Subjective perception of nasal breathing; identifying patient at risk of a poor surgical outcome

Mr. Dichapong Kanjanawasee

A Dissertation Submitted in Partial Fulfillment of the Requirements

for the Degree of Doctor of Philosophy in Clinical Sciences

Common Course

FACULTY OF MEDICINE

Chulalongkorn University

Academic Year 2021

การรับรู้ความรู้สึกของการหายใจ; การระบุผู้ป่วยที่มีโอกาสได้รับผลของการผ่าตัดที่ไม่พึงประสงค์

นายดิชพงศ์ กาญจนวาสี

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
สาขาวิชาเวชศาสตร์คลินิก ไม่สังกัดภาควิชา/เทียบเท่า
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2564

Thesis Title	Subjective perception of nasal breathing; identifying patient at risk of a poor surgical outcome
By	Mr. Dichapong Kanjanawasee
Field of Study	Clinical Sciences
Thesis Advisor	Assistant Professor JESADA KANJANAUMPORN
Thesis Co Advisor	Associate Professor KORNKIAT SNIDVONGS

Accepted by the FACULTY OF MEDICINE, Chulalongkorn University in Partial Fulfillment of the Requirement for the Doctor of Philosophy

..... Dean of the FACULTY OF MEDICINE
(Associate Professor CHANCHAI SITTIPUNT)

DISSERTATION COMMITTEE

..... Chairman
(Professor Saowaros Patarapak)

..... Thesis Advisor
(Assistant Professor JESADA KANJANAUMPORN)

..... Thesis Co-Advisor
(Associate Professor KORNKIAT SNIDVONGS)

..... Examiner
(Associate Professor SONGKLOT AEUMJATURAPAT)

..... External Examiner
(Associate Professor PONGSAKORN TANTILIPIKORN)

ดิชพงศ์ กาญจนวาสี : การรับรู้ความรู้สึกของการหายใจ; การระบุผู้ป่วยที่มีโอกาสได้รับผลของการผ่าตัดที่ไม่พึงประสงค์. (Subjective perception of nasal breathing; identifying patient at risk of a poor surgical outcome) อ.ที่ปรึกษาหลัก : ผศ. นพ. เจษฎา กาญจนอัมพร, อ.ที่ปรึกษาร่วม : รศ. ดร.นพ. ม.ล.กรเกียรติ์ สนิทวงศ์

-

สาขาวิชา	เวชศาสตร์คลินิก	ลายมือชื่อนิสิต .....
ปีการศึกษา	2564	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....
		ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

5974655530 : MAJOR CLINICAL SCIENCES

KEYWORD: nasal perception, empty nose syndrome, surgical outcome, pathophysiology, nasal breathing, nasal airway assessment

Dichapong Kanjanawasee : Subjective perception of nasal breathing; identifying patient at risk of a poor surgical outcome. Advisor: Asst. Prof. JESADA KANJANAUMPORN Co-advisor: Assoc. Prof. KORNKIAT SNIDVONGS

-

Field of Study:	Clinical Sciences	Student's Signature .....
Academic Year:	2021	Advisor's Signature .....
		Co-advisor's Signature .....

ACKNOWLEDGEMENTS

I would like to express my deep and sincere gratitude to all my supervisor Asst. Prof. Jesada Kanjanaumporn, Assoc. Prof. Kornkiat Snidvongs and Prof. Richard Harvey for the continuous support throughout my study. Their dynamism, vision, sincerity and motivation have deeply inspired me. They are like role models on every aspect not only in academic work but also a dedication to the family showing greatness in work life-balance. It was a great privilege and honor to work and study under their guidance. Also, thank for my associate supervisor Prof. Raymond Sacks for his kindness and willingness to guide me through the research study as well as great advice and guidance for staying oversea. My completion of this project could not have been accomplished without the support of the sinus and skullbase research team, especially Dr. Raquel Alvarado. She always guides and supports me on every step. Also, thanks to other members of the team, Assoc. Prof. Larry Kalish, Dr. Raewyn Campbell and Prof. Janet Rimmer for prompt response, great advice and support.

Dichapong Kanjanawasee

TABLE OF CONTENTS

Page

3

LIST OF TABLES

Page

LIST OF FIGURES

Page

Subjective perception of nasal breathing

Dichapong Kanjanawasee, MD.

Department of Otolaryngology
Faculty of medicine
Chulalongkorn University

Department of Clinical Medicine
Faculty of Medicine, Health and Human Sciences
Macquarie University

Abstract

Nasal obstruction is a very common nasal complaint in clinical practice. The mechanism of nasal breathing perception is poorly understood and controversial. Currently, there is no reliable tool for measuring nasal perception of air flow. This thesis aims to develop an understanding of nasal perception pathway, identify factors contributing to nasal perception and develop a new reliable measuring tool.

Empty nose syndrome (ENS) is a well-known condition characterized by paradoxical sensation of nasal obstruction despite wide empty nasal space. The explanation of this condition can enhance the understanding of nasal perception mechanism, therefore pathophysiology of ENS was studied. (Chapter 2) The nasal perception is driven by the nasal mucosal 'cooling' which connected to brainstem control center and specific region of cerebral cortices including emotional processing area. Our experiment found that the effect of emotional control and psychogenic modulation on nasal perception is likely to be the explanation of the discordance between subjective and objective findings in ENS and may potentially be its cause.

The utility of objective airway test on structural obstruction was studied in patients who underwent nasal obstruction surgery. (Chapter 3) Nasal resistance demonstrates higher correlation of the impact of surgery with patient reported outcomes on the obstructed side. The control of 'disease factor' is deemed successful when an improvement in unilateral nasal resistance by 0.2 Pa/cm^3/s or total resistance by 0.1 Pa/cm^3/s is achieved.

Despite achieving the desired outcome in controlling the 'disease factor', persistent nasal obstruction also depends on 'patient factor.' The 'patient factor' associated with poor surgical outcome from the turbinate surgery was studied by comparing ENS and non-ENS patients. (low or high benefit) (Chapter 4) High psychogenic function, disproportionate subjective nasal complaints and the presence of reflux symptoms were shown to be characteristic of ENS. The new measuring tool called ENS12Qs was developed accordingly. (Chapter 5) This 12-item questionnaire utilized in this study to differentiate ENS from non-ENS cases can potentially be used to clinically identify patients at risk of developing poor surgical outcome 'before' it occurs.

In conclusion, this thesis provides the understanding and insight of subjective nasal perception. Psychogenic factor is the major contributor on subjective nasal perception and could explain the paradoxical finding between subjective perception and objective nasal airway test. The poor psychogenic function found in ENS led to the development of subjective measurement tool which provides a comprehensive and reliable subjective nasal perception assessment.

Declaration

Statement of Originality

This thesis is being submitted to Macquarie University and Chulalongkorn University in accordance with the Cotutelle agreement dated 07 January 2019.To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

_____

Date:_____08_NOV_2021_____

Chapter 1. General introduction

1.1 Nasal obstruction: Definition, prevalence and burden

Nasal obstruction is defined as the subjective perception of insufficient airflow through the nose. *Nasal congestion* is another term used to describe nasal turbinate mucosa swelling on clinical examination, which is caused by dilatation of the capacitance vessels in the turbinate tissue that is a key component of sinonasal pathology such as rhinitis.[1] In other words, the term *congestion* describes both subjective perceptions in mucosal pathology and the outcomes of objective nasal airway measurements, such as nasal airway resistance or nasal airflow.[2] Decongestants act by constricting these blood vessels and restoring nasal patency perception. Therefore, nasal congestion causes nasal obstruction, but not all nasal obstruction is caused by congestion.

Nasal obstruction is one of the most common complaints in rhinology practice.[3] It is estimated that nasal obstruction can affect at least 30% of the general population.[4] The two most common causes are inflammatory disease and nasal obstruction due to anatomical abnormality. Most studies of nasal obstruction have been conducted in patients with sinonasal inflammatory disease, and common conditions are allergic rhinitis and rhinosinusitis, with allergic rhinitis (AR) being the most common sinonasal inflammatory condition. The prevalence of allergic rhinitis varies across studies, ranging from 10% to 40%.[5] Up to 85% of patients with allergic rhinitis reported nasal obstruction, and it has been reported as the most problematic symptom in 50%–78% of cases. The prevalence of rhinosinusitis was reported by over 10% of the population, with an incidence of nasal obstruction observed in 66% to 70% of patients.[6-8]

In Australia, the health utility values (HUV), a measure of preference-based health-related quality of life used in cost-utility analyses, were studied in patients with nasal airway obstruction. The results show similar HUV to those in individuals with chronic diseases in the Australian population, including chronic obstructive pulmonary disease, diabetes mellitus

and renal disease requiring dialysis.[9] In 2007, approximately 13 million out-patient visits for the assessment of nasal congestion took place in the United States.[10] The monetary cost of nasal obstruction is significant – approximately 30 years ago, an estimated $5 billion was spent for medical management annually, and another $60 million was spent on surgical intervention. [11,12]

1.2 Nasal anatomy

Anatomical obstruction is one of the most common causes of nasal obstruction. Anatomical structures contributing to nasal airway obstruction include the nasal framework and cartilage, internal and external valve, nasal septum and nasal turbinate. The abnormality of these structures can be measured through objective airflow assessment.

1.2.1 Framework and cartilage

The nasal framework and nasal septum form a major support of the nose. The framework is rigid and separated into three parts. The nasal bones are in the upper third, the middle third comprises the upper lateral cartilage (ULCs) and the lower lateral cartilages (LLCs) are situated in the lower third. The paired nasal bones form a pyramidal shape structure, they attach to the frontal bone superiorly and to the frontal process of the maxilla laterally. The caudal edge of the nasal bone forms the superior border of the pyriform aperture and articulates with the nasal septum to create the *keystone area,* which is an important area determining the stability and dorsal aesthetic of the nose.

The middle and lower thirds of the nose are formed by nasal cartilage. The middle third is composed of paired ULCs. Laterally, the ULCs are connected with the pyriform aperture, while the lower third of the nose is composed of the paired LLCs or alar cartilage. The LLCs are separated into the medial crus and the lateral crus, with the LLCs and nasal septum providing the nasal tip support. The shape and position of the nasal tip is determined by the configuration of these cartilages.

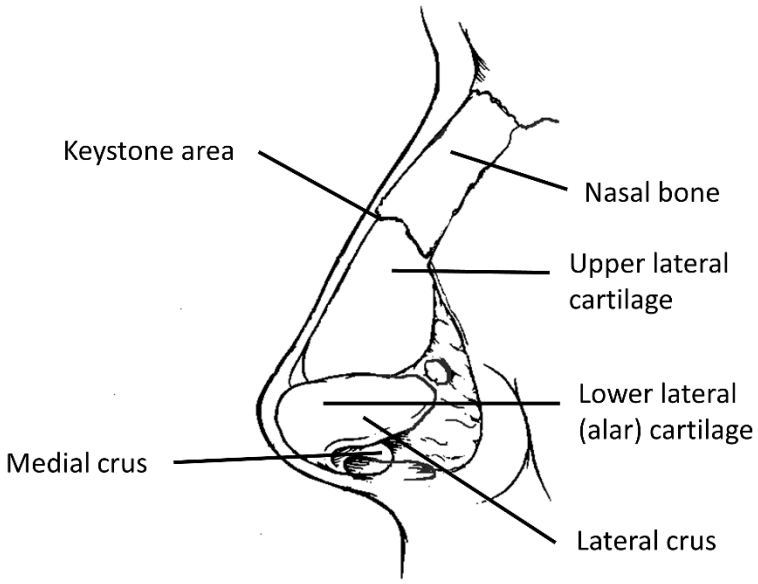


Figure 1. Anatomy of nasal framework and cartilage

1.2.2 Internal and external nasal valve

The nasal valve is the narrowest portion of the human airway. Nasal valve collapse, or stenosis, is a common structural cause of nasal obstruction.[13,14] The nasal valve is separated into an internal and external nasal valve. The anatomic boundaries of the internal nasal valve are the dorsal nasal septum medially, the internal caudal edge of the ULCs laterally and the anterior head of the inferior turbinate posteriorly. The normal angle between the nasal septum and ULCs is 10° to 15°. It has a cross-sectional area of approximately 40 to 60 mm^2. This anatomic area is the narrowest portion of the nasal airway and comprises the area of greatest overall nasal airflow resistance.[15]

The external nasal valve is the area under the nasal alar, also known as the nasal vestibule. Its anatomical boundaries are the medial crus of the alar cartilages and the membranous septum medially, the caudal edge of the lateral crus of the lower lateral cartilages, the alar rim laterally and the nasal sill inferiorly. This is the first region in creating nasal airflow resistance. The external nasal valve is dilated and supported by the nasalis muscle. The external nasal valve assessment is highly complicated when both dynamic and static disturbances occur simultaneously in this area. [16,17]

1.2.3 Nasal septum

The two nasal cavities are divided by nasal septum. From anterior to posterior, the nasal septum consists of membranous septum, cartilaginous septum and bony septum. The membranous septum is fibrofatty tissue located between the columella and the septal cartilage. The cartilaginous part of the septum is known as the quadrangular cartilage, and the posterior bony septum is composed of the perpendicular plate of ethmoid and the vomer. The nasal septum functions to support the structure of the nose. Abnormalities in its shape and configuration can alter nasal airflow and cause nasal obstruction. A deviated nasal septum (DNS) is the most common structural cause of nasal obstruction[18] and affects approximately 80% of the population.[19] Although septal deformities are common, they are often asymptomatic. Trauma is a common cause reported in many patients, but there is no clear trigger event in most cases. Birth trauma or microfractures occurring early in life were associated with this abnormal septal growth.[20]

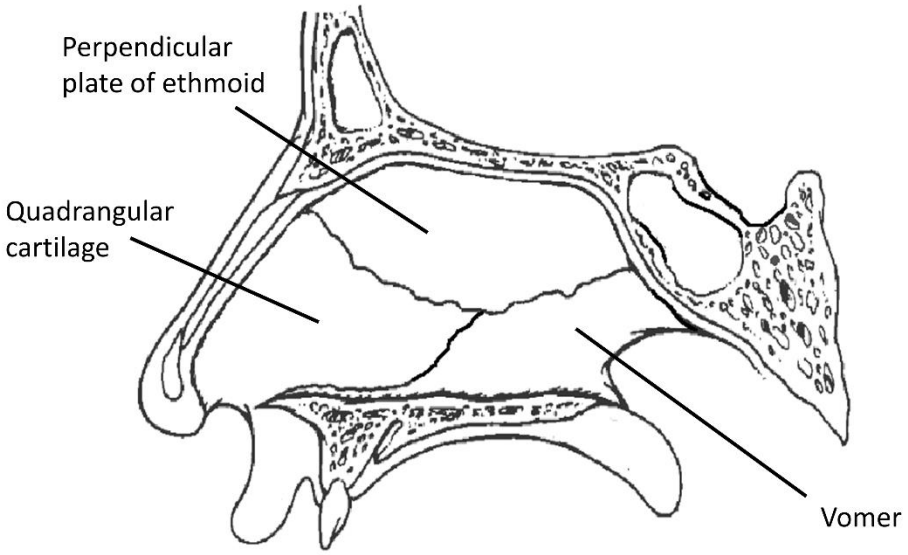


Figure 2. Anatomy of nasal septum

1.2.4 Septal swell body

The nasal septal swell body is an enlarged area of the anterior nasal septum also called the septal turbinate. The septal swell body is a different condition from septal deviation.[21] It is located anterior to the middle turbinate, close to the distal part of the internal nasal valve

and might contribute to the site of the obstruction. A large proportion of venous sinusoids and seromucous glands found in this area potentially affect nasal airflow.[22]

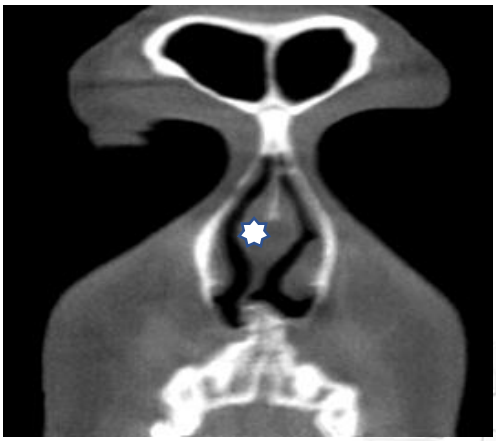


Figure 3. Coronal computed tomography (CT) with septal swell body

1.2.5 Turbinates

Nasal concha or nasal turbinates are located at the lateral nasal wall. Generally, three nasal turbinates are identified: superior, middle and inferior. The superior and middle turbinates originate from the ethmoid bone, whereas the inferior turbinates are discrete structures. The turbinate consists of a bony structure and soft tissue. The inferior turbinate tissue contains a rich supply of resistance blood vessels and venous sinusoids, which are controlled by the autonomic nervous system. An alteration in autonomic activity contributes to congestion, or decongestion, of the inferior turbinate. Hypertrophy of the inferior turbinate, in response to chronic inflammatory processes, leads to a decrease in cross-section area and increase in nasal resistance. Similarly, polypoid edema of middle turbinate is reported in allergic rhinitis patients. [23]

The middle turbinate serves as an important surgical landmark, but less so for determining nasal resistance. A concha bullosa represents pneumatization of the middle turbinate and is a common anatomic variant found in approximately 25% of the population.[24] A large concha bullosa can increase nasal airflow resistance and contribute to nasal obstructive symptoms.[25] Contralateral septal deviation commonly coexists with unilateral concha bullosa.

1.3 The nasal airflow

Bernoulli's principle states that the faster a fluid moves, the more its pressure decreases. This concept explains the decline in intraluminal pressure when air passes at high speed through the nasal valve during inspiration, leading to collapse of the upper lateral cartilage.[14] However, the strength of the upper and lower lateral cartilages helps maintain the integrity of the internal nasal valve and prevents it from collapsing, even on deep inspiration. Nasal obstruction, caused by internal nasal valve collapse, is often seen where internal nasal valve laxity occurs due to previous trauma or aging. In comparison, external nasal valve collapse is prevented by activation of the dilator nasalis muscle during inspiration and by positive airway pressure during expiration.

The nasal airflow passes the nasal valve and runs towards the nasal turbinate, septum, floor of the nose and nasopharynx. Airflow velocity is proportional to the nasal cross-sectional area radius to the fourth power (radius^4), as stated in Poiseuille's principle.[13] Poiseuille's law explains the effect on airflow velocity when there is a decrease in nasal diameter caused by structural abnormalities. A reduction in diameter of the affected structure can exponentially reduce nasal airflow.

The effect of airflow sensing was studied on computational fluid dynamic models. Nasal wall shear stress is used to study the effect of airflow on mechanoreceptors stimulation in the nasal mucosa. The result demonstrates no correlation between subjective sensation of nasal airflow and nasal wall shear stress.[26] In addition, basic research on animal models also found no activation of nasal mechanoreceptors during breathing.[27,28] From these results, it is concluded that the mechanoreceptor of airflow is not involved in the mechanism of nasal breathing. The true role of airflow in nasal perception is to initiate water evaporation from the epithelial lining, which mediates the *cooling* radiant effect. This temperature gradient then triggers the trigeminal cool receptor and interprets the *cool* message as patency breathing perception.[29-33]

1.4 Nasal physiology

Sinonasal inflammatory diseases, such as rhinitis and rhinosinusitis, are common causes of nasal obstruction. The inflammatory process alters the normal nasal physiologic function in different ways, including mucociliary clearance and vascular tissue complex.

1.4.1 Mucociliary function

Nasal mucosa is comprised of pseudostratified ciliated columnar respiratory cells, goblet cells and the seromucous submucosal glands. Both seromucous glands and goblet cells secrete mucus and the secretion forms a layer that covers nasal mucosa like a blanket throughout the nasal cavity and sinuses. Seromucous glands in the submucosa layer are responsible for mucus production in the nasal cavity, whereas goblet cells are found mainly in the sinuses. The mucus blanket comprises two distinct layers: the inner periciliary layer, or sol layer, and the outer viscous layer, or gel layer. The liquid sol layer provides an optimal environment for cilia to recover from active beating, whereas the outer, thicker and more viscous gel layer is transported along with each coordinated ciliary beat. This mucous blanket functions to trap foreign particles and remove them toward the nasopharynx. This mucociliary clearance is an essential protective function that helps clear out allergens and microbes. Thus, it slows down the inflammatory response and prevents upper respiratory infections.[34] The blanket changes in the nasal cavity every 20–30 minutes, and has an average speed of 6 mm/min. The cilia of the lower septum and inferior turbinate beat at 12–15 Hz (beats/sec) under normal circumstances.[35]

The autonomic nervous system is the primary controller of mucus production. Parasympathetic stimulation, increasing mucus secretion, is mediated through the nerve to the pterygoid canal (vidian nerve). Conversely, sympathetic stimulation reduces mucus secretion from the seromucous glands. Prolonged mucociliary clearance transit times are associated with sinonasal pathologies, such as ciliary dysfunction in ciliary dyskinesia, increased mucus viscosity in cystic fibrosis and increased mucus production in rhinitis and rhinosinusitis. Mucociliary function can be improved with anti-inflammatory medication in chronic rhinosinusitis and rhinitis patient.[36-38]

1.4.2 Vascular complex

A complex vascular structure in the nasal cavity serves to modify the nasal cavity morphology [39] and maintain normal nasal air conditioning. The vascular complex is prominent in the septum, inferior and middle turbinate. It is the arterial and venous anastomosis consisting of precapillary resistance vessels, capillaries, venous sinusoids and venule. The venous sinusoids are interposed between capillaries and venules and act as capacitance vessels.[35,40,41] The blood flow of the anastomoses is regulated by smooth muscle

surrounding the endothelial layer, enabling the resistance vessel and venous sinusoids capacitance vessel to control blood volume according to the state of congestion/decongestion.[42,43] The change in the congestion/decongestion states is largely responsible for nasal airflow resistance.[35] The vascular tone in the capacitance and resistance vessels is influenced by sympathetic and parasympathetic agents.

The autonomic nervous system controls the vascular tone and level of congestion. The adrenergic sympathetic pathway stimulation induces vasoconstriction of the arteriovenous anastomoses and collapse of the venous sinusoid capacitance vessel, resulting in nasal airspace volume expansion and perception of nasal patency. Adrenergic receptors are present on the anastomoses and are the target of topical and systemic vasoconstricting decongestants.[44] Conversely, sympathetic tone loss generates an increase in nasal resistance and in the sensation of nasal congestion, as found in patients with cervical sympathectomy and Horner's syndrome.

Cholinergic parasympathetic fibers are found around seromucous glands, blood vessels, and nasal mucosa. Presynaptic parasympathetic fibers originate from the geniculate ganglion, travel along the greater superficial petrosal nerve and join the deep petrosal nerve, which contains sympathetic fiber, to form the vidian nerve. The vidian nerve travels to the sphenopalatine ganglion where parasympathetic axon synapses with the postganglionic neurons before innervating the nasal mucosa. Nasal congestion/decongestion is determined by a fluctuation in the balance between parasympathetic and sympathetic nervous activity.

Regulation of this autonomic nervous system may play an important role in the normal physiologic nasal cycle. The nasal cycle is a spontaneous phenomenon of cyclic unilateral nasal mucosa congestion due to an asymmetrical venous sinusoid engorgement that alternates from one nasal passage to the other over a period of time.[45] The nasal cycle was presented in about 70%–90% of adults,[46] but some studies reported a true periodicity exists only in 21%–39% of the population.[47,48] The nasal cycle periodicity ranges from 25 minutes to 8 hours. During waking hours, the average interval is between 1.5 and 4 hours.[49] In the normal population, the cycle generally goes unnoticed, with unchanged total airflow and resistance, but in patients with nasal pathologies, such as anatomical obstruction or sinonasal inflammation, this alternating obstruction can be detected.

