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ORIGINAL ARTICLE

Orthonasal and retronasal olfactory function in patients with chronic rhinosinusitis without nasal polyps undergoing endoscopic sinonasal surgery

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Abstract

Background: Olfactory dysfunction (OD) is a key symptom of chronic rhinosinusitis (CRS). Although extensively studied in CRS with nasal polyps (CRSwNP), OD in CRS without nasal polyps (CRSsNP) remains under-researched. This study aims to assess the prevalence of OD and its evolution in surgically naïve patients with CRSsNP undergoing endoscopic sinus surgery (ESS).

Methods: This prospective study included 97 participants with CRSsNP (mean age, 46.5 years; 70.1% men) and 97 healthy controls (mean age, 46.5 years; 70.1% men). Participants underwent psychophysical evaluations of orthonasal (using the Sniffin' Sticks test) and retronasal olfaction (using powdered aromas) at enrolment and 6 months post-ESS.

Results: Out of 97 patients, 81 (83.5%) completed all assessments. At enrolment, 23 (28.4%) CRSsNP patients had OD based on composite threshold, discrimination, identification scores, compared with 7 (8.6%) controls (absolute % difference, 19.8% [95% CI, 8.2–31.4]). Retronasal olfactory function was also significantly worse in CRSsNP patients. Six months post-ESS, 30 patients (37.0%) experienced a clinically significant improvement in olfactory, whereas nonsignificant changes were observed in retronasal olfactory score, and 3.7% of patients experienced a deterioration of the olfactory function.

Conclusions: In conclusion, although 37% of patients experienced a clinically significant improvement in their sense of smell following ESS, the overall prevalence of OD in this surgically naive population appears relatively low, especially when compared to that observed in patients with CRSwNP. Therefore, ESS may offer some benefits for enhancing orthonasal olfactory function, but the extent of these improvements appears to be limited.

KEYWORDS
anosmia, chronic rhinosinusitis, CRSsNP, endoscopic sinus surgery, smell

1 | INTRODUCTION

Chronic rhinosinusitis (CRS) is a highly prevalent inflammatory disease affecting the nasal mucosa and paranasal sinuses.[1] The prevalence of CRS in Europe and the United States measured in epidemiologic study is around 10%,[2,3] whereas the prevalence based on sinus radiology and symptomatology was estimated to be 3%–6%.[4] CRS is characterized by symptoms persisting for at least 12 weeks, including facial pain or pressure, nasal discharge, congestion, and olfactory dysfunction (OD).[1] The condition is typically classified into two main phenotypes: CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP), which differ with regards to symptoms, CT findings, treatments, and risks of recurrence and comorbid asthma.[5] Additionally, based on the inflammatory pathway, CRS can be further stratified into two main endotypes. In Western countries, around 80% of patients with CRSwNP have a Type 2 inflammatory signature,[6] whereas only 50% of patients with CRSsNP have a Type 2 inflammatory reaction, but less pronounced than in CRSwNP.[7]

OD, while often considered trivial, can severely impact patients' quality of life, leading to mood changes, difficulties with food enjoyment, safety concerns, and challenges in social interactions.[8,9] However, particularly following the SARS-CoV-2 pandemic, the importance of OD has gained increased recognition.[10,11] The pathophysiology of OD in CRS is complex, involving conductive problems, inflammation of the olfactory neuroepithelium, and potential central nervous system abnormalities.[12] Current treatment options include topical or systemic corticosteroid administration, surgery, and more recently biologic therapies targeting Type 2 inflammation, with medical therapy being more supported by evidence in CRSwNP.[1,13] Although OD has been extensively studied in CRSwNP patients, with reported prevalence rates over 90%,[14] there is a significant gap in our understanding of OD in CRSsNP patients. Studies conducted so far to evaluate OD in patients with CRSsNP offer only limited insights, either because they do not classify this phenotype as a separate subgroup in their analyses[14,15] or rely on self-assessments[7] or limited psychophysical tests focusing solely on odor identification skills.[16]

Previous investigations have observed that the prevalence of measured OD in mixed CRS populations strongly depends on the psychophysical evaluation method used and varies from 30% using brief odor identification tests to 78% when using the extended Sniffin' Sticks test (SST) battery.[14] Therefore, it is essential to assess the prevalence of OD in the distinct phenotype of CRSsNP through a comprehensive evaluation of olfactory function.

