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Empty Nose Syndrome Pathophysiology: A Systematic Review

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Abstract

Objective. The pathophysiology of empty nose syndrome (ENS) remains unclear despite significant research. The pathophysiologic mechanism of ENS was systematically reviewed.

Data Sources. MEDLINE and Embase.

Review Methods. Data were systematically reviewed for studies that provided original data on pathophysiology.

Results. A total of 2476 studies were screened, and 19 met the inclusion criteria: 13 case-control and 6 cross-sectional. Nine pathophysiologic themes were identified.

- Demographics: ENS symptoms had no relationship with climatic factors.
- Symptomatology: ENS patients demonstrated high symptom severity.
- Mental health: Anxiety and depression including hyperventilation were reported in >50% of ENS patients and correlated with ENS symptom severity.
- Anatomic features: Structural changes in response to turbinate surgery were similar between ENS and non-ENS patients.
- Airflow analysis: Airflow parameters were similar between ENS and non-ENS patients after turbinate surgery. On computational fluid dynamic analysis, differences were found on multiple outcomes.
- Diagnostic testing: The menthol detection test was impaired in ENS, and cotton placement in the airway improved ENS symptoms.
- Cognitive function: Functional magnetic resonance imaging showed activation in emotional processing area during breathing.
- Olfactory function: Subjective impairment was reported in ENS, but quantitative measures were similar to non-ENS patients.
- Mucosal physiology/innate immunity: Turbinate histopathology in ENS showed a tissue-remodeling pattern. Nasal nitric oxide level was lower in ENS patients.

Conclusion. There is evidence of high comorbid mental health disorders in ENS patients. An abnormal trigeminal-thermoreceptor response may be present in some patients. The influence of altered airflow and the evidence of surgery as the cause for ENS are unclear.

Keywords

empty nose syndrome, nasal perception, psychogenic comorbidity, neurogenic dysfunction

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Empty nose syndrome (ENS) is a rare but relevant clinical entity. It was first described in 1994 by Kern and Stenkvist[1,2] as a syndrome of paradoxical nasal obstruction. Patients had persisting symptoms, with an ''empty nasal space'' in those who received interventions for nasal obstruction, such as turbinate surgery. Turbinate procedures generally have good outcomes[3]; however, the classic presentation of ENS is a patient who has undergone surgery to relieve nasal obstructive symptoms but whose symptoms deteriorate, despite achieving the desired anatomic outcome. Patients with ENS generally have an unremarkable examination apart from evidence of prior surgery, thus the term

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''paradoxical obstruction.'' Other symptoms include sensation of crusting, dryness, diminished airflow, nose feeling too open, and suffocation.[4] ENS is not synonymous with atrophic rhinitis, which is a well-described condition with extensive mucosal crusts, cacosmia, and *Klebsiella ozaenae* colonization.[5] The absence of clinical findings differentiates it from atrophic rhinitis.

ENS carries a significant burden on mental health and psychogenic function, with anxiety, depression, and even suicidality.[6,7] When compared with patients with physical nasal obstruction from other sinonasal conditions, such as polyps, septal deviation, and tumor, ENS patients have much greater symptom awareness and express high impact on quality of life.

While surgery appears to make the symptoms deteriorate, the pathophysiology behind ENS is poorly defined and controversial. Theories include alteration of nasal perception by airflow dynamics, neurosensory decline and psychogenic dysfunction.[8-10]

Turbinate tissue changes do not explain ENS, as patients do not develop ENS symptoms after tumor surgery, pituitary surgery with middle turbinate resection, or radical sinus surgery with extensive nasal tissue removed.[11-17] It is often overlooked that almost all ENS patients present with nasal obstruction, at the outset, often leading to the initial surgery, making the role of surgery in their condition uncertain. Although there have been reviews on the diagnostic methods of ENS,[18] these tools have not advanced our understanding of ENS pathophysiology. This study aimed to systematically and objectively review the literature on investigated pathophysiologic mechanisms in ENS.

Methods

A systematic review was performed to identify peer-reviewed and published studies with original data on the pathophysiologic mechanism of ENS. The systematic review was structured in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[19] and the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*.[20]

Eligibility Criteria

Any study design was considered. Review articles, case series, and case reports were excluded. The target population was adults ($\geq$18 years) diagnosed with ENS. Since there is no gold standard for ENS diagnosis, the diagnostic criteria used by the study authors were collated and categorized into 4 groups: symptoms, endoscopy, imaging, and ENS-specific tests. Studies relating to only ENS treatment were excluded, due to a potential risk of attribution bias in a condition with an uncertain origin and to a placebo effect related to motivation by surgical candidacy.

Information Sources and Search Strategy

A systematic electronic search was performed through MEDLINE (1946–), Embase (1947–), and manual identification from the references of studies. The search was performed on the January 23, 2021. The search was limited to English-only and human studies. A search strategy was designed for each database (Supplement Table S1, available online).

Study Selection and Data Collection Process

Two authors (D.K., L.K.) reviewed the search results by screening titles, abstracts, and then full text based on predetermined eligibility criteria. A structured Excel (Microsoft 365) data collection sheet was used to extract data from full texts. The characteristics of studies comprised study design, number of participants, ENS diagnostic criteria (4 groups as indicated earlier), type of surgery (inferior, middle turbinate, or both), and outcomes measured. Articles providing insufficient information for complete data extraction or containing conflicting data were assessed by additional authors (R.A., R.S., R.J.H., R.G.C., J.R., J.K., K.S.). Any disagreements were resolved by discussion among the authors.

Risk of Bias in Individual Studies

The quality assessment followed the COSMOS-E guidelines for assessment in observational studies.[21] Four constructs of bias were adapted from the ROBINS-I tool (Risk of Bias in Non-randomized Studies of Interventions)[22]: confounding, selection bias, information bias, and reporting bias. ''Causal/association bias'' was included as a fifth element in quality assessment, as it was deemed important in etiologic studies.[23]

Data Synthesis

Given the range of investigational types, methods, and outcomes, data were qualitatively reviewed and categorized into pathophysiologic themes. After thematic grouping, the studies were then secondarily arranged by the outcome investigated. Where there was uniformity of outcomes and theme, a meta-analysis was performed with a random effects model and presented as a forest plot with mean difference and 95% CI.[19]

Results

Study Selection

The search strategy yielded 2950 articles (MEDLINE, n = 638; Embase, n = 2308; reference search, n = 4), reducing to 2476 studies after duplicates were removed. Title and abstract screening produced 84 full texts assessed for eligibility. Nineteen studies were included for qualitative analysis (**Figure 1**). Two studies were available for a meta-analysis.[24,25]

Characteristics of Studies

The studies (n = 19) consisted of 13 case-control[7,24-35] and 6 cross-sectional[4,6,36-39] designs (Supplement Table S2, available online). There were 489 adult ENS patients. The definition of ENS differed among studies: by self-identification in 2 (11%) studies,[6,39] per paradoxical obstruction in 10 (53%),[4,7,25,27,28,33,35-38] and with the Empty Nose Syndrome 6 Questionnaire (ENS6Q) in 8 (42%).[6,24,29-32,34,39] In 9 (47%) studies, endoscopic examination confirmed a widely patent nasal airway and a lack of other pathology.[4,25,27-29,31,35-37] In 9 (47%) studies, imaging was used to confirm an unobstructed nose and the absence of other sinonasal disease.[4,6,24,29,31,32,34,37,39] The ''cotton test'' was used as a diagnostic criterion in 7 (37%)

