Olfaction after endoscopic surgery for sellar and parasellar disease: an updated systematic review and meta-analysis*

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Rhinology 60: 3, 177 - 187, 2022
https://doi.org/10.4193/Rhin21.348

***Received for publication:**
September 27, 2021
Accepted: January 30, 2022

Abstract

Background: Whether endoscopic surgery for sellar/parasellar disease causes significant deficits in olfactory function remains unclear. We aimed to systematically review the olfactory outcomes in such settings based on the evidence up to date.

Methods: PubMed, EMBASE, and CENTRAL were searched through February 1, 2021. Included studies were limited to endoscopic surgery for sellar/parasellar disease with follow-up olfactory function measured by standardized olfactory testing methods or subjective assessment. The primary outcome was the change in olfactory function after surgery assessed by standardized olfactory testing methods. The secondary outcome was the change in subjective olfactory function. Random-effects model was used in obtaining combine effects. Study quality was assessed using the Newcastle–Ottawa scale. Sensitivity analysis was carried out using the leave-one-out approach, and publication bias was assessed using Egger's test.

Results: The results show no significant difference in olfaction assessed by standardized olfactory testing methods at 1–3 months post-surgery (880 patients in 16 studies) or at 6–12 months post-surgery (1320 patients in 16 studies) compared to pre-surgery, whereas a significantly lower subjective olfaction at 3 months was observed. In addition, the lack of significant change in olfaction as assessed by standardized olfactory testing methods was observed regardless of whether patients were treated with or without the nasoseptal flap (NSF) harvesting. Heterogeneity and publication bias were observed, whereas sensitivity analysis showed the meta-analysis results are robust.

Conclusion: The findings of this updated systematic review and meta-analysis support the conclusion that endoscopic surgery for sellar and parasellar pathology may pose no greater risk of olfactory dysfunction. In addition, the current evidence does not support there is an increased risk of diminished olfaction among patients treated with NSF during surgery.

Key words: endoscopic, endonasal surgery, pituitary tumor, olfaction, smell, complication

Introduction

Technological advancements have revolutionized, making the endoscopic endonasal management of skull base pathologies increasingly routine [(1,2)]. Among the late postoperative complications after endoscopic surgery of the skull base, most attention is paid to cranial complications, such as cerebrospinal fluid leak, meningitis, massive hemorrhage, and endocrinologic deficits [(3,4)]. However, it is recognized that the endoscopic endonasal access to the skull base carries risks in terms of olfactory disturbance [(3,5-7)]. In addition to its essential role in smell, olfaction is critical to the formation of emotion and memory. It is reported that olfactory dysfunction is increasingly recognized, associated with

greatly diminished quality of life, depression, neurodegeneration and even death [8-10].
Endoscopic transnasal access to the skull base requires the removal and disruption of structures containing olfactory neuroepithelium [11-15]. The nasoseptal flap (NSF), used in the reconstruction of the skull base defect, can aggravate this reduction in olfaction because its construction requires manipulation of the olfactory neuroepithelium or regions close to it [14]. However, the actual olfactory outcome after such procedure and its associative factors need further examination. Individual studies on the topic vary widely in several variables, making accurate comparisons difficult and precluding consensus on the degree of olfactory risk posed by the procedure.
Olfaction after endoscopic endonasal access to the skull base has been investigated in several recent reviews, with inconsistent results. Yin et al. reported no significant change in objective olfaction after endoscopic surgery to the skull base, in which resections for sellar/parasellar lesions were the major focus [16]. In contrast, Zhu et al. reported a pooled incidence of 18% for decreased olfactory function in patients who underwent the same procedure [17]. Both reviews included literature published only up to 2017. Several eligible studies have been published more recently, providing the opportunity for a more comprehensive data synthesis.
To gain further insights into this important topic, this updated meta-analysis aims to summarize the current evidence on olfaction after endoscopic surgery for sellar/parasellar disease in a larger cohort than in previous studies. This larger cohort allows for subgroup analysis of the timepoint of outcome evaluation, which was not investigated in the previous reviews, and the effect of NSF on the outcomes.

Materials and methods

Search strategy and selection criteria

This present meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. PubMed, EMBASE, and CENTRAL were searched through February 1, 2021, using a combination of keywords 'skull base', 'olfaction', and 'endoscopic surgery' properly combined with Boolean operators and using Medical Subject-Headings (MeSH) terms where appropriate. For the PubMed search, we used the following search string: ("skull base"[MeSH] AND endoscopic [MeSH] AND (olfactory OR olfaction [MeSH]))
The inclusion criteria were: 1) prospective or retrospective studies reported follow-up of patients undergoing endoscopic surgery for disease involved only sellar/parasellar regions; and 2) studies must report outcome using standardized olfactory testing methods or subjective olfactory function before and after surgery.
The exclusion criteria were: 1) studies for lesions not limited to sellar/parasellar regions such as olfactory groove meningiomas or neuroblastomas; 2) no quantitative outcomes; 3) letters, commentaries, editorials, case reports, and personal communications; 4) non-English articles. The reference lists of included studies were hand-searched to identify other potentially relevant studies.

