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Olfactory Function After Surgical Treatment of CRS: A Comparison of CRS Patients to Healthy Controls

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Abstract

Background: Many patients with chronic rhinosinusitis (CRS) have persistent olfactory dysfunction (OD) following endoscopic sinus surgery (ESS). Few studies compare outcomes to control subjects so it is unknown if residual OD is due to persistent CRS.

Objective: Compare postoperative measures of OD in case patients with CRS to healthy controls without sinonasal disease.

Methods: Prospective, observational, multicenter cohort study between October, 2016 and May, 2019. Case participants were selected from referred adult patients diagnosed with CRS, with or without nasal polyposis (NP), electing ESS as subsequent treatment modality. Controls voluntarily enrolled from a community-based sample without a history of CRS. Primary outcomes included measures of preoperative and postoperative OD using "Sniffin' Stick" pens which summarize odorant threshold (T), discrimination (D), and identification (I) scores. Secondary outcomes included the Questionnaire of Olfactory Disorders-Negative Statements (QOD-NS) survey and olfactory cleft endoscopy scores (OCES).

Results: Outcomes were compared between 113 cases and 164 controls of similar average age and gender. Cases reported significantly worse baseline Sniffin' Sticks TDI total scores (-6.8[SE $\pm$ 1.0]; 95% CI: -4.9 to -8.7), QOD-NS (8.9[SE $\pm$ 1.1]; 95% CI: 6.8–10.9), and OCES (3.5[SE $\pm$ 0.4]; 95% CI: 2.9–4.2) on average. Cases reported significant postoperative improvement in TDI total score (3.7[SD $\pm$ 8.2]; 95% CI: 2.2–5.2), QOD-NS (-5.9[SD $\pm$ 8.7]; 95% CI: -7.6 to -4.3), and OCES (-1.7[SD $\pm$ 3.8]; 95% CI: -2.7 to -0.8) on average, while 63% of anosmics reported improved postoperative olfaction. Multivariate regression identified that NP (OR = 0.4; 95% CI: 0.2–1.0) and previous ESS (OR = 0.3; 95% CI: 0.1–0.8) decreased the odds of postoperative improvement equal to mean TDI scores of controls, while septoplasty increased those odds (OR = 4.5; 95% CI: 1.5–13.7).

Conclusion: ESS improved olfactory metrics and restored olfactory function in approximately 50% of patients with CRS to that of healthy controls. Concurrent septoplasty increased the likelihood of achieving normal olfaction, while NP and previous ESS decreased those odds.

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sinusitis, chronic disease, patient reported outcome measures, smell, risk, endoscopy, olfactory perception, olfaction disorders

Introduction

Olfactory dysfunction (OD) is associated with multiple adverse effects ranging from decreased nutrition to impaired quality-of-life (QOL) and even increased mortality.[1–4] Numerous factors contribute to OD, including sinonasal inflammation, advanced age, head trauma, and neurodegenerative disorders.[2] Olfactory dysfunction is also a primary characteristic and defining symptom of chronic rhinosinusitis (CRS).[5,6]

Meta-analysis has identified that between 25% and 75% of patients with CRS have OD, while other literature reviews have reported that up to 100% of patients with CRS have olfactory impairment.[7,8] Medical therapy for CRS, most notably oral corticosteroids, improves olfaction.[9] In patients with medically refractory CRS, endoscopic sinus surgery (ESS) can improve OD in a majority of cases.[8,10] Factors associated with a greater likelihood of postoperative olfactory improvement include nasal polyposis (NP) and more severe preoperative OD.[8,10]

While ESS improves OD for many patients, a proportion of patients have a degree of persistent OD postoperatively.[8] It is currently unknown if this residual OD is related to CRS, potentially from on-going sinonasal inflammation or permanent damage to the olfactory epithelium or if it is related to non-CRS factors such as aging. Further limiting our understanding of the prevalence, incident rates, and causes of persistent postoperative OD is the fact that existing studies on olfactory improvement following ESS have not incorporated control populations to aid in determinations of relative risk measures associated with CRS. Therefore, the objective of this investigation was to compare olfaction after ESS in subjects with CRS to olfaction in healthy, control subjects without sinonasal disease.