Furthermore, evaluating the impact of endoscopic sinus surgery (ESS) on olfactory function in CRSsNP patients is crucial, despite the lower prevalence of OD compared to CRSwNP, as patients with CRSsNP currently cannot benefit from biological therapies, which have shown outstanding results in managing OD in CRSwNP patients,[17] as the use of biologics is not licensed in this group.

The aim of this study was to address this knowledge gap by conducting a prospective study, including a healthy control group, to assess the prevalence of OD and its evolution after ESS in patients with CRSsNP.

2 | METHODS

2.1 | Study design

This prospective study was conducted in accordance with the Declaration of Helsinki guidelines and received approval from the ethics committee for clinical experimentation at Trieste University Hospital. All participants provided both verbal and written informed consents.

Ninety-seven cases (mean [SD] age, 46.5 [12.6] years; 68 [70.1%] men) were recruited prospectively from the University Hospital of Trieste, Italy, and Treviso General Hospital, Italy, from May 2021 to December 2023. Inclusion criteria for cases were adults aged 18–70 years with a diagnosis of CRSsNP and appropriate candidacy for ESS. The diagnosis of CRSsNP, including unilateral and bilateral disease, was confirmed on clinical symptoms, nasal endoscopy, and CT imaging. Both the diagnosis of CRSsNP and the indication for ESS were based on guidelines published in the EPOS 2020.[1] A procedure was classified as ESS if at least one sinus was surgically treated. Patients who also underwent concurrent septoplasty and/or turbinate surgery were considered eligible.

All patients were advised to perform nasal irrigation with saline solutions for at least 1-month post-ESS. Conversely, due to the limited evidence supporting their efficacy in the treatment of CRSsNP, the use of oral corticosteroids was not recommended,[1,18] whereas the use of topical steroids was determined on an individualized basis by the ENT surgeon.

Ninety-seven controls (mean [SD] age, 46.5 [12.3] years; 68 [70.1%] men) were recruited on voluntary basis from the staff of Trieste University Hospital and Treviso General Hospital. Cases were matched 1:1 with controls for sex and age (±3 years). The inclusion criteria for healthy control subjects included no history of recurrent acute or CRS and any other nose/sinus disorders.

The study excluded individuals with CRSwNP, odontogenic sinusitis, secondary CRS, diagnosis of aspirin-exacerbated respiratory disease, allergic fungal sinusitis, cystic fibrosis, immunosuppression, previous ESS, a history of head trauma, congenital anosmia, post-viral OD, or neurodegenerative disorders such as Alzheimer's or Parkinson's disease.

The study sample size was calculated on the primary outcome, that is, the prevalence of threshold, discrimination, identification (TDI) composite score <30.75. Assuming the a priori error probabilities $\alpha = 0.05$ and $\beta = 0.20$, at least 77 patients per group are required to detect an absolute difference of 17.5% through the Z-test (expected prevalence: $p_{\text{controls}} = 0.10$ and $p_{\text{cases}} = 0.275$). To account for a lost-at-follow-up rate of 20%, the sample size was increased to 97 cases and 97 controls.

