1.1.2 Definition and diagnosis

Non-allergic rhinitis often has onset after the age of 20 [9] and can have nasal hyperreactivity [10] and perennial symptoms [11]. The accurate diagnosis of non-infectious, non-allergic rhinitis requires a medical history to ascertain relevant symptoms, frequency, time of year and aggravating triggers in conjunction with a physical examination (including nasal) and skin prick or specific IgE testing. Exclusion of relevant differential diagnoses, e.g. hormonally induced and drug-induced rhinitis, is fundamental [3]. However, physicians are often unaware of how to differentiate between allergic and non-allergic forms of this disease [12, 13] and opinion leaders have not reached a consensus on how to define non-allergic rhinitis [3].

1.1.3 Health related quality of life

QoL instruments measure the impact of a disease in relation to various physical and mental functions. Health related quality of life (HRQoL) instruments are divided into generic and disease specific. One of the most extensively used generic HRQoL instruments is the Medical Outcomes Trust Short Form 36-Item Health Survey (SF-36)[14]. This contains 36 items in eight domains covering both physical and mental health and shows good reproducibility and validity[15]. It was developed after interviews with patients asking about relevant symptoms and disabilities that they can cause. There are also disease specific HRQoL instruments, e.g. for rhinitis [16, 17] and rhinosinusitis [18, 19]. As the SF-36 is a generic HRQoL instrument it makes it possible to compare the results with other diseases [14]. However, there are no robust HRQoL data on non-allergic rhinitis as measured by validated generic HRQoL instrument and there is no disease-specific HRQoL instruments for non-allergic rhinitis [20]. Data from studies of allergic rhinitis show that rhinitis predominantly affects mental HRQoL [21, 22]. The burden of rhinitis is associated with sleep impairment, daytime sleepiness, concentration problems and irritability [20].

1.1.4 Treatment

In general, the less is known about a disease the more treatment options are available. This also applies to non-allergic rhinitis. There is no obvious first line treatment for non-infectious non-allergic rhinitis. Evidence level Ib has been reached by the following treatments; Intranasal corticosteroids, decongestants, ipratropium bromide nasal spray, capsaicin nasal spray, intranasal azelastine and outpatient inferior turbinate surgery [3]. In contrast to allergic rhinitis, the studies supporting intranasal corticosteroids are limited and inconclusive. The largest is a randomised placebo-controlled study showing efficacy in 56% of the patients treated with mometasone furoate nasal spray (MFNS) and in 49% in the placebo group [23]. However, usage of the rescue medication (loratadine) at least once during the double-blind period was high: 38% in the MFNS group and 41% in the placebo group. This makes it harder to interpret results.

Goals for the future include reaching a consensus on the definitions of rhinitis and rhinitis subtypes. Only then can research results be compared and the most appropriate treatments presented.

1.2 NASAL POLYPOSIS

Nasal polyps are a sign of inflammation in the nose and can be associated with nasal polyps. Chronic rhinosinusitis with or without nasal polyps is a significant health problem which results in a large financial burden on society [24-26]. Health economy data on nasal polyposis are limited [27] and the available limited data are difficult to interpret and extrapolate [28].

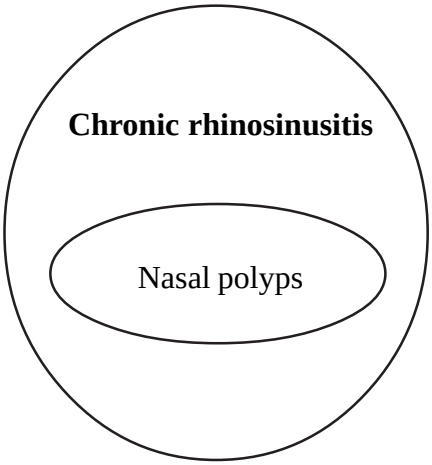


Figure 1. The spectrum of chronic rhinosinusitis and nasal polyps.

1.2.1 Epidemiology

Nasal polyposis is a common chronic inflammatory disorder of the upper airway and it has been estimated that approximately 2-4% of the general population in Europe suffer from nasal polyposis [29-31]. Men outnumber women in the occurrence of nasal polyposis, with the great majority of polyps appearing after 40 years of age [30, 32]. The condition is rare in children [33].

In a population-based study in Skövde, Sweden, Johansson et al. reported a prevalence of nasal polyps of 2.7% of the total population [30]. In that study, nasal polyps were diagnosed by nasal endoscopy without decongestant and were more frequent in men (2.2 to 1), the elderly (5% at 60 years of age and older) and asthmatics (OR 5.2). In a survey in Korea, the overall prevalence of polyps diagnosed by endoscopy was 0.5% of the total population [34]. Based on a postal questionnaire survey in Finland, Hedman et al. found that 4.3% of the adult population answered positively to the question as to whether polyps had been found in their nose [29]. Using a questionnaire, Klossek et al reported a prevalence of nasal polyposis of 2.1% in France [31].

1.2.2 Pathophysiology

The pathophysiology of nasal polyposis is yet to be defined: it involves inflammation of the nasal and paranasal sinus mucosa originating from within the ethmoid region. Histologically, nasal polyps are benign growths of the mucosa characterised by proliferation of the epithelial layer, few mucous glands, thickening of the basement membrane, oedema, stromal fibrosis, and cellular infiltration of the stromal layer with a reduced number of vessels and glands, but virtually no neural structure [35, 36]. Infiltrating inflammatory cells include eosinophils, mast cells, neutrophils, lymphocytes and plasma cells with eosinophils most often predominating [37-39]. Expression of cytokines and chemokines, such as interleukin-5 and eotaxin, which are involved in the regulation of migration, survival and activation of inflammatory cells, is increased in nasal polyposis [40-42].

Bacterial colonisation of the nasal cavity, resulting in the synthesis and release of enterotoxins that act as superantigens may be involved in the pathogenesis [43]. It has also been proposed that most patients with chronic rhinosinusitis exhibit eosinophilic infiltration with presence of fungi by histology or culture [44]. However, the same percentage of positive fungi cultures was also found in normal controls [45] and two prospective clinical trials [46, 47] with antifungals have given no effect on the polyposis itself, indicating that fungal driven inflammation is a parallel phenomenon.

Bacterial communities adherent to a mucosal surface (biofilms) are associated with chronic rhinosinusitis [48]. However, little research is available to define their exact role in the pathogenic process. There is tremendous potential for future research as bacterial biofilms may be a factor in the inflammatory process [49].

Although the mechanisms involved in the pathogenesis remain largely unclear, there are suggestions of an underlying genetic predisposition [50]. This thesis does not include nasal polyps in cystic fibrosis, which is a hereditary monogenetic disease with genetic variations and multi-organ involvement.

Inflammation of the nose and the para-nasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/ congestion or nasal discharge (anterior/ posterior nasal drip):
- ± facial pain/pressure
- ± reduction or loss of smell

and either

Endoscopic signs of:
- polyps and/or;
- mucopurulent discharge primarily from middle meatus

and/or

Oedema/mucosal obstruction primarily in middle meatus

and/or

Computed tomography changes:
- mucosal changes within the ostiomeatal complex and/or sinuses

1.2.3 Diagnosis, staging and assessments

1.2.3.1 Clinical and research definitions

According to current European guidelines, EP^{3}OS 2007 [28], rhinosinusitis (including nasal polyps) is defined as:

According to the same guidelines the disease can be divided into mild, moderate or severe based on total severity visual analogue scale (VAS) score (0-10); where mild = VAS 0-3, moderate = VAS >3-7 and severe = VAS >7-10. To evaluate the total severity, the patient is asked to indicate on a VAS the response to the question: ”How troublesome are your symptoms of rhinosinusitis?”. A VAS > 5 affects patient QoL [51]. Duration of the disease is classified as: acute (< 12 weeks) with complete resolution of symptoms or chronic (>12 weeks symptoms) without complete resolution of symptoms [28]. Chronic rhinosinusitis may also be subject to exacerbations.

For research purposes chronic rhinosinusitis is defined by EP^{3}OS 2007 as above. Chronic rhinosinusitis is defined as the major finding and nasal polyps/polyposis is considered a subgroup of this entity (Fig 1). For the purpose of a study, the differentiation between chronic rhinosinusitis and nasal polyposis must be based on out-patient endoscopy. The definition by EP^{3}OS 2007 of the two types of chronic rhinosinusitis when no earlier sinus surgery has been performed is [28]:

Chronic rhinosinusitis with nasal polyposis
Polyps bilaterally, endoscopically visualised in middle meatus.

Chronic rhinosinusitis without nasal polyposis
No visible polyps in middle meatus, if necessary following decongestant.

In this thesis we use nasal polyposis for the diagnosis defined as chronic rhinosinusitis with nasal polyposis/nasal polyps by EP^{3}OS 2007. We believe that decongestion always should precede nasal endoscopy.

EP^{3}OS 2007 states that the following conditions should be considered for sub-analysis in research: 1. Aspirin sensitivity, based on positive oral, bronchial or nasal provocation or an obvious history; 2. Asthma/bronchial hyper-reactivity/ chronic obstructive pulmonary disease/ bronchiectasis, based on symptoms, respiratory function tests; 3. Allergy, based on specific serum IgE or skin prick tests [28].

Patients with the following diseases should be excluded from general studies, but may be the subject of a specific study on chronic rhinosinusitis and/or nasal polyposis:
1. Cystic fibrosis, 2. Gross immunodeficiency 3. Congenital mucociliary problems e.g. primary ciliary dyskinesia (PCD), 4. Non-invasive fungal balls and invasive fungal disease, 5. Systemic vasculitis and granulomatous diseases, 6. Cocaine abuse, 7. Neoplasia [28].

1.2.3.2 Symptoms
Subjective assessment of nasal polyposis is based on symptoms:

- nasal blockage, congestion or stuffiness,
- rhinorrhoea, or nasal discharge
- facial pain or pressure, headache, and
- reduction/loss of sense of smell

Nasal polyps may cause constant nasal blockage. Nasal polyps often cause nasal congestion, which can be a feeling of fullness in the nose and paranasal cavities. This is typical of ethmoidal polyposis, which in severe cases can cause widening of the nasal and paranasal cavities. Reduced or absent sense of smell are more prevalent in patients with nasal polyps than in other chronic rhinosinusitis patients [52]. As increased nasal resistance has been linked to snoring and obstructive sleep apnoea [53], questions regarding sleep impairment should also be asked.

1.2.3.3 Symptom assessment
Subjective assessment of the symptoms should consider the severity and duration. During the last decade more attention has been paid not only to symptoms but also to their effect on the patient's QoL [19, 54]. The assessment of symptoms is done using questionnaires or in clinical studies recorded in report forms. Symptoms are usually evaluated once or twice daily. The severity of the symptoms can be estimated using many different grading tools [55]:

- recorded as such: severe, moderate, slight and no symptom
- recorded as numbers: from 0 to 4 or as many degrees as needed
- recorded as VAS score on a line giving a measurable continuum (0 -10).

1.2.3.4 Validation of subjective symptoms
Nasal blockage
In patients, interpretation of nasal obstruction varies from true mechanical obstruction of airflow to the sensation of fullness in the face. Generally, the subjective sensation of nasal obstruction and objective evaluations show a good intra-individual correlation in studies [56-59] . However, there are also some studies where this correlation is not seen [60] or the correlation was poor [61, 62]. The interpatient variation in subjective scoring suggests that every nose is "unique", which makes interpatient comparisons less reliable but still significant [56, 57]. Subjective nasal obstruction correlates better with objective measurements of nasal airflow resistance (rhinomanometry, PNIF) than with measurements of nasal cavity width, such as acoustic rhinometry [59, 63].

Rhinorrhoea
Tools for objective assessment of nasal discharge are not as good as for nasal obstruction: validating correlation studies between on "objective" discharge measures (collecting and measuring amount or weight of nasal secretion) and subjective scoring of rhinorrhoea has not been performed.

Smell abnormalities
Fluctuations in the sense of smell are associated with nasal polyposis. Please see chapter 1.4 Olfaction.

1.2.3.5 Clinical examination

Anterior rhinoscopy

Anterior rhinoscopy is the first step in examining a patient with this disease. However, as it doesn't cover the whole nasal cavity, it is inadequate if nasal polyps are to be totally ruled out.

Nasal endoscopy

Nasal endoscopy should be performed with decongestion. A number of staging systems for polyps have been proposed [64-68]. Johansson et al. showed good correlation between a 0-3 scoring system and their own system in which they estimated the percentage projection of polyps from the lateral wall and the percentage of the nasal cavity volume occupied by polyps [64]. However, they did not find a correlation between polyp size and symptoms.

Nasal biopsy

Biopsy of nasal polyp tissue may be indicated to exclude more severe conditions such as neoplasia.

Imaging

Sinus x-rays are of limited usefulness for the diagnosis of nasal polyposis due to the number of false positive and negative results [69]. Computed tomography is the modality of choice confirming the extent of pathology and anatomy. However, it should not be regarded as the primary step in the diagnosis of the condition, except where there are unilateral signs and symptoms or other pathological signs, but rather as aid to the surgeon as pre-operative guidance. A computed tomography scan is nowadays standard in the pre-operative assessment and is especially important in revision surgery where image guidance has a role.

1.2.3.6 Nasal airway assessment

Peak nasal inspiratory flow

In 1980, Youlten developed a peak nasal inspiratory flow (PNIF) meter which was non-invasive and had the advantages of simplicity, portability and economy [70]. PNIF allows maximum inhalations through the nose [71]. This quick and easy test is a useful estimate of airflow which can be performed at home as well as in the hospital setting. However, it measures both sides together and has little direct role in the assessment of nasal polyposis. PNIF is an emerging endpoint used as an objective measure of nasal patency. It could be used to assess gross reduction in nasal polyps and compares well with rhinomanometry and also with subjective assessments of nasal congestion by patients [72-77]. Normative data is now available in an adult Caucasian population [78]. PNIF is assessed using a PNIF meter; the normal range is 100-300 l/min [79]. In nasal polyposis clinical trials, PNIF has been shown to be a useful tool for the detection of a treatment response [67, 80, 81]. An increase in PNIF supports the clinical efficacy of the study drug tested.

Peak nasal expiratory flow

Peak nasal expiratory flow is less often used as nasal secretion is expelled into the mask.

Rhinomanometry

Rhinomanometry is the measurement of nasal airway resistance by assessing nasal flow at a constant pressure. It is of limited use in nasal polyposis, but can be useful in confirming that improvement in nasal congestion is the result of reduction in inflammation rather than mechanical obstruction [82].

Acoustic rhinometry

Acoustic rhinometry is based on a sound wave distortion by nasal topography and allows quantification of area at fixed points in the nose from which volume may be derived. It can be used to demonstrate subtle changes, both as a result of medical and surgical intervention [73, 83-85].

1.2.3.7 Olfaction

Threshold Testing

The estimation of olfactory thresholds by the presentation of serial dilutions of pure odorants has been used in a number of clinical studies in nasal polyposis [67, 86, 87].

Other quantitative olfactory testing

Scratch and sniff tests using patches impregnated with microencapsulated odorants are available [88] and have been utilised in studies of nasal polyposis [73]. A cruder screening test, the Zurich Smell Diskette test may also be used and has the advantage of pictorial representation of the items [89]. Also on a national level, the

Barcelona Smell Test has been developed, comprising 24 odorants and has been compared with the Zurich Smell Diskette Test [90]. More complex tests exist, e.g. 'Sniffin' sticks', application of which is limited to the research setting [91]. A combined supra-threshold detection and identification test has been presented as a cross-cultural test in the European population [92]. For more on olfaction, please see chapter 1.4 Olfaction.

1.2.4 Health related quality of life

Health related quality of life questionnaires are tools to evaluate the impact of a disease on daily life and well-being as perceived by the patient [93]. However, it is of interest that the severity of nasal symptoms has been reported not to correlate with HRQoL scales [94, 95]. Until recently, there has been a lack of randomised study data on nasal polyposis and HRQoL. Only a few studies have provided information on the effect of treatment of nasal polyposis.

1.2.4.1 Generic HRQoL instruments

Generic measurements enable the comparison of patients suffering from nasal polyposis with other patient groups. Of these, the Medical Outcomes Study Short Form 36 (SF-36) [14] is by far the most widely used and well validated and this has been used both pre- and post-operatively in chronic rhinosinusitis [83, 100]. It includes eight domains: physical functioning, role functioning physical, bodily pain, general health, vitality, social functioning, role functioning emotional and mental health. Many other generic measurements are also available (Table 1) [101].

1.2.4.2 Disease specific HRQoL instruments

Several disease specific questionnaires for evaluation of HRQoL in chronic rhinosinusitis have been published [19, 102-107]. Specific symptoms for rhinosinusitis are included in these questionnaires. Such areas include headache, facial pain or pressure, nasal discharge or postnasal drip, and nasal congestion. Disease specific questionnaires are usually used to measure effects within the disease in response to interventions. They are usually more sensitive than general health status instruments. However, no validated disease specific HRQoL instrument exists for nasal polyposis alone.

1.2.4.3 Results; Generic questionnaires

In three generic SF-36 surveys the scores of chronic rhinosinusitis patients were compared to those of a healthy population. The results showed statistically

Table 1. Selection of generic HRQoL questionnaires for adults, modified from Alobid et al. [96].

Questionnaire	Number of items	Number of domains	Time to complete	Type	Original language	Scoring
SF-36 [14]	36	8	10-20 min	Self-report	English	0-100
SF-12 [97]	12	8	5-10 min	Self-report	English	0-100
MPQ [98]	78	20	10-20 min	Interviewer	English	5 point scale
EQ-5D [99]	15	5	5-10 min	Self-report	English Dutch Finnish Norwegian Swedish	0-100

SF-36, short form-36 health survey, SF-12, short form-12 health survey,
MPQ, McGill pain questionnaire, EQ-5D, EuroQol 5 D.

significant differences in seven of eight domains [24, 108, 109]. Two studies have reported that patients with chronic rhinosinusitis, *without* nasal polyps, have more bodily pain and worse social functioning than for example patients with chronic obstructive pulmonary disease, congestive heart failure, diabetes or back pain [108, 110]. The effect of surgical treatment was studied with generic questionnaires preoperatively and usually 3, 6 or 12 months after the operation [109, 111]. Following endoscopic sinus surgery, the SF-36 questionnaire demonstrated a return to normality in all eight domains six months post-operatively which was maintained at twelve months [100]. In a study by Gliklich and Metson after the sinus surgery significant improvements in QoL and reduction of the symptoms and medications needed were found [112].

Radenne et al. have, in a prospective study, studied the QoL of 49 nasal polyposis patients using a generic SF-36 questionnaire [95]. Polyposis impaired the QoL more than for example perennial rhinitis (n= 111). Treatment (14 had intranasal steroids and 14 had intranasal steroids and surgery) significantly improved the symptoms and the QoL of 28 polyposis patients after 10 months. FESS surgery on asthmatic patients with massive nasal polyposis in a retrospective study improved nasal breathing and HRQoL, and the use of asthma medications was also significantly reduced [113].

In nasal polyposis studies, when the effect of medical treatment or surgery has been evaluated, HRQoL has been considered to be an important outcome measurement as distinct from classic symptom parameters. HRQoL has been shown to improve significantly with both medical and surgical treatment [109]. In that randomised study on 109 patients with nasal polyposis by Alobid et al. the surgical (FESS) group was treated with intranasal steroid beginning 14 days after surgery and SF-36 was measured at 6 and 12 months (Table 2).