The physiologic mechanism of the nasal cycle is still unknown but may be related to fluctuations in autonomic nervous systems. The sympathetic stimulation on one side

promotes vasoconstriction, while parasympathetic function causes vasodilation and congestion on the contralateral side. Evidence confirms that the nasal cycle is centrally controlled and persists even after total laryngectomy, when nasal airflow ceases.[50] The nasal cycle is affected by changes in blood pressure rate, blood glucose level, age or positional changes.[49] The purpose of the nasal cycle is thought to be an evolutionary adaptation that allows for optimal regeneration, moisturising and cleaning of nasal mucosa.[46]

1.5 Theory of nasal sensation

Historically, physicians have relied on physical assessments and nasal objective airflow measurements, such as rhinomanometry, acoustic rhinometry and nasal peak inspiratory flow to evaluate nasal patency and guide for surgical decisions. Studies have shown that most nasal obstruction surgery is successful in improving nasal airflow.[51] Despite an improvement in nasal airflow and resistance, evidence suggests that these objective measurements often poorly correlate with the subjective sensation of nasal airflow.[52,53] This discrepancy explains the report of surgical failure rates being as high as 28%–33%.[54-56] Evidence now suggests that the primary mechanism of nasal airflow sensation is not airflow resistance but rather the nasal mucosal cooling activation of the trigeminal nerve.

1.5.1 Mechanism of nasal airflow perception

The primary pathophysiological mechanism of nasal breathing perception is trigeminal cool thermoreceptor activation. The current theory of nasal sensation was developed based on the understanding of the effect of menthol. It was shown that menthol vapor improves the subjective sensation of nasal airflow without altering nasal resistance. [57-59] The sensation of nasal patency is derived from a cooling of the nasal lining, which is detected by cool thermoreceptors.[60] The relationship between nasal temperature and nasal perception was studied, and the evidence shows that cooler nasal lining temperature is correlated with the greater subjective perception of nasal breathing.[31-33] The combination of evaporative heat loss and conductive heat loss drives the cooling of nasal mucosa, and this change in temperature or temperature gradient provides nasal patency perception.[30]

The specific receptors stimulated by cold temperature were identified on trigeminal nerve endings.[61] Schafer et al. provided evidence on the existence of the cold receptors that respond to chemical compounds such as menthol.[62] Cold receptors belong to the transient receptor potential (TRP) protein family. The general role of the TRP protein family is

thermosensation.[63] TRP proteins respond to a different specific temperature and to different types of aromatherapy. TRPV1 responds to temperatures ≥ 42 °C, while TRPV2 responds to dangerously high tissue-damaging temperatures ≥ 52 °C. TRPV3 and TRPV4 respond to ambient temperatures (25–35 °C). TRPM8 responds to temperatures around 8–22 °C, menthol and other cooling agents, such as icilin, eucalyptol, WS-3, lysophosphatidylinositol, lysophosphatidyl choline and lysophosphatidyl serine. TRPA1 responds to very cold temperatures, mustard oil, garlic isocyanate compounds and tetrahydrocannabinol.[64] The thermoreceptor Transient Receptor Potential Melastatin-8 (TRPM8) was shown to be responsible for the cooling signal in nasal perception. TRPM8 is predominantly expressed in a primary afferent sensory neuron within the trigeminal ganglia found in the nasal epithelium, mucous glands and vessels.[65-68]

When high-speed air moves through the nostril and induces evaporation of water from the epithelial lining fluid, the cooling signal is sensed and activated by TRPM8 receptors, causing depolarization of neurons that connect to the brainstem respiratory center and the cool message is interpreted as patent nostrils.[2,69] A normal nasal-cooling effect requires an adequate airflow-mucosa surface contact area and a normal mucosal vascular condition. Less mucosal–airflow contact area in structural obstruction and a higher local temperature from mucosal inflammatory disease can contribute to ineffective nasal cooling activation. [29,70]

The cool stimulus to the nasal mucosa activates the primary trigeminal sensory neurons synapse in the spinal trigeminal nucleus, and the secondary neurons cross the midline and ascend via trigemino-spinothalamic tracts to the thalamus and brainstem. The brainstem reticular formation could trigger arousal and cerebral cortex activity, as demonstrated on electroencephalogram and functional magnetic resonance imaging.[71,72] The specific cortical activation areas include somatosensory cortex regions of the rostral insula, which involve sensory and emotional processing, anterior cingulate cortex area, which relates to decision making, the insula cortex and pre-central gyrus of the frontal lobe, which is the motor cortex. [2,69,73] The involvement of the limbic system or emotional processing area indicates the impact of cognitive function and emotional control on nasal perception. Therefore, an emotional regulation deficit in a psychogenic disorder may lead to poor nasal perception.

1.5.2 The control of respiration

Breathing is centrally controlled by a pontomedullary respiratory center that receives afferent information from many sources. The breathing pattern is mainly controlled by acid-based homeostasis, which is detected by CO_2 receptors on the medulla's surface and on the carotid bodies. For example, hyperventilation is induced to restore pCO_2 hemostasis during hypocapnia or respiratory alkalosis. However, there is a common condition termed *dysfunctional breathing disorder,* in which metabolic control does not determine breathing patterns. It describes a group of breathing disorders in patients where chronic changes in the breathing pattern result in dyspnoea in the absence of organic respiratory or cardiovascular disease.[74-76] Hyperventilation syndrome (HVS) is the most well recognized form of dysfunctional breathing and was first described in 1938.[77] HVS is defined as the condition of increased minute ventilation or hyperventilation exceeding metabolic requirements from hypocapnia (a reduction in arterial pCO_2) and respiratory alkalosis.[75,76,78,79] Symptoms include palpitations, chest pain, breathlessness, chest tightness, tingling of the lips and fingers, tetany, paresthesia, light-headedness and dizziness. The pathogenesis of hyperventilation syndrome is unclear.[80] Previously, it was assumed that the hyperventilation provocation test (HVPT),[81] where patients are instructed to hyperventilate for a period of time, could generate a fall in arterial CO_2 and produce symptoms, and was considered a diagnostic requirement.[82] However, recent research doubts the role of hypocapnia in triggering the HVS symptoms. The CO_2 levels do not always relate to the breathing pattern, and the reproduction of symptoms during the HVPT is poorly correlated with a decrease in end-tidal pCO_2.[47,83-85]

The behavioral/emotional pathway was proposed to control respiration, in addition to the metabolic pathway, in similar fashion with the nasal perception mechanism.[81] This pathway presumably controls the ventilatory drive when the pCO_2 hemostasis is maintained. It could explain the difference between pCO_2 levels between sleep and awake states. During sleep, the subject relies on CO_2 chemoreceptor feedback to maintain ventilation, but the behavioral pathway overrides the CO_2 hemostasis when awake, which then alters the breathing pattern and pCO_2 level. The association of HVS and emotional stress, or psychogenic disorder, such as anxiety disorders, depression and panic disorder support this theory.[75,78,86] Initiation of attacks is possibly generated by emotional distress, but the neurophysiology of emotional disturbance is poorly understood. However, emotional factors

may stimulate nervous activity, which influences the behavioral pathway by activating the breathing muscular apparatus in an irregular, disorganized way that is unrelated to metabolic need and results in a fluctuation in the tidal volume, breathing frequency and end-tidal CO_2 levels.[81]

1.6 Measurement of nasal breathing

Measuring nasal obstruction is complex due to the nature of its varied etiology. The common etiology ranges from well described structural cause and inflammatory cause to an unsettled cause of empty nose syndrome. Since there are many causes of nasal obstruction, there are many available measuring tools. Various measuring instruments have been used, including objective and subjective measurements. Anatomical obstruction is usually measured objectively to determine the nasal morphology, nasal volume and resistance. The patient-reporting outcome measure has been used for subjective obstruction evaluation. Currently, there is no accurate test to measure nasal obstruction due to a poor correlation between subjective and objective measurements. Therefore, clinicians rely more on subjective assessments when making therapeutic decisions.

1.6.1 Subjective test

The patient reporting outcome measure (PROM) is a validated questionnaire, or instrument, developed to capture patients' self-reported perceptions of the severity of their specific diseases or symptom, and evaluate the impact on quality of life (QoL). PROM is usually used to evaluate disease progression and gauge the success of medical or surgical treatment. PROMs are recommended for routine use in rhinoplasty and rhinosinusitis clinical practice guidelines. [17,87]

The Nasal Obstruction Symptom Evaluation (NOSE) score is a validated questionnaire designed to measure the impact of nasal obstruction on QoL. The NOSE score was initially validated in patients undergoing septoplasty, but is now most commonly used in functional rhinoplasty.[88-90] The questionnaire contains five questions on a five-point Likert scale, and the total reported score ranges from 0 to 100. The severity of the NOSE score is classified into mild (5–25), moderate (30–50), severe (55–75) and extreme (> 80). The classification was shown to have high sensitivity and specificity in over 90% of the assessments of nasal airway obstruction.[91]

Another common measurement is the visual analogue scale (VAS). The VAS is used to subjectively assess the severity of all nasal symptoms, including nasal obstruction. VAS is scored on a continuous scale from 0 to 10, where 0 indicates the absence of symptoms and 10 indicates maximum severity. The marking on the point representing the severity of symptoms on a horizontal 10 cm line is usually the way to measure. The severity of nasal obstruction on VAS has been validated with reference to other subjective measures and correlated with successful surgical outcomes.[92-95] It is estimated that the average VAS in asymptomatic patients is 2.1 ±1.6, and the average VAS in patients with nasal obstruction is 6.9 ±2.3.[90] The advantage of using this scale in nasal obstruction over other commonly used PROMs is that it can evaluate unilateral symptoms by separating them into left- and right-sided obstruction scales.

Many PROMs have been developed to evaluate impact on QoL of specific diseases. The widely used disease-specific questionnaires on nasal inflammatory diseases are the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and the 22-item Sinonasal Outcome Test (SNOT-22).[96,97] These questionnaires are primarily used to evaluate disease-specific QoL, whereas nasal obstruction assessed by these instruments are more commonly the secondary aim.

RQLQ is the most common PROM used in allergic rhinitis throughout clinical studies and clinical practice.[98] It is a comprehensive survey that asks the patient to indicate disease-specific QoL and symptom severity based on the previous week. The questionnaire contains 28 items in seven domains. There are four items related to nose symptoms, four to eye symptoms, three to practical problems, three to sleep impairment, seven to non-hay fever symptoms, three to activity limitations and four to emotional states. Each item is scored on a seven-point Likert scale. The overall QoL is presented as the mean of these seven domains.[96] It has been extensively validated and translated to multiple languages.[99-101]

SNOT-22 is a 22-item validated tool that is widely used among clinicians and researchers to assess health-related QoL and symptom severity in chronic rhinosinusitis (CRS).[97] It was initially developed from the Rhinosinusitis Outcome Measure (RSOM-31)[102] and was reduced to SNOT-20, and then modified into SNOT-22. The SNOT-22 questionnaire was validated in pre- and post-operative sinus surgery patients[97,103] and has been validated and translated to multiple languages.[104-108] SNOT-22 is correlated with the degree of the sinus disease severity measure with a visual analogue scale[109] which is recommended to

measure sinus symptom severity in the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) guidelines.[87] SNOT-22 evaluates major and minor CRS symptom severity, divided into four subscales, including nasal symptoms, sleep dysfunction, emotional/psychological dysfunction and aural/facial symptoms.[110,111] Patients score each of the 22 items on a six-point Likert scale, with a total score ranging from 0–110. SNOT-22 can be classified into mild (8–20), moderate (20–50) and severe (> 50).[112] The minimal clinically important difference (MCID) can be used to monitored disease severity and health-related QoL over time. A MCID of 8.9 points for patients undergoing sinus surgery, and 12 points for patients undergoing medical intervention has been proposed.[113]

SNOT-22 is the instrument recommended by the EPOS2020 steering group for specific rhinology health-related QoL evaluation in CRS.[87] Additionally, the systematic review of PROMs used in chronic rhinosinusitis rated SNOT-22 as the highest quality PROM amongst 15 validated PROMs using standardized quality assessment.[110]

1.6.2 Objective test

Objective tests are used to measure nasal airway resistance, nasal airflow, nasal volume and nasal geometry. The current objective nasal airway measurement includes rhinomanometry, acoustic rhinometry and nasal peak inspiratory flow.

Rhinomanometry measures nasal airway resistance, while acoustic rhinometry assess the minimum cross-sectional area at different points inside the nostril, and nasal peak inspiratory flow (NPIF) detects the maximum nasal flow rate during inspiration. These objective tests have been generally used in the evaluation of anatomical obstruction and predict the possible efficacy of medical and surgical therapies by comparing tests before and after the application of nasal decongestant. Objective tests can also be used to interpret the outcome of nasal provocation test in patients with suspected allergic rhinitis.

Rhinomanometry

Rhinomanometry is a functional assessment of airflow that involves measuring transnasal pressure and nasal airflow to determine nasal airway resistance during the breathing cycle.[114]

Total resistance, and resistance from each side of the nose, can be compared, enabling the physician to identify how each nasal passage contributes to the patient's complaint. It is currently considered the gold standard technique by the International Committee on Standardization of Rhinomanometry for the assessment of nasal patency.[115,116] Techniques include active or passive and anterior or posterior methods. The active technique uses the subject's own breath to generate airflow, whereas for the passive technique the subject is in apnoea, and airflow is applied to the nasal cavity via a face mask.[116-119] The passive technique does not mimic true nasal physiology, and the propelled airflow could increase mucosal thickness, which affects the accuracy of the measurement. The measuring instruments are placed at the level of the nasal nostril in the anterior method. The posterior method requires the placement of an intra-oral device to record choanal pressure and flow. The active anterior method is more commonly used because it is more physiological, well tolerated and easier to cooperate with.[120] For this method, the transducer is placed in the nostril not being tested, and the nostril is sealed. When there is no flow, the pressure at the anterior and posterior end of the nostril is equal. After the patient breathes through one nasal cavity, transnasal pressure differences and nasal airflow between the posterior and anterior of the nose are recorded simultaneously for each side and the airway resistance changes are calculated.[117,121,122]

Four-phase rhinomanometry is the instrument of choice because it has the ability to display changes throughout all phases of the breathing cycle. The measurement resembles pulmonary flow-volume loops since it measures an accelerating inspiratory phase, a decelerating inspiratory phase, an accelerating expiratory phase and a decelerating expiratory phase. The resulting plot, with the x-axis representing the pressure differential and the y-axis representing the airflow, produces an S-shaped curve.

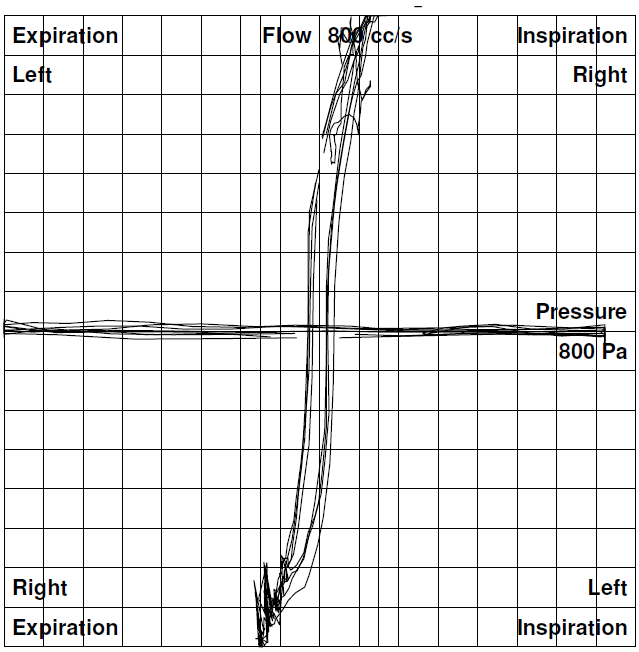


Figure 4. Rhinomanometry curve; demonstrating high nasal resistance of left nasal cavity and normal nasal resistance of right nasal cavity

The test is performed under baseline conditions and after vasoconstriction. This comparison with baseline results can guide the assessment of the nasal obstruction cause, and predict the response to treatment.[123,124] The International Standardisation Committee recommends active anterior rhinomanometry as the test to use in clinical practice.[118,123] Using active anterior rhinomanometry, the nasal response can also be quantified after exposure to irritants or allergens (nasal provocation test). If nasal flow decreases by 20% or more, the result is considered positive.[125] Rhinomanometry may detect nasal valve dysfunction, but it requires forced respiration to obtain the measurements.[120]

The reference nasal resistance values obtained by rhinomanometry have not been fully agreed. In the geographical area of a leptorrhine population, the normal values of unilateral and total nasal resistance reported at 150 Pa are < 0.45 and < 0.22 Pa/cm3/s, respectively.[126]

The limitations of this technique include the inability to specify the site of obstruction, it is time-consuming (usually takes 20–30 minutes) and operator dependent. Active anterior rhinomanometry cannot be used when insufficient airflow and pressure are generated, such as in a subject with a total or near-total nasal obstruction, and in the presence of a septal perforation.[13,120] Additionally, the total nasal resistance is calculated without direct measurement because each nostril is measured separately. Several factors

were shown to cause inconsistencies in the test. The nasal cycle causes a variation in nasal resistance, especially for unilateral interpretation.[127] Exercise is shown to reduce nasal resistance.[128,129] Ethnicity is another factor that affects nasal resistance. Nasal resistance is highest in Caucasian and lowest in African Americans, while in Asians it is in-between.[130] Supine position, the use of aspirin and smoking are also found to increase nasal resistance.[131,132] Age and weight also contribute to the variability.[118]

Acoustic rhinometry

Acoustic rhinometry is a device using the acoustic reflection of sound waves to analyze nasal cavity geometry.[133-135] Acoustic rhinometry devices transmit sound waves to a subject's nasal cavity and then record the sound waves that are reflected. Changes in acoustic impedance are used to calculate the nasal airway cross-sectional area and nasal volume at different points along the nasal passage. The amplitude of the reflected sound waves determines the nasal airway cross-sectional area, and the time delay of reflections represents the different distances from the nasal opening.[124,136-138]
The results are constructed into a rhinogram that provides a two-dimensional cross-sectional area at different distances from the nasal rim.[139] The test is compared between baseline and after nasal decongestant is applied.

On the rhinogram, there are two notches representing two common anatomic restriction areas in the nasal cavity. The first notch or I-notch (isthmus) indicates the nasal valve and the minimal cross-sectional area (MCA) of the nasal airway. This area is not affected by the vasoconstrictive property of the nasal decongestant. The second notch or C-notch (concha) represents the head of the inferior turbinate.[140] A cross-sectional area < 0.4 cm^2 on the C-notch has been shown to correlate with nasal obstruction symptoms.[135] Acoustic rhinometry is the most sensitive measurement for showing changes in response to nasal decongestants.[141] It is appropriate for assessment of the nasal airway structure, to locate the site of nasal airflow restriction and to evaluate changes in response to medical and surgical treatment.[133,142,143] Acoustic rhinometry can also be used to quantify the degree of nasal response on the nasal provocation test. It is considered positive if the MCA or the nasal volume between 2 and 6 cm from nasal opening decreases by at least 27%. [125]

Acoustic rhinometry has been validated against computed tomography (CT), magnetic resonance imaging (MRI) and nasal endoscopy, and a high correlation has been reported.[133,144-149]

Acoustic rhinometry takes very little time (usually ten seconds for each nostril), requires little instruction, is minimally invasive, has better tolerance and can be used in young children. Most importantly, the benefit over rhinomanometry is the ability to precisely identify the site of obstruction in the nose.[150] Disadvantages include its inability to measure dynamic changes with breathing. Due to a loss of acoustic energy, the accuracy of the measurement is lower, especially in an area beyond the narrow part in the posterior aspect of the nasal cavity.[123] Several factors that interfere with accuracy are ethnic/racial characteristics, age, weight, facial growth and development.[135]

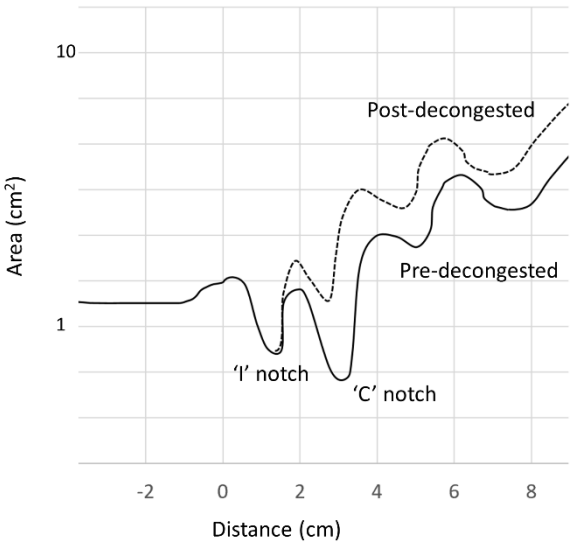


Figure 5. Acoustic rhinometry: rhinogram

Nasal peak inspiratory flow

Nasal peak inspiratory flow (NPIF) is a non-invasive, simple, rapid and affordable method used to assess nasal patency. The test does not need a computer for data analysis nor technical expertise to perform.[151] NPIF measures the maximum nasal airflow in liters per minute achieved during forced nasal inspiration.[122]The procedure requires an inverted flow meter; the device is a portable plastic tube (20 cm long, 3–4 cm in diameter) attached to a face mask that is placed over the subject's nose and mouth. The subject then made a force inspiration through their nostrils with their lips closed.[152] The method is accepted as reliable

for assessment of structural nasal obstruction[153] and of benefit to medical or surgical therapy when performed after nasal decongestion.

NPIF has been validated against nasal resistance measured on rhinomanometry, and a significant correlation was reported. [92,154] It can be used in measuring the outcome of nasal provocation test, and a ≥ 20% reduction in NPIF is considered positive.[125] NPIF is reproducible with an intraclass correlation coefficient ranging from 0.89 to 0.92.[155,156] A wide range of values of normality has been published for adults and children.[92,152,157-159] Recent systematic review suggest that the mean value of subjects with no nasal obstruction is 138.4 L/min, and the mean value of nasal-obstructed populations is 97.5 L/min.[160] A MCID was established at 20 L/min.[161] Cut-off values of 115–120 L/min have been suggested as the distinction between normality and obstruction.[122,152,156] NPIF is susceptible to high variability due to differences in technique and patients' cooperation. NPIF variability was shown within the first four attempts with a coefficient of variation of 15%.[162] Therefore, repeatability is more acceptable between the fourth and fifth attempts.

A number of factors that may influence NPIF results include age, height, gender, method of administration and respiratory effort. [152,163,164] Another concern with NPIF is that it does not represent normal physiologic breathing because forceful inspiration is not frequently made during daily activity.

1.6.3 Other tests

Computed tomography (CT) and magnetic resonance imaging (MRI) can directly demonstrate the nasal cavity space and volume. Imaging is a standard tool used for diagnosis and assessing the extension of nasal pathology. CT is preferred imaging for anatomical assessment.[165] Sinus CT is useful in evaluating nasal polyps, other pathologic masses and to determine the presence of a concha bullosa or other anatomic variations that may contribute to nasal obstruction. For sinonasal malignancy, CT and MRI are complementary in providing both soft tissue and bony structure information.

The limitations include poor correlation with subjective measurements. Symptom scores were poorly correlated with CT findings, and there was discordance between the patients' reported side of the obstruction and the side of septal deviation.[166] Imaging is a static measurement and has a limited role in evaluating dynamic nasal pathology such as rhinitis, which is prone to changes in volume and area depending on the level of nasal

congestion.[17,133,167]Also, CT is not recommended for evaluation of the nasal valve function when an abnormality is detected during dynamic nasal breathing – simple physical examination is usually preferred.[17]

Computational fluid dynamics (CFD) is a simulation model of nasal airflow. CFD involves creating three-dimensional computational models that are generated from the CT imaging data. The software generates a computational mesh, and normally millions of elements are generated. The airflow is simulated by applying a pressure drop between two anatomical points. Fluid dynamic parameters such as nasal airflow, velocities, streamlines, nasal resistance, heat transfer and wall shear stress are computed by software. CFD is still mostly performed in a research setting.[168-172] More evidence on validation with other nasal obstruction subjective and objective measurements are needed before it is used in a clinical setting.