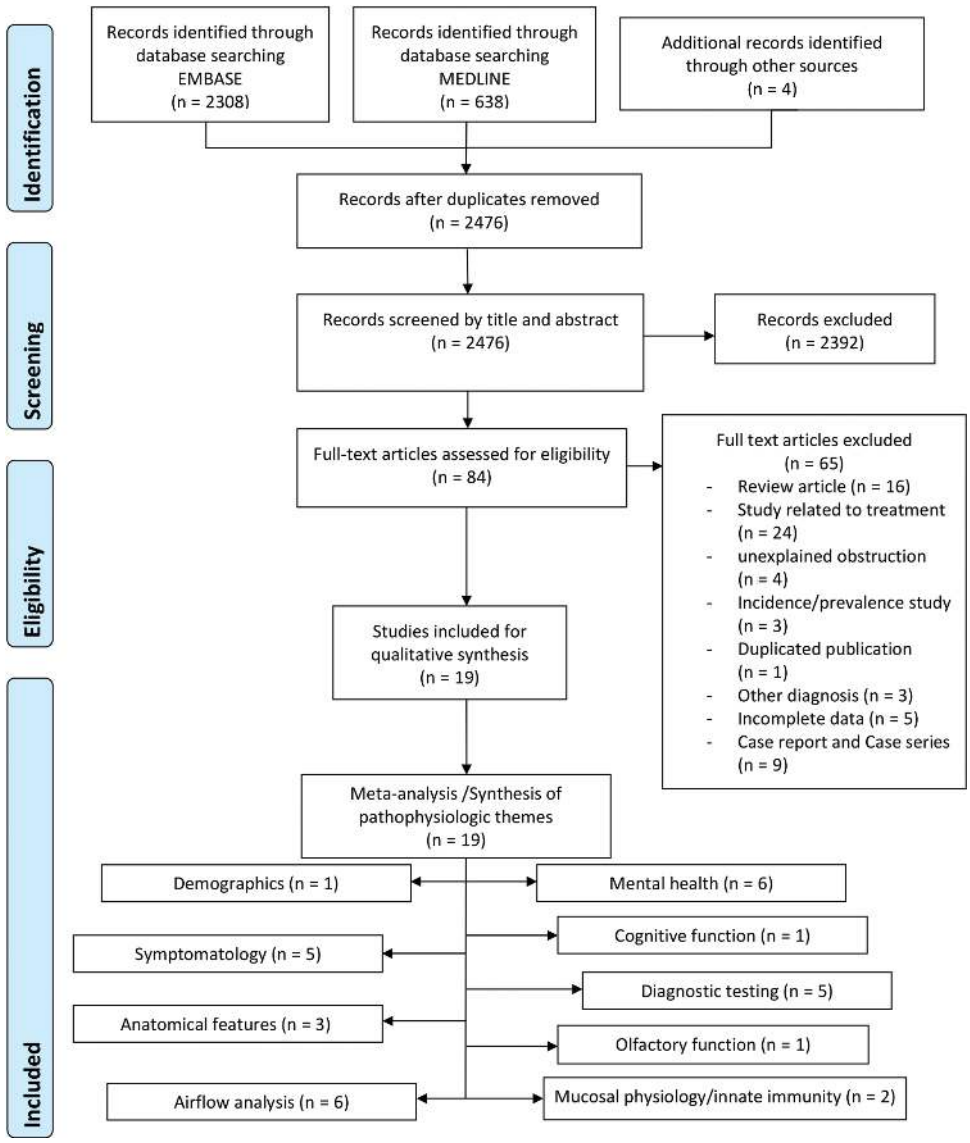

Figure 1. PRISMA flowchart of study selection process.

studies.[4,7,29,33,35,36,38] Nasal resistance was assessed to confirm the absence of anatomic obstruction in 2 (11%) studies.[25,37] Overall, studies diagnosed ENS based on 1 criterion in 1 (5%) study,[30] 2 criteria in 11 (58%),[6,7,24,27,28,31-34,38,39] 3 criteria in 5 (26%),[4,25,29,36] and all 4 criteria in 1 (5%).[37]

All studies considered patients who had undergone inferior turbinate reduction (ITR), with or without septoplasty, and 6 studies included patients with middle turbinate reduction (MTR).[24,26,32,34,35,37] No study included ENS patients without turbinate surgery. Most studies combined degrees of turbinate reduction, either partial or subtotal resection. Through this study we refer to either ITR or MTR. Where comparisons were made between post–turbinate surgery populations, patients with ENS are referred to as ITRwENS, and those without ENS symptoms are referred to as ITRsENS.

There were 454 control participants. Control groups included ITRsENS in 3 (16%) studies,[24,25,29] sinonasal disease without ENS in 4 (21%),[4,7,31,33] and healthy surgically naive patients, referred as ''controls'' in this review, in 11 (58%).[4,24-30,32,34,35]

Pathophysiologic Themes

Nine proposed pathophysiologic themes for the etiology of ENS were identified: demographics (n = 1),[39] symptomatology (n = 5),[4,6,26,31,33] anatomic features (n = 3),[27-29] airflow analysis (n = 6),[24-26,30,32,34] mental health (n = 6),[6,7,33,36-38] cognitive function (n = 1),[26] diagnostic testing (n = 5),[24,25,30-32] olfactory function (n = 1),[25] and mucosal physiology/innate immunity[33] (n = 2; **Table 1**). Some of the studies with multiple outcomes contributed data to >1 thematic group.

Demographics. Patients self-reporting ENS did not have disease-specific quality of life influenced by climatic region.

One study assessed the association of climatic factors with ENS via the ENS6Q in 53 self-reporting ENS patients from an international database[39] (**Table 2**). No correlation was

Table 1. Nine Pathophysiologic Themes for the Etiology of Empty Nose Syndrome Based on Primary Outcomes Assessed by Studies.

Pathophysiologic Themes	Outcomes Investigated
Demographics	*Climate and geographic factors:* dew point, humidity, temperature, precipitation, altitude data, pollution data (PM10, PM2.5)
Symptomatology	*Any sinonasal symptom rating:* Sinonasal Outcome Test, Empty Nose Syndrome 6 Questionnaire, sinonasal patency rating, sinonasal symptom severity score
	General health: Epworth Sleepiness Scale, Work Productivity and Impairment questionnaire, 5-dimension EuroQol General Health State Survey
Anatomic features	*Computed tomography findings:* history of turbinate surgery, nasal cavity airspace, nasal mucosa thickness, inferior turbinate volume, other abnormal finding
Airflow analysis	*Computational fluid dynamic modeling:* cross-sectional area, nasal resistance, airflow rate, airflow distribution, wall shear stress/force, humidification efficiency, heating efficiency, surface area stimulated by mucosal cooling.
	Airway function analysis: Minimal cross-sectional area (acoustic rhinometry), nasal resistance (rhinomanometry), airflow rate
Mental health	*Anxiety:* generalized anxiety disorder questionnaire, Beck Anxiety Inventory
	Depression: Patient Health Questionnaire, Beck Depression Inventory
	Hyperventilation syndrome: hyperventilation provocation test, pulmonary function
Cognitive function	Functional magnetic resonance imaging
Diagnostic testing	Menthol detection threshold / menthol detection test
	Cotton test
Olfactory function	Visual analog scale of olfactory function
	Odor threshold, discrimination test, identification test
Mucosal physiology / innate immunity	Histopathology
	Nasal nitric oxide level

Abbreviations: PM10, particulate matter of aerodynamic diameter <10 μm; PM2.5, particulate matter of aerodynamic diameter <2.5 μm.

Table 2. Demographics in Empty Nose Syndrome.

Study (Year): Design (Participants)	Clinical End Points	Results
Manji (2019)[39]: cross-sectional (ENS, n = 53)	*Climate factors at point of residence and ENS6Q correlation:*	Patients self-reporting ENS did not have disease-specific quality of life influenced by climatic region.
	Dew point, °C	*Climate factors did not correlate with ENS6Q:*
	Humidity, %	Dew point: $r = -0.22$, $P = .19$
	Precipitation, mm/d	Morning humidity: $r = -0.002$, $P = .94$
	Temperature, °C	Afternoon humidity: $r = 0.06$, $P = .75$
	Pollution, PM10 and PM2.5	Relative humidity: $r = -0.08$, $P = .61$
	Altitude, m	Annual precipitation: $r = 0.09$, $P = .53$
		Precipitation days per year: $r = 0.27$, $P = .07$
		Average temperature: $r = 0.002$, $P = .99$
		High temperature: $r = -0.06$, $P = .69$
		Low temperature: $r = -0.003$, $P = .99$
		PM10: $r = -0.12$, $P = .42$
		PM2.5: $r = -0.13$, $P = .39$
		Altitude: $r = -0.16$, $P = .25$

Abbreviations: ENS, empty nose syndrome; ENS6Q, Empty Nose Syndrome 6 Questionnaire; PM10, particulate matter of aerodynamic diameter <10 μm; PM2.5, particulate matter of aerodynamic diameter <2.5 μm.

identified between ENS6Q and climatic factors such as dew point, humidity, precipitation, temperature, pollution, altitude, and climatic/geographic region. This study highlighted the occurrence of ENS in any ethnic groups and independent of geographic region.

Symptomatology. ENS patients reported higher symptom severity, impaired daily activity, and worse sleep function. An ENS symptom–based questionnaire (ENS6Q) defined patients with ENS as compared with other sinonasal disease.

Five studies assessed symptomatology in ENS, of which 3 were case-control[26,31,33] (ENS, n = 44; other sinonasal disease, n = 30; controls, n = 15) and 2 were cross-sectional[4,6] (ENS, n = 68; **Table 3**). Outcome measures included the Sinonasal Outcome Test–22 (SNOT-22), ENS6Q, nasal patency subjective rating scale (4-point Likert scale), and general health questionnaires (Epworth Sleepiness Scale, Work Productivity and Impairment, and the EQ-5D-5L [5-Dimension EuroQol General Health State Survey]).