Main outcome measures

Primary outcome. The primary outcome was the change in olfactory function after surgery measured by the following standardized olfactory testing methods or scales: University of Pennsylvania Smell Identification Test (UP-SIT), Cross Cultural Smell Identification Test (CC-SIT), Connecticut Chemosensory Clinical Research Center (CCCRC), Butanol Threshold Test (BTT), Brief Smell Identification Test (B-SIT), Smell diskettes Olfaction Test (SDOT), Barcelona Smell Test (BAST-24), and the Sniffin' Sticks test.
Secondary outcome. The secondary outcome was the change in subjective olfactory function after surgery, as measured by the Likert scale or visual analog scale (VAS).

Data extraction

Studies were identified using the above search strategy by two independent reviewers (CCL and CCH). Uncertainty was resolved by a third reviewer (CCC). The following information was extracted: first author name, year of publication, study design, number of patients, specific technique, patient ages, sex, type of NSF, tumor type, timepoint of outcome evaluation, and measures of olfactory function.

Ethical statement

This review was a secondary analysis on published studies and did not directly involved patient consent. Raw patient data and private information were neither required nor used. The protocol of this study was approved by Chang Gung Medical Foundation (202101256B1) and it is exempt from IRB review and informed consent is not required.

Quality assessment

Quality of the included studies were assessed using the Newcastle–Ottawa scale (NOS) as recommended by the Cochrane Non-Randomized Studies Methods Working Group [19]. This scale awards a maximum of nine stars to each study: four for the adequate selection of cohort participants, two for comparability, and three for the adequate ascertainment of outcomes.

Statistical analysis

For the measurements of olfactory function, the mean and standard deviation (SD) were calculated. If lacking, the median, range, and sample size were used to estimate the mean and variance [20]. We assumed that the median was equal to the mean

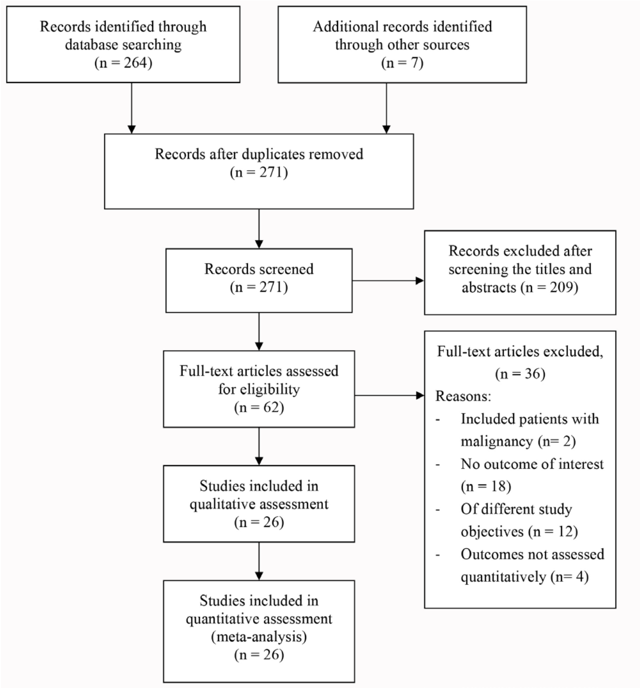


Figure 1. PRISMA flow diagram of study selection.

response, and the width of the interquartile range is approximately 1.35 standard deviation [21]. Considering that olfactory function was determined by a variety of instruments, the standardized mean difference (SMD) with corresponding 95% confidence interval was calculated for each study and for all studies combined under the guidance of the Cochrane handbook [21]. This approach is used as a summary statistic in meta-analysis when the same outcome is assessed but measured in different continuous scales, as elaborated elsewhere [22]. A χ^2-based test of homogeneity was performed, and the inconsistency index (I^2) and Q statistics were determined. Study heterogeneity was defined as follows: homogeneous, $I^2 < 25\%$; heterogeneous, $I^2 > 50\%$; highly heterogeneous, $I^2 > 75\%$. A random-effects model (DerSimonian–Laird method) was used because of the diversity of scales used to measure olfactory function. Two-sided P value <0.05 was considered statistically significant. Sensitivity analysis was carried out using the leave-one-out approach. Publication bias was assessed by constructing funnel plots for outcomes using Egger's test. If publication bias existed, adjusted effect sizes were calculated after consideration of publication bias using Duval and Tweedie's 'trim and fill' procedure [23]. Publication bias analysis was waived when the number of studies was too small to detect an asymmetric funnel [24]. Subgroup analysis was conducted according to whether or not the surgery included NSF harvesting. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ, USA).

