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Prospective evaluation of multidimensional health-related quality of life after endoscopic endonasal surgery for pituitary adenomas using the endoscopic endonasal sinus and skull base surgery questionnaire

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Abstract

Objective: Social functioning is an important factor in the evaluation of postoperative health-related quality of life (HRQoL) for pituitary adenoma patients. In a prospective cohort study multidimensional HRQoL of non-functioning (NFA) and functioning (FA) pituitary adenoma patients were evaluated following endoscopic endonasal surgery using the endoscopic endonasal sinus and skull base surgery questionnaire (EES-Q).

Methods: Prospectively, 101 patients were included. The EES-Q was completed preoperatively and postoperatively (2 weeks, 3 months, 1 year). Sinonasal complaints were completed daily during the first week postoperatively. Preoperative and postoperative scores were compared. A generalized estimating equation (uni- and multivariate) analysis was performed to identify significant HRQoL changes related to selected covariates.

Results: Two weeks postoperatively, physical ($p < .05$) and social ($p < .05$) HRQoL are worse and psychological ($p < .05$) HRQoL improved compared with preoperatively. Three months postoperatively, psychological HRQoL ($p = .01$) trended back to baseline and no differences in physical or social HRQoL were reported. One year postoperatively, psychological ($p = .02$) and social ($p = .04$) HRQoL improved while physical HRQoL remained stable. FA patients report a worse HRQoL preoperatively (social, $p < .05$) and 3 months postoperatively (social, $p < .02$ and psychological, $p < .02$). Sinonasal complaints peak in the first days postoperatively and gradually return to presurgical levels 3 months postoperatively.

Conclusions: The EES-Q provides meaningful information on multidimensional HRQoL to improve patient-centred health care. Social functioning remains the most difficult area in which to achieve improvements. Despite the relatively modest sample size, there is some indication that the FA group continues to show a downward

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trend (and thus improvement) even after 3 months, when most other parameters reach stability.

Level of evidence: Level II–B.

KEYWORDS

anterior skull base, endoscopic endonasal sinus and Skull Base surgery questionnaire (EES-Q), endoscopic skull base surgery, patient reported outcome measure, quality of life

1 | INTRODUCTION

Pituitary adenomas are among the most common intracranial tumors, with an overall estimated prevalence of around 17% based on radiologic and autopsy studies.¹ They are classified by size and functional status, presenting with endocrinological or ophthalmological compressive effects. The pathology and treatment of pituitary adenomas may cause changes in health-related quality of life (HRQoL). Pituitary adenomas can be safely and effectively treated by endoscopic endonasal surgery (EES).²

Objective endpoints have always been important to assess the effect of treatment. Today, the value of the patient's perspective on health outcomes is recognized and can be addressed.^{3–5} HRQoL is a patient-reported outcome measure that aims to describe to which extent the patient's perception of well-being is affected by a medical condition or treatment.⁶ This helps both physicians and patients to better understand of the factors that influence the patient-reported HRQoL. This improves preoperative counseling and patient-centered health care. HRQoL should be evaluated in physical, psychological and social domains.^{4,7} Other frequently used disease-specific instruments to evaluate the effect of EES on HRQoL do not capture all relevant HRQoL domains, do not assess nasal morbidity, or are not validated for EES or pituitary adenomas.^{8,9}

Our research group developed and validated the endoscopic endonasal sinus and skull base surgery questionnaire (EES-Q) to assess HRQoL after EES.^{8,10} It is a reliable and comprehensive instrument including physical, social and psychological domains. The EES-Q provides meaningful information on the burden of EES in all three health domains in one single instrument, suitable for daily practice and scientific research.^{10,11}

This study prospectively evaluated the effect of EES on overall HRQoL of pituitary adenoma patients (non-functioning (NFA) and functioning (FA)) using the EES-Q to improve patient monitoring, counseling and shared-decision making. Factors that influence the postoperative HRQoL are identified with use of uni- and multivariate analyses. Finally, we specifically set out to map patient-perceived nasal symptoms during the first week postoperatively.

2 | MATERIALS AND METHODS

A prospective study was performed at the Department of Otorhinolaryngology – Head and Neck Surgery and Neurosurgery in a tertiary

referral center. Local institutional review board approval was obtained before commencing.