1.6.4 The correlation between subjective and objective tests

Many studies have been performed to correlate objective and subjective measurements. Most studies demonstrated improved nasal obstruction outcomes following nasal obstruction surgery, but correlation between changes in objective and subjective outcome measures varied across the studies.[52]

The majority of studies found a poor correlation between subjective patient complaints and objective tests.[94,95,173-181] Lam et al.[53] found no significant correlation of acoustic rhinometry and nasal peak inspiratory flow with nasal obstruction VAS and the NOSE scale. Mozzanica et al. [182] demonstrated weak correlations between the objective and subjective methods using NOSE, VAS and active anterior rhinomanometry. Tomkinson and Eccles[183] found a poor correlation between subjective measurements and acoustic rhinometry, despite a significant correlation of acoustic rhinometry with CT, MRI and rhinoscopy. Andrews et al.[184] compared NPIF with SNOT-22, NOSE and nasal obstruction VAS after nasal surgery and found no significant correlation between outcomes, despite both objective and subjective outcome measures improved postoperatively. Mendes et al.[185] compared active anterior rhinomanometry, acoustic rhinometry and a symptom scale in children with allergic rhinitis and found no significant correlation between the objective and subjective methods. Kjaergard et al. [143] demonstrated a significant correlation between nasal

obstruction VAS and acoustic rhinometry and NPIF. However, the reported correlation coefficients were relatively low.

In 2009, a systematic review was conducted on 16 studies regarding the correlation between objective and subjective nasal obstruction outcome measures. The results demonstrated both correlation and lack of relation between the outcomes. The data also suggested that correlation is higher when the assessment is performed unilaterally, especially on the side of the obstruction.[52] There is no proven explanation for this lack of correlation between subjective and objective outcome measures. The understanding of the nasal breathing pathway possibly addresses this phenomenon and further study is needed.

1.7 Causes of nasal obstruction

Multiple factors are involved in the normal breathing pathway. Normal nasal perception of breathing requires normal function of the cooling system. The cause of nasal obstruction is based on the mechanism that interferes with it. The major causes are structural abnormality and sinonasal inflammation. Airflow restriction in structural obstruction, and high local temperature from nasal mucosal pathology, contributes to ineffective mucosal cooling and nasal obstruction perception. The differential diagnosis of nasal obstruction is displayed in Table 1. Potential causes include structural, inflammatory and other etiologies.[12]

Table 1. Differential diagnosis of nasal obstruction

Structural cause
Deviate nasal septum
Inferior turbinate hypertrophy
Middle turbinate hypertrophy/concha bullosa
Internal nasal valve abnormality
External nasal valve abnormality
Neoplasm
Trauma
Deformity of nasal bones
Septal hematoma
Inflammatory cause
Allergic rhinitis
Nonallergic rhinitis
Vasomotor rhinitis
Occupational rhinitis
Smoking rhinitis
Hormonal related rhinitis
Acute rhinosinusitis
Chronic rhinosinusitis
Allergic fungal sinusitis
Autoimmune disease
Granulomatosis With polyangiitis
Sarcoidosis
Eosinophilic granulomatosis with polyangiitis (Churg- Strauss syndrome)
Vestibulitis
Rhinosporidiosis
Rhinoscleroma
Cystic fibrosis
Primary ciliary dyskinesia

Other cause
Gastroesophageal reflux disease
Rhinitis medicamentosa
Other medications
Atrophic rhinitis
Empty nose syndrome

1.7.1 Structural cause

Anatomical obstruction hinders the optimal nasal airflow and produces inadequate radiant airflow cooling leading to the perception of nasal obstruction. Common causes of a structural problem are nasal valve collapse, DNS and turbinate hypertrophy. Nasal anatomy was discussed in Section 1.2.

A thorough physical examination and nasal endoscopic examination is essential for diagnosis, therapeutic consideration and surgical planning. Objective assessment has been widely used to evaluate nasal geometry in anatomical obstruction. However, the inability to detect nasal valve defects and the poor correlation of subjective and objective assessments limits its use in clinical practice. (Section 1.6.3)

1.7.2 Inflammatory cause

Sinonasal inflammatory disease is one of the most common causes of nasal obstruction. The mechanism of nasal blockage is produced by a combination of mucus hypersecretion or mucociliary dysfunction and soft tissue edema from venous sinusoid engorgement. Mucus overproduction hinders the airflow-mucosa contact surface and vascular engorgement produces high local temperature, with both effects leading to poor mucosal cooling. Common sinonasal inflammatory disorders are rhinitis and rhinosinusitis.

Rhinitis

Rhinitis is an extremely common cause of nasal congestion – it is an inflammation of the nasal mucous membrane and refers to a group of nasal diseases characterized by sneezing, nasal itching, rhinorrhea, and nasal congestion.[186] The two major causes of rhinitis are allergic rhinitis (AR) and non-allergic rhinitis (NAR).

Allergic rhinitis (AR) significantly impairs general and disease-specific QoL, sleep quality and daily function.[98,187] The prevalence of allergic rhinitis varies across studies,

ranging from 10% to 40%[5] Nasal obstruction is one of the most annoying symptoms of allergic rhinitis and is a key factor affecting sleep quality.[188] Physical examination may reveal nasal mucosa congestion, inferior turbinate hypertrophy, middle turbinate edema/polypoid change and clear watery discharge.[23,98] Decongesting the mucosa can help evaluate the effect of mucosal inflammation on nasal obstruction.

AR is an immunoglobulinE (IgE)-mediated inflammation resulting from allergen introduced in a sensitized individual. [98,189] The mechanism of allergic rhinitis is primarily due to a combination of early- and late-phase allergic inflammatory response.[190-194] In the early phase, allergen comes into contact with the nasal mucosa, are recognised by immunoglobulin E (IgE)-coded mast cells and degranulate. This degranulation releases preformed inflammatory mediators, such as histamine and proteases.[190-192] In addition, mast cell synthesize and secrete a number of mediators, including leukotrienes, prostaglandins, tumor necrosis factor (TNF)-α and interleukin (IL)-4.[190,195,196] The release of these inflammatory mediators leads to swelling/edema and increased venous engorgement/fluid secretion, resulting in congestion as well as other nasal symptoms.[195] The chronic, late-phase inflammatory response involves cellular infiltration with eosinophils, neutrophils, basophils, mast cells and lymphocytes as a result of cytokine or mediator release in the early phase. This cellular-driven inflammatory reaction sustains nasal tissue swelling and edema.[190-192,196] If allergic rhinitis is suspected as a potential cause of obstruction, in vitro or skin allergy testing and topical and/or systemic therapy is suggested. In patients with both a distinct anatomic obstruction and chronic rhinitis, structural surgery may be considered as an adjunctive treatment.[98,189,197]

In contrast, NAR is a non-IgE-mediated inflammatory response composed of a wide range of medical conditions, such as vasomotor rhinitis, infectious rhinitis, rhinitis due to hormonal changes, occupational rhinitis, smoking or rhinitis due to a systemic disease.

Rhinosinusitis

Rhinosinusitis is an inflammation of the paranasal sinuses characterized by nasal obstruction, nasal discharge, facial pain and reduction or loss of smell. Symptoms with either endoscopic exam or sinus computed tomography (CT) change fulfilled the definition of rhinosinusitis.[87] Nasal endoscopy may reveal evidence of significant inflammation, including polyps, edema, and mucopurulent discharge from middle meatus. Rhinosinusitis is a

common condition in ear nose and throat clinics, imposing a significant burden on QoL, healthcare consumption and productivity loss.[198-201] Rhinosinusitis is typically classified as acute (< 12 weeks) or chronic (≥ 12 weeks), depending on the duration of symptoms and with distinctive pathophysiology.[202]

Acute rhinosinusitis is classified as originating from a virus or bacterial infection. Host responses against the pathogen trigger an inflammatory cascade and lead to nasal epithelial damage by the infiltrating cells, causing edema, engorgement, fluid extravasation, mucus production and sinus obstruction.

Chronic rhinosinusitis (CRS) is estimated to affect 5%–12% of the general population.[87] CRS is classified into primary or secondary pathologic characteristics.[203] Primary CRS is defined as an inflammatory disorder that is only limited to the airway or respiratory system and is divided into different phenotypes by anatomical distribution (localized or diffused) and endotype predominant (type 2 or non-type 2 inflammation). Common phenotypes are localized CRS, central compartment atopic disease and eosinophilic CRS.[203] Secondary CRS represents sinus disease that arises as a part of other clinical entities and is simply an expression of another condition. The primary treatment is to control the underlying condition. The clinical phenotypes are considered by four types of mechanism: local pathology, mechanical, inflammatory and immunological factors. Examples of secondary CRS are odontogenic sinusitis, fungal mycetoma, sinonasal tumor, cystic fibrosis, primary ciliary dyskinesia, granulomatosis with polyangiitis and common variable immunodeficiency.[203]

CRS is multifactorial in origin, resulting in a dysfunctional interaction between various environmental factors and the host immune system. CRS is subdivided into different inflammatory endotypes in response to pathogen penetration across mucosal barriers. Type 1 immune responses target viruses, type 2 responses target parasites, and type 3 target extracellular bacteria and fungi. Immunological responses to each pathogen generate different cytokine and T helper (Th) responses to eliminate the identified class of pathogen with minimal collateral tissue damage, all of which resolve with the elimination of the pathogens and the restoration of barrier integrity. CRS results when the inflammatory response fails to resolve. Type 2 inflammation is associated with Th2 response, characterized by cytokines IL-4, IL-5, IL-13 local immunoglobulinE(IgE) and activation of eosinophils and mast cells.[204] Non–type 2 inflammation in the CRS setting is a mix of type 1 and type 3

inflammation. Type 1 is related to Th1 response with production of IL-2 and IFN-γ interferon gamma (IFN-γ). Type 3 inflammation involves Th17 responses that induce the production of IL-17 and IL-22. Both type 1 and 3 responses lead to neutrophil activation.[205] In addition to the immune response, the role of sinonasal tissue remodelling is significant. It is often presented as nasal polyps, goblet cell hyperplasia and epithelial barrier abnormalities. However, the precise relationship between the endotype and the remodelling pattern is not completely clear.

The immunologic response and tissue remodelling work in concert and account for most of the CRS characteristics. The delineation of these clinical phenotypes and endotypes allows physicians to deploy specific therapeutic regimens based on the endotype to improve the treatment outcome.

1.7.3 Other cause

Gastroesophageal reflux (GERD)

Previous studies suggested there is a relation between gastroesophageal reflux and nasal obstructive symptoms.[206] GERD patients may not necessarily characterize with typical symptoms such as heartburn, dysphagia and acid regurgitation. Other related extra-symptoms include the sensation of postnasal drip, globus sensation, frequent throat clearing and nasal obstruction. Nasal obstruction related to reflux should be suspected in patients who report symptoms of nasal obstruction at night or after awakening in the morning. GERD may be present in up to 45% of the general population[207] and can be as high as 78% in CRS patients.[208]

There are significant associations between gastroesophageal reflux disease and rhinosinusitis. CRS subjects have greater prevalence of intranasal *Helicobacter pylori* and acid reflux than subjects without CRS.[209] CRS patients with GERD reported a higher sinonasal symptom score and required more CRS medication and sinus surgery than CRS patients without GERD.[210] GERD treatment improves nasal obstructive and sinus symptoms in CRS[206,211]

The relationship between GERD and rhinosinusitis remains unclear due to its complexity. [212,213] A few mechanisms regarding this relationship have been reported. The first mechanism involves the direct reflux effect on nasal mucosa. Nasopharyngeal reflux leads to gastric acid, pepsin reflux, and local eosinophilic infiltration directly in the nasal

cavity and induced nasal inflammation that worsens CRS.[209,214,215] The other hypothesis involves the potential role of *Helicobacter pylori* that is detected in the nasal cavity.[214] It has been shown to play a major role in stomach ulcers, gastritis and gastric cancers, but the connection with CRS remains unknown. [216,217]

Medication induced

Systemic medical therapies may result in increased nasal obstructive symptoms. These medicines include antihypertensive medications such as reserpine, hydralazine, guanethidine, methyldopa and prazosin, Beta-blockers, such as propranolol and nadolol, and antidepressants and antipsychotics, including thioridazine, chlordiazepoxide amitriptyline and perphenazine.[13]

Chronic use of topical nasal decongestant, including sympathomimetic amines (ephedrine/phenylephrine) and imidazoline derivatives (oxymetazoline and xylometazoline), may result in significant rebound congestion (rhinitis medicamentosa).[218] The risk of developing rhinitis medicamentosa typically occurs at five to seven days after using intranasal medication.

Pathophysiology is still unknown – possible hypotheses are ischemia of the nasal mucosa from chronic vasoconstriction, adrenoreceptor sensitivity reduction and imbalance of vasomotor activity. The condition can be treated by discontinuing the offending agent and the use of topical and/or systemic steroids. Combining the use of topical steroids and nasal decongestants has been shown to delay the rebound effect.

Atrophic rhinitis

Atrophic rhinitis is a chronic, progressive degenerative condition of the nasal mucosa. Atrophy of all nasal mucosa constituents include epithelium, seromucous gland and cilia are major characteristics.[219,220] The loss of glandular function and mucociliary dysfunction leads to the clinical presentation of thick secretion dryness, crusts, foul odor (fetor) and nasal congestion. Thick, stagnated secretions promote superimposed bacterial colonization that may become a source of recurrent bacterial infection. The common pathogenic organisms in atrophic rhinitis include Klebsiella ozaenae, Staphylococcus species, Proteus mirabilis and Escherichia coli. Atrophic rhinitis is classified into primary and secondary forms. The cause of primary atrophic rhinitis is unknown, while secondary

atrophic rhinitis is often found following surgical trauma, granulomatous inflammation or irradiation.

Nasal endoscopic examination reveals a wide nasal cavity as a result of atrophic turbinate tissue accompanied by dry mucosa and yellowish-green crusts. Histopathologic analysis of biopsy tissue reveals typical findings, including atrophy of serous and mucinous glands, loss of cilia and goblet cells, respiratory epithelium metaplastic changes, diminished vascular density and inflammatory cell infiltration.[219] The management includes nasal saline irrigation, antibiotics and surgical techniques that restore nasal mucosal function.

Empty nose syndrome

Empty nose syndrome (ENS) is first described in 1994 by Kern and Stenkvist[1-2] as a condition with paradoxical nasal obstruction in patient who had received interventions for nasal obstruction, such as turbinate surgery. The presenting symptoms include nasal obstruction, sensation of suffocating crusting, dryness and anosmia. Patients suffering from ENS, generally have an unremarkable examination except the evidence of 'empty nasal space' as a result of prior nasal procedure. The absence of examination findings differentiates it from atrophic rhinitis. ENS is not synonymous with atrophic rhinitis, which is a well described condition.

ENS sufferers have much greater symptom awareness and express high impact on quality of life compared to patients with physical nasal obstruction, from other sinonasal conditions such as polyps, septal deviation and tumour. ENS also carries a significant burden on psychogenic function, with anxiety, depression and somatic symptom disorder.[221,222]

Despite ENS patients become fixated to the surgical procedure as the cause of current deteriorating situation, the pathophysiology is poorly defined. Few theories have been speculated including the nasal airflow alteration after surgery, dysfunction of trigeminal nerve and psychogenic dysfunction.[223-225] Diagnostic methods recently developed include cotton test and 6-Item Empty Nose Syndrome Questionnaire (ENS6Q). 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.[226] The validated ENS6Q consisting of 6 questions evaluating ENS-specific symptoms derived from common presentation in ENS patients include 'dryness,' 'suffocation,' 'nose feels too open,' 'nasal crusting,' 'sense of

diminished airflow' and 'nasal burning'.[227] The recent systematic review on the diagnostic methods of ENS recommended using ENS6Q and cotton test to identify patients suspected of ENS.[228]

However, these diagnostic tools do not advance the understanding of ENS pathophysiology and controversies still exist. Further study is needed to address the pathophysiology and develop understanding in nasal perception of breathing.

Chapter 2. Empty nose syndrome pathophysiology: a systematic review

2.1 Introduction

Empty nose syndrome (ENS) is a rare but significant clinical entity. First described in 1994 by Kern and Stenkvist [219,229] as a syndrome of unexplained or paradoxical nasal obstruction. Patient had persisting symptoms, with an 'empty nasal space', in those who had already received interventions for nasal obstruction, such as turbinate surgery. While acknowledging that patients who have turbinate surgery generally have good outcomes [230], the classic presentation of ENS is a patient who has had surgery to relieve nasal obstructive symptoms and whose symptoms deteriorate, despite achieving the desired anatomical outcome. Patients suffering from ENS, generally have an unremarkable examination, apart from evidence of prior surgery, thus the term 'paradoxical obstruction'. Other symptoms include crusting, dryness, and sensation of suffocation, in the absence of examination findings, differentiating it from conditions such as atrophic rhinitis. ENS is not synonymous with atrophic rhinitis, which is a well described condition with crusting, cacosmia and *Klebsiella ozaenae* colonization. [231]

ENS carries a significant burden on mental health and psychogenic function, with anxiety, depression and even suicidality. [221,222] Compared to patients with near complete physical nasal obstruction, from other sinonasal conditions such as polyps, septal deviation, tumour and even choanal atresia, ENS sufferers have much greater awareness of their symptoms and express a higher impact on their quality of life.

While surgery appears to make the symptoms deteriorate, the pathophysiology behind ENS is poorly defined, and there is controversy in this field. Theories proposed or speculated include; alteration in nasal airflow dynamics, neurogenic and psychogenic dysfunction of nasal perception. [223-225]

While widely acknowledged that many patients who have tumour surgery, and postoperatively have much more nasal tissue removed, do not develop such ENS symptoms.

[232,233] Additionally, it is often overlooked that almost all ENS patients present with nasal symptoms, including obstruction, often begetting the initial surgery, making the role of surgery in their condition uncertain. Although there have been reviews on the diagnostic methods of ENS, [228] these diagnostic tools do not advance our understanding of ENS pathophysiology. This study aimed to systematically, and objectively, review the literature on the investigated pathophysiologic mechanisms in ENS.

2.2 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 the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [234] and the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. [235]

Eligibility criteria

Any study design was considered. Case control studies between patients with ENS and any non-ENS control, or cross-sectional studies, were primarily sought. Review articles, case series and case reports were excluded. Participants were adults (≥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, endoscopic findings, imaging and ENS-specific tests. Studies which related only to ENS treatment were excluded.

Information sources and search strategy

A systematic electronic search was performed using MEDLINE (1946-), EMBASE (1947-) and manual identification from the bibliography of included studies. The search was performed on the 20 September 2019. The search was limited to English-only and human studies. A search strategy was designed for each database (Appendix 1).

Study selection and data collection process

Two authors (DK, LK) reviewed the search results by screening titles, abstracts and then full text based on predetermined eligibility criteria. A structured Excel (Microsoft 365, Microsoft, Redmond, WA, USA) data collection sheet was used to extract data from full texts that fulfilled the inclusion criteria. The characteristics of included studies comprised study design,

age, number of participants, ENS diagnostic criteria (4 groups as above), type of surgery, and outcomes measured. Articles providing insufficient information for complete data extraction or containing conflicting data were further assessed by additional authors (RS, RJH, RGC, JR, JK, KS). Any disagreements were resolved by discussion among authors.

Risk of bias in individual studies

The quality assessment followed the COSMOS-E guidelines for assessment in observational studies [236] Four constructs of bias were adapted from The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool. [237] These biases consisted of; 1. confounding, 2. selection bias, 3. information bias and 4. reporting bias. 'Causal/Association bias' was included, as a fifth element in quality assessment, as it was deemed important in etiological studies. [238]

Data synthesis

Given the wide range of investigational types, methods and outcomes, data was 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% confidence interval (CI). [234]

2.3 Results

Study selection

The search strategy yielded 2591 articles (MEDLINE n=577, EMBASE n=2010, bibliographic search n=4), reducing to1847 studies after duplicates removal. Title and abstract screening produced 69 full texts assessed for eligibility. 18 studies were included for qualitative analysis (Figure 6). Two studies were available for a meta-analysis. [239,240]

Characteristics of included studies

The included studies(n=18) consisted of 12 case control [222,226,239-248] and 6 cross-sectional studies[221,227,249-252] (Appendix 2). The definition of ENS patients differed between studies.

ENS was defined using self-identification in 2(11%) studies [221,252], paradoxical obstruction in 9(50%) studies [222,227,240,242,243,247,249-251] and with the Empty Nose Syndrome 6 Questionnaire (ENS6Q) in 8(44%) studies. [221,226,239,244-246,248,252] Endoscopic examination confirming a widely patent nasal airway and a lack of other pathology in 8(44%) studies. [226,227,240,242-244,249,250] Imaging was used to confirm an unobstructed nose and absence of other sinonasal disease in 9(50%) studies. [221,226,227,239,244,246,248,250,252] The "cotton test" was used as diagnostic criteria

in 6(33%) studies. [222,227,244,247,249,251] Nasal resistance was assessed to confirm the absence of anatomical obstruction in 2(11%) studies. [240,250] Overall, included studies diagnosed ENS based on 1 criteria in1(6%) study [245], 2 criteria in 11(61%) studies [221,222,226,239,242,243,246-248,251,252], 3 criteria in 4(22%)studies [227,240,244,249], and all 4 criteria in 1(6%)study. [250] All studies assumed prior turbinate surgery as intrinsic to the diagnosis of ENS.

All studies considered patients who had undergone inferior turbinate reduction (ITR), and 5 studies included patients with middle turbinate reduction (MTR). [239,241,246,248,250] Although some studies tried to define a turbinectomy over turbinate reduction, most studies combined surgical concepts of reduction, partial or subtotal resection. Thus, this has been referred to as either inferior or middle turbinate reduction (ITR and MTR). Where comparisons were made between post-turbinate surgery populations, patients suffering from ENS are refer to as ITRwENS and those without ENS symptoms are referred to as ITRsENS.

Control groups included ITRsENS in 3(17%) studies [239,240,244], sinonasal disease without ENS in 4(22%) studies [222,226,227,247] , and healthy surgically naive patients in 10(55%) studies [227,239-246,248] (referred as “healthy controls” in this review).

Pathophysiologic Themes

Nine proposed pathophysiologic themes for the etiology of Empty Nose Syndrome were identified from the included studies: demographics (n=1) [252], symptomatology (n=5) [221,226,227,241,247], anatomical features (n=3) [242-244], airflow analysis (n=6) [239-241,245,246,248], mental health (n=6) [221,222,247,249-251], cognitive function (n=1) [241], diagnostic testing (n=5) [226,239,240,245,246], olfactory function (n=1) [240], and mucosal physiology/innate immunity (n=1) [247](Table 2). As some of the included studies (n=18) reported multiple outcomes, they contributed data to more than one thematic group.

<u>Demographics</u>

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 using the ENS6Q in 53 ENS patients [252] (Table 3). Patients self-reporting ENS from an international database were

recruited. No correlation was identified between ENS6Q and climatic factors which included: dew point, humidity, precipitation, temperature, pollution, altitude, and climatic/geographic region.

Symptomatology

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

Five studies assessed symptomatology in ENS, of which 3 were case control [226,241,247] (ENS, n= 44; other sinonasal disease, n=30; healthy controls, n=15) and 2 cross-sectional studies [221,227] (ENS, n=68) (Table 3). Outcome measures included the Sinonasal Outcome Test (SNOT-22), Empty Nose Syndrome 6 Questionnaire (ENS6Q), nasal patency subjective rating scale (4-point Likert scale) and general health questionnaires (Epworth Sleepiness Scale (ESS), Work Productivity and Impairment questionnaire (WPAI) and the 5-dimension EuroQol General Health State Survey (EQ-5D-5L)).

While an ENS6Q validation study [227] reported higher SNOT-22 scores in ENS patients compared to chronic rhinosinusitis without nasal polyps patients, other investigators have shown similar SNOT-22 scores between ENS and chronic rhinitis patients. [247] Higher ENS6Q scores, as expected, have been reported when comparing ENS patients to non-ENS sinonasal disease and healthy controls. [226,227] This highlights the role of the ENS6Q as seeking specific questions to the ENS entity and not those typical of other sinonasal diseases.