Table 2. Selection of studies with generic HRQoL questionnaires in nasal polyposis, modified from Alobid et al. [96]

Study	N	Treatment	Length of treatment	HRQoL questionnaire	Impact on HRQoL	Level of evidence
Radenne et al. [95]	49	INS vs INS + Ethmoidectomy + OCS	2-19 months	SF-36	Decrease pretreatment, improve posttreatment	IIa
Alobid et al. [109]	109	OCS + INS vs ESS + INS	6, 12 months	SF-36	Decrease pretreatment, improve posttreatment	Ib
Alobid et al. [114]	130	Not defined*	Not applicable	SF-36	Negative impact of asthma	III
Alobid et al. [115]	109	No	Not applicable	SF-36	Negative impact of atopy	III

N, Number of patients, INS, Intranasal corticosteroids, OCS, Oral corticosteroids, ESS, Endoscopic sinus surgery, * Both treated and untreated patients.

1.2.5 Medical treatment

The objective of management of nasal polyposis is to reduce the symptoms and size of polyps, restore the sense of smell, and reduce the incidence of relapse. Grade A recommended evidence based medical treatments are, according to current European guidelines [28], intranasal corticosteroids, OCS and nasal douche for symptomatic relief (but not in single use). After consideration of the underlying aetiology, nasal polyposis is normally managed by a combination of medical and surgical interventions [116-118]. Of these, intranasal corticosteroids and functional endoscopic sinus surgery (FESS), a minimally invasive technique that uses an endoscope to improve ventilation and drainage, have proved to be the medical and surgical treatments of choice, respectively [28]. However, surgical treatment, i.e. nasal polypectomy as well as FESS, is proposed to only be indicated in patients who are not sufficiently responsive to medical treatment in nasal polyposis as surgery has not been sufficiently studied [28].

1.2.5.1 Treatment with corticosteroids

Approved glucocorticosteroid treatment for nasal polyposis can be administered as nasal drop or nasal spray formulations. The effect of OCS on nasal polyposis is poorly documented [119], but a short (14 day) course of oral steroids may be considered [103] where the effect is maintained by long-term treatment with intranasal steroids [120, 121]. Intranasal corticosteroids may reduce the need for surgery [122]. However, this has not been studied with intranasal corticosteroid sprays, which are considered – by many – to be more convenient to use than drops. Studies have shown that MFNS administered once (QD) or twice daily (BID), produces statistically significant reductions in nasal polyp size and congestion/obstruction score, relative to placebo as a medical treatment of nasal polyps [67, 81, 122-125]. However, studies carried out with fluticasone propionate (fluticasone propionate nasal drops, FPND or fluticasone propionate aqueous nasal spray, FPANS) failed to show a consistent effect on polyp size [73, 81, 125, 126]. Both FPND and MFNS have low systemic bioavailability and are approved for the treatment of nasal polyposis in Sweden [127, 128].

1.2.5.2 Postoperative treatment with intranasal corticosteroids to prevent relapse of nasal polyps

The relapse rate after treatment for nasal polyps is high, even after surgery, and the majority of patients require long term follow-up. Twenty years after surgery, 85% of patients who had surgery for nasal polyposis disease were found to have active nasal polyps [52]. Small studies have demonstrated that intranasal corticosteroids are effective in reducing the recurrence of nasal polyps following simple polypectomy (Table 3) [32, 129-133]. These benefits are, at least in part, believed to be attributable to the effect of topical corticosteroids in reducing eosinophilic infiltration of the nasal mucosa. Beclomethasone and budesonide nasal spray have been approved in Sweden for the prevention of nasal polyp relapse following polypectomy.

Recently, two studies have evaluated the efficacy of FPANS among subjects who have undergone FESS [134, 135] (Table 4) although with inconsistent results. Dijkstra et al. performed a double-blind placebo-controlled randomised study in 162 patients with chronic rhinosinusitis with (n=55) *or without* nasal polyps after FESS following failure of nasal steroid treatment [134]. Patients were randomised and given FPANS 400 µg BID, FPANS 800 µg BID or placebo for the duration of 1 year after FESS combined with peri-operative OCS. No differences in the number of patients withdrawn because of recurrent or persistent diseases were found between the patients treated with FPANS and patients treated with placebo. Nor was any positive effect found for FPANS compared with placebo in several subgroups such as patients with nasal polyps, high score at FESS or no previous sinus surgery. Rowe Jones et al studied a similar group of 109 patients (77 with nasal polyps) studied prospectively for 5 years

postoperatively [135]. Seventy two patients attended the 5 year follow-up visit. The patients were entered into a randomised, stratified, prospective, double-blind placebo controlled study of FPANS 200 µg BID, commencing 6 weeks after FESS. The change in overall visual analogue score was significantly better in the FPANS group at 5 years. The changes in endoscopic oedema and polyp scores and in total nasal volumes were significantly better in the FPANS group at 4 years but not 5 years. Last value carried forward analysis demonstrated that changes in endoscopic polyp score and in total nasal volume was significantly better in the FPANS group at 5 years. Significantly more OCS rescue medication courses were prescribed in the placebo group. Thus, these two studies describe the effect after FESS in a group of patients with *and without* nasal polyps who underwent FESS after inadequate response to at least three months intranasal corticosteroid treatment. The reasons why the studies show conflicting results are not clear. But the lack of distinction between nasal polyposis and chronic rhinosinusitis without polyps probably makes it very difficult to assess and define relapse of disease. The studies also had somewhat different designs.

Table 3. Treatment evidence and recommendations for postoperative treatment to in nasal polyposis (Note: some of these studies included patients with chronic rhinosinusitis *without* nasal polyps). Adapted from EP^{3}OS 2007 [28].

Treatment	Level of evidence	Grade of recommendation	Relevance and comments
Oral antibiotics < 2 weeks	No data	D	If pus seen during operation, treatment post op
Oral antibiotics > 12 weeks	Ib	A	Yes, but patients had no polyps in study
Intranasal corticosteroids after FESS	Ib (2 studies, one +, one -)	B	Yes, but patients both with or without polyps
Intranasal corticosteroids after simple polypectomy	Ib	A	Yes
Oral corticosteroids	No data	D	Yes
Nasal douche	No data	D	Yes

Table 4. Treatment evidence for intranasal corticosteroids in the post-FESS management of nasal polyposis to prevent relapse of nasal polyps (Note: both of these studies included patients with chronic rhinosinusitis *without* nasal polyps). Adapted from EP^{3}OS 2007[28].

Study	Drug	N (with nasal polyps)	Treatment time in years	Effect on polyp relapse	Level of evidence	Comments
Dijkstra et al. [134]	FPANS 400 µg or 800 µg BID	55	1	No effect vs placebo	Ib	2 weeks of OCS peri-FESS
Rowe-Jones et al. [135]	FPANS 200 µg BID	77	5	Yes, (polyp) score and total nasal volume	Ib	3 weeks of OCS + 2 weeks of amox-C or vibra

N, number of patients, FPANS, fluticasone propionate aqueous nasal spray, BID, twice daily, OCS, Oral corticosteroids, amox-C, amoxicillin-clavulanic acid, vibra, vibramycin.

1.2.5.3 Side effects of intranasal and oral corticosteroids

Regarding adverse effects of corticosteroids, it is obvious that a distinction needs to be made between intranasal and oral corticosteroids (OCS). Intranasal corticosteroid treatment represents a long-term treatment choice in patients with nasal polyposis. There is insufficient evidence from the literature to relate the use of intranasal corticosteroids at licensed doses to changes in bone mineral biology, cataract or glaucoma. The anti-inflammatory effects cannot be separated from their metabolic effects as all cells use the same glucocorticoid receptor. Therefore when corticosteroids are prescribed measures should be taken to minimise their side effects. Clearly, the chance of significant side effects increases with the dose and duration of treatment. So the minimum dose necessary to control the disease should be given. It is obvious that repeated or prolonged use of OCS is associated with a significantly enhanced risk of change in bone mineral density and fractures [136]. Patients with severe nasal polyposis and a high OCS consumption have a high prevalence of glucocorticoid-induced osteoporosis and secondary adrenal insufficiency [137].

1.2.6 Surgery

FESS focuses on re-establishing communication between the sinuses and the nasal cavity through the natural ostia [138, 139]. Generally, the surgery should focus on, and be limited to, the affected sinuses, leaving the unaffected areas alone. This is to obtain maximum efficacy with minimal risk. FESS is, as mentioned earlier, not superior to medical treatment in patients with nasal polyposis.

It is difficult to generalise about surgery studies because surgery is usually indicated in selected patients who are unresponsive to medical treatment. Moreover, only a few publications on sinus surgery qualify for evidence based evaluation [140] and frequently studies included in systematic reviews are assigned low evidence levels [141]. This is in part due to specific problems in conducting surgical trials. In general, surgery is difficult to estimate or standardise, and the type of treatment is difficult to conceal (blinding). Randomisation may pose ethical problems unless narrow inclusion criteria are set [142]. In addition, a variety of confounders make it difficult to obtain homogenous patient groups with comparable procedures for unbiased evaluation of surgery outcomes. Moreover, type and duration of pre- and post-operative medical treatment may alter the outcome.

One outcomes study and more than a hundred reviewed case series with consistent results suggest that patients with chronic rhinosinusitis with and *without* polyps benefit from sinus surgery [143-145]. Major complications occur in less than 1%, and revision surgery is performed in approximately 10% within 3 years [144] . History of previous sinus surgery or asthma predicted higher recurrence and revision surgery rates. History of allergy also predicted recurrence and need for revision [145].

1.2.6.1 Surgical treatment versus sole medical treatment

Sinus surgery is often preceded and/or followed by various forms of medical treatment including nasal lavage, intranasal corticosteroids, OCS, and antibiotics. No studies have in a randomised controlled way compared sinus surgery, without concomitant medical treatment, versus sole medical treatment.

1.2.6.2 Conventional Endonasal surgery versus FESS

Conventional sinus surgery is a term for surgical techniques used before the development of FESS. They include external approaches, simple (snare) polypectomy, inferior meatal antrostomy, and radical transnasal spheno-ethmoidectomy with or without middle turbinate resection. Unlike FESS, conventional sinus procedures do not proceed along the natural pathways of sinus ventilation and mucociliary transport revealed by the work of Messerklinger [146]. Restoring ventilation and mucociliary transport by functional surgery along the natural sinus ostia allows recovery of the diseased mucosa, which is not resected [147]. With the development of FESS, rigid endoscopes became available, which improved visualization. The evolving concept of FESS spread worldwide through the efforts of Stammberger and Kennedy [138, 148]. In the National Health Service Health Technology Assessment Programme evaluation polyp relapse was 28% following FESS compared to 35% following simple polypectomy [143]. FESS has thus not been studied sufficiently, but EP^{3}OS 2007 concludes that FESS is superior to polypectomy [28].

1.3 NASAL POLYPOSIS WITH ASTHMA

1.3.1 Epidemiology

Asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough, and chest tightness [149] and is reported by 26% of patients with nasal polyps, compared to 6% of controls in a questionnaire survey in France [31]. According to a Danish meta analysis, asthma was found in 30% of those referred to ENT physicians and in more than 70% of those referred to an allergy clinic [150].

Seven to 15 percent of asthma patients have nasal polyps [150-153] and in non-atopic asthma and late onset asthma, polyps are diagnosed more frequently (10-15%). ASA-induced asthma is a distinct clinical syndrome characterised by the triad ASA-intolerance, asthma and nasal polyposis (Samters triad) and has an estimated prevalence of 1% in the general population and 10% among asthmatics [154]. The prevalence of nasal polyps rises up to 60% in studies of the asthma subgroup associated with intolerance to ASA and NSAID [155, 156]. The unusual severity of the upper airway disease in these patients is reflected by high relapse of nasal polyps, and frequent need for endoscopic sinus surgery [52, 157]. Increased nasal colonisation by Staphylococcus aureus and presence of specific IgE directed against Staphylococcus aureus enterotoxins was found in nasal polyposis patients [158]. Rates of colonisation and IgE presence in polyp tissue were increased in subjects with nasal polyposis and co-morbid asthma or ASA-intolerance.

Concerning hereditary factors, HLA A1/B8 has been reported as having a higher incidence in patients with asthma and ASA-intolerance [159].

1.3.2 Treatment effects

1.3.2.1 Effect of medical treatment of nasal polyposis on asthma

No prospective trials on the effects of medical therapy alone for nasal polyposis alone on asthma, as a primary objective, have been conducted to date.

1.3.2.2 Effect of FESS on bronchial asthma in nasal polyposis

There is no evidence that patients with nasal polyposis and concurrent asthma benefit less from FESS than patients without asthma with regard to their polyposis symptoms. Various confounders influence the effects of surgical polyposis treatment on concomitant asthma. In studies published in recent years, predominantly positive effects of surgical polyp treatment on concomitant asthma severity were reported [160, 161]. However, the level of evidence is low.

The question of how sinus surgery and medical treatment may alter the course of asthma, was reviewed by Lund [162] and Scadding [163]. These authors describe the somewhat intricate base of evidence and conclude that the weight of evidence suggests a beneficial effect. However, once again, the authors did not differentiate between chronic rhinosinusitis with or *without* polyps.

After FESS for nasal polyposis in patients with concomitant asthma in a retrospective study of 17 patients, a significant improvement in lung function and a reduction of OCS use were noted, whereas this was not the case in ASA-intolerant asthma patients [164]. It is unclear how the diagnosis of ASA-intolerance was obtained. In a retrospective series of 34 patients with nasal polyposis, FESS did not affect the asthma state [113]. However, nasal breathing and quality of life improved in most patients.

Ragab and co-workers report a prospective evaluation of a subgroup of 43 asthma patients [165] joining a randomised trial comparing the effects of endoscopic sinus surgery (n=23) and medical treatment (n=20) in chronic rhinosinusitis with and *without* polyps [83]. Outcome parameters included asthma symptoms, FEV_1, PNIF, exhaled nitric oxide, medication use and hospitalisation at 6 and 12 months from the start of the study. Overall asthma control improved significantly following both treatment modalities, but was better maintained after medical therapy, where improvement could also be demonstrated in the subgroup with nasal polyps. Medical treatment (n=8) was superior to surgery (n= 12) with respect to a decrease in exhaled nitric oxide and increase in FEV_1, but not in PEFR in the sub-subgroup of polyp patients at 12 months. However, the "surgical" group had quite extensive medical treatment with a 6-week regimen of dexamethasone-tramazoline spray and an alkaline nasal douche preop as well as a 12-week course of erythromycin, alkaline nasal douche and intranasal corticosteroid preparations. Furthermore, following endoscopic sinus surgery, all patients were prescribed a 2-week course of 500 mg erythromycin, dexamethasone-tramazoline spray and alkaline nasal douche b.i.d. This was followed by a 3-month course of 100 mg (two sprays) fluticasone propionate nasal spray (FPANS) into each nostril and alkaline nasal douche BID. In summary, in the Ragab et al study, medical or adapted medical with endoscopic sinus surgery treatment of *chronic rhinosinusitis*, may benefit concomitant asthma. If there are associated nasal polyps, patients may benefit more from medical therapy, only. More and larger randomised controlled studies are needed.

1.3.3. Health related quality of life

No randomised prospective study has exclusively studied the nasal polyposis with asthma population from a HRQoL aspect [96]. Bousquet and co-workers showed that the SF-36 was reliable and valid when used for the assessment of HRQoL impairment in subjects with moderate asthma [21, 166]. HRQoL in patients with nasal polyposis associated with asthma was worse than that found in subjects with NP without asthma [95]. HRQoL scores in asthmatic patients without nasal polyps [21] are better than those of patients with isolated nasal polyposis, suggesting that nasal polyposis impairs HRQoL to a higher degree than asthma. However, NP and asthma seem to have a cumulative negative effect on HRQoL [95].

1.4 OLFACTION

One of the most important sensory functions of the human being is olfaction. The olfactory airway is 1-2 mm wide and lies above the middle turbinate in the nose. The olfactory mucosa has a surface of approximately 400 mm^2 and contains numerous odour-receptor cells with thin cilia [3]. The area were the olfactory epithelium is located is poorly ventilated as most of the inhaled air passes through the lower aspect of the nasal cavity (Fig. 2).

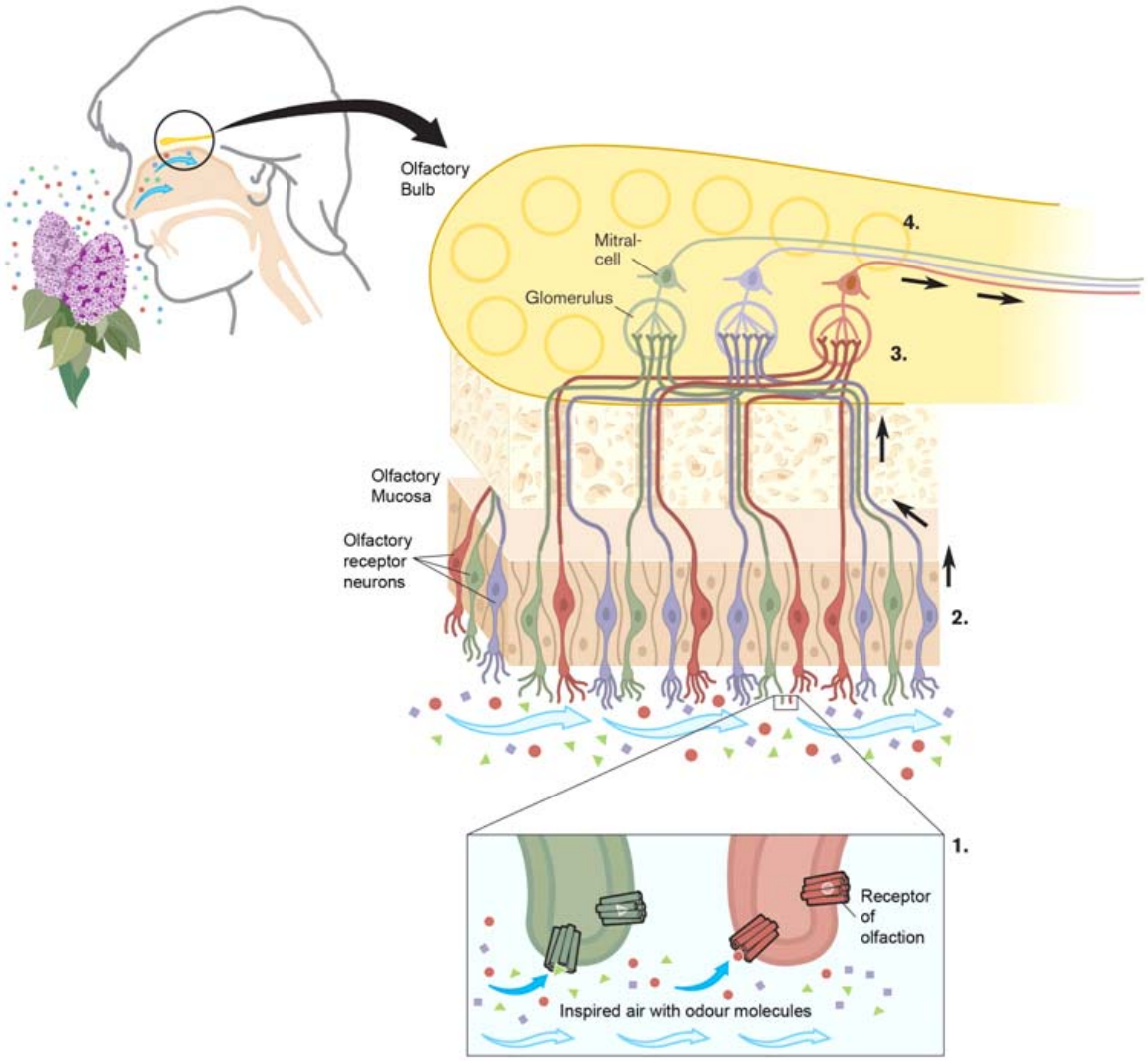


Figure 2. Olfaction: (1) Odours reach the receptors of olfaction on the olfactory receptor neurons (2). Depolarisation of the membrane occurs and transmits a signal that is forwarded to glomeruli (3) in the olfactory bulb through neurotransmission via synapses and from the olfactory bulb signals are transmitted to higher centres of the brain (4) via the olfactory nerve (cranial nerve # 1).

