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Clinical Outcomes of Endoscopic Transsphenoidal Resection of Pituitary Adenoma in Patients With Tobacco Smoking or Nicotine Dependence

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Abstract

Background: While the endoscopic endonasal approach has revolutionized pituitary surgery, postoperative complications contribute to significant morbidity. Tobacco smoking is a well-established risk factor for poor wound healing and adverse outcomes in other skull base procedures, yet its direct influence following transsphenoidal resection is largely unaddressed. This study seeks to define the association between smoking history and adverse outcomes in this population.

Methods: This is a retrospective cohort study utilizing the TriNetX global federated research network (2011–2024) to identify adults undergoing primary endoscopic transsphenoidal resection for benign pituitary tumors. Patients were stratified by tobacco use or nicotine dependence. To control for confounding, cohorts were matched via 1:1 propensity score matching (PSM). A panel of outcomes, defined by the PitCOP Delphi consensus, was analyzed. Time-to-event analysis for reoperation was performed, and survival distributions were compared between cohorts.

Results: The study population included 11,376 patients: 3,597 smokers and 7,779 non-smokers. Following PSM, 3,219 well-balanced pairs were established. In the matched cohorts, smoking was associated with significantly higher odds of postoperative cerebrospinal fluid leak (OR 1.30; p=0.006), 30-day hospital readmission (OR 1.33; p<.001), and new postoperative hypopituitarism (OR 1.23; p=.0086). Rates of infection and in-hospital mortality were similar. The time-to-event analysis for reoperation showed a higher cumulative incidence in the smoking cohort at 2-year follow-up; however, this difference in survival distributions was not significant after PSM.

Conclusions: This large, population-based study suggests that smoking may be associated with adverse outcomes following endoscopic pituitary surgery. Our findings indicate a significant correlation between tobacco use and a triad of major complications: impaired healing of CSF leak repairs, increased morbidity requiring early hospital readmission, and a risk of new-onset hypopituitarism. This evidence reinforces the importance of smoking as a critical, modifiable risk factor and warrants greater emphasis on cessation during preoperative counseling and patient optimization.

INTRODUCTION

Pituitary adenomas represent approximately 10% to 20% of all primary intracranial neoplasms.[1,2] While histologically benign, these tumors often present with significant clinical morbidity, including progressive visual field loss, secondary endocrine dysfunction, and debilitating headaches due to local mass effect.[3–5] Endoscopic transsphenoidal hypophysectomy (TSH) has emerged as the contemporary standard of care for surgical resection, offering superior visualization, shortened operative times, and higher rates of gross total resection compared to traditional microscopic approaches.[6,7]

Despite the high technical success rates associated with endoscopic TSH, the procedure is not without risks. Postoperative complications such as cerebrospinal fluid (CSF) leaks, electrolyte imbalances, and intracranial infections remain significant challenges that can necessitate a return to the operating room,

prolong hospitalization, and lead to unplanned readmissions.[3,7–10] Identifying modifiable risk factors that influence these outcomes is essential for optimizing preoperative patient selection and intraoperative management.

Tobacco smoking is a well-established driver of perioperative morbidity across various surgical disciplines.[11–13] However, within the specific context of endoscopic skull base surgery and pituitary resection,[14,15] the existing literature is sparse and often conflicting. This significant knowledge gap, combined with the small sample sizes of previous single-institution studies,[15] necessitates a more robust, large-scale investigation. Utilizing a large, multicenter dataset, this study aims to comprehensively analyze the impact of nicotine dependence or smoking on postoperative outcomes after endoscopic TSH for pituitary adenoma. We hypothesized that smoking history would negatively affect surgical healing, particularly regarding the stability of CSF leak repairs, and increase the overall burden of perioperative complications.

