


Predictors of olfactory improvement after endoscopic sinus surgery in chronic rhinosinusitis with nasal polyps

A K Hernandez¹ , O Wendler², S Mayr², H Iro², T Hummel^{1,*} and S K Mueller^{2,*}

¹Smell and Taste Clinic, Department of Otorhinolaryngology, Technische Universität Dresden, Dresden, Germany and ²Department of Otorhinolaryngology, University of Erlangen–Nuremberg, Erlangen, Germany

Main Article

*These authors contributed equally as last authors to this work.

Dr A K Hernandez takes responsibility for the integrity of the content of the paper

Cite this article: Hernandez AK, Wendler O, Mayr S, Iro H, Hummel T, Mueller SK. Predictors of olfactory improvement after endoscopic sinus surgery in chronic rhinosinusitis with nasal polyps. *J Laryngol Otol* 2023;**137**:524–531. <https://doi.org/10.1017/S0022215122001633>

Accepted: 28 June 2022

First published online: 6 July 2022

Key words:

Nasal Polyps; Rhinitis; Sinusitis; Smell; Natural Orifice Endoscopic Surgery

Author for correspondence:

Dr A K Hernandez, Smell and Taste Clinic, Department of Otorhinolaryngology, Technische Universität Dresden, Fetscherstrasse 74, 01307 Dresden, Germany
E-mail: akmhernandezmd@gmail.com
Fax: +49 351 458 4326

Abstract

Objective. This study aimed to determine the predictors of olfactory improvement after endoscopic sinus surgery among patients with chronic rhinosinusitis with nasal polyps.

Method. This prospective cohort study included patients admitted to a university hospital between 2006 and 2012. Assessment using odour identification testing, a sinonasal symptom questionnaire, the Rhinosinusitis Disability Index and mucus biomarker levels was performed at various time points. Correlation of variables with identification score differences at six post-operative time points and at baseline was performed, followed by multiple linear regression to determine significant predictors at each of the six post-operative time points.

Results. Baseline absence of acute sinusitis, elevated serpin F2 and anterior rhinorrhoea predict early olfactory improvement, whereas baseline allergic rhinitis predicts late olfactory improvement. Baseline odour identification score was the strongest predictor across all time points.

Conclusion. Patients with chronic rhinosinusitis and nasal polyps with worse disease or baseline olfactory function may benefit more from endoscopic sinus surgery in terms of olfactory improvement.

Introduction

Olfactory loss is among the four main symptoms of chronic rhinosinusitis.¹ Aside from chronic rhinosinusitis, there can be a wide variety of differential diagnoses for smell loss, including viral infections, trauma, neurodegenerative disease and idiopathic causes among others.²

Mechanisms of olfactory dysfunction in chronic rhinosinusitis include an obstructive and inflammatory component, leading to interference with odorant binding to the olfactory receptor sites and possible epithelial remodelling.^{3–5} Olfactory deficits in patients with chronic rhinosinusitis appear to be caused by a summation of multiple factors, including diminished airflow, damage to the olfactory neuroepithelium and alteration to the local ionic microenvironment.⁶

In sinus disease refractory to medical management, endoscopic sinus surgery must be considered to improve patients' symptoms.¹ Through endoscopic sinus surgery, it is possible to restore mucociliary drainage pathways for the paranasal sinuses and to optimise sinonasal mucosal distribution of topical therapies.^{7–9} Chronic rhinosinusitis related olfactory loss has a good success rate for improvement if chronic rhinosinusitis is treated, although most will not return to normosmic levels.^{1,10}

Most studies that explore predictors of olfactory dysfunction are among patients with chronic rhinosinusitis. Some factors that have been cited include: nasal polyps,^{4,7,11–13} age,^{5,7,11,12} smoking,^{11,12} asthma,^{5,7,11} diabetes,⁷ aspirin intolerance,^{4,5,12} duration of symptoms,⁵ prior surgical procedures,^{5,12,13} status of the olfactory cleft, posterior ethmoid and frontal sinus,¹⁴ corticosteroid use,¹² eosinophilic chronic rhinosinusitis,¹⁵ and inflammatory disease severity (as measured by computed tomography (CT) scan or nasal endoscopy scores).¹² There have been some studies on post-operative olfactory improvement predictors, such as eosinophilic chronic rhinosinusitis,¹⁶ pre-operative presence and size of nasal polyps,^{4,5,17} pre-operative Lund–Mackay score,⁵ pre-operative nasal congestion,⁵ systemic steroid use,^{18–20} and severe pre-operative olfactory dysfunction.^{5,14} However, most of these studies only had short-term follow up, were examining different sets of factors and were using various measures of olfactory function with some of them relying on self-rating.

The aim of this study was to explore possible predictors of olfactory function after endoscopic sinus surgery among those with chronic rhinosinusitis with nasal polyps.

Materials and methods

This was a prospective study approved by the institutional review board of the University of Erlangen–Nuremberg. The study included patients who had chronic rhinosinusitis with

nasal polyps who were admitted from 2006 to 2012. The development of non-invasive biomarkers and the analysis of the results were conducted between 2013 and 2022. Possible risks and benefits related to participation in the study were explained to patients on the day of recruitment. All participants provided their written informed consent. Data were previously collected from another study exploring steroid effects on chronic rhinosinusitis and were re-analysed to explore potential predictors of olfactory improvement in the same sample.