1.4.1 Epidemiology

Olfactory disturbance is common. The high prevalence of olfactory disorders becomes clearer with results from population-based studies. In one study 24% of individuals aged 53 to 97 were found to have impaired olfaction [167]. A recent Swedish study of 1,900 individuals showed a prevalence of 13% (81 women and 104 men) with hyposmia and 6% (33 women and 47 men) with anosmia among individuals aged 20 or older [168]. Regarding risk of olfactory dysfunction (both hyposmia and anosmia), the prevalence increased with age in that study and a recent longitudinal study of adults age 19-95 followed over a three-year period showed the same result [169]. Prevalence of anosmia *per se* seems to be related to high age [168]. Olfactory dysfunction is more common in men than in women (OR for men = 1.7), and more common in individuals with nasal polyps (OR = 2.1) [168]. There does not seem to be an increased risk of olfactory dysfunction in people with diabetes mellitus or in smokers [168]. Apart from aging, the 3 other major causes of olfactory disorders are: head trauma, upper respiratory tract

infections and disease in nose and sinuses [170, 171]. The olfactory dysfunction in nose and sinus disease may be due to mucosal obstruction of the olfactory niche (conductive loss; e.g. nasal polyposis, allergic or non-allergic rhinitis) and/or degenerative alterations in the olfactory mucosa due to the disease or its treatment e.g. repeated nasal surgery.

1.4.2 Classification and assessment of olfactory function

1.4.2.1 Classification

Non-conductive disorders

Most of these cases are probably of sensorineural origin. They are caused by head trauma, neurodegenerative diseases, exposure to toxic substances, medical or surgical treatment, metabolic disorders, congenital disorders and idiopathic conditions. The aetiology may be conductive and sensorineural in the rare cases of tumours.

Conductive disorders

These conditions are usually regarded as treatable and they are often caused by various inflammatory disorders in the nose and sinuses, e.g. nasal polyposis and non-allergic rhinitis.

1.4.2.2 Definitions

A normal sense of smell is called normosmia. Impaired sense of smell can be quantitative or qualitative. Quantitatively, we call a reduced sensitivity to one or more odorants hyposmia, and the inability to detect any olfactory sensation anosmia. Anosmia can also be selective to one or more odorants. Individuals sometimes experience a sense of smell in spite of having anosmia because odorants (e.g. menthol, ammonia) may stimulate the sensory nerves of the nasal mucosa.

Qualitatively, olfactory dysfunctions are classified as parosmia or phantosmia. Parosmia is a perception of an atypical or distorted odour in response to a particular stimulus. Phantosmia is perception of an unpleasant odour when there is no odour present. Quantitative and qualitative olfactory disturbances are found in combination.

1.4.2.3 Assessment

Subjective scoring of olfaction is a commonly used, but not validated assessment method [67, 86, 172].

Psychophysical tests

A procedure that provides a quantitative measurement of sensory function and requires a verbal or conscious overt response on the part of the examinee is considered to be a psychophysical procedure. The most widely used methods for diagnosing olfactory dysfunction are detection and identification tests, which are relatively easy to perform but many are too time consuming to be practical in clinical work. Discrimination tests are also available. For a selection of published olfactory tests, se Table 5. One of the best known and evaluated procedures is the butanol odour detection threshold test. In this thesis the Connecticut Chemosensory Clinical Research Center (CCCRC) threshold test with butanol was used [173].

The most commonly used identification tests are the University of Pennsylvania Smell Identification Test (UPSIT) and Sniffin´ Sticks [88, 91, 174]. Odour identification (by e.g. odour naming, yes/no identification or multiple choice) is related to recognition of aromatic items. This might limit the use of a test to a geographical region. The Scandinavian Odor-Identification Test (SOIT) was developed to address the needs of clinical odour identification for application to a Scandinavian population [175].

Neurophysiological tests

Neurophysiological tests [176] are objective in the respect that they do not always demand active participation of the person. However, they are still largely experimental.

Table 5. Selection of published olfactory tests, adapted from EP^{3}OS 2007 [28].

Author(s)	Test	Test-Time	Country	Sample size	Test retest	Subject differences	Method
Cain [173] 177, 178]	CCCRC	35 min	USA	>700		Age, gender, disease, olfactory disorders.	1/ Threshold for n-butanol. 4-correct-in-a-row method. Odours in squeeze bottles. 2/ Identification. 10 odours. Forced choice from 20 descriptors. Odours in jars.
Doty et al. [88]	UPSIT	15 min	USA	>3000	r=0.981	Age, gender, culture, smoker disease, olfactory disorders.	Identification of 40 encapsulated odours. Scratch and sniff technique.
Doty et al. [179, 180]	CC-SIT MOD-SIT	5 min	USA Europe Asia	>3000	r=0.71	Age, gender olfactory disorders.	Identification of 12 encapsulated odours. Scratch and sniff technique.
Hummel et al. [174] **Kobal et al.** [91]	Sniffin´ Sticks	30 min	Germany Switzerland Austria Australia Italy USA	>1000	r=0.72	Age, olfactory disorders.	Odours in pens. 1/ Threshold for n-butanol. Triple forced choice paradigm. Single staircase method. 2/Discrimination: 16 odorant triplets. Identify the pen with the different smell. Forced choice. 3/ Identification: 16 odours.
Nordin et al. [175]	SOIT	15 min	Sweden Finland	>600	R=0.79	Age, gender olfactory disorders.	Identification of 16 odours in bottles.
Cardesin et al. [90]	BAST-24		Spain	120			24 odours scoring smell detection, identification, and forced choice

1.5 RESEARCH NEEDS AND PRIORITIES ACCORDING TO EP³OS 2007

The following suggestions should highlight some areas of interest for further investigation, according to current European recommendations [28]:

1. Surgical management for nasal polyposis will probably continue to play a role in the management of the disease. In the future, rather than attempting to demonstrate superiority of one therapy over another, studies should target selected patient populations or situations so as to guide the clinician to rational use of medical and/or surgical therapy as part of a comprehensive treatment plan individualised to stage of disease and patient needs.

2. Most HRQoL and symptom-specific questionnaires have been designed for a North American population and need to be validated for European patients.

3. The relationship between the upper and lower respiratory tract needs further investigation and will offer further insight into pathophysiology of inflammation and therapeutic options.

2 AIMS

The aims of this thesis were:

To estimate the prevalence of self-reported non-allergic nasal symptoms in an adult Swedish population.

To explore relations of self-reported non-allergic nasal symptoms to age and sense of smell.

To study the effects of FESS and the intranasal corticosteroid FPND 400 µg BID on lower airway and nasal parameters in patients with nasal polyposis and asthma.

To investigate the health burden incurred by nasal polyposis with asthma compared with the Swedish general population.

To study the effects of FESS, as well as addition of FPND 400 µg BID, on HRQoL in patients with nasal polyposis and asthma.

To study the efficacy of the intranasal corticosteroid MFNS 200 µg QD in reducing relapse of nasal polyps in subjects with endoscopically verified nasal polyposis who have undergone FESS.

To study the effect of FESS on sense of smell and olfactory thresholds in patients with nasal polyposis.

3 SUBJECTS AND METHODS

3.1 SUBJECTS

3.1.1. Paper I

A questionnaire survey was sent to a stratified random sample of 15,000 individuals, aged 19-80 years, out of 1.3 million in this age group in Stockholm County, Sweden. 14,622 individuals received the questionnaire and 10,680 individuals answered. Ten responses were excluded because of incomplete answering, which left a total of 10,670 individuals in the analysis, corresponding to a response rate of 73%. The response rate was lower among persons born outside Sweden, males, and people in the 19-29 years age group.

3.1.2 Paper II

A total of 201 subjects aged ≥18 years with endoscopically verified bilateral nasal polyps fulfilling the criteria for FESS were screened, of whom 162 were randomised to treatment. Of these, 80 were randomised to the study drug MFNS 200 µg QD and 82 were randomised to placebo. For inclusion and exclusion criteria please see Table 6. Asthmatic subjects could be included if they had not had an exacerbation of their asthma since visit 1 (see 3.2.1.2). Baseline exclusion criteria were similar to those for study entry. For baseline characteristics please see Table 7. For study flow chart, please see Figure 3.

3.1.3 Paper III

Of the 201 subjects in paper II, 199 patients were included in a post hoc analysis of which 160 patients (54 women and 106 men) had undergone FESS. All patients who had pre-surgery and post-surgery data (Visit 1-4, please see 3.2.1.3) before randomisation to treatment, as described in Paper II, were included in the statistical analyses. Inclusion and exclusion criteria were the same as in Paper II (Table 6). The age distribution and the percentage of smokers were similar for men and women. Moreover, there were no obvious differences between men and women, or between patients with or without previous surgery, with respect to polyp or congestion scores.

3.1.4 Paper IV and V

Eighty-two patients, aged 18 years or older, with a diagnosis of nasal polyposis and asthma, were recruited and assessed for eligibility. The asthma diagnosis was based on history and lung function tests, as assessed by a pulmonologist. All but one patient were on inhaled corticosteroids at the start of the study. They were also required to have bilateral nasal polyps upon endoscopic examination by an otorhinolaryngologist. After wash-out for nasal medical treatment, 68 patients were randomised to treatment. Of these, 30 were randomised to the study drug FPND 400 µg BID and 38 were randomised to placebo. For inclusion and exclusion criteria please see Table 6. Investigators were instructed not to change the medical treatment for asthma throughout the study. ASA/NSAID intolerance was not an exclusion criterion, and this specific history was not investigated. For baseline characteristics see Table 7. For study flow chart, please see Figure 4.

Figure 3. Paper II. Study flow, ITT population.

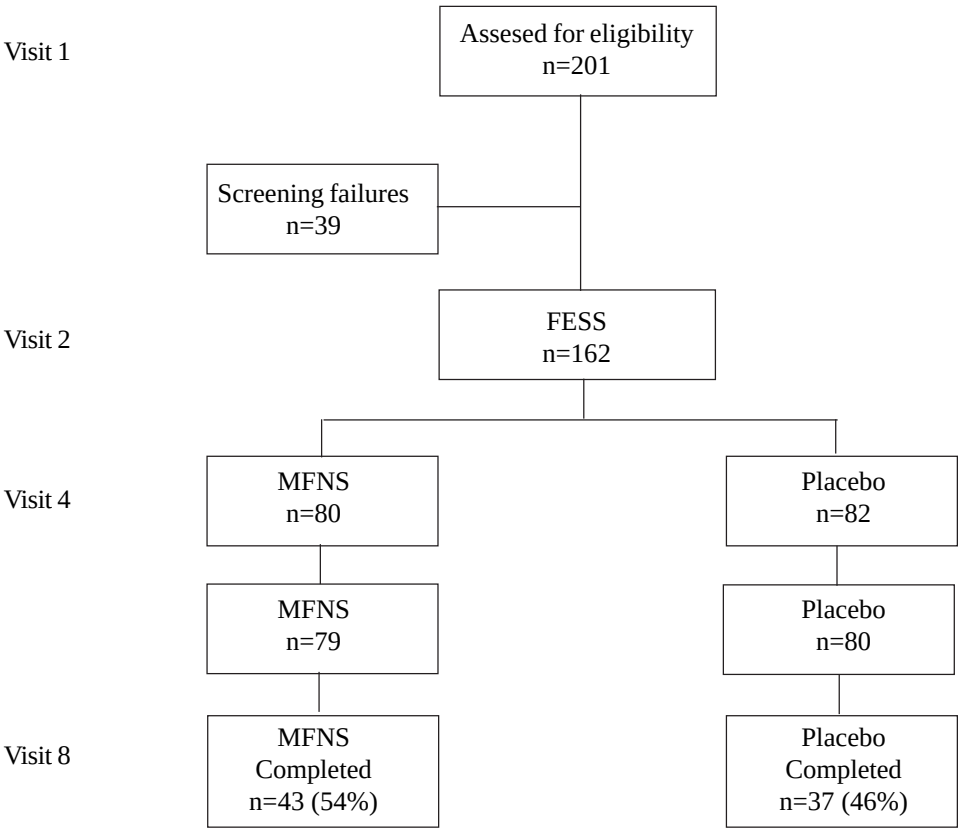


Figure 4. Papers IV and V. Study flow, ITT population.

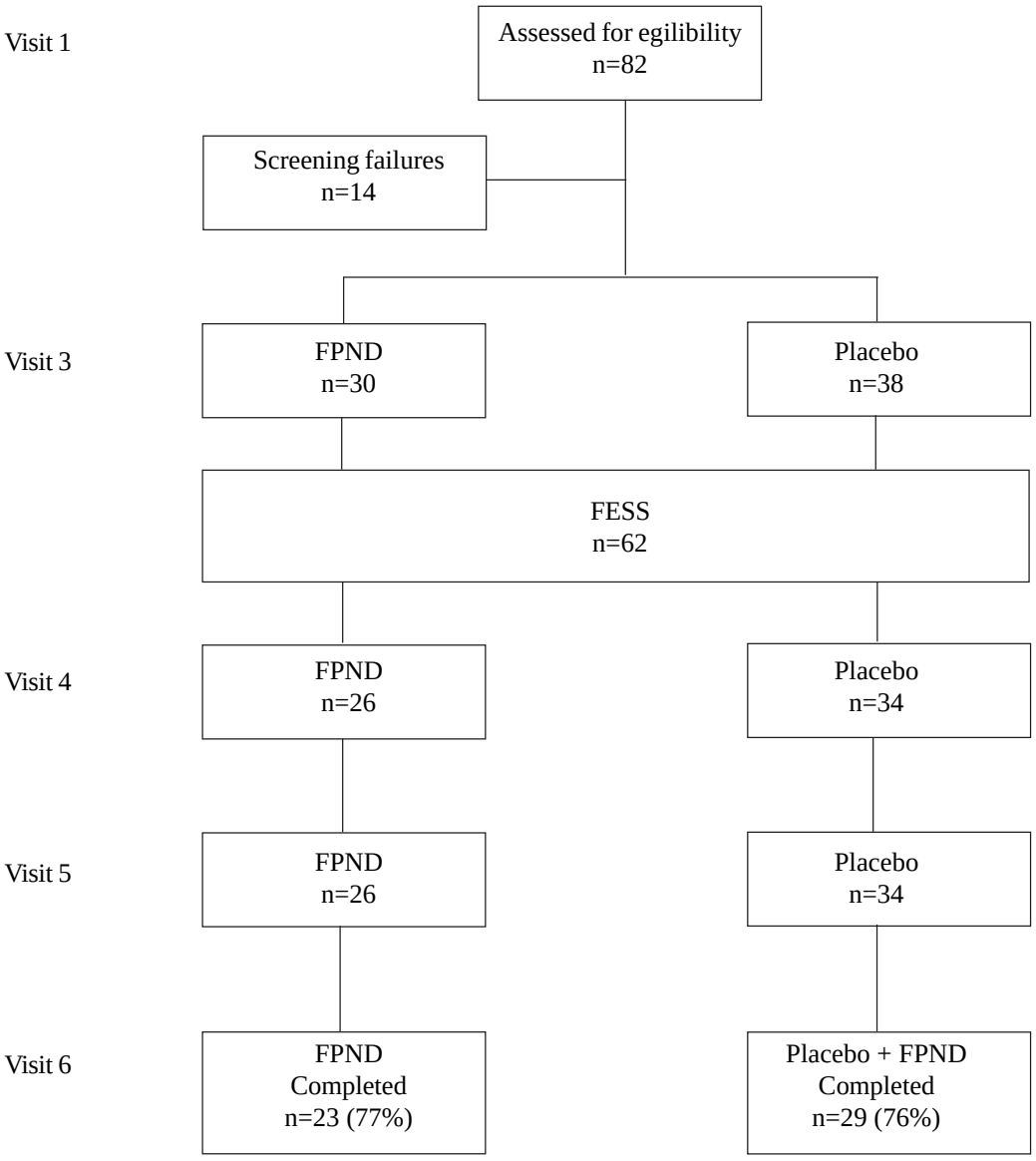


Table 6. Inclusion and exclusion criteria in Papers II, III, IV and V.

Inclusion criteria	**Paper II and III**	**Paper IV and V**
Age ≥18	X	X
Bilateral nasal polyps	X	X
Asthma		X
Capable of recording symptoms in diary	X	X
Capable of complying with dosing regiment	X	X
Exclusion criteria		
Asthma attack within the past 30 days	X	
Asthmatics on ICS >1000 µg beclomethasone/day or equivalent, or not stable on corticosteroid therapy	X	
Polypectomy within the previous 6 months	X	X
Unhealed nasal surgery or trauma	X	
>5 previous polypectomies	X	
Ongoing concurrent nasal infection	X	
Rhinitis medicamentosa	X	
Hereditary mucociliary dysfunction	X	
Nasal structural abnormalities	X	
Idiosyncratic reaction to corticosteroids	X	X
Active/latent pulmonary tuberculosis	X	
Significant medical condition that could interfere with evaluations, e.g. cystic fibrosis	X	X
Immunocompromised	X	
Pregnant or lactating woman, or not using an adequate contraceptive	X	X
Study personnel or persons related to study personnel	X	X
Enrolled more than once	X	X
Unfit for general anaesthesia		X

Table 7. Baseline characteristics of treatment groups in Papers II (n=162), IV and V (n= 68), obtained at Visit 1 in both studies, except for polyp score, rhinorrhea, sense of smell, olfactory threshold test, shortness of breath, cough and FEV_1 % of predicted, which were obtained at Visit 2 in paper IV and V. Data are described as mean (range) or n (%).

	Placebo (II)	**MFNS (II)**	**Placebo +FPND (IV, V)**	**FPND(IV, V)**
Age, years	51 (19-76)	46* (17-80*)	52 (24-78)	51 (19-73)
Males	56 (68%)	51 (64%)	28 (67%)	21 (53%)
Smokers	8 (10%)	8 (10%)	3 (7%)	3 (7%)
SPT positive	52 (63%)	46 (57%)	18 (43%)	15 (42%)
> 2 polyp surgeries	10 (12%)	9 (11%)	6 (15%)	8 (20%)
Polyp score	L: 2.5, R: 2.4	L: 2.3, R:2.4		
(0-6, paper II)	SUM: 4.9 (2-6)	SUM: 4.6 (2-6)		
(0-3, paper IV/V)			2.2 (1-3)	2.3 (1-3)
Nasal congestion (0-3)	2.3 (0-3)	2.1 (1--3)	1.8 (0-3)	1.9 (0-3)
Rhinorrhoea (0-3)	1.3 (0-3)	1.3 (0-3)	1.0 (0-3)	1.1 (0-3)
Sense of smell (0-3)	2.3 (0-3)	2.3 (0-3)	2.3 (0-3)	2.2 (0-3)
Olfactory threshold test				
(0-13)	1.9 (0-9)	2.3 (0-12)	2.0 (0-7)	2.4 (0-7)
ICS, budesonide or eq.				
µg/day	ND	ND	661 (100-1600)	598 (0-1600)
Shortness of breath (0-3)	ND	ND	0.8 (0-3)	0.6 (0-3)
Cough (0-3)	ND	ND	0.6 (0-3)	0.6 (0-3)
FEV_1 % of predicted	ND	ND	82 (44-112)	86 (40-120)
Asthma, by history	29 (34%)	32 (40%)	38 (100%)	30 (100%)
ASA/NSAID intolerance				
by history	17 (20%)	11 (14%)	ND	ND

* One subject had her 18th birthday 8 days after screening. This subject was included in the study.
ICS, Inhaled corticosteroids; SPT, Skin prick test; ND, No data; L, Left nasal cavity;
R, Right nasal cavity; SUM, Summary of left and right nasal cavities.

