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Impact of patient-reported nasal symptoms on quality of life after endoscopic pituitary surgery: a prospective cohort study

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Abstract

Purpose Endoscopic transsphenoidal surgery causes nasal morbidity and negatively affects health-related quality of life (HRQoL). Knowledge on actionable symptoms that could improve postoperative HRQoL is therefore important. This study assessed the impact of nasal symptoms on postoperative HRQoL.

Methods This perioperative cohort study included 103 adult patients undergoing endoscopic pituitary adenoma resection (August 2016–December 2018), with measurements preoperatively, and 5 days, 6 weeks and 6 months after surgery. Nasal symptoms were measured with the Anterior Skull base nasal inventory-12, and HRQoL with the Short Form-36 (SF-36) physical (PCS) and mental component scores (MCS). Linear regression analysis was used to assess (1) determinants of postoperative nasal morbidity, (2) associations between number of symptoms or (3) individual symptoms and HRQoL, and (4) the percentage of variance of HRQoL explained by nasal symptoms.

Results The number of nasal symptoms transiently increased after surgery. No significant treatment- or disease-related determinants of nasal morbidity were identified. The number of nasal symptoms was significantly associated with a lower PCS ($\beta = -1.0$; 95%CI -1.5, -0.4), but not with MCS at 6 weeks. Similar results were observed at 6 months. Headaches (42.2%), problems with smell (42.0%), and taste (36.0%) were the most prevalent symptoms, while sense of smell and taste, and nasal discharge showed the strongest associations with HRQoL.

Conclusions Postoperative nasal symptoms, in particular problems with smell and taste, significantly affect pituitary patients' physical HRQoL. Monitoring of these symptoms may aid in determining which patients may benefit from intensified follow-up and treatment, aiming to optimize HRQoL.

Keywords Pituitary adenoma · Endoscopic surgery · Nasal symptoms · Health-related quality of life

Introduction

It is increasingly recognized that patients with pituitary adenomas experience substantial short- and long-term morbidity, which often leads to a reduced health-related quality of life (HRQoL), even after tumor resection and biochemical remission [1, 2]. Surgery plays a key role in the treatment of pituitary adenomas, as current guidelines advise surgery as first-line treatment for almost all pituitary tumor subtypes [3–5], with the exception of prolactinomas, for which recent studies suggest that surgery might be an equal treatment option compared to dopamine agonists [6]. However, surgery carries a risk of transient and permanent complications. Specifically, postoperative nasal symptoms are a common adverse effect of (endoscopic) transsphenoidal tumor

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resection [7–9]. However, the impact of nasal symptoms on postoperative HRQoL remains unclear.

In patients with a pituitary adenoma, HRQoL may be affected by systemic symptoms of hormone excess, hypopituitarism, or medication, as well as by local symptoms caused by the tumor mass effects or surgical treatment [1]. Headache is the only self-reported local symptom of which the impact on general HRQoL has been evaluated in this patient group [10–12]. While quite some studies have investigated patient-reported nasal morbidity in the perioperative period, the association between actionable nasal symptoms and general HRQoL has not yet been comprehensively investigated [13, 14]. It would be valuable to gain insight into the impact of these symptoms on general HRQoL, as this would indicate which symptoms require interventions to improve postoperative general HRQoL.

The aim of this study was therefore to assess to what extent postoperative patient-reported nasal symptoms affect pituitary patients' general HRQoL, and to determine which individual nasal symptoms are most important to monitor and to act upon in order to improve pituitary patients' general HRQoL. The secondary aim was to assess which disease- and treatment-related variables may affect the number of nasal symptoms.

Methods

Study design

For the analyses presented in this study, data of a previously published perioperative longitudinal cohort [15] were used, consisting of 103 consecutive pituitary adenoma patients who were operated endoscopically between August 2016 and December 2018. Starting point of this cohort is the launch of our value-based health care pathway, with structured measurement of clinician- and patient-reported outcome measures (PROMs), plan-do-check-act (PDCA) cycles to evaluate care, and initiatives to improve HRQoL through symptom management. Patients were recruited at our tertiary referral center, the Leiden University Medical Center in the Netherlands. The study was approved by the institutional ethical committee (p16.091).

Patient population

Patients were eligible if they had a radiologically confirmed pituitary tumor, were at least 18 years of age, fluent in Dutch, and had an indication for endoscopic transsphenoidal pituitary tumor resection. Patients were excluded if post-surgical follow-up was shorter than 6 months, or if they lived abroad. Patients were enrolled after providing informed consent.

Surgical procedure

A detailed description of surgical indications and techniques at our center has been described elsewhere [16]. In short, all patients are operated by two surgeons (i.e., two neurosurgeons, or a neurosurgeon with an ear, nose, and throat (ENT) surgeon) using a three- or four-hands technique and electromagnetic neuronavigation. Using the natural ostium of the sphenoid as a landmark, a "cranial" septal incision is routinely made for the possibility of a rescue septal vascularized mucosa flap before opening of the sphenoid sinus. A part of the mucosa superior of the natural ostium is used as a free mucosal graft. For large supra- or parasellar adenomas, extended approaches are used, including removal of the tuberculum sellae and sometimes part of the planum sphenoidale. Closure mainly depends on cerebrospinal fluid (CSF) leakage. For the resection of a small adenoma without CSF leakage, closure consists of collagen foam material placement. In case of CSF leakage with small arachnoidal defects, a combination of abdominal fat, fascia lata and the free mucosa graft is used, while for large arachnoidal defects, a vascularized septum mucosa (Hadad) flap is used. Following surgery, all patients start with nasal rinsing with saline for 6 weeks, and the majority also received xylometazoline nasal spray. Only if symptoms persisted, nasal corticosteroid spray was prescribed.