2.1 | Subjects

Between April 2014 and December 2016, 119 pituitary adenoma patients were enrolled in this study. Patients included were (1) aged ≥18 years; (2) able to read and write Dutch; (3) treated by EES. Thirteen patients were excluded because of large amount of missing data at several time points.¹⁰ Five patients were included twice in the study, the second surgery was used as baseline. Data of the remaining 101 patients were analyzed.

Sinonasal complaints during the first postoperative week were assessed in subgroups. As a rule of thumb, a subgroup of approximately 50 was considered adequate. They were included chronologically. Four patients were excluded because of missing data. The remaining 46 patients were included for statistical analyses.

2.2 | Study design

One day preoperatively, eligible patients were informed and asked to participate. Written informed consent was obtained. The EES-Q was completed 1 day preoperatively and during postoperative follow-up (2 weeks, 3 months and 1 year). The sinonasal items were also completed daily during the first week. Patient received the EES-Q per mail.

2.2.1 | The Endoscopic Endonasal Sinus and Skull Base Surgery Questionnaire

The EES-Q is a validated, disease-specific instrument for patients undergoing endoscopic endonasal sinus or skull base surgery, comprising a physical, psychological and social domain with 30 items.^{8,10} Completing the EES-Q takes 3–5 min.¹⁰ Items are formulated as complaints or activities with a five-point Likert response scale ranging from not at all (1), mildly (2), moderately (3), severely (4) to very severely (5) to indicate the degree of inconvenience, with lower scores indicating better HRQoL (Data S1).

Easily interpretable *Domain scores* ranging from 0 (not at all) to 100 (very severe inconvenience) were calculated by summing the

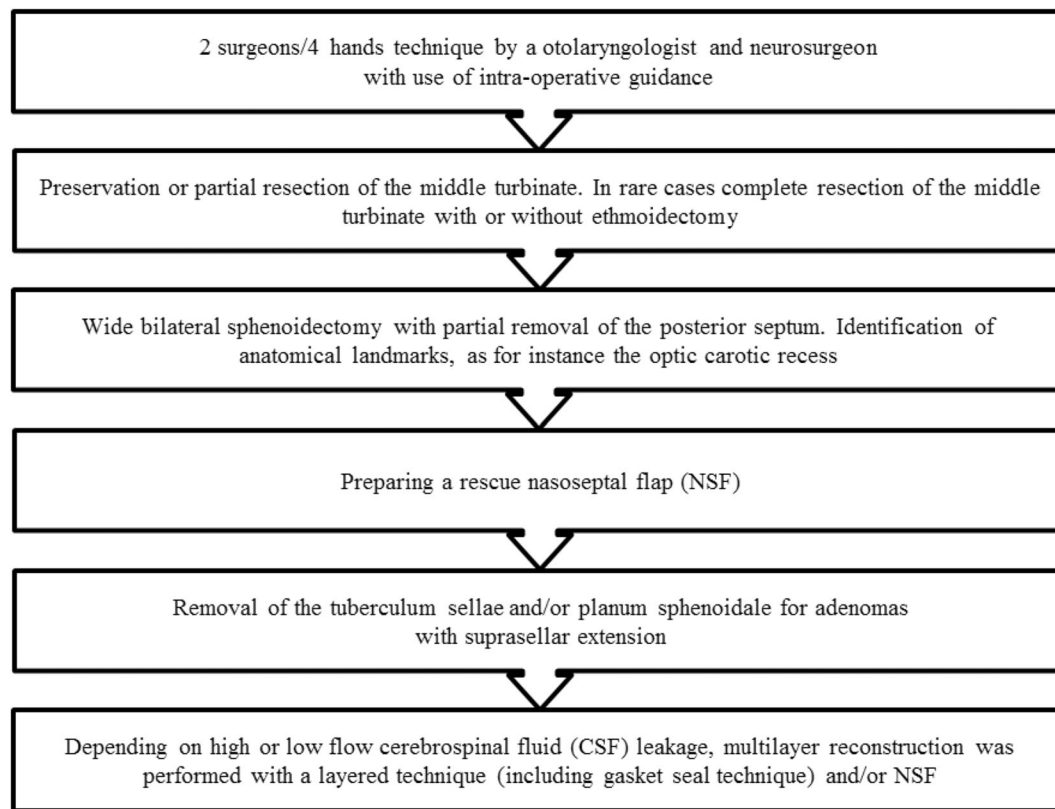


FIGURE 1 Surgical procedure. The endoscopic transsphenoidal approach used in our clinic is shown step by step^{2,15}