METHODS

Data Source and Ethical Compliance

Patient data for this analysis were extracted from the TriNetX Global Collaborative Network, a federated health research platform encompassing de-identified electronic health records from 146 healthcare organizations. This multicenter repository provides a longitudinal view of clinical care, including International Classification of Diseases, Tenth Revision (ICD-10-CM) diagnoses, Current Procedural Terminology (CPT) codes, laboratory results, and pharmacy records. The platform operates in strict compliance with the Health Insurance Portability and Accountability Act (HIPAA) and the General Data Protection Regulation (GDPR). As the network provides only de-identified, aggregated statistical data, the Western Institutional Review Board (IRB) granted a waiver of informed consent. This study is reported following the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Study Population and Cohort Selection

We performed a retrospective, multicenter cohort study of adult patients (> 18 years) undergoing primary surgical intervention for benign pituitary neoplasms (ICD-10: D35.2) between January 2011 and January 2025. The study focused specifically on individuals who underwent neuroendoscopic transnasal or transsphenoidal resection (CPT-4: 62165).

Initially, 11,565 patients were identified. Patients who had a craniotomy within 6 months before or on the index surgical date were excluded. Patients were also required to have at least 6 months of continuous clinical data before (look-back period) and after (follow-up period) the index surgical date. These exclusion criteria were critical to ensuring the homogeneity of the endoscopic approach within the study cohort. This resulted in a final study population of 11,376 patients.

Exposure Definition: Nicotine Dependence

The index date was established as the date of primary endoscopic transsphenoidal surgery. The study population was stratified into two distinct groups based on tobacco use history:

- **Tobacco/Nicotine Dependence (Smokers) Group:** Patients with a documented clinical history of nicotine dependence or active smoking status at the time of the index procedure.
- **Control Group:** Patients undergoing the same neurosurgical intervention without any recorded history of nicotine dependence or tobacco use.

Standardized Outcome Measures

To facilitate high-quality evidence synthesis and clinical benchmarking, the primary and secondary endpoints were selected based on the international core outcome set (COS) for pituitary surgery research (PitCOP).[16] The primary outcome was the postoperative recovery or improvement of pituitary function. This was defined as the Recovery/Improvement of pituitary function post-operatively, including hypopituitarism, hyperprolactinemia, or Cushing's disease, at last follow-up (defined as the study sample minus codes E22, E23, E24.0, E89.3, E29.1, and E28.8).

Secondary outcomes were organized into the following COS domains:

- **Perioperative Surgical Events:** Postoperative CSF leak (ICD-10: G96.0), intraoperative arterial injury (ICD-10: I60–I69, I97.821, I97.51, G91), and intracranial infection (including meningitis) (ICD-10: G00–G09).
- **Systemic and Recovery Outcomes:** 30-day perioperative morbidity, including unplanned 30-day readmission, 30-day reoperation, and in-hospital mortality.
- **Nasal and Sensory Outcomes:** New onset, reduced or absent sense of smell or taste (ICD-10: R43.0, R43.1, R43.2, R43.8, R43.9).
- **Ophthalmic Outcomes:** Documented deterioration of visual acuity (ICD-10: H54.1, H54.2, H54.3, H54.6) or visual fields (ICD-10: H53.4).
- **Extended Endocrine Outcomes:** Postoperative dysnatremia (ICD-10: E87.0, E87.1), new-onset hypopituitarism (ICD-10: E89.3), and sexual or reproductive health issues (ICD-10: E29.1, N52.9, N46.9, E28.2, E28.8, N91.1).
- **Disease Control:** Delayed reoperation occurring beyond the initial 30-day postoperative window up to 3 years.

Propensity Score Matching and Statistical Analysis

To mitigate the impact of baseline clinical and demographic heterogeneity between smokers and non-smokers, a 1:1 propensity score matching (PSM) protocol was implemented. Cohorts were balanced on age, sex, race, and ethnicity, as well as an extensive array of comorbidities, including BMI, hypertension,

diabetes mellitus, ischemic heart disease, and history of malignancy. Furthermore, matching accounted for baseline endocrine status, preoperative medication use (e.g., steroids, thyroid supplements), and preoperative laboratory values (sodium, glucose, and hemoglobin).