Data collection

Baseline characteristics

The following baseline characteristics were collected from the patients' medical records: age, sex, marital status, education level, tumor type, tumor size, tumor invasion, date of diagnosis, prior treatment of the tumor, preoperative pituitary function, preoperative visual field defects, preoperative visual acuity, cranial nerve deficits, comorbidities, work status, and surgical and postoperative complications (including epistaxis, CSF leak, transient and permanent diabetes insipidus, delayed hyponatremia, new-onset pituitary deficiencies). Detailed information on the collection and classification of these data has been reported previously [15].

Health-related quality of life

General HRQoL was measured using the Short Form-36 (SF-36) [17], the most frequently used generic questionnaire in patients with a pituitary tumor [1]. It consists of 36 questions covering eight domains and generating a physical component score (PCS) and mental component score (MCS). All scores range from 0 to 100, higher scores indicating a better general HRQoL. Patients completed the SF-36 preoperatively, and 6 weeks and 6 months postoperatively, either digitally or on paper. The Dutch version of the SF-36 was validated in the Netherlands [18].

Nasal symptoms

Patients completed the Anterior Skull base nasal inventory-12 (ASK-12) before, and 5 days, 6 weeks, and 6 months after surgery, either digitally or on paper. The ASK-12 was chosen because it is a short but comprehensive questionnaire that has shown good validity and reliability among patients with pituitary adenomas [19, 20]. It consists of 12 items assessing the presence and severity of 12 nasal symptoms on a six-point Likert scale (0 = No problem, to 5 = Severe problem). The total score is the mean of all item scores and ranges from 0 to 5, higher scores indicating worse nasal functioning. For the analyses of this study, it was decided to dichotomize the ASK-12 score, since this would not only facilitate interpretation of the results for clinicians not familiar with the ASK-12, but would also be more applicable to clinical practice, as not all pituitary centers use questionnaires such as the ASK-12 to monitor nasal symptoms. Therefore, in this study, the presence of a nasal symptom was defined as a score of 2 or higher for that symptom on the ASK-12, indicating that the patient considered the symptom at least a minor problem. This was considered clinically relevant by the research team, because in practice, if no questionnaire is used, patients likely do not mention all symptoms that they only consider a very minor problem (= score 1). To show the results for a milder definition, the analyses were repeated for a cut-off of 1, indicating that the patient considered the symptom at least a very minor problem. These are presented in Supplements 7 to 15.

Statistical analysis

All statistical analyses were performed using IBM SPSS 25.0 software (IBM, Armonk, NY). Normality of the data was assessed using the Shapiro–Wilk test. Missing values of SF-36 items were imputed using parcel summary imputation. All tests were two-sided and P values < 0.05 were considered statistically significant.

Description of symptoms

The number of nasal symptoms and HRQoL scores (SF-36) were presented for all time points for the total cohort. Since these were non-normally distributed, the Friedman test was used to compare the number of nasal symptoms and the HRQoL scores between the different timepoints. Post-hoc pairwise comparisons between the different timepoints were made using the Wilcoxon signed rank test with Bonferroni correction for multiple testing.

Determinants of number of symptoms

Linear regression analyses were used to assess possible disease- or treatment-related determinants of the number of nasal symptoms at 6 weeks and 6 months. These were performed both unadjusted and adjusted for the potential confounders age and sex. These analyses were not performed for the measurement at 5 days postoperatively, because a proportion of the symptoms present at 5 days disappears relatively quickly, and no data on HRQoL were available for this time point. To account for multiple testing, P values were false discovery rate (FDR)-corrected according to the Benjamini–Hochberg method.

Associations between the number of nasal symptoms and general HRQoL

In order to assess the impact of nasal symptoms on PCS and MCS, linear regression analyses were performed to calculate the association between the number of nasal symptoms and the PCS and MCS separately for the measurements at 6 weeks and 6 months, adjusted for the confounders age, sex, education level, comorbidities, tumor type, and tumor size. These associations are presented as betas, which represent the change in PCS or MCS if a patient has one additional nasal symptom.

Association between individual nasal symptoms and general HRQoL

To determine which specific nasal symptoms were most strongly associated with HRQoL, the association of the presence of every symptom with the SF-36 component scores was estimated using univariable linear regression analyses, for both 6 weeks and 6 months, again adjusted for the possible confounders age, sex, education level, comorbidities, tumor type, and tumor size. A beta of more than 5 or less than − 5 was considered clinically relevant for the PCS and MCS. Since the clinically important differences of SF-36 subscales have not been determined in pituitary patients yet, the cutoff of 5 was based on the minimal clinically important differences of SF-36 subscales found in other patient populations [21, 22]. This cutoff also corresponds to the clinically relevant change we found in this cohort of pituitary patients [23] using the definition of 0.5 SD of the observed change, which is typically regarded as the minimal important difference for HRQoL instruments in chronic disease populations [24]. Benjamini–Hochberg FDR-correction was applied to account for multiple testing.