Methods

Case Subjects

Case study participants were prospectively recruited from a patient population presenting to academic, rhinology centers located in at Oregon Health and Science University (OHSU, Portland, OR.), the Medical University of South Carolina (MUSC, Charleston, SC.), the University of Utah (Salt Lake City, UT.), the University of Colorado (Aurora, CO.), and the University of Virginia (UVA, Charlottesville, VA.). Enrollment was conducted as part of an investigator-monitored, observational research study funded by a grant from the National Institute on Deafness and Other Communication Disorders (Bethesda, MD.).

Adult patients ($\geq$18 years of age) received a confirmed diagnosis of symptomatic CRS, with or without NP, from a fellowship trained rhinologist following practice guidelines.[5] Patients had been treated with medical therapy regimens including: systemic corticosteroids, broad-spectrum or culture directed antibiotics, and topical corticosteroid sprays/irrigations. Subjects provided written, informed consent after clinical appointments and preliminary enrollment meetings to ensure voluntary participation without deviation from the standard of care (SOC). The Institutional Review Board at each enrollment site provided ethical oversight in accordance with guidelines established by the Declaration of Helsinki.

Endoscopic Sinus Surgery

Prior to study invitation, the enrolling physician at each performance site completed patient counseling regarding treatment options for recalcitrant CRS. Case subjects voluntarily elected surgery as the primary intervention, which was either primary or revision ESS. Postoperative therapeutics included nasal saline irrigation, topical corticosteroid sprays/rinses, oral corticosteroid tapers and broad-spectrum antibiotics, depending on the surgeon's clinical judgement.

Control Subjects

Simultaneous control study enrollment was conducted using a community-based sample of adults at MUSC and UVA without a history or current diagnosis of CRS or previous ESS. Control participants were prospectively enrolled on a voluntary basis as part of an investigator-initiated study. Adult, study volunteers were recruited locally using advertisements, word-of-mouth, and self-referral techniques.

Exclusion Criteria

Case and control study participants were excluded based on comorbid conditions associated with an increased

prevalence of OD involving: sarcoidosis, granulomatosis with polyangiitis, dementia, aphasia, Alzheimer's disease, other non-specified neurocognitive disorders, Parkinson's disease, major head trauma/traumatic brain injury, or immunosuppression. Additionally, control subjects with a history of vasovagal syncope and/or adverse reaction to local anesthetics or decongestants, were also excluded. Study candidates were also required to demonstrate strong fluency in English as a first or second language.

Clinical Measures of Olfactory Function

Both case and control subjects completed evaluations of bilateral olfactory function at the time of enrollment using "Sniffin' Stick" pens (Burghart Messtechnik, Wedel, Germany).[11,12] This examination evaluated three separate domain items of olfactory function including: odorant threshold (T, score range: 1–16), odorant discrimination (D, score range: 0–16), and odorant identification (I, score range: 0–16). Threshold scores (n-butanol target) were evaluated in a 'staircase procedure' using pen triplets in which odorant threshold scores are identified on a continuum of dilution steps until the odorant can be correctly distinguished from 2 additional blank pens offered in random sequence. Discrimination scores were determined using a presented sequence of pen triplets in which 2 pens have identical odorants. Identification was evaluated using 16 pens containing common odorants presented individually. Correct responses from threshold, discrimination, and identification scores are summarized into a composite TDI total score (range: 1–48) with higher scores reflecting superior olfaction. Diagnostic interpretations of TDI normative value scores are: normosmia (range: 31–48), hyposmia/microsmia (range: 16–30), and anosmia (range: 1–15).[13] Olfactory testing was conducted on case subjects both before ESS and approximately 6 months postoperatively.

Sinonasal endoscopy was conducted for all case and control subjects near the time of study enrollment using a rigid endoscope (Karl Storz, Tuttlingen, Germany). Physicians quantified the severity of discharge, edema, NP, crusting and scarring of the olfactory cleft using a Likert score (range: 0–2) for each attribute. Results for each side were recorded separately and combined for a final Olfactory Cleft Endoscopy Scale (OCES; range: 0–20), with higher scores representing increased disease severity.[14] Bilateral visualization was not always possible in case subjects due to the presence of NP or severe nasal septum deviation.