While an ENS6Q validation study[4] reported higher SNOT-22 scores in ENS versus chronic rhinosinusitis without nasal polyps, other investigators have shown similar SNOT-22 scores between ENS and chronic rhinitis patients.[33] Higher ENS6Q scores have been cited in ENS as compared with non-ENS sinonasal disease and controls.[4,31]

Self-perception of nasal patency between ENS and control groups was compared under 3 conditions: during free breathing and following menthol or lemon oil inhalation. The ENS and control groups perceived higher patency following menthol and lemon oil inhalation. The ENS group reported worse patency than controls under all conditions.[26]

Functional impairments in self-identified ENS patients from the Epworth Sleepiness Scale, Work Productivity and Impairment, and EQ-5D-5L questionnaires demonstrated impaired sleep, work productivity, and non–work activity and greater pain/discomfort as compared with normative data.[6]

Anatomic Features. Inferior turbinate volume was similar, after turbinate reduction, between patients with and without ENS symptoms. The turbinate volume after reduction did not correlate with ENS symptoms.

The intranasal anatomy was assessed between ITRwENS and ITRsENS patients in 1 case-control study[29] and between ITRwENS patients and controls in 2 case-control studies (**Table 4**).[27,28] All measurements were based on computed tomography image analysis.

In comparing ITRwENS (n = 32 sides) and ITRsENS (n = 34 sides), no difference in nasal cavity airspace was demonstrated (septum–inferior turbinate, lateral wall–inferior turbinate, floor–inferior turbinate, and septum–lateral wall). Nasal mucosal thickness between groups was similar. Of 10 measures taken, only the central and posterior septal area had thicker nasal mucosa in ITRwENS patients, and no multiple-outcome adjustment (or Bonferroni adjustment) was included.[29]

Axiomatically, when ITRwENS patients (n = 34) were compared with controls (n = 10), the inferior turbinate volume was smaller in the ITRwENS group. There was no correlation between turbinate volume and ENS-specific quality-of-life scores (SNOT-25).[28] In a similar study of 14 sides, ITRwENS patients had thicker nasal mucosa as compared with controls.[27] This study also found that 50% of ITRwENS patients had coexisting radiologic evidence of sinus disease.

Airflow Analysis. Nasal airflow and resistance were similar after turbinate reduction between patients with and without ENS symptoms. Based on computational fluid dynamic (CFD) analysis, differences were found on multiple-outcome analyses with modeling by a single research center.

For airflow analysis, there were 6 case-control studies (**Table 5**). Human research was performed in 3 studies.[25,26,30] CFD simulation/modeling was performed in 4 studies,[24,30,32,34] and 1 study used both.[30]

In the 3 studies on human subjects, 123 patients were assessed (ITRwENS, n = 37; ITRsENS, n = 18; controls, n = 68). Analysis of the human nasal airway with rhinomanometry and acoustic rhinometry demonstrated similar nasal airflow between ITRwENS and ITRsENS patients (mean ± SD, 485 ± 3 vs 490 ± 28 cm^3/s; $P = .95$).[25] When ITRwENS patients were compared with controls, lower nasal resistance was reported (expressed as flow rate), consistent with the postoperative state (163.9 ± 62.8 vs 120.9 ± 67.5 mL/s, P value not cited).[30] Surprisingly, 1 study indicated a similar nasal airflow rate between ITRwENS patients and unoperated controls (median [interquartile range], 593 [636] vs 700 [653] cm^3/s, $P > .05$).[26]

In CFD studies, 242 models were analyzed (ITRwENS, n = 89 possible duplicates; ITRsENS, n = 5; controls, n = 148). All CFD studies were from the same research group,[24,30,32,34] and 3 studies had the same number of model analyses.[24,32,34] The computational model simulating airflow was based on computed tomography scans. Only 1 CFD study compared ITRwENS and ITRsENS.[24] When compared with ITRsENS and controls, ITRwENS patients demonstrated decreased nasal airflow rate at the inferior region of the nasal cavity, and airflow distribution shifted upward to the middle region.[24,30,32,34] Mucosal-airflow interaction, measured as wall shear stress at the inferior region, was decreased in the ITRwENS group as compared with the ITRsENS group and controls.[24,30,32,34] There was a weak correlation between ENS6Q and wall shear stress ($r = -0.398$, $P = .003$).[40] Neither the number of samples nor multiple-outcome adjustment was defined.

Mental Health. Patients with ENS were affected by anxiety (73%), depression (71%), and hyperventilation syndrome (77%). The condition was not related to the extent of surgery. Mental health comorbidities were correlated with ENS-specific questionnaire scores (higher ENS6Q/SNOT-25 scores reflected greater mental health burden).

There were 2 case-control[7,33] and 4 cross-sectional[6,36-38] studies that assessed anxiety (ENS, n = 160; sinonasal disease, n = 12),[6,33,36,38] depression (ENS, n = 184; sinonasal disease, n = 82),[6,7,33,36,38] and hyperventilation syndrome (ENS, n = 22; **Table 6**).[37]

Table 3. Symptomatology in Empty Nose Syndrome.[a]

Study (Year): Design (Participants)	Clinical End Points	Results
Fu (2019)[33]: case-control (ENS, n = 19; chronic rhinitis, n = 12)	SNOT-22, 0-110	Sinonasal-specific quality of life (SNOT-22) was similar between patients with ENS and chronic rhinitis (65 [74] vs 51 [62], $P = .156$).
Thamboo (2017)[31]: case-control (ENS, n = 15; sinonasal disease, n = 18)	ENS6Q, 0-30	ENS symptom–based questionnaire defined patients with ENS and not other sinonasal disease. *ENS vs sinonasal disease:* ENS6Q score: 18.87 ± 7.54 vs 4.72 ± 3.39, $P < .001$ Dryness: 3.80 ± 1.14 vs 1.11 ± 1.32, $P < .001$ Lack of sensation: 3.87 ± 1.30 vs 1.33 ± 1.32, $P < .001$ Suffocation: 2.47 ± 2.16 vs 0.56 ± 1.04, $P = .002$ Nose feels too open: 3.33 ± 1.44 vs 0.22 ± 0.73, $P < .001$ Nasal crusting: 2.73 ± 1.79 vs 1.39 ± 1.50, $P = .025$ Nasal burning: 2.93 ± 1.79 vs 0.17 ± 0.38, $P < .001$
Freund (2011)[26]: case-control (ENS, n = 10; controls, n = 15)	Patient-reported nasal patency scale: better, same, worse, very bad After exposure to room air; menthol, 10%; and lemon oil, high grade	ENS patients perceived better breathing with menthol and lemon oil over room air. The relative change of perception after exposure to menthol, and lemon oil was not compared between controls and ENS patients. *ENS group reported (%; worse, very bad):* Room air vs menthol: 48.2% vs 35%, $P < .04$[b] Room air vs lemon oil: 48.2% vs 50%, $P < .01$[b] *Control group reported (%; worse, very bad):* Room air vs menthol: 15% vs 12.2%, $P < .01$[b] Room air vs lemon oil: 15% vs 12.2%, $P < .01$[b] ENS group reported worse breathing than controls (%; worse, very bad): room air, 48.2% vs 15%; menthol inhalation, 35% vs 12.2%; lemon oil inhalation, 50% vs 12.2% (reported as a group, $P < .01$)
Manji (2018)[6]: cross-sectional (ENS, n = 53)	ESS, 0-24 WPAI, % EQ-5D-5L General health–ENS6Q correlation	Patients self-reporting ENS had impaired sleep, work productivity, non–work activity, and pain/discomfort. *ENS patients are affected by* ESS: score ≥8 in 42% WPAI: 62% reduction in productivity at work WPAI: 65% reduction in all other non-work-related activities EQ-5D-5L: moderate difficulties with household and/or leisure activities and moderate levels of pain/discomfort *ENS symptom severity (ENS6Q) correlation:* ESS scores: $r = 0.21$, $P = .14$ WPAI: work, $r = 0.64$, $P < .001$; activity, $r = 0.41$, $P < .001$ EQ-5D-5L: overall pain/discomfort, $r = 0.43$, $P = .002$; impairment in activities of daily living, $r = 0.4$, $P = .003$
Velasquez (2017)[4]: cross-sectional (ENS, n = 15; CRSsNP, n = 30; controls, n = 30)	ENS6Q, 0-30 SNOT-22, 0-110	Patients self-reporting ENS (and candidates for an augmentation procedure) had higher ENS6Q and SNOT-22 scores than CRSsNP vs controls: ENS6Q, 18.9 ± 7.5 vs 4.7 ± 4.3 vs 1.8 ± 2.8, $P < .001$; SNOT-22, 50.2 ± 26.6 vs 33.4 ± 18.3 vs 17.9 ± 16.2, $P < .001$

Abbreviations: CRSsNP, chronic rhinosinusitis without nasal polyp; ENS, empty nose syndrome; ENS6Q, Empty Nose Syndrome 6 Questionnaire; EQ-5D-5L, 5-Dimension EuroQol General Health State Survey; ESS, Epworth Sleepiness Scale; ITR, inferior turbinate resection; SNOT, Sinonasal Outcome Test; WPAI, Work Productivity and Impairment questionnaire.

[a]Data format: mean ± SD and median [interquartile range].

[b]Statistical error is likely.