Relative importance of nasal symptoms in the context of other sociodemographic and clinical variables

Finally, to determine the relative importance of symptoms in explaining general HRQoL compared to comorbidities, tumor characteristics, clinician-reported deficits, treatment characteristics, and complications, the explained variance (adjusted R^2) was calculated. This indicates the percentage of the variance of HRQoL that can be explained by nasal symptoms and other variable clusters. The following variable clusters were defined: patient-reported nasal symptoms, demographics (age, sex, education level, relationship status, work status), comorbidities (diabetes mellitus, cardiovascular disease, neurovascular disease, malignancies), tumor characteristics (tumor type, tumor size, tumor invasion), clinician-reported deficits (cranial nerve deficits, preoperative pituitary function, preoperative visual field defects, preoperative visual acuity), treatment characteristics (prior treatment, time since diagnosis), and complications. The explained variance was determined for all clusters separately in univariable analyses.

Results

Patient population

Of the 142 patients who visited the outpatient clinic during the inclusion period, 103 patients were eligible and willing to participate (see reference [15]). The median age was 52.9 years (IQR 37.0–65.0 years) and 39 patients (38%) were male (Table 1). Most patients were diagnosed with a non-functioning pituitary adenoma (n = 47, 46%), followed by functioning pituitary adenomas (n = 45, 44%, comprising 14 (14%) patients with acromegaly, 15 (15%) with Cushing's disease, and 16 (16%) with a prolactinoma), and Rathke's cleft cysts or craniopharyngiomas (n = 11, 11%). Median time between diagnosis and surgery was 0.8 years (IQR 0.1–4.8 years). Sixteen patients (16%) required an extended surgical approach and a pedicled mucoseptal flap was used in 8 (8%) patients. None of the patients were lost to follow-up.

Health-related quality of life over time

The median PCS remained relatively stable with values of 40.2 preoperatively, 39.8 at 6 weeks, and 42.1 at 6 months, although there was a significant increase (improvement) between 6 weeks and 6 months ($P = 0.001$). The median MCS significantly increased (improved) from 44.6 preoperatively to 50.9 at 6 weeks and 51.1 at 6 months (Fig. 1, Supplement 1, Supplement 2).

Nasal symptoms over time

The median number of nasal symptoms increased from 1.0 (interquartile range [IQR] 1.0–3.0) preoperatively, to 7.0 (IQR 5.0–10.0) at five days, and thereafter decreased again to 3.0 (IQR 1.0–5.0) at 6 weeks and 1.0 (IQR 0.0–4.0) at 6 months (Fig. 1, Supplement 1). The number of symptoms at 5 days was significantly higher compared to the other time points ($P < 0.001$) (Supplement 1, Supplement 2).

Determinants of number of nasal symptoms

Linear regression analysis showed that patients who had received a mucoseptal flap during surgery had significantly more nasal symptoms at 6 weeks (adjusted analysis: $\beta = 2.8$; 95%CI 0.1, 5.4) (Table 2), but not at 6 months (Supplement 3). Moreover, patients with a prolactinoma experienced significantly more symptoms than patients with a non-functioning adenoma at 6 weeks (adjusted analysis: $\beta = 2.2$; 95%CI 0.1, 4.4). However, after FDR correction, the P values for these associations were no longer significant (Table 2). No other significant determinants of the number of nasal symptoms at 6 weeks (Table 2) or 6 months (Supplement 3) were found.

Association between number of nasal symptoms and general HRQoL

Linear regression analysis showed that with every extra nasal symptom experienced by a patient, PCS significantly decreased with 1.0 at 6 weeks (95%CI − 1.5, − 0.4), and 1.4 at 6 months (95%CI − 2.3, − 0.4). In contrast, the associations were not significant for the MCS (Supplement 4).

Prevalence of individual nasal symptoms

At 6 weeks, *headache* (42.4%) and *problems with sense of smell* (42.0%) and *sense of taste* (36.0%) were the most common symptoms (Fig. 2). At 6 months, *headaches* (33.3%), *problems with sense of smell* (27.3%) and *nasal crusting* (27.3%) were the most prevalent (Table 3).

Association between individual nasal symptoms and general HRQoL

At 6 weeks, seven nasal symptoms (*postnasal drip*, *thick drainage from nose, headaches, nasal crusting, sense of smell, sense of taste, overall functioning of nose*) showed significant and clinically relevant associations with a decreased PCS, whereas none of the symptoms were associated with

Table 1 Baseline characteristics

	Total cohort (N = 103)	Missing data, N (%)
Sociodemographic characteristics		
Sex: male, N (%)	39 (38)	0
Age in years, median (IQR)	52.9 (37.0; 65.0)	2 (2)
Marital status: relationship/married, N (%)	74 (72)	0
Education level, N (%)		0
Low	29 (28)	
Intermediate	29 (28)	
Tertiary	45 (44)	
Comorbidities*		
Diabetes mellitus	5 (5)	3 (3)
Neurovascular disease	2 (2)	3 (3)
Cardiovascular disease**	41 (41)	2 (2)
Malignancies	14 (14)	4 (4)
Paid job, N (%)	59 (59)	3 (3)
Disease-specific characteristics		
Tumor type, N (%)		0
Nonfunctioning adenoma	47 (46)	
Acromegaly	14 (14)	
Cushing's disease	15 (15)	
Prolactinoma	16 (16)	
Rathke's cleft cyst	6 (6)	
Craniopharyngioma	5 (5)	
Tumor size, N (%)		0
Micro	22 (21)	
Macro	58 (56)	
Giant	8 (8)	
Residual < 1 cm	5 (5)	
Residual > 1 cm	10 (10)	
Tumor invasion: Knosp grade		0
0	30 (29)	
I	43 (42)	
II	21 (20)	
IIIA	3 (3)	
IIIB	4 (4)	
IV	2 (2)	
Time since diagnosis, in years, median (IQR)	0.8 (0.1; 4.8)	0
Prior treatment, N (%)		0
No treatment	59 (57)	
Medication	29 (28)	
Surgery	15 (15)	
Radiotherapy	0	
Preoperative pituitary function, N (%)		0
No deficits	48 (47)	
Hypopituitarism	50 (49)	
Panhypopituitarism	5 (5)	
Preoperative visual fields, N (%)		0
No defects	56 (54)	
Mild visual defects (quadrantanopia)	19 (18)	
Severe visual defects (hemianopia)	28 (27)	