All participants were asked to complete a self-administered survey of olfaction-related symptom severity and impact during baseline enrollment meetings. As a secondary outcome, responses to 17 negatively termed questions of the Questionnaire of Olfactory Dysfunction (QOD-NS) were compared between case and control subjects. The QOD-NS is a validated, olfactory-specific survey which summarizes Likert scale responses from 0 ("Disagree") to 3 ("Agree") whereas higher total scores (range: 0–51) represent higher global impacts of olfactory impairment.[15] Previous research using the QOD-NS applied to an outpatient population with smell and taste disorders has previously identified total scores of 12.5 or higher to reflect abnormal olfactory function.[16] Survey responses were also completed by case subjects both before ESS and approximately 6 months postoperatively.

Data Management and Biostatistics

All biostatistics were completed using SPSS software (version 26.0; IBM Corporation, Armonk, NY.). Two-sided t testing and Pearson's chi-square (χ^2) were selected to evaluate bivariate differences between case and control subjects. Unadjusted odds ratio (OR) values, with corresponding 95% confidence intervals (CIs), were also used to quantify relative effect sizes of olfactory diagnoses. Mean (±SD) within-subject postoperative differences were assessed using two-tailed paired samples t-testing in case subjects.

Multivariate logistic regression modeling was used to identify independent cofactors associated with TDI postoperative score improvement in cases equal to control subjects on average. Cofactor screening selected variables from Table 1 with univariate significance ($p < 0.200$). Final models manually controlled for enrollment location, age, and gender. Surgical procedures (Table 2) were also screened for univariate associations. Final models were built using forward inclusion of screened cofactors and manual, backwards elimination ($p < 0.010$) technique in a stepwise process. Goodness of final model fit was determined using Hosmer-Lemeshow (H-L) χ^2 statistics. Adjusted OR values with corresponding 95% CIs are reported with type-I error probabilities (p-values).

Results

Final Study Population and Surgical Intervention

Baseline enrollment was conducted between October, 2016 and May, 2019 which captured a total of 277 study participants who met inclusion criteria, consisting of 113/277 (41%) case subjects electing ESS and 164/277 (59%) control subjects without CRS. Comparisons of patient characteristics and comorbid conditions, between cases and controls, are described in Table 1. Overall, both case and control cohorts had similar average age and gender prevalence. Anticipated baseline

Table 1. Comparison of Patient Characteristics and Comorbid Conditions Between Case and Control Subjects.

