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

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## 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.

## 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

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## 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 criteria[21] 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 history[23] 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

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**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) |
| 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).

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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

| | Time points (months)† | | | | | | |
|---|---|---|---|---|---|---|---|
| Variable* | 0.75 | 1.5 | 3 | 6 | 9 | 12 | Correlated with |
| **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.

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**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; $R^2$ 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

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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 groups[44] 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.

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