2.2 | Clinical and survey-based indicators of disease severity

A practicing rhinologist performed sinonasal endoscopy with the use of 2.7–4.0-mm-diameter rigid endoscopes and preoperative bilateral assessments of the paranasal sinuses by reviewing CT scans in the coronal plane. The Lund–Kennedy score evaluated five endoscopic parameters (polyps, edema, drainage, crusting, and scarring) for each side of the nose, assigning a rating between 0 and 2, for a maximum total score of 20 points.[19] CT findings were quantified using the Lund–Mackay scoring system.[20] The Lund–Mackay staging system scores each sinus (anterior ethmoid, posterior ethmoid, maxillary, frontal, and sphenoid sinuses) according to the following scale: 0 (no opacification), 1 (partial opacification), or 2 (complete opacification). The ostiomeatal complex is scored as 0 (not occluded) or 2 (occluded). Left and right sides are staged separately, and the scores are summed so that the total Lund score may range from 0 to 24 for each patient. Sinonasal health-related quality of life was assessed using SNOT-22 score. The SNOT-22 questionnaire, consisting of 22 items each rated from 0 to 5, has a total possible score ranging from 0 to 110, with higher scores indicating poorer quality of life. Both Lund–Kennedy and Lund–Mackay staging scores were recorded at enrolment, whereas the SNOT-22 was recorded at enrolment and 6 months after ESS. A change in SNOT-22 score of 8.9 points is generally regarded as the minimal clinically important difference. Controls underwent a brief medical examination, including nasal endoscopy to confirm the absence of CRS and other sinonasal diseases.

2.3 | Evaluation of the nasal patency

To assess nasal obstruction, the peak nasal inspiratory flow (PNIF) was measured using the in-check portable inspiratory flow meter (GM Instruments). Measurements were taken with a tight-fitting anesthetic mask that preserved the natural shape of the nose. Patients were asked to inhale as forcefully and quickly as possible through the mask while keeping their mouths closed. During formal testing, each patient completed three seated trials at maximum effort. The highest flow rate (liters per minute [L/min]) from these three attempts was recorded.

2.4 | Self-assessment of chemosensory perception

Participants self-evaluated their olfactory ability by answering the question, "How would you rate your sense of smell?" They used a 10 cm olfaction visual analog scale (VAS), with 0 representing no perception and 10 indicating excellent perception. The experimental group (cases) provided self-assessments at enrolment and 6 months after ESS, whereas the control group only assessed at enrolment.

2.5 | Psychophysical evaluation

Assessments were conducted in quiet, well-ventilated rooms. The experimental group underwent evaluations at enrolment and 6-month post-ESS, whereas the control group was assessed only at enrolment. To prevent chemosensory desensitization, all participants were instructed to refrain from eating, drinking, smoking, or brushing their teeth for at least 2 h prior to the evaluation.

2.6 | Orthonasal olfactory function

Orthonasal olfactory function was measured using the validated extended SST battery (Burghart Messtechnik), including phenylethyl alcohol odor thresholds (T), odor discrimination (D), and odor identification (I).[21] The maximum score for each of the three subsections of the SST is 16. Results are combined for a composite TDI score

(range 1–48) and categorized as anosmia (TDI ≤ 16.0), hyposmia (16.25–30.5), or normosmia (TDI ≥ 30.75).[22] A compromised orthonasal identification ability was defined as a score <12.[23] An variation in TDI score of at least 5.5 points was considered clinically significant.[24] The test has been validated and shown to have high test–retest reliability.[25] Testing was performed by a standardized testing protocol.[21]

2.7 | Retronasal olfactory function

Retronasal olfactory function was tested using 20 tasteless grocery store condiments and food items available in powder form as described by Heilmann et al.[26] For each trial, participants were blindfolded and occluded their nostrils before delivering each stimulus, in powdered form (approximately 0.05 g), to the mid-dorsal section of the participant's anterior tongue. The tongue was withdrawn into the mouth, the nostrils were unblocked, and participants then exhaled through their nostrils. After exhalation, participants identified the odor from a list of four verbal descriptors. The total score ranged between 0 and 20 and was based on the sum of correctly identified flavors. A compromised retronasal smell was defined as a score <12.[23]

2.8 | Statistical analysis

Statistical analysis was carried out using GraphPad Prism version 8.4.3 (GraphPad Software Inc.). Standard descriptive statistics were used to characterize the study sample. Comparisons between groups were performed using *t* test for unpaired and pair samples. The intervention effect was estimated as absolute differences before and after the intervention, with corresponding 95% confidence intervals (CIs). Pearson's correlation coefficient was used to evaluate the correlation among the variables.