10-item score of each domain, subtracting 10 points from this total and multiply this by 2.5. Domain scores were corrected for missing answers by adjusting the subtracted value and the multiplication factor accordingly. For example, for patients with 1 missing answer domain scores were calculated by summing the 10-item score of each domain, subtracting 9 points from this total and multiply this by 2.779, and so on. To calculate the total EES-Q score, ranging from 0 (not at all) to 100 (very severe inconvenience), the sum of the domain score was divided by 3, indicating that each of the EES-Q domains are equally important. The maximum number of missing answers is three per subject per domain.¹⁰

2.3 | Preoperative evaluation

Patients underwent rigid nasal endoscopy to identify septal deviation and/or signs of infection and/or nasal polyps. Ophthalmic examination (including visual acuity and visual field testing) and endocrinological evaluation to assess pituitary functional derangement were performed. Magnetic resonance imaging (MRI) with gadolinium and conventional sinonasal computed tomography (CT) were obtained. Adenomas were classified into microadenomas (<10 mm), macroadenomas (≥10 mm) or giant adenomas (>35 mm). Parasellar invasion and suprasellar extension were analyzed by a neuroradiologist according to the Knosp or Hardy-Wilson classification.¹²⁻¹⁴

2.4 | Surgical procedure

The main technical aspects of the surgical procedure are listed in Figure 1.^{2,15}

2.5 | Follow-up

Saline rinsing 4–6 times and a topic nasal decongestant 3–4 times daily were prescribed. During postoperative controls (2 weeks, 3 months) nasal debridement was performed. The EES-Q was completed postoperatively at 2 weeks, 3 months and 1 year. Postoperative MRI scans were done to check for residual pituitary adenoma, regrowth or recurrence during follow-up by the endocrinologist. Patients were “in remission” if clinical symptoms had disappeared and serum hormone levels were within normal ranges 6 months postoperatively. Patients with a (biochemical) residual adenoma were closely monitored.

2.6 | Statistical analysis

Descriptive statistics were used to summarize patient's demographics. Mean and standard deviation (SD) were calculated for all domains separately at every follow-up point to indicate the trend in HRQoL. Distributions of domain and total EES-Q scores were checked and

TABLE 1 Covariates

Covariate		
Gender	Male	Female
Age	≤60 years	≥60 years
Postoperative CSF leakage	Yes	No
Prior EES	Yes	No
Parasellar invasion (Knosp)	≥grade III	<grade III
Suprasellar extension (Hardy-Wilson)	≥C	<C
Tumor size	<10 mm	≥10 mm
Non-functioning adenoma	Yes	No
Endocrine remission within 6 months postoperatively	Yes	No
Adjuvant radiotherapy	Yes	No
Need for reoperation	Yes	No
Body mass index	<30 kg/m ²	≥30 kg/m ²

Note: Covariates selected to assess their effect on the trend in HRQoL over time are shown.

Abbreviations: CSF, cerebrospinal fluid; EES, endoscopic endonasal surgery.

appropriate tests were performed (Wilcoxon signed rank test or Mann-Whitney for skewed data and independent t test for normally distributed data). For means of interpretability the mean (SD) is reported instead of the median score. Several covariates based on clinical relevance and previous studies^{5,16,17} were selected to assess their effect on the trend in HRQoL over time (Table 1). A generalized estimating equation (GEE) (univariate and multivariate) analysis was performed on the selected covariates to identify significant longitudinal changes in HRQoL during 1-year follow-up. GEE analysis takes the correlation of responses for an individual patient into account and is suitable for handling missing data and calculates unbiased regression coefficients (β).¹⁸ N varies because of missing data (>3 missing items per domain).¹⁰ A *p*-value <.05 was considered statistically significant. The statistical analyses were performed with IBM SPSS Statistics version 22.0 (SPSS IBM, Inc.).