Self-perception of nasal patency between ENS and healthy control groups was compared under 3 conditions in a case control study: during free breathing and following menthol or lemon oil inhalation. ENS and healthy control groups both perceived higher patency following menthol and lemon oil inhalation. The ENS group reported worse patency than healthy controls in all conditions. [241]

Functional impairments in self-identified ENS patients from the ESS, WPAI and EQ-5D-5L questionnaires, demonstrated impaired sleep, work productivity, non-work activity and greater pain/discomfort compared to normative data. [221]

Anatomical features

Inferior turbinate volume was similar, post- turbinate reduction, between patients with or 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 [244] and between ITRwENS patients and healthy controls in 2 case control studies (Table 4). [242,243] All measurements were based on computed tomography (CT) image analysis.

In comparing ITRwENS (n=32(sides)) and ITRsENS (n = 34(sides)), no difference in nasal cavity airspace (septum-inferior turbinate, lateral wall-inferior turbinate, floor-inferior turbinate and septum-lateral wall) was demonstrated between groups. Nasal mucosal thickening between groups was also similar. Of ten measures taken, only the central and posterior septal area had thicker nasal mucosa in ITRwENS patients, no multiple outcome adjustment (or Bonferroni adjustment) was included. [244]

Axiomatically, when ITRwENS patients (n=34) were compared with healthy 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). [243] In a similar study of 14(sides) ITRwENS comparing with healthy controls, ITRwENS patients had thicker nasal mucosa. [242] It is unclear if this represents mucosal hypertrophy often seen after surgery. This study also found that 50% of turbinate surgery patients had co-existing radiologic evidence of sinus disease.

Airflow analysis

The nasal airflow and resistance were similar post- turbinate reduction, between patients with or without ENS symptoms. Using computation fluid dynamic analysis, differences have been found on multiple outcome analyses with modelling by a single research center.

For airflow analysis, there were six case control studies (Table 4). Human research was performed in 3 studies. [240,241,245] Computational fluid dynamic (CFD) simulation/modeling was performed in 4 studies [239,245,246,248] and 1 study used both. [245] Airflow analysis was compared between ITRwENS, and ITRsENS patients in 2 studies (Human n=1, CFD n=1)[239,240] and 6 studies compared to healthy controls (Human n=3, CFD n=3). [239-241,245,246,248]

In the 3 studies on human subjects, there were 123 total patients assessed (ITRwENS, n=37; ITRsENS, n=18; healthy control, n=68). Analysis of the human nasal airway using rhinomanometry and acoustic rhinometry demonstrated similar nasal airflow between ITRwENS and ITRsENS patients.(485±3 v 490±28 cm^3/s, p=0.95) [240] When ITRwENS patients were compared with healthy controls, lower nasal resistance was reported, and consistent with the post-operative state (163.9±62.8 v 120.9±67.5 mL/s, p-value not reported). [245] Surprisingly, one study reported a similar nasal airflow rate between ITRwENS patients and unoperated healthy controls (593[636]cm^3/s v 700[653]cm^3/s, $p > 0.05$). [241]

In CFD studies, 242 models were analyzed (ITRwENS, n=89 (possible duplicates); ITRsENS, n=5; healthy controls, n=148). All CFD studies were from the same research group [239,245,246,248] and three studies had the same number of model analyses. [239,246,248] The computational model simulating airflow was based on CT scans. Only one CFD study compared ITRwENS to ITRsENS. [239] ITRwENS patients demonstrated decreased nasal airflow rate at the inferior region of nasal cavity and airflow distribution shifted upward to middle region when compared to both ITRsENS and healthy controls. [239,245,246,248] Mucosal-airflow interaction, measured as wall shear stress force (WSS) at the inferior region was decreased in the ITRwENS group compared to ITRsENS patients and healthy controls.[239,245,246,248] There was a weak correlation between ENS6Q and WSS ($r = -0.398$, $p = 0.003$). [253] However, the number of sample subsites in the nasal airway was not declared in these studies and it is unclear how many measures were taken. Also, no data was available on multiple outcome adjustment for repeated measures.

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/SNOT25 scores reflected greater mental health burden).

There were 2 case control [222,247] and 4 cross-sectional studies [221,249-251] that assessed anxiety (ENS n=160, sinonasal disease n=12) [221,247,249,251], depression (ENS n=184, sinonasal disease n=82) [221,222,247,249,251], and hyperventilation syndrome (ENS n= 22) (Table 5). [250]

ENS patients scored higher on anxiety and depression-validated questionnaires compared to other sinonasal diseases without ENS.[221,222,247,249,251] Anxiety was reported as high as 65-73% in the ENS group. Likewise, depression was reported in 51-71% in ENS patients with comparable rates of 15-27% in other sinonasal disease.[222]

No correlation was demonstrated between depression severity (BDI) and extent of turbinate surgery , nasal volume (cm^3), or sinonasal specific quality of life (SNOT-22) scores.[222] However, a moderate correlation was demonstrated between ENS-specific quality of life scores (ENS6Q/SNOT-25) and anxiety ($r=0.499$, $p<0.001$; $r=0.54$, $p<0.001$) and depression ($r=0.48$, $p<0.001$; $r=0.53$, $p<0.001$).[221,251]

Cross-sectional assessment of ENS patients (n=22) with both hyperventilation provocation testing and pulmonary function measures defined hyperventilation syndrome in 77% of ENS patients.[250]

Cognitive function

ENS patients demonstrated qualitatively different f-MRI patterns to healthy controls. Activation in the emotional processing areas of the temporal lobe was seen in ENS patients compared to controls on normal breathing and deactivation in this area was shown after menthol stimulation.

Cognitive function was assessed by functional Magnetic Resonance Imaging (f-MRI) in 1 case control study. (ENS, n= 10; healthy controls, n=15) [241] (Table 5) f-MRI qualitatively compared ENS patients to a normal, surgically naive, control group in three conditions: during free breathing, and after menthol or lemon oil inhalation. Lemon oil was used because it has fresh fragrance and no pseudo-decongestant properties. Qualitative data showed specific differing areas of activation/deactivation between ENS and healthy controls. During free breathing, specific activation of the temporal areas and amygdala was seen in ENS patients compared to healthy controls. After menthol inhalation, specific 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 compared to healthy 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 healthy 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[226,239,240,245,246] with 4 studies assessing menthol detection (ITRwENS, n=80; ITRsENS, n=13; healthy control, n=129) and 1 study assessing the perception of airway occlusion with cotton, the 'cotton test', (ITRwENS, n=15; sinonasal disease, n=18) (Table 6).

In the 4 case control studies[239,240,245,246] assessing menthol detection, 2 studies[239,240] used ITRwENS and ITRsENS patients (ITRwENS, n=48; ITRsENS, n=23) and a further 2 studies[245,246] only compared ITRwENS patients to healthy controls (ITRwENS, n=32; healthy controls, n=55). Menthol detection was utilized to evaluate trigeminal nerve function as menthol is thought to activate the Transient Receptor Potential Melanostatin 8 (TRPM8) receptor.[64] It was performed by introducing a menthol vapor into nasal cavity via sniffing. The menthol test required reporting either a detectable threshold (concentration (g/mL)) in ordinal scales; a higher scale requires lower concentration of menthol for detection) or the localization of which nostril was being stimulated (number of correct localizations).

ITRwENS reported worse menthol detection on both identification and detection threshold compared to ITRsENS patients (21±8 v 29±8, p =0.021; 10.2±3.87 v 15.2±1.23 *, p* < 0.0001)[239,240] and healthy controls (10.3±3.9 v 14.0±1.8, *p* < 0.0001; 9.2±4.6v 14.8±1.6, p< 0.05).[245,246] When comparing menthol detection in ITRsENS patients and healthy controls, there was conflicting data with one study showing similar localization (29±8 v 34±5,p=0.067)[240] and the other with better menthol detection in ITRsENS group (15.2±1.23 v 14.8±1.59, *p* < 0.05).[239] However, the 95% CIs overlapped from this data and a statistical error was assumed. When data was pooled for meta-analysis, menthol detection scores were lower in ITRwENS compared to ITRsENS patients (SMD -1.09; 95%CI: -1.65, -0.53) (Figure 7).[239,240]

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 using the pressure of the instrument placement without leaving cotton behind.

Thamboo et al.[226] performed the 'cotton test' validation study with ENS6Q and participants also completed a subjective rating scale. With the cotton in-situ (for 10 minutes), ENS patients reported an improvement in ENS6Q. (19.13±7.91 v 6.00 ±5.75, p<0.01) and all ENS patients rated improved breathing. Healthy controls reported a worse ENS6Q (5.06 ±3.94 v 2.94±3.36, p=0.034) and nearly all healthy control patients 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 compared to those without ENS, the objective olfaction is similar.

A single case control study compared both subjective olfaction scoring visual analogue scale (VAS) and functional assessment with a validated threshold, discrimination, identification (TDI) score between ITRwENS, ITRsENS patients and healthy controls[240] (ITRwENS, n=21; ITRsENS, n=18; healthy controls, n=31) (Table 6). The ENS group reported poorer subjective olfaction scoring than ITRsENS and healthy controls (35.7±6.3 v 72.2±5.5 v 81.1±4.9; p <0.001). However, on functional assessment, ITRwENS and ITRsENS patients had a similar TDI score which were lower than healthy controls (28.1±3.5 v 30.5±4.1 v 35.5±3.2; ENS v ITRsENS, p=0.62, ENS v healthy controls, p=0.028). ITRwENS patients may have other sinonasal disease that might account for the difference with healthy controls however, this data was not reported.

Mucosal physiology/Innate immunity

ENS patients had lower nNO than non-ENS controls.

Nasal nitric oxide (nNO) levels was assessed in 1 case control study between ITRwENS patients and chronic rhinitis[247] (ITRwENS, n=19; chronic rhinitis, n=12) (Table 6). The nNO assessment was performed using an electrochemical analyzer (NIOX MINO®; Phadia AB/Aerocrine AB, Sweden). ENS patients had lower nNO levels compared to chronic rhinitis patients (85.5[327.5] v 231.3[312] ppb, p<0.001). The study's authors discussed a possible association between nNO and psychiatric conditions, such as depression and anxiety.

Risk of Bias assessment

Five type of biases were assessed in individual studies (Tables 3-6). Association bias existed throughout most studies as causality between ITR and ENS was assumed but not proven, and pre-operative data was not available. Common bias found included selection bias related to highly symptomatic selection in ENS. ENS patients were motivated by surgical candidacy and the use of surgically naive participants as a comparison. The potential for placebo effect was high in some interventions such as diagnostic testing.

2.4 Discussion

The current concepts regarding the perception of nasal breathing is important when speculating on the potential pathophysiology of ENS. There are no described tactile or airflow receptors in the nose.[29] The perception of nasal patency is believed to be triggered through cool-thermo receptors in the nasal mucosa.[31,32,64] The high speed nasal airflow creates evaporation of water from nasal epithelial lining and activates TRPM8 receptors through temperature gradient. TRPM8 receptor is located on sensory endings of the trigeminal nerve within the nasal mucosa. This induces depolarization of neurons and stimulates the brainstem respiratory center and specific regions of the cerebral cortex .[69,73,254] The temperature gradient cool sensing is thus interpreted as clear breathing. Menthol stimulation provides a good example of this mechanism. It creates enhanced breathing without altering nasal airflow.[59] Dysfunction at any level of this pathway affects nasal breathing perception. This review's outcomes are incorporated into the nasal perception pathway (Figure 8). The pathophysiologic defect for ENS is likely to reside in this pathway and the evidence for each is summarized.

Mucosal thermal state (radiant airflow dynamics and thermovascular conditions)

The mucosal temperature gradient activation of TRPM8 is likely a combination of mucosal vasculature (thermovacular conditions) and the influence of radiant cooling by airflow. Thus, congestive states, such as allergic rhinitis, create mucosal inflammation and vascular dilatation, leading to a 'warmer' baseline and impaired influence from radiant airflow cooling, Likewise, a simple septal deviation may produce loss of radiant air cooling in otherwise normal nasal mucosa.

By the nature of ENS, these patients have normal mucosa on examination and thus, the absence of disease that influences thermovascular condition is assumed. Only studies on airflow dynamics and radiant cooling were identified. Human studies have confirmed that similar improvements in nasal airspace, minimal cross-sectional area, airflow rate and nasal resistance were observed between patients with and without ENS after ITR. [239,240,248] Mucosal thickening has been observed in ENS patients on CT scans compared to ITRsENS patients.[242,244] However, only 2 of the 10 studied areas were different in the ENS patient group and they had a longer timepoint from their surgery. Mucosal hypertrophy overtime may lead to bias in patient selection and lack of adjustment for repeated outcome measures may contribute to such findings.

Despite all ENS studies on human assessments being similar, simulated nasal airflow on CFD modeling demonstrated decreased nasal airflow at the region where the inferior turbinate previously resided.[239,245,246,248,255] However, there is incongruity with this theory of airflow dynamic alteration as a cause of ENS. Firstly, ENS was only reported in a very small proportion of patients following turbinate surgery[256] and is independent of the extent of surgery such as turbinectomy and turbinoplasty.[223,257,258]Secondly, airflow analysis generated in CFD modeling in this review was reported from a single research group with potential bias in CT data selection. Additionally, the modelling of CFD potentially creates many data points for analysis lead to a type 1 error and repeated outcome measure adjustments are 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. Some authors have investigated, menthol detection to subjectively evaluate trigeminal sensitivity. These data suggest a lower subjective menthol detection in ITRwENS compared to ITRsENS patients and healthy controls.[239,240,245,246] It is proposed that ENS pathophysiology maybe dysfunction in trigeminal temperature cool sensing 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,[259,260] 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 suffer these symptoms.[232,233] Pre-surgical impairment

leading an ENS sufferer to their first presentation, and subsequent surgery, would be plausible.

Pathways of nasal perception are triggered at the trigeminal nucleus, brainstem, and cerebral cortex centrally. Centrally affected areas may also be a potential etiological contributor for ENS and may result in similar perceptive deficits possibly explaining the menthol detection data. However, apart from some limited f-MRI data, studies in this area are lacking and this again would suggest a pre-existing deficit.

Psychogenic dysfunction in nasal patency perception

There are examples of disorders in many specialties which are thought to have a strong psychogenic etiology especially when symptoms are incompatible with observed examination, for example, tinnitus, irritable bowel syndrome and fibromyalgia.[261-266]

Evidences exists for a strong association in ENS patients with mental health, poor sleep function, reduced work productivity, and general health.[221] Co-morbidities such as anxiety, depression and hyperventilation syndrome have been reported in a majority of ENS patients.[221,222,247,249-251] In addition, an association between ENS and somatic symptom disorder and panic disorder have been suggested[267], as many ENS patients fulfil the criteria for somatic symptom disorder.[268] As a result, symptom severity is expectedly high in ENS.[221,226,227,241] ENS6Q and SNOT-25 representing ENS symptom severity correlate with anxiety and depression.[221,251] 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, [222,243,269] and demonstrates emotional regulation deficits.[270] Connection between emotion control and nasal perception was evident, with a f-MRI study demonstrating the deactivation of emotional processing areas after the successful pseudo-decongestant stimulatory effects of menthol in ENS patients.[241]

Psychogenic influence on nasal perception, would explain the discordance between the subjective and objective findings between ITRwENS and ITRsENS patients. The discordance between subjective and objective findings in ENS is shown in appendix 3. 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' reported in ENS may be the result of attempts to manage these pre-surgical symptoms. The exacerbation of ENS symptom after surgery remains questionable. Stressful and emotional life events, potentially such as a surgical intervention with unrealized 'hopes and dreams' of benefit, have been associated with triggering a conversion disorder.[271,272]

Previous systematic reviews have recommended mental health screening in the rhinology workflow.[228] ENS6Q may be useful screening tool for anxiety and depression due to its correlation with these mental conditions, especially when the examination is discordant. The authors have used a guide to screen a turbinate reduction candidate, referred to as "Ray's rules", based on intact 'sensory' nasal perception of the Mucosal Thermal State: 1. the patient is aware of fluctuating or 'cycling' nasal congestion, 2. Postural congestion is perceived and 3. There is a subjective response to topical nasal decongestant.

There is a clinical need for diagnostic tools that could more accurately reflect subjective nasal perception, both to assess the impact of our interventions and also to avoid surgery on those who are unlikely to benefit, or potentially decline in health from interventions.

2.5 Conclusion

Alterations of the nasal airspace are similar between patients after turbinate surgery with and without ENS. The extent of the 'empty space' described in ENS does not influence the symptoms of ENS. The influence of an 'airflow' basis for ENS is unlikely. Neurogenic dysfunction of temperature-gradient cool sensing is subjectively reported in ENS patients compared to controls. However, discordance between subjective and objective constructs in ENS extended beyond breathing to olfaction as well. There is evidence of high psychogenic comorbidities in patients with ENS. No data offered causality between ITR and ENS as pre-operative data was not available. The assumption of surgery as the *raison d'etre* for ENS is unclear, but the surgery may be a trigger for conversion event for comorbid conditions.

Table 2. Pathophysiologic themes for the etiology of ENS

Pathophysiologic theme	**Outcome investigated**
Demographics	*Climate and geographic factors:* Dew point, humidity, temperature, precipitation, altitude data, pollution data (PM-10, PM 2.5)
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
Anatomical 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 Analogue Scale of olfactory function Odor Threshold, Discrimination test, Identification test
Mucosal physiology/Innate immunity	Nasal Nitric Oxide level

Abbreviations: PM-10, particulate matter of aerodynamic diameter less than 10 µm; PM2.5, particulate matter of aerodynamic diameter less than 2.5 µm

Table 3. Demographics and symptomatology in empty nose syndrome.

Study, Year	Design	Participants	Clinical endpoint	Result	Bias assessment
Demographics					
Manji 2019[252]	Cross-sectional	ENS = 53	Climate factors at point of residence and ENS6Q correlation: - Dew point (° c) - Humidity (%) - Precipitation (mm, day) - Temperature (° c) - Pollution (PM-10, PM-2.5) - Altitude (m)	Patients self-reporting ENS did not have disease specific Quality of Life influenced by climatic region. Climate factors did not correlate with ENS6Q.: Dew point (r= −0.22, p=0.19) Morning humidity (r= −0.002, p=0.94) Afternoon humidity (r=0.06, p=0.75) Relative humidity (r= −0.08, p=0.61) Annual precipitation (r=0.09, p=0.53) Precipitation days per year	Confounding ? Selection bias ? Information bias + Reporting bias + Causal bias + Selection bias: - ENS was diagnosed by self-reporting.

				(r=0.27, p=0.07) Average temperature (r= 0.002, p=0.99) High temperature (r= −0.06, p=0.69) Low temperature (r= −0.003, p=0.99) PM-10 (r= −0.12, p=0.42) PM-2.5 (r= −0.13, p=0.39) Altitude (r= −0.16, p=0.25)	
Symptomatology					
Fu 2019[247]	Case control	ENS = 19 Chronic rhinitis = 12	SNOT-22 (0-110)	Sinonasal specific quality of life (SNOT-22) was similar between patients with ENS and chronic rhinitis (65[74] v 51[62], p=0.156).	Confounding ? Selection bias - Information bias ?

					Reporting bias: + Causal bias: ? Selection bias: - ENS group may be motivated by surgical candidacy.
Thamboo 2017[226]	Case control	ENS = 15 Sinonasal disease = 18	ENS6Q (0-30)	ENS-symptom based questionnaire defined patients with ENS and not other sinonasal disease. ENS compared to sinonasal disease: ENS6Q score (18.87±7.54 v 4.72±3.39, p<0.001)	Confounding: ? Selection bias: - Information bias: ? Reporting bias: + Causal bias: ?

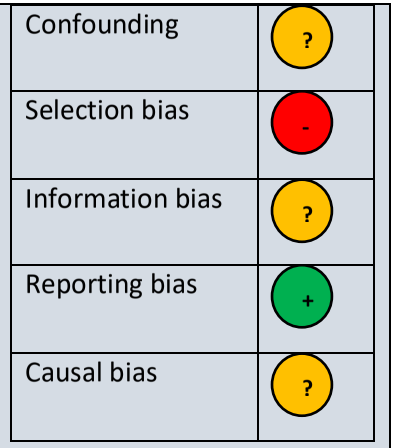
				Dryness (3.80±1.14 v 1.11±1.32, p<0.001) Lack of sensation (3.87±1.30 v 1.33±1.32, p<0.001) Suffocation (2.47±2.16 v 0.56±1.04, p=0.002) Nose feels too open (3.33±1.44 v 0.22±0.73, p<0.001) Nasal crusting (2.73±1.79 v 1.39±1.50, p=0.025) Nasal burning (2.93±1.79 v 0.17±0.38, p<0.001)	Selection bias: -ENS6Q ≥ 11 was an inclusion criterion for ENS; ENS group was highly symptomatic compare to non-ENS sinonasal disease. -Post turbinate surgery patients were compared to surgically naive patients.

Freund 2011[241]	Case control	ENS = 10 Healthy controls = 15	Patient reported nasal patency scale ('better', 'same', 'worse', 'very bad') After exposure to - Room air - Menthol (10%) - 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 healthy controls and ENS patients. ENS group reported (% 'worse', 'very bad'): -Room air v menthol: 48.2% v 35%, p<0.04† -Room air v lemon oil: 48.2% v 50%, p<0.01†	Confounding ? Selection bias - Information bias - Reporting bias - Causal bias ? Selection bias: -Post turbinate surgery patients were compared to surgically naive patients. Information bias: - Outcome measurement had unbalance rating scale.

				Healthy control group reported (% 'worse', 'very bad'): -Room air v menthol: 15% v 12.2%, p<0.01† -Room air v lemon oil: 15% v 12.2%, p<0.01† ENS group reported worse breathing than healthy controls (% 'worse', 'very bad').: -Room air 48.2% v 15% -Menthol inhalation 35% v 12.2% -Lemon oil inhalation 50% v 12.2% (reported as a group p<0.01)	Reporting bias: -Within group change was not compared. -statistical error is likely; analysis within scale only was potentially performed.

Manji 2018[221]	Cross-sectional	ENS = 53	ESS (0-24) WPAI (%) EQ-5D-5L General health and ENS6Q correlation	Patients self-reporting ENS had impaired sleep, work productivity, non-work activity and pain/discomfort. ENS patients are affected by 1. ESS: score ≥8 in 42% 2. WPAI: 62% reduction in productivity at work 3. WPAI: 65% reduction in all other non-work-related activities 4. EQ-5D-5L: moderate difficulties with household	Confounding: ? Selection bias: ? Information bias: ? Reporting bias: + Causal bias: ? Selection bias: - ENS was diagnosed by self-reporting. Reporting bias: -Reference range was used (normative data) without control group.

				and/or leisure activities, and moderate levels of pain/discomfort 5. ENS symptom severity (ENS6Q) correlation: - ESS scores (r=0.21, p=0.14) - WPAI (work, r=0.64, p<0.001; activity, r=0.41, p<0.001) - EQ-5D-5L; overall pain/discomfort (r=0.43, p=0.002) and impairment in activities of daily living (r=0.4, p=0.003)	Causality: -ENS symptoms and general health may not be related.

Velasquez 2017[227]	Cross-sectional	ENS = 15 CRSsNP = 30 Healthy controls = 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 and healthy controls (ENS v CRSsNP v healthy controls: ENS6Q 18.9±7.5 v 4.7±4.3 v 1.8±2.8, $p<0.001$; SNOT-22: 50.2±26.6 v 33.4±18.3 v 17.9±16.2, $p<0.001$).	 Selection bias: - ENS group may be motivated by surgical candidacy. Reporting bias: - subgroup analysis data between CRSsNP and healthy controls was not shown.