The study included patients aged 18 to 80 years who were diagnosed with chronic rhinosinusitis with nasal polyps based on the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis criteria²¹ and who had not undergone prior sinus surgery. All patients were treated with saline rinses and topical intranasal steroid spray (mometasone furoate, 200 µg) twice a day for three months and systemic steroids and/or antibiotics as needed. If the patients did not respond to medical treatment, a CT scan was performed, and those with persistent chronic rhinosinusitis symptoms were recommended to undergo functional endoscopic sinus surgery. Exclusion criteria were based on a prior study that the data were collected for and included: ciliary dysfunction, autoimmune disease, cystic fibrosis and immunodeficiency. Additionally, pregnant women, patients less than 18 years and more than 80 years old, those who failed to complete the 2-year follow up, and those with significant cognitive impairment or a poorly controlled psychiatric disorder were excluded.

Surgery

Functional endoscopic sinus surgery was performed following the surgical technique described by Wigand *et al.*²² (complete functional endoscopic sinus surgery with opening of the maxillary sinus, the anterior and posterior ethmoid sinus, the sphenoid sinus, and the frontal sinus (Draf IIa)). Septoplasty, turbinate reduction or both were performed as needed.

Variables and patient follow up

A standardised, structured history²³ was taken. Variables considered are summarised in Tables 1 and 2.

All patients were followed over a 2-year period at 10 different time points. However, only data from baseline until 12 months after surgery (a total of 8 time points) were used for the analysis. Time point 1 was the day of recruitment or baseline. Time point 2 was the day of surgery. The remaining 6 post-operative time points were at 0.75, 1.5, 3, 6, 9 and 12 months after surgery. All variables were measured at eight time points, except for nasal polyp score, which was measured only from the day of surgery.

Questionnaires

Patients were asked to answer questionnaires at the beginning of each visit. These included questions on sinonasal symptoms, such as nasal congestion, anterior rhinorrhoea, posterior rhinorrhoea and sneezing. Patients were also asked to rate their sense of smell. The Rhinosinusitis Disability Index, a validated 30-item Likert-type scale that assesses the impact of sinusitis on three subscales was also used.²⁴ Higher total and subscale Rhinosinusitis Disability Index scores indicate a worse impact of sinus disease (0 = no impact; 120 = highest impact).

Table 1. Frequencies and means of independent variables based on history

Variable	Frequency
Age (mean (SD); years)	50 (12.33)
Sex (n (%))	
– Men	53 (87)
– Women	8 (13)
Allergic rhinitis (n (%))	
– No	27 (44)
– Yes	34 (56)
Anti-histamine use (n (%))	
– No	59 (97)
– Yes	2 (3)
Steroid use (n (%))	
– No	3 (5)
– Topical	52 (85)
– Topical + systemic	6 (10)
Previous surgery (n (%))	
– No	52 (85)
– Yes	9 (15)
Non-steroidal anti-inflammatory drug tolerance (n (%))	
– No	11 (18)
– Yes	50 (82)
Asthma (n (%))	
– No	42 (69)
– Yes	19 (31)
Frequency of acute sinusitis per year (n (%))	
– None	19 (31)
– 0–3	21 (34)
– 4–6	12 (20)
– >6	9 (15)

n = 61. SD = standard deviation

Mucus biomarkers

For biomarkers, the proteins cystatin 2, pappalysin-1, periostin, serpinE1 and serpinF2 were assessed based on previous studies^{25–32} and were selected because of their potential to monitor disease severity over time (cystatin SN, pappalysin 1, periostin) and their role in inflammation and fibrinolysis (serpinE1, serpinF2).

Nasal polyp score

The endoscopic nasal polyp score was assessed using a 30° endoscope (Karl Storz, Tuttlingen, Germany) for each nostril separately. The highest score per side was graded. Each nostril was scored from 0 to 4 (0 = no polyps, 1 = small polyps confined to the middle meatus, 2 = blocked middle meatus, 3 = polyps extending beyond middle meatus and 4 = large polyps causing almost complete nasal obstruction). Simultaneously, endoscopic pictures were taken for documentation purposes.

Biomarker analysis

Mucus collection technique

Mucus samples were taken at each time point using a polyvinyl alcohol sponge (Medtronic, Minneapolis, USA) applied to the