Table 4. Anatomic Features in Empty Nose Syndrome.[a]

Study (Year): Design (Participants)	Clinical End Points	Results
Hong (2016)[28]: case-control (ENS, n = 34; controls, n = 10)	*CT:* ITV, mL; ITV and SNOT-25 correlation	Patients who had ITR had smaller ITV vs those without ITR: 1.81 ± 0.92 vs 7.35 ± 1.28 mL, $P < .001$. *Within ENS group:* There was no correlation between ITV and SNOT-25 score: anterior, $r = 0.142$, $P = .211$; posterior, $r = 0.145$, $P = .207$; total, $r = 0.223$, $P = .1$ Nasal dryness score weakly correlated with smaller total ITV: $r = -0.327$, $P = .03$ Reduced productivity and fatigue score weakly correlated with larger total ITV: reduced productivity, $r = 0.318$, $P = .033$; fatigue, $r = 0.383$, $P = .025$.
Thamboo (2016)[29]: case-control (ITRwENS, n = 32 sides; ITRsENS, n = 34 sides; controls, n = 58 sides)	*CT:* nasal cavity airspace, mm; nasal mucosa thickness, mm	Nasal cavity airspace measures were similar between patients with ITRwENS and ITRsENS. *Nasal cavity airspace, mm:* Septum–IT air space: 4.13 ± 0.4 vs 4.25 ± 0.4, $P = .83$ Lateral wall–IT air space: 1.54 ± 0.2 vs 1.91 ± 0.17, $P = .16$ Floor–IT air space: 6.4 ± 0.71 vs 5.35 ± 0.68, $P = .29$ Septum–lateral wall air space: 9.58 ± 0.34 vs 9.65 ± 0.38, $P = .9$ Of the 10 mucosal measures, 2 areas showed differences between ITRwENS and ITRsENS patients. *Nasal mucosa thickness, mm:* IT mucosa: 6.27 ± 0.44 vs 6.65 ± 0.35, $P = .51$ *Floor* Anterior: 3.24 ± 0.12 vs 2.89 ± 0.20, *P* value NR[b] Central: 2.33 ± 0.16 vs 1.92 ± 0.15, $P = .07$ Posterior: 1.09 ± 0.12 vs 0.93 ± 0.1, *P* value NR[b] *Septum* Anterior: 3.00 ± 0.13 vs 3.04 ± 0.16, *P* value NR[b] Central: 3.08 ± 0.17 vs 2.42 ± 0.17, $P < .01$ Posterior: 2.20 ± 0.17 vs 1.36 ± 0.15, $P < .01$ *Lateral wall* Anterior: 1.19 ± 0.13 vs 0.99 ± 0.08, *P* value NR[b] Central: 1.44 ± 0.14 vs 1.40 ± 0.11, *P* value NR[b] Posterior: 0.71 ± 0.12 vs 0.61 ± 0.09, *P* value NR[b]
Jang (2011)[27]: case-control (ENS, n = 14 sides; controls, n = 14 sides; unilateral CRS, n = 20 sides)	*CT:* nasal mucosa thickness, mm	Nasal mucosa thickness was greater in patients with ENS vs controls: 3.01 ± 0.76 vs 1.80 ± 0.43 mm, $P < .001$

Abbreviations: CRS, chronic rhinosinusitis; CT, computed tomography; ENS, empty nose syndrome; IT, inferior turbinate; ITR, inferior turbinate resection; ITRwENS, inferior turbinate resection with empty nose syndrome; ITRsENS, inferior turbinate resection without empty nose syndrome; ITV, inferior turbinate volume; NR, not reported; SNOT, Sinonasal Outcome Test.
[a]Data format: mean ± SD.
[b]*P* value across group was not significant.

ENS patients scored higher on anxiety- and depression-validated questionnaires as compared with other sinonasal diseases without ENS.[6,7,33,36,38] Anxiety was reported as high as 65% to 73% in the ENS group. Likewise, depression was cited in 51% to 71% in ENS patients with comparable rates of 15% to 27% in other sinonasal disease.[7]

No correlation was demonstrated between depression severity (Beck Depression Inventory) and extent of turbinate surgery, nasal volume (cm^3), or sinonasal-specific quality-of-life scores (SNOT-22).[7] However, there was a moderate correlation between ENS-specific quality-of-life scores (ENS6Q/SNOT-25) and anxiety ($r = 0.499$, $P < .001$; $r = 0.54$, $P < .001$) and depression ($r = 0.48$, $P < .001$; $r = 0.53$, $P < .001$).[6,38]

Cross-sectional assessment of ENS patients (n = 22) with hyperventilation provocation testing and pulmonary function

Table 5. Airflow Analysis in Empty Nose Syndrome.[a]

Study (Year): Design (Participants)	Clinical End Points	Results
Malik (2019)[24]: case-control (ITRwENS, n = 27; ITRsENS, n = 5; controls, n = 42)	*CFD modeling:* Cross-sectional area, cm^2 (inferior, middle, superior) Nasal resistance, $Pa/cm^3/s$ Airflow rate, m^3/s (inferior, middle, superior) Airflow distribution, % (inferior, middle, superior) Wall shear force distribution, % (anterior, MT, IT)	*Airflow and airway parameters on CFD modeling were altered in patients with ITRwENS vs ITRsENS.* Cross-sectional area (1.19 ± 1.05 vs 0.94 ± 0.21 cm^2, *P* = NS) and nasal resistance (0.052 ± 0.015 vs 0.051 ± 0.020 $Pa/cm^3/s$, *P* = NS) in ITRwENS were similar to ITRsENS patients. In ITRwENS: airflow rate was lower than ITRsENS patients at inferior region (3.69 ± 2.58 × 10^{-5} vs 6.96 ± 4.12 × 10^{-5} m^3/s, $P < .05$). Airflow distribution was lower than ITRsENS patients at inferior region (25.8% ± 17.6% vs 47.7% ± 23.6%, $P < .01$) but higher at middle region (66.5% ± 18.3% vs 49.1% ± 10.6%, $P < .05$). Wall shear force distribution was lower at inferior region than ITRsENS patients (32.24 ± 12.64 vs ~40%, $P < .05$) but higher at middle region (39.88% ± 6.96% vs 25.3% ± 12.74%, $P < .05$).
Maza (2019)[34]: case-control (EEAwENS, n = 2; EEAsENS, n = 2; non-EEAwENS, n = 27; controls, n = 42)	*CFD modeling:* Cross-sectional area, cm^2 Airflow distribution, % (inferior, middle, superior) WSS, Pa (anterior, MT, IT)	*Airflow and airway parameters on CFD modeling were altered in patient with EEAwENS vs EEAsENS.* EEAwENS patients had a history of submucosal ITR in attempts to treat nasal obstruction. In EEAwENS: Cross-sectional area was similar to EEAsENS patients (3.47 ± 0.23 vs 3.79 ± 1.20 cm^2, *P* = NR). Airflow distribution was lower than EEAsENS patients through inferior region (17.74% ± 4.00% vs 51.25% ± 3.33%, $P < .002$). WSS at inferior region was lower than EEAsENS patients (0.30 ± 0.13 vs 0.61 ± 0.03 Pa, *P* = .003). Airflow parameters between non-EEAwENS and EEAwENS patients were not compared.
Li (2018)[32]: case-control (ENS, n = 27; controls, n = 42)	*CFD modeling:* Cross-sectional area, cm^2 Nasal resistance, $Pa/cm^3/s$ Airflow rate, % (inferior, middle, superior) WSS, Pa (anterior, MT, IT) WSS and ENS6Q correlation	*Airflow and airway parameters on CFD modeling were altered after ITR in ENS patients vs controls.* In ENS: Cross-sectional area was higher than controls (~3.5 vs ~1.0 cm^2, $P < .001$). Nasal resistance was lower than controls (0.052 ± 0.01 vs 0.070 ± 0.02 $Pa/cm^3/s$, $P < .001$). Airflow rate decreased through inferior region (25.8% ± 17.6% vs 36.5% ± 15.9%, $P < .001$) while increased at middle region vs controls (66.5% ± 18.3% vs 49.9% ± 15.1%, $P < .001$). WSS was lower in inferior region (0.58 ± 0.24 vs 1.18 ± 0.81 Pa, *P* = .014) and middle region (0.70 ± 0.31 vs 1.20 ± 0.82 Pa, *P* = .038) vs controls. Peak WSS in the inferior region is weakly correlated with ENS6Q (total score, $r = -0.398$, *P* = .003; suffocation, $r = -0.295$, *P* = .031; nose feels too open, $r = -0.388$, *P* = .004).
Konstantinidis (2017)[25]: case-control (ITRwENS, n = 21; ITRsENS, n = 18; ; controls, n = 31)	Rhinomanometry: Nasal resistance, $Pa/cm^3/s$ Airflow rate, cm^3/s	Nasal resistance (0.20 ± 0.04 vs 0.21 ± 0.03 $Pa/cm^3/s$, *P* = .97) and airflow rate (485 ± 3 vs 490 ± 28 cm^3/s, *P* = .95) were similar between ITRwENS and ITRsENS patients.