3 | RESULTS

3.1 | Patient characteristics

A total of 101 patients (54.5% female) were included. The mean age was 56.5 ± 13.0 years. Seventy-four (73.3%) patients were diagnosed with a macroadenoma (mean 25.1 ± 8.5 mm) and 27 (26.7%) patients with a microadenoma (mean 6.3 ± 2.1 mm). Fifty-nine (58.4%) patients were diagnosed with a NFA and 42 (41.6%) with a FA. Prior EES was performed in 16 (15.8%) patients (Table 2).

The 74 macroadenoma patients presented initially with ophthalmological complaints (45.9%), hypersecretion syndrome (17.6%) hypopituitarism (12.2%) or facial pain in the area supplied by the maxillary nerve (1.4%). Seventeen (23.0%) patients underwent EES because of

TABLE 2 Patients' characteristics

Characteristics	n (%)
Gender	
Male	46 (45.5)
Female	55 (54.5)
Mean (SD) age (in years)	56.5 (13.0)
ASA	
I	21 (20.8)
II	65 (64.3)
III	14 (13.9)
IV	1 (1.0)
Mean (SD) BMI (in kg/m ²)	29.2 (5.9)
Prior EES	16 (15.8)
Macroadenoma	74 (73.3)
NFA	59 (79.7)
Cushing	1 (1.4)
Acromegaly ^a	10 (13.5)
Prolactinoma	4 (5.4)
Microadenoma	27 (26.7)
Cushing	19 (70.4)
Acromegaly	4 (14.8)
Prolactinoma	3 (11.1)
TSH	1 (3.7)
Complications, postoperative ^b	
None	56 (55.4)
CSF leakage ^c	5 (5.0)
Epistaxis	9 (8.9)
Sinusitis	5 (5.0)
Diabetes insipidus (transient ^d ; persistent)	10 (9.9); 5 (5.0)
SIADH (transient) ^d	13 (12.9)
Urinary tract infection	1 (1.0)
AF de novo	1 (1.0)
Apoplexy	1 (1.0)

Abbreviations: AF, atrial fibrillation; ASA, American Society of Anesthesiologists; BMI, body mass index; CSF, cerebrospinal fluid; EES, endoscopic endonasal surgery; NFA, non-functioning adenoma; SD, standard deviation; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TSH, thyroid-stimulating hormone.

^aOne silent somatotroph.

^bSix patients presented with more than one complication.

^cOne patient with meningitis.

^dDefined as recovery within 6 months.

an endangered optic chiasm on MRI without ophthalmological complaints yet. Eight of the 74 (7.9%) macroadenomas were giant adenomas. Parasellar invasion (≥Knosp Grade 3) and suprasellar extension (≥Hardy-Wilson Grade C) was present in 21 (28.4%) and 9 (12.2%) patients, respectively.

All 27 microadenoma patients presented with a hypersecretion syndrome: Cushing's disease (19; 70.4%), acromegaly (4; 14.8%), prolactinoma (3; 11.1%) and thyrotropin-secreting pituitary adenoma (1; 3.7%).

FIGURE 2 Mean domain and EES-Q scores—all patients. The mean domain and EES-Q scores of the physical, psychological and social domain of the EES-Q preoperatively and postoperatively (2 weeks, 3 months, 1 year) are shown. Lower scores represent better HRQoL