Results

The search and study selection process is shown in Figure 1. Finally, 26 studies [3,5-7,11-15,25-42] (6 retrospective, 18 prospective, and 2 RCTs) met the eligibility criteria and were included in this review. The characteristics of the studies are summarized in Table 1. A total of 1858 patients were enrolled (mean age, 37.5–65.8 years; % male, 16–76.5%. The olfactory function reported using standardized olfactory testing methods included UPSIT outcomes (8 studies [6,11,12,15,25-27,32]), CCSIT outcomes (8 studies [28-30,36-39,42]), Sniffin's Sticks outcomes (5 studies [3,34,35,40,41]), CCCRC outcomes (2 studies [5,13]), SDOT outcomes (2 studies [7,33]) and the BAST-24 identification test (1 study [31]).

Meta-analysis

Olfactory function 1–3 months after surgery assessed by standardized testing methods

Sixteen of the 26 studies [3,5,6,11,13, 25-30,34-36,41,42], including 880 patients, provided quantitative data for olfactory function evaluated prior to surgery and 1-3 months after surgery (Table 2, A). Evidence indicated heterogeneity across the 16 studies (Q statistic = 49.39; $I^2 = 69.63$; $P < 0.001$). The combined difference (pooled SMD = –0.07; 95% CI = –0.20 to 0.06) indicated no significant difference between the olfaction measured before and after surgery (Figure 2).

Olfactory function 6–12 months after surgery assessed by standardized testing methods

Sixteen of the 26 studies [3,5-7,12,13,15,27,31-33,37-41], including 1320 patients, provided numerical data for olfaction measured preoperatively and 6–12 months after surgery (Table 2, B). Substantial heterogeneity was observed (Q statistic = 290.09; $I^2 = 98.83$; $P < 0.001$). Again, the result showed no significant difference between pre- and postoperative olfaction (pooled SMD = –0.19; 95% CI = –0.48 to 0.09) (Figure 3).

Subjective olfaction after surgery

Only 5 studies [28-30,36,42], including 413 patients, reported subjective olfaction preoperatively and 3 months postoperatively (Table 2, C). Moderate heterogeneity was observed (Q statistic = 6.85; $I^2 = 41.56$; $P = 0.144$). The combined difference (pooled SMD = –0.54; 95% CI, –0.68 to –0.40) indicated a significantly lower subjective olfaction after surgery (Figure 4).

Sensitivity analysis and publication bias

In sensitivity analyses, the direction and magnitude of combined estimates did not vary markedly, indicating that the meta-analysis was robust, and the data were not overly influenced by any one study (Table 2).

No publication bias was observed regarding 1–3 months olfactory outcome measured by standardized testing methods ($t = 0.299$; $P = 0.384$) (Figure 5A). However, publication bias was observed in 6–12 months olfaction outcome measured by standardized testing methods ($t = 2.240$; one-tailed $P = 0.021$) (Figure 5B). Simulation by the 'trim and fill' method to look for missing studies based on the random-effects model showed

Table 1. Characteristics of the included studies.

First author (year)	Study design	No. of pts	Specific technique	Male (%)	Age (years)	Naso-septal flap (NSF)	Tumor type	Time-point of outcome evaluation	Measure of olfaction	NOS score
Carvalho (2020) [13]	Prospective	17		77%	NA	All NSF	PA and others	3mo	CCCRC	7
Dolci (2020) [5]	Prospective	40		NA	NA	All NSF	PA, others	6mo	CCCRC	6
Gong (2020) [34]	Prospective	15		27%	38.7	NSF in some	PA, others	2mo	Sniffin' Sticks	7
Li (2020) [40]	Retrospective	74	Partial resection of the superior turbinate	49%	46.0	NSF in some	PA	6mo	Sniffin' Sticks	6
		74	Intentional lateralization of the superior turbinate							
Noh (2020) [28]	Prospective	46	Single neuro-surgeon	57%	48.5	No NSF	PA	3mo	CC-SIT, BTT, Likert	6
		106	Neurosurgeon and ENT surgeon	48%	49.8					
Seo (2020) [42]	Retrospective	96		47%	51.6	All NSF	PA, RCC, others	3mo	Likert, CC-SIT	6
Garzaro (2019) [3]	Retrospective	85		43%	52.3	NSF in some	PA	6mo	Sniffin' Sticks	7
Netuka (2019) [41]	Prospective	143		51%	50.0	No NSF	PA	12mo	Sniffin' Sticks	8
Puccinelli (2019) [6]	RCT	12	Cautery	46%	50.2	NSF in some	PA, RCC, others	12mo	UP-SIT	6
		10	Cold knife			NSF in some				
Cingoz (2018) [35]	Prospective	30		53%	37.5	NSF in some	PA	2mo	Sniffin Sticks	6
Kim,DH (2018) [38]	Retrospective	112		57%	48.1	all rescue NSF	PA	6mo	CC-SIT	6
Schreiber (2018) [12]	Prospective	28		41%	52.6	NSF in some	PA, RCC, others	6mo	UP-SIT	7
Eördögh (2017) [33]	Retrospective	17		50%	50.3	No NSF	PA	12mo	SDOT	6
Kim, DH (2017) [37]	Retrospective	535		NA	NA	rescue NSF in most	PA, RCC, others	6mo	CC-SIT	7
Upadhyay (2017) [27]	Prospective	35		51%	48.9	all rescue NSF	PA, RCC	6mo	UP-SIT	6
Hong (2016) [30]	Prospective	30		51%	49.7	No NSF	PA	3mo	CC-SIT, VAS	6
		51	Modified endoscopic approach							
Chaaban (2015) [25]	Prospective	18		33%	58.2	NSF in some	PA	3mo	UP-SIT	6
Harvey (2015) [32]	Prospective	40		52%	51.0	All NSF	PA, others	6mo	UP-SIT	6
Hong (2015) [36]	Prospective	35		46%	50.8	No NSF	PA	3mo	CC-SIT, BTT, VAS	7