The efficacy of the matching process was validated using standardized mean differences (SMD), with a threshold of SMD < 0.1 utilized to define negligible imbalance between groups. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to evaluate the association between smoking and the defined outcomes. Time-to-event outcomes, specifically reoperation rates, were analyzed using Kaplan-Meier survival curves and compared via the log-rank test. To estimate the relative risk over time, a Cox proportional hazards regression model was utilized to calculate hazard ratios (HR) and 95% CIs. The proportional hazards assumption was verified for the primary exposure using Schoenfeld residuals.

Statistical significance was set at a two-sided $P < .05$. All computational analyses were conducted on the TriNetX platform utilizing R (version 4.5.2), with figures produced using ggplot2 and GraphPad Prism (version 9.0).

RESULTS

Participants and Descriptive Data

A total of 11,565 adult patients undergoing primary endoscopic transsphenoidal resection for benign pituitary tumors were identified in the TriNetX Global Collaborative Network between January 2011 and January 2025. Following the exclusion of 189 patients who underwent a craniotomy before or on the index surgery date, 11,376 patients were included in the final analysis. Of these, 3,597 patients were smokers, and 7,779 were non-smokers (**Figure 1)**. Before matching, smokers were significantly older (55.7 ± 14.9 years vs. 51.8 ± 16.2 years; $P < .0001$) and more likely to identify as male (60.45% vs. 44.38%; $P < .0001$). Significant racial disparities were noted, with smokers more likely to identify as White (67.06% vs. 61.37%; $P < .0001$) or Black/African American (19.02% vs. 16.82; $P = .0041$). Clinical comorbidities were significantly different between the groups, as the smokers cohort exhibited a higher prevalence of hypertension (58.72% vs. 47.17%; $P < .0001$), ischemic heart disease (10.73% vs. 6.02%; $P < .0001$), and diabetes mellitus (25.39% vs. 21.37%; $P < .0001$). Following 1:1 PSM, two balanced cohorts of 3,219 patients each were generated, which eliminated significant differences in demographics, major comorbidities, and baseline laboratory values (SMD < 0.1) (**Table 1, Figure 2)**.

Outcomes Before and After PSM

Smoking was associated with several adverse outcomes that maintained statistical significance both before and after PSM. Smokers demonstrated a significantly increased risk of CSF leak, with rates of 8.6% compared to 6.7% in the matched control group (OR = 1.30; 95% CI: 1.08–1.57; $P = .0056$). Similarly, the risk for 30-day readmission remained significantly higher for smokers after matching, at 25.1% versus 20.1% (OR = 1.33; 95% CI: 1.18–1.50; $P < .0001$). Regarding morbidity, smoking was consistently

associated with a higher risk of new-onset postoperative hypopituitarism, occurring in 13.3% of smokers compared to 11.1% of matched non-smokers (OR = 1.23; 95% CI: 1.06–1.42; P = .0086) (**Table 2)**.

Several outcomes initially associated with smoking status in the crude analysis became non-significant after adjusting for baseline characteristics through PSM. Intraoperative arterial injury (P = .031 to P = 1.00), new visual acuity deterioration (P = .0124 to P = .0773), and postoperative dysnatremia (P = .0051 to P = .1284) all lost statistical significance following the matching protocol. Similarly, sexual and reproductive health issues, which were significantly higher in smokers before matching (18.4% vs. 14.7%; P < .0001), showed no difference between groups post-matching (17.2% vs. 17.9%; P = .5336).

In contrast, several outcomes showed no significant association with smoking status in either the unmatched or matched cohorts. Specifically, there were no significant differences observed both before and after matching for infection and meningitis (matched P = .6885), 30-day reoperation (matched P = .5207), in-hospital mortality (matched P = 1.00), and new sense of smell/taste deficits (matched P = .2198). Furthermore, while the recovery of pituitary function was initially lower in smokers (P = .0214), this difference also resolved after matching (P = .422) (**Table 2)**.

The time-to-event analysis for reoperation showed a lower cumulative incidence in the non-smoking cohort at 2-year follow-up; however, this difference in survival distributions was not statistically significant after PSM (log-rank P = 0.12). The proportional hazards assumption was assessed using Schoenfeld residuals, which confirmed that the assumption was not violated for the smoking status variable (P > .05) (**Figure 3**).