(continued)

Table 5. (continued)

Study (Year): Design (Participants)	Clinical End Points	Results
Li (2017)[30]: case-control (ITRwENS, n = 6; pre-ITR ENS, n = 3; controls, n = 22)	Acoustic rhinometry: minimal cross-sectional area, cm^2 Rhinomanometry: nasal resistance, mL/s *CFD modeling:* Nasal resistance, mL/s[b] Airflow rate, % (inferior, middle, superior) WSS, Pa (inferior, middle, superior)	Airflow and airway parameters on acoustic rhinometry, rhinomanometry and CFD modeling were altered after ITR vs controls. In ITRwENS: Minimum cross-sectional area on acoustic rhinometry was higher than controls (0.68 ± 0.36 vs 0.51 ± 0.18 cm^2, *P* = NR). Nasal resistance on rhinomanometry (163.9 ± 62.8 vs 120.9 ± 67.5 mL/s, *P* = NR) and CFD modeling (173.1 ± 41.4 vs 116.0 ± 41.7 mL/s, $P < .05$) was lower vs controls. Nasal flow rate was lower than pre-ITR and controls at inferior region (~20% vs ~40% vs ~ 40%, $P < .05$) but higher at middle region (75.6% ± 14.6% vs 56.2% ± 14.7% vs ~50%, $P < .05$). Average WSS was lower than controls at inferior region (~0.03 vs ~0.07 Pa, $P < .05$).
Freund (2011)[26]: case-control (ENS, n = 10; controls, n = 15)	Rhinomanometry: airflow rate, cm^3/s	Airflow rate was similar between patients with ENS and controls (593 [636] vs 700 [653] cm^3/s, $P > .05$).

Abbreviations: CFD, computational fluid dynamics; EEA, endoscopic endonasal approach (skull base); EEAsENS, endoscopic endonasal approach without empty nose syndrome; EEAwENS, endoscopic endonasal approach with empty nose syndrome; ENS, empty nose syndrome; ENS6Q, Empty Nose Syndrome 6 Questionnaire; IT, inferior turbinate; ITR, inferior turbinate resection; ITRsENS, inferior turbinate resection without empty nose syndrome; ITRwENS, inferior turbinate resection with empty nose syndrome; MT, middle turbinate; NR, not reported; NS, not significant; WSS, wall shear stress.
[a]Data format: mean ± SD and median [interquartile range].
[b]Nasal resistance was expressed as flow rate at specific pressure.

measures defined hyperventilation syndrome in 77% of ENS patients.[37]

Cognitive Function. ENS patients had qualitatively different functional magnetic resonance imaging (fMRI) patterns to healthy controls. Activation in the emotional processing areas of the temporal lobe was seen in ENS patients as compared with controls on normal breathing, and deactivation in this area was shown after menthol stimulation.

Cognitive function was assessed by fMRI in 1 case-control study (ENS, n = 10; controls, n = 15)[26] (**Table 7**). fMRI qualitatively compared ENS patients with surgically naive controls in 3 conditions: during free breathing and after menthol or lemon oil inhalation. Qualitative data showed differing areas of activation/deactivation between ENS and controls. During free breathing, activation of the temporal areas and amygdala was seen in ENS patients as compared with controls. After menthol inhalation, deactivation in these areas was found in ENS patients. Both areas belong to the limbic system and are involved in emotional processing. With lemon oil inhalation, deactivation was seen in the caudate nucleus, middle frontal gyrus, and superior temporal gyrus when compared with controls. This included the prefrontal secondary sensory area, which is activated during odor presentation.

Diagnostic Testing. The subjective perception of menthol is lower in ENS patients than controls (with or without prior turbinate resection). ENS patients had "symptom improvement" from cotton placed in their airway.

Diagnostic methods were assessed in 5 case-control studies,[24,25,30-32] with 4 studies assessing menthol detection (ITRwENS, n = 80; ITRsENS, n = 13; controls, n = 129) and 1 study assessing the nasal perception on the cotton test (ITRwENS, n = 15; sinonasal disease, n = 18; **Table 8**).

Menthol detection was utilized to evaluate trigeminal nerve function, as menthol activates the TRPM8 temperature receptor (transient receptor potential melanostatin 8).[41] Menthol vapor was introduced into nasal cavity via sniffing. The menthol test reflected either a detectable threshold (higher ordinal values reflect lower concentration detected) or the localization of the nostril stimulated (number of correct localizations).

ITRwENS had worse menthol detection on identification and detection threshold as compared with ITRsENS (21 ± 8 vs 29 ± 8, $P = .021$; 10.2 ± 3.87 vs 15.2 ± 1.23, $P < .05$)[24,25] and controls (10.3 ± 3.9 vs 14.0 ± 1.8, $P < .001$; 9.2 ± 4.6 vs 14.8 ± 1.6, $P < .05$).[30,32] When menthol detection was compared in ITRsENS patients and controls, there were conflicting data, with 1 study showing similar localization (29 ± 8 vs 34 ± 5, $P = .067$)[25] and the other with better menthol detection in the ITRsENS group (15.2 ± 1.23 vs 14.8 ± 1.59, $P < .05$).[24] However, the 95% CIs overlapped from these data, and a statistical error was assumed. When data were pooled for meta-analysis, menthol detection

Table 6. Mental Health in Empty Nose Syndrome.[a]

Study (Year): Design (Participants)	Clinical End Points	Results
Fu (2019)[33]; case-control (ENS, n = 19; chronic rhinitis, n = 12)	BAI (0-63), BDI (0-63)	Anxiety and depression severity was higher in patients diagnosed with ENS than chronic rhinitis: BAI, 21.0 [41.0] vs 2.5 [26.0], $P = .005$; BDI, 15.0 [47.0] vs 8.0 [18.0], $P = .007$
Kim (2021)[7]; case-control (ENS, n = 24; CRSwNP, n = 16; CRSsNP, n = 20; AR, n = 34)	BDI (0-63), BDI and nasal volume correlation, BDI and SNOT-22, correlation	Although depression was high in patients with ENS, depression severity did not correlate to extent of ITR surgery. Depression was reported at 71% (ENS) vs 19% (CRSwNP), 15% (CRSsNP), and 27% (AR). *Within the ENS group:* BDI score was not different between conservative and radical ITR surgery: 14.88 ± 6.81 vs 17.69 ± 18.21, $P = .92$ BDI score did not correlate with nasal volume after surgery: right, $r = 0.26$, $P = 0.95$; left, $r = 0.47$, $P = .83$ BDI score did not correlate with SNOT-22 score: $r = 0.1$, $P = .62$
Huang (2019)[38]; cross-sectional (ENS, n = 68)	BAI (0-63), BDI (0-63), BAI, BDI and SNOT-25 correlation,	Anxiety and depression were high in patients with ENS: 73.5% and 51.5% Anxiety and depression correlated with SNOT-25: BAI, $r = 0.499$, $P < .001$; BDI, $r = 0.526$, $P < .001$
Manji (2018)[6]; cross-sectional (ENS, n = 53)	GAD-7 (0-21), PHQ-9 (0-27), GAD-7, PHQ-9 and ENS6Q correlation,	Anxiety and depression were high in patients self-reporting ENS: 65.9% and 67.9% Anxiety and depression correlated with ENS6Q: GAD-7: $r = 0.54$, $P < .001$; PHQ-9, $r = 0.48$, $P < .001$
Mangin (2017)[37]; cross-sectional (ENS, n = 22)	HVPT (positive or negative), lung function (spirometry, plethysmography, and diffusing capacity of the lung for carbon monoxide measurement),	Hyperventilation syndrome (with normal lung function) was found in 77.3% of patients with ENS.
Lee (2016)[36]; cross-sectional (ENS, n = 20)	BAI (0-63), BDI (0-63)	Anxiety and depression were high in patients with ENS: 70% and 65%

Abbreviations: AR, allergic rhinitis; CRSwNP, chronic rhinosinusitis with nasal polyp; CRSsNP, chronic rhinosinusitis without nasal polyp; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; ENS, empty nose syndrome; ENS6Q, Empty Nose Syndrome 6 Questionnaire; GAD-7, Generalized Anxiety Disorder questionnaire; HVPT, hyperventilation provocation test; ITR, inferior turbinate resection; PHQ-9, Patient Health Questionnaire; SNOT, Sinonasal Outcome Test.
[a]Data format: mean ± SD and median [interquartile range].

Table 7. Cognitive Function in Empty Nose Syndrome.