3.2. METHODS

3.2.1 Study design

3.2.1.1 Paper I

Self-judged health and environmental exposures were investigated in a questionnaire survey. The survey was distributed in order to estimate the occurrence of environmental exposures and the prevalence of possibly environmentally related diseases and disturbances in general. To be able to make comparisons between different areas of the Stockholm County, mainly of traffic and noise related exposures, a simple random sample was taken in each of 17 geographical areas. Questionnaire management was performed by Statistics Sweden. The first date of distribution was February 26th; the last date for acceptance was June 19th, 1997.

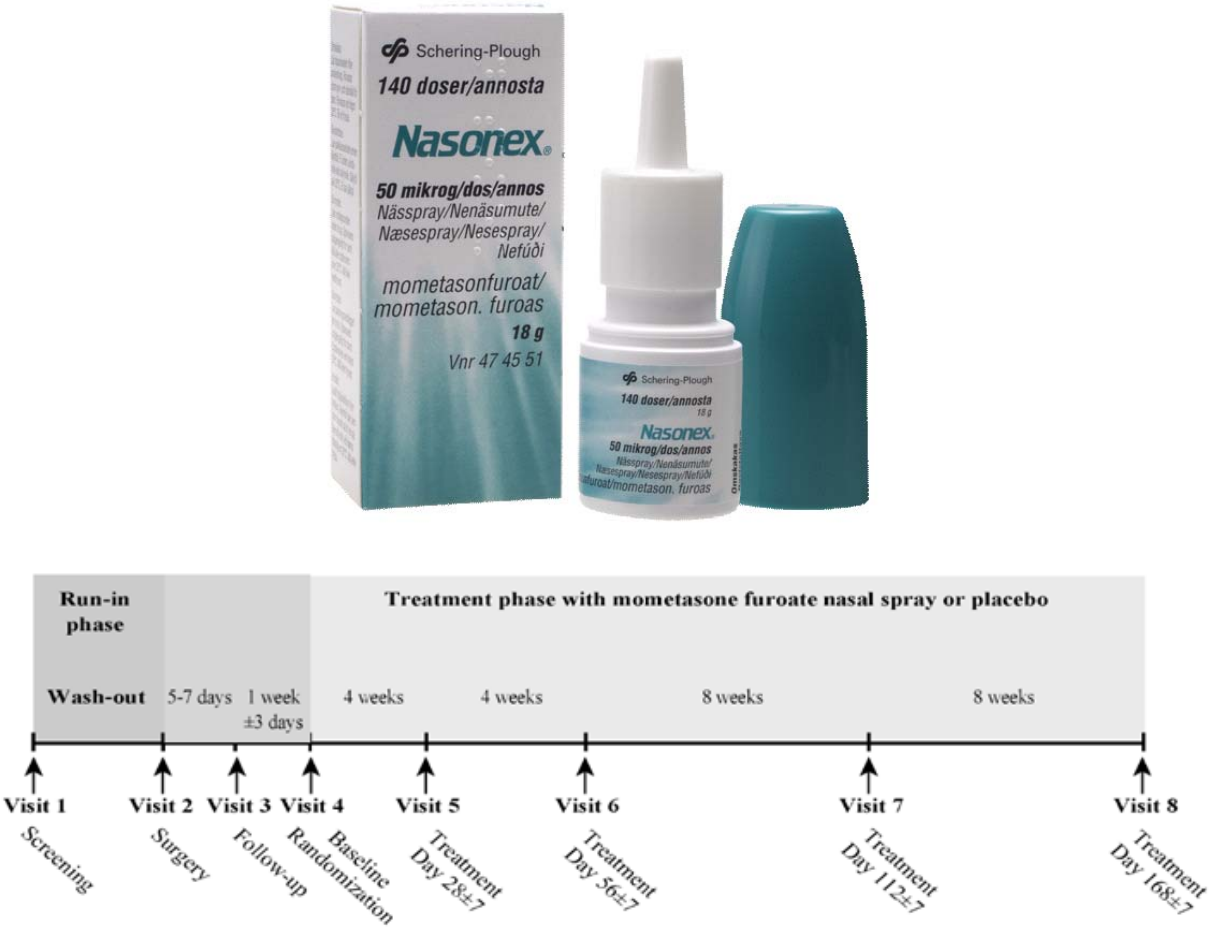
3.2.1.2 Paper II

This randomised, double-blind, placebo-controlled, multicenter study was conducted at 10 ENT clinics in Sweden. Following entry assessments at Visit 1, qualifying subjects entered a washout phase of varying duration depending on prestudy drug(s). At Visit 2, patients underwent FESS. Approximately 2 weeks after surgery (baseline, Visit 4), patients were reassessed and those who met entry criteria were assigned a study number and randomised in a 1:1 ratio to receive either MFNS 200 µg QD (2 sprays in each nostril once daily) or matching placebo nasal spray, according to a computer-generated code created by a statistician. Treatment continued for 24 weeks if no relapse occurred. Patients were also supplied with 20 pipettes containing oxymetazoline (0.5 mg/ml) as rescue medication in the event of worsening symptoms. Follow-up assessments were conducted at 28, 56, 112, and 168 days after randomisation to therapy, with a ± 7-day window for each visit. The study was conducted from September, 2003 to September, 2005 (Fig. 5).

The MFNS dose assessed was 200 µg QD, the approved and recommended dose for treatment of allergic rhinitis. The recommended dosages for beclomethasone and budesonide in the post surgical (simple polypectomy) treatment of nasal polyposis in Sweden are the same as for the treatment of seasonal allergic rhinitis. Hence it was assumed that the same was also applied to mometasone, which was the reason for the selection of dose. A placebo nasal spray matching the MFNS in colour and packaging was utilised. A placebo control was justified, and approved by the MPA and the Ethics Committee, since no evidence based comparator could be used in post-FESS treatment and the subjects could discontinue if necessary.

The prespecified primary endpoint was the time to relapse from baseline, with relapse defined as an increase in polyp score of ≥1, where baseline scores were ≤1. The score was recorded as the sum of scores from both nostrils from assessments by endoscopy of the nasal cavity (see 3.2.5.1). Secondary endpoints included PNIF, olfactory threshold test, QoL scores and diary symptom scores (nasal congestion, rhinorrhoea, loss of sense of smell). Safety evaluations included adverse event documentation, vital signs, and the results of physical examinations.

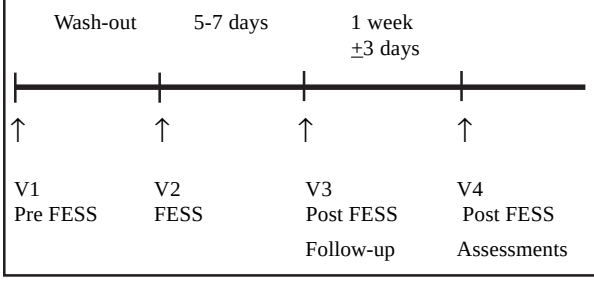
Figure 5. Paper II. Mometasone furoate nasal spray and (below) study design.



3.2.1.3 Paper III

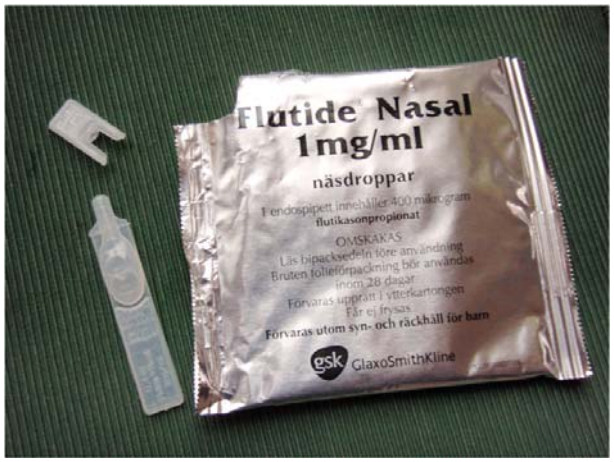
This was a post-hoc analysis of unpublished data from the study presented in Paper II. Following entry assessments at Visit 1, qualifying patients entered a washout phase of varying duration depending on pre-study drug(s). Inhaled (unless on a stable dose for treatment of asthma), oral, IV, rectal, intranasal or ocular corticosteroids were not allowed for at least 3 weeks pre-FESS (Visit 2). As in Swedish clinical practice, nasal saline was allowed from Visit 1 to Visit 4. Between Visit 2 and Visit 4, lavage with nasal saline was recommended twice daily using a device. Nasal endoscopy was performed at all study visits. For details on endoscopy and polyp scoring please see 3.2.5.1. The patients recorded their sense of smell in the diary once daily, and at each visit the patient and physician performed a joint evaluation of QoL. A butanol olfactory threshold test was performed prior to decongestant at Visit 1 and Visit 4 as described by the CCCRC [173]. At Visit 2 patients underwent FESS. Visit 3 was a post-FESS visit for nasal debridement. At Visit 4, approximately 2 weeks after surgery, the assessments were performed again in order to compare pre- and post-FESS data (Fig. 6).

Figure 6. Paper III. Study design. V=Visit.



3.2.1.4 Paper IV and V

This was a prospective 21 week single-centre study (Visits 1-6), conducted at the ENT and Pulmonary Departments of Karolinska University Hospital, Huddinge from January 2002 to September 2004, in order to evaluate possible bronchial and nasal benefits of treatment with FESS. A randomised, double-blind, placebo-controlled treatment phase of 14 weeks (Visits 1-5) was included because we also wanted to evaluate whether FPND had additional benefits regarding the same parameters (fig. 7).



At Visit 1 the patients were evaluated by a pulmonologist and an otorhinolaryngologist. Thereafter, they underwent four weeks' wash-out from nasal medical treatment until Visit 2, when those who met entry criteria were assigned a study number and randomised in a 1:1 ratio to receive either FPND 400 µg BID (1 pipette divided into each nostril twice daily) or matching placebo pipette, according to a computer-generated code created by a statistician. The FPND dose assessed was 400 µg BID, the approved and recommended higher dose for the treatment of nasal polyposis in Sweden. Patients were not supplied with any formal rescue medication, but the prohibited medication nasal decongestant was permitted to be used for one period of a maximum of 5 consecutive days. The patients, regular asthma medication, i.e. inhaled corticosteroids, was used throughout the entire study, and patients completed the daily symptom scores in the diary on nasal and bronchial parameters, as well as morning and evening PEFR. After four weeks of treatment and prior to surgery, the patients were examined at Visit 3. Thereafter all patients underwent FESS, and a few days later they underwent post-surgical follow-up (nasal debridement) at Visit 4. Then they continued with

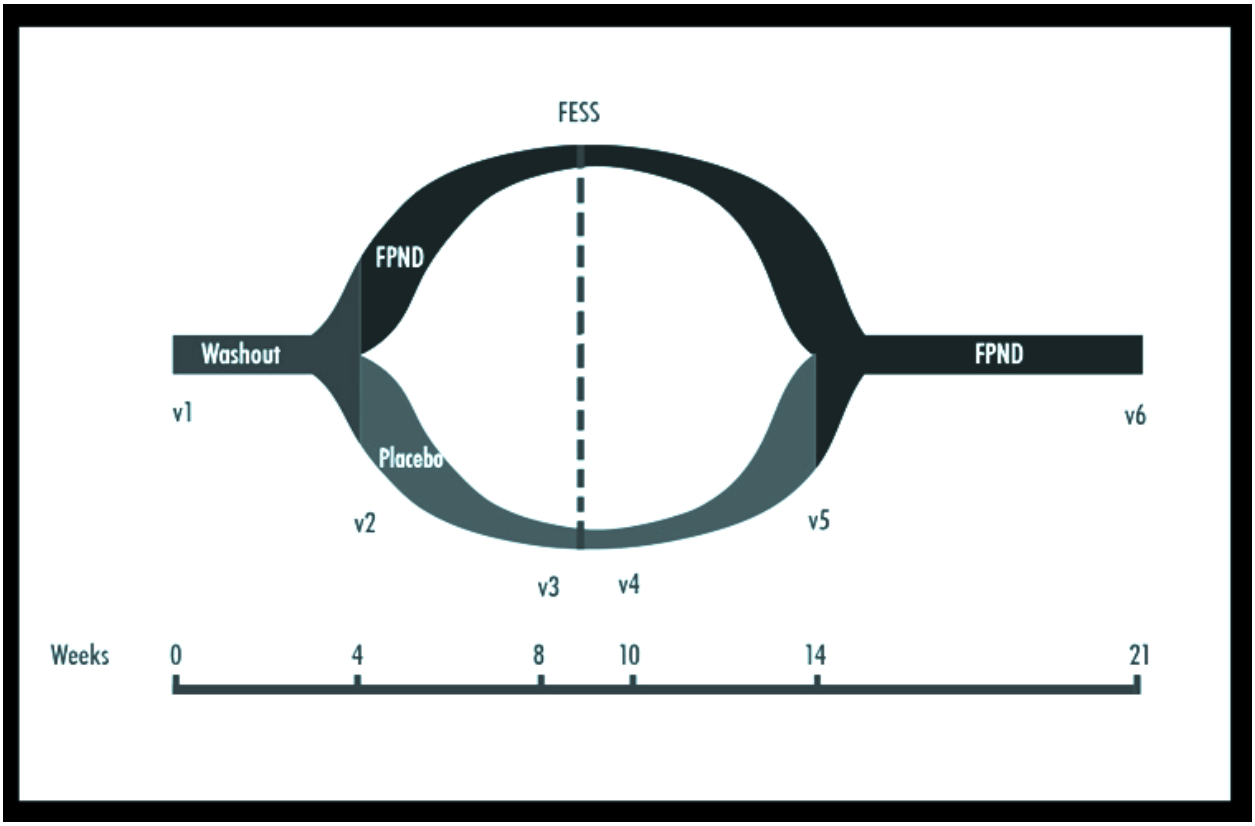


Figure 7. Papers IV and V. Fluticasone propionate nasal drops and (below) study design.

FPND or placebo approximately 4 weeks in the same manner as pre-surgery until Visit 5, when they were again examined with regard to nasal and bronchial parameters as at Visits 1, 2 and 3. After Visit 5 all patients were treated with FPND for another approximately 7 weeks until completion of the study at Visit 6. Visits 2 and 3 had a time window of ± 7 days, Visit 4 ± 3 days, Visit 5 ± 7 days and, finally Visit 6 ± 14 days.

The primary endpoint of this study was the change in the lower airway symptom scores after FESS, compared with before FESS. Secondary endpoints included PEFR, FEV_1, histamine PD_{20} FEV_1, as needed β2-agonists, nasal symptom scores, olfactory threshold test, PNIF, and endoscopy with polyp score. Safety evaluations included adverse event documentation, vital signs, and the results of physical examinations.

3.2.2. Questionnaire

In Paper I the questionnaire contained 87 questions on general and specific health, housing, symptoms, diet, recreation, family, profession, income, residence and education.
In response to the question; ”are you suffering from or have you had any of the following diseases?” the individual could check each of the following;

1. Asthma
2. Allergic eye symptoms
3. Hay fever or any other allergic rhinitis
4. Other nasal symptoms (recurrent sneezing, itching, nasal blockage etc.)
5. Chronic bronchitis or emphysema

Concerning smoking habits the individual could check ”yes” or ”no” in response to the question; ”do you smoke on a daily - or almost daily - basis?”. In response to the question; ”have you earlier been smoking on a daily basis for at least one year?”; the individual could check ”yes” or ”no”. Concerning sense of smell, the individual could check ”yes/often”, ”yes/from time to time” or ”no/never” in response to the question; ”are you suffering from reduced sense of smell or have you had a reduced sense of smell in the last three months”?
In the further analysis in Paper I of age, smoking habits and olfaction we compared self-reported allergic rhinoconjunctivitis symptoms only (”unique”) and self-reported non-allergic nasal symptoms only (”unique”) in order to try to exclude individuals with self-reported allergic rhinoconjunctivitis from the self-reported non-allergic nasal symptoms group. However, this approach excluded persons answering yes to the alternative ”Chronic bronchitis or emphysema” (5.), were there is a high representation of smoking prevalence. In new analyses, presented under 4.1.1, we excluded the ”unique” approach in order to avoid this exclusion of smokers.

Also in Paper I, the definition of allergic rhinoconjunctivitis symptoms as a positive response to 2. *or* 3., included persons only responding to 2. *or* 3 with yes, that is persons *without* obvious allergic eye symptoms or *only* allergic eye symptoms. In order to redefine the allergic rhinoconjunctivitis group to a more clinically realistic group we conducted new analyses, presented under 4.1.1, with the definition: Allergic rhinoconjunctivitis: positive response to 2. *and* 3. Subjects with allergic rhinitis, allergic rhinoconjunctivitis as well as non-allergic rhinitis, as defined by Tables 3 and 4, in new analysis of relation to age, smoking habits and sense of smell are also presented under 4.1.1.

The definitions of different types of rhinitis in this study are made by the authors as seen in Table 8 and 9 to be able to analyze the rhinitis symptom data from the extensive questionnaire survey.

Table 8. Modified from Table I in Paper I.

New definitions of self-reported rhinitis symptoms by the author, based on answers in the Stockholm County population survey in 1997
Allergic rhinitis symptoms
Positive response to 3.
Allergic rhinoconjunctivitis symptoms
Positive response to 2. *and* 3.
Non-allergic nasal symptoms
Positive response to 4.
Healthy
No positive response to 1.-5.
1. Asthma
2. Allergic eye symptoms
3. Hay fever or any other allergic rhinitis
4. Other nasal symptoms (recurrent sneezing, itching, nasal blockage etc.)
5. Chronic bronchitis or emphysema

Table 9. Modified from Table II in Paper I.

New definitions by the author
Allergic rhinitis Suffers from or has experienced hay fever or any other allergic rhinitis.
Allergic rhinoconjunctivitis Suffers from or has experienced hay fever or any other allergic rhinitis *and* suffers from, or has experienced, allergic eye symptoms.
Non-allergic rhinitis Suffers from, or has experienced, other nasal symptoms (recurrent sneezing, itching, nasal blockage etc).
Normal sense of smell Never had reduced olfactory sense during the last three months.
Reduced sense of smell, often Often had reduced olfactory sense (every week) during the last three months.
Reduced sense of smell, from time to time From time to time had reduced olfactory sense during the last three months.
Current smoker (cigarettes, cigars, pipe) Daily or practically daily smoking.
Former smoker Formerly daily smoker for at least one year.
Never smoker No daily or practically no daily smoking.
Healthy Never suffered from asthma, allergic eye symptoms, allergic rhinitis symptoms, other nasal symptoms, bronchitis or emphysema.

3.2.3 Short form 36 (SF-36)

This method was used in the study reported in Paper V. The health survey SF-36 [14] takes approximately 10 minutes to complete [181] and consists of 36 self-administered questions that cover eight health domains reflecting different aspects of physical and mental health: physical functioning (PF) , role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). Scale scores range from 0 to 100 and higher scores indicate better HRQoL. To summarise data in two main scores, the physical component summary (PCS) and the mental component summary (MCS), scores can be calculated from the eight dimensions of the questionnaire [182]. The Swedish version of SF-36 has been translated from the original English and validated, so that normative population data are available in Sweden [183, 184].

3.2.4 FESS

FESS (Fig. 8) was performed on patients as reported in Papers II, III, IV and V. All patients were under general anaesthesia. Intranasal local anaesthetic with decongestant was also used to minimise bleeding and improve visibility. The procedure was tailored to the extent of the disease as indicated by clinical and computed tomography-scan findings, but included the removal of polyps and usually uncinectomy with anterior ethmoidectomy. If the posterior cells and sphenoid were involved, surgery was continued posteriorly with posterior ethmoidectomy and sphenoidotomy. Care was taken to preserve intact mucosa. For subjects who had previously undergone FESS, the extent of surgery depended on clinical findings, and in some cases simple removal of polyps was sufficient.