DISCUSSION

This multicenter analysis of 11,376 patients represents the largest investigation to date on the impact of tobacco use or nicotine dependence on clinical outcomes following endoscopic transsphenoidal resection of pituitary adenoma. Our findings demonstrate that smoking is an independent predictor of specific postoperative morbidities after adjustment for demographic and clinical baseline heterogeneity. Specifically, smokers exhibited a significantly higher risk of postoperative CSF leak, unplanned 30-day readmission, and new-onset postoperative hypopituitarism. Tobacco use did not significantly increase the risk of intraoperative arterial injury, in-hospital mortality, or 30-day reoperation rates in our matched cohorts.

The observed increase in postoperative CSF leak risk in smokers aligns with the established pathophysiology of nicotine-induced microvascular compromise.[17,18] Nicotine is a potent vasoconstrictor that reduces peripheral tissue perfusion,[19] while carbon monoxide, a byproduct of combustible tobacco, impairs oxygen delivery by forming carboxyhemoglobin. At the cellular level, chronic tobacco exposure desensitizes the alpha 7 nicotinic acetylcholine receptors (α7-nAChR), which are critical for the angiogenic response to surgical ischemia.[19–21] This creates a hostile

microenvironment for skull base reconstruction, where the rapid integration of mucosal grafts or vascularized nasoseptal flaps is required to provide a permanent barrier against the pulsatile pressures of the CSF. When compared to the single-center study by Min et al.[15], which reported a higher odds ratio for reoperation due to CSF leak (OR = 5.25) in a smaller cohort of 398 patients, our results confirm the clinical reality of impaired healing on a much larger scale, albeit with a more nuanced effect size. The discrepancy in reoperation rates between our large-scale data and smaller series may reflect institutional variations in the threshold for surgical re-intervention versus conservative management of "low-flow" leaks.[22,23]

The significantly higher rate of 30-day unplanned readmission in the smoking cohort (25.1%) represents a substantial healthcare burden and a critical metric of surgical quality.Our results are consistent with broader surgical meta-analyses, indicating that smokers face higher odds of readmission due to a blunted physiological response to surgical stress.[14,17]In the specific context of pituitary surgery, readmissions are most commonly driven by hyponatremia and the evaluation of suspected CSF leaks.[24]While our study did not find a significant difference in postoperative dysnatremia after PSM ($p = 0.1284$), the overall higher readmission rate in smokers suggests they may experience a higher frequency of other systemic complications, such as respiratory complications or delayed wound disruption, that necessitate a return to the hospital. This underscores that the "neurosurgical smoker" requires more intensive post-discharge surveillance to navigate the high-risk window of the first two weeks postoperatively.

A novel and clinically significant finding in our analysis is the increased incidence of new-onset postoperative hypopituitarism in the smoking cohort (13.3% vs. 11.1%). While nicotine acutely stimulates the hypothalamic-pituitary-adrenal axis, driving the release of adrenocorticotropic hormone, cortisol, and Arginine vasopressin, chronic use leads to complex dysregulation of these axes.[25] The localized vascular compromise induced by tobacco may further jeopardize the perfusion of the residual normal pituitary gland during the mechanical stress of tumor resection.[25–27] This finding is particularly relevant given that endocrine recovery and the avoidance of new hormone deficiencies are top priorities within the international PitCOP.[16] Our results suggest that smoking status should be considered a critical prognostic variable when discussing the likelihood of long-term hormonal replacement with patients preoperatively.

From a clinical management perspective, the increased risk of CSF leak in smokers (8.6 %) warrants a more aggressive primary reconstructive strategy. Surgeons should have a lower threshold for utilizing multilayered repairs or vascularized nasoseptal flaps in this population, even in cases where intraoperative leak grade is low. Furthermore, the increased 30-day readmission risk suggests a need for specific discharge protocols, potentially including extended outpatient electrolyte monitoring and earlier clinic follow-up.Preoperative nicotine cessation should be advocated as a mandatory component of surgical optimization, though clinicians must recognize that the physiological disadvantage of a tobacco history persists even in former smokers.[17]