Study (Year): Design (Participants)	Clinical End Points	Results
Freund (2011)[26]: case-control (ENS, n = 10; controls, n = 15)	fMRI: after exposure to free breathing; menthol, 10%; lemon oil, high grade	ENS patients expressed different patterns on fMRI vs controls. During free breathing, there was ENS-specific activation at cerebellum, amygdala, and temporal area vs controls. *In ENS patients:* After menthol inhalation, specific deactivation mainly in bilateral temporal pole (superior temporal gyrus), which is emotional processing area After lemon oil inhalation, deactivation in caudate nucleus, middle frontal gyrus, and superior temporal gyrus, which is activated during odor presentation

Abbreviations: ENS, empty nose syndrome; fMRI, functional magnetic resonance imaging.

Table 8. Diagnostic Testing in Empty Nose Syndrome.[a]

Study (Year): Design (Participants)	Clinical End Points	Results
Malik (2019)[24]: case-control (ITRwENS, n = 27; ITRsENS, n = 5; controls, n = 42)	Menthol detection threshold,[b] 1-20	Menthol detection was lower in patients with ITRwENS vs ITRsENS and controls: 10.2 ± 3.87 vs 15.2 ± 1.23 vs 14.8 ± 1.59, $P < .05$ for both comparison ITRsENS patients reported better mental detection than controls: 15.2 ± 1.23 vs 14.8 ± 1.59, $P < .05$[c]
Li (2018)[32]: case-control (ENS, n = 27; controls, n = 42)	Menthol detection threshold,[b] 1-20	Menthol detection was lower in patients with ENS vs controls: 10.3 ± 3.9 vs 14.0 ± 1.8, $P < .001$
Konstantinidis (2017)[25]: case-control (ITRwENS, n = 21; ITRsENS, n = 18; controls, n = 31)	Menthol identification test,[d] 0-40	Menthol detection was lower in patients with ITRwENS vs ITRsENS and controls: 21 ± 8 vs 29 ± 8 vs 34 ± 5; ITRwENS vs ITRsENS, $P = .021$, ITRwENS vs controls, $P = .004$ ITRsENS patients reported similar menthol detection vs controls: 29 ± 8 vs 34 ± 5, $P = .067$
Li (2017)[30]: case-control (ENS, n = 5; controls, n = 14)	Menthol detection threshold,[b] 1-20	Menthol detection was lower in patients with ENS vs controls: 9.2 ± 4.6 vs 14.8 ± 1.6, $P < .05$
Thamboo (2017)[31]: case-control (ENS, n = 15; sinonasal disease, n = 18)	Cotton test ENS6Q, 0-30 Overall severity score: much better, a little better, about the same, a little worse, much worse	ENS patients reported ENS symptom improvement on cotton test vs non-ENS controls. *In ENS:* Total ENS6Q reduced to normal level during cotton in situ: cotton in situ (6.00 ± 5.75) vs cotton removed (19.13 ± 7.91, $P < .01$) All ENS patients (15/15) reported "a little better" or "much better" during cotton in situ. *In sinonasal disease:* Total ENS6Q increased during cotton in situ (5.06 ± 3.94) vs cotton removed (2.94 ± 3.36, $P = .034$). Majority of patients (16/18) reported "about the same" or worse during cotton in situ.

Abbreviations: ENS, empty nose syndrome; ENS6Q, Empty Nose Syndrome 6 Questionnaire; ITR, inferior turbinate resection; ITRsENS, inferior turbinate resection without empty nose syndrome; ITRwENS, inferior turbinate resection with empty nose syndrome.
[a]Data format: mean ± SD.
[b]Menthol detection threshold: lower score required higher concentration of menthol for detection.
[c]Statistical error is likely.
[d]Menthol identification test: higher score indicated better function.

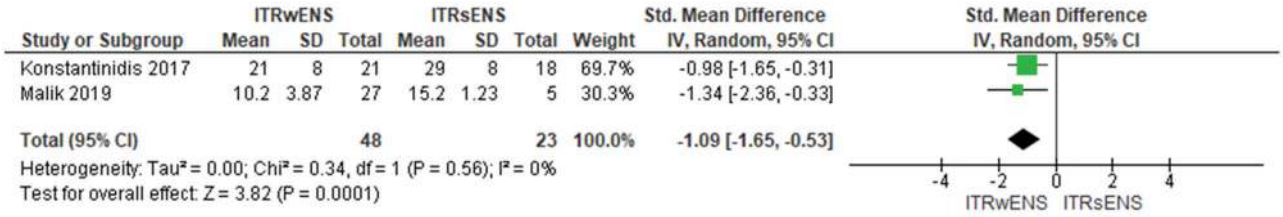

Figure 2. Forest plot representing menthol detection test in ITRwENS and ITRsENS. ITRwENS, inferior turbinate reduction with empty nose syndrome; ITRsENS, inferior turbinate reduction without empty nose syndrome.

scores were lower in ITRwENS than in ITRsENS patients (standardized mean difference, –1.09; 95% CI, –1.65 to –0.53; **Figure 2**).[24,25]

The cotton test involved placing dry cotton into the region where the turbinate tissue has been removed. The test was considered positive when a patient reported any subjective nasal breathing improvement with the cotton in situ. A pseudo-placebo test was performed by using the pressure of the instrument placement without leaving cotton behind.

Thamboo et al[31] performed the cotton test validation study with ENS6Q, and participants completed a subjective rating scale. With the cotton in situ for 10 minutes, ENS patients reported an improvement in ENS6Q (19.13 ± 7.91 vs 6.00 ± 5.75, $P < .01$), and all ENS patients indicated improved

Table 9. Olfactory Function in Empty Nose Syndrome.[a]

Study (Year): Design (Participants)	Clinical End Points	Results
Konstantinidis (2017)[25]: case-control (ITRwENS, n = 21; ITRsENS, n = 18; controls, n = 31)	*Olfactory function:* Visual analog scale, 0-100 TDI score, 1-48	Subjective olfactory rating was impaired in ITRwENS patients, but TDI score showed no different vs ITRsENS patients. *In ITRwENS:* Subjective olfaction rating was lower than ITRsENS patients and controls: 35.7 ± 6.3 vs 72.2 ± 5.5 vs 81.1 ± 4.9, $P < .001$ for both comparison TDI score was similar to ITRsENS patients but lower than controls: 28.1 ± 3.5 vs 30.5 ± 4.1 vs 35.5 ± 3.2; ITRwENS vs ITRsENS, $P = .62$; ITRwENS vs controls, $P = .028$

Abbreviations: ITRsENS, inferior turbinate resection without empty nose syndrome; ITRwENS, inferior turbinate resection with empty nose syndrome; TDI, odor threshold, discrimination, and identification test.
[a]Data format: mean ± SD.

Table 10. Mucosal Physiology/Innate Immunity in Empty Nose Syndrome.[a]

Study (Year): Design (Participants)	Clinical End Points	Results
Wu (2020)[35]: case-control (ENS, n = 17; controls, n = 6)	Histopathology	Histopathology was different between ENS patients and controls. ENS patients presented with more squamous metaplasia (76% vs 17%, $P = .018$), more submucosal fibrosis (94% vs 33%, $P = .008$), and lower submucosal gland number grading (0-4; 1.71 ± 1.13 vs 3.17 ± 0.69, $P = .013$) vs controls. The expression level of TRPM8 was scored via immunohistochemical staining intensity and percentage of stained cells (0-300). The expression level was lower in the ENS group vs controls (129.68 ± 56.91 vs 251.67 ± 27.94, $P < .001$).
Fu (2019)[33]: case-control (ENS, n = 19; chronic rhinitis, n = 12)	nNO	ENS patients had lower nNO than chronic rhinitis patients (85.5 [327.5] vs 231.3 [312] ppb, $P < .001$).

Abbreviations: ENS, empty nose syndrome; nNO, nasal nitric oxide; TRPM8, transient receptor potential melanostatin 8 receptor.
[a]Data format: mean ± SD and median [interquartile range].

breathing. Controls cited worse ENS6Q (2.94 ± 3.36 vs 5.06 ± 3.94, $P = .034$), and nearly all controls rated their breathing as ''about the same'' or worse during cotton in situ.

Olfactory Function. While subjective olfaction is impaired in post–turbinate reduction patients with ENS as compared with those without ENS, the objective olfaction is similar.

Whether cause, effect, or association, olfaction was studied in a single case-control study, which compared subjective olfaction scoring with a visual analog scale and functional assessment with a validated TDI score (threshold, discrimination, identification) among ITRwENS patients (n = 21), ITRsENS patients (n = 18), and controls (n = 31)[25] (**Table 9**). The ENS group reported poorer subjective olfaction scoring than ITRsENS and controls (35.7 ± 6.3 vs 72.2 ± 5.5 vs 81.1 ± 4.9, $P < .001$). However, on functional assessment, ITRwENS and ITRsENS patients had a similar TDI score, which was lower than controls (28.1 ± 3.5 vs 30.5 ± 4.1 vs 35.5 ± 3.2; ITRwENS vs ITRsENS, $P = .62$; ITRwENS vs controls, $P = .028$). ITRwENS patients may have other sinonasal disease that might account for the difference with controls; however, these data were not reported.