First author (year)	Study design	No. of pts	Specific technique	Male (%)	Age (years)	Naso-septal flap (NSF)	Tumor type	Time-point of outcome evaluation	Measure of olfaction	NOS score
Rioja (2015) [31]	Prospective	38		NA	NA	NSF in some	PA	12mo	BAST-24, VAS	7
Hong (2014) [29]	Prospective	19	Cautery	43%	49..0	all rescue NSF	PA	3mo	CC-SIT, VAS	6
		30	Cold knife							
Kahilogullari (2013) [7]	Prospective	25		16%	40.8	No NSF	PA, RCC, others	6mo	SDOT	7
Kim,SW (2013) [39]	Prospective	15		60%	53.4	All NSF	PA	6mo	CC-SIT	6
Sowerby (2013) [11]	Prospective	17		41%	49.0	NSF in some	PA, RCC	1-3mo	UP-SIT	6
Tam (2013) [15]	RCT	10		40%	54.1	All NSF	PA	6mo	UP-SIT	6
		10		60%	65.8	No NSF				
Hart (2010) [26]	Prospective	45		51%	51.2	No NSF	PA, RCC	3mo	UP-SIT	6

UP-SIT, University of Pennsylvania Smell Identification Test; CC-SIT, Cross Cultural Smell Identification Test; CCCRC, Connecticut Chemosensory Clinical Research Center; NSF, nasoseptal flap; VAS, visual analog scale; BTT, Butanol Threshold Test; B-SIT, Brief Smell Identification Test; PA, pituitary adenoma; RCC, Rathke's cleft cyst; SDOT, Smell Diskettes Olfaction Test; BAST-24, Barcelona Smell Test.

that the imputed point estimate changed to –0.30 (95% CI, –0.55 to –0.01).

Endoscopic surgery with / without NSF elevation

No significant difference between pre- and postoperative olfaction outcome measured by standardized olfactory testing methods among patients with NSF elevation (7 studies (5,13,15,25,32,39,42); 224 patients; pooled SMD, –0.15; 95% CI, –0.61 to 0.31) was observed. The analysis also reveals no significant difference in olfaction before and after surgery in patients without NSF elevation (8 studies (7,15,26,28,30,33,36,41); 508 patients; pooled SMD, –0.06; 95% CI, –0.26 to 0.13) (Table 3).

Quality assessment

The quality ratings for each individual study are shown in Table 1. The average NOS score was 6.4 (range, 6–8), suggesting that the studies included were of moderate quality.

Discussion

In this updated meta-analysis of the most recent studies investigating patient olfactory outcomes after endoscopic surgery for sellar/parasellar disease, we observed no significant difference in olfaction outcome as assessed by standardized olfactory testing methods at 1–3 months post-surgery (880 patients in 16 studies) or at 6–12 months post-surgery (1320 patients in 16 studies) compared to pre-surgery. This lack of significant change in olfactory function was observed regardless of whether patients were treated with or without NSF. Sensitivity analysis of the included studies showed the meta-analyses are robust. These findings suggest that endoscopic surgery for sellar/parasellar lesions may pose no greater risk of diminished olfaction and those treated with NSF elevation during surgery are at no increased risk of olfactory dysfunction as those without.

This comprehensive analysis in the largest cohort to date expands upon the findings of previous reviews investigating the effects of endoscopic surgery for sellar/parasellar lesions on olfaction. In a prior review focusing on olfaction, Yin et al. also reported no significant difference between pre- and postoperative olfaction using the UPSIT or CCSIT (16). As their quantitative analysis only included 739 patients in 8 studies published before 2017, the present meta-analysis included all relevant newly published studies up to 2021, largely expanding the analytic sample size (1320 patients in 16 studies at 6-12 months follow-up, nearly doubling the patient number) that not only added reliability to the statistical analyses but also allowed for further subgroup analysis based on the timing of post-surgical assessment and on surgical technique with or without NSF. The results of the present meta-analysis have strengthened the evidence and added new insights to the relevant issue.