3 | RESULTS

Of 97 patients initially recruited, 81 (83.5%) completed all assessments and were included in the final analysis. Thus, the study cohort comprised 81 patients with CRSsNP (mean [SD] age, 46.0 [12.9] years; 56 [69.1%] men) and 81 matched healthy controls (mean [SD] age, 46.0 [12.5] years; 56 [69.1%] men). Seventy-eight patients (96.3%) had undergone at least one course of topical corticosteroid therapy in the year preceding surgery.

3.1 | Indicators of disease severity

Among the 81 patients, the majority had bilateral disease, accounting for 73 patients (90.1%). At enrolment, patients with CRSsNP demonstrated significant sinonasal disease, with a mean (SD) Lund–Kennedy endoscopic score of 3.8 (2.5) and a mean (SD) Lund–Mackay CT score of 7.5 (4.9). The mean (SD) SNOT-22 score was 46.5 (22.0), indicating substantial disease-specific quality of life impairment (Table 1). Additionally, the mean (SD) PNIF for patients was significantly lower at 87.4 (36.1) compared to 128.1 (41.4) in healthy controls, with an absolute difference of 40.8 (95% CI, 28.8–52.9). The analysis of the correlation matrix (Figure S1) revealed that TDI exhibited moderate positive correlations with PNIF (Pearson $r = 0.45$) and a strong negative correlation with the Lund-Mackay radiograph score (Pearson $r = -0.68$).

3.2 | Prevalence of olfactory dysfunction

Healthy controls reported significantly higher self-rated olfactory function compared with cases (mean [SD] olfaction VAS score, 8.3 [1.4] vs. 5.9 [2.9]; mean difference, 2.5 [95% CI, 1.8–3.2]) (Table 1). Cases obtained significantly worse scores in all domains of psychophysical assessment compared to controls (Table 1). Psychophysical assessment revealed a mean (SD) TDI score in CRSsNP patients of 32.8 (6.5) compared with 36.4 (4.0) in controls (mean difference, −3.7 [95% CI, −5.4 to −2.0]). Based on TDI scores, 23 (28.4%) CRSsNP patients were classified as hyposmic/anosmic compared with 7 (8.6%) controls (absolute difference, 19.8% [95% CI, 8.2–31.4]) (Figure 1). Retronasal olfactory function was also significantly worse in CRSsNP patients (mean [SD] retronasal score, 15.1 [3.5] vs. 17.3 [3.1] in controls; difference, −2.2 [95% CI, −3.1 to −1.3]), with 13 (16.0%) patients demonstrating compromised retronasal smell (score < 12).

3.3 | Changes in olfactory function after ESS

All cases underwent ESS under general anesthesia. The types of sinus surgical procedures performed are detailed in Table 2. Additionally, concurrently with ESS, 26 patients (32.1%) underwent both septoplasty and turbinate surgery, whereas 19 patients (23.5%) underwent only septoplasty, and 5 patients (6.1%) underwent only turbinate surgery. Changes in olfactory function after ESS are reported in Figures 1 and 2 and Table S1.

TABLE 1 Sociodemographic and clinical characteristics of cases and age- and sex-matched healthy controls at enrolment.