Table 2. Frequencies and means of other independent variables

Parameter	Variable*	Value
Sinonasal Symptom Questionnaire	Nasal congestion	(n (%))
	- No	5 (8)
	- Mild	17 (28)
	- Moderate	32 (52)
	- Severe	7 (12)
	Anterior rhinorrhoea	(n (%))
	- No	9 (15)
	- Mild	28 (46)
	- Moderate	18 (30)
	- Severe	6 (10)
	Posterior rhinorrhoea	(n (%))
	- No	15 (25)
	- Mild	26 (43)
	- Moderate	17 (28)
	- Severe	3 (5)
	Headache	(n (%))
	- No	24 (39)
	- Mild	20 (33)
	- Moderate	16 (26)
	- Severe	1 (2)
Subjective smell rating	(n (%))	
- Normal	10 (16)	
- Mild problem	27 (44)	
- Could not smell	24 (39)	
Sneezing	(n (%))	
- No	9 (15)	
- Mild	25 (41)	
- Moderate	0 (0)	
- Severe	27 (44)	
Rhinosinusitis Disability Index (mean (SD); score)	- Overall	66.85 (24.99)
	- Functional	22.39 (8.25)
	- Emotional	18.15 (8.86)
	- Physical	23.05 (8.79)
Mucus biomarkers (mean (SD), units are specified for each biomarker)	- SerpinE1 (pg/ml) (n = 45)	194.48 (184.85)
	- SerpinF2 (pg/ml) (n = 59)	2648.03 (1756.73)
	- Cystatin 2 (pg/ml) (n = 59)	341.02 (422.39)
	- Periostin (ng/ml) (n = 58)	199.54 (293.69)
	- Pappalysin-1 (pg/ml) (n = 58)	112.47 (82.74)
Baseline Identification Score (mean (SD); score)		7.25 (3.54)

(Continued)

Table 2. (Continued.)

Parameter	Variable*	Value
Olfactory function (n (%))	- Anosmia	25 (41)
	- Hyposmia	32 (52)
	- Normosmia	4 (7)
Nasal polyp score (mean (SD); score)		5.15 (2.29)

*n = 61 unless otherwise stated

anterior internal valve, taking care not to abrade the mucosa or contaminate the sponge with blood. The sponges were weighed before and after insertion into the nose. Next, 3 ml of phosphate-buffered saline were added. After 10 minutes, the sponges were centrifuged for 10 minutes at 2000 ×g. The eluate was frozen immediately into aliquots at -80°C and was stored at -80°C until analysis.

Protein biomarker analysis

After thawing of the aliquots, the five proteins were quantified in the nasal mucus using enzyme-linked immunosorbent assay and normalised to total protein (BCA-Assay, Life Technologies, Darmstadt, Germany). All enzyme-linked immunosorbent assays were performed according to the manufacturer's protocols. For cystatin 2, the nasal mucus was diluted 1:5 with 0.1 per cent bovine serum albumin in phosphate-buffered saline. The human cystatin SA CST2 enzyme-linked immunosorbent assay pair set (number SEK11567, Sino Biological, Beijing, China) was used. For pappalysin-1, the nasal mucus was measured undiluted. The human pappalysin-1 DuoSet (number DY2487-05, R&D Systems, Bio-Techne, Wiesbaden, Germany) was used. For periostin, the nasal mucus was diluted 1:800 with reagent diluent (included in the kit). The human periostin DuoSet (number DY3548B, R&D Systems, Bio-Techne, Wiesbaden, Germany) was used. For serpinE1, the nasal mucus was diluted 1:3 with 0.1 per cent bovine serum albumin in phosphate-buffered saline. The human serpinE1 enzyme-linked immunosorbent assay pair set (number SEK10296, Sino Biological, Beijing, China) was used. For serpinF2, the nasal mucus was diluted 1:2 with reagent diluent. The human serpinF2 DuoSet (number DY1470-05, R&D Systems, Bio-Techne, Wiesbaden, Germany) was used.

Outcome measures

The primary outcome measure (dependent variable) was the difference in odour identification score between baseline and 0.75, 1.5, 3, 6, 9 and 12 months after surgery. For olfactory testing, the 16-item "Sniffin' Sticks" identification test was used.³³ Each patient had to correctly identify and label each pen containing common and familiar odours. A list of four descriptors were presented to the participants as verbally labelled pictures, and they had to match one of these descriptors to the odour of the pen. The identification score was the sum of correctly identified odour pens, with scores ranging between 0 and 16. Anosmia was defined as a score equal to or less than 8, hyposmia as a score of 9 to 11, and normosmia as a score of 12 or higher.^{34,35}

Data collection and statistical analysis

Patient records were assigned codes and anonymised. Data analysis was performed using SPSS® (version 28.0).

Independent variables were variables measured at baseline and on the day of surgery, which were found to have significant correlation with the dependent variables.

Phase 1: variable analysis

Point biserial correlation was performed on all dichotomous nominal variables. Pearson's r was computed for age, mucus biomarkers, Rhinosinusitis Disability Index and subtests (functional, emotional and physical), nasal polyp score and odour identification score. Spearman's rho (r_s) was computed for type of steroid use, frequency of acute sinusitis and the sinonasal symptom questionnaire.

Correlative analyses were performed for all independent variables that were found to be correlated with identification score differences at the six predetermined time points. Independent variables that were highly correlated with other independent variables (r or $r_s \geq 0.4$) at the same time point were excluded from the regression analysis, based on which independent variable had a lower r or r_s value.

Phase 2: regression analysis

Multiple linear regression analysis was performed separately for all six time points. Independent variables determined from phase 1 (Table 3) were entered as predictors using the standard method. Frequency of acute sinusitis and steroid use were recoded as dichotomous variables to better determine the trend and effects of each group in the model.