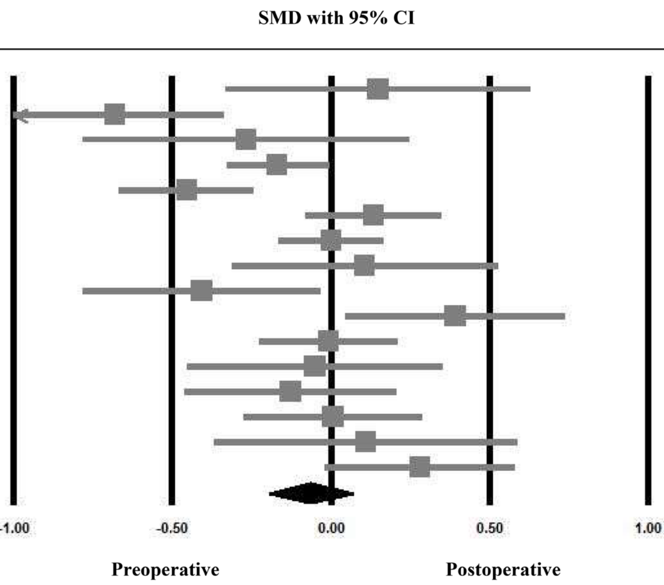
Our investigation shows no significant decrease in olfaction at either 1–3 months 6–12 months after endoscopic surgery. Several studies have suggested that endoscopic pituitary surgery can cause a transient decrease in olfaction at 1–3 months that improves by 6 months after surgery (25,26), and that it took approximately 6 weeks for mucosal regeneration and 3 months for recovery of ciliary function (27).

Table 2. Sensitivity analysis.

First author (year)	Statistics with study removed				
	SMD	Lower limit	Upper limit	Z-Value	P-Value
A. Olfactory function - standardized testing methods (1 to 3 Months after operation)					
Carvalho (2020)	-0.08	-0.21	0.06	-1.10	0.272
Dolci (2020)	-0.03	-0.15	0.09	-0.48	0.628
Gong (2020)	-0.06	-0.19	0.08	-0.84	0.402
Noh (2020)	-0.06	-0.20	0.09	-0.76	0.448
Seo (2020)	-0.03	-0.15	0.09	-0.51	0.609
Garzaro (2019)	-0.08	-0.22	0.05	-1.19	0.236
Netuka (2019)	-0.07	-0.22	0.07	-0.96	0.335
Puccinelli (2019)	-0.07	-0.21	0.06	-1.08	0.279
Cingoz (2018)	-0.05	-0.18	0.09	-0.68	0.497
Upadhyay (2017)	-0.09	-0.22	0.03	-1.45	0.147
Hong (2016)	-0.07	-0.21	0.07	-0.97	0.331
Chaaban (2015)	-0.07	-0.20	0.07	-0.95	0.340
Hong (2015)	-0.06	-0.20	0.08	-0.88	0.381
Hong (2014)	-0.07	-0.21	0.07	-1.00	0.318
Sowerby (2013)	-0.07	-0.21	0.06	-1.07	0.284
Hart (2010)	-0.09	-0.22	0.04	-1.35	0.176
B. Olfactory function - standardized testing methods (6 to 12 Months after operation)					
Carvalho (2020)	-0.22	-0.52	0.07	-1.48	0.139
Dolci (2020)	-0.19	-0.50	0.11	-1.25	0.210
Li (2020)	-0.16	-0.47	0.15	-1.01	0.315
Garzaro (2019)	-0.22	-0.52	0.07	-1.46	0.143
Netuka (2019)	-0.21	-0.52	0.09	-1.36	0.175
Puccinelli (2019)	-0.22	-0.52	0.07	-1.48	0.139
Kim, DH (2018)	-0.15	-0.45	0.16	-0.95	0.344
Schreiber (2018)	-0.20	-0.50	0.10	-1.32	0.188
Eördögh (2017)	-0.23	-0.52	0.07	-1.52	0.130
Kim, DH (2017)	-0.13	-0.40	0.13	-0.99	0.323
Upadhyay (2017)	-0.24	-0.53	0.05	-1.63	0.103
Harvey (2015)	-0.21	-0.51	0.08	-1.40	0.160
Rioja (2015)	-0.23	-0.52	0.07	-1.50	0.132
Kahilogullari (2013)	-0.19	-0.49	0.11	-1.22	0.223
Kim, SW (2013)	-0.23	-0.52	0.06	-1.53	0.127
Tam (2013)	-0.09	-0.37	0.19	-0.64	0.524
C. Subjective olfactory function					
Noh (2020)	-0.55	-0.75	-0.34	-5.25	<0.001*
Seo (2020)	-0.50	-0.65	-0.34	-6.31	<0.001*
Hong (2016)	-0.60	-0.71	-0.48	-9.98	<0.001*
Hong (2015)	-0.54	-0.71	-0.37	-6.22	<0.001*
Hong (2014)	-0.51	-0.67	-0.35	-6.34	<0.001*

Endoscopic endonasal approach for tumor resection can result in defects that require extensive dural repair to prevent cerebrospinal fluid leak. The NSF is one of the available repair techniques used for such reconstruction [43], which allowing