†statistical error is likely

Data format: mean±SD, median [IQR], Bias assessment: 

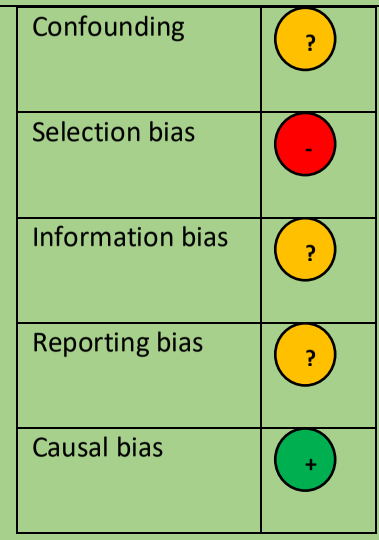
, low risk; 

, high risk; 

, unclear risk

Abbreviations: ENS, Empty Nose Syndrome; ITR, Inferior Turbinate Resection; CRSsNP, Chronic Rhinosinusitis without Nasal Polyp; ENS6Q, Empty Nose Syndrome 6 Questionnaire; PM-10, particulate matter of aerodynamic diameter less than 10 µm; PM-2.5, particulate matter of aerodynamic diameter less than 2.5 µm; SNOT, Sinonasal Outcome Test ;; ESS, Epworth Sleepiness Scale; WPAI, Work Productivity and Impairment questionnaire; EQ-5D-5L, 5-dimension EuroQol General Health State Survey

Table 4. Anatomical features and airflow analysis in empty nose syndrome.

Study, Year	Design	Participants	Clinical endpoint	Result	Bias assessment
Anatomical features					
Hong 2016[243]	Case control	ENS = 34 Healthy controls = 10	CT: - ITV (mL) - ITV and SNOT-25 correlation	Patients who had ITR had smaller ITV compare to those without ITR (1.81±0.92mL v 7.35±1.28mL, p<0.001). Within ENS group: 1. There was no correlation between ITV and SNOT-25 score	

				(anterior r=0.142, p=0.211; posterior r=0.145, p=0.207; total r=0.223, p=0.1). 2. Nasal dryness score weakly correlated with smaller total ITV (r= -0.327, p=0.03). 3. Reduced productivity and fatigue score weakly correlated with larger total ITV (reduced productivity r=0.318,	- Post turbinate surgery patients were compared to surgically naive patients. Reporting bias: - Multiple outcome measure may require p value adjustment.

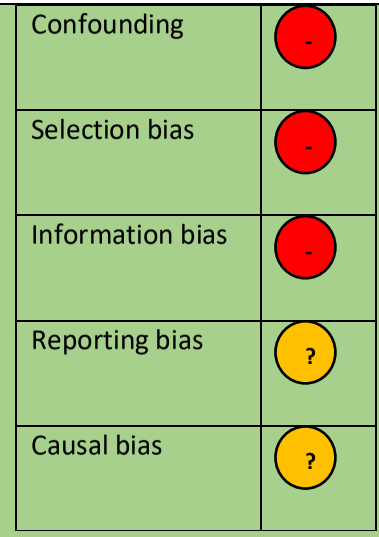
				p=0.033; fatigue r=0.383, p=0.025).	
Thamboo 2016[244]	Case control	ITRwENS = 32 (sides) ITRsENS = 34 (sides) Healthy controls = 58 (sides)	CT: - Nasal cavity airspace (mm) - Nasal mucosa thickness (mm)	Nasal cavity airspace measures were similar between patients with ITRwENS and ITRsENS. Nasal cavity airspace: - septum-IT air space (4.13±0.4 v 4.25±0.4mm, p=0.83) - lateral wall-IT air space (1.54±0.2 v 1.91±0.17mm, p=0.16)	Confounding: ? Selection bias: - Information bias: ? Reporting bias: ? Causal bias: ? Confounding: - Mucosal re-hypertrophy could be confounded with different

				- floor-IT air space (6.4±0.71 v 5.35±0.68mm, p=0.29) - septum-lateral wall air space (9.58±0.34 v 9.65±0.38mm, p=0.9) Of the ten mucosal measures, two areas showed differences between ITRwENS and ITRsENS patients. Nasal mucosa thickness:	timing after ITR between both groups. Selection bias: - The selection of ITRsENS patients was not reported and potentially represented ideal comparison. Reporting bias: - Multiple outcome measure may require p value adjustment - Statistical data were not completely reported.

				- IT mucosa (6.27±0.44 v 6.65±0.35mm, p=0.51) - floor (anterior) (3.24±0.12 v 2.89±0.20mm, p value =NR)† - floor (central) (2.33±0.16 v 1.92±0.15mm, p=0.07) - floor (posterior) (1.09±0.12 v	Causality: - Association between ENS and mucosal thickness may be related to evidence prior surgery.

				0.93±0.1mm, p value =NR)† - septum (anterior) (3.00±0.13mm v 3.04±0.16mm, p value =NR)† - *septum (central)* (3.08±0.17 v 2.42±0.17mm, p<0.01) - *septum (posterior)* (2.20±0.17 v 1.36±0.15mm, p<0.01)	

				- lateral wall (anterior) (1.19±0.13 v 0.99±0.08mm, p value =NR)† - lateral wall (central) (1.44±0.14 v 1.40±0.11mm, p value =NR)† - lateral wall (posterior) (0.71±0.12 v 0.61±0.09mm, p value =NR)†	

Jang 2011[242]	Case control	ENS = 14(sides) Healthy controls = 14(sides) Unilateral CRS = 20(sides)	CT: - Nasal Mucosa thickness (mm)	Nasal mucosa thickness was greater in patients with ENS compared to healthy controls (3.01±0.76 v 1.80±0.43mm, p <0.001).	 Confounding: -50% of ENS patients had co-existing sinus changes. Selection bias:

					- Post turbinate surgery patients were compared to surgically naive patients. Information bias: - Examiner was not blind to evidence of ITR. Reporting bias: - Comparison between CRS and ENS patients was not shown. Causality: - Association between ENS and mucosal thickness may be

					related to evidence prior surgery.
Airflow analysis					
Malik 2019[239]	Case control	ITRwENS = 27 ITRsENS= 5 Healthy controls = 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 and airway parameters on CFD modeling were altered in patients with ITRwENS compared to ITRsENS. Cross-sectional area and nasal resistance in patients with ITRwENS were similar to ITRsENS (cross-sectional area:	Confounding ? Selection bias ? Information bias ? Reporting bias ? Causal bias ? Selection bias: - ITRsENS patients potentially represented ideal comparison.

			- Airflow distribution (%) (inferior, middle, superior) - Wall shear force distribution (%) (anterior, MT, IT)	1.19±1.05 v 0.94±0.21 cm^2, p= NS; nasal resistance: 0.052±0.015 v 0.051±0.020 $Pa/cm^3/s$, p=NS). In ITRwENS, - Airflow rate was lower than ITRsENS patients at inferior region ($3.69±2.58x10^{-5}$ v $6.96± 4.12x10^{-5}$ m^3/s, $p<0.05$) while it was	Information bias: - CFD modeling is not validated to patient's symptom. - CFD modeling used sampling area for testing. Reporting bias: - Statistical data were not completely reported Causality: - Association between ENS and airflow change may be related to evidence prior surgery.

				similar at middle and superior region. - Airflow distribution was lower than ITRsENS patients at inferior region (25.8± 17.6 v 47.7±23.6%, $p<0.01$) but it was higher at middle region (66.5± 18.3 v 49.1±10.6%, $p<0.05$). - Wall shear force distribution was lower at inferior region than	

				ITRsENS patients (32.24±12.64 v ~ 40%, p<0.05) but it was higher at middle region (39.88±6.96 v 25.3±12.74%, p<0.05).	
Maza 2019[248]	Case control	EEAwENS = 2 EEAsENS = 2 non-EEAwENS = 27 Healthy controls = 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 compared to EEAsENS. Both EEAwENS patients had a prior history of	Confounding ? Selection bias - Information bias ? Reporting bias ? Causal bias ? Selection bias:

				submucosal ITR in attempts to treat nasal obstruction. In EEAwENS, - Cross-sectional area was similar to EEAsENS patients (3.47±0.23 v 3.79±1.20 cm^2, p=NR). - Airflow distribution was lower than EEAsENS patients through inferior region	-EEAwENS patients had prior inferior turbinate surgery and potential a history of nasal obstructive symptoms. Information bias: - CFD modeling is not validated to patient's symptom. - CFD modeling used sampling area for testing. Reporting bias: - Statistical data were not completely reported. Causality:

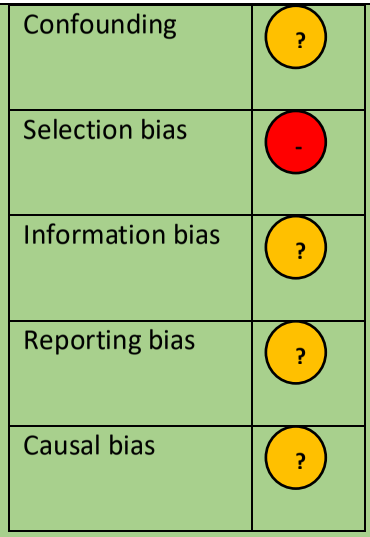
				(17.74±4.00 v 51.25±3.33%, p<0.002). - WSS at inferior region was lower than EEAsENS patients. (0.30±0.13 v 0.61±0.03Pa, p=0.003) Airflow parameters between non-EEAwENS and EEAwENS patients were not compared.	- Association between ENS and airflow change may be related to evidence prior surgery.
Li 2018[246]	Case control	ENS = 27 Healthy controls = 42	CFD modeling - Cross-sectional area(cm^2)	Airflow and airway parameters on CFD modeling were altered	Confounding: ? Selection bias: -

			- Nasal resistance ($Pa/cm^3/s$) - Airflow rate (%) (inferior, middle, superior) - WSS (Pa) (anterior, MT, IT) WSS and ENS6Q correlation	after ITR in ENS patients compared to healthy controls. In ENS, -Cross-sectional area was higher than healthy controls (~3.5 v ~1.0 cm^2, $p<0.001$). -Nasal resistance was lower than healthy controls (0.052±0.01 v 0.070±0.02 $Pa/cm^3/s$, $p<0.001$).	<table><tr><td>Information bias</td><td>?</td></tr><tr><td>Reporting bias</td><td>?</td></tr><tr><td>Causal bias</td><td>?</td></tr></table> Selection bias: -Post turbinate surgery patients were compared to surgically naive patient. Information bias: - CFD modeling is not validated to patient's symptom. - CFD modeling used sampling area for testing. Reporting bias:

				- Airflow rate decreased through inferior region (25.8±17.6 v 36.5±15.9%, p<0.001) while increased at middle region compared to healthy controls (66.5±18.3 v 49.9±15.1%, p<0.001). -WSS was lower in both inferior and middle region compared to healthy	- Statistical data were not completely reported. Causality: - Association between ENS and airflow change may be related to evidence prior surgery.

				controls (Inferior: 0.58±0.24 v 1.18±0.81Pa, p=0.014; Middle: 0.70±0.31 v 1.20±0.82Pa, p=0.038). Peak WSS in the inferior region is weakly correlated with ENS6Q total score, 'suffocation' and 'nose feels too open' (ENS6Q r= −0.398, p=0.003; suffocation r= −0.295, p=0.031; and nose	

				feels too open r= −0.388, p=0.004).	
Konstantinidis 2017[240]	Case control	ITRwENS = 21 ITRsENS = 18 Healthy controls = 31	Rhinomanometry: -Nasal resistance (Pa/cm^3/s) -Airflow rate (cm^3/s)	Nasal resistance and airflow rate were similar between ITRwENS and ITRsENS patients (nasal resistance: 0.20±0.04 v 0.21±0.03 Pa/cm^3/s, p=0.97; airflow rate: 485±3 v 490±28 cm^3/s, p=0.95).	Confounding ? Selection bias ? Information bias + Reporting bias + Causal bias ? - No data is provided as to how ITRsENS patients were selected.

Li 2017[245]	Case control	ITRwENS = 6 Pre-ITR ENS = 3 Healthy controls = 22	Acoustic rhinometry: - Minimal cross-sectional area(cm^2) Rhinomanometry: - Nasal resistance (expressed as flow rate@75 Pa(mL/s)) CFD modeling: -Nasal resistance (expressed as flow rate@15 Pa(mL/s)) - Airflow rate (%)	Airflow and airway parameters on acoustic rhinometry, rhinomanometry and CFD modelling were altered after ITR compared to healthy controls. In ITRwENS: -Minimum cross-sectional area on acoustic rhinometry was higher than healthy controls	 Selection bias: - Pre-ITR ENS group had lower nasal resistance than healthy controls (without ITR) -Post turbinate surgery compared to surgically naive patient.

			(inferior, middle, superior) - WSS (Pa) (inferior, middle, superior)	(0.68±0.36 v 0.51±0.18cm^2, p=NR). - Nasal resistance on both rhinomanometry and CFD modeling was lower compared to healthy controls (rhinomanometry: 163.9±62.8 v 120.9±67.5 mL/s, p=NR; CFD: 173.1±41.4 v 116.0±41.7 mL/s, p<0.05).	Information bias: - CFD modeling is not validated to patient's symptom. - CFD modeling used sampling area for testing. Reporting bias: - Statistical data were not completely reported.

				-Nasal flow rate was lower than pre-ITR and healthy controls at inferior region (~ 20 v ~ 40 v ~ 40%, p<0.05) but higher at middle region (75.6±14.6 v 56.2±14.7 v ~50%, p<0.05). - Average WSS was lower than healthy controls at inferior region (~0.03 v ~0.07Pa, p<0.05).	

Freund 2011[241]	Case control	ENS= 10 Healthy controls = 15	Rhinomanometry: -Airflow rate (cm^3/s)	Airflow rate was similar between patients with ENS and healthy controls (593[636] v 700[653]cm^3/s, p>0.05).	Confounding: ? Selection bias: - Information bias: + Reporting bias: + Causal bias: ? Selection bias: -Post turbinate surgery compared to surgically naive patient.

† p value across group was not significant

Data format: mean±SD, Bias assessment: 

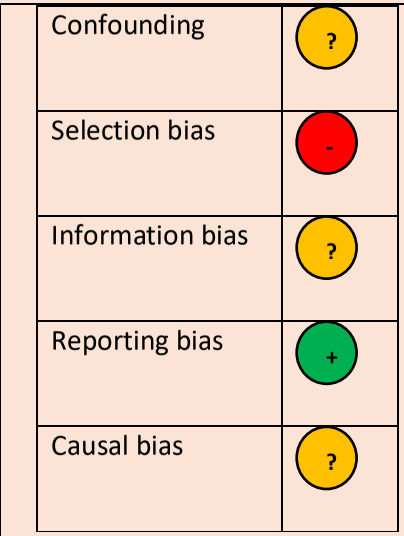
, low risk; 

, high risk; 

, unclear risk

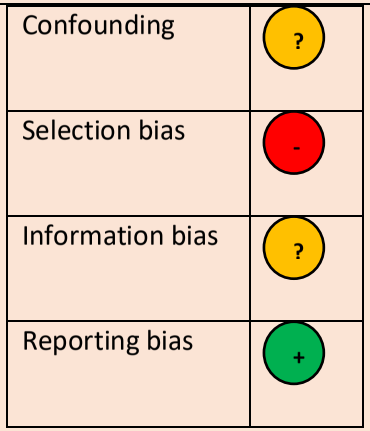
Abbreviations: ENS, Empty Nose Syndrome; ITR, Inferior Turbinate Resection; MTR, Middle Turbinate Resection; ITRwENS, Inferior Turbinate Resection with Empty Nose Syndrome; ITRsENS, Inferior Turbinate Resection without Empty Nose Syndrome; CRS, Chronic Rhinosinusitis; EEA, Endoscopic Endonasal Approach (skull base); EEAwENS, Endoscopic Endonasal Approach with Empty Nose Syndrome; EEAsENS, Endoscopic Endonasal Approach without Empty Nose Syndrome; CT, Computed Tomography; SNOT, Sinonasal Outcome Test; IT, Inferior Turbinate; MT, Middle Turbinate; ITV, Inferior Turbinate Volume; CFD, computational fluid dynamics; WSS, wall shear stress; ENS6Q, Empty Nose Syndrome 6 Questionnaire; NR, Not Reported; NS, Not Significant.

Table 5. Mental health and cognitive function in empty nose syndrome.

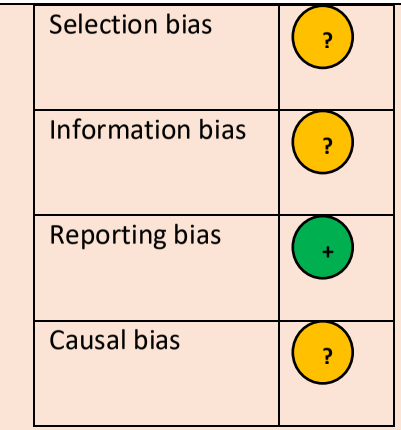
Study, Year	Design	Participants	Clinical endpoint	Result	Bias assessment
Mental health					
Fu 2019[247]	Case control	ENS = 19 Chronic rhinitis = 12	BAI (0-63) BDI (0-63)	Anxiety and depression severity were higher in patients diagnosed with ENS than chronic rhinitis (BAI 21.0[41.0] v 2.5[26.0], p=0.005; BDI 15.0 [47.0] v 8.0[18.0], p=0.007).	 Selection bias: - ENS group may be motivated by surgical candidacy.

					Causality: -Association between ENS symptoms and anxiety/ depression may be related to pre-existing evidence.
Kim 2019[222]	Case control	ENS = 24 CRSwNP = 16 CRSsNP = 20 AR = 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)	Confounding: ? Selection bias: - Information bias: ? Reporting bias: ? Causal bias: ?

				compared to 19%(CRSwNP), 15%(CRSsNP) and 27% (AR). Within the ENS group: 1.BDI score was not different between conservative and radical ITR surgery (14.88±6.81 v 17.69±18.21, p=0.92). 2. BDI score did not correlate with nasal	Selection bias: -ENS patients were selected based on depression symptom. Reporting bias: -The correlation between BDI/nasal volume and BDI/SNOT-22 in non- ENS groups were not reported. Causality: -Association between ENS symptoms and depression may

				volume after surgery (Rt: r=0.26, p=0.95; Lt: r=0.47, p=0.83). 3. BDI score did not correlate with SNOT-22 score (r=0.1, p=0.62).	be related to pre-existing evidence.
Huang 2019[251]	Cross-sectional	ENS = 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<0.001; BDI: r=0.526, p<0.001).	Causal bias ? Selection bias: - ENS group may be motivated by surgical candidacy. Causality: -Association between ENS symptoms and anxiety/ depression may be related to pre-existing evidence.
Manji 2018[221]	Cross-sectional	ENS = 53	GAD-7 (0-21) PHQ-9 (0-27)	Anxiety and depression were high	Confounding ?

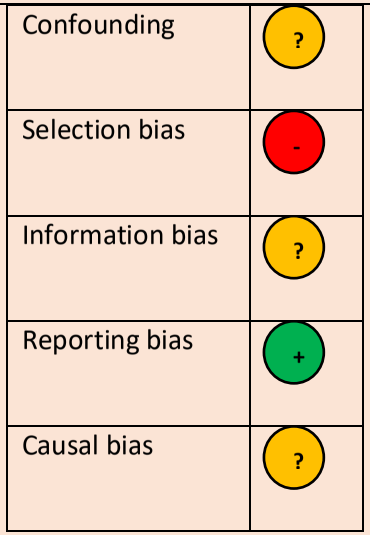
			GAD-7, PHQ-9 and ENS6Q correlation	in patients self-reporting ENS (65.9% and 67.9%). Anxiety and depression correlated with ENS6Q (GAD-7: r=0.54, p<0.001; PHQ-9: r=0.48, p<0.001).	 Selection bias: -ENS was diagnosed by self-reporting. Causality: -Association between ENS symptoms and anxiety/

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>depression may be related to pre-existing evidence.</td></tr>
<tr><td>Mangin 2017[250]</td><td>Cross-sectional</td><td>ENS = 22</td><td>HVPT (positive or negative)

Lung function (spirometry, plethysmography

and diffusing capacity of the lung for carbonmonoxide (DLCO) measurement)</td><td>Hyperventilation syndrome (with normal lung function) was found in 77.3% of patients with ENS.</td><td><table><tr><td>Confounding</td><td>+</td></tr><tr><td>Selection bias</td><td>?</td></tr><tr><td>Information bias</td><td>+</td></tr><tr><td>Reporting bias</td><td>+</td></tr><tr><td>Causal bias</td><td>?</td></tr></table>Causality:

-Association between ENS symptoms and hyperventilation</td></tr>
</table>

					syndrome may be related to pre-existing evidence.
Lee 2016[249]	Cross-sectional	ENS = 20	BAI (0-63) BDI (0-63)	Anxiety and depression were high in patients with ENS (70% and 65%).	 Selection bias: - ENS group may be motivated by surgical candidacy.

					Causality: -Association between ENS symptoms and anxiety/ depression may be related to pre-existing evidence.
Cognitive function					
Freund 2011[241]	Case control	ENS = 10 Healthy controls = 15	f-MRI After exposure to - free breathing - menthol (10%) -lemon oil (high grade)	ENS patients expressed different patterns on f-MRI compared to healthy controls. During free breathing, there was ENS-	Confounding: ? Selection bias: - Information bias: ? Reporting bias: ? Causal bias: ?

				specific activation at cerebellum, amygdala, and temporal area compared to healthy controls. In ENS patients - After menthol inhalation, specific deactivation mainly in bilateral temporal pole (superior temporal gyrus) which is emotional	Selection bias: -Post turbinate surgery patients were compared to surgically naive patient. Information bias: -f-MRI is qualitatively assessed.

				processing area was shown. - After lemon oil inhalation, deactivation in caudate nucleus, middle frontal gyrus, and superior temporal gyrus which is activated during odor presentation was shown.	

Data format: mean±SD, median [IQR] , Bias assessment: +, low risk; -, high risk; ?, unclear risk

Abbreviations: ENS, Empty Nose Syndrome; ITR, Inferior Turbinate Resection; CRSwNP, Chronic Rhinosinusitis with Nasal Polyp; CRSsNP, Chronic Rhinosinusitis without Nasal Polyp; AR, Allergic Rhinitis; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; Sinonasal Outcome Test; GAD-7, Generalized Anxiety Disorder questionnaire; PHQ-9, Patient Health Questionnaire; ENS6Q, Empty Nose Syndrome 6 Questionnaire; HVPT, Hyperventilation Provocation Test; f-MRI, functional Magnetic resonance imaging

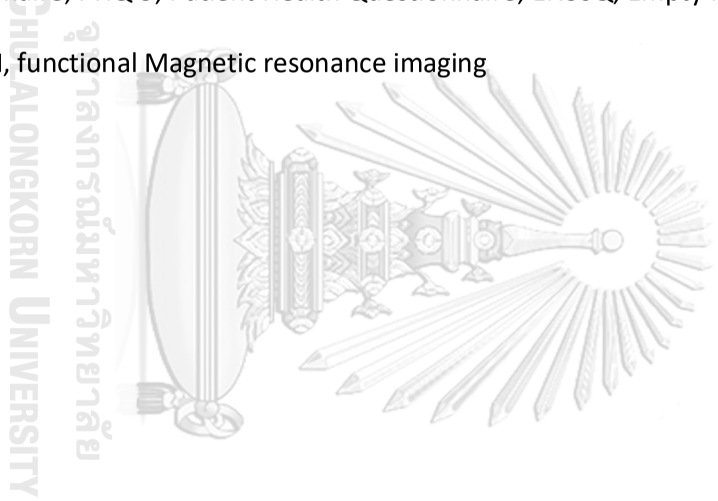


Table 6. Diagnostic testing, olfactory function and mucosal physiology/innate immunity in empty nose syndrome

Study, Year	Design	Participants	Secondary Outcomes	Result	Bias assessment
Diagnostic testing					
Malik 2019[239]	Case control	ITRwENS = 27 ITR sENS= 5 Healthy controls = 42	Menthol detection threshold† (1-20)	Menthol detection was lower in patients with ITRwENS compared to ITRsENS and healthy controls (10.2±3.87 v 15.2±1.23 v 14.8±1.59, *p*<0.05 for both comparison). ITRsENS patients reported better mental detection than healthy controls (15.2±1.23 v 14.8±1.59, p<0.05).§	Confounding: ? Selection bias: - Information bias: ? Reporting bias: ? Causal bias: ? Selection bias:

					- ITRsENS reported lower symptom score than healthy controls Information bias: - Menthol detection threshold is considered as subjective measurement. Reporting bias: - Statistical error is likely Causality:

					- Association between ENS and menthol detection may be related to evidence prior surgery.
Li 2018[246]	Case control	ENS = 27 Healthy controls = 42	Menthol detection threshold† (1-20)	Menthol detection was lower in patients with ENS compared to healthy controls (10.3±3.9 v 14.0±1.8, p<0.001).	Confounding: ? Selection bias: - Information bias: ? Reporting bias: ? Causal bias: ? Selection bias:

					-Post turbinate surgery patients were compared to surgically naive patient. Information bias: - Menthol detection threshold is considered as subjective measurement. Causality: - Association between ENS and menthol detection may be related to evidence prior surgery.