Results

The study included 61 patients, with a mean age of 50 years (range, 19 to 75 years), most of whom were men ($n = 53$, 86.9 per cent), did not take antihistamines ($n = 59$, 96.7 per cent), used topical corticosteroids only ($n = 52$, 85.2 per cent), had not undergone prior nasal surgery ($n = 52$, 85.2 per cent), could tolerate non-steroidal anti-inflammatory drugs ($n = 50$, 82 per cent) and did not have asthma ($n = 42$, 68.9 per cent). Frequencies and means of the independent variables are listed in Tables 1 and 2. The majority of the participants had hyposmia ($n = 32$, 52.5 per cent) and functional anosmia ($n = 25$, 41 per cent) at baseline.

Table 4 summarises the significant models that were found. Predictors of early olfactory improvement included absence of acute sinusitis, elevated baseline serpinF2 in mucus and baseline anterior rhinorrhoea. Concomitant allergic rhinitis was found to be a predictor of late olfactory improvement. Baseline odour identification score appeared to be the strongest and most reliable predictor across all time points.

Those with baseline functional anosmia had a significantly higher olfactory score improvement post-operatively across all time points ($F_{5,54} = 2.90$, $p < 0.022$). Those who took topical and systemic steroids pre-operatively had a tendency for increased improvement ($F_{5,54} = 2.34$, $p = 0.054$), but the failure to reach significance may be because of the low sample size ($n = 6$, 9.8 per cent). Other predictors had a significant effect for particular time points but not for all (Table 4). Those with higher baseline serpinF2 had significantly greater improvement at 3 weeks after surgery ($F_{1,57} = 10.30$, $p = 0.002$).

Table 3. Initial variables for regression analysis

Variable*	Time points (months) [†]						Correlated with
	0.75	1.5	3	6	9	12	
Allergic rhinitis					x	x	
Steroid use		x	x	x	x	x	
– No steroid							Topical only
– Topical only							No steroid, topical + systemic
– Topical + systemic							Topical only
Frequency of acute sinusitis per year	x			x	x	x	
– No sinusitis							0-3/year
– 0-3							No sinusitis
– 4-6							
– >6							
Identification score 1	x	x	x	x	x	x	Smell rating 2
Identification score 2	o	o	o	o	o	o	Identification score 1
Nasal congestion 2				x			
Anterior rhinorrhoea 1		x	x				
Anterior rhinorrhoea 2		o	o				Anterior rhinorrhoea 1
Posterior rhinorrhoea 1						x	
Smell rating 1					x		
Smell rating 2	o	o	o	o	o [‡]	o	Identification score 1
							[‡] Smell rating 1
Serpin F2	x						

*1: measured at baseline, 2: measured on the day of surgery; [†]x: included in regression analysis, o: excluded in regression analysis because of high correlation with other independent variables; [‡]indicates a link to 'smell rating 1' in the 'correlated with' column.

Table 4. Predictors of post-operative olfactory score improvement

Time point (months)	F-value	df	P-value	R ²	Percentage variance explained (%)	Predictors*	B	SE B	Beta	P-value	Correlated variables	r _{pb}	P-value
0.75	16.161	5	<0.001	0.604	36.48	No sinusitis	-1.365	0.612	-0.224	0.03	No sinusitis – 0–3/year	-0.487	<0.001
						Identification score 1	-0.499	0.073	-0.618	<0.001			
						Serpin F2 1	0.001	0	0.342	<0.001			
1.5	14.023	4	<0.001	0.5	25	Identification score 1	-0.579	0.093	-0.62	<0.001	No steroid – topical steroid	-0.547	<0.001
											Topical steroid – topical + systemic	-0.794	<0.001
3	17.047	4	<0.001	0.549	30.14	Identification score 1	-0.556	0.087	-0.602	<0.001	No steroid – topical steroid	-0.547	<0.001
						Anterior rhinorrhoea 1	0.738	0.362	0.193	0.046	Topical steroid – topical + systemic	-0.794	<0.001
6	9.669	7	<0.001	0.561	31.47	Identification score 1	-0.567	0.091	-0.613	<0.001	No steroid – topical steroid	-0.547	<0.001
											Topical steroid – topical + systemic	-0.794	<0.001
											No sinusitis – 0–3/year	-0.487	<0.001
9	11.255	8	<0.001	0.634	40.20	Allergic rhinitis	1.349	0.587	0.207	0.026	No steroid – topical steroid	-0.547	<0.001
						Identification score 1	-0.631	0.89	-0.684	<0.001	Topical steroid – topical + systemic	-0.794	<0.001
											No sinusitis – 0–3/year	-0.487	<0.001
12	9.018	8	<0.001	0.581	33.76	Allergic rhinitis	1.275	0.596	0.205	0.037	No steroid – topical steroid	-0.547	<0.001
						Identification score 1	-0.567	0.085	-0.644	<0.001	Topical steroid – topical + systemic	-0.794	<0.001
											No sinusitis – 0–3/year	-0.487	<0.001

*Measured at baseline. Those with positive values for beta are positive predictors (leads to an increase in score), and those with negative values for beta are negative predictors (leads to a decrease in score). df = degrees of freedom; R² = proportion of the variance in olfactory score difference accounted for by the model; B = unstandardised regression coefficient; SE B = standard error of the unstandardised regression coefficient; beta = standardised regression coefficient; r_{pb} = point-biserial correlation of the correlated variables

Those with baseline moderate anterior rhinorrhoea had greater improvement at 1.5 months than those with no anterior rhinorrhoea ($F_{3,57} = 2.851$, $p = 0.045$). Those with allergies had greater improvement at 9 months ($F_{1,59} = 5.00$, $p = 0.029$) and 12 months ($F_{1,59} = 4.29$, $p = 0.043$) compared with those without allergic rhinitis. Those with no episodes of acute sinusitis had significantly lower improvement at 3 weeks after surgery compared with those with more than 6 episodes of acute sinusitis per year ($F_{3,57} = 2.97$, $p = 0.039$).