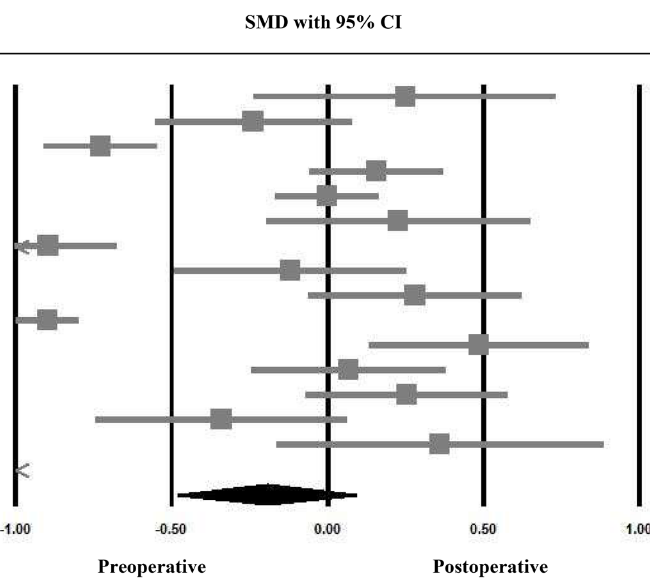
First author (year)	Statistics for each study					Relative weight
	SMD	Lower limit	Upper limit	Z-Value	P-Value	
Carvalho (2020)	0.15	-0.33	0.63	0.61	0.544	4.264
Dolci (2020)	-0.68	-1.03	-0.34	-3.88	<0.001*	5.887
Gong (2020)	-0.27	-0.78	0.25	-1.02	0.308	3.904
Noh (2020)	-0.17	-0.33	-0.01	-2.07	0.039*	8.656
Seo (2020)	-0.46	-0.67	-0.25	-4.25	<0.001*	7.913
Garzaro (2019)	0.13	-0.08	0.35	1.23	0.220	7.861
Netuka (2019)	0.00	-0.16	0.16	0.00	1.000	8.604
Puccinelli (2019)	0.11	-0.31	0.53	0.50	0.617	4.914
Cingoz (2018)	-0.41	-0.78	-0.04	-2.15	0.032*	5.499
Upadhyay (2017)	0.39	0.05	0.73	2.23	0.026*	5.890
Hong (2016)	-0.01	-0.23	0.21	-0.07	0.942	7.791
Chaaban (2015)	-0.05	-0.45	0.35	-0.24	0.807	5.118
Hong (2015)	-0.13	-0.46	0.20	-0.75	0.450	6.046
Hong (2014)	0.01	-0.27	0.29	0.04	0.966	6.821
Sowerby (2013)	0.11	-0.37	0.59	0.45	0.650	4.276
Hart (2010)	0.28	-0.02	0.58	1.85	0.065	6.556
Pooled effect	**-0.07**	**-0.20**	**0.06**	**-0.99**	**0.322**	



Heterogeneity test: Q=49.39, df = 15, P < 0.001, I-square = 69.63%

Figure 2. Forest plot of pooled meta-analysis for olfactory function assessed with standardized olfactory testing methods before and after endoscopic skull base surgery (1–3 months after surgery).

First author (year)	Statistics for each study					Relative weight
	SMD	Lower limit	Upper limit	Z-Value	P-Value	
Carvalho (2020)	0.25	-0.23	0.73	1.02	0.310	5.860
Dolci (2020)	-0.24	-0.55	0.08	-1.48	0.138	6.483
Li (2020)	-0.73	-0.91	-0.55	-7.86	0.000	6.839
Garzaro (2019)	0.16	-0.05	0.37	1.46	0.144	6.769
Netuka (2019)	0.00	-0.16	0.16	0.00	1.000	6.874
Puccinelli (2019)	0.23	-0.20	0.65	1.06	0.291	6.094
Kim,DH (2018)	-0.90	-1.11	-0.68	-8.01	<0.001*	6.754
Schreiber (2018)	-0.12	-0.49	0.25	-0.62	0.535	6.286
Eördögh (2017)	0.28	-0.06	0.62	1.61	0.108	6.388
Kim,DH (2017)	-0.90	-1.00	-0.80	-17.54	<0.001*	6.972
Upadhyay (2017)	0.49	0.14	0.84	2.72	0.007*	6.362
Harvey (2015)	0.07	-0.24	0.38	0.42	0.671	6.495
Rioja (2015)	0.26	-0.07	0.58	1.55	0.122	6.454
Kahilogullari (2013)	-0.34	-0.74	0.06	-1.65	0.099	6.171
Kim,SW (2013)	0.36	-0.16	0.88	1.36	0.175	5.697
Tam (2013)	-3.09	-4.17	-2.00	-5.58	<0.001*	3.502
Pooled effect	**-0.19**	**-0.48**	**0.09**	**-1.34**	**0.182**	