3.2.5 Nasal assessments

3.2.5.1 Endoscopy with polyp score

A nasal endoscopy was performed by otorhinolaryngologists on specified visits, in Papers II, III, IV and V, and was scheduled after PNIF and the butanol threshold test, when performed (Fig. 9). The nasal cavity was decongested prior to endoscopy. In Papers II and III the polyps were scored for each nasal cavity on a 4-point scale; 0 = no polyps; 1 = polyps in the middle meatus, not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate; 3 = large polyps reaching to or below the inferior border of the inferior turbinate or polyps medial to the middle turbinate [67]. Polyp size and extension were drawn on a diagram representing the coronal view (Fig. 10). In Papers IV and V nasal polyp size was scored on the same 0-3 scale as in Papers II and III, however not for each nasal cavity [86].

Figure 8. Endoscopic sinus surgery at the Karolinska University Hospital.

Figure 9. Papers II, III, IV, V. Endoscopic examination of the nasal cavities.
A polyp score of 3 is seen in the left nasal cavity of this patient (with permission).

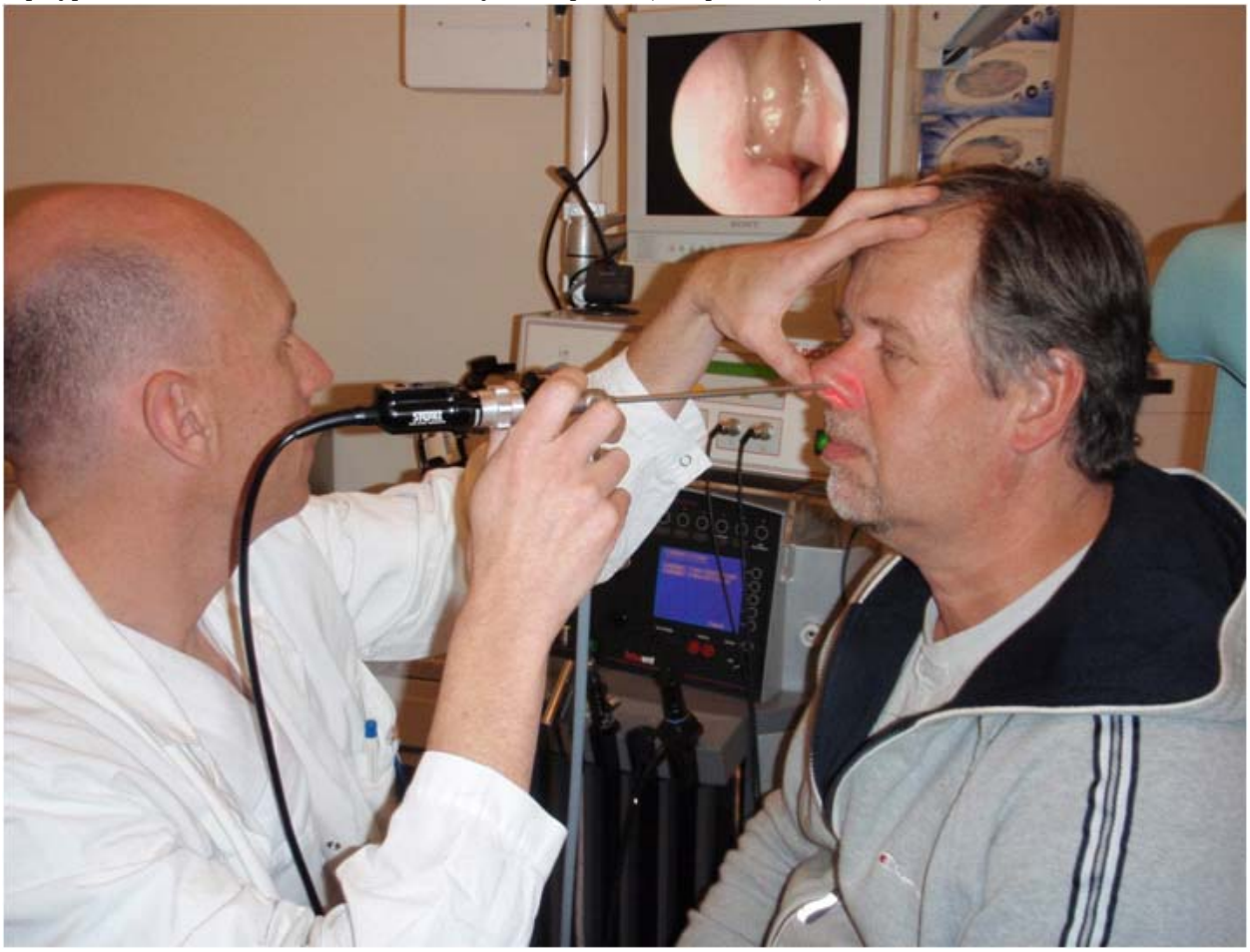
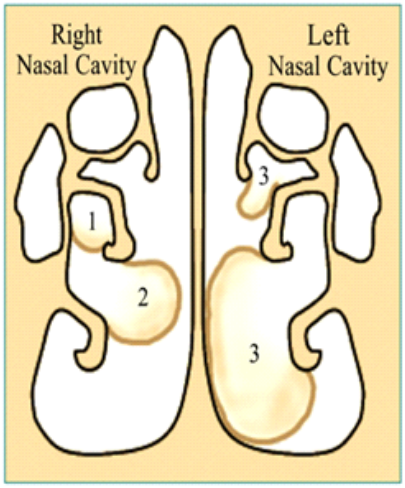


Figure 10. Papers II and III. Endoscopic findings of polyp size and extension in nasal cavities.



Score		
Right	Left	
0	0	No polyps
≤1	≤1	Polyps in the middle meatus, not reaching below the inferior border of the middle turbinate
≤2	≤2	Polyps reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate
≤3	≤3	Large polyps reaching to or below the lower border of the inferior turbinate or polyps medial to the middle turbinate
___	___	Sum of scores from both cavities

3.2.5.2 Nasal symptom scores

Severity of nasal stuffiness/congestion, rhinorrhoea and sense of smell were individually scored in Papers II, III, IV and V on a 4-point scale. Patients graded the symptoms of nasal congestion and rhinorrhoea, respectively; 0 = no symptoms, 1 = mild symptoms/tolerable, 2 = moderate symptoms/ still tolerable, and 3= severe symptoms/affects daily activity [67, 185]. The sense of smell was scored 0 = normal, 1 = mild reduction, 2 = moderate reduction, 3 = absent sense of smell [67] .

3.2.5.3 Peak nasal inspiratory flow (PNIF)

An In-check™ Portable Inspiratory Flow-meter (Clement Clark Int., Ltd., Essex, UK) was used in Papers II, IV/V in order to measure the nasal inspiratory airflow [67, 70] (Figure 11). First, the patient was instructed how to use the equipment. The patients exhaled deeply and then inhaled to the maximum through the nose with the mouth closed and the mask sealed tightly over the face. When the investigator judged the technique to be adequate, the best value from three consecutive inhalations was recorded.

3.2.5.4 Olfactory threshold test

The olfactory threshold test, as described by CCCRC [173, 177], uses aqueous dilutions of 1-butanol (n-butyl alcohol) as the odorant. Butanol is reported not to affect the trigeminal nerve at the concentrations used [186]. The sensitivity for the test is 86% and the specificity 94 % in patients with nasal polyposis [187]. The test is as valid as the Cross Cultural Smell Identification Test (CC-SIT)

Figure 11. Paper II, IV and V, PNIF, investigation situation

Figure 12. Papers II, III, IV and V. Olfactory threshold test, investigation situation.

to be administered to patients with nasal polyposis [187]. The highest concentration (4%) in deionised water is called dilution step 0; then the solution is diluted by successive factors of three to step 13. The test solutions were presented in squeezable polyethylene bottles. Prior to a decongestant, the olfactory threshold was determined in Papers II, III, IV and V using butanol in dilutions ranging from 0.000008% to 4%. The olfactory threshold was identified when the subject was able to distinguish the same butanol concentration from a blank control on five consecutive attempts (Fig. 12) [86, 173].

3.2.6 Lower airway assessments

3.2.6.1 Lower airway symptom scores

In Papers IV and V, from the screening Visit 1 to the end of the study (except between Visits 3 and 4) patients were asked to record symptom scores on a daily basis before going to bed. Patients were asked about their asthma symptoms: shortness of breath and cough. The symptoms were scored on a four point scale: 0 = no symptoms, 1 = mild symptoms/tolerable, 2 = moderate symptoms/still tolerable, and 3 = severe symptoms/affects daily activity [188]. We calculated the mean daily symptom scores from the diary cards in the last 7 days prior to Visit 2 (baseline recordings) and compared them to scores of the last 7 days prior to Visits 3, 5 and 6.

3.2.6.2 As-needed β2-agonists for asthma

In papers IV and V patients were instructed to use short-acting β2-agonists for as-needed asthma medication, and to register the number of inhalations in their diary scores on a daily basis before going to bed. The frequency of inhalations was scored as follows:

0 inhalations = 0 points
1-2 inhalations = 1.5 points
3-5 inhalations = 4 points
>5 inhalations = 5 points

We calculated the mean number of inhalations with short acting β2-agonists from the diary cards in the last 7 days prior to Visit 2 (baseline recordings) and compared to scores of the last 7 days prior to Visits 3, 5 and 6.

3.2.6.3 Lung function tests; PEFR and spirometry

In Papers IV and V, from screening during Visit 1 to the end of the study (except between Visits 3 and 4) patients had diary cards on a daily basis in order to register PEFR. The morning and evening PEFR were measured (Personal Best®, Health Scan, Cedar Grove, NJ, U S A) [189] (Fig. 13) and the results were filled in at that time. We calculated the mean daily PEFR, from the diary cards in the last 7 days prior to Visit 2 (baseline recordings) and compared to scores of the last 7 days prior to Visits 3, 5 and 6. Lung function was also measured as forced expiratory volume in one second (FEV_1) in Papers IV and V at Visits 1, 2, 3, and 5 on a spirometer (Spirolab®, MIR, Rome, Italy) according to the standards laid down by the American Thoracic Society [190].

Figure 13. Papers IV and V. PEFR, Investigation situation

3.2.6.4 Bronchial challenge by inhalation of histamine

A dosimeter-controlled jet nebulizer (Spira Elektro 2™, Respiratory Care Center Ltd, Hemeenlinna, Finland) was used in Paper IV for the bronchial histamine challenge, with inhalation of first saline and then histamine, as previously described [191, 192]. We used PD_{20} FEV_1 for evaluation of the histamine sensitivity. To determine baseline, the best of three FEV_1 measurements was registered. The test was terminated when FEV_1 had fallen at least 20 % from the post-diluents' baseline, or the maximum cumulative dose of histamine had been reached (7,027 μg). After the challenge the patient was observed until FEV_1 had returned to within 90 % of baseline. The histamine PD_{20} FEV_1 values were calculated from the log-dose response curves by linear interpolation [192].

3.3 STATISTICAL ANALYSES

The tool for data handling and statistical analyses was SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) except for data handling and analyses in Paper I, where Stata 6.0 (StataCorp LP**,** College Station, Texas, USA) was used. All statistical analyses were performed at a two-sided significance level of 0.05.

3.3.1 Paper I

Prevalence figures were computed with 95% confidence intervals (CIs) using the stratified sampling procedure. Chi-square-tests were performed to test the independence of variables, and p-values are presented. A logistic regression model was fitted and predicted probabilities for self-reported rhinoconjunctivitis and self-reported non-allergic nasal symptoms as a function of age were calculated and presented graphically with 95% confidence bands in order to obtain the slope of the plot of age against prevalence. Pearson correlation coefficients were calculated for prevalence and age in 1-year classes.

3.3.2 Paper II

All subjects who had received ≥1 dose of the study drug were included in the safety population. The ITT population included all subjects who received ≥1 dose of the study medication and had baseline and post-baseline data. The PP population included all subjects who met inclusion/exclusion criteria, took the study medication as specified in the protocol, and did not take a prohibited concomitant medication during the study.

Kaplan-Meier curves were generated for the time to relapse and the 2 groups were compared using a log-rank test. Subjects who terminated the study prematurely and had a relapse recorded at the time of dropout or withdrawal were included in the analysis as relapse; subjects who prematurely ended the study without having a relapse were included in the analysis as censored observations. Binary variables were compared using the Mantel-Haenzel chi-square test, stratified by centre. Continuous and ordinal variables were compared using Wilcoxon rank-sum test.

At a sample size of 62 subjects per treatment arm, a 0.05 level two-sided log-rank test for equality of survival curves was estimated to have 80% power to detect the difference between a Group 1 proportion of 0.65 and a Group 2 proportion of 0.40 (a constant hazard ratio of 0.46). With an estimated fraction of 15% non-evaluable subjects, it was estimated that 146 subjects needed to be included in the trial.

3.3.3 Paper III

All subjects who underwent FESS and had pre-surgery and post-surgery data were included in the statistical analyses. The statistical analyses of changes within the study population were performed using the Wilcoxon signed-rank test. The power calculation for determination of sample size was not based on the variables described in this paper.

3.3.4 Paper IV

All subjects who had received ≥1 dose of the study drug were included in the safety population. The ITT population included all randomised subjects in the study population who were given at least one dose of the study treatment and had baseline and post-baseline data. For continuous variables and ordinal variables including symptom scores, changes were calculated and analysed within groups with Wilcoxon signed-rank tests. Inter-group comparisons were performed using Wilcoxon rank-sum tests. For study of correlations, Spearman rank-correlation coefficients were calculated. The power analysis was based upon a frequency of improvement in lower airway symptoms in the placebo group of 30% and in the FPND group of 60%, which implied that 78 patients should be studied to achieve a power of 80% so that the null hypothesis (p1 = p2) would be falsified at a 5% significance level.

3.3.5 Paper V

The reference was an exact sex- and age-matched reference population (n = 340), randomly selected from the Swedish SF-36 norm data base (n = 8,930). Five reference persons were selected for each patient (quota = 5:1). The quota was decided from

the smallest quota principle, i.e. the smallest number of reference persons corresponding to one patient [193]. According to the ITT principle, all randomised subjects in the study population who were given at least one dose of the study treatment and had baseline and post-baseline data were included in the statistical analyses. Student's t-test was used to compare the SF-36 scores with the Swedish reference population. Changes within groups were analysed using Wilcoxon signed-rank tests and Wilcoxon rank-sum tests were applied for comparisons of the two treatment groups. For each scale, Cronbach´s coefficient was calculated to estimate internal consistency. For study of correlations Spearman rank-correlation coefficients were calculated. The power calculation for determination of sample size was based on clinical symptoms and not on SF-36.

3.4 ETHICS

3.4.1 Paper I

The Ethics Committee at Karolinska Hospital reviewed the study design and judged that formal approval was not required for the study.

3.4.2 Papers II, III, IV and V

The final study protocols, including amendments and final versions of the subject information and consent forms, were reviewed and approved by the Ethics Committee at Karolinska Institutet and the MPA prior to enrolment of subjects. All subjects gave written informed consent to participate in the studies.

4 RESULTS WITH COMMENTS

4.1 PAPER I

4.1.1 Results including additional findings

The prevalence of self-reported non-allergic rhinitis was 19.3 % (95% CI 18.4-20.2) in new analyses. The prevalence of allergic rhinoconjunctivitis was 9.9 % (95% CI 9.3-10.6), and the prevalence of self-reported allergic rhinitis was 18.4 % (95% CI 17.6-19.3) in new analyses (Fig 14 and 15, Table 10). The prevalence of self-reported non-allergic nasal symptoms did not change with age in new analyses compared to a slight increase with age reported in Paper I (Fig. 16).

Figure 14. Prevalence of self-reported rhinitis symptoms (Allergic rhinitis, Allergic rhinoconjunctivitis, Non-allergic rhinitis) with 95% CIs. New analysis of data from a population survey of adults in Stockholm County in 1997 (n =10,670).

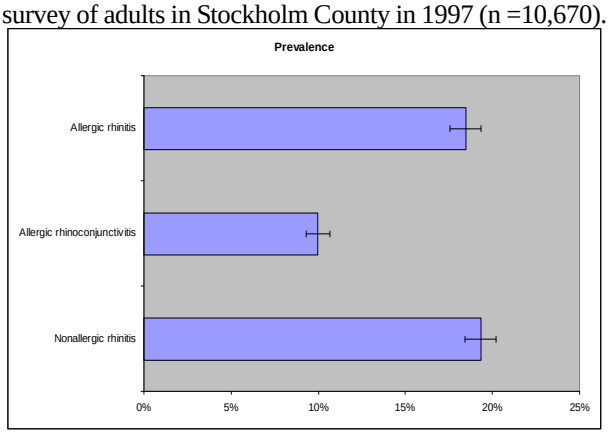


Figure 15. Non-proportional Venn diagram showing subsets of self-reported non-allergic, allergic and allergic rhinoconjunctivitis symptoms. New analysis of data from a population survey of adults in Stockholm County in 1997 (n =10,670).
AR, Allergic rhinitis, ARC, Allergic rhinoconjunctivitis, NAR, Non-allergic rhinitis.

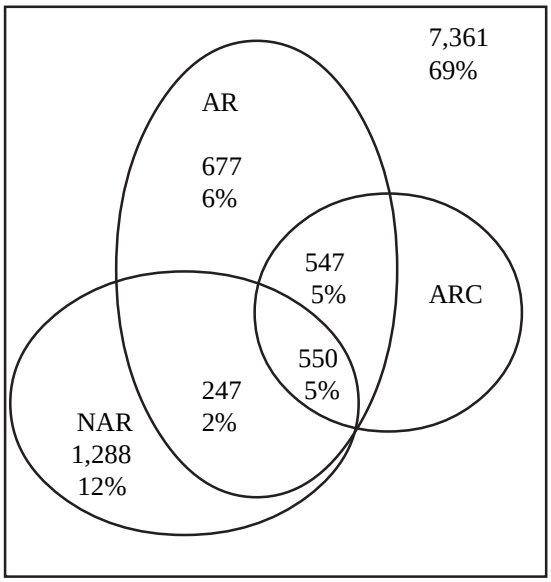
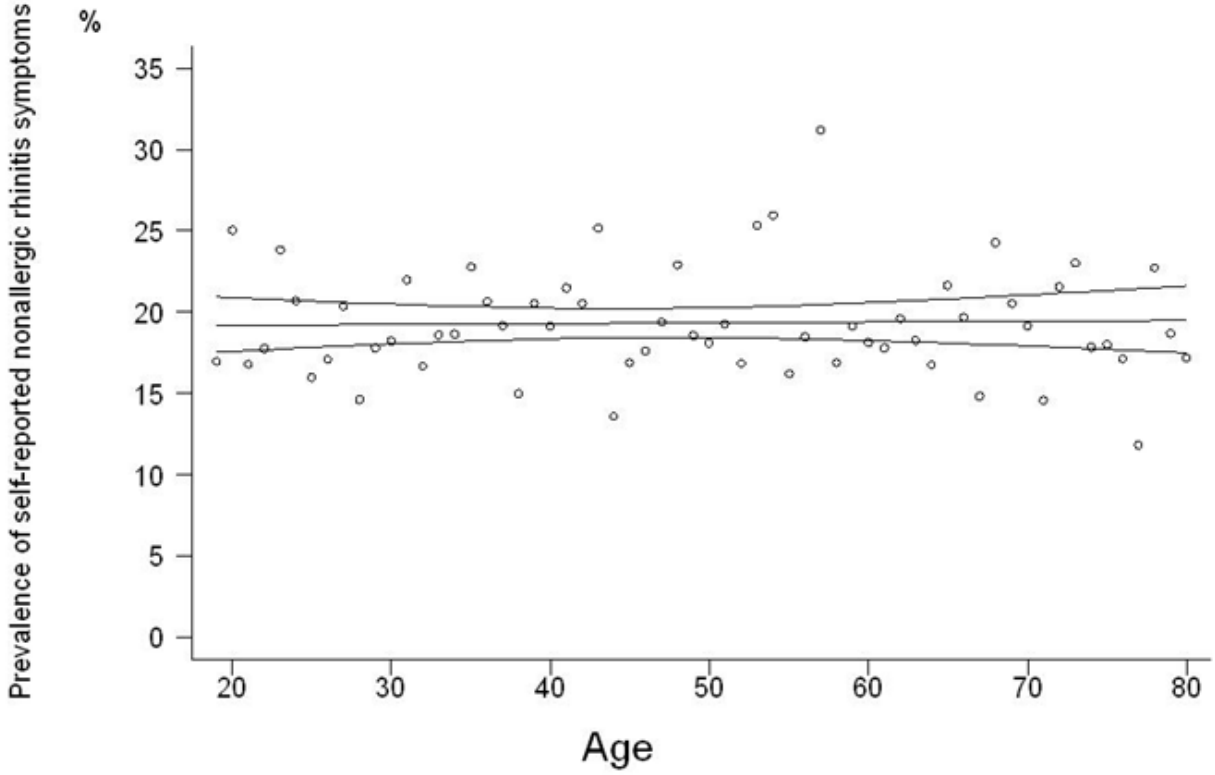


Table 10. Subsets of self-reported non-allergic, allergic and allergic rhinoconjunctivitis symptoms. New analysis of data from a population survey of adults in Stockholm County in 1997 (n =10,670, answered the 3 questions). AR, Allergic rhinitis, ARC, Allergic rhinoconjunctivitis, NAR, Non-allergic rhinitis. Please observe that AR is part of the definition of ARC.