Table 1 (continued)

	Total cohort (N = 103)	Missing data, N (%)
Preoperative visual acuity, median (IQR)		
Vision right eye	1.0 (1.0; 1.2)	11 (11)
Vision left eye	1.0 (0.9; 1.0)	11 (11)
Preoperative cranial nerve palsy, N (%)	3 (3)	0
Extended surgical approach, N (%)	16 (16)	0
Application of mucoseptal flap, N (%)	8 (8)	1 (1)
Postoperative CSF leak, N (%)	7 (7)	0
Postoperative epistaxis, N (%)		0
None	96 (93)	
Mild (not requiring surgery)	5 (5)	
Severe (requiring surgery)	2 (2)	
Postoperative referral to ENT specialist, N (%)	43 (42)	0

Percentages are calculated over the number of patients with available data

N number, *SD* standard deviation, *IQR* interquartile range, *CSF* cerebrospinal fluid

*More than one comorbidity could be present per patient

**Cardiovascular disease includes hypertension, atherosclerosis and myocardial infarction

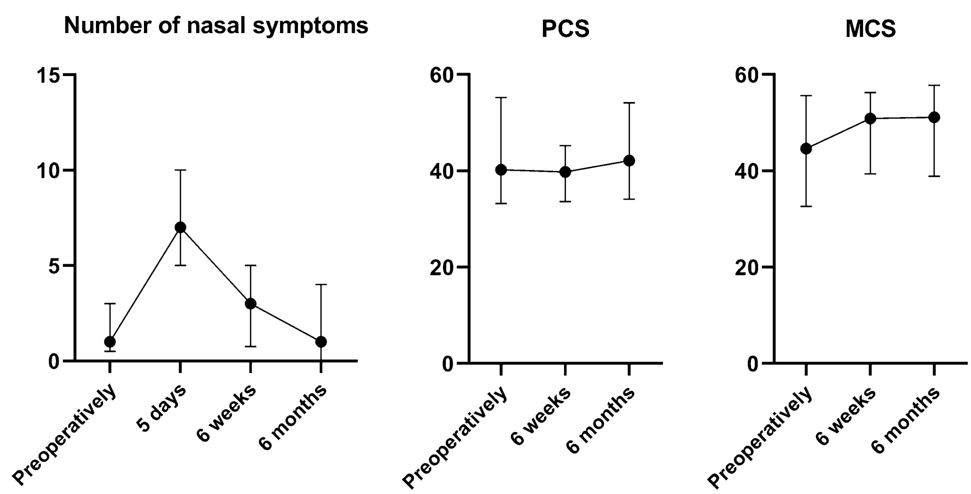

Fig. 1 Number of nasal symptoms and Short Form-36 component scores (median and interquartile range) per timepoint. *PCS* physical component score, *MCS* mental component score

the MCS in the adjusted analysis (Table 3; see Supplement 5 for the P values and FDR-corrected P values, and Supplement 6 for the unadjusted analysis). The strongest association was found between the symptom *problems with sense of taste* and PCS (β = − 7.6; 95%CI − 11.2, − 4.0), followed by *thick drainage from the nose* (β = − 7.4; 95%CI − 11.6, − 3.1) and *sense of smell* (β = − 6.7; 95%CI − 10.1, − 3.2). After FDR correction, the associations for *postnasal drip* and *headaches* were no longer significant.

At 6 months, five of these symptoms were still associated with decreased PCS (*thick drainage from nose, headaches, sense of smell, sense of taste, overall functioning of the nose),* but only the associations for *headaches, sense of smell, and sense of taste* remained significant after FDR correction (Table 3, Supplement 5).

Importance of symptoms in explaining quality of life

Nasal symptoms contributed substantially to the variance of the PCS 6 weeks after surgery (R^2 = 15.7%), but less at 6 months postoperatively (R^2 = 4.6%) (Table 4). Compared to the PCS, the MCS was influenced less by nasal symptoms (R^2 = 3.5% at 6 weeks, R^2 = − 0.6% at 6 months) at both time points, whereas demographics (R^2 = 15.1% at 6 weeks, R^2 = 12.9% at 6 months) and tumor characteristics (R^2 = 9.5% at 6 weeks, R^2 = 14.7% at 6 months) influenced the MCS more. Complications, comorbidities, and clinician-reported deficits contributed only marginally to the variance of the PCS and MCS (Table 4).