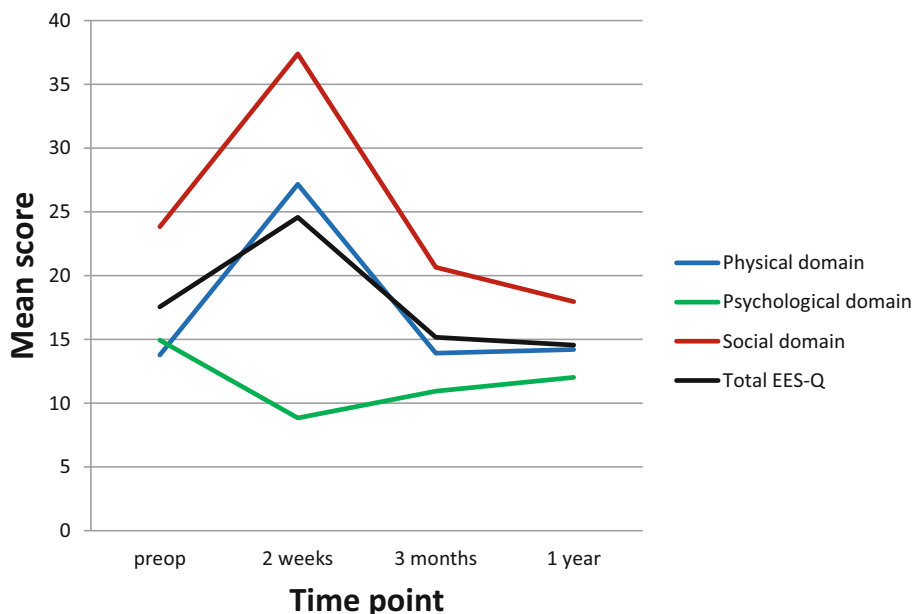
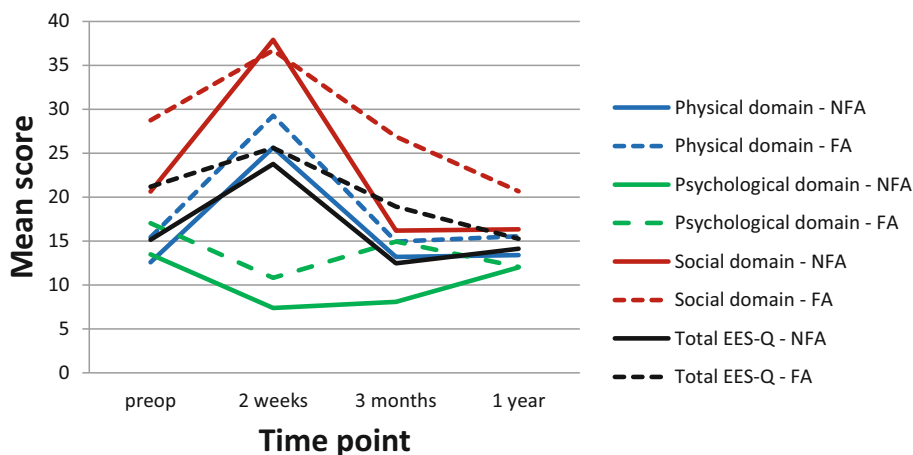


FIGURE 3 Mean domain and EES-Q scores—NFA versus FA. The mean domain and EES-Q scores of the physical, psychological and social domain of the EES-Q preoperatively and postoperatively (2 weeks, 3 months, 1 year) are shown. Lower scores represent better HRQoL



The most common postoperative complication was diabetes insipidus (Table 2). Five (5.0%) patients had postoperative CSF leakage. Bed rest and external lumbar drainage for 3 days were necessary for three patients. Two patients required reoperation for reconstruction of the defect using fascia lata and fat (1) and a NSF (1). All patients recovered completely. For 5 (5.0%) patients reoperation was due to postoperative epistaxis, corrected with bipolar coagulation of the septal branches of the sphenopalatine artery (4) or clipping of the sphenopalatine artery on both sides (1).

Of the 42 patients with FA, endocrine remission was achieved in 24 (47.6%) patients. Two of these 24 patients had recurrent biochemical activity requiring reoperation or radiotherapy, respectively 2 and 4 years postoperatively. Eighteen of the 42 (42.9%) patients did not achieve endocrinological remission within 6 months. Despite suppression therapy, 12 (66.7%) patients underwent adjuvant postoperative therapy: transsphenoidal reoperation (1), radiotherapy (9) or transsphenoidal reoperation followed by radiotherapy (2). Two patients refused adjuvant therapy.

3.2 | Health-related quality of life

3.2.1 | Effect of EES on HRQoL during follow-up

Two weeks postoperatively

In the physical and social domain, a worse HRQoL was reported 2 weeks postoperatively compared with preoperative scores (both $p < .01$). In the psychological domain, a HRQoL improvement was reported ($p < .01$) (Figure 2).

NFA patients reported a worse HRQoL in the physical, psychological and social domain (all $p < .01$) compared with preoperative scores. FA patients reported a worse HRQoL in the physical ($p < .01$) and psychological domain ($p < .05$) (Figure 3).