AR	ARC	NAR	n	%	% *	Note
No	No	No	7,361	69.0	69.5	"Healthy"
No	No	Yes	1,288	12.1	12	
No	Yes	No	0	0	0	
No	Yes	Yes	0	0	0	
Yes	No	No	677	6.3	6.2	
Yes	No	Yes	247	2.3	2.3	
Yes	Yes	No	547	5.1	5.0	
Yes	Yes	Yes	550	5.2	5.0	
			10,670	*100*	*100*	*Total*

* Percentage from the survey estimator where n = total population. These percentages differ somewhat from the percentages based on the sample of 10,670 individuals.

Figure 16. Predicted probabilities and 95% confidence bands from a logistic regression model of age on self-reported non-allergic rhinitis symptoms. Dots show prevalence in one-year classes. New analysis of data from a population survey of adults in Stockholm County in1997 (n =10,670). Age in years. The Pearson correlation coefficient is 0.02 (p=0.85).



The differences in prevalence between self-reported allergic rhinoconjunctivitis and non-allergic rhinitis symptoms according to smoking habits both in Paper I and the new analyses were statistically significant. Prevalence of self-reported allergic rhinoconjunctivitis was highest among never smokers (11.3%, 95% CI 10.3-12.3), lowest among current smokers (7.7%, 95% CI 6.5-9.0) and intermediate among former smokers (9.8%, 95% CI 8.5-11.0). For non-allergic nasal symptoms the lowest prevalence (18.2%, 95% CI 17.0-19.5) was found among never smokers, the highest among former smokers (21.8 %, 95% CI 17.3-21.2) and intermediate among current smokers (19.2%, 95% CI 17.3-21.2) (Fig. 17).

In new analyses the prevalence of reduced sense of smell in the group of self-reported allergic rhinoconjunctivitis symptoms (19.6%, 95%CI 16.7-22.4, from time to time and 7.8%, 95%CI 5.7-9.9, often) was more than two times higher to that in the healthy group (8.7%, 95%CI 7.8-9.5 and 1.9%, 95%CI 1.5-2.3), respectively. However, in the group with self-reported non-allergic nasal symptoms, the prevalence of reduced olfactory sense was 3-6 times higher than that in the healthy group (25.6%, 95% CI 23.3-28.0, and 12.1%, 95% CI 10.2-14.0, respectively) (Fig.18). In Paper I we reported, in contrast, that the prevalence of reduced sense of smell in the group of self-reported allergic rhinoconjunctivitis was similar to that in the healthy group.

4.1.2 Comments

The only major difference in the new data compared to prevalence data reported in Paper I is the prevalence of allergic rhinoconjunctivitis, which dropped from 24.0% to 9.9%. This was expected as we in new analyses of the group of allergic rhinoconjunctivitis only included subjects with positive answers to both 2 (allergic eye symptoms) *and* 3 (hay fever or any other allergic rhinitis) instead of 2 or 3, as reported in Paper I. Three minor differences can be noted between data in Paper I and our new data. Adults with allergic rhinoconjunctivitis symptoms also have a reduced sense of smell compared to the ”healthy” population, Non-allergic rhinitis symptoms did not change with age, and prevalence by smoking habits were, as expected, lowered in the group with allergic rhinoconjunctivitis symptoms. The 95 per-cent confidence intervals were narrow and far from overlapping in fig. 17 and 18.

Figure 17. Prevalence of self-reported allergic rhinoconjunctivitis symptoms and non-allergic nasal symptoms, with 95% CIs, according to smoking habits. New analysis of data from a population survey of adults in Stockholm County in 1997 (n =10,670).

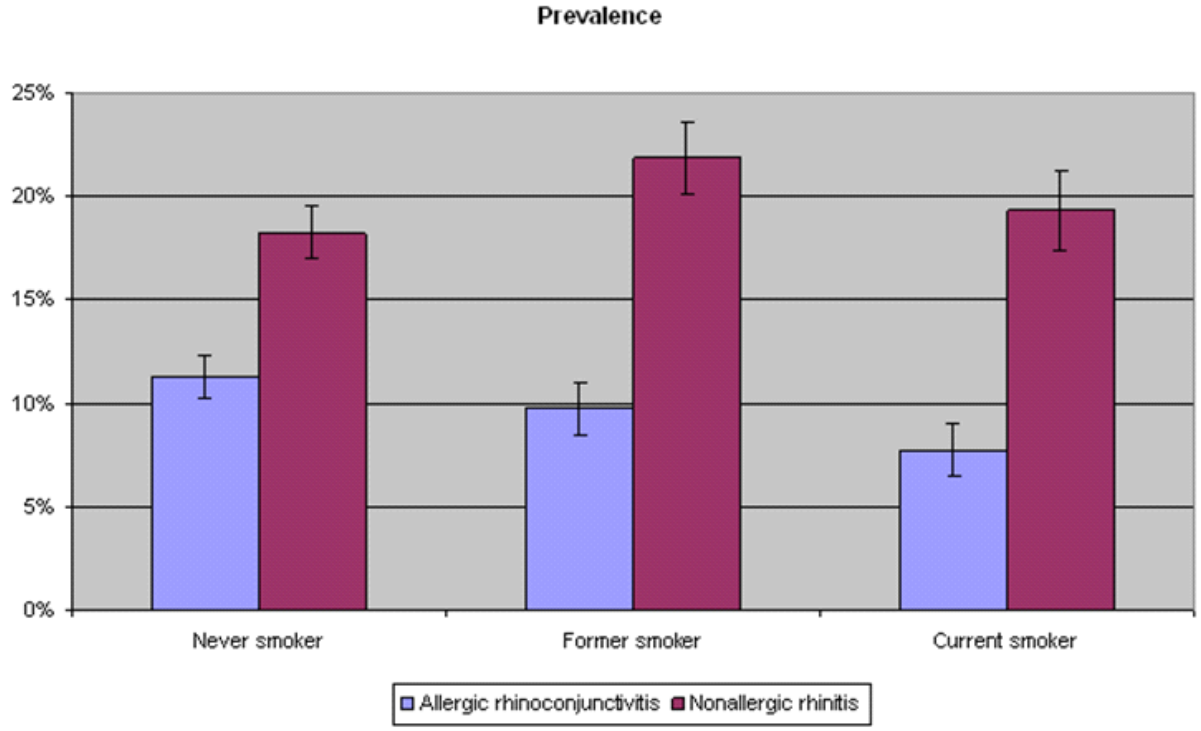
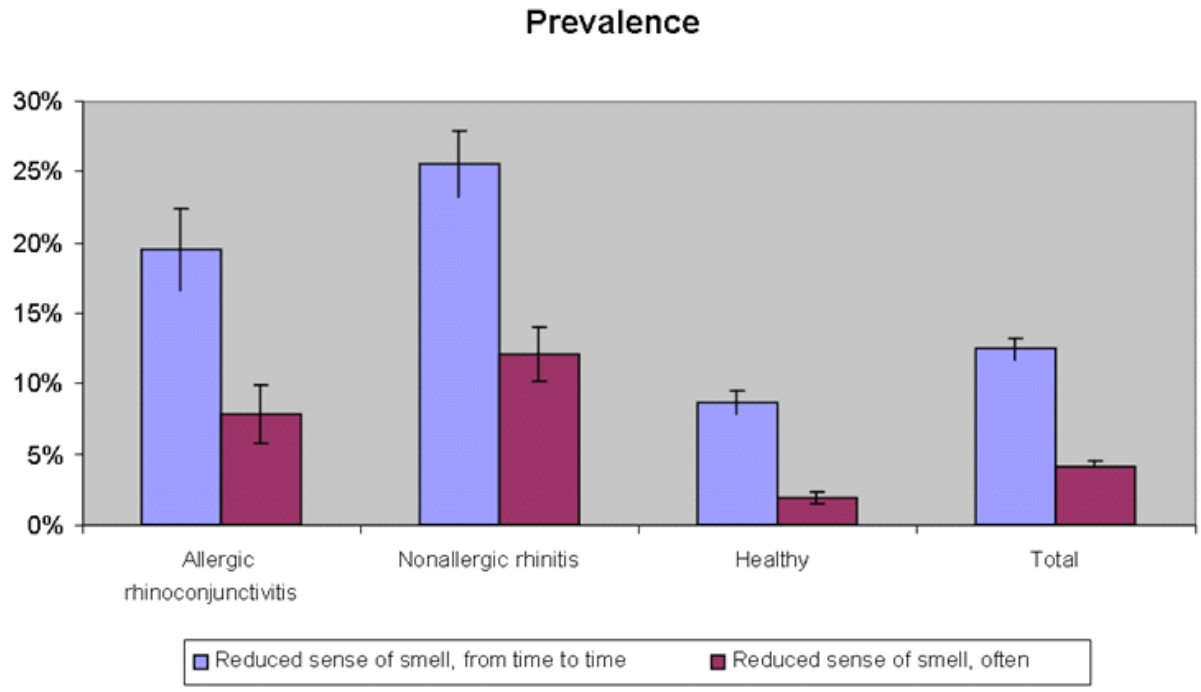


Figure 18. Prevalence of reduced sense of smell, with 95%CIs, among adults with self-reported allergic rhinoconjunctivitis symptoms, those with self-reported non-allergic nasal symptoms and healthy individuals (never suffered from asthma, allergic eye symptoms, allergic rhinitis, other nasal symptoms, bronchitis or emphysema). New analysis of data from a population survey of adults in Stockholm County in 1997 (n =10,670).



A strength of this study is that we studied a large random population sample, in contrast to some previous studies involving selected groups. The survey was, as mentioned, distributed in order to estimate the prevalence of possible environment-related diseases in general, which is why the risk of individuals over-reporting nasal complaints is probably lower than that in specific rhinitis questionnaires. The response rate was high, but was lower among young males born outside Sweden.

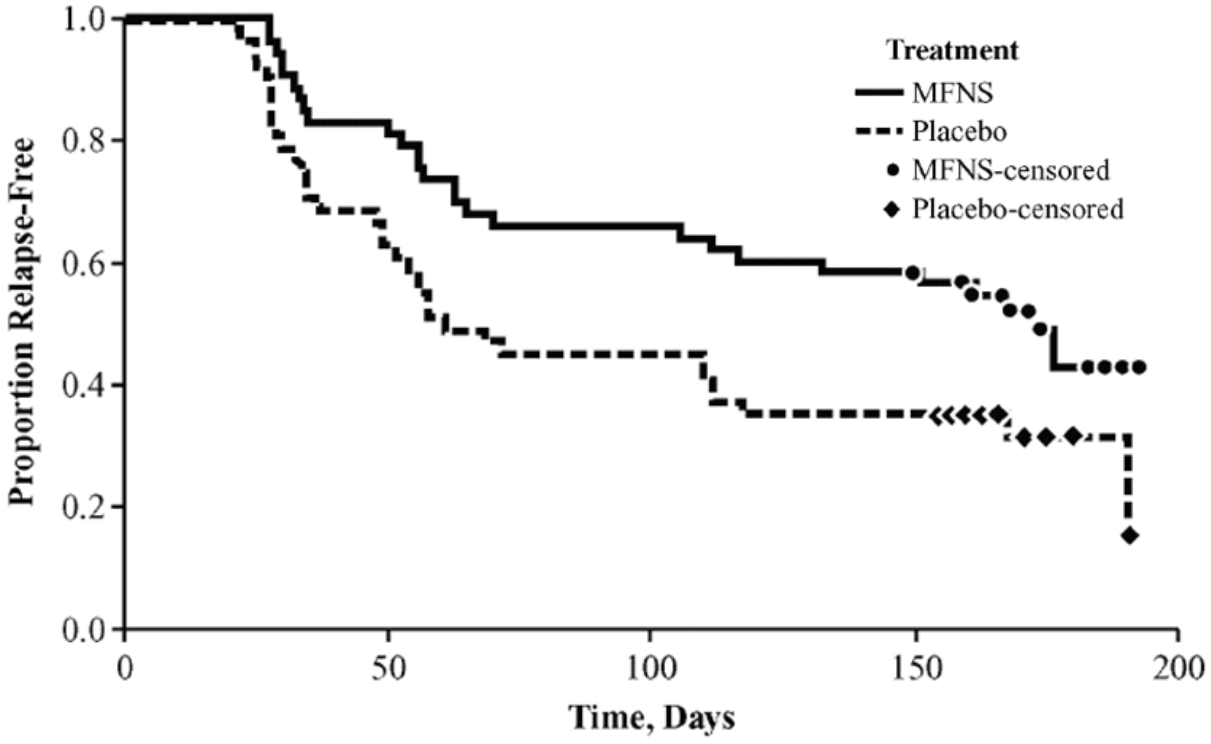
Our study has weaknesses apart from those that always exist in questionnaires based on self-reporting. We have no information that could be used to exclude, for instance, nasal polyposis from the group of individuals who selected ‘‘other nasal symptoms’’. The time aspect was only considered in questions on sense of smell, which makes prevalence estimates harder. Additionally, the questionnaire was distributed in Stockholm during the season of our most common airborne pollens, such as birch. Separation of seasonal allergic symptoms from non-allergic symptoms may thus be harder. Another weakness is that the questionnaire is not validated.

4.2 PAPER II

4.2.1 Results

The relapse-free period was significantly longer among subjects who received MFNS in both the ITT and PP data sets. For the PP analysis, the prespecified primary endpoint, median time to relapse was 173 days in the MFNS group and 61 days in the placebo group (Fig. 19, p = 0.007; hazard ratio and 95% confidence interval [CI], 0.72 [0.55-0.93]). Median time to relapse in the ITT population was >175 days in the MFNS group and 125 days in the placebo group (p = 0.049; hazard ratio and 95% CI, 0.79 [0.62-0.99]). With the exception of rhinorrhoea (as measured by both physician and subject), there were no differences between the 2 groups for all other secondary outcomes (PNIF, olfactory threshold test, QoL scores etc).

Figure 19. Paper II, Post-FESS use of MFNS 200µg QD gave a twofold longer time to relapse of polyps in patients with nasal polyposis. Kaplan-Meier plots of time to relapse. In the PP data set, median time to relapse was 173 days in the MFNS group and 61 days in the placebo group (log-rank statistic = 7.18; p = 0.007).



4.2.2 Comments

In the present study of postsurgical subjects who underwent FESS, MFNS 200 µg QD resulted in a significantly longer relapse-free period compared with placebo. With the exception of rhinorrhoea, there were no differences between the groups for secondary outcomes. The lack of impact on most secondary outcome measures is unsurprising as it is most likely related to the effect of FESS, i.e. the impact of FESS on many signs and symptoms of nasal polyposis gave little room for additional improvement and thus may have obscured differences between MFNS and placebo on these measures.

The inclusion and exclusion criteria were carefully chosen in order to select a representative target population, and to evaluate the results of the study without confounding issues. Subjects with unilateral polyps were excluded due to the possibility of a higher risk of malignant tumours [194]. The age of subjects enrolled in the study represents the relevant population. A review of the literature shows that nasal polyposis is very rare in children, with a prevalence of about 0.1% [33]. The nature, histology, and pathology of nasal polyps that occur most frequently in children (nasal polyps and antrochoanal polyps) are different from bilateral nasal polyps in adults [38, 52]. Since more than 20% of patients with nasal polyps have concurrent asthma [33, 152, 195, 196] subjects with asthma were not excluded if they had not had an exacerbation of their asthma within ≤30 days of study entry. However, their concomitant inhaled corticosteroid dose must have been lower than 1000 µg beclomethasone per day or equivalent, and this dose must have been maintained consistently throughout the study to avoid a confounding effect from possible systemic absorption. Subjects with cystic fibrosis were excluded because the pathogenesis, nature and course of nasal polyps in these patients are different [33, 197] As a safety precaution, subjects with glaucoma or a history of subcapsular cataract were excluded from the study since corticosteroids have been associated with the development of glaucoma and/or cataracts, although no particular safety concerns have been directly attributed to the use of MFNS in clinical programs or in post-marketing safety surveillance. To avoid confounding effects from other treatments, adequate washout periods of varying duration were required for subjects who were on additional medications at study entry, and certain medications were prohibited during the study.

There were more males than females in both treatment groups, which is similar in pattern to that reported for nasal polyps in the literature [30, 195]. The subjects' mean ages were 46 and 51 years for MFNS 200 mcg QD and placebo. Five subjects in the MFNS group and 9 subjects in the placebo group were older than 65 years. Approximately 50% of the subjects had had no prior polyp surgery. Overall, the two treatment groups were well matched with regard to baseline and disease characteristics.

A total of 7 adverse events, including 3 in the MFNS group and 4 in the placebo group, led to discontinuation during the treatment period. One serious adverse event, nasal bleeding, was related to FESS.

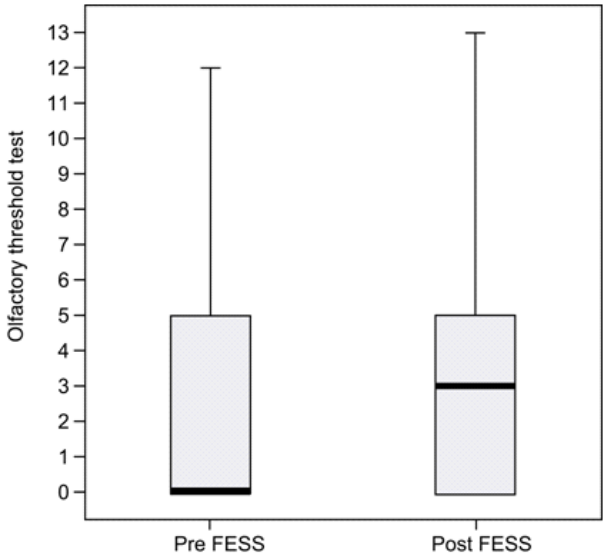
The deterioration of symptoms after FESS in patients with nasal polyposis is hard to capture within the study period of a maximum of six months. Hence, the "time to relapse" in polyp size was chosen as primary end point. For ethical reasons, to conduct a longer placebo-controlled study was not an option in Sweden.

4.3 PAPER III

4.3.1 Results

The median olfactory threshold increased from 0 pre-FESS to 3.0 ($p<0.001$; Figure 20), 2 weeks post-FESS. The results were similar when performing separate analyses for patients with (median 0.0 pre-FESS vs 0.0 post FESS; $p=0.003$) and without (2.0 vs 4.0; $p=0.003$) previous polyp surgery. Moreover, the same effect was found for both men (1.0 vs 3.0; $p<0.001$) and women (0.0 vs 3.0; $p=0.048$). The sense of smell decreased from 3.0 pre-FESS to 1.7 ($p<0.001$) post-FESS, i.e. an improvement was found.