Characteristics at Enrollment	Case Subjects With CRS (n=113)	Control Subjects Without CRS (n=164)	Test Statistics	Unadjusted OR	95% CI	P-Value
Age (years) [Mean ± SD]	50.2 ± 15.8	51.5 ± 17.3	t= 0.61	–	–	0.55
Males N (%)	53 (47%)	61 (37%)	χ^2= 2.60	0.67	0.41–1.09	0.11
Females	60 (53%)	103 (63%)				
White/Caucasian	102 (90%)	117 (71%)	χ^2= 14.47	3.73	1.84–7.56	<0.001
African American	7 (6%)	38 (23%)	χ^2= 14.17	0.22	0.09–0.51	<0.001
Asian	2 (2%)	4 (2%)	χ^2= 0.14	0.72	0.13–4.00	0.71
Hispanic/Latino ethnicity	6 (5%)	6 (4%)	χ^2= 0.44	1.48	0.46–4.70	0.51
Education years completed						
High School	32 (28%)	48 (29%)	χ^2= 0.16	–	–	0.92
Post-secondary/College/University	53 (47%)	73 (45%)				
Graduate/professional degree	28 (25%)	43 (26%)				
Nasal polyposis	61 (54%)	0 (0%)	χ^2= 113.53	0.24	0.19–0.31	<0.001
Previous sinus surgery/ESS	55 (49%)	0 (0%)	χ^2= 99.60	0.26	0.21–0.33	<0.001
Asthma	55 (49%)	14 (9%)	χ^2= 57.62	10.16	5.25–19.67	<0.001
Diabetes mellitus (Type I/II)	11 (10%)	15 (9%)	χ^2= 0.03	1.07	0.47–2.43	0.87
Depression (history/self-reported)	33 (29%)	27 (17%)	χ^2= 6.40	2.09	1.17–3.73	0.01
Anxiety (history/self-reported)	28 (25%)	20 (12%)	χ^2= 7.40	2.37	1.26–4.47	0.007
OSA	20 (18%)	15 (9%)	χ^2= 4.43	2.14	1.04–4.38	0.04
Smoking/tobacco use (current)	4 (4%)	19 (12%)	χ^2= 5.69	0.28	0.09–0.85	0.02
Alcohol use (current)	58 (52%)	99 (60%)	χ^2= 2.23	0.69	0.43–1.12	0.14
Allergic rhinitis	60 (53%)	49 (30%)	χ^2= 14.53	2.61	1.59–4.30	<0.001
GERD	33 (29%)	18 (11%)	χ^2= 14.80	3.35	1.77–6.32	<0.001
Oral corticosteroid use (past 30 days)	30 (27%)	1 (1%)	χ^2= 45.29	58.92	7.90–439.63	<0.001
TDI total score	22.0 ± 9.2	28.8 ± 7.0	t= 6.96	–	–	<0.001
Threshold score	3.6 ± 3.0	6.1 ± 2.7	t= 7.04	–	–	<0.001
Discrimination score	9.0 ± 3.5	10.9 ± 2.7	t= 4.80	–	–	<0.001
Identification score	9.4 ± 4.1	11.8 ± 2.8	t= 5.38	–	–	<0.001
OCES total score	4.3 ± 3.5	0.6 ± 1.1	t= -8.53	–	–	<0.001
QOD-NS total score	13.2 ± 10.5	4.4 ± 6.9	t= −7.83	–	–	<0.001
Olfactory diagnoses						
Normosmia	26 (23%)	83 (51%)	χ^2=21.36	0.29	0.17–0.50	<0.001
Hyposmia/microsmia	49 (43%)	71 (43%)	χ^2=<0.00	1.00	0.62–1.63	>0.99
Anosmia	38 (34%)	10 (6%)	χ^2=35.40	7.80	3.69–16.51	<0.001

SD, standard deviation; CRS, chronic rhinosinusitis; ESS, endoscopic sinus surgery; OSA, obstructive sleep apnea; GERD, gastroesophageal reflux disease; t, independent samples t-test statistic for unadjusted, between-subjects comparisons of average scores; χ^2, chi-square test statistic; reported p-values correspond to two-sided asymptotic significance; TDI, threshold, discrimination, identification; OCES, olfactory cleft endoscopy scale; QOD-NS, Questionnaire of Olfactory Dysfunction-Negative Statements; OR, odds ratio; CI, confidence interval of OR. Empty cells indicate that summary statistics are not applicable to the measure/characteristic listed.

differences between case and control subjects included the prevalence of NP, previous ESS, comorbidities, and recent oral corticosteroid use. Additional descriptions of surgical procedures completed for case subjects is provided in Table 2.

Comparing Baseline Factors Associated with Olfactory Function

Bivariate comparisons of average measures of olfactory function at enrollment were compared between case and control subjects without covariate adjustment (Table 1). Endoscopic visualization and staging for OCES were possible for 79 cases and 123 control subjects. Compared to control subjects, cases had significantly worse function across all measures of olfaction on average. The prevalence of anosmia was also significantly higher, and the prevalence of normosmia significantly lower, in case subjects with CRS (Table 1).

Postoperative Improvement in Case Subjects

Case subjects completed olfactory evaluations during routine clinical appointments an average of 7.0 (SD = 2.4) months postoperatively. Without covariate adjustment, case subjects reported statistically significant

postoperative improvement across all olfactory metrics (Table 3). The prevalence of anosmia in case subjects significantly decreased after ESS from 34% to 18% ($n = 20$; $\chi^2 = 14.40$) while the percentage of patients with normosmia increased from 23% to 39% ($n = 44$; $\chi^2 = 20.49$) and the prevalence of postoperative hyposmia remained unchanged at 43% for all case subjects ($p = 0.29$). Further description of outcome measures associated with postoperative olfactory diagnoses, stratified across preoperative olfactory categories, are described for case subjects (Table 4). While on average subjected reported improved olfaction, a smaller percentage reported worsen olfaction.