Characteristic	Cases at enrolment	Healthy controls	Difference (95% CI)[a]
Participants, *n*	81	81	
Age, mean (SD), year	46.0 (12.9)	46.0 (12.5)	
Male sex, no. (%)	56 (69.1)	56 (69.1)	
Ethnicity			
White non-Hispanic	81 (100)	81 (100)	0.0 (0.0–0.0)
Smokers, no. (%)	26 (32.1)	29 (35.8)	3.7 (−18.3 to 10.9)
Olfaction VAS score, mean (SD)	5.9 (2.9)	8.3 (1.4)	2.5 (1.8–3.2)
Orthonasal olfactory function, mean (SD)			
Threshold	7.2 (2.5)	9.0 (3.1)	1.8 (0.9–2.7)
Discrimination	12.8 (2.7)	13.7 (1.2)	0.9 (0.2–1.6)
Identification	12.7 (3.2)	13.7 (1.5)	1.0 (0.2–1.7)
TDI composite score	32.8 (6.5)	36.4 (4.0)	3.7 (2.0–5.4)
Retronasal identification score, mean (SD)	15.1 (3.5)	17.3 (2.1)	2.2 (1.3–3.1)
Orthonasal identification score < 12, no. (%)	16 (19.8)	7 (8.6)	−11.2 (−21.8 to −0.6)
TDI composite score < 30.75, no. (%)	23 (28.4)	7 (8.6)	−19.8 (−31.4 to −8.2)
Retronasal identification score < 12, no. (%)	13 (16.0)	3 (3.7)	−11.1 (−19.8 to −2.3)
PNIF, mean (SD), L/min	87.4 (36.1)	128.1 (41.4)	40.8 (28.8–52.9)
Preoperative score, mean (SD)			
SNOT-22	46.5 (22.0)	NA	
Lund–Kennedy endoscopy	3.8 (2.5)	NA	
Lund–Mackay radiograph	7.5 (4.9)	NA	

Abbreviations: CI, confidence interval; PNIF, peak nasal inspiratory flow; TDI, threshold, discrimination, identification; VAS, visual analogue scale.
[a]Mean difference for continuous variables: absolute percent difference for categorical variables.

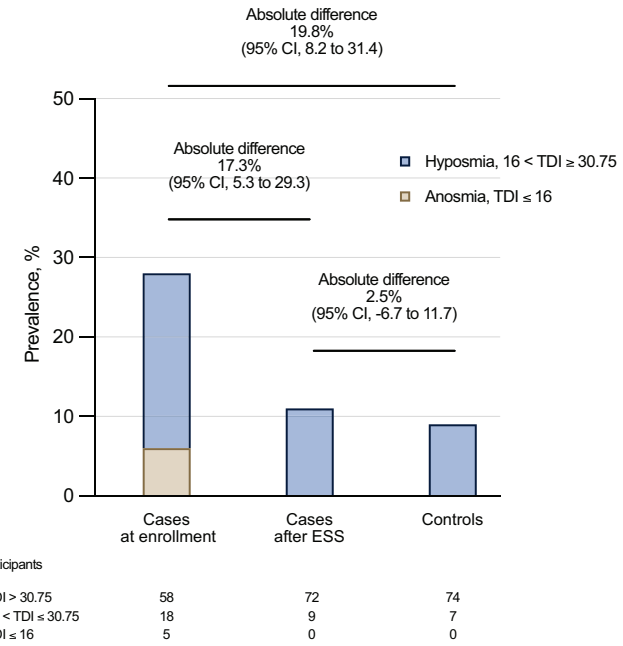

FIGURE 1 Prevalence of psychophysically assessed olfactory orthonasal dysfunction according to threshold, discrimination, identification (TDI) score. CI, confidence interval; ESS, endoscopic sinus surgery.

TABLE 2 Distribution of endoscopic sinus surgery procedures.

Procedure	No.	%
Maxillary antrostomy	71	87.7
Partial ethmoidectomy	15	18.5
Total ethmoidectomy	48	59.3
Sphenoidotomy	19	23.5
Frontal sinusotomy	24	29.6
Inferior turbinate reduction	31	38.3
Septoplasty	45	55.6

Post-operatively, 70 patients (86.4%) used topical steroids. Six-month post-ESS, CRSsNP patients showed significant improvement in self-reported olfactory function (mean [SD] olfaction VAS score increase, 1.3; 95% CI, 0.4–2.2). Orthonasal olfactory function also improved significantly, with a mean (SD) TDI score increase of 4.0 (95% CI, 2.5–5.5). The distribution of olfactory function categories improved after ESS. Prior to surgery, 23 patients (28.4%) were classified as hyposmic (18 patients) or anosmic (5 patients) based on TDI score. At 6-month post-ESS, this number decreased to 9 hyposmic patients (11.1%), with the remaining 72 (88.9%) patients classified as normosmic, making the prevalence of OD in cases