Limitations

This study is limited by the retrospective nature of electronic health record data provided by TriNetX, which relies on the accuracy of ICD-10 and CPT coding and may be susceptible to reporting bias.Additionally, we were unable to differentiate between the impact of combustible tobacco and alternative nicotine delivery systems such as electronic cigarettes or "vaping," which are increasingly prevalent.[28,29]While PSM accounts for documented comorbidities, unmeasured variables such as Knosp grade, tumor consistency, and surgeon-specific technical variations remain potential confounders. Future prospective studies utilizing objective biomarkers like serum cotinine are necessary to further elucidate the dose-dependent relationship between nicotine exposure and pituitary surgical recovery.

CONCLUSION

This multicenter analysis of 11,376 patients demonstrates that tobacco smoking is a significant independent driver of morbidity following endoscopic transsphenoidal pituitary surgery, specifically increasing the risk of postoperative CSF leaks, unplanned 30-day readmissions, and new-onset hypopituitarism. These findings suggest that nicotine-induced microvascular compromise impairs skull base healing and the preservation of residual pituitary function. Consequently, smoking status should be integrated into preoperative risk stratification.

Abbreviations

CI
confidence intervals
COS
core outcome set
CPT
Current Procedural Terminology
CSF
cerebrospinal fluid
HR
hazard ratios
ICD
International Classification of Diseases
IRB
Institutional Review Board
OR
odds ratios
PitCOP
core outcome set for pituitary surgery research
PSM

propensity score matching
SMD
standardized mean differences
TSH
transsphenoidal hypophysectomy

Declarations

Data availability statement:

Template data collection forms, data extracted from included studies, data used for all analyses, analytic code, and other materials used in this study are available from the corresponding author upon reasonable request.

Human Ethics and Consent to Participate declarations:

not applicable

Clinical Trial Registration

This manuscript is a **retrospective study based on claims database**, not a clinical trial. Therefore, clinical trial registration is **not applicable**.

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Disclosures

No disclosures are relevant to this study.

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Tables

Tables are available in the Supplementary Files section.

Figures

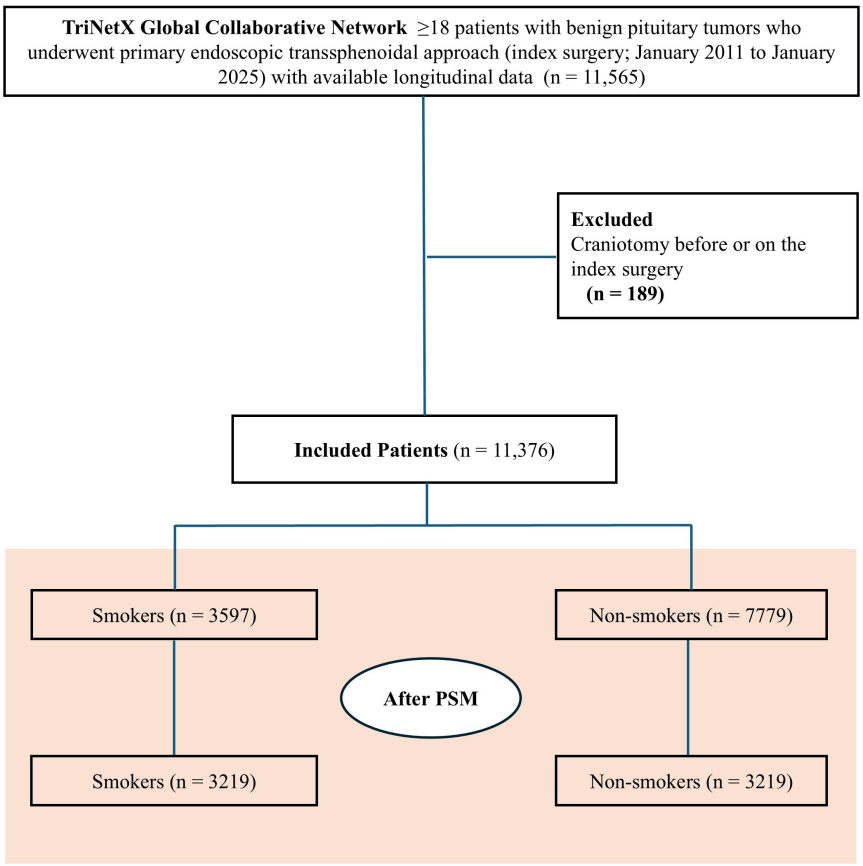


Figure 1

Flowchart of Patient Selection and Attrition.