Fig. 20. Olfactory Threshold test pre-FESS and post-FESS (N=158). Box-whisker plots. Data are presented as median, 25% and 75% percentiles, minimum and maximum values. The change from Visit 1 (Pre-FESS) to Visit 4 (Post-FESS) was statistically significant, p<0.001.



4.3.2 Comments

This study showed, for the first time in a large multi-centre trial, that FESS without concomitant medical treatment improves both sense of smell and olfactory thresholds in patients with nasal polyposis with or without asthma. This finding further indicates that FESS reduces anosmia and hyposmia in nasal polyposis. Earlier prospective clinical studies on the effects of FESS on sense of smell and olfactory thresholds in nasal polyposis have been confounded with the lack of control of concomitant medications or a study design that included co-treatment with intranasal and/or oral steroids [86, 87, 120, 135]. This has made it impossible to differentiate the effects of FESS from concomitant medical treatment.

This study was multi-centre, post-hoc in design, but included 160 patients, compared to the 68 in Paper IV. The patient population was somewhat different in Paper IV, as asthma was not an inclusion criterion in this study. Both median nasal polyp and congestion score and olfactory thresholds at baseline were nevertheless similar with this study, measured by a similar scoring system and an identical olfactory threshold assessment. Five weeks after FESS the median olfactory threshold had improved from 0 to 4 in Paper IV. In this study we note an effect of FESS on median olfactory threshold (from 0 to 3) already 2 weeks after FESS, even though at this time point the nasal cavity is not totally healed. The slightly better result for Paper IV study could be a result of observation time.

There was no concomitant medical treatment for at least 3 weeks before FESS and up until the assessments at 2 weeks post surgery. The only nasal treatment allowed was nasal lavage, which does not have an evidence-based effect on sense of smell or olfactory thresholds in nasal polyposis [28]. A general weakness with our study design is that it was a post-hoc analysis without a control group and that we only have data on olfaction without influence of concomitant medication two weeks after FESS. However, it will be a challenge, from an ethical standpoint, to follow nasal polyposis patients without medical treatment post FESS for longer periods than 2 weeks, as Paper II shows that MFNS prolongs time to relapse compared to placebo when started 2 weeks after FESS.

4.4 PAPER IV

4.4.1 Results

The symptoms scores of shortness of breath and cough were decreased after FESS in both FPND and placebo groups at Visits 5 (p=0.007), and the daily PEFR was increased in the placebo group at Visit 5 (p=0.010) (Fig. 21). All nasal parameters, including the daily symptoms scores of nasal congestion, rhinorrhoea, sense of smell as well as PNIF and olfactory threshold test improved in both groups after FESS surgery (p= 0.015 – 0.001). However, there were no statistically significant differences between the two treatment groups in the mentioned variables, nor were there any significant differences between or within each treatment group in FEV_1, airway responsiveness to histamine or as needed β2-agonist use, from Visit 2 to Visit 5. There were statistically significant correlations between the sense of smell score versus the olfactory threshold test at Visit 2 (R= -0.81, p<0.001), 3 (R= -0.85, p<0.001), 5 (R= -0.71, p<0.001) and 6 (R= -0.71, p<0.001).

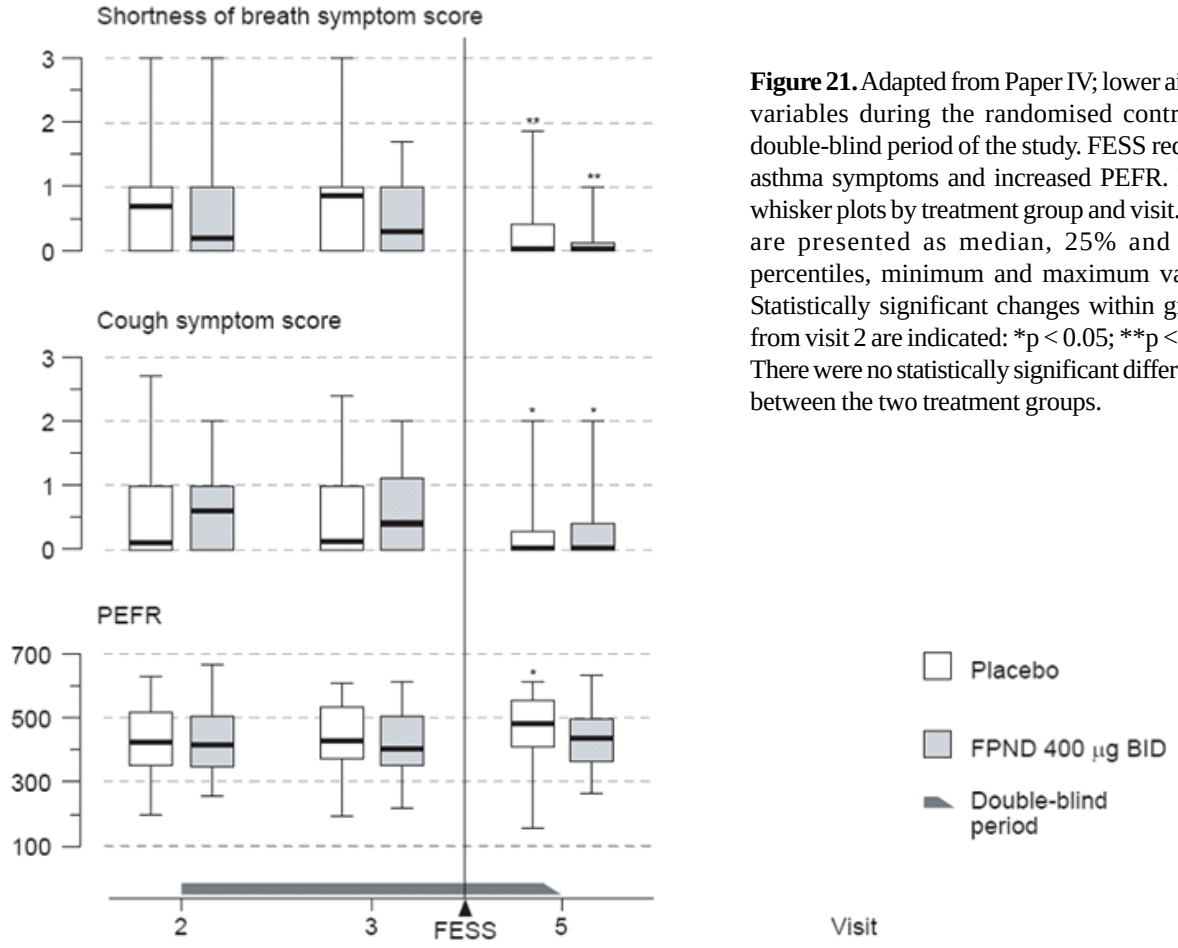


Figure 21. Adapted from Paper IV; lower airway variables during the randomised controlled double-blind period of the study. FESS reduced asthma symptoms and increased PEFR. Box–whisker plots by treatment group and visit. Data are presented as median, 25% and 75% percentiles, minimum and maximum values. Statistically significant changes within groups from visit 2 are indicated: *p < 0.05; **p < 0.01. There were no statistically significant differences between the two treatment groups.

4.4.2 Comments

In this randomised, controlled trial of 68 patients, without a non-surgical control, we found that FESS significantly improved asthma symptoms and PEFR as well as all nasal parameters, including sense of smell and butanol tests. This is the first published prospective study that shows the benefits of FESS on olfactory threshold tests in patients with nasal polyposis and asthma. We found no statistically significant additional benefit of intranasal treatment with FPND versus placebo in the nasal or lower airways variables.

In this study, we investigated patients with bronchial asthma and nasal polyposis, by evaluating the benefits of FESS surgery and intranasal steroid treatment on nasal and lower airway, clinical as well as subjective parameters. As well as for nasal congestion and asthma, hyposmia also reduces the quality of life in this patient group. Medical treatment with intranasal and oral steroids has been shown to have positive effects on the olfactory function, as evaluated by both subjective methods and threshold tests [67, 86]. Klimek et al. have reported benefits of surgery on the olfaction function, as measured by a modified CCCRC butanol test, after including 31 patients with nasal polyposis in a prospective study, which was less than half the number of patients included in Paper IV [198]. In this study, published 1997, they used Microscopic Endonasal Sinus Surgery (MES) without endoscopy, including a total sphenoethmoidectomy with an enlargement of the frontal recess - a more radical surgical method compared to modern FESS. It is unclear whether OCS was used, but ”medication that might influence olfaction” was prohibited. The authors found a significant improvement in the olfactory function, as measured by butanol tests 4, 8 and 12, but not 24 weeks post-surgery. The olfactory function of patients was probably better at baseline in that study, with a mean CCCRC butanol test score

of 4.19, in contrast to data from Paper IV where the mean value in the two groups was 2.0 and 2.4, respectively. Today FESS or ESS (endoscopic sinus surgery) is the gold standard among the surgery techniques in nasal polyposis, and to our knowledge no major studies have evaluated the benefits of FESS on olfaction, using threshold tests such as butanol. Therefore we also wanted to study the olfactory function in Paper IV. OCS is a potent treatment. Combined with intranasal steroids and surgery, OCS has a potential to influence most outcomes. Therefore we excluded patients with aggravations of disease that demanded treatment with OCS.

When designing this study, before the first EP^{3}OS guidelines were published in 2005 [55], our hypothesis was that FESS is an anti-inflammatory treatment and the effects in the upper airways might also result in the reduction of lower airways inflammation. Therefore, we decided to include the whole range of patients suffering from nasal polyposis entering the clinic, from severe to mild, with the diagnosis of bronchial asthma. Moreover, after confirming the asthma diagnosis, the pulmonologists did not alter the asthma treatment throughout the study, if the pulmonary function was judged to be stable enough for surgery. All patients but one were on inhalation steroids when entering the study, and the average FEV_1 % of predicted was 82 and 86, respectively, in the two groups at baseline. Despite the fact that the patients' asthma was well controlled with inhaled corticosteroids, we noted statistically significant improvements in asthma symptom scores and PEFR with no increase in the use of β2-agonists. However, in contrast to Batra and co-workers [164] we did not find any post-surgery improvements in the spirometry nor in the histamine challenge tests, although our patient group was larger. Our interpretation is that daily PEFR and symptom scores registered in the diary captures a longer period of time as an indicator of asthma severity than spirometry and histamine challenge tests in this study, performed only on two single occasions, approximately 5 and 12 weeks after surgery.

Of the five serious adverse events reported. one, nasal bleeding leading to hospitalisation, was judged to be related to FESS. Three subjects in the FPND group and four in the placebo (+ FPND) group were discontinued because of adverse events, and in five of these seven patients the reason for discontinuation was OCS treatment due to asthma exacerbation or onset of acute bacterial rhinosinusitis.

This study, the largest of its kind to our knowledge, provides important data suggesting FESS can be considered earlier in the treatment of the disease with concomitant asthma. In addition, the study provides new data with statistically significant improvements in both olfactory threshold tests as well as subjective parameters of olfactory function, including a statistically significant correlation between the two after endoscopic surgery.

4.5 PAPER V

4.5.1 Results

At baseline HRQoL was significantly decreased with regard to both PCS (45 vs 48, p=0.049) and MCS (43 vs 51, p<0.001), and six (RP, 66 vs 80, p=0.0048; RE, 69 vs 85, p<0.001; MH, 73 vs 81, p=0.0015; VT, 49 vs 69, p<0.001; GH, 56 vs 72, p<0.001; SF, 73 vs 87, p<0.001) out of eight domains compared with the Swedish reference population (Fig. 22).

FESS (placebo group) significantly improved five (PF, p=0.002; RE, p=0.021; MH, p=0.009; VT, p<0.001; GH, p=0.005) out of eight domains as well as PCS (44 to 48, p=0.027) and MCS (42 to 47, p=0.021) after approximately 5 weeks. Seven (PF, p<0.001; RP, p<0.001; RE, p=0.002; VT, p<0.001; GH, p=0.001, SF=0.02, BP, p=0.003) out of eight domains, as well as both PCS (p<0.001) and MCS (p=0.046) were significantly improved by FESS (placebo) at Visit 6. We found significant benefit of the addition of FPND 400µg BID versus placebo in three (RP, p=0.025; VT, p= 0.007 (Fig. 23); SF, p=0.002 (Fig. 23)) out of eight domains as well as in MCS (52 versus 47, p=0.013) but not in PCS (50 versus 48, p=0.081).

Fig. 22. Paper V. Baseline SF-36 scores from the study population and reference population. Six out of eight domains are significantly lower in the study sample. PCS and MCS are significantly lower in the study sample. Data are presented as mean values. Statistically significant differences are indicated; *) p<0.05, **) p<0.01, and ***) p<0.001.

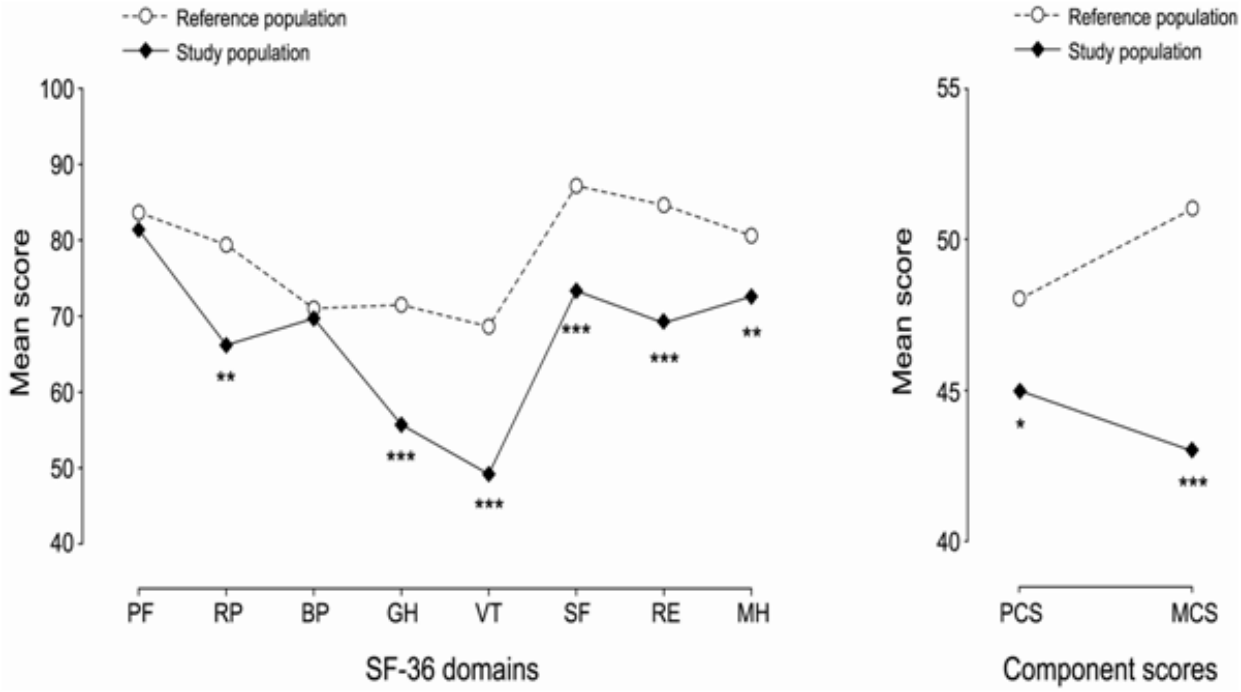
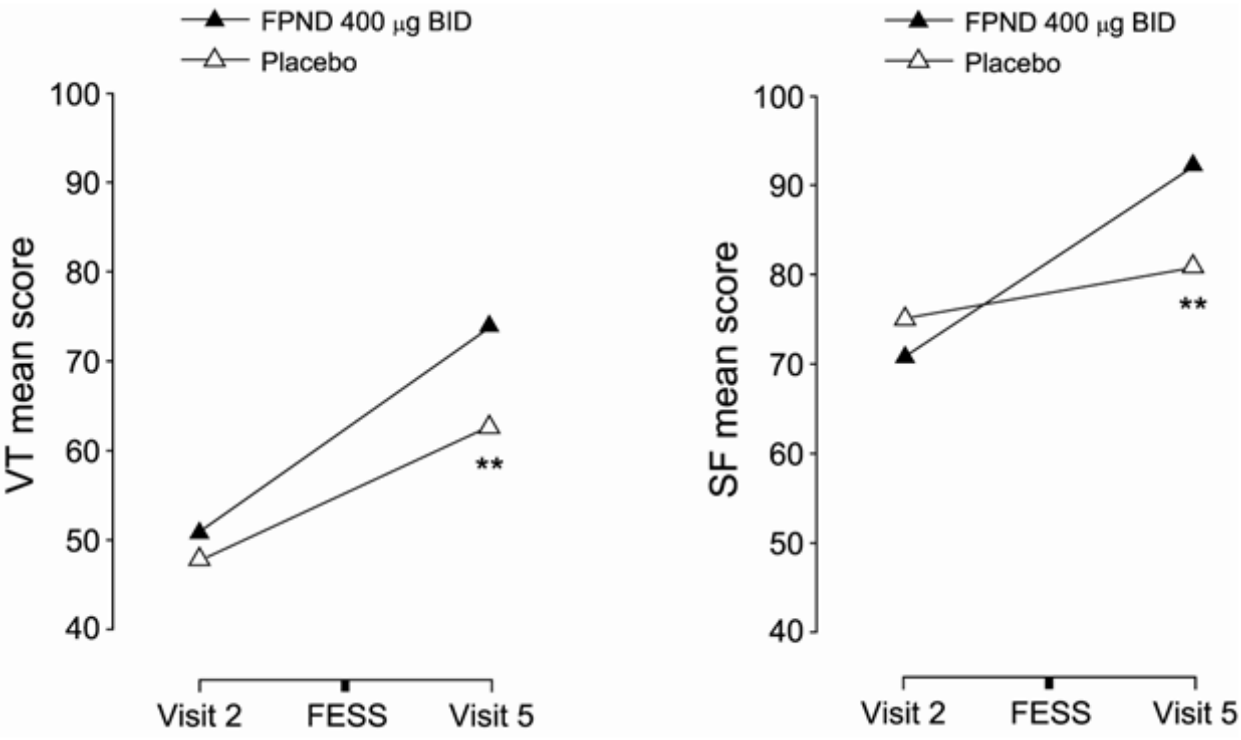


Fig. 23. Paper V, Effects of FESS and FPND or placebo on VT and SF domains. FPND 400µg b.i.d. gave significant additional benefit versus placebo on three (RP, VT, SF) out of eight domains. Displayed are VT and SF. Data are presented as mean values. Statistically significant differences between the groups at Visit 5 are indicated; **) p<0.01.



4.5.2 Comments

In this study we found that FESS in patients with nasal polyposis and concomitant asthma had a statistically significant and clinically relevant positive effect on HRQoL. The randomised, double-blind, placebo-controlled 14-week part of the study showed that FPND 400µg BID can be added to improve, and to reach population levels of, HRQoL 5 weeks after surgery. Impairment of HRQoL - before treatment - compared to the general population was found in all SF-36 domains except for PF and BP.

Despite the fact that the patients´ asthma was well controlled we noted statistically significant and clinically relevant improvements after FESS in five out of eight SF-36 domains, as well as in MCS and PCS, after FESS, without an increase in the use of β2-agonists. The results suggest that FESS has statistically significant positive effects on physical functioning, emotions, mental health, vitality (tiredness, energy level), and general health, according to both the specific and summarised domains of SF-36, already after 5 weeks.

We found significant benefit of the addition of FPND 400µg BID on perceiving physical limitations, vitality and social functioning as well as on mental health in general. The increase in HRQoL with FPND reached population levels in all domains as well as in both PCS and MCS approximately 5 weeks after FESS, which is much earlier that in other studies that have included patients with NP with or without asthma [95, 109, 115]. The additional effect of FPND was not seen when we studied clinical parameters, such as asthma and nasal symptoms in Paper IV.