Table 2 Associations between disease- and treatment-related determinants and number of nasal symptoms experienced at 6 weeks

Determinant	Unadjusted			Adjusted for age and sex		
	β (95%CI)	P value	P_{FDR}	β(95% CI)	P value	P_{FDR}
Tumor type (reference: Non-functioning adenoma)						
Acromegaly	− 0.4 (− 2.3, 1.5)	0.66	0.93	− 0.7 (− 2.7, 1.4)	0.54	0.97
Cushing's disease	0.8 (− 1.1, 2.8)	0.40	0.82	0.7 (− 1.3, 2.8)	0.48	0.97
Prolactinoma	**2.2 (0.4, 4.0)**	**0.016**	0.38	**2.2 (0.1, 4.4)**	**0.045**	0.54
Rathke's cleft cyst	0.1 (− 2.6, 2.7)	0.97	0.97	0.1 (− 2.6, 2.8)	0.95	0.99
Craniopharyngioma	2.5 (− 0.8, 5.7)	0.13	0.76	2.4 (− 0.9, 5.7)	0.15	0.97
Tumor size (reference: Micro)						
Macro	− 0.9 (− 2.5, 0.8)	0.29	0.82	− 0.6 (− 2.4, 1.1)	0.49	0.97
Giant	− 0.2 (− 3.0, 2.6)	0.89	0.97	0.4 (− 2.7, 3.4)	0.81	0.99
Residual < 1 cm	1.2 (− 1.9, 4.4)	0.44	0.82	1.4 (− 1.8, 4.7)	0.38	0.97
Residual > 1 cm	− 0.2 (− 2.7, 2.3)	0.87	0.97	0.1 (− 2.5, 2.8)	0.93	0.99
Tumor invasion: Knosp grade (reference: 0)						
I	− 0.1 (− 1.7, 1.4)	0.85	0.97	0.2 (− 1.5, 1.9)	0.82	0.99
II	− 0.7 (− 2.6, 1.1)	0.44	0.82	− 0.2 (− 2.3, 1.9)	0.83	0.99
IIIA	− 0.3 (− 4.2, 3.7)	0.90	0.97	− 0.0 (− 4.0, 4.0)	0.99	0.99
IIIB	− 1.3 (− 5.2, 2.7)	0.53	0.82	− 0.1 (− 4.4, 4.1)	0.96	0.97
IV	− 1.6 (− 6.3, 3.1)	0.51	0.82	− 1.4 (− 6.2, 3.4)	0.56	0.97
Time since diagnosis, in years	0.1 (− 0.1, 0.3)	0.19	0.76	0.1 (− 0.1, 0.3)	0.20	0.97
Prior treatment (reference: None)						
Medication	1.0 (− 0.5, 2.5)	0.18	0.76	0.7 (− 0.9, 2.3)	0.39	0.97
Surgery	0.6 (− 1.3, 2.5)	0.55	0.82	0.6 (− 1.3, 2.5)	0.55	0.97
Preoperative pituitary function (reference: No deficits)						
Hypopituitarism	− 0.5 (− 1.8, 0.8)	0.48	0.82	0.1 (− 1.4, 1.7)	0.88	0.99
Panhypopituitarism	0.2 (− 3.1, 3.6)	0.89	0.97	0.8 (− 2.6, 4.3)	0.64	0.99
Application of mucoseptal flap: yes	**2.7 (0.1, 5.3)**	**0.044**	0.53	**2.8 (0.1, 5.4)**	**0.043**	0.54
Extended approach: yes	0.1 (− 1.8, 1.9)	0.94	0.97	0.3 (− 1.6, 2.2)	0.76	0.99
Postoperative CSF leak: yes	0.5 (− 0.9, 1.9)	0.47	0.82	0.5 (− 0.9, 1.9)	0.48	0.97
Postoperative epistaxis (reference: None)						
Mild	− 1.1 (− 4.0, 1.8)	0.46	0.82	− 1.1 (− 4.1, 1.8)	0.45	0.97
Severe	3.2 (− 1.3, 7.7)	0.16	0.76	2.7 (− 1.9, 7.3)	0.25	0.97

Linear regressions presented as β (95% CI)

Values in bold are statistically significant ($P < 0.05$)

95% CI 95% confidence interval, *CSF* cerebrospinal fluid, P_{FDR} false discovery rate corrected P values

Discussion

This study shows that pituitary patients experience a transient increase in self-reported nasal symptoms 5 days and 6 weeks following endoscopic transsphenoidal surgery, which decrease to preoperative levels at 6 months after surgery. Patients with a mucoseptal flap reported more nasal symptoms at 6 weeks compared to patients without a mucoseptal flap, but this association was not significant anymore after FDR correction. Likewise, prior treatment or postoperative complications were not significantly associated with nasal morbidity. In turn, nasal symptoms did have substantial impact on postoperative physical HRQoL, particularly 6 weeks after surgery, and especially the symptoms *problems with sense of taste* and *thick drainage from the nose* were strongly associated with general HRQoL. Therefore, these symptoms deserve more attention in this population, and we hypothesize that they can differentiate between patients who could benefit from intensified ENT consultation and those who do not. A summary of the main results is presented in Fig. 3.