Three months postoperatively

Improvement in the psychological domain was reported 3 months postoperatively compared with preoperatively ($p = .01$) in our entire group because of the NFA patients but not the FA patients (Figure 2, Figure 3).

One year postoperatively

Patients reported a HRQoL improvement in the psychological domain ($p = .02$) and in the social domain ($p = .04$) (Figure 2).

The physical, psychological and social domain scores of the NFA patients return to their preoperative baseline. It was the better psychological and social HRQoL scores (both $p = .03$) of the FA patients that caused the general group result to be significant. The physical domain scores remained largely unchanged.

3.2.2 | NFA versus FA patients

Total EES-Q scores—all time points

FA patients reported a significantly worse EES-Q score preoperatively ($p < .03$) and 3 months postoperatively ($p < .01$) compared with NFA patients (Figure 3).

Domain scores—all time points

Preoperatively, a worse social HRQoL was reported by FA patients compared with NFA patients ($p < .04$). Three months postoperatively, a worse psychological and social HRQoL was reported by FA patients (both $p < .02$) (Figure 3).

3.2.3 | Longitudinal patterns of HRQoL—univariate analysis

Univariate GEE analysis showed that only the covariates “gender” and “age” significantly influence HRQoL during follow-up.

Gender

Two weeks postoperatively, males reported a significantly better physical HRQoL compared with females ($\beta = -15.10, p < .01$). During 1 year

follow-up, all patients report a significant improvement in the physical domain compared with 2 weeks postoperatively, ($\beta = -8.20, p < .01$) yet, males maintain their better physical HRQoL while females do not.

Age

Two weeks postoperatively, patients ≤ 60 years old reported a significantly worse physical HRQoL ($\beta = 11.10, p = .02$) and social HRQoL ($\beta = -16.72, p = .04$) compared with patients > 60 years old. At 1 year follow-up, all patients reported a significant improvement in physical ($\beta = -5.46, p < .01$) and social ($\beta = -6.19, p < .01$) domain scores compared with 2 weeks postoperatively. Patients > 60 years old maintain a better physical and social HRQoL during follow-up compared with patients ≤ 60 years old. Age did not significantly influence the psychological domain.

3.2.4 | Longitudinal patterns of HRQoL—multivariate analysis

Multivariate GEE analysis showed a significantly better physical HRQoL for males compared with females 2 weeks postoperatively ($\beta = -14.30, p < .01$). Additionally, males > 60 years old reported a significantly better physical HRQoL compared with males ≤ 60 years old ($\beta = -9.99, p < .03$). During follow-up, both males and females of all ages report a significant improvement in physical HRQoL compared with 2 weeks postoperatively ($\beta = -9.22, p < 0.01$). Yet, males > 60 years old maintain a better physical HRQoL compared with males ≤ 60 years old during follow-up.

3.2.5 | Sinonasal symptoms during the first week postoperatively

All sinonasal items showed a significantly worse (all $p < .03$) HRQoL 1 day postoperatively compared with preoperatively. Over the next