After ESS, case subjects reported olfactory measures slightly worse than those of control subjects on average for TDI total scores, threshold domain scores, OCES, and QOD-NS (Table 5). The prevalence of case subjects improving to at least average scores of control subjects after ESS for TDI total score was 51/113 (45%), 36/113 (32%) for threshold scores, 65/113 (58%) for discrimination scores, 61/113 (54%) for identification scores, 49/94 (52%) for OCES measures, and 55/108 (51%) for QOD-NS scores.

Table 2. Frequency of Surgical Procedures Completed For Case Subjects With CRS ($n = 113$).

Surgical Procedures	N (%)
Maxillary antrostomy	108 (96%)
Partial ethmoidectomy	12 (11%)
Total ethmoidectomy	100 (89%)
Sphenoidotomy	98 (87%)
Middle turbinate resection	55 (49%)
Inferior turbinate reduction	21 (19%)
Frontal sinusotomy (*Draf* 2a)	71 (63%)
Frontal sinusotomy (*Draf* 2b)	16 (14%)
Frontal sinusotomy (*Draf* 3)	15 (13%)
Septoplasty	37 (33%)
Image guidance	104 (92%)

N, sample size.

Multivariate Modeling of Postoperative Olfactory Status in CRS

Logistic regression modeling was completed within the case subject population to identify cofactors predictive of differences in postoperative improvement in olfactory function. Models were not adjusted for preoperative TDI measures due to evidence of multi-collinearity with nasal polyposis. Final multivariate modeling (Table 6) found that the presence of NP and previous ESS decreases the odd of postoperative olfactory improvement equal to at least that of control subjects on average, while concurrent septoplasty significantly improves the odds.

Discussion

Olfactory dysfunction is a "cardinal" symptom in CRS and affects the majority of patients with this disease.[7,8] Furthermore, patients identify OD as one of the top three most important symptoms in which they would like to see post-treatment improvement.[17] Prior work suggests that some amount of the OD seen in patient with CRS may be related to non-CRS factors such as age and medical comorbidity.[18] While ESS improves olfaction for certain patients, the results can be unpredictable and difficult to counsel patients surrounding post-operative expectation.[8] One primary limitation evident within the available literature on this subject is the lack of comparisons of OD in healthy, control populations. As such, previous findings of olfactory outcomes after ESS may be confounded by the fact that OD is multi-factorial and that some patients with CRS suffer from levels of OD similar to normative data.[18]

This study is the first attempt to our knowledge to compare ESS olfaction outcomes between a CRS cohort and a simultaneously recruited cohort of healthy individuals. In our control population with an average age of 51.5 (±17.3) years the mean TDI total score was 28.8 (Table 1), similar to normative data for patients

Table 3. Unadjusted, Within-Group Comparisons of Outcome Measures Before and After ESS in Case Subjects With CRS.

Outcome Measures	N	Preoperative Mean ± SD	Postoperative Mean ± SD	Difference Mean ± SD	95% CI	Test Statistic	P-Value
TDI total score	113	22.0 ± 9.2	25.7 ± 8.6	3.7 ± 8.2	2.2–5.2	t= −4.79	<0.001
Threshold	113	3.6 ± 3.0	4.4 ± 3.1	0.8 ± 3.4	0.2–1.5	t= −2.63	0.01
Discrimination	113	9.0 ± 3.5	10.5 ± 3.4	1.4 ± 3.7	0.7–2.1	t= −4.07	<0.001
Identification	113	9.4 ± 4.1	10.8 ± 3.6	1.4 ± 3.4	0.8–2.0	t= −4.40	<0.001
OCES	70	4.3 ± 3.5	2.6 ± 3.8	1.7 ± 3.8	0.8–2.7	t= 3.82	<0.001
QOD-NS	109	13.2 ± 10.5	7.3 ± 8.0	5.9 ± 8.7	4.3–7.6	t= 7.12	<0.001

ESS, endoscopic sinus surgery; SD, standard deviation; LL, lower limit; UL, upper limit; TDI, threshold, discrimination, identification; OCES, olfactory cleft endoscopy scale; QOD-NS, Questionnaire of Olfactory Dysfunction-Negative Statements. t, paired samples t-test statistic for within subject comparison; CRS, chronic rhinosinusitis; N, sample size; CI, confidence interval of average difference.