Previous research has shown that nasal symptoms are common following transsphenoidal surgery, with nasal crusting (50.8%), nasal discharge (40.4%), and airflow blockage (40.1%) reported most commonly [9]. Changes in taste and smell are also frequent symptoms in patients undergoing endoscopic resection of skull base lesions (8–46%) [9], especially in functioning pituitary adenomas

Table 3 Association between individual nasal symptoms (items of the Anterior Skull base nasal inventory) and Short Form-36 component scores at 6 weeks and 6 months

	6 weeks postoperatively			6 months postoperatively		
	PCS, β (95% CI)	MCS, β (95% CI)	% of patients with symptom (%)	PCS, β (95% CI)	MCS, β (95% CI)	% of patients with symptom (%)
Urge to blow nose	− 1.1 (− 5.0, 2.9)	− 4.9 (− 9.8, − 0.1)	35.0	− 3.5 (− 9.2, 2.2)	− 0.7 (− 6.6, 5.2)	25.5
Postnasal drip	**− 5.5 (− 10.6, − 0.4)**	− 3.1 (− 9.6, 3.4)	16.0	− 13.0 (− 26.6, 0.6)	− 3.2 (− 17.6, 11.1)	5.2
Thick drainage from nose	**− 7.4 (− 11.6, − 3.1)**	− 2.3 (− 8.0, 3.3)	24.0	**− 6.0 (− 11.8, − 0.1)**	− 2.0 (− 8.2, 4.2)	23.2
Headaches	**− 5.1 (− 8.9, − 1.2)**	− 2.3 (− 7.3, 2.7)	42.4	**− 9.1 (− 14.3, − 4.0)**	− 2.2 (− 8.0, 3.5)	33.3
Whistling sound through nose	− 4.3 (− 10.0, 1.3)	0.6 (− 6.5, 7.8)	13.0	− 0.4 (− 11.1, 10.4)	− 2.7 (− 13.7, 8.3)	8.2
Nasal crusting	**− 5.3 (− 9.2, − 1.4)**	− 1.6 (− 6.6, 3.4)	32.3	0.1 (− 5.7, 5.9)	− 1.1 (− 7.1, 4.8)	27.3
Trouble breathing through nose during day	1.4 (− 4.7, 7.4)	− 5.0 (− 12.5, 2.5)	10.0	− 3.2 (− 10.5, 4.1)	2.1 (− 5.4, 10.0)	14.1
Trouble breathing through nose during night	− 1.0 (− 5.9, 3.8)	− 5.0 (− 11.0, 0.9)	18.0	− 2.1 (− 7.9, 3.8)	− 1.1 (− 7.1, 4.9)	22.2
Not breathing equally through both nostrils	− 2.3 (− 7.0, 2.5)	− 2.1 (− 8.0, 3.9)	22.0	− 2.0 (− 8.9, 5.0)	− 1.8 (− 9.0, 5.3)	16.2
Sense of smell	**− 6.7 (− 10.1, − 3.2)**	− 3.7 (− 8.4, 0.9)	42.0	**− 9.3 (− 15.0, − 3.7)**	− 2.2 (− 8.4, 4.0)	27.3
Sense of taste	**− 7.6 (− 11.2, − 4.0)**	− 2.3 (− 7.2, 2.7)	36.0	**− 9.3 (− 15.7, − 2.9)**	− 3.7 (− 10.7, 3.2)	22.2
Overall functioning of nose	**− 6.5 (− 10.0, − 3.0)**	− 2.1 (− 6.9, 2.7)	34.0	**− 6.6 (− 12.4, − 0.8)**	− 3.5 (− 9.7, 2.6)	20.4

Linear regressions presented as β (95% CI), adjusted for age, sex, education level, tumor type, tumor size, and comorbidities

Values in bold are both statistically significant ($P < 0.05$) and clinically relevant

95% CI 95% confidence interval, *PCS* physical component score, *MCS* mental component score

as compared to non-functioning adenomas [25]. Previous studies identified various factors contributing to postoperative nasal morbidity, such as surgical approach (more extensive and invasive approaches were associated with more nasal symptoms) [26–28], use of splints and absorbable nasal packing [29], and tumor type (functioning tumors [30], specifically ACTH-secreting tumors [31] were associated with higher morbidity). Several studies also investigated differences in outcomes between endoscopic versus microscopic techniques, showing that these techniques can achieve similar sinonasal results [32], with potentially superior olfactory outcomes in endoscopic techniques [33]. In the present study, patients who had received a mucoseptal flap during surgery had more nasal symptoms at 6 weeks but not at 6 months, although this association was not significant anymore after FDR correction. This is in line with the literature, as most published studies indeed report that the use of a mucoseptal flap is not or only transiently associated with increased nasal morbidity [31, 34–36]. We believe that these results are driven by the improved technique to harvest mucoseptal flaps, including the well-defined boundaries to prevent damage of the olfactory nerves. Furthermore, we did not find an association between prior surgical treatment and nasal morbidity, which is also in line with the literature [37]. Potentially, this could be explained by the great regenerative properties of the nasal mucosa [38].

We showed that with every symptom experienced by a patient, the physical HRQoL (PCS) decreased by one point, meaning that a patient experiencing at least five symptoms as a minor problem following surgery would experience a clinically significant decrease of five points in HRQoL. Our finding that disturbances in sense of smell and taste have important impact on general HRQoL is supported by previous literature in patients with olfactory disorders from any cause [39]. Although interventions such as olfactory training and steroid use appear promising to improve these symptoms, evidence for the prevention or management of changes in taste and smell is generally weak [40], with the strongest evidence for olfactory training [41]. In a recent randomized controlled trial, omega 3-supplementation has also been shown to have a protective effect on the olfactory system following endoscopic resection of sellar or parasellar tumors, including pituitary adenomas [25]. Moreover, since around 25% of patients still experience problems with sense