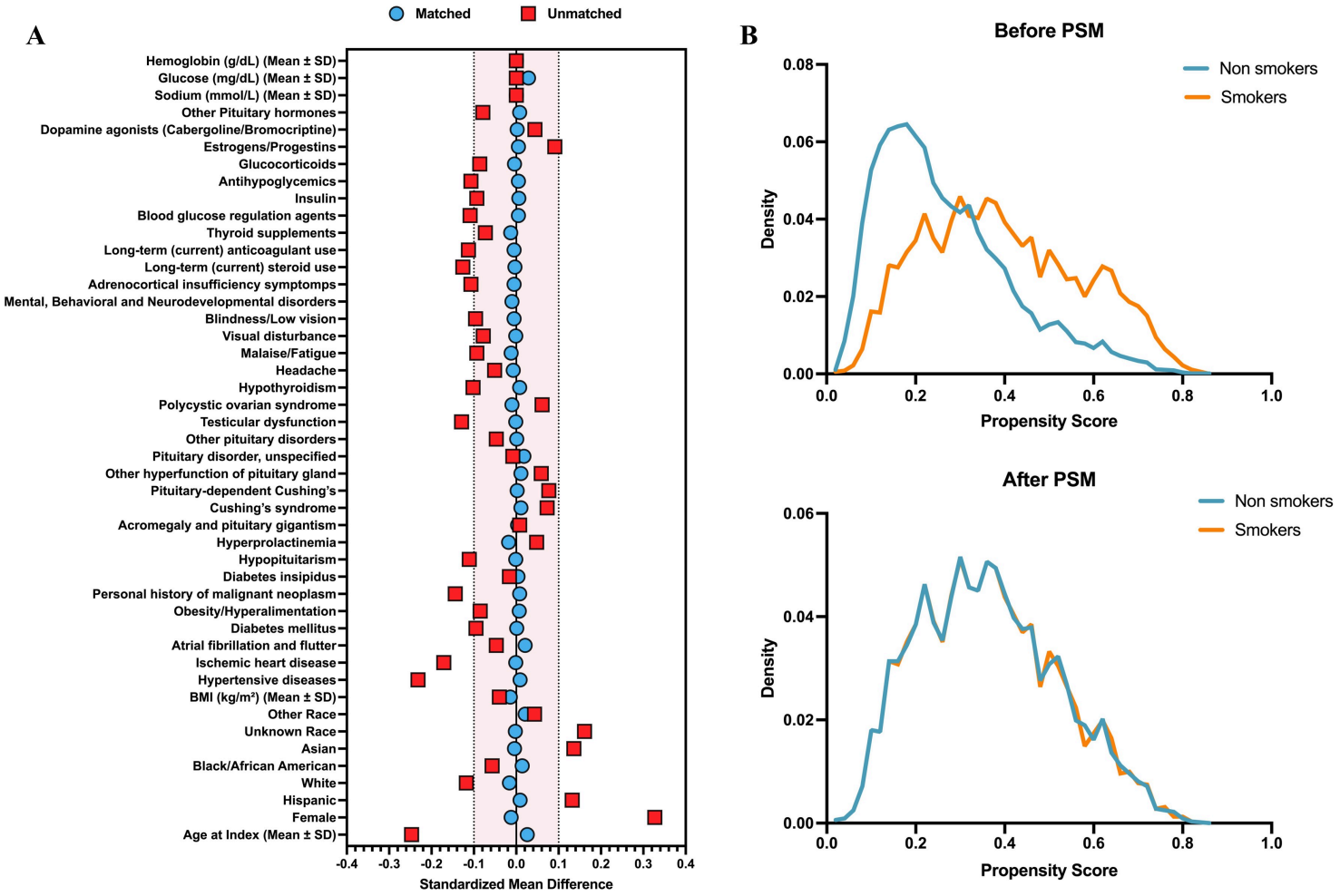


Figure 2

Assessment of Covariate Balance Before and After Propensity Score Matching.