Discussion

Our study basically highlights two main ideas related to olfactory improvement after endoscopic sinus surgery: that more severe disease leads to greater olfactory improvement, and conversely, that less severe disease improves less. Litvack *et al.*³⁶ hypothesised that chronic rhinosinusitis patients with a mild olfactory deficit would benefit more from endoscopic sinus surgery compared with those with severe olfactory deficits, but they found the reverse to be true in their study. Similar to their findings, we found that those with anosmia had significantly greater improvement after surgery.

Chronic rhinosinusitis associated olfactory dysfunction is related to both an obstructive and inflammatory component. Surgery may help to improve the obstructive component; however, recovery may likely depend on the severity of disease and chronicity of inflammation. Significant local activation of the coagulation system in the upper airways of patients with chronic rhinosinusitis with nasal polyps through the activation of thrombin, a proteolytic enzyme that catalyses the conversion of fibrinogen to fibrin, can promote tissue remodelling by stimulating vascular endothelial growth factor secretion from airway epithelial cells.^{37,38} Irreversible damage to the olfactory neuroepithelium may occur during the chronicity of the disease process, thereby preventing the return of olfactory function to normal levels despite surgical management.¹⁰ Those who have mild olfactory loss likely do not improve to the point of normal olfaction, which showed as the decreased benefit in this subgroup in the present study (which was consistent with 'no episodes of acute sinusitis' being a predictor of less olfactory improvement at three weeks after surgery) compared with those with functional anosmia improving to hyposmic levels.

SerpinF2 (also known as alpha-2-antiplasmin) is an extracellular plasmin inhibitor that impairs fibrinolysis and signals mucosal dysregulation of the coagulation system. Studies have previously shown that impaired fibrinolysis can lead to excessive fibrin deposition in nasal polyps, leading to mucosal oedema and tissue remodelling.^{39,40} Excessive fibrin deposition may have proinflammatory effects in patients with nasal polyps, but fibrin production was also found to be important for airway epithelial repair after epithelial damage.⁴⁰ Pre-operative serpinF2 is expected to be elevated in patients with chronic rhinosinusitis with nasal polyps. The observed decrease of this mucosal biomarker at three weeks after surgery may indicate post-surgical improvement of inflammation secondary to the removal of nasal polyps and inflammatory tissue as well as from improved circulation of corticosteroids in the nasal cavity. We hypothesised that this decrease in serpinF2 may signal a period of decreased inflammation, allowing the recovery and repair of the olfactory epithelium in the setting of an intact olfactory system, leading to improved olfactory function.

Anterior rhinorrhoea may be a marker of disease severity or poor control, especially when it is mucopurulent and

occurring on most days of the week.¹ Increased secretions may also interfere with binding of odorant molecules to the olfactory epithelium. In as much as polyps may prevent odorant molecules from reaching the olfactory epithelium, chronic nasal inflammation resulting in the disturbance of olfactory mucus may also be a significant factor leading to olfactory dysfunction. Olfactory mucus, which usually covers the apical receptor surface of the olfactory neuroepithelium, has been regarded as the primary source of ions that are necessary for odour transduction.^{41,42} Olfactory dysfunction may result from hypersecretion as a result of chronic nasal inflammation, with associated presence of inflammatory mediators in diseased olfactory mucosa.⁴¹ Given that surgery likely contributes to removal of inflammatory tissue and allows for improved delivery of intranasal corticosteroids post-operatively, it is possible that hypersecretion is reversed and patients with these symptoms gain more in terms of olfaction in the early phase of recovery.

Allergic rhinitis is not typically associated with severe olfactory dysfunction. However, severe olfactory dysfunction may be observed in more severe allergic disease and those with longer disease duration.⁴³ In a study by Apter *et al.*,⁴⁴ patients with allergic rhinitis and chronic rhinosinusitis had worse olfactory thresholds compared with those with allergic rhinitis only, whereas those with allergic rhinitis and chronic rhinosinusitis with nasal polyps generally had anosmia. This severe olfactory dysfunction may explain the increased improvement post-operatively. Inflammatory conditions of allergic origin may contribute to the reversible olfactory loss through obstruction of the olfactory epithelium or other factors related to the inflammatory process.⁴⁵ However, the exact reason why allergic rhinitis was a significant predictor at 9 and 12 months after surgery is unclear. There have been conflicting findings as to the effect of allergy on chronic rhinosinusitis related olfactory dysfunction. A study by Schlosser *et al.*⁷ found that the presence of allergy led to higher threshold scores, but a study by Litvack *et al.*¹¹ did not find any relationship between allergy and olfaction in chronic rhinosinusitis. It has been proposed that the link between allergic rhinitis and olfactory loss may be because of the association of allergic rhinitis with frequent respiratory tract infections, leading to irreversible damage to the olfactory mucosa.⁴⁴ We propose that the presence of allergic rhinitis as a co-morbid condition in chronic rhinosinusitis may have led to a protracted course of recovery as a result of recurrent infection or persistent inflammation. Inflammation may block the proliferation of basally located progenitors, restricting the repopulation by new olfactory receptor neurons.³ In addition, procoagulant activity has also been observed in allergic rhinitis.³⁸ Thrombin activation and decreased fibrinolysis in nasal polyps may lead to a proinflammatory state that might not immediately resolve with surgery alone, allowing greater olfactory improvement to be experienced more at a later period during recovery.