Mucosal Physiology/Innate Immunity. ENS patients had different histopathology and expressed lower nasal nitric oxide than non-ENS controls.

Mucosal physiology/innate immunity was assessed in 2 case-control studies. Histopathology and TRPM8 immunohistochemical staining scores were compared in 1 case-control study between ENS patients and controls (ITRwENS, n = 17; controls, n = 6; **Table 10**). Tissue biopsy was performed at the midpoint of the residual inferior turbinate. Duration after previous surgery was not reported. The ENS group presented with more squamous metaplasia (76% vs 17%, $P = .018$), more submucosal fibrosis (94% vs 33%, $P = .008$), and lower submucosal gland number grading (0-4; 1.71 ± 1.13 vs 3.17 ± 0.69, $P = .013$) when compared with controls. The expression level of TRPM8 was scored by using a combination of immunohistochemical staining intensity and percentage of

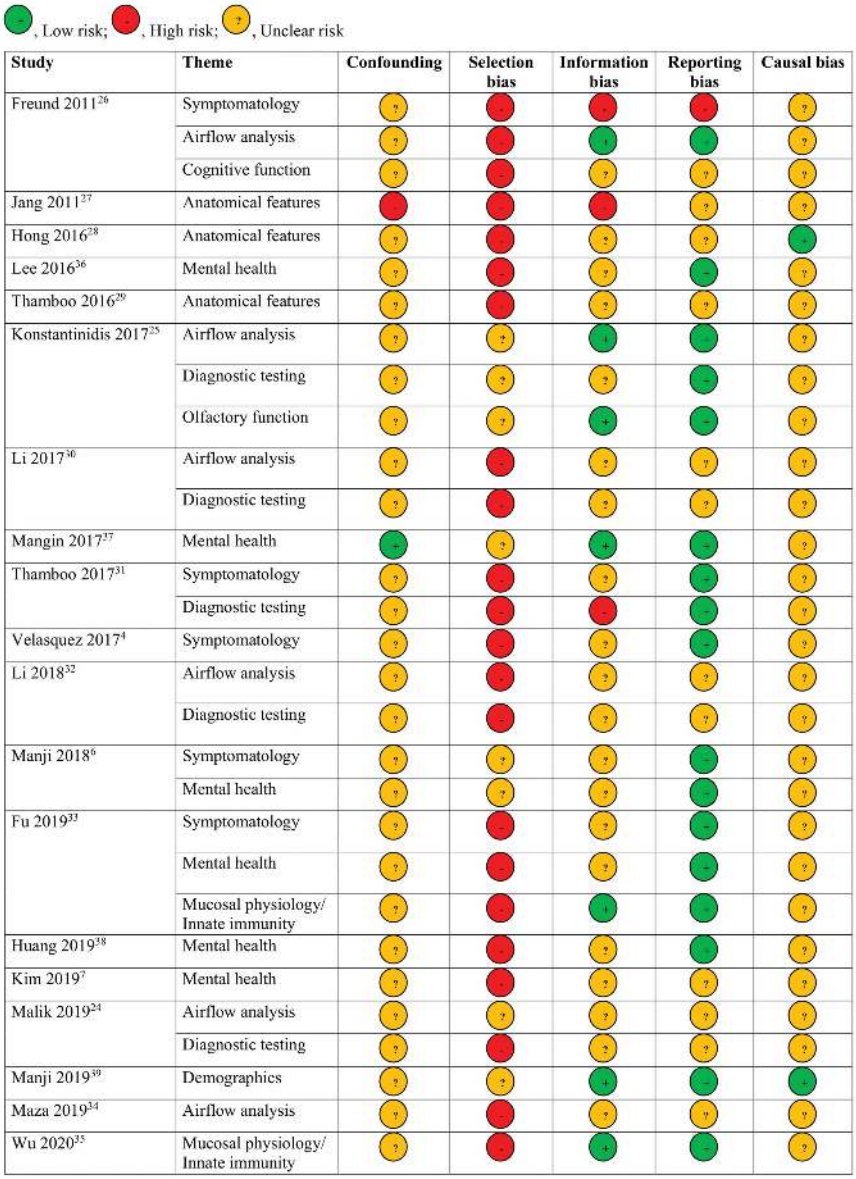

Figure 3. Risk-of-bias assessment.

stained cells (0-300). The TRPM8 expression level had a lower score in the ENS group than in the control group (129.68 ± 56.91 vs 251.67 ± 27.94, $P < .001$).

Nasal nitric oxide level was assessed in 1 case-control study between ITRwENS patients (n = 19) and chronic rhinitis (n = 12)[33] (**Table 10**). The nasal nitric oxide assessment was performed via an electrochemical analyzer (NIOX MINO; Phadia AB/Aerocrine AB). ENS patients had lower nasal nitric oxide levels when compared with chronic rhinitis patients (85.5 [327.5] vs 231.3 [312] ppb, $P < .001$). The study's authors discussed a possible association between nasal nitric oxide and psychiatric conditions, such as depression and anxiety.

Risk-of-Bias Assessment

Five types of bias were assessed in individual studies (**Figure 3**). Association bias existed throughout most studies, as causality between ITR and ENS was assumed but not proven and preoperative data were not available. Common bias included selection bias related to the use of surgically naive participants as a comparison, ENS patients were motivated by surgical candidacy and highly symptomatic selection in ENS on ENS6Q comparison. The potential for a placebo effect was high in some interventions, such as diagnostic testing.

Discussion

Human perception of nasal breathing is important when speculating on the potential pathophysiology of ENS. There are no described airflow receptors in the nose.[42] The perception of nasal patency is triggered through cool thermoreceptors (TRPM8) in the nasal mucosa.[41,43,44] The nasal airflow creates evaporation of water from nasal epithelial lining and activates trigeminal TRPM8 receptors through a temperature

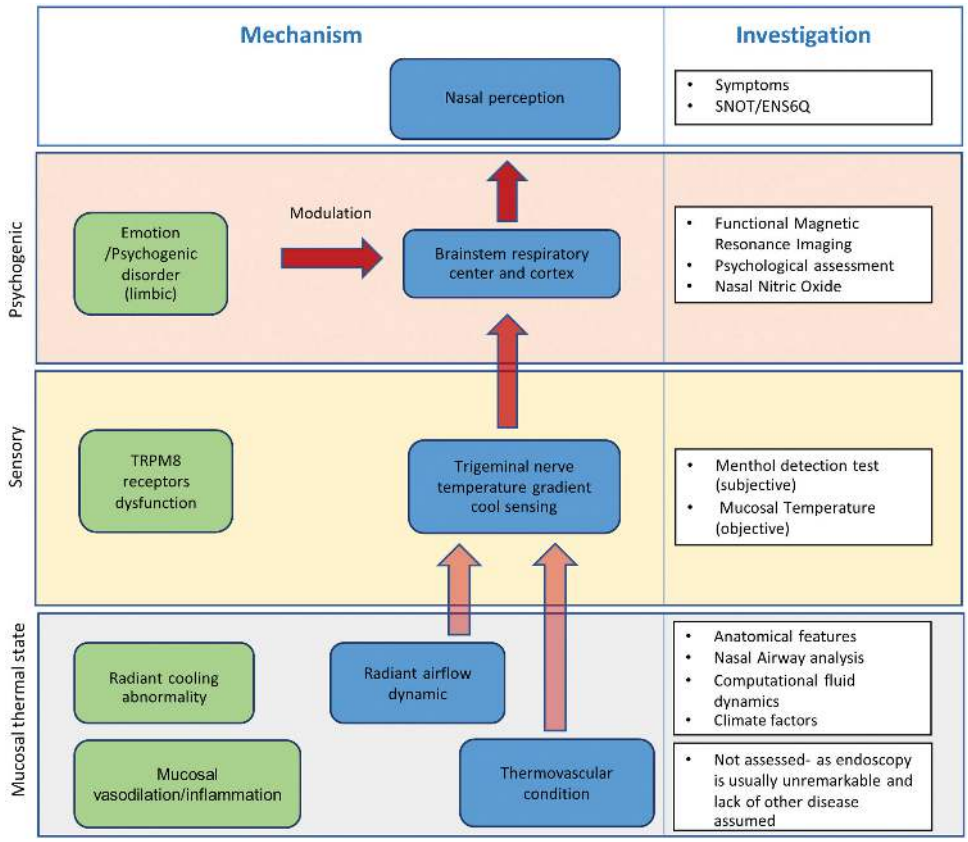

Figure 4. Illustrated model of pathophysiologic evidence in ENS. ENS6Q, Empty Nose 6-Item Questionnaire; SNOT, Sinonasal Outcome Test; TRPM-8, transient receptor potential melanostatin 8.

gradient in the range of 8 to 22 °C. This induces neuronal depolarization and stimulates the brainstem respiratory center and specific regions of the cerebral cortex.[45-47] The temperature-gradient cool sensing is thus interpreted as clear breathing. Menthol stimulation provides a good example of this mechanism, creating enhanced breathing without altering nasal airflow.[48] Dysfunction at any level of this pathway affects nasal breathing perception. This review's outcomes are incorporated into the nasal perception pathway (**Figure 4**). The pathophysiologic defect for ENS is likely to reside in this pathway, and the evidence for each is summarized.