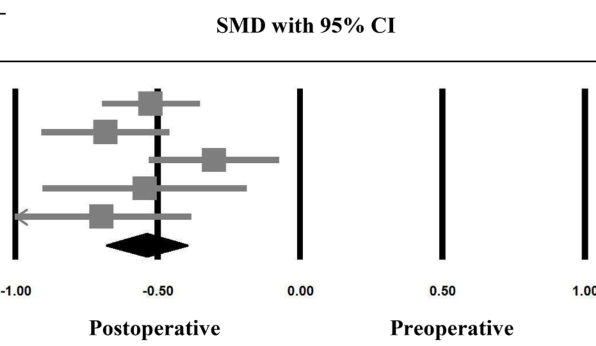


Heterogeneity test: Q=290.09, df = 15, P < 0.001, I-square = 98.83%

Figure 3. Forest plot of pooled meta-analysis for olfactory function assessed with standardized olfactory testing methods before and after endoscopic skull base surgery (6–12 months after surgery).

for a vascularized graft which could enhance reconstruction as compared to free grafting [44,45]. Elevation of the NSF involves cutting in the superior septal mucosa, which is associated with an increased chance of nasal crusting [17]. The major approach of NSF, the Hadad-Bassagasteguy (HB) flap, is harvested at the beginning of the operation [46]. A less common variation is the 'rescue' flap which can be created at the end of the procedure if any unexpected CSF leak occurs [47]. Whether NSF elevation increases the risk of olfactory deficit after endoscopic surgery for sellar/parasellar lesions is not fully clear. Our subgroup meta-

First author (year)	Statistics for each study					Relative weight
	SMD	Lower limit	Upper limit	Z-Value	P-Value	
Noh (2020)	-0.52	-0.69	-0.35	-6.06	<0.001*	28.982
Seo (2020)	-0.68	-0.91	-0.46	-6.03	<0.001*	22.375
Hong (2016)	-0.30	-0.53	-0.08	-2.63	0.009*	21.987
Hong (2015)	-0.55	-0.90	-0.19	-3.01	0.003*	12.101
Hong (2014)	-0.70	-1.01	-0.38	-4.37	<0.001*	14.554
Pooled effect	**-0.54**	**-0.68**	**-0.40**	**-7.43**	**<0.001***	



Heterogeneity test: Q=6.85, df = 4, P = 0.144, I-square = 41.56%

Figure 4. Forest plot of pooled meta-analysis for subjective olfactory function before and after endoscopic skull base surgery (3 months after surgery).

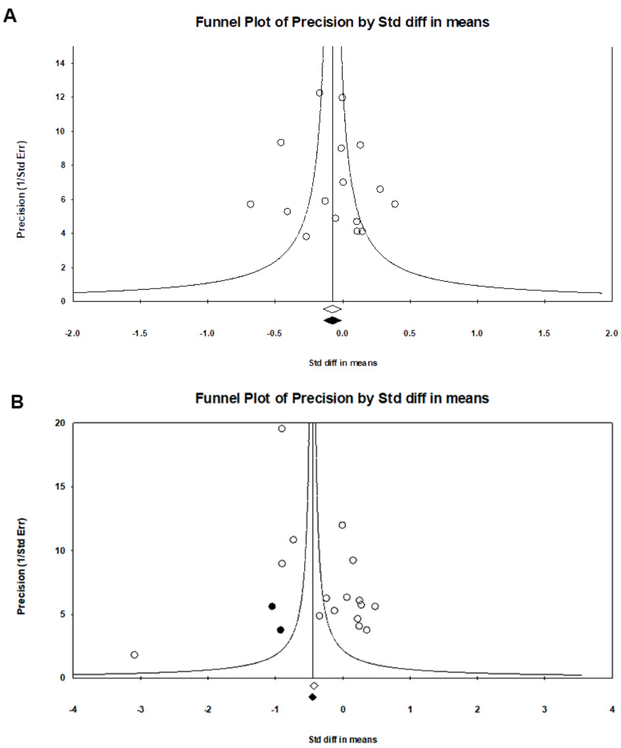


Figure 5. Funnel plots for (A) olfactory function (1–3 months after surgery) and (B) olfactory function (6–12 months after surgery) assessed with standardized olfactory testing methods, showing the distribution of published study outcomes (open circles) and simulated outcomes (black circles) estimated by "trim and fill "procedure.