Table 4. Postoperative Olfactory Diagnoses Stratified Across Preoperative Olfactory Diagnoses in Case Subjects With CRS.

		Postoperative Olfaction		Mean Postoperative Improvement		
Preoperative Olfactory Classification/Category	Total N	Diagnosis	N (%)	TDI Total Score Mean ± SD	OCES Mean ± SD	QOD-NS Mean ± SD
Normosmia	26	Normosmia	20 (77%)	−0.1 ± 3.8	−1.5 ± 2.7	−4.1 ± 6.3
		Hyposmia / microsmia	6 (23%)	−5.6 ± 2.1	−3.7 ± 2.3	−3.3 ± 8.2
		Anosmia	0 (0%)	–	–	–
Hyposmia/microsmia	49	Normosmia	19 (39%)	7.7 ± 4.6	−1.8 ± 2.5	−10.5 ± 12.4
		Hyposmia / microsmia	24 (49%)	1.2 ± 5.2	0.4 ± 4.6	−4.5 ± 6.8
		Anosmia	6 (12%)	−10.5 ± 8.2	–	−4.8 ± 5.8
Anosmia	38	Normosmia	5 (13%)	21.6 ± 4.1	−3.4 ± 4.4	−13.3 ± 8.3
		Hyposmia / microsmia	19 (50%)	11.1 ± 4.5	−5.1 ± 2.9	−7.1 ± 8.0
		Anosmia	14 (37%)	1.4 ± 4.1	−1.2 ± 3.9	−2.0 ± 7.8

N, sample size; SD, standard deviation; TDI, threshold, discrimination, identification; OCES, olfactory cleft endoscopy scale; QOD-NS, Questionnaire of Olfactory Dysfunction-Negative Statements. Empty cells indicate that patient data was not available for that measure of interest.

Table 5. Average Postoperative Outcome Measures in Cases With CRS Compared to Control Subject Averages Without CRS.

Outcome Measures	Case Subject Postoperative Scores (n=113) Mean ± SD	Control Subjects (n=164) Mean ± SD	Difference Mean ± SE	95% CI	Test Statistic	P-Value
TDI total score	25.7 ± 8.6	28.8 ± 7.0	3.1 ± 0.9	1.2–5.0	t= 3.20	0.002
Threshold	4.4 ± 3.1	6.1 ± 2.7	1.6 ± 0.4	0.9–2.4	t= 4.62	<0.001
Discrimination	10.5 ± 3.4	10.9 ± 2.7	0.5 ± 0.4	−0.3 to 1.2	t= 1.18	0.24
Identification	10.8 ± 3.6	11.8 ± 2.8	1.0 ± 0.4	0.2–1.8	t= 2.50	0.01
OCES	2.6 ± 3.8	0.6 ± 1.1	2.0 ± 0.3	0.9–2.4	t= 4.50	<0.001
QOD-NS	7.3 ± 8.0	4.4 ± 6.9	2.8 ± 0.9	1.0–4.7	t= 3.03	0.003

CRS, chronic rhinosinusitis; SD, standard deviation; SE, standard error; CI, confident interval of the mean difference; TDI, threshold, discrimination, identification; OCES, olfactory cleft endoscopy scale; QOD-NS, Questionnaire of Olfactory Dysfunction-Negative Statements.

Table 6. Final, Adjusted Logistic Regression Model for TDI Total Score Improvement in Case Subjects With CRS Equal to That of Control Subjects on Average.