Mucosal Thermal State

The mucosal temperature-gradient activation of TRPM8 is likely a combination of mucosal vasculature (thermovascular conditions) and the influence of radiant cooling by airflow (radiant airflow dynamics). Thus, allergic rhinitis creates a thermal effect from vasodilation and secondary poor radiant airflow cooling. Likewise, septal deviation may produce loss of radiant air cooling in otherwise normal nasal mucosa.

By definition, the absence of disease that influences thermovascular condition is assumed in ENS. Only studies on radiant airflow cooling were identified. Human studies have confirmed that similar improvements in nasal airspace, airflow rate, and nasal resistance were observed between ITRwENS and ITRsENS patients.[24,25,34] Mucosal thickening was observed at the septal area in ITRwENS when compared with ITRsENS, but patients had a longer time point from their surgery. Mucosal hypertrophy over time may have led to bias, and a lack of adjustment for repeated outcome measures may also contribute to such findings.

Despite all ENS studies on human assessments being similar, simulated nasal airflow on CFD modeling after ITR demonstrated decreased nasal airflow at the region where the inferior turbinate previously resided.[24,30,32,34,49] Contrasting findings were noted in another CFD model, which showed increased nasal airflow at an inferior region after ITR.[50] CFD modeling after MTR was also studied. Aerodynamic changes of an MTR model resulted in a slight decrease in wall shear stress at the region where the middle turbinate previously resided.[49,50] Nevertheless, MTR does not affect ENS risk after partial middle turbinate resection in humans.[51]

The effect of airflow alteration led clinicians to the use of nasal implants with the purpose to replace the missing nasal tissue.[52] The utility of nasal implants are based on potential changes in airflow dynamics.[53,54] A number of studies and systematic reviews of surgical intervention in ENS noted improvement in patient-reported sinonasal symptoms after surgical implants.[55-59]

While these data support a role for an airflow redistribution procedure, there is incongruity with this theory of airflow dynamic alteration as a cause of ENS. First, a multitude of

alterations in airflow patterns was reported in CFD modeling after ITR. Second, ENS was indicated in a very small proportion of patients following turbinate surgery[60] and is independent of the extent of surgery.[8,52,61] Third, around 20% of patients reported minimal or no improvement after surgical implants.[55] Finally, the modeling of CFD potentially creates many data points for analysis to lead to a type 1 error, and repeated outcome measure adjustments were not often reported.

Sensory Dysfunction in Nasal Patency Perception

Trigeminal innervation plays a major role in the perception of nasal breathing through the TRPM8 cool temperature receptor. Trigeminal sensitivity is evaluated by a subjective menthol detection test and an objective TRPM8 expression level on immunohistochemical staining. These data suggested a lower subjective menthol detection in ITRwENS versus ITRsENS and healthy controls.[24,25,30,32] On objective evaluation, ENS patients expressed a lower TRPM8 level on the remnant inferior turbinate as compared with healthy controls.[35] It is proposed that dysfunction in trigeminal temperature cool sensing is brought about by nerve damage or poor nerve regeneration following turbinate surgery. However, this has been disputed by the fact that nasal trigeminal receptors are widely distributed throughout the nasal cavity,[62,63] not just along the inferior turbinate. Additionally, ENS patients were not distinguished by the extent of surgery, and patients with extensive tumour resection do not experience these symptoms.[11,12] Presurgical impairment leading an ENS patient to first presentation and subsequent surgery or secondary to histological changes after surgery would be plausible.

Pathways of nasal perception are triggered at the trigeminal nucleus, brainstem, and cerebral cortex. Centrally affected areas may be an etiologic contributor for ENS and may result in similar perceptive deficits and menthol detection data. However, apart from some limited fMRI data, studies in this area are lacking.

Psychogenic Dysfunction in Nasal Patency Perception

There are examples of disorders in many specialties that are thought to have a strong psychogenic etiology, especially when symptoms are incompatible with observed examination—for example, tinnitus, irritable bowel syndrome, and fibromyalgia.[64-69]

Evidences exists for a strong association in ENS patients with impaired mental health.[6] Comorbidities such as anxiety, depression, and hyperventilation syndrome have been reported in a majority of ENS patients.[6,7,33,36-38] Many ENS patients fulfilled the criteria for somatic symptom disorder and gained benefit from psychiatric treatment, including cognitive behavioral therapy.[70-72] The extent of turbinate tissue loss does not appear to be related to the symptom burden in the studies within this review. As a result, symptom severity is high in ENS.[4,6,26,31] ENS6Q and SNOT-25 representing ENS symptom severity correlate with anxiety and depression.[6,38] These questionnaires may be detecting an underlying mental health impairment as much as any local airflow dysfunction.

Poor mental health status has been linked to poor nasal perception, disproportionate to objective findings,[7,28,73] and emotional regulation deficits.[74] Connection between emotional control and nasal perception was evident, with an fMRI study demonstrating the deactivation of emotional processing areas after the successful pseudo-decongestant stimulatory effect of menthol in ENS patients.[26]

The psychogenic influence on nasal perception would explain the discordance between the subjective and objective findings between ITRwENS and ITRsENS patients (Supplement Table S3, available online). However, it is challenging to prove which disease has given rise to the other. An alteration in nasal perception due to psychogenic conditions may exist prior to turbinate surgery. Findings of an ''empty nasal space'' in ENS may be the result of attempts to manage these presurgical symptoms. The exacerbation of ENS symptoms after surgery remains questionable. Stressful and emotional life events, potentially such as a surgical intervention, with an overexpectation of benefit have been associated with triggering a conversion disorder.[75,76]

Mucosal physiology in ENS showed low nitric oxide expression and a tissue-remodeling pattern on histopathology. Extracellular matrix and vascular remodeling have been found to be associated with an increased level of nitric oxide in animal and human models. The association between nitric oxide and tissue remodeling in ENS is unlikely. Nitric oxide level may rather be associated with downregulation of neurotransmitters involved in psychogenic disorders.[77-81]

Previous systematic reviews have recommended mental health screening in the rhinology workflow.[18] ENS6Q may be a useful screening tool for anxiety and depression due to its correlation with these mental conditions, especially when the examination is discordant. We have used a guide to screen a turbinate reduction candidate, referred to as ''Ray's rules'': (1) The patient is aware of fluctuating or ''cycling'' nasal congestion. (2) Postural congestion is perceived. (3) There is a subjective response to topical nasal decongestant. These physiologic responses feature an intact ''sensory'' nasal perception of the mucosal thermal state.

Conclusion

Alterations of the nasal airspace are similar between patients after turbinate surgery with and without ENS. The extent of the measured ''empty space'' described in ENS does not influence the symptoms of ENS. The influence of a altered airflow basis for ENS is unlikely. Neurogenic dysfunction of temperature-gradient cool sensing is reported in ENS patients as compared with controls. However, discordance between subjective and objective constructs in ENS extended beyond breathing to include olfaction. There is evidence of high psychogenic disorder comorbidities in patients with ENS. No data offered causality between ITR and ENS as preoperative data were not available. The assumption of surgery as the raison d'être for ENS is unclear.

Author Contributions

Dichapong Kanjanawasee, conception of the work, records screening, data extraction and analysis, manuscript preparation; **Raewyn G. Campbell**, conception of the work, data extraction, manuscript revising; **Janet Rimmer**, conception of the work, conflicting data management, manuscript revising; **Raquel Alvarado**, conception of the work, conflicting data management, manuscript revising; **Jesada Kanjanaumporn**, conception of the work, conflicting data management, manuscript revising; **Kornkiat Snidvongs**, conception of the work, conflicting data management, manuscript revising; **Larry Kalish**, screening: conception of the work, records screening, data extraction, manuscript revising; **Richard J. Harvey**, conception of the work, data extraction and analysis, manuscript revising; **Raymond Sacks**, conception of the work, data extraction, manuscript revising.

Disclosures

Competing interests: Kornkiat Snidvongs is on the speakers bureau for Merck Sharp Dohme, Sanofi Aventis, and Menarini (Mylan). Larry Kalish is on the speakers bureau for Care Pharmaceuticals, Sequiris, and Meda Pharmaceuticals. Janet Rimmer has honoraria with Sanofi Aventis, Novartis, Mundipharma, GSK, and Stallergenes. Richard J. Harvey is consultant with Medtronic, Stryker, Novartis, Meda, and NeilMed Pharmaceuticals; he has received research grant funding from Glaxo-Smith-Kline and Stallergenes; and he has been on the speakers bureau for Glaxo-Smith-Kline, Meda Pharmaceuticals, and Seqirus. Raymond Sacks is a consultant for Medtronic and is on the speakers bureau for Meda Pharmaceuticals.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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