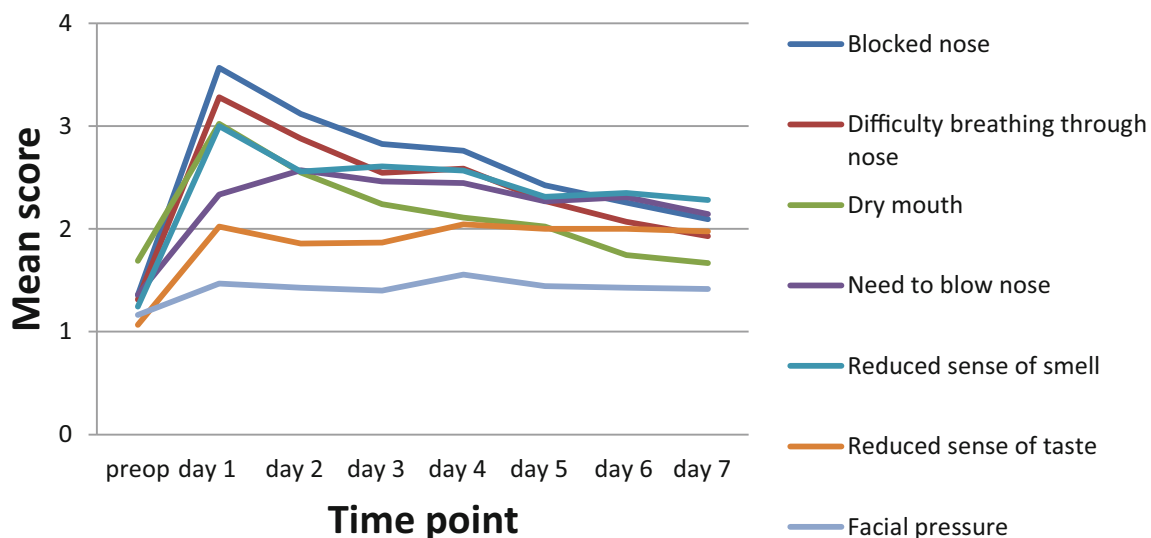


FIGURE 4 The sinonasal-related physical complaints of the EES-Q the first week postoperatively. The mean sinonasal-related physical complaints scores preoperatively and the first 7 days postoperatively are shown. Lower scores represent better HRQoL

days, sinonasal HRQoL gradually improved. After the first postoperative day, four sinonasal-related physical items were significantly better at 7 days postoperatively: “blocked nose” ($p < .01$), “difficulties in breathing” ($p < .01$), “dry mouth” ($p < .01$) and “sense of smell” ($p = .01$) (Figure 4).

4 | DISCUSSION

4.1 | Key findings

Our results emphasize the value of assessment via a multidimensional HRQoL scale including social, psychological and psychological domains. Compared with physical and psychological HRQoL, patients experience the most inconveniences in social HRQoL 1 year postoperatively. FA patients report a significantly worse HRQoL preoperatively and 3 months postoperatively compared with NFA patients, due to impaired social HRQoL, which does continue improving over a year. As expected a significantly worse sinonasal HRQoL was reported 1 day postoperatively, gradually improving in time.

4.2 | Health-related quality of life

4.2.1 | Social domain

Social life and work are essential contributors to HRQoL.¹⁹ Positive social relations are predictors of happiness and work performance is associated with perceived health.^{20,21} Patients in our study reported the most inconveniences in social functioning 1 year postoperatively compared with physical and psychological issues. A trend toward significant improvement in social functioning is shown 1 year postoperatively. Limited literature is available on social HRQoL in this population. Available results are based on individual items in HRQoL instruments or on a generic HRQoL instrument, making comparisons with our instrument difficult. Some studies show significant improvement in social functioning 6 months and 1 year after EES^{17,22–25} whereas others find no significant differences.^{26–28} Little et al.²⁹ showed a correlation between sinonasal QoL and overall health status after EES. In our study, the trend of social limitations follows the changes in physical complaints. This suggests that subjective impairment in carrying out activities could be the indirect effect of physical complaints.^{22,29}

The worse social HRQoL preoperatively and 3 months postoperatively in our FA patient population might be explained by the negative impact of hormonal imbalances.^{24,30–32}

Our study reports a greater absolute difference in improvement in the social domain for patients with a FA compared with NFA indicating that the effect of EES is greater for FA patients. However, this result is not significant. This might be caused by the probable lack of power in this specific analysis. Change-scores could only be calculated for completers at 1 year follow-up.

4.2.2 | Psychological domain

Our study shows a significant improvement in psychological HRQoL 2 weeks postoperatively, which continues during 1 year follow-up. An improvement in psychological health has previously been reported 3 to 6 weeks postoperatively.^{5,17,22,25,33}

Three months postoperatively, we found a significantly worse psychological HRQoL for FA patients compared with NFA patients. At 1 year follow-up no difference was observed. Mental health of NFA patients tends to recover between 1 and 6 months postoperatively with a clear tendency to further improvement during 1 year follow-up.^{22,23,34,35} NFA patients tend to recover sooner than FA patients, possibly due to postoperative hormonal imbalance for patients with FA.^{24,30–32} We speculate that the improvement in psychological HRQoL shortly after EES is the result of the relief of anxiety around surgery.