5 GENERAL DISCUSSION

Non-allergic rhinitis is a very prevalent disease that is often trivialised and therefore inaccurately diagnosed, leading to inadequate management and unnecessary health care expenditures [3]. In Paper I our aim was to estimate the prevalence of self-reported non-allergic nasal symptoms in an adult Swedish population. We found that the prevalence of non-allergic nasal symptoms was 19% in the largest questionnaire study to date addressing self-reported non-allergic nasal symptoms, performed by us on 10,670 randomly selected adult individuals. The results are in line with prevalence data found by other Swedish questionnaire studies [7, 8, 199] even though our definition of non-allergic rhinitis symptoms is different from e.g. Jessen et al. [7]. Approximately 30% of our study population reported some kind of rhinitis symptoms. Hellgren et al. reported a prevalence of 40% with non-infectious rhinitis, including both allergic and non-allergic rhinitis, which rose to 47% when the ”runny nose” was included in their question [200]. Our question did not either have a ”runny nose”- part nor did it exclude the common cold. Still we only reached a prevalence of 30% rhinitis. The difference probably lies in the wording of the question.

We also wanted to explore relations of non-allergic nasal symptoms to age and sense of smell. Our main findings were that reduced sense of smell is a three to six times more common complaint among subjects with self-reported non-allergic rhinitis symptoms than observed for individuals without nasal symptoms and that the non-allergic symptoms in adults seem to occur independent of age. In a new post-hoc analysis of our results (see 4.1.1) the group that reported allergic rhinoconjunctivitis symptoms had a twofold greater prevalence of self-reported reduced sense of smell than the ”normal” individuals. Mann and co-workers, utilizing multiple test odorants, compared olfactory status in both allergic and non-allergic rhinitis patients, to normal healthy controls and confirmed that non-allergic subjects had a greater olfactory loss compared to controls and allergic rhinitis subjects [201]. Simola and Malmberg, utilizing a commercially available odour test kit, also found that subjects with non-allergic

rhinitis had a diminished sense of olfaction compared to allergic rhinitis subjects independent of gender [202]. Threshold studies have reported that olfaction diminishes with age, with significant reductions occurring after age 50 [202, 203]. These findings may be age dependent rather than a manifestation of non-allergic rhinitis itself. But when we, post-hoc, analyzed subjective sense of smell in our non-allergic symptom population, by age intervals of 9 years, we did *not* observe an increase in prevalence of loss of smell with increasing age.

The diagnosis of non-allergic rhinitis appears to be more frequently made in older individuals compared to allergic rhinitis. In a chart review of a large patient population in an allergy clinic 95% of patients with allergic rhinitis received the diagnosis during the first decade of life, whereas 60% of patients with non-allergic rhinitis were given the diagnosis in their fifth decade of life [204]. Our post-hoc data of adults 19-80 years do not demonstrate a variation in non-allergic rhinitis symptoms with age and show a decrease in allergic rhinoconjunctivitis symptoms over age. This is in contrast to the Jessen and Janzon questionnaire study from the 1980´s of 1,469 randomly selected individuals age 16-82. They found the prevalence of non-allergic rhinitis symptoms being U-shaped, with the lowest prevalence at middle age [7]. In another Swedish study Lindberg and Malm, in a computerised questionnaire to patients at an allergologist's office, found median ages for allergic rhinitis and vasomotor rhinitis to be 26 and 32, respectively [205]. However, there was overlap in triggers for the two populations indicating that many of these patients had "mixed rhinitis". Nonetheless, it appears that most of these questionnaire studies confirm that non-allergic rhinitis begins later in life than allergic rhinitis.

A few epidemiological studies designed to distinguish between subtypes of rhinitis found differences in non-allergic rhinitis prevalence in females versus males, with a female: male ratio ranging from 1.4:1 to 2.8:1 [6, 206]. Neither we, Jones et al. nor Lindberg and Malm found any gender differences in the populations studied [205, 207].

To date, there are no validated questionnaires specifically designed for non-allergic rhinitis [3]. Brandt and Bernstein found certain characteristics in rhinitis patients in an allergologist's office that could be part of a consensus definition of non-allergic rhinitis. These include absence of positive skin prick or specific IgE tests, late age of symptom onset, symptoms during the spring (in the US) or around furry animals and aggravation of symptoms around irritants like perfumes or fragrances [208]. Lager studies using validated questionnaires that include characteristics predictive of non-allergic rhinitis should be conducted in primary care to determine whether such an instrument could improve diagnosis and treatment.

A limited number of cross-sectional epidemiological studies have sought to establish the concordance of rhinitis and asthma in nonatopic patients. Leynaert et al. assessed a large group of randomly selected adults from the European Community Respiratory Health Survey database using a questionnaire, skin prick test, total as well as specific IgE testing, and bronchoprovocation challenge with methacoline. As might be expected, the frequency of asthma was higher in subjects with rhinitis (16%) versus those without (1%) [4]. Asthma was strongly associated with non-allergic rhinitis (OR =11.6). In a later study Leynaert et al. again demonstrated that asthma and bronchial hyperreactivity were significantly more common in subjects with rhinitis than those without (OR=6.6 and 3.0, respectively) [209]. A Swedish nested case-control study of adult-onset asthma was performed in a random sample from the general population (n=15,813), aged 21 to 51 years. Adult-onset physician-diagnosed asthma was associated with occurrence of non-infectious rhinitis before asthma onset (OR=5.4), especially among smoking non-atopics (OR=9.1) [210].

Longitudinal studies are required to define whether rhinitis is a risk factor for developing asthma. Plaschke and co-workers examined a cohort of Swedish adults over a period of three years. Rhinitis strongly predicted the development of asthma in non-allergic patients (OR= 3.5). Guerra et al studied, as part of the

Tuscon Epidemiology Study of Obstructive Lung Diseases, 173 adult patients with newly diagnosed asthma compared to 2177 controls without asthma and found that rhinitis was a significant risk factor for asthma, even after adjustment for atopic status. In non-allergic patients rhinitis increased the risk of developing asthma approximately threefold [211].

One of the most common types of severe chronic non-allergic nasal inflammation is nasal polyposis, with population prevalence on the same level as diabetes [30, 212]. Nasal polyposis, or chronic rhinosinusitis with nasal polyps, is a quite "unknown" disease despite the level of prevalence, and has a substantial impact on HRQoL [95, 109] and activity in 85% of patients after 20 years.

In Paper II we wanted to study the efficacy of the intranasal corticosteroid MFNS in reducing relapse of nasal polyps in subjects with endoscopically verified nasal polyposis who underwent FESS. The median time to relapse with nasal polyps after FESS in the untreated placebo group of the PP population was just over 2 months. As we now know from our 6-month multi-centre randomised placebo-controlled study, we can double the time to relapse after FESS by treatment with the intranasal steroid MFNS at a low dose. This will make in virtually impossible in the future - from an ethical standpoint - to conduct a clinical study after FESS in nasal polyposis without an active treatment group with MFNS. Because patients with polyposis frequently need repeat surgeries due to regrowth of nasal polyps and worsening of symptoms, the ability of MFNS to extend time to relapse has direct positive implications for patients and physicians, as well as the potential to reduce overall costs related to the management of this condition.

No published data on direct or indirect costs are available distinguishing costs of nasal polyps from chronic rhinosinusitis. A Swedish study reported the expected reduction in cost from using intranasal budesonide compared with inpatient FESS to be 9,760 Swedish kronors (1998 values) [213]. Unpublished data exist from a retrospective cohort study documenting costs for patients with newly diagnosed nasal polyposis in the US. Patients who undergo surgery have significantly higher costs and a greater frequency of outpatient visits and surgery-related procedures in the year following the diagnosis than nonsurgery patients. [27]. More studies on the indirect and direct costs related to FESS, the pre- and post-operative management of nasal polyposis with or without asthma are needed in order to present to stakeholders in evaluating different treatment strategies for nasal polyposis.

Our Paper II also sheds light on the conflicting data of the efficacy of FPANS on relapse of polyps after FESS. The recent European guidelines on rhinosinusitis and nasal polyps, EP^{3}OS, in their next update may perhaps upgrade the grade of recommendation for post-FESS treatment in adults with chronic rhinosinusitis with nasal polyps from B to A in their Table 13-6, based on our new Ib evidence (*two* +, one -) [28]. Our data also supports earlier statements that these patients require follow-up for the rest of their lives due to high recurrence tendency and insidious symptoms [52].

In Paper IV we wanted to study the effects of FESS and the intranasal corticosteroid FPND on bronchial and nasal parameters in patients with nasal polyposis and asthma. The recommended treatment strategy for nasal polyposis is anti-inflammatory, with an Evidence A treatment recommendation for topical and oral corticosteroids, and surgical treatment is proposed to be reserved for patients who do not satisfactorily respond to medical treatment [28]. This is because the benefits of surgical treatment have not yet been sufficiently studied, and therefore Papers IV and V are intended to contribute in this aspect. We found it relevant to evaluate the surgical treatment (FESS) with or without concomitant treatment with intranasal corticosteroids by randomising to either FPND or placebo, including surgery in both groups. For some patients, four weeks of wash-out from nasal steroids before surgery (between Visits 1 and 2) caused heavy local symptoms forcing them to drop-out from the study. We did not include wash-out from asthma treatment (except for OCS) in the study design, because this would probably have further increased the drop-outs. Most importantly, it would have been unethical to wash-out from asthma treatment before anaesthesia, risking lower airway complications pre- and post-surgery.

Non-allergic rhinitis, and in particular nasal polyposis, is associated with an impaired sense of smell. In Paper III we wanted to reproduce a positive effect of ”stand-alone” FESS on sense of smell and olfactory thresholds in patients with nasal polyposis found in Paper IV. ”Stand-alone” FESS is our definition of FESS without concomitant medical treatment. In Papers III and IV we found that FESS improved olfactory function, as evaluated by both subjective scoring and by a butanol threshold test. This is interesting because no major study has been performed until now that demonstrates positive effects on olfactory threshold after FESS in nasal polyposis [198], and repeated sinus surgery is meant to be a risk factor for hyposmia [172].

Subjective scoring of olfaction is a commonly used assessment method, and in validating clinical settings, subjective scores have been found to significantly correlate to objective measurements of the olfactory function [90, 173]. In Paper IV we also found a significant correlation between subjective scoring and the threshold test. Other clinical studies have shown that MFNS in nasal polyposis had statistically significant and clinically relevant effects on the subjective sense of smell [67, 124]. OCS are associated with adverse reactions such as osteoporosis and negative systemic effects on the hypothalamic-pituitary adrenal axis [137]. Our results, with positive effects on both subjective sense of smell and olfactory thresholds, might to some extent contribute to considering FESS in patients with nasal polyposis, moderate nasal congestion and hyposmia, after treatment with intranasal corticosteroids, to improve sense of smell and to reduce need of OCS. At least our results should first inspire future planning of a randomised placebo-controlled study on effects of OCS on olfactory thresholds in patients with nasal polyposis.

We also investigated the health burden incurred by nasal polyposis with asthma compared with the Swedish general population in Paper V. We found that the lower airway symptoms ”shortness of breath”, ”cough” and the upper airway symptom ”nasal congestion”, after washout from upper airway treatment for four weeks, were correlated to generic QoL. This may indicate that these three specific symptoms of NP and asthma account for an important part of the effects on QoL in the patient population. We also found a correlation between the symptom sense of smell and the SF-36 domain SF, confirming the finding of others that olfactory disorders could alter quality of life [214].

In Paper V, we wanted to study the effects of FESS, as well as addition of FPND 400 µg BID, on HRQoL in patients with nasal polyposis and asthma. The additional effect of FPND was not seen when we studied clinical parameters, such as asthma and nasal symptoms in Paper IV. In patients with nasal polyposis, concomitant asthma and atopy had an additional negative impact on QoL scores on RP, BP, VT, and MH [114]. Alobid et al. [109] also demonstrated a significant improvement in patients with nasal polyposis on all SF-36 domains after both medical (OCS and intranasal steroids) and surgical (FESS followed by 12 months of intranasal steroid) treatment reaching the HRQoL level of the general population at 6 months later than in our sample. Despite the fact that the SF-36 is a validated and well-established questionnaire, the interpretation of results is somewhat controversial. A numerical difference on a HRQoL scale may be large enough to be significant, but will not necessarily have clinical relevance. A minimal important difference of 5 scale points has been suggested to be of clinical relevance [181]. In Paper V MCS and all 6 out of 8 domains with statistically significant differences between the study population vs the reference population at baseline also had a clinical relevant difference of $\geq$ 5 points. This also applies to 6 out of 8 domain-improvements in the FESS (placebo) group after surgery. Johansson et al. [215] found impairment in only three (PF, GH, VT) out of eight domains in a group of 44 patients with nasal polyposis (36% with asthma). The difference in that finding, as well as the lack of major impact on mental health domains compared to our data, might be explained by the fact that their patients were on treatment and that a minority of them were asthmatics.

Nasal polyposis, with reduced sense of smell, is a common airway disease which impairs HRQoL. Our data support the need for early and proper evaluation of sense of smell, HRQoL and lower airways to tailor treatment for patients with or without asthma.

6 CONCLUSIONS

Based on the studies in this thesis, the following conclusions can be drawn:

- Self-reported non-allergic rhinitis symptoms are highly prevalent independent of age, and reduced sense of smell is a common complaint among these subjects.
- FESS, but not addition of FPND 400µg BID, improved asthma symptoms as well as sense of smell, olfaction and PEFR in patients with nasal polyposis and asthma.
- HRQoL is impaired in patients with nasal polyposis and concomitant asthma.
- FESS seems to have benefits on HRQoL in patients with nasal polyposis and asthma.
- FPND 400µg BID can be added to FESS in nasal polyposis with asthma, to improve perception of physical limitations, vitality and social functioning as well as mental health in general, and also to reach population levels of HRQoL already at 5 weeks post-FESS.
- Post-FESS use of MFNS 200µg QD increases time to relapse of polyps in patients with nasal polyposis.
- There are indications of a positive effect of FESS on sense of smell and olfactory thresholds in nasal polyposis with moderate nasal congestion.
- FESS can be considered early in the course of treatment of nasal polyposis with concomitant asthma.
- FESS can be considered, after treatment with intranasal corticosteroids, in patients with nasal polyposis and moderate nasal congestion to improve sense of smell and to reduce the need for oral corticosteroids.
- Nasal polyposis, with reduced sense of smell, is a common airway disease which impairs HRQoL. Our data support the need for early and proper evaluation of sense of smell, HRQoL and lower airways to tailor treatment for patients with or without asthma.

7 FUTURE PERSPECTIVES

There is a need of;

- A study to examine and interview a random sample of the general population with self-reported non-allergic nasal symptoms in order to validate questions on non-allergic rhinitis.
- A randomised controlled study on effects of FESS without concomitant medical treatment versus sole medical treatment on upper and lower airways in patients with nasal polyposis and concomitant asthma.
- A randomised controlled study on effects of FESS without concomitant medical treatment versus sole medical treatment on upper airways in nasal polyposis patients without asthma.
- A randomised controlled study on effects of oral corticosteroids versus placebo on olfactory thresholds in patients with nasal polyposis.
- Studies on the indirect and direct costs related to FESS and the pre- and post-operative management of nasal polyposis with or without asthma.

8 POPULÄRVETENSKAPLIG SAMMANFATTNING

Icke-allergisk inflammation i näsan, icke-allergisk rinit, är en vanlig sjukdom som ofta banaliseras, trots att den är en riskfaktor för att utveckla astma. Det kan medföra en felaktig behandling av sjukdomen och onödiga kostnader för patient och samhälle. En av de vanligare typerna av kraftig icke-allergisk inflammation i näsan är näspolypos. Näspolypos är en kronisk övre luftvägsinflammation med polyper i näsan som ofta ger nästäppa, rinnsnuva, tryckkänsla i ansiktet, sömnstörningar och luktnedsättning. Cirka 3 procent av den svenska befolkningen har näspolyper. Det är vanligare hos män än kvinnor och sjukdomen debuterar oftast efter 40-årsåldern. Ungefär 1 av 4 patienter med näspolypos har astma.

Syftena med den här avhandlingen var följande; att uppskatta hur vanliga icke-allergiska näsbesvär är i befolkningen, att undersöka hur denna grupp människor ser ut vad gäller åldersfördelning och besvär med luktnedsättning, att undersöka näspolypos och astmans påverkan på patienternas livskvalitet, att undersöka effekterna på astman och livskvaliteten av titthålskirurgi i näsa-bihålor (s.k. FESS) tillsammans med behandling med kortisonnäsdroppar hos en grupp patienter med näspolypos och astma, att undersöka om kortisonnässpray kan förlänga tiden till återfall av näspolyper efter titthålskirurgi i näsa-bihålor och att undersöka hur titthålskirurgi i näsa-bihålor kan påverka luktsinnet hos patienter med näspolypos.

Resultaten är sammanställda i fem delarbeten, varav ett är publicerat och två snart skall publiceras i internationella vetenskapliga tidskrifter.

I delarbete I använde vi en frågeenkät till en slumpvis utvald grupp av 15 000 individer mellan 19 och 80 år. Vi fann att nästan 1 av 5 (19 %) personer uppger icke-allergiska näsbesvär och att det verkade vara lika vanligt hos vuxna oavsett ålder. Hos dem med icke-allergiska näsbesvär hade 1 av 4 (25 %) besvär med nedsatt luktsinne.

I delarbete IV och V genomförde vi en klinisk studie under totalt nästan 4 månader där 68 patienter 18 års ålder med näspolyper och astma slumpades till antingen titthålskirurgi i näsa-bihålor med tillägg av kortisonnäsdroppar eller titthålskirurgi i näsa-bihålor med tillägg av droppar utan aktiv substans. Vi undersökte både näsa och lungor samt frågade efter symptom och livskvalitet före och efter titthålskirurgin. Vi såg att astmasymptomen minskade och lungfunktionen (mätt med s.k. PEF) samt luktsinnet förbättrades 5 veckor efter kirurgi. Vi såg ingen skillnad på astma- och näsparametrar mellan de som fick tillägg av kortisonnäsdroppar och de som fick icke-aktiv substans. Däremot gav tillägg av kortisonnäsdroppar en ytterligare förbättring av livskvaliteten utöver titthålskirurgin i näsa-bihålor. Vi såg också att patienter med näspolypos och astma har en nedsatt livskvalitet jämfört med normalbefolkningen och att livskvaliteten förbättras till normalbefolkningens nivåer redan 5 veckor efter titthålskirurgin i näsa-bihålor med tillägg av kortisonnäsdroppar.

I delarbete II genomförde vi en annan klinisk studie där 162 patienter från 18 års ålder med näspolyper slumpades till antingen kortisonnässpray eller spray utan aktiv substans cirka 2 veckor efter titthålskirurgi i näsa-bihålor och följde dem till återfall av näspolyper eller till maximalt 6 månader efter kirurgin. Vi fann att kortisonnässpray kan förlänga tiden till återfall av näspolyper efter titthålskirurgi i näsa-bihålor, från drygt 4 månader (125 dagar) till minst 6 månader (>175 dagar).

I delarbete III följde vi 160 patienter från delarbete II som hade genomgått titthålskirurgi i näsa-bihålor och undersökte deras luktsinne med både frågor och lukttest före och cirka 2 veckor efter kirurgin. Vid lukttestet förbättrades gruppen, från avsaknad av luktsinne (0 i testet) till nedsatt luktsinne (3 i testet) redan 2 veckor efter titthålskirurgin i näsa-bihålor. Patienterna märkte också själva av en förbättring av luktsinnet (från 3 till 1,7 poäng på en skala från 3 till 0, där 0 är normalt luktsinne) efter kirurgin.

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