Steroids have been mentioned to influence post-operative olfactory improvement. In our study, we observed a tendency for higher score improvement among those receiving both topical and systemic steroids pre-operatively. Although the sample of patients who received combined steroid treatment was low in our population, a previous study by Alobid *et al.*⁴⁶ found evidence that combined oral and intranasal steroids improved olfaction and nasal congestion as well as decreased nasal inflammation in patients with severe nasal polyps. Systemic steroids have been found to have benefit for chronic rhinosinusitis-related olfactory dysfunction.^{47,48} The addition

of systemic steroids pre-operatively may be a viable adjunct treatment option for chronic rhinosinusitis patients who do not have any contraindications to receiving this treatment.

Limitations to this study included the low sample size, reliance on only the odour identification test to represent olfactory function, a predominantly male population, a varying number of patients for some factor groups (e.g. steroid use, antihistamine use) and that the data were re-analysed from another study. Odour threshold scores may be more sensitive to differences between groups⁴⁴ and are often the most sensitive to change in olfactory dysfunction.³⁵ Our study may have been limited in discriminating between olfaction differences because of our choice of test. Chronic rhinosinusitis with nasal polyps has been found to be predominant in men in prior studies^{44,49,50}; thus, our study is reflective of what is observed in the population despite the observed skewness of data. Future studies may be performed with a larger sample size, include tests for odour threshold and have a more heterogeneous distribution for investigated factors.

- Many studies have explored possible predictors of olfactory improvement after endoscopic sinus surgery
- Anosmia, nasal polyposis and previous surgery are examples of predictors that have been reported in the literature, but results have been conflicting
- This study is the first to explore mucus biomarkers as possible predictors of olfactory improvement in patients with chronic rhinosinusitis
- Chronic rhinosinusitis with nasal polyps patients with poorer baseline olfactory function or more severe disease may benefit more from endoscopic sinus surgery in terms of olfactory function
- Chronic rhinosinusitis with nasal polyps patients with no or mild olfactory loss may have little or no olfactory benefit from endoscopic sinus surgery

In summary, chronic rhinosinusitis with nasal polyps patients with poorer baseline olfactory function or more severe disease (frequent episodes of acute sinusitis on top of chronic rhinosinusitis, anterior rhinorrhoea, concomitant allergic rhinitis) may benefit more from endoscopic sinus surgery in terms of olfactory function. Chronic rhinosinusitis with nasal polyps patients with no or mild olfactory loss may have little or no benefit from endoscopic sinus surgery from an olfactory standpoint.

Acknowledgements. The authors would like to acknowledge Anna Oleszkiewicz for her valuable comments and guidance in the process of statistical analysis. This work was supported by Merck, Darmstadt, Germany (reference: NCT04915456).

Competing interests. Since 2018, TH did research together with or received funding from Sony, Stuttgart, Germany; Smell and Taste Lab, Geneva, Switzerland; Takasago, Paris, France; Aspuraclip, Berlin, Germany; Bayer Healthcare, Berlin, Germany; Baia Foods, Madrid, Spain; Frequency Therapeutics, Farmington, CT, USA; Primavera, Oy-Mittelberg, Germany; Novartis, Nürnberg, Germany; Verlag für chemische Industrie H. Ziolkowsky, Thannhausen, Germany; Ismar Healthcare NV-SA, Lier, Belgium. All other authors have no conflicts of interest to declare.