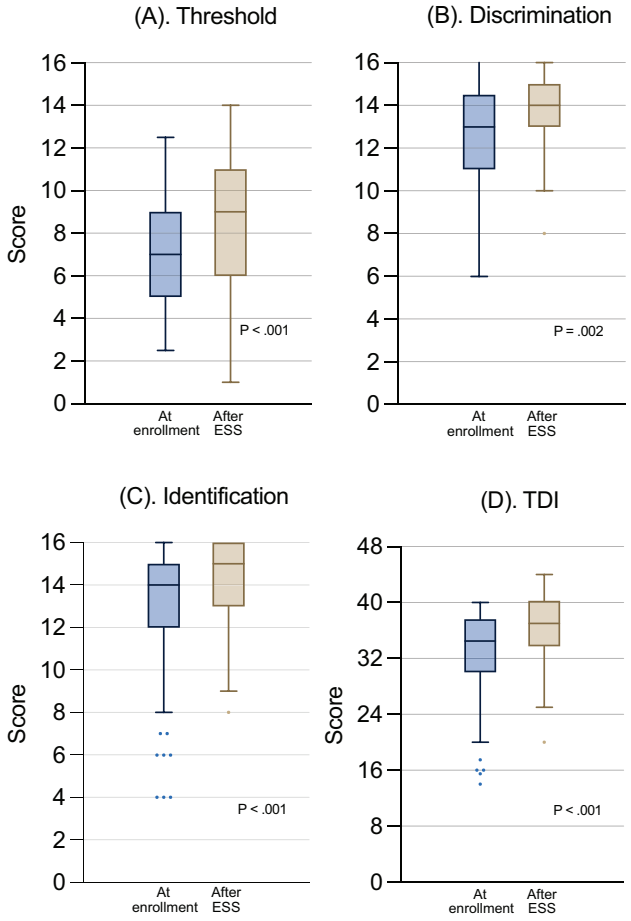

FIGURE 2 Box and whiskers representing ratings for threshold (A), discrimination (B), identification (C), and composite threshold, discrimination, identification (TDI) score (D) in cases at enrolment and 6 months after endoscopic sinus surgery (ESS). The horizontal line in each box indicates the median, and the top and bottom borders of each box indicate the 25th and 75th percentiles, respectively. The whiskers above and below each box indicate the minimum and maximum, respectively. The circles beyond the whisker represent outliers that are 1.5 more than the upper quartile or 1.5 less than the lower quartile.

after ESS comparable to that observed in the controls (Figure 1). Overall, 30 patients (37.0%) experienced a clinically significant improvement in olfactory function 6 months after ESS, as indicated by an increase in TDI score of 5.5 or more, whereas 3 patients (3.7%), normosmic at enrolment, exhibited a significant deterioration in their sense of smell following surgery. Nonsignificant changes were observed in retronasal olfactory score, with a mean score increase of 0.4 (95% CI, −0.4 to 1.3).

3.4 | Changes in nasal patency and quality of life outcomes

The mean PNIF increased by 40.9 L/min after ESS (95% CI, 33.2–48.5). Improvements in TDI scores after surgery correlated positively with an increase in nasal patency (Pearson r = 0.57; 95% CI, 0.41–0.71; R squared = 0.33) (Figure S2). A mean PNIF increased by 47.4 L/min was observed in patients undergoing concurrent septoplasty and/or turbinate surgery compared with 30.3 observed in patients who did not undergo septoplasty and/or turbinate surgery (mean difference, 17.1 [95% CI, 1.8–32.4]). A greater, yet nonsignificant, mean increase of 4.7 points in the TDI score was observed in patients who underwent concurrent septoplasty, compared to a 3.1-point increase in those who did not undergo this procedure (mean difference, 1.67; 95% CI, −1.49 to 4.8). The mean SNOT-22 score decreased by 14.9 points post-ESS (95% CI, −18.3 to −11.5), with 62 (76.6%) patients achieving the minimal clinically important difference of 8.9 points or greater.