Cofactors	OR	95% CI	P-Value	H-L Test (P-Value)
Enrollment location	0.59	0.39–0.89	0.01	χ^2=8.12
Age	0.98	0.95–0.1.01	0.19	(p=0.42)
Gender	2.00	0.77–5.17	0.15	
Preoperative nasal polyposis	0.40	0.16–1.01	0.05	
Previous sinus surgery / ESS	0.31	0.11–0.82	0.02	
Septoplasty during ESS	4.49	1.48–13.65	0.008	

OR, odds ratio; CRS, chronic rhinosinusitis; CI, confidence interval of OR; H-L, Hosmer-Lemeshow test statistic for goodness of model fit; ESS, endoscopic sinus surgery.

aged >55 years (mean: 29.8) and lower, as expected, than values for groups containing younger patients.[12] This suggests that a degree of OD, which is independent of sinonasal disease, may exist in similar control populations. Controlling for CRS alone would likely not improve olfactory function above that of a non-CRS cohort. Our data show that the majority of patients can expect some degree of improvement in OD after ESS, which is consistent with prior studies.[8] Additionally, up to 50% of patients can expect a return of smell function to a degree comparable to those without CRS and patients with NP and those

with a history of previous ESS were less likely to achieve normal, control-like levels of olfaction.

The primary issue this study addresses is how likely a CRS patient is to achieve a level of olfaction postoperatively that is comparable to healthy control subjects. Our data found that cases without NP (CRSsNP) are most likely to achieve olfaction similar to controls. This does not infer however that all CRSsNP patients regained normal olfaction postoperatively. In fact, 49% of our control population was either anosmic or hyposmic. Therefore, even if all CRSsNP related OD is resolved, many patients with CRS would still not regain normosmia.

Several prior studies have suggested that the presence of NP is associated with increased olfactory improvement postoperatively.[8,19,20] This has been corroborated by both recent international consensus guidelines and meta-analyses, which evaluated multiple subjective and objective measures of olfaction.[10,21] The current finding that NP is associated with a lower likelihood of attaining control-like olfaction is interesting. This suggests some degree of on-going OD which may be related to persistent inflammation or it may reflect a more permanent change to the olfactory mechanism. Taken together, this suggests that patients with NP are likely to experience improved olfaction after ESS but remain unlikely to achieve control-like olfactory function. For example, removal of physical obstruction may permit an improvement in olfaction due to maximized ventilation to the olfactory cleft, but chronic inflammation may have injured the olfactory epithelium which is less easily reversed with ESS. Revision surgery also seems to predict a lower likelihood of return to control-like levels of olfaction. This may represent a marker of more severe or refractory disease, but it is also possible that these patients are more likely to have more permanent olfactory loss, whether from long-standing disease or prior surgical intervention.

The performance of concomitant septoplasty at the time of ESS seems to improve the odds of achieving control-like olfactory functioning. Septoplasty, concurrent within ESS, has also been linked to improved surgical outcomes and a decreased rate of revision surgery.[22] This may relate to improved topical steroid delivery or improved airflow to the olfactory cleft. These multivariate findings, coupled with an understanding of the multi-factorial nature of OD in CRS, allows us to better counsel patients on expected surgical outcomes and may help guide surgical decision-making.

Limitations

For the cases and controls, while the data were prospectively gathered in a multi-institutional cohort, these patients were recruited from tertiary care rhinology clinics at academic medical centers, and may not be representative of the broader population. This study also has an average follow-up time period of 7 months which may limit our observed benefit of ESS in the setting of a chronic disease. While longer follow-up may better elucidate postoperative olfactory outcomes, it may result in worse subject retention. While the control group was similar in distribution of age and gender to the cases, there are several differences between case and control populations which need to be considered. Cases had higher rates of anxiety/depression, reflux disease, and allergic rhinitis, and lower rates of smoking, than the control group. These comorbidities may associate with worse postoperative olfactory outcomes among case subjects. Additionally, the control group did not undergo any sinonasal surgical procedure. Targeting patient groups who underwent sinonasal surgery, such as pituitary adenoma resection or septorhinoplasty, may be a viable alternative as a control population. Future investigations should also involve larger population samples from diverse practice settings.