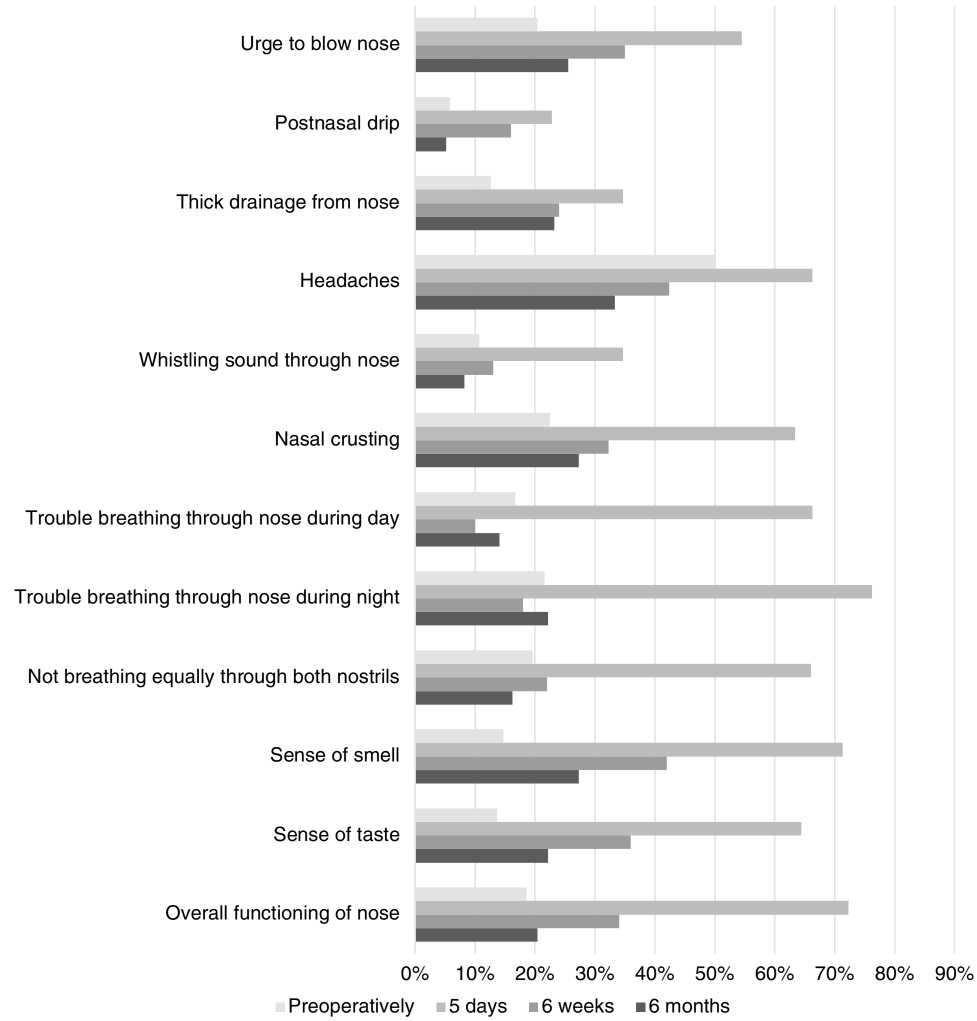

Fig. 2 Prevalence of nasal symptoms, preoperatively, at 5 days, 6 weeks, and 6 months

Table 4 Explained variance (adjusted R^2 presented as %) of PCS and MCS, for separate variable clusters

	6 weeks		6 months	
	R^2 PCS (%)	R^2 MCS (%)	R^2 PCS (%)	R^2 MCS (%)
Number of patient-reported nasal symptoms	15.7	3.5	4.6	− 0.6
Tumor characteristics	8.2	9.5	5.7	14.7
Demographics	5.1	15.1	6.0	12.9
Comorbidities	0.9	− 3.9	− 2.1	1.3
Clinician-reported deficits	− 5.3	1.3	− 3.1	3.8
Treatment characteristics	− 0.4	0.4	2.6	7.5
Complications	5.1	0.0	0.3	0.0

Tumor characteristics include tumor type, tumor size, and tumor invasion. Clinician-reported deficits include cranial nerve deficits, preoperative pituitary function, preoperative visual defects, and preoperative visual acuity. Treatment characteristics include prior treatment and time between diagnosis and surgery. A negative percentage in adjusted R^2 analyses means that that variable cluster does not have any association with the Short Form-36 component score

PCS physical component score, *MCS* mental component score

of smell and taste 6 months after surgery, more attention should be paid to these symptoms when counselling the patients before surgery.

Postoperative nasal discharge and crusting were two other symptoms significantly associated with general HRQoL in our study. For these symptoms, nasal saline