4 | DISCUSSION

The findings of this study highlight the significant prevalence of OD in patients with CRSsNP and the potential benefits of ESS in improving olfactory function. At enrolment, surgically naïve CRSsNP patients exhibited significantly reduced olfactory function compared to healthy controls, as evidenced by both self-reported measures and comprehensive psychophysical assessments.

Our results demonstrate indeed that OD is a common symptom in CRSsNP, affecting approximately 28% of patients. Although this prevalence is significantly lower than in CRSwNP, where OD affects approximately 70%–90% of patients[6,14,17] and about 75% are classified as anosmic based on UPSIT psychophysical assessments,[17] it still represents a substantial proportion of patients with CRSsNP. Patients with CRSwNP were indeed observed to have a composite TDI score approximately 10 points lower than patients with CRSsNP.[27] Studies focusing specifically on CRSsNP patients have reported prevalence rates ranging from 17%[16] to 44%.[28] The variation in our prevalence rate of OD compared to the higher estimate (44%) and the observed higher overall TDI scores compared with previous reports[27–29] may be explained by differences in patient characteristics, including the exclusion of previously operated patients in our study, a younger average age, and the lower disease severity, as evidenced by the comparison of Lund–Mackay scores. Consistently, a strong negative correlation was observed in the present study between Lund–Mackay radiograph score and TDI at enrolment, suggesting that olfactory function is inversely related to the severity of radiographic sinonasal disease.

The significant improvements in olfactory function observed 6-month post-ESS are encouraging. The mean

TDI score increase of 4.0 points and the 17% reduction in the prevalence of OD demonstrate the potential of ESS as an effective intervention for OD in CRSsNP. Notably, 37% of patients experienced a clinically significant improvement in olfactory function, whereas only 3.7% showed a significant deterioration in their sense of smell following surgery. These improvements, coupled with the significant enhancement in nasal patency and quality of life, provide support for considering ESS as a therapeutic option in CRSsNP patients with olfactory complaints, although normosmia was not restored in all patients.

These results are consistent with findings reported in a recent study, which highlighted that patients with CRSsNP benefit more from surgery in terms of olfactory recovery compared to patients with CRSwNP.[29] A key driver of OD in patients with CRSwNP is the Type 2 inflammatory signature that characterizes the predominant CRSwNP endotype in Western populations.[5] The mediators of Type 2 inflammation appear to directly compromise the integrity of the olfactory neuroepithelium. In CRSwNP, therefore, OD could stem from both conductive issues and inflammation-induced damage to the olfactory neuroepithelium. Notably, patients with CRSwNP exhibit improvements in olfactory function when treated with biological drugs targeting Type 2 inflammatory signatures, particularly Dupilumab, a monoclonal antibody specifically targeting and interfering with the signaling pathways of both IL-4 and IL-13, key cytokines involved in Type 2–mediated inflammatory responses.[17] These improvements occur independently of the drugs' effects on nasal patency, highlighting the critical role of specific inflammatory signatures in the pathogenesis of CRSwNP-associated OD.[30] Conversely, in patients with CRSsNP, OD may predominantly result from conductive issues. In these cases, ESS could potentially resolve the olfactory impairment by addressing the mechanical obstruction. This hypothesis is supported by our observation that improvements in TDI scores after surgery correlated positively with an increase in nasal patency, indicating a strong relationship between restored nasal airflow and improved olfactory function in these patients. Patients who underwent concurrent septoplasty and/or turbinate surgery experienced a greater improvement in nasal airflow compared to those who did not undergo these additional procedures. In this regard, a previous study on patients undergoing surgical treatment for CRS demonstrated that concurrent septoplasty significantly increased the likelihood of achieving normal olfaction.[29] However, in the present investigation, although a larger increase in the TDI score was observed in patients who had undergone concurrent septoplasty compared to those who had not, the difference was not statistically significant, likely due to the reduced statistical power.