A: Love plot displaying standardized mean differences (SMDs) across all matched variables (negative values represent higher incidence in smokers). B: Density plot of propensity score distributions before and after matching.

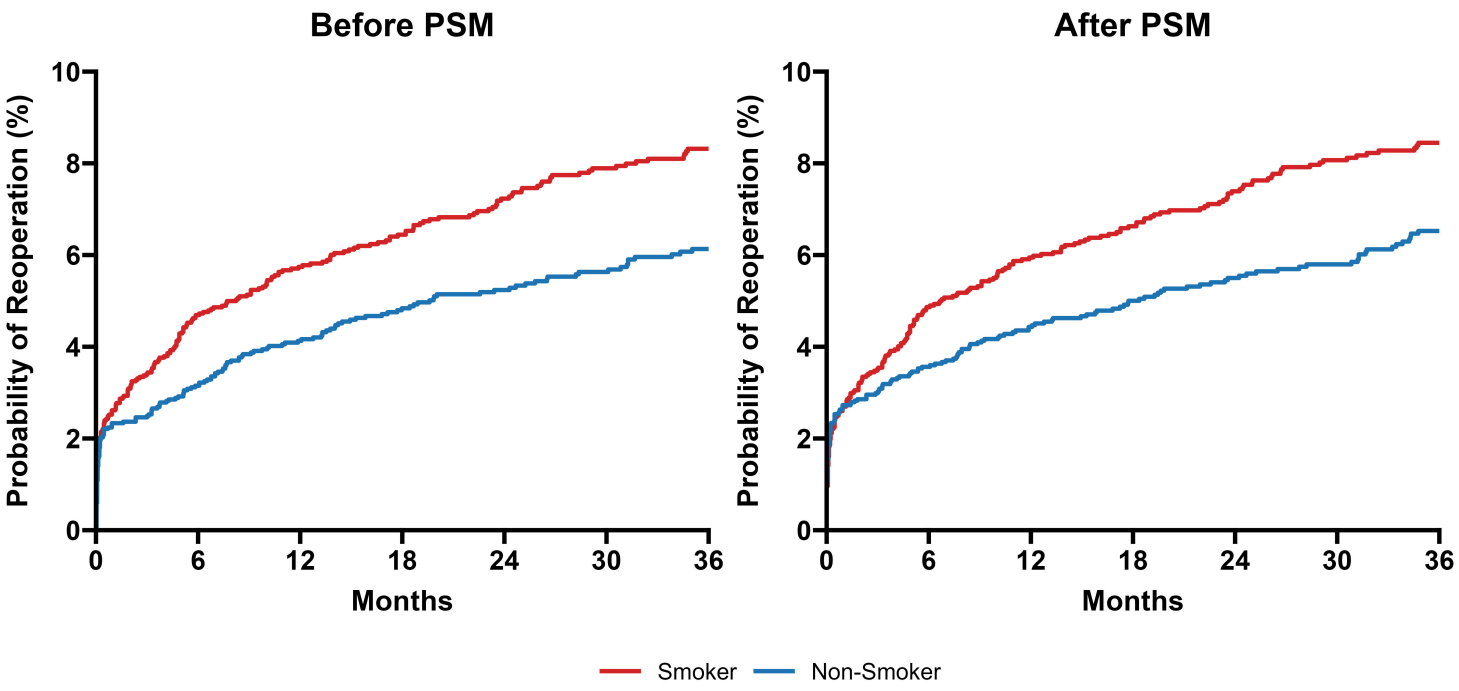


Figure 3

Cumulative Incidence of Reoperation Following Endoscopic Transsphenoidal Resection. *Kaplan-Meier curves comparing smokers and non-smokers before PSM (left) and after PSM (right).*

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- Table2.docx