Conclusions

Endoscopic sinus surgery improves most olfactory metrics in CRS patients. However, patient and surgeon expectations should be that OD improvement cannot be greater than control-like levels of olfaction. Patients with CRSsNP and those who undergo concomitant septoplasty are more likely to reach this threshold, while patients with nasal polyps and prior surgery are less likely to do so. ESS restored olfaction in CRS patients to levels similar to controls in half of the cases.

Declaration of Conflicting Interests

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References

1. Mattes RD, Cowart BJ. Dietary assessment of patients with chemosensory disorders. *J Am Diet Assoc*. 1994;94(1):50–56.
2. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life-an updated review. *Chem Senses*. 2014;39(3):185–194.
3. Liu B, Luo Z, Pinto JM, et al. Relationship between poor olfaction and mortality among community-dwelling older adults: a cohort study. *Ann Intern Med*. 2019;170(10):673–681.
4. Kohli P, Soler ZM, Nguyen SA, Muus JS, Schlosser RJ. The association between olfaction and depression: a systematic review. *Chemse*. 2016;41(6):479–486.
5. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis executive summary. *Otolaryngol Head Neck Surg*. 2015;152(4):598–609.
6. Orlandi RR, Kingdom TT, Hwang PH, et al. International consensus statement on allergy and rhinology: rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6(Suppl 1):S22–S209.
7. Kohli P, Naik AN, Harruff EE, Nguyen SA, Schlosser RJ, Soler ZM. The prevalence of olfactory dysfunction in chronic rhinosinusitis. *Laryngoscope*. 2017;127(2):309–320.
8. Haxel BR. Recovery of olfaction after sinus surgery for chronic rhinosinusitis: a review. *Laryngoscope*. 2019;129(5):1053–1059.
9. Banglawala SM, Oyer SL, Lohia S, et al. Olfactory outcomes in chronic rhinosinusitis with nasal polyposis after medical treatments: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. 2014;4(12):986–994.
10. Kohli P, Naik AN, Farhood Z, et al. Olfactory outcomes after endoscopic sinus surgery for chronic rhinosinusitis: a meta-analysis. *Otolaryngol Head Neck Surg*. 2016;155(6):936–948.
11. Kobal G, Hummel T, Sekinger B, Barz S, Roscher S, Wolf S. "Sniffin' sticks": screening of olfactory performance. *Rhinology*. 1996;34(4):222–226.
12. Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the "sniffin sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. *Eur Arch Otorhinolaryngol*. 2007;264(3):237–243.
13. 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(3):719–728.
14. Soler ZM, Hyer JM, Karnezis TT, Schlosser RJ. The olfactory cleft endoscopy scale correlates with olfactory metrics in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6(3):293–298.
15. Simopoulos E, Katotomichelakis M, Gouveris H, Tripsianis G, Livaditis M, Danielides V. Olfaction-associated quality of life in chronic rhinosinusitis: adaptation and validation of an olfaction-specific questionnaire. *Laryngoscope*. 2012;122(7):1450–1454.
16. Frasnelli J, Hummel T. Olfactory dysfunction and daily life. *Eur Arch Otorhinolaryngol*. 2005;262(3):231–235.
17. Mattos JL, Rudmik L, Schlosser RJ, et al. Symptom importance, patient expectations, and satisfaction in chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2019;9(6):593–600.
18. Schlosser RJ, Smith TL, Mace JC, et al. Factors driving olfactory loss in patients with chronic rhinosinusitis: a case control study. *Int Forum Allergy Rhinol*. 2020;10(1):7–14.
19. Litvack JR, Mace J, Smith TL. Does olfactory function improve after endoscopic sinus surgery? *Otolaryngol Head Neck Surg*. 2009;140(3):312–319.
20. Soler ZM, Sauer DA, Mace JC, Smith TL. Ethmoid histopathology does not predict olfactory outcomes after endoscopic sinus surgery. *Am J Rhinol Allergy*. 2010;24(4):281–285.
21. Fokkens WJ, Lund VJ. Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps 2020. *Rhin* . 2020;58(1):1–464.
22. Rudmik L, Xu Y, Alt JA, et al. Evaluating surgeon-specific performance for endoscopic sinus surgery. *JAMA Otolaryngol Head Neck Surg*. 2017;143(9):891–898.