4.2.3 | Physical domain

Few detailed descriptions of patients' early postoperative symptoms are available, despite these problems being self-evident. In our study, all items of the physical domain showed a significantly worse HRQoL on 1 day postoperatively compared with preoperatively. Scores gradually improve through the first postoperative week. Two other studies showed a peak onset of nasal symptoms 1 to 3 days after transsphenoidal pituitary surgery.^{22,36} Castle-Kirsbaum et al.²⁴ also showed a significantly worse sinonasal QoL at day 1, 3 and 7 postoperatively compared with preoperatively. In our study, worse physical HRQoL is reported 2 weeks postoperatively compared with preoperative scores with a return to baseline (preoperative scores) after 3 months. This correlates with previous studies evaluating the HRQoL after EES for pituitary adenomas.^{5,22,24,26,29,34,37–39} The peak incidence of such complaints come in the first days postoperatively and as expected return to preoperative scores between 2 weeks and 3 months postoperatively.

We found no significant difference in the physical domain between NFA and FA patients preoperatively and during follow-up. This is in accordance with other studies.^{5,29,38,39}

Worth noting is that acromegaly patients reported worse physical HRQoL compared with other pituitary adenoma patients in our study. This could potentially be caused by the high incidence of polyp formation and mucosal hypertrophy within in the nose and paranasal sinuses in these patients.⁴⁰ Unfortunately, the number of patients is too small to perform subgroup analyses.

4.3 | Longitudinal patterns of HRQoL

In accordance with previous studies, female gender was a negative factor for physical HRQoL.^{16,17,24,25,41} In our study, older males reported better physical HRQoL during 1 year follow-up. In some studies^{35,36,42} age was not associated with nasal symptoms, whereas

Little et al.²⁹ showed that older age negatively correlated with sinonasal QoL. It is possible that an individual's attitude toward the physical complaints varies over time and experience and is influenced by psychological phenomena such as adaptation, coping, and expectation.⁴³

One might consider intra-operative CSF leakage a complication and therefore not presenting numbers on this type of CSF leakage a limitation of the study. However, considering the disease characteristics of this patient group, intra-operative CSF leakage might be inevitable to successfully operate on these patients. Therefore, only postoperative CSF leakage is considered a complication and is taken into account in this study.

4.4 | Limitations

In absence of a reasonable effect size estimation performing a formal sample size calculation was not possible. From our experience, however, we find the number of 100 to be generally sufficient to show clear direction in these types of studies. We restricted enrolment to pituitary adenomas. This limits the confounding influence of a heterogeneous group with a variety of skull base pathologies.^{33,39,42,44-47} It does not eliminate the confounding effect of various pituitary adenoma types on HRQoL. NFA's tend to be larger than FA's when treated by EES and patients cured from FA can continue to suffer from the irreversible effects of hormonal dysregulation.^{30,47} Furthermore, our study was not specifically designed to assess the effect of hormonal therapy. No FA subgroup analysis was performed due to the small number of patients in the FA subgroups. Ophthalmologic examination was not consistently documented, or was assessed in a different hospital with different parameters and is therefore not included in the univariate analysis. The number of included patients varies in the analyses due to missing data. Although this number is explainable and the GEE can validly handle missing data, we aim at higher rates of completed questionnaires. The EES-Q is now digitally available with an automatic control to prevent missing items, only a completed form can be submitted. The EES-Q is a relatively new instrument, reference values and the minimal clinically important difference are not yet available which may hamper interpretation of single scores. However, interpretation of score differences is possible and informative. Additional research with larger subgroups is necessary to confirm our results, to keep improving patient-centered health care.

5 | CONCLUSION

This study emphasizes the importance of multidimensional HRQoL, including a social domain. The EES-Q provides meaningful information on the burden of EES, combining all three health domains in one single instrument. Preoperatively and during one-year follow-up pituitary adenoma patients undergoing EES experience the worst HRQoL in the social domain. As expected, sinonasal symptoms peak the first day postoperatively and gradually improve in the first week with a return to preoperative scores after 3 months. The total EES-Q score

improved 1 year postoperatively compared with preoperatively. The EES-Q plays an important role in patient monitoring, disease screening, shared decision-making, counseling and research.

CONFLICT OF INTEREST

The authors have no financial or other conflicts to report.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available upon request from the authors. The data are not publicly available due to privacy or ethical restrictions.

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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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