References

- 1 Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology* 2020;**11**(suppl 29):1–464
- 2 Hummel T, Whitcroft KL, Andrews P, Altundag A, Cinghi C, Costanzo RM et al. Position paper on olfactory dysfunction. *Rhinology* 2017;**54**:1–30
- 3 Lane AP, Turner J, May L, Reed R. A genetic model of chronic rhinosinusitis-associated olfactory inflammation reveals reversible functional impairment and dramatic neuroepithelial reorganization. *J Neurosci* 2010;**30**:2324–9
- 4 Alt JA, Mace JC, Buniel MCF, Soler ZM, Smith TL. Predictors of olfactory dysfunction in rhinosinusitis using the brief smell identification test. *Laryngoscope* 2014;**124**:259–66
- 5 Szalenciec J, Wróbel A, Stręk P, Kowalczyk M, Bylica E, Przeklasa M et al. Smell impairment in chronic rhinosinusitis – evaluation of endoscopic sinus surgery results and review of olfactory function predictors. *Otolaryngol Pol* 2015;**69**:33–44
- 6 Damm M, Leung RM, Kern RC. Sinonasal Olfactory Disorders. In: Welge-Lüssen A, Hummel T, eds. *Management of Smell and Taste Disorders: A Practical Guide for Clinicians*. Stuttgart: Thieme, 2013;76–90
- 7 Schlosser RJ, Smith TL, Mace JC, Alt J, Beswick DM, Mattos JL et al. Factors driving olfactory loss in patients with chronic rhinosinusitis: a case control study. *Int Forum Allergy Rhinol* 2020;**10**:7–14
- 8 Asai K, Haruna SI, Otori N, Yanagi K, Fukami M, Moriyama H. Saccharin test of maxillary sinus mucociliary function after endoscopic sinus surgery. *Laryngoscope* 2000;**110**:117–22
- 9 Harvey RJ, Goddard JC, Wise SK, Schlosser RJ. Effects of endoscopic sinus surgery and delivery device on cadaver sinus irrigation. *Otolaryngol Head Neck Surg* 2008;**139**:137–42
- 10 Doty RL, Mishra A. Olfaction and its alteration by nasal obstruction, rhinitis, and rhinosinusitis. *Laryngoscope* 2001;**111**:409–23
- 11 Litvack JR, Fong K, Mace J, James KE, Smith TL. Predictors of olfactory dysfunction in patients with chronic rhinosinusitis. *Laryngoscope* 2008;**118**:130–4
- 12 Ramakrishnan VR, Arbet J, Mace JC, Suresh K, Shintani Smith S, Soler ZM et al. Predicting olfactory loss in chronic rhinosinusitis using machine learning. *Chem Senses* 2021;**46**:bjab042
- 13 Mattos JL, Soler ZM, Schlosser RJ, Mace JC, Alt JA, Ramakrishnan VR et al. Olfactory function after surgical treatment of CRS: a comparison of CRS patients to healthy controls. *Am J Rhinol Allergy* 2021;**35**:391–8
- 14 Kim BG, Kang JM, Shin JH, Choi HN, Jung YH, Park SY. Do sinus computed tomography findings predict olfactory dysfunction and its postoperative recovery in chronic rhinosinusitis patients? *Am J Rhinol Allergy* 2015;**29**:69–76
- 15 Mori E, Matsuwaki Y, Mitsuyama C, Okushi T, Nakajima T, Moriyama H. Risk factors for olfactory dysfunction in chronic rhinosinusitis. *Auris Nasus Larynx* 2013;**40**:465–9
- 16 Im D, Yang YS, Choi HR, Han K, Hong S-C, Cho JH et al. Do eosinophilic polyps act as a reliable predictor of olfactory dysfunction and postoperative recovery in chronic rhinosinusitis? *Korean J Otorhinolaryngol Neck Surg* 2018;**61**:300–7
- 17 Andrews PJ, Poirrier AL, Lund VJ, Choi D. Outcomes in endoscopic sinus surgery: olfaction, nose scale and quality of life in a prospective cohort study. *Clin Otolaryngol* 2016;**41**:798–803
- 18 Ecevit MC, Erdag TK, Dogan E, Sutay S. Effect of steroids for nasal polypoid surgery: a placebo-controlled, randomized, double-blind study. *Laryngoscope* 2015;**125**:2041–5
- 19 Kirtsreesakul V, Wongsritrang K, Ruttanaphol S. Does oral prednisolone increase the efficacy of subsequent nasal steroids in treating nasal polypoid? *Am J Rhinol Allergy* 2012;**26**:455–62
- 20 Hissaria P, Smith W, Wormald PJ, Taylor J, Vadas M, Gillis D et al. Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. *J Allergy Clin Immunol* 2006;**118**:128–33
- 21 Orlandi RR, Kingdom TT, Smith TL, Bleier B, DeConde A, Luong AU et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. *Int Forum Allergy Rhinol* 2021;**11**:213–739
- 22 Wigand M, Steiner W, Jaumann M. Endonasal sinus surgery with endoscopic control: from radical operation to rehabilitation of the mucosa. *Endoscopy* 1978;**10**:255–60
- 23 Hummel T, Hummel C, Welge-Luessen A. Assessment of olfaction and gustation. Welge-Lüssen A, Hummel T, editors. *Management of Smell and Taste Disorders: A Practical Guide for Clinicians*. Stuttgart: Thieme, 2013;58–75
- 24 Benninger MS, Senior BA. The development of the rhinosinusitis disability index. *Arch Otolaryngol Head Neck Surg* 1997;**123**:1175–9
- 25 Mueller SK, Nocera AL, Dillon ST, Gu X, Wendler O, Otu HH et al. Noninvasive exosomal proteomic biosignatures, including cystatin SN, peroxiredoxin-5, and glycoprotein VI, accurately predict chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol* 2019;**9**:177–86
- 26 Mueller SK, Wendler O, Nocera A, Grundtner P, Schlegel P, Agaimy A et al. Escalation in mucus cystatin 2, pappalysin-A, and periostin levels over time predict need for recurrent surgery in chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol* 2019;**9**:1212–9
- 27 Mueller SK, Nocera AL, Dillon ST, Libermann TA, Wendler O, Bleier BS. Tissue and exosomal serine protease inhibitors are significantly overexpressed