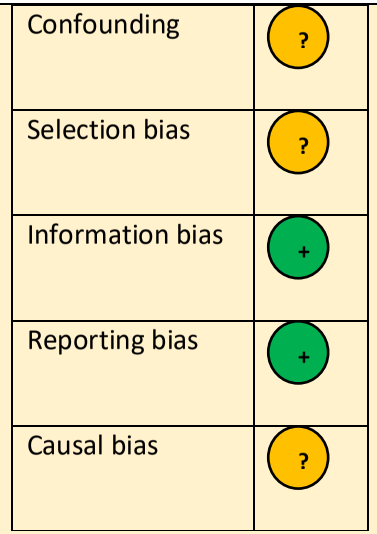
Konstantinidis 2017[240]	Case control	ITRwENS = 21 ITRsENS = 18 Healthy controls = 31	Menthol identification test‡ (0-40)	Menthol detection was lower in patients with ITRwENS compared to ITRsENS and healthy controls (21±8 v 29±8 v 34±5; ITRwENS v ITRsENS, p=0.021, ITRwENS v healthy controls, p=0.004). ITRsENS patients reported similar menthol detection compared to healthy controls (29±8 v 34±5, p=0.067).	Confounding: ? Selection bias: ? Information bias: ? Reporting bias: + Causal bias: ? Information bias: - Menthol detection threshold is considered as subjective measurement. Causality:

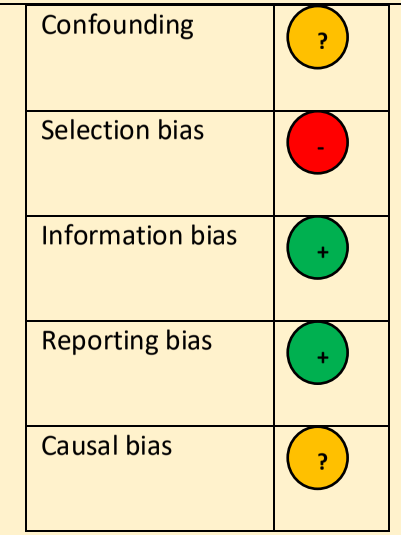
					- Association between ENS and menthol detection may be related to evidence prior surgery.
Li 2017[245]	Case control	ENS = 5 Healthy controls = 14	Menthol detection threshold† (1-20)	Menthol detection was lower in patients with ENS compared to healthy controls (9.2±4.6 v 14.8±1.6, p<0.05).	Confounding: ? Selection bias: - Information bias: ? Reporting bias: ? Causal bias: ? Selection bias:

					-Post turbinate surgery patients were compared to surgically naive patient. Information bias: - Menthol detection threshold is considered as subjective measurement. Causality: - Association between ENS and menthol detection may be related to evidence prior surgery.
	Case control	ENS = 15	Cotton test		Confounding ?

Thamboo 2017[226]		Sinonasal disease = 18	- 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 compared to non-ENS controls. In ENS: - Total ENS6Q reduced to normal level during cotton in situ. (cotton in situ 6.00 ±5.75 v cotton removed 19.13±7.91, p<0.01). - All ENS patients (15/15) reported 'A little better' or 'much better' during cotton in situ. In sinonasal disease:	Selection bias: - Information bias: - Reporting bias: + Causal bias: ? Selection bias: -ENS6Q ≥ 11 was an inclusion criterion for ENS; ENS group was highly symptomatic compare to non-ENS sinonasal disease.

				- Total ENS6Q increased during cotton in situ (cotton in situ 5.06 ±3.94 v cotton removed 2.94±3.36, p=0.034). - Majority of patients (16/18) reported 'about the same' or worse during cotton in situ.	-Post turbinate surgery patients were compared to surgically naive patients. Information bias: - Assessor and patient were not blinded despite authors' effort to reduce the bias. - Test result on symptom improvement was subjectively performed.
Olfactory function					

Konstantinidis 2017[240]	Case control	ITRwENS = 21 ITRsENS = 18 Healthy controls= 31	Olfactory function: -Visual Analogue Scale (0-100) -TDI score (1-48)	Subjective olfactory rating was impaired in ITRwENS patients, but TDI score showed no different compared to ITRsENS patients. In ITRwENS, - Subjective olfaction rating was lower than ITRsENS patients and healthy controls (35.7±6.3 v 72.2±5.5 v 81.1±4.9; p <0.001 for both comparison). - TDI score was similar to ITRsENS patients but lower than healthy controls (28.1±3.5 v 30.5±4.1 v	 Causality: - Association between ENS and olfactory impairment may be related to evidence prior surgery.

				35.5±3.2; ITRwENS v ITRsENS, p=0.62, ITRwENS v healthy controls, p=0.028).	
Mucosal physiology/innate immunity					
Fu 2019[247]	Case control	ENS = 19 Chronic rhinitis = 12	nNO	ENS had lower nNO than chronic rhinitis patients (85.5[327.5] v 231.3[312], p<0.001).	 Selection bias:

					-Post turbinate surgery patients were compared to surgically naive patient. - ENS group may be motivated by surgical candidacy. Causality: - Association between ENS and nNO may be related to evidence prior surgery.

†Menthol detection threshold: lower score required higher concentration of menthol for detection

‡Menthol identification test: higher score indicated better function

§Statistical error is likely

Data format: mean±SD, Bias assessment: 

, low risk; 

, high risk; 

, unclear risk

Abbreviations: ENS, Empty Nose Syndrome; ITR, Inferior Turbinate Resection; ITRwENS, Inferior Turbinate Resection with Empty Nose Syndrome; ITRsENS, Inferior Turbinate Resection without Empty Nose Syndrome; ENS6Q, Empty Nose Syndrome 6 Questionnaire; TDI, Odor Threshold, Discrimination, and Identification test; nNO, nasal nitric oxide.

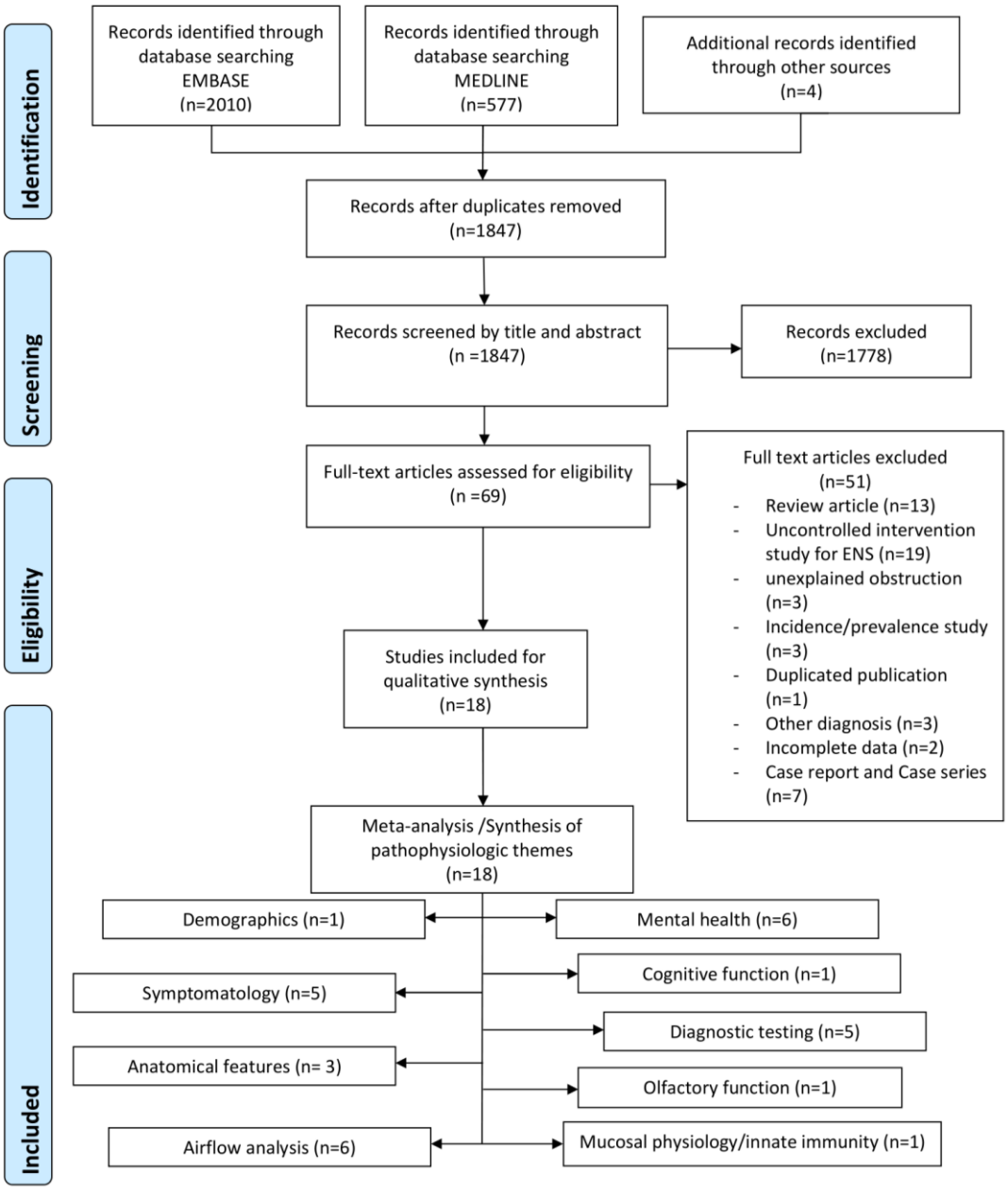


Figure 6. PRISMA flowchart of study selection process

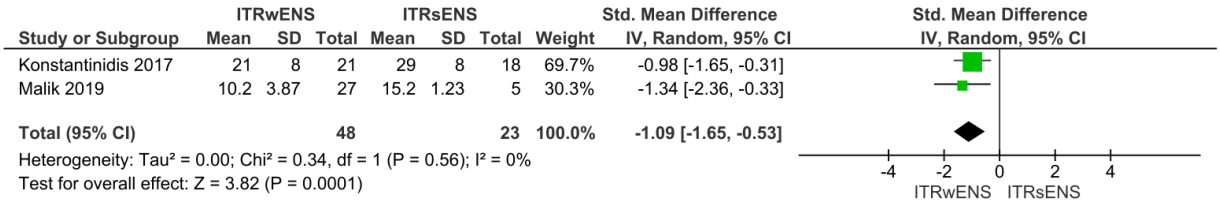


Figure 7. Forest plot representing menthol detection test in ITRwENS and ITRsENS.

Abbreviations: ITRwENS, Inferior turbinate reduction with Empty nose syndrome; ITRsENS, Inferior turbinate reduction without empty nose syndrome

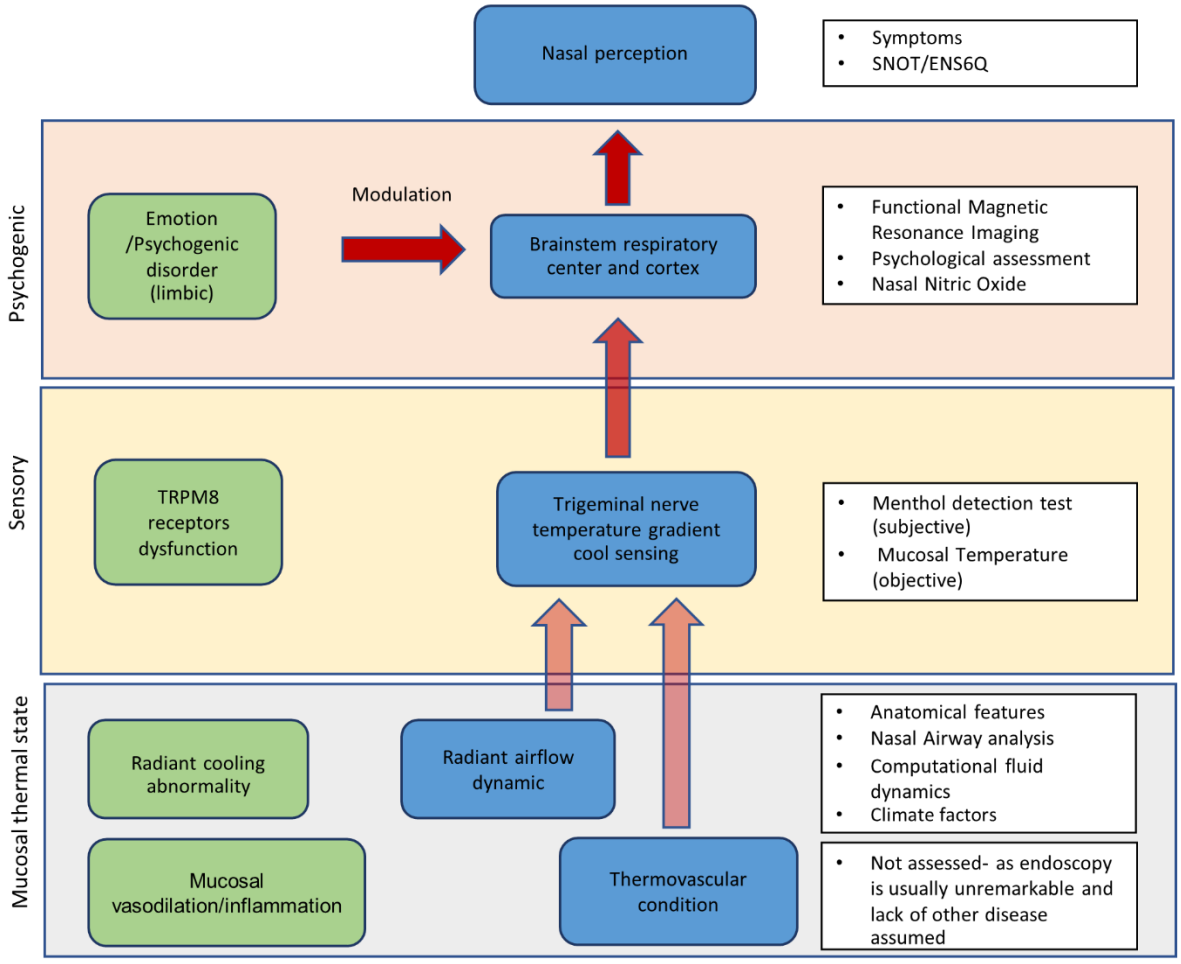


Figure 8. Illustrated model of pathophysiologic evidence in ENS

Abbreviations: SNOT, Sinonasal Outcome Test; ENS6Q, Empty Nose 6-item Questionnaire;

TRPM-8, transient receptor potential melanostatin-8

Table 7. Supplementary: Search strategy

Search strategy for MEDLINE
1. empty nose syndrome.mp. 2. ENS.mp. NOT enteric nervous system.mp 3. empty nose.mp. 4. OR /1-3 5. exp ANXIETY/ 6. exp ANXIETY DISORDERS/ 7. exp DEPRESSIVE DISORDER/ 8. DEPRESSION/ 9. exp SUICIDE/ 10. exp MENTAL DISORDERS/ 11. exp BEHAVIORAL SYMPTOMS/ 12. exp SOMATOFORM DISORDERS/ 13. exp HYPERVENTILATION/ 14. Hyperventilation Syndrome.mp. 15. Suffocation.mp. 16. OR/5-15 17. Paradoxical.mp. 18. Blockage.mp. 19. Obstruction.mp. 20. Congestion.mp. 21. OR/18-20 22. 17 ADJ1 21

23. 16 OR 22
24. *NOSE DISEASE/
25. NASAL SURGICAL PROCEDURES/
26. TURBINATE/
27. NASAL OBSTRUCTION/
28. OR/24-27
29. 23 AND 28
30. 4 OR 29 =988
31. Limited 30 to English language and human study = 577

Modified version was used for EMBASE

Table 8. Supplementary: Characteristics of included study

Study, Year	Design	Pathophysiologic theme	Participants	Definition of ENS	Type of turbinate surgery	Primary outcome	Secondary outcome
Freund 2011[241]	Case control	Cognitive function Symptomatology Airflow analysis	ENS = 10 Healthy controls = 15	-Physician diagnosed (unspecified) -History of turbinate surgery	IT+MT	Functional Magnetic Resonance Imaging	Rhinomanometry: -Airflow rate Nasal patency rating scale
Jang 2011[242]	Case control	Anatomical features	ENS = 14 (side) Healthy controls	-Symptoms (excessive airflow, nasal congestion,	IT	CT: -Nasal mucosa thickness	None

			= 14 (side) Unilateral CRS = 20 (side)	nasal or facial pain on inspiration, excessive crusting or discharge, and headache) -Endoscopic finding -History of turbinate surgery			
Hong 2016[243]	Case control	Anatomical features	ENS = 34 Healthy controls = 10	-Symptoms (excessive nasal crusting or discharge, paradoxical nasal obstruction, excessive	IT	CT: -ITV ITV/ SNOT-25 correlation	None

				airflow, facial or nasal pain on inspiration, and depression) -Endoscopic finding -History of turbinate surgery			
Lee 2016[249]	Cross-sectional	Mental health	ENS = 20	-Symptoms (paradoxical nasal obstruction, breathing discomfort, pharyngeal dryness, and other related discomfort)	IT	BAI BDI	None

				-Endoscopic finding -Cotton test -History of turbinate surgery			
Thamboo 2016[244]	Case control	Anatomical features	ITRwENS = 32 (side) ITRsENS = 34 (side) Healthy controls = 58 (side)	-Symptoms (ENS6Q) -Endoscopic finding or Imaging -Cotton test -History of turbinate surgery	IT	CT: -Nasal cavity airspace -Nasal mucosa thickness	None

Konstantinidis 2017[240]	Case control	Diagnostic testing Olfactory function Airflow analysis	ITRwENS = 21 ITRsENS = 18 Healthy controls = 31	-Symptoms (sense of nasal obstruction, nasal or facial pain on inspiration, persistent crusting or discharge, and headache) -Endoscopic finding -Nasal resistance -History of turbinate surgery	IT	Menthol identification test	Rhinomanometry: -Nasal resistance -Airflow rate Olfactory function: -Visual Analogue Scale -Odor Threshold, Discrimination test, Identification test
Li 2017[245]	Case control	Airflow analysis Diagnostic testing	ITRwENS = 6 Pre-ITR ENS	-Symptoms (ENS6Q, SNOT22, NOSE)	IT	Acoustic rhinometry:	Menthol detection threshold

			= 3 Healthy controls = 22	-History of turbinate surgery		-Minimal cross-sectional area Rhinomanometry: -Nasal resistance CFD modeling: -Nasal resistance -Airflow rate -Wall shear stress	
Mangin 2017[250]	Cross-sectional	Mental health	ENS = 22	-Symptoms (paradoxical nasal obstruction, nasal pain, rhinopharyngeal	IT±MT	HVPT Lung function	none

				dryness, lack of nasal airflow sensation, hypersensitivity to cold air, sleep disorder, and dyspnea) -Endoscopic finding -Imaging -Nasal resistance -History of turbinate surgery			
Thamboo 2017[226]	Case control	Diagnostic testing Symptomatology	ENS = 15 Sino-nasal disease	-Symptoms (ENS6Q) -Endoscopic finding or Imaging	IT	Cotton test ENS6Q	Nasal breathing rating scale

			= 18	-History of turbinate surgery			
Velasquez 2017[227]	Cross-sectional	Symptomatology	ENS = 15 CRSsNP = 30 Healthy controls = 30	-Symptoms (patients presenting with nasal discomfort and/or paradoxical nasal obstruction) -Endoscopic finding or Imaging -Cotton test -History of turbinate surgery	IT	ENS6Q SNOT-22	None

Li 2018[246]	Case control	Airflow analysis Diagnostic testing	ENS = 27 Healthy controls = 42	-Symptoms (ENS6Q, SNOT22, NOSE) -Imaging -History of turbinate surgery	IT±MT	CFD modeling: -Cross-sectional area -Nasal resistance -Airflow rate -Wall shear stress Wall shear stress/ ENS6Q correlation	Menthol detection threshold
Manji 2018[221]	Cross-sectional	Mental health Symptomatology	ENS = 53	Self-reporting -Symptoms (ENS6Q) -Imaging -History of turbinate surgery	IT	GAD-7 PHQ-9 ESS WPAI EQ-5D-5L	General health/ ENS6Q correlation

Fu 2019[247]	Case control	Symptomatology Mental health Mucosal physiology/Innate immunity	ENS = 19 Chronic rhinitis = 12	-Symptoms (paradoxical nasal obstruction, breathing difficulty, and other related discomforts) -Cotton test -History of turbinate surgery	IT	Nasal Nitric Oxide	SNOT-22 BAI BDI
Huang 2019[251]	Cross-sectional	Mental health	ENS = 68	-Symptoms (paradoxical nasal obstruction, breathing discomfort,	IT	BAI BDI BAI, BDI/ SNOT-25 correlation	None

				and other related discomfort) -Cotton test -History of turbinate surgery			
Kim 2019[222]	Case control	Mental health	ENS = 24 CRSwNP = 16 CRSsNP = 20 AR = 34	-Symptoms (excessive nasal crusting or discharge, paradoxical nasal congestion, headache, hoarseness, excessive airflow,	IT	BDI	BDI/Nasal volume correlation BDI/SNOT-22 correlation

				facial or nasal pain on inspiration, and *depression*) -Cotton test -History of turbinate surgery			
Malik 2019[239]	Case control	Airflow analysis Diagnostic testing	ITRwENS = 27 ITRsENS = 5 Healthy controls = 42	-Symptoms (ENS6Q, SNOT22, NOSE) -Imaging -History of turbinate surgery	IT±MT	CFD modeling: -Cross-sectional area -Nasal resistance -Airflow rate -Airflow distribution	Menthol detection threshold

						-Wall shear force distribution	
Manji 2019[252]	Cross-sectional	Demographics	ENS = 53	Self-reporting -Symptoms (ENS6Q) -Imaging -History of turbinate surgery	IT	Climate factors At point of residence/ ENS6Q correlation	none
Maza 2019[248]	Case control	Airflow analysis	EEAwENS = 2 EEAsENS = 2 Non-EEAwENS = 27	-Symptoms (ENS6Q, SNOT22, NOSE) -Imaging -History of turbinate surgery	IT±MT	CFD modeling: -Cross-sectional area -Airflow distribution -Wall shear stress	None

			Healthy controls = 42				

Abbreviations: ENS, Empty Nose Syndrome; ITR, Inferior Turbinate Resection; ITRwENS, Inferior Turbinate Resection with Empty Nose Syndrome; ITRsENS, Inferior Turbinate Resection without Empty Nose Syndrome; CRS, Chronic Rhinosinusitis; CRSwNP, Chronic Rhinosinusitis with Nasal Polyp; CRSsNP, Chronic Rhinosinusitis without Nasal Polyp; AR, Allergic Rhinitis; EEA, Endoscopic Endonasal Approach(skull base); EEA, Endoscopic Endonasal Approach (skull base); EEAwENS, Endoscopic Endonasal Approach with Empty Nose Syndrome; EEAsENS, Endoscopic Endonasal Approach without Empty Nose Syndrome; ENS6Q, Empty Nose Syndrome 6 Questionnaire; SNOT, Sino-nasal Outcome Test; NOSE, Nasal Obstruction and Septoplasty Effectiveness; IT, Inferior Turbinate; MT, Middle Turbinate; CT, Computed Tomography; CFD, Computational Fluid Dynamics; ITV, Inferior Turbinate Volume; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; HVPT, Hyperventilation Provocation Test; GAD-7, Generalized Anxiety Disorder questionnaire; PHQ-9, Patient Health Questionnaire; ESS, Epworth Sleepiness Scale; WPAI, Work Productivity and Impairment questionnaire; EQ-5D-5L, 5-dimension EuroQol General Health State Survey

Table 9. Supplementary: Comparison between subjective and objective findings on Empty Nose Syndrome constructs

Construct	**ENS subjective finding**	**ENS objective finding**
Nasal perception pathway		
Nasal airflow dynamic	'Empty' nasal space is presented in ENS patients. Nasal breathing perception is bad despite wide patency nasal cavity.	Nasal volume and airspace are similar between ITRwENS and ITRsENS patients. There is no described airflow-mechano receptor. Nasal perception and nasal airflow are not correlated. Human airflow assessment demonstrated similar nasal airflow and resistance between ITRwENS and ITRsENS patients.
Nasal airflow related effect	Cotton test subjectively improved nasal breathing perception.	No objective test was compared.