analysis of 224 patients with HB flap usage and 508 with no NSF elevation both showed no significant change in olfaction. Lavigne et al. reviewed the complications of NSF reconstruction and documented NSF as a safe and reliable procedure but did not go deep into olfaction [48]. A previous study of NSF use in 27 patients among 91 patients receiving extended endonasal surgery for pituitary adenoma concluded that NSF appears to have a limited negative impact in nasal quality of life. Although reduced smell was observed, it tended to improve with time [49]. Several previous studies had suggested NSF usage as a factor that caused olfactory discrimination. Zhu et al. reported an 18.48% incidence for decreased olfaction among 211 patients and concluded that NSF was an unfavorable factor for olfactory recovery and indicated the rescue flap ought to be preferred compared with the planned flap [17]. However, no quantitative analysis was performed to support their conclusion. In a short review, Majovsky et al. also suggested that the endoscopic transsphenoidal surgery without creating NSF might lead to the best olfactory results [50]; however, they also reported the quality of included studies were generally poor. Yin et al. did not conduct analysis on NSF outcomes because of too small sample size [16]. A recent doubled blind RCT compared the effect of NSF elevation on olfaction and sinonasal quality of life. They concluded no significant effect of NSF usage on olfaction or quality of life, and the sidedness of NSF harvesting was not a major concern, either [51]. Another study with a 31.1-month follow-up reported NSF harvest was not an unfavorable factor on olfactory dysfunction after controlled for confounding factors [52]. In addition, minor variations of NSF technique exist. A study included in our analysis reported tissue damage may be reduced thus led to better olfactory outcome with the usage of cold knife in superior incision than electrocautery [39]. Future studies are warranted to gain more evidence.

In the small subset of analysis that used subjective assessment of olfactory changes (Likert or VAS), we observed a significant decrease in subjective olfaction 3 months after endoscopic surgery for sellar/parasellar lesions. A previous study focused on sinus-specific quality of life based on the validated, commonly utilized 22-item Sino-Nasal Outcome Test (SNOT-22) and concluded that patients' sinonasal quality of life achieved baseline level within 3 months following a temporary declined [1]. However, only composite scores were assessed in that study and data of smell subdomain in SNOT-22 was not separately reported. Ne-

Table 3. Subgroup analysis: endoscopic skull base surgery with/without NSF elevation.

	Number of studies	Number of patients	Q statistics	I-square	Pooled SMD with 95%CI
All NSF	7	224	23.8	70.00%	-0.15 (-0.61, 0.31)
No NSF	8	508	27.84	74.86%	-0.06 (-0.26, 0.13)

NSF, nasoseptal flap; SMD, Standardized mean difference.

vertheless, Yin et al. documented the study-specific VAS remains an unvalidated measurement of subjective olfaction with unknown correlations to patient quality of life [16]. Another study also mentioned that subjective olfactory assessment should not be undertaken in isolation, given its poor reliability [10], indicating that subjective olfactory results should be interpreted with caution, especially considering conflicting outcome with standardized olfactory testing results.

The present meta-analysis has some weakness. It is known that a major challenge to any meta-analysis is heterogeneity among the included studies. In this review, a wide range of factors contribute to heterogeneity among studies of olfactory outcomes after endoscopic surgery for sellar/parasellar disease, including variations in tumor pathology, details of surgical techniques and the level of experience of surgeons. Although lesion sites were restricted, and efforts were made to accommodate olfactory tests by applying the standardized difference approach on the numerical values, heterogeneity was observed in the meta-analysis. In addition, evidence of publication bias was observed in the meta-analysis of the 6–12-month olfactory outcomes. Further categorization of patients to minimize heterogeneity was not possible because the small number of patients in each subgroup would have been insufficient for accurate analysis. Despite the observed heterogeneity, sensitivity analysis showed that the meta-analysis results are robust, without undue influence by any one study.

Despite the limitations mentioned above, this report is the most up-to-date and comprehensive meta-analysis of olfactory outcomes following endoscopic surgery for sellar/parasellar disease. Our analysis includes the most recent studies, published in 2017 through February 2021, which were not included in previous reviews. These additional studies increase the data available for analysis, thereby increasing the power of the results. The inclusion of only sellar/parasellar pathologies strengthened the analyses by avoiding disparities in tumor pathology, surgical technique, and extent of surgical dissection. Another unique strength of this review is the separate analysis of short- and long-term quantitative olfactory measures, which for the first time suggest that assessment after 3 months may not be necessary to accurately determine the olfactory outcomes. We were also able to conduct subgroup analysis of patients treated with and without NSF numerically in the largest cohort to date.

Conclusion

This updated systematic review and meta-analysis indicates that endoscopic surgery for sellar/parasellar lesions results in no significant change in patients' olfaction as assessed with standardized olfactory testing methods, whether or not the procedure involves NSF. These findings from our comprehensive cohort may better inform physician choices in surgical planning. As additional data become available, further meta-analyses with more homogeneity within and between studies are warranted.

Acknowledgements

We would like to acknowledge Chang Gung Memorial Hospital and Chang Gung University for supporting this research and thank CONVERGENCE CT, INC. for English language editing.

Authorship contribution

Conception and design: CCL and CCC. Acquisition of data: CCL, CCH, TJL, YCW, YTL, TWC and APHH. Analysis and interpretation of data: CCL, CCH, TJL and CCC. Drafting of the manuscript: CCL, CCH, YCW and YTL. Critical revision of the manuscript: CCL, TJL, TWC, APHH and CCC. All authors approved the final version of the manuscript.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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