- in chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy* 2019; **33**:359–68
- 28 Miyake MM, Workman AD, Nocera AL, Wu D, Mueller SK, Finn K *et al*. Discriminant analysis followed by unsupervised cluster analysis including exosomal cystatins predict presence of chronic rhinosinusitis, phenotype, and disease severity. *Int Forum Allergy Rhinol* 2019; **9**:1069–76
- 29 Maxfield AZ, Landegger LD, Brook CD, Lehmann AE, Campbell AP, Bergmark RW *et al*. Periostin as a biomarker for nasal polyps in chronic rhinosinusitis. *Otolaryngol Head Neck Surg (United States)* 2018; **158**:181–6
- 30 Mueller SK, Nocera AL, Dillon ST, Wu D, Libermann TA, Bleier BS. Highly multiplexed proteomic analysis reveals significant tissue and exosomal coagulation pathway derangement in chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol* 2018; **8**:1438–44
- 31 Mueller SK, Nocera AL, Workman A, Libermann T, Dillon ST, Stegmann A *et al*. Significant polyomic and functional upregulation of the PAPP-A/IGFBP-4/5/IGF-1 axis in chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol* 2020; **10**:546–55
- 32 Workman AD, Nocera AL, Mueller SK, Otu HH, Libermann TA, Bleier BS. Translating transcription: proteomics in chronic rhinosinusitis with nasal polyps reveals significant discordance with messenger RNA expression. *Int Forum Allergy Rhinol* 2019; **9**:776–86
- 33 Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' sticks'. Olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chem Senses* 1997; **22**:39–52
- 34 Kobal G, Klimek L, Wolfensberger M, Gudziol H, Temmel A, Owen CM *et al*. Multicenter investigation of 1,036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. *Eur Arch Otorhinolaryngol* 2000; **257**:205–11
- 35 Oleszkiewicz A, Schriever VA, Croy I, Hähner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. *Eur Arch Otorhinolaryngol* 2019; **276**:719–28
- 36 Litvack JR, Mace J, Smith TL. Does olfactory function improve after endoscopic sinus surgery? *Otolaryngol Head Neck Surg* 2009; **140**:312–9
- 37 Shimizu S, Gabazza EC, Ogawa T, Tojima I, Hoshi E, Kouzaki H *et al*. Role of thrombin in chronic rhinosinusitis-associated tissue remodeling. *Am J Rhinol Allergy* 2011; **25**:7–11
- 38 Shimizu S, Shimizu T, Morser J, Kobayashi T, Yamaguchi A, Qin L *et al*. Role of the coagulation system in allergic inflammation in the upper airways. *Clin Immunol* 2008; **129**:365–71
- 39 Takabayashi T, Kato A, Peters AT, Hulse KE, Suh LA, Carter R *et al*. Excessive fibrin deposition in nasal polyps caused by fibrinolytic impairment through reduction of tissue plasminogen activator expression. *Am J Respir Crit Care Med* 2013; **187**:49–57
- 40 Kim DY, Cho SH, Takabayashi T, Schleimer RP. Chronic rhinosinusitis and the coagulation system. *Allergy, Asthma Immunol Res* 2015; **7**:421–30
- 41 Robinson AM, Kern RC, Foster JD, Fong KJ, Pitovski DZ. Expression of glucocorticoid receptor mRNA and protein in the olfactory mucosa: physiologic and pathophysiologic implications. *Laryngoscope* 1998; **108**:1238–42
- 42 Drescher DG, Kerr TP. Na⁺, K⁺-activated adenosine triphosphatase and carbonic anhydrase: inner-ear enzymes of ion transport. In: Drescher DG, ed. *Auditory Biochemistry*. Springfield, IL: Charles C. Thomas, 1986;436–73
- 43 Stuck BA, Hummel T. Olfaction in allergic rhinitis: a systematic review. *J Allergy Clin Immunol* 2015; **136**:1460–70
- 44 Apter AJ, Gent JF, Frank ME. Fluctuating olfactory sensitivity and distorted odor perception in allergic rhinitis. *Arch Otolaryngol Head Neck Surg* 1999; **125**:1005–10
- 45 Cowart BJ, Flynn-Rodden K, McGeady SJ, Lowry LD. Hyposmia in allergic rhinitis. *J Allergy Clin Immunol* 1993; **91**:747–51
- 46 Alobid I, Benitez P, Cardelus S, De Borja Callejas F, Lehrer-Coriat E, Pujols L *et al*. Oral plus nasal corticosteroids improve smell, nasal congestion, and inflammation in sino-nasal polyposis. *Laryngoscope* 2014; **124**:50–6
- 47 Wolfensberger M, Hummel T. Anti-inflammatory and surgical therapy of olfactory disorders related to sino-nasal disease. *Chem Senses* 2002; **27**:617–22
- 48 Bogdanov V, Walliczek-Dworschak U, Whitcroft KL, Landis BN, Hummel T. Response to glucocorticosteroids predicts olfactory outcome after ESS in chronic rhinosinusitis. *Laryngoscope* 2020; **130**:1616–21
- 49 Moloney JR. Nasal polyps, nasal polypectomy, asthma, and aspirin sensitivity. Their association in 445 cases of nasal polyps. *J Laryngol Otol* 1977; **91**:837–46
- 50 Busaba NY, Sin HJ, Salman SD. Impact of gender on clinical presentation of chronic rhinosinusitis with and without polyposis. *J Laryngol Otol* 2008; **122**:1180–4