	Olfactory function rating was impaired in ENS patients.	Objective olfactory function (TDI score) was similar between ITRwENS and ITRsENS patients.
Neuro-sensory function	Menthol detection was lower in ENS patients.	No objective test was compared.
Cortex and higher control	ENS patients were associated with anxiety (73%), depression (71%).	Hyperventilation syndrome diagnosed by hyperventilation provocation test and pulmonary function test was reported in 77% of ENS patients. f-MRI demonstrated relation between emotional processing area and nasal breathing perception.
Cause and impact of ENS		
Cause of the event	ENS is an iatrogenic condition following excessive nasal turbinate tissue removal.	Patients initial indication for surgery is often forgotten and surgical failure to improve nasal perception potentially increased perception severity.

		ENS is possibly a form of functional neurological disorder (conversion disorder), characterized by neurological symptoms incompatible with known neurological pathology. Stressor related to surgical event is considered triggering the event.
Impact of the event	ENS patients self-reported mental health disorder, functional and sleep function impairment.	It is unclear whether these conditions were predisposing, or resultant of the ENS. ENS as a cause of these conditions cannot be inferred. when pre-surgical data were not compared.

Abbreviations: ENS, Empty Nose Syndrome; ITR, Inferior Turbinate Resection; ITRwENS, Inferior Turbinate Resection with Empty Nose Syndrome; ITRsENS, Inferior Turbinate Resection without Empty Nose Syndrome; f-MRI, functional Magnetic Resonance Imaging

Chapter 3. Defining the minimal clinically important difference in rhinomanometry from nasal airway surgery

3.1 Introduction

Nasal obstruction has a significant impact on patient quality of life and patients often seek treatment through medical or surgical interventions.[273] It is a multifactorial phenomenon resulting from an interplay of structural, mucosal, thermo-sensing and psychological factors.[274,275] Patient reported outcome measures (PROMs) such as the Nasal Obstruction Symptom Evaluation (NOSE) are often utilized in clinical practice to assess patient's subjective feelings of nasal patency [89], however these do not always reflect nasal airflow patency. Additionally, adaptation to changes in nasal breathing can occur and objective measures therefore remain an integral part of clinical assessment. Objective tools are also important in demonstrating the degree of relief following surgical intervention.

Active anterior rhinomanometry (AAR) is considered to be the gold standard technique by the International Committee on Standardization of Rhinomanometry for the assessment of nasal patency [115] and provides a measure of nasal airway resistance (NAR). Although there have been several studies reporting normative AAR values in patient populations, the minimal clinically important difference (MCID) remains to be established. Thus, the changes in airflow due to a medical or surgical intervention and how they reflect patient's subjective feelings of patency remain difficult to interpret.

Although there have been several studies published assessing the correlations between NAR and patient perceptions of nasal patency, the results of these have been inconsistent. A meta-review noted that the assessment of airflow unilaterally demonstrated consistent positive correlations but there were inconsistencies when total NAR was assessed. [52,93,94,276] In addition, there has been no consensus on the most suitable PROMs appropriate for use in the clinical assessment of nasal obstruction.

The aims of this study were therefore twofold: to determine whether the change in patient subjective scores demonstrated correlation with the change in NAR and to define an MCID following surgical intervention. Correlation analyses were performed using a range of subjective measurement tools, and both total and unilateral NAR were assessed.

3.2 Methods

Population

A prospective case series of adult patients (age > 18 years) from two tertiary clinics undergoing any turbinate, septal and/or rhinoplasty surgery for nasal obstruction was performed. Patients had a mix of turbinate, septal and nasal valve disorders, but all were nasal airway pathologies only. Patients with significant sinus disease, tumour or other inflammatory disorders were not included. Recruitment was consecutive from October 2009 to October 2015 and ethics approval was granted by St Vincent's Hospital Human Research Ethics Committee (SVH 09/083). The assessment of NAR and PROMs were performed prior to surgery and at least 6 months post-surgery.

Outcome measures

Four-phase AAR was performed at the international standard of 150 Pa pre- and post-surgery using an NR6 Rhinomanometer (GM Instruments, UK). Measurements were taken

after resting for at least 10 minutes in a climate-controlled room (22 ℃), and with the patient seated. No exercise was allowed during the 4 hours prior to assessment. Decongestants (oral and topical) were avoided for at least 3 days prior to testing.

An anaesthetic mask was held airtight around the nose, with the nostril contralateral to the testing side sealed with a foam nasal plug. The patient was instructed to breathe normally through the nose with the mouth closed. The opposite side was then tested using the same method. At least two readings of NAR within 15% of each other were obtained on each side.

Total NAR was calculated by combining representative readings for both sides using NARIS software (GM Instruments, Bristol, UK) and reported in $Pa/cm^3/s$. The obstructed side was defined as the side of higher resistance at baseline. Values were defined for NAR Total, NAR Obstructed and NAR less obstructed at pre- and post-surgery. Change in NAR (ΔNAR) was determined using patient matched data pre- and post-surgery.

Defining a clinically important change

The clinically relevant changes were calculated by two ways, using a half standard deviation of baseline method as previously described [161,277] and based on 1-point improvement on nasal function scale. On continuous measures, linear regression analysis was used to calculate MCID by the estimate change in NAR corresponding to minimum improvement in PROMs.

Distribution-based method

MCID was calculated using half Standard Deviation (SD) and Standard Error of measurement (SEM). SEM = SD × √ (1 – [test-retest reliability]). The test-retest reliability was acquired from previous data (0.83).[278]

Anchor-based method

The change in NAR was anchored against patient reported ordinal scales: 13-point Likert score of overall nasal function ranging from +6 (*excellent*) to +4 (*good*), +2 (*fair*), 0 (*neither good nor bad*), -2 (*poor*), -4 (*bad*), and -6 (*terrible*) and nasal obstruction six-point Likert score composed of 0 (*no problem*), 1 (*very mild problem*), 2 (*mild or slight problem*), 3 (*moderate problem*), 4 (*severe problem*), and 5 (*problem as bad as it can be*). MCID was then determined by the change in NAR based on 1- point improvement on each ordinal scale.

Continuous measures

MCID was also calculated from continuous measures: Nasal Obstruction Symptom Evaluation (NOSE)[89], Sinonasal Outcome Test 22 (SNOT-22)[97], visual analogue scales (VAS) on unilateral obstruction ranging from 0 (no nasal obstruction) to 100 (complete obstruction). Patients were stratified according to whether they had achieved a clinically important change for any of the utilised PROMs. These resulted in two groups of patients; those who had achieved a clinically important change for each PROM and those who had not. These groups varied by the PROM that was used to define them. Published clinically relevant change values were used to assess NOSE (8.5)[90] and SNOT-22 (8.9)[97]. For VAS, clinically important changes were calculated by half of standard deviation of pre-operative VAS and VAS change in corresponding to 1-categorical improvement in overall nasal function. The calculation yield VAS change of 9 and 13 mm, respectively. Linear regression analysis was used to estimate the change in NAR corresponding to minimum improvement in PROMs and MCID was estimated using the slope of linear regression (Beta coefficient).

Statistical analysis

Data was collated and analysed using SPSS v22 software (IBM, Australia). The data categories were analysed for normality using a Shapiro-Wilk test and histogram analysis. Parametric data was analysed using paired t-tests for matched data or independent t-tests for unrelated groups. Correlations for parametric data were examined using a Pearson's test for continuous variables or Spearman's analysis for ordinal variables. Values of $p<0.05$ were considered significant.

3.3 Results

One hundred and seventy-one patients were recruited (age 37.2±13.4 years, 59.6% female), with 46.6% having undergone prior nasal surgery. Body mass index was 23.4±4.0 kg/m^2. Time from surgery to post-operative follow-up was 11.2±8.8 months.

Comparison of pre- and post-operative nasal function

Significant improvements were observed in nasal function scores for the total population when pre- and post-operative measures were compared (Table 10). NAR Total decreased post-operatively (0.440±0.253 Pa/cm^3/s vs 0.382±0.346 Pa/cm^3/s, $p<0.001$), as did NAR on obstructed side (1.282±1.210 Pa/cm^3/s vs 0.907±1.070 Pa/cm^3/s, $p=0.001$). Improvements post-surgery were observed in NOSE (59.0±26.2 vs 34.2±28.0, $p<0.001$), SNOT22 (36.2±19.0 vs 21.2±17.6, $p<0.001$) and VAS (48.2±25.2 vs 31.2±25.9, $p<0.001$). Higher number of patients reported their Nasal Obstruction as a *'mild problem'* or better (34.5% vs 73.4%, $p<0.001$), or Overall Nasal Function as *'fair'* or better (26.2% vs 81.0%, $p=0.001$).

Correlations between patient reported measures and nasal airflow

ΔSNOT22 score only correlated with ΔNAR Total ($r= 0.246$, $p<0.001$) (Table 11). There were weak correlations observed between the ΔVAS and total ΔNAR ($r=0.216$, $p<0.001$), ΔNAR Obstructed ($r=0.292$, $p<0.001$) and ΔNAR less obstructed side ($r=0.242$, $p=0.003$) (Table 11).

ΔOverall nasal function and ΔNasal obstruction score showed higher degree of correlation with ΔNAR Total (r=-0.329, p<0.001; r=0.326, p<0.001 respectively) and ΔNAR Obstructed (r=-0.342, p<0.001; r=0.421, p<0.001 respectively). NOSE scores demonstrated no correlations with ΔNAR.

Minimal Clinically important difference in NAR

Distribution based method

For NAR Total, the half standard deviation of the baseline was 0.127 Pa/cm3/s and standard error of measurement was 0.103 Pa/cm3/s. For unilateral NAR, the half standard deviation was 0.509 Pa/cm3/s and, standard error of measurement was 0.449 Pa/cm3/s.

Anchor based method

ΔNAR was assessed according to achievement of 1-point categorical ordinal scale improvement in overall nasal function and nasal obstruction score. On overall nasal function, 1 categorical improved NAR Total by 0.093±0.307 Pa/cm3/s and NAR Obstructed by 0.180±0.397 Pa/cm3/s. For nasal obstruction score, 1 categorical scale improved NAR Total by 0.091±0.290 Pa/cm3/s and NAR Obstructed by 0.221±0.684 Pa/cm3/s.

Continuous measures

PROMs which showed linear correlated with NAR were used to estimate MCID. For NAR Total, the Beta coefficient indicated a MCID of 0.154 Pa/cm3/s on SNOT-22, 0.132 Pa/cm3/s on VAS (9 mm) and 0.138 Pa/cm3/s on VAS (13mm), and for NAR Obstructed, data showed 0.669 Pa/cm3/s on VAS (9mm) and 0.742 Pa/cm3/s on VAS (13mm). (Table 12)

Recommended MCID

All MCID values from three methods were shown in table 13. The recommended MCID of total NAR is 0.1 Pa/cm^3/s ranging from 0.091 to 0.154 Pa/cm^3/s and of obstructed NAR is 0.2 Pa/cm^3/s ranging from 0.180 to 0.742 Pa/cm^3/s.

3.4 Discussion

Nasal airway resistance is affected by thermo-vascular changes in nasal mucosal and anatomical obstruction.[279-281] Rhinomanometry is a useful tool that enables the evaluation of nasal airway resistance based on airflow and pressure, and thus is recommended for use in investigations of candidacy for nasal surgery and interventional outcomes.[5,17] However, difficulties in the interpretation of rhinomanometry values exist, due to variability in correlation with patient reported symptom scores and lack of well-established MCID values. This study found a correlation between NAR and overall patient reported nasal function and nasal obstruction scores, and proposed MCID values of 0.1 Pa/cm^3/s for total NAR and 0.2 Pa/cm^3/s for obstructed NAR following surgical intervention.

A unique feature of this investigation was the assessment of both functional and subjective parameters before and after surgery, and analysis of correlations pertaining to the overall changes in these values. This is clinically relevant, as it provides a comprehensive assessment of patient satisfaction with their nasal function post-intervention, using a range of outcome measures. There has been conflicting evidence regarding the validity of commonly used patient symptom reporting tools and nasal functional assessment techniques.

NOSE score demonstrated no correlation with ΔNAR assessed either bilaterally, or unilaterally in line with the previous study.[282] Also, the correlation between SNOT-22 and

minimal cross-sectional area (MCA) measured by acoustic rhinometry was not shown in previous study.[283] However, in the presented study, a correlation between SNOT-22 and ΔNAR Total but not unilateral ΔNAR was observed.

Outcomes focused on nasal obstruction severity were rated by VAS score, Nasal obstruction, and Overall nasal function scores. This study demonstrated significant correlation between ΔNAR and ΔVAS in line with previous reports in patients with acute viral rhinitis, following histamine challenge, or before and after the application of a topical decongestant.[284-286] However, conflicting evidences has also been observed between MCA or NAR and VAS pre- or post- septoplasty, during the nasal cycle, or during routine clinic attendance.[287-289] The ΔNasal obstruction and ΔOverall nasal function scores demonstrated superior correlations with ΔNAR compared with other outcomes, resulting in improved correlation coefficients with ΔNAR for total and obstructed measures. Thus, the outcome tool selection is likely to be an important factor when assessing improvements in nasal obstruction, and validated tools such as NOSE and SNOT-22 may not be the most appropriate to use alongside rhinomanometric assessment for evaluation of nasal obstruction. These tools may poorly reflect the degree of nasal obstruction due to the incorporation of additional quality of life aspects.

Furthermore, a recurring observed theme was the stronger relationship between ΔNAR and subjective outcome measures on the side of greater nasal obstruction. Notably, previous studies supported the assessment of NAR unilaterally, demonstrating stronger correlations with patient VAS scores.[93,94,290]

In defining MCID of NAR, an MCID of 0.1 Pa/cm^3/s for total NAR and the MCID of 0.2 Pa/cm^3/s for obstructed NAR is suggested to serve as a threshold to aid clinicians in the interpretation of successful nasal surgical outcomes in nasal obstruction patients.

Correlation between subjective nasal breathing measures and NAR only shows the association between nasal perception of breathing and structural patency. Other factors involved in nasal perception need to be addressed. Nasal thermo-sensing through trigeminal nerve cooling receptor, and its control centre in the cerebral cortex and limbic system, have proposed to play roles when determining subjective nasal perception. Trigeminal sensory dysfunction and psychogenic comorbidities could modify the correlation between patient reported and functional nasal airway measurement. Thus, the practical application of NAR MCID is recommended when there is consistency between subjective and objective outcomes, without the effect of other nasal perception modifiers.

3.5 Conclusion

The relationship between rhinomanometry measurements and patient derived outcomes is likely to be influenced by a range of factors, including the tools used for subjective measure assessment. Overall nasal function and Nasal obstruction scores may be more useful in representing subjective nasal obstruction than validated NOSE or SNOT22 questionnaires. Use of these parameters demonstrated an MCID of 0.1 Pa/cm^3/s for total NAR and 0.2 Pa/cm^3/s for obstructed NAR following surgical intervention and these may serve as a useful threshold for investigators assessing rhinomanometry outcomes post-surgery.

Table 10. Comparison of nasal function pre- and post-surgery.

Outcome measure	Pre-operative	Post-operative	p-value
Total nasal airway resistance	0.440±0.253 Pa/cm^3/s	0.382±0.346 Pa/cm^3/s	p<0.001
Obstructed nasal airway resistance	1.282±1.210 Pa/cm^3/s	0.907±1.070 Pa/cm^3/s	p=0.01
NOSE (0-100)	59.0±26.2	34.2±28.0	p<0.001
SNOT-22 (0-110)	36.2±19.0	21.2±17.6	p<0.001
VAS	48.2±25.2 mm	31.2±25.9 mm	p<0.001
Nasal obstruction score (%≤ mild)	34.5%	73.4%	p<0.001
Overall Nasal Function (% fair or better)	26.2%	81.0%	p=0.001

Abbreviations: NOSE, Nasal Obstruction Symptom Evaluation; SNOT2, Sinonasal Outcome Test 22; VAS, Visual Analogue Scale assessing nasal obstruction

Table 11. Assessment of the correlations between change in nasal airway resistance and patient reported outcome measures

Outcome measure (Δ)	**Total nasal airway resistance (Δ)**	**Obstructed nasal airway resistance (Δ)**	**Less obstructed nasal airway resistance (Δ)**
NOSE (0-100)	r= 0.107 p= 0.069	r= 0.072 p= 0.380	r= 0.075 p= 0.390
SNOT-22 (0-110)	r= 0.246 p<0.001	r= 0.204 p= 0.061	r = 0.186 p= 0.100
VAS (0-100)	r= 0.216 p<0.001	r= 0.292 p<0.001	r= 0.242 p= 0.003
Overall nasal function (terrible to excellent – 13 ordinal score)	r =-0.329 p<0.001	r =-0.342 p<0.001	r =-0.236 p= 0.003
Nasal obstruction score (no problem to as bad as it can be – 6 ordinal score)	r=0.326 p<0.001	r=0.421 p<0.001	r=0.177 p= 0.072

Abbreviations: NOSE, Nasal Obstruction Symptom Evaluation; SNOT-22, Sinonasal Outcome Test 22; VAS, Visual Analogue Scale assessing nasal obstruction

Table 12. Minimal Clinically Important Difference in nasal airway resistance calculated with continuous measures

Outcome measure	Threshold	Total nasal airway resistance ($Pa/cm^3/s$)		Obstructed nasal airway resistance ($Pa/cm^3/s$)	
		MCID (95% CI)	**P value**	**MCID (95% CI)**	**P value**
NOSE	Δ8.5*	-0.056 (-0.16, 0.049)	p= 0.294	-0.159 (-0.479, 0.224)	p= 0.575
SNOT-22	Δ8.9*	-0.154 (-0.277, -0.031)	p= 0.014	-0.719 (-1.471, 0.033)	p= 0.061
VAS	Δ9mm†	-0.132 (-0.213, -0.052)	p= 0.001	-0.669 (-1.116, -0.221)	p= 0.004
VAS	Δ13mm‡	-0.138 (-0.221, -0.055)	p= 0.001	-0.742 (-1.190, -0.294)	p= 0.001

Abbreviations: MCID, Minimal Clinically Important Difference; NOSE, Nasal Obstruction Symptom Evaluation; SNOT22, Sinonasal Outcome Test 22; VAS, Visual Analogue Scale assessing nasal obstruction. * threshold determined by reference value; † threshold determined by half of standard deviation of pre-operative data; ‡ threshold determined by 1-categorical improvement in overall nasal function

Table 13. Summary of Minimal Clinically Important Difference in nasal airway resistance

Outcome measure/Technique	**MCID Total NAR (Pa/cm³/s)**	**MCID Obstructed NAR (Pa/cm³/s)**
Distribution-based method (0.5 SD)	0.127	0.535
Distribution-base method (SEM)	0.103	0.441
Overall nasal function/ Anchor-based method (Δ one category)	0.093	0.180
Nasal obstruction score/ Anchor-based method (Δ one category)	0.091	0.221
NOSE/Anchor-base method (Threshold Δ8.5*)	n/a	n/a
SNOT-22 / Anchor-base method (Threshold Δ8.9*)	0.154	n/a
VAS/ Anchor-base method (Threshold Δ9mm†)	0.132	0.669
VAS/ Anchor-base method (Threshold Δ13mm‡)	0.138	0.742
Recommended MCID	0.1 (0.091-0.154)	0.2 (0.180-0.742)

Abbreviations: NAR, nasal airway resistance; MCID, Minimal Clinically Important Difference; NOSE, Nasal Obstruction Symptom Evaluation; SNOT22, Sinonasal Outcome Test 22; VAS, Visual Analogue Scale assessing nasal obstruction; SD, Standard Deviation; SEM, Standard Error of Measurement; * threshold determined by reference value[90,97]; † threshold determined by half of standard deviation of pre-operative data; ‡ threshold determined by 1-categorical improvement in overall nasal function

Chapter 4. Patient factors associated with empty nose syndrome and poor surgical outcome

4.1 Introduction

Nasal obstruction is a condition in which the body perceives a sensation of insufficient airflow. It is one of the most common complaints in rhinological practice, estimated to be affecting at least 30% of the general population.[4] The burden of cost of nasal obstruction is significant. Approximately $5 billion were spent annually for symptomatic relief and another $60 million on surgical procedures to address anatomic causes of obstruction in the US in the 1990s.[11]

Two common etiologies include anatomical obstruction and sinonasal inflammation. Initial treatment is usually medical therapy. In more severe cases when medical therapy fails, surgical reduction of the inferior turbinate is performed.

Historically, physicians have relied on methods of measuring nasal airflow, such as rhinomanometry and acoustic rhinometry, as objective tools to evaluate nasal patency and guide surgical planning. However, current evidence suggests that the primary mechanism of nasal airflow sensation is not airflow resistance, but rather mucosal cooling by inspired air.[29,64] Transient receptor potential melanostatin 8 (TRPM8) in nasal mucosa activates the cool signal when high-speed air induces water evaporation from the epithelial lining fluid. This activation causes depolarization of neurons that connect to the brainstem respiratory center and being interpreted as patent nostrils.[31,59] The cooling system has been demonstrated to have more significant clinical correlation than nasal resistance and cross-sectional area.[30,33]

This new paradigm explains the observed poor correlations between subjective sensation of nasal airflow and objective measurements[52,53], despite turbinate surgery generally achieving a successful surgical outcome in decreasing nasal airway resistance.[51] This discrepancy might also explain the report of apparent surgical failure rates being as high as 28% to 33%.[54-56] In this surgical failure group, there are patients receiving suboptimal

surgery (surgeon factor), patient with uncontrolled rhinitis or rhinosinusitis and structural obstruction (disease factor) and on the other end, patient with unsettling cause of poor nasal breathing perception mainly psychogenic disorder and 'empty nose syndrome' (patient factor). Empty nose syndrome (ENS) was first described in 1994 by Stenrkvist and Kern as paradoxical persistence of nasal obstruction sensation with an 'empty nasal space' in patients who have already received interventions for nasal obstruction, such as turbinate surgery. The classic presentation of ENS is a patient who has had surgery to relieve nasal obstructive symptoms and whose symptoms deteriorate, despite achieving the desired anatomical outcome. Patients suffering from ENS, generally have an unremarkable examination, apart from prior evidence of surgery.[219,291] ENS carries a significant burden on health-related quality of life and psychogenic function.