Previous studies on retronasal olfactory function in patients with CRS have shown that this sensory modality is more significantly impaired in CRSwNP compared to CRSsNP.[31] An interesting aspect of our findings is the discrepancy between improvements in orthonasal and retronasal olfaction following ESS. Although retronasal olfactory function was less compromised at enrollment, it did not show significant improvement following ESS. This differential response warrants further investigation and may have implications for patient counseling and expectations regarding post-surgical outcomes. This discrepancy might be due to several factors: different mechanisms mediate orthonasal and retronasal olfaction; although surgery can clear obstructions and reduce inflammation in the nasal passages, it may not sufficiently address factors affecting retronasal olfaction. Persistent inflammation and changes in the mucosal lining, even after surgery, might continue to impair retronasal olfaction.

Moreover, future research should investigate the potential of intranasal corticosteroids administered through devices that enhance drug distribution to the olfactory neuroepithelium, which were not employed in this study.[32–34]

This study has several limitations worth noting. One is the lack of endotype characterization. Although previous studies based on olfactory assessment using the olfaction VAS score did not find differences in self-reported OD between Type 2 and non-Type 2 endotypes in CRSsNP,[7] other investigations observed that the presence of OD was significantly associated with the presence of T2 endotype also in patients with CRSsNP.[35] The follow-up period of 6 months, although providing valuable short-term data, may not capture long-term changes in olfactory function following ESS. A longer follow-up period would be beneficial to assess the durability of improvements. Furthermore, the study did not include a control group of CRSsNP patients who did not undergo surgery, which limits our ability to definitively attribute olfactory improvements to the surgical intervention alone. Because our cohort is entirely Caucasian, reflecting the typical patient population we encounter, the generalizability of our findings may be limited. Finally, the control group was not re-evaluated 6 months after the enrollment. However, we believe that within 6 months there are no significant spontaneous changes in chemosensory function.[21,36]

In conclusion, this study suggests that OD may be an important concern in a subgroup of patients with CRSsNP. Although 37% of patients did experience a clinically significant improvement in their sense of smell following ESS, the overall prevalence of OD in this surgically naive population appears relatively low, especially when compared to that observed in patients with CRSwNP. Therefore, ESS

may offer some benefits for enhancing orthonasal olfactory function, but the extent of these improvements should be interpreted with caution, considering the variability of outcomes among patients. Furthermore, ESS does not seem to improve retronasal olfaction, and a marginal proportion of subjects may experience a decline in their olfactory function. This information may be useful for counseling CRSsNP patients on the expected outcomes of ESS in managing olfactory impairment. Future research should focus on optimizing patient selection, refining surgical techniques, and developing complementary interventions to maximize olfactory recovery in this patient population.

AUTHOR CONTRIBUTIONS

Paolo Boscolo-Rizzo had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design*: Paolo Boscolo-Rizzo, Claire Hopkins, Thomas Hummel, Anna Menini, and Giancarlo Tirelli. *Acquisition of data*: Paolo Boscolo-Rizzo and Francesco Uderzo. *Analysis and interpretation of data*: All authors. *Drafting of the manuscript*: Paolo Boscolo-Rizzo. *Critical revision of the manuscript for important intellectual content*: Paolo Boscolo-Rizzo, Claire Hopkins, Thomas Hummel, Anna Menini, and Giancarlo Tirelli. *Statistical analysis*: Paolo Boscolo-Rizzo. *Supervision*: Claire Hopkins, Thomas Hummel, and Giancarlo Tirelli.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available upon reasonable request.

ETHICS STATEMENT

The study was approved by the Ethics Committees of the Trieste University Hospital.

INFORMED CONSENT

Informed consent was obtained from all individual participants in the study.

CODE AVAILABILITY

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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