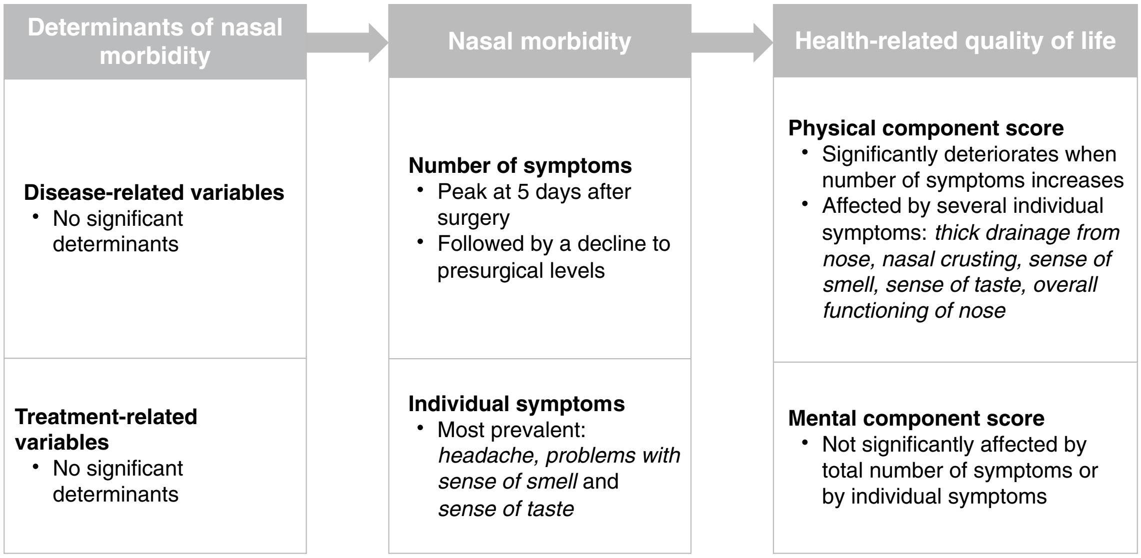

Fig. 3 Summary of the main results

irrigation may effectively decrease the symptom burden [42]. In our clinical practice, all patients receive nasal saline and instructions for nasal irrigation following endoscopic surgery, and the great majority adheres to this treatment. Additionally, postoperative assessment and treatment by an ENT specialist may be beneficial. To determine which patients could benefit from intensified consultation with an ENT specialist, PROMs can play an important role, potentially using a small number of screening questions based on the results of this study.

Although headache is included in the ASK-12, it is not a purely sinonasal symptom. In line with our findings, previous studies reported a preoperative headache prevalence ranging from 37 to 70% in pituitary patients 41 [43], and demonstrated that headache can significantly affect HRQoL [10–12]. It should however be noted that headache is very common in the general population, with 50% of adults reporting headache in the last year [44]. Because the relation between pituitary adenomas and headache is often not evident, except in the case of pituitary apoplexy, headache alone is a controversial indication for surgery and requires thorough investigation [45].

Our finding that complications only marginally affected general HRQoL at 6 weeks and 6 months after surgery is in agreement with a previous study assessing the impact of surgical complications on pituitary patients' HRQoL [46]. A possible explanation is that the highest burden of complications is experienced directly after surgery as delayed complications are rare [47], resulting in a low impact of complications on general HRQoL 6 weeks or 6 months after surgery.

Strengths and limitations

A few previous studies investigated the relation between symptoms and HRQoL following transsphenoidal pituitary surgery, but only considered one self-reported symptom, i.e. headache [10–12], or only measured sinonasal symptoms instead of general HRQoL [13, 14], while general HRQoL provides a more comprehensive view of patients' functioning and wellbeing than questionnaires limited to sinonasal problems. The relation between nasal symptoms and general HRQoL following transsphenoidal surgery has never been studied before. Therefore, a strength of this study is the focus on a variety of patient-reported nasal symptoms as measured by a validated questionnaire, which gives a more comprehensive overview of the relation between self-reported perioperative symptoms and general HRQoL than previously reported [10–12]. However, some limitations must be noted. First of all, because scaled questionnaire items were used, the presence of a symptom was based on a cut-off value deemed clinically relevant by the research team, i.e., if the patient considered a symptom at least a minor problem. Results might differ slightly for different cut-offs (≥ 1 vs. ≥ 2, on a scale of 0–5); however, our sensitivity analyses as shown in Supplements 7–15 show similar results. In addition, whereas symptoms were measured five days after surgery, no HRQoL data were measured at this timepoint, because the SF-36 asks about the patient's experiences in the past four weeks, which would mainly cover the period before surgery. Data on HRQoL at 5 days would have been relevant since nasal symptoms were most pronounced directly after surgery. However, as many of these symptoms tend to resolve within the first weeks after surgery [8, 35], the relation between symptoms and HRQoL is more relevant at 6 weeks. Finally, despite the validation of the SF-36 in several countries, some differences in SF-36 outcomes may exist between countries, which might limit the international generalizability of the results presented in this study [18].

Conclusion

Endoscopic transsphenoidal surgery plays an important role in the treatment of pituitary adenomas and is associated with temporary deterioration of nasal symptoms. Here, we demonstrated that pituitary patients' physical HRQoL is significantly affected by postoperative nasal symptoms, especially problems with sense of smell and taste, and nasal discharge. Therefore, attention for and treatment of these symptoms is essential, especially if the nasal symptoms persist for several weeks, as these are a potential target for improvement of patients' HRQoL. Since the use of a mucoseptal flap was not associated with more nasal symptoms, these results also indicate that mucoseptal flaps can be used safely for intraoperative reconstruction techniques of dural defects without compromising patients' HRQoL on the long term.

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Author contributions NRB, WRF, DJL, contributed to the study conception and design. Data collection was performed by DJL. Data analysis was performed by MM. The first draft of the manuscript was written by MM and AHZN and all authors commented on previous versions of the manuscript. All authors provided input on the interpretation of the analyses and results, and read and approved the final manuscript.

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Data availability Data requests can be directed to DJL: d.j.lobatto@lumc.nl.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Medical Ethical Committee of the Leiden University Medical Center (No. p12.067).

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

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