The actual cause of ENS is controversial, as there are several constructs with the recurring inconsistency between subjective and objective outcomes. Patients are often led to believe that the surgery is the cause. More discussions can be found in the ENS pathophysiology section (Chapter 2). Evidence showed a strong relation between ENS and psychogenic conditions such as hyperventilation syndrome, anxiety and somatic symptom disorder.[250,292] Functional brain imaging suggests that ENS may share some psychophysiological mechanisms, including increased limbic reactivity, which is the emotional control area.[241] Modulation of nasal perception by psychogenic factor is likely the primary pathogenesis of ENS. Whether surgical interventions contribute to the cause of ENS is unclear. Current evidence seems to suggest that ENS is mainly caused by the pre-existing alteration in nasal perception by the psychogenic condition. These patients would not be suitable candidates for turbinate surgery at the beginning and undergoing turbinate surgery worsen their symptoms due to their over expectation of benefit.

Currently, there is no accurate approach for nasal obstruction evaluation. A reliable tool is needed to measure the subjective perception (patient factor) and guide for surgical candidate selection to avoid surgery on patients at risk of poor surgical outcome. Therefore, the objective of this study was to identify distinctive clinical characteristics between patients with ENS and poor surgical outcomes compared to those with successful turbinate surgery.

4.2 Methods

Study design

An online questionnaire survey on post turbinate surgery patients was conducted. All participants filled out the online questionnaire to define the population group and compare characteristics among groups. This study had ethical approval from Macquarie University and St Vincent's Hospital Human Research Ethics Committee (2019/ETH13672). The online questionnaire contains a consent statement and completion of the questionnaire will imply consent for research data collection. The survey's webpage link was distributed to the participant through social media/ social forum, public announcement, and post-operative clinic.

Study population

Adult (Age ≥ 18 years old) patients who had previous nasal surgery primarily performed for inferior turbinate reduction surgery more than three months were recruited. Turbinate surgery is defined as any turbinate resection or turbinate volume reduction involving either unilateral or bilateral inferior turbinate. Patients who were unable to provide informed consent or complete the questionnaire because of age, mental illness, dementia, communication difficulties or other reasons were excluded.

Outcome measures

Patient reported outcome measures were selected based on existing validated tools. The selected tools could measure subjective nasal breathing perception on every aspect involved in the nasal breathing pathway including sinonasal inflammation, anatomical obstruction, and psychogenic modulation of nasal perception (Chapter 2). The outcome measures are divided into five categories: patient definition, demographics, sinonasal function, nasal pathophysiology, and psychogenic function. The final questionnaire was created by mixing multiple previously validated questionnaires to create a comprehensive one containing a total 115 Items (Appendix 1).

1. Patient Definition

Since there is no gold standard diagnostic tool for ENS, the satisfaction of surgery and ENS specific questionnaire are used to diagnose ENS. Patient sample is then divided into

three groups based on outcome experienced: ENS, low benefit, and high benefit. Satisfaction measurements include the overall satisfaction scale (Likert scale) ranges from -6(terrible) to +6(excellent) and the Glasgow Benefit Inventory (GBI).

The Glasgow Benefit Inventory (GBI) is a validated, generic patient-recorded outcome measure that was invented by Robinson et al. in 1996. Widely used in otolaryngology, it is designed to measure a change in health-related quality of life after a specific surgical or medical treatment.

The questionnaire consists of 18 questions answered using a five-point Likert scale. The responses are then scaled and averaged to give a score ranging from −100 (poorest outcome) through 0 (no change) to +100 (best outcome).[293] The Glasgow Benefit Inventory is subdivided into three distinct subscales consist of 'general', 'social' and 'physical' subscales. Twelve questions focused on general changes in health status, including psychosocial health status. Three questions were related to the amount of social support needed. The remaining three questions addressed changes in physical health status including medications requirement and number of visits to doctors required.

The ENS-specific questionnaire of Empty nose syndrome 6 questionnaires (ENS6Q)[227] is a validated questionnaire consisting of 6 questions evaluating ENS-specific symptoms. Four of the questions were derived from the Sinonasal outcome test 25 (SNOT-25) which are 'dryness,' 'suffocation,' 'nose feels too open,' and 'nasal crusting'. SNOT-25 is an extended version of SNOT-22 with added of ENS-specific symptoms.[294] The next question is regarding the perception of nasal breathing in which the questionnaire developer specified the 'sense of diminished airflow' (cannot feel air flowing through your nose). Lastly, 'nasal burning' was added according to common symptoms experienced by this group of patients. A score of 10.5 is used as the cut-off value to identify ENS.

<u>Criteria defining patient population</u>

Post turbinate surgery patients will be separated into

ENS or Poor outcome group:

1. Negative score on the Glasgow Benefit Inventory
2. Negative score on overall nasal function
3. Score of ≥10.5 on ENS6Q

High benefit group:

1. Positive score on Glasgow Benefit Inventory
2. Positive score on overall nasal function
3. Score of <10.5 on ENS6Q

And the group of patients who have mixed results on these three criteria are categorized as having 'Low benefit' from the surgery. This group may include patients with suboptimal surgical results, nasal valve compromise and ongoing underlying sinonasal inflammation.

2.Demographics

Demographic data collected include age, type of surgery, duration after surgery, ancestry, smoking status, asthma, self-diagnosed on the cause of nasal obstruction (snoring, sinusitis, allergy [inhalant/eye/skin], post trauma, not otherwise specified). Gastro-esophageal reflux (GERD) symptoms were included, as GERD is one factor that can potentially increase nasal resistance and results in nasal congestion.[206,295-297] There is also an association between GERD and allergic rhinitis and sinusitis.[298,299] Additionally, the anti-reflux treatment was shown to improve the obstructive symptoms.[206,297,300] GERD was assessed using the validated Reflux Symptom Index questionnaire.[301]

3.Sinonasal function

Sinonasal outcome test 22 (SNOT-22) and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) were selected to evaluate symptom-specific severity and overall health-related quality of life caused by inflammatory process and anatomical obstruction.

SNOT22 is a 22-item, validated tool that is widely used among clinicians and researchers in assessing health related quality of life and symptom severity in chronic rhinosinusitis.[97] It was initially developed from the Rhinosinusitis Outcome Measure (RSOM-31)[102] and was reduced to SNOT-20, then modified into SNOT-22 in 2009. It has been validated in multiple languages.[104-108] SNOT-22 evaluates major and minor CRS symptom severity via four subscales including nasal symptoms, sleep dysfunction, emotional / psychological dysfunction and aural/ facial symptoms.[110,111] Patients score each of the 22 items on the six-points Likert scale, or 0 to 5, ending with a total score range of 0-110.

Overall symptoms can be interpreted from SNOT-22 score as being 'mild' (8-20), 'moderate' (>20-50), or 'severe' (>50).[112]

A systematic review of patient-reported outcome measures (PROM) used in chronic rhinosinusitis assessed the quality of each validated tools using COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN)[302] and SNOT-22 was rated as the highest quality PROM among 15 validated PROMs.[110] Additionally, it is the recommended instrument used by the majority of the EPOS2020 steering group for specific rhinologic health-related quality of life evaluation in CRS.[87]

Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) is the most common PROM used in allergic rhinitis throughout clinical studies and clinical practice.[98] It is a comprehensive survey that asks the patient to reflect disease-specific quality of life and symptom severity based on the past week. This questionnaire contains 28 items in seven domains. Four items are related to nose symptoms, four to eye symptoms, three to practical problems, three to sleep impairment, seven to non-hay-fever symptoms, three to activity limitations and four to emotional. Each item was scored on a seven-point Likert scale. The overall quality of life is presented as the mean of these seven domains.[96] RQLQ results were well correlated with symptom severity score.[303] RQLQ has been extensively validated and translated into 16 languages.[98] Due to the overlapping domain of RQLQ with other questionnaires, only nose symptoms, eye symptoms, practical problem and activity limitation domain were included in our questionnaire.

4.Nasal pathophysiology

Nasal pathophysiologic responses could assist in the diagnosis of mucosal pathology and anatomical obstruction. The three typical pathophysiologic responses of nasal turbinate to look for are called 'Ray's rule'.

The *first rule* is the response to nasal decongestant. Vasoconstrictive property of topical nasal decongestant improves nasal congestion by reducing the volume of soft tissue swelling of the inferior turbinate. Oxymetazoline is the commonly used decongestant; it is an α1 receptor agonist and a partial α2 receptor agonist. When oxymetazoline binds the alpha receptors on the inferior turbinate vasculature, vasoconstriction occurs, the turbinate decongests, and nasal resistance decreases.[304,305] The effect of nasal decongestion is also

found in normal healthy, but it is more pronounced in patients with turbinate hypertrophy. It is used to predict the therapeutic response from medical or surgical intervention. The *second rule* is the nasal cycle or perception of switch side nasal obstruction. The nasal cycle refers to the asymmetrical, spontaneous changes in congestion or vasodilation and decongestion or vasoconstriction of venous sinusoid and capacitance vessel of nasal mucosal. As one side of the inferior turbinate becomes more congested with a blood-filled venous sinusoid, nasal resistance increases. Simultaneously, the other side of inferior turbinate decongests, airflow increases through the nasal cavity. An estimation of at least 80% of the population reported this perception of switch side nasal obstruction. The nasal cycle lasts between 50 minutes and 4 hours before alternating congestion and decongestion occur.[306] The *third rule* is postural congestion. The effect of posture on nasal airway resistance has been demonstrated in healthy participants.[127,307] The change in venous hydrostatic pressure of venous sinusoid of turbinate tissue results in different nasal breathing perception related to gravity. The increase in hydrostatic venous pressure when changing posture from sitting to supine causes subsequent nasal congestion. Again, the effect of this phenomenon is more prominent in patient with turbinate hypertrophy or anatomical problem.[308] The nasal response following 'Ray's rule' potentially indicates real sinonasal mucosal pathology or anatomical obstruction without other nasal perception modifiers. Therefore, we hypothesize that the high benefit group would show a higher response to 'Ray's rule'.

5.Psychogenic function

The psychogenic component has been shown to be a factor in modulating nasal breathing perception at higher respiratory central control. (Chapter 2) Depression, anxiety and somatic symptom disorder (SSD) are the most common psychogenic disorders in primary care and many medical specialties.[309-313] The overlapping of mental disorders are common; most patients diagnosed with one condition also have one or both of the other two conditions[312,314,315]

In a rhinology practice, Alam et al. investigated the incidence of psychological disorders and demonstrated 9%, 14%, and 21% moderate-to-severe anxiety, depressive, and SSD, respectively. Out of all the rhinology presenting symptoms, nasal obstruction/congestion is the most highly associated with these three most common

psychogenic disorders.[316] In addition to assessing these three disorders, hyperventilation was also included in the questionnaire, as emotional control may involve in its pathophysiology similar to ENS and it is highly associated with psychogenic disorders.

The 7-item General Anxiety Disorder scale (GAD-7) is principally a measure of anxiety severity, developed and validated in 2006.[317] It demonstrated good correlations with other anxiety scales and general health-related quality of life score. Each item scored in three Likert scales, total GAD-7 scores can range from 0 to 21, with 5, 10 and 15 represent mild, moderate and severe levels of anxiety symptoms[317,318] A cut point of ≥10 is considered clinically significant and provides high sensitivity and specificity. GAD-7 has been widely used in many research studies.[319-322]

The 9-item Patient Health Questionnaire (PHQ-9) is used as a diagnostic and severity measurement tool for major depressive disorder (MDD). The scores range from 0 to 27 and cut points of 5, 10, 15 and 20 represent mild, moderate, moderately severe and severe levels of depressive symptoms, respectively. Similar to all three common psychogenic disorders, a threshold of ≥10 is considered clinically significant. The PHQ-9 has been largely utilized in clinical studies across many medical specialties and discipline.[316,319,323-329]

The current criteria for Somatic Symptom Disorder (SSD) in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) require the presence of somatic symptoms (criterion A), excessive thoughts, feelings or behaviors related to these symptoms (criterion B), and presence of these symptoms for>6 months.[268] Regarding Criterion A, 40 questionnaires were identified to quantify the presence of somatic symptoms.[330] The 15-item Patient Health Questionnaire (PHQ-15)[331] is considered one of the most useful tools in epidemiological studies. The PHQ-15 includes 15 symptoms that account for more than 90% of symptoms seen in primary care (exclusive of upper respiratory symptoms such as cough, nasal symptoms, sore throat, otalgia). The PHQ-15 asks patients to rate how much they have been bothered by each symptom during the past month on a 0 (“not at all”) to 2 (“bothered a lot”) scale. The total score ranges from 0 to 30, with cut points of 5, 10 and 15 representing thresholds for mild, moderate and severe somatic symptom severity, respectively. A score ≥10 is recommended clinically significant cut point. PHQ-15 has been widely used in clinical and research settings.[313,314,332-334]

Criterion B explores the impact of SSD on general wellbeing such as excessive cognitive, affective and behavioral aspects associated with somatic symptoms.[335,336] Toussaint et al. recently developed 12-item Somatic Symptom Disorder – B Criteria Scale (SSD-12) with promising psychometric and validity characteristics. [337] It was developed as a direct measure of the new B criteria of SSD according to DSM-V. The scale is composed of 12 items, divided into three psychological subscales: cognitive, affective and behavioral aspects. Each subscale contains four items with all item scores ranging between 0 and 4. SSD-12 has excellent validity, reliability and It was shown to correlate with the 15-item Patient Health Questionnaire,[331] the 7-item Generalized Anxiety Disorder Scale[338] and the 9-item Patient Health Questionnaire.[339] The SSD-12 score of ≥23 is suggested in combination with PHQ-15 to identify somatic symptom disorder.[340]

Hyperventilation syndrome (HVS) is the most well recognized form of dysfunctional breathing.[341] First described in 1938[77], HVS is defined as the condition of increased minute ventilation or hyperventilation exceeding metabolic requirements from hypocapnia and respiratory alkalosis.[75] Symptoms include palpitations, chest pain, breathlessness, chest tightness, tingling of the lips and fingers, tetany, paresthesia, light-headedness, and dizziness. HVS is significantly related to sinonasal disease[342] and nasal obstruction is considered one of the HVS symptoms as a high number of patients (25-85%) with nasal obstruction complaint were diagnosed with HVS.[343,344] The pathogenesis of hyperventilation syndrome is unclear.[80] However, it is believed that an emotional/behavioral pathway are involved, explaining the connection with psychogenic disorders, such as depression, anxiety disorders, and panic disorder[75,86] The most common method to aid clinical diagnosis of dysfunctional breathing relies on a positive Nijmegen questionnaire. A group in the Netherlands developed this questionnaire. It consists of a list of 16 symptoms ranked on a 5 Likert scale according to frequency. Of the 16 questions, three domains were identified, seven related to respiratory symptoms, four to excessive ventilation and five to central nervous system symptoms. [345] A score of >23 is considered significant for HVS diagnosis. It was shown to have a sensitivity of 91% and specificity of 95%.[345]

Statistical analysis

All statistics and graphic representations were generated using SPSS version 24 (IBM Corp., Armonk, NY). The clinical characteristics between groups were compared using chi square analysis for binary outcome and 1-way analysis of variance (ANOVA) test for continuous variable. A p-value of < 0.05 was defined as statistically significant. The outcome measurements which demonstrated significant differences among the three comparisons were then analyzed with post hoc Bonferroni test.

4.3 Results

A total of 97 patients were recruited (42.8±13.8 years old, 55.7% female). The population definition identified n=15 (15.5%) ENS or poor surgical outcome group, n=12 (12.4%) low benefit group and n=70 (72.2%) high benefit group. The satisfaction assessing tools were compared (Table 14) and a model showing the separation of three defining group was illustrated. (Figure 9)

Demographics

The characteristic differences between three groups were presented in Table 15. Comparing between ENS or poor surgical outcome, low benefit and high benefit groups, patients with ENS were more likely to be self-diagnosed with sinusitis (80.0% vs 50.0% vs 30.4%, p=0.001) and report higher reflux score (19.6±13.0 vs 4.7±4.6 vs 4.5±6.5, p<0.001). There were no differences in age, gender, smoking, and other self-diagnosed sinonasal conditions between groups. ENS reported a longer duration after turbinate surgery (11.9±12.9 vs 3.8±2.2 vs 3.2±3.1 years, p<0.001). Difference in duration after surgery was expected as most of ENS participants were recruited from social platform announcements while the other groups were from the post-operative clinic.

Sinonasal function

SNOT-22 and all RQLQ domains scores were significantly different across the three groups. (RQLQ: Practical problem 10.3±4.4 vs 4.5±4.8 vs 3.0±3.6, p<0.001; Nasal symptoms 8.3±7.0 vs 6.8±5.9 vs 3.2±3.6, p <0.001; Ocular symptoms 8.7±9.4 vs 5.9±7.1 vs 1.9±3.5, p<0.001; Activities 13.1±4.5 vs 9.1±4.4 vs 2.2±3.8, p<0.001; SNOT-22 63.2±15.9 vs 29.2±6.6 vs 12.6±13.9, p<0.001) (Table 16). On post-hoc analysis, ENS reported higher scores than the high benefit group in all RQLQ domains and SNOT-22. RQLQ practical problem and SNOT-22 were reported higher in ENS than low benefit group. Low benefit group reported higher score than high benefit group on nasal symptom, activities and SNOT-22. This highlighted the possible ongoing or uncontrolled sinonasal disease in this low benefit group.

Turbinate pathophysiology

On turbinate pathophysiology, ENS demonstrated lower response to nasal decongestant compared with high benefit but no different to low benefit group. (33.3% vs 54.5% vs 76.9%, p=0.007; ENS vs High benefit, p=0.02; ENS vs low benefit, p=0.305) Surprisingly, nasal cycle and postural congestion were not different among three comparisons. (Presence of nasal cycling 66.7% vs 45.5% vs 34.4%, p=0.104; postural congestion 46.7% vs 33.3% vs 29.0%, p=0.413) (Table 17)

Psychogenic function

Psychogenic function was significantly associated with poor surgical outcome. ENS reported higher scores compared with low benefit and high benefit groups on all evaluated questionnaires: Nijmegen questionnaire (29.4±14.0 vs 10.6±8.9 vs 5.4±9.1, p <0.001), GAD-7

(12.1±5.5 vs 5.1±4.3 vs 2.2±3.7, p <0.001), PHQ-9 (17.3±6.2 vs 6.4±4.8 vs 2.0±2.7, p<0.001), PHQ-12(12.3±6.4 vs 5.1±2.5 vs 3.9±4.5, p<0.001), and SSD-12(33.3±10.9 vs 19.5±9.8 vs 5.7±7.1, p<0.001) (Table 18). Additionally, all the mean values demonstrated in ENS group reached the clinically significant level in each psychogenic questionnaire assessed. Low benefit group also reported higher scores than high benefit group on PHQ-9 (p<0.001) and SSD-12 (p= 0.001) questionnaire. However, the reported score did not meet the clinically significant cut-off value in the low benefit group.

4.4 Discussion

Turbinate surgery is the preferred surgical management in patients with turbinate hypertrophy often presented in sinonasal inflammatory disease. It is considered an adjunctive approach with medical treatment when medical treatment alone fails to control nasal obstructive symptoms. The success of this combination approach is the goal for patient and ENT surgeon. It is acknowledged that despite anatomically successful surgery, the failure rate of turbinate reduction can be as high as 33%.[54,55] This discordance between subjective and objective measurement shows that the current evaluation during surgical planning and patient selection is inaccurate.[52] The best approach to avoid having poor surgical outcome is to identify unsuitable candidates before the surgery is performed. This study compared the characteristics of patent who report successful surgical outcome to those reported disastrous outcome.

ENS group demonstrated higher score on psychological symptoms, sinonasal symptoms and reflux symptoms than low benefit and high benefit groups. Psychogenic related conditions, including HVS, anxiety, depression, and somatic symptom disorder, were significantly more reported in ENS group as expected. The high incidence report of psychogenic events in rhinology practice and previous ENS studies support the finding.[221,250,316] Previous studies on ENS showed a strong correlation with anxiety, depression and HVS. The diagnosis of SSD in ENS has also been reported anecdotally; many ENS patients fulfill the criteria for somatic symptom disorder.[267]

Poor mental health status has been linked to poor nasal perception[269],and both conditions are not related to the nasal airspace measured on CT scan.[222,243]. A f-MRI study demonstrated the deactivation of emotional processing areas upon successful pseudo-decongestant stimulatory effects of menthol in ENS patients.[241] This shows a probable connection between emotional control and nasal perception. Therefore, the modulation of psychogenic component on subjective nasal perception could be the potential cause of ENS and described the contrast between patient-reported outcome and nasal airway resistance.

Nasal symptom severity was higher in ENS group than the low benefit and high benefit groups. Considering 'empty nasal space' described in ENS, this phenomenon resembles the 'out of proportion' symptom severity reported in many disorders which are thought to have a strong psychogenic etiology, especially when symptoms are paradoxical to the observed examination, for example, tinnitus, irritable bowel syndrome, fibromyalgia, somatic symptom disorder and body dysmorphic disorder. This finding is in line with previous studies in which ENS patients reported higher symptom severity compared to that experienced in other sinonasal diseases including rhinitis, rhinosinusitis and structural obstruction.[226]

80% of ENS group self-identified themselves as 'sinusitis' sufferers. The complaint of 'sinusitis' is widespread in rhinology practice, especially for unexplained sinonasal symptoms by the fact that sinusitis symptoms overlap with other common conditions. For this reason, the diagnosis of CRS is often inaccurate, particularly with self-diagnosis. Even with CRS diagnosed by non-otolaryngologist, real CRS was identified in only less than 1%.[346]

The ENS group also scored high on reflux symptom index. This is in accordance with previous studies which suggests the relation between gastroesophageal reflux and nasal obstructive symptom. Additionally, the correlation of reflux symptoms with anxiety and depression were reported, possibly explaining the presence of nasal obstruction in reflux disease. Thus, reflux symptoms may be one of the predictive symptoms of poor surgical outcome.[347]

On nasal pathophysiology, greater response to nasal decongestant is demonstrated in high benefit group compared to the ENS group. Surprisingly, the presence of nasal cycling and postural congestion failed to show any differences among groups and even showed

slightly greater response in ENS group, though not statistically significant. A possible explanation for this unexpected finding is the coexistence of nasal inflammatory condition in the ENS group. It is often overlooked that almost all ENS patients initially presented with nasal obstruction, possibly mild inflammatory disease, which led them to the surgery. Despite the minimal disease, response to nasal pathophysiology was shown in ENS.

Poor psychogenic function, out of proportion subjective complaints discordance to objective measure, and reflux symptoms are red flags of patients at risk of poor surgical outcome. Avoidance should be implemented in this group of patients. Furthermore, the development of new reliable screening tools would be highly beneficial.

4.5 Conclusion

Poor psychogenic function, disproportionate subjective nasal complaint and reflux symptoms are clinical characteristics of poor surgical outcome from turbinate surgery. These warning signs may be used as a guide in identifying patient at risk of poor surgical outcome. A surgical decision should be cautiously made upon the presence of any of these clinical features.

Table 14. Comparison of satisfaction criteria and Empty nose syndrome specific questionnaire (ENS6Q)

	ENS	Low benefit	High benefit	p-value
n	15	12	70	
GBI (-100 - +100)	-39.1±22.3*†	-4.4±12.9†‡	24.6±13.6*‡	<0.001
Overall nasal function score (% < "poor")	100%*†	10%†‡	0%*‡	<0.001
ENS6Q (0-30)	17.2±4.7*†	5.0±3.7†	1.7±4.0*	<0.001

Abbreviations: GBI, Glasgow Benefit Inventory; ENS6Q, Empty Nose Syndrome 6-item Questionnaire

Table 15. Demographics comparison of ENS, Low benefit and High benefit group

	ENS	Low benefit	High benefit	p-value
n	15	12	70	
Age (yrs)	50.±13.1	46.8±16.5	40.9±13.2	0.075
Gender (%F)	60.0	50.0	55.1	0.873
Asthma (%)	33.3	16.7	13.0	0.161
Reflux (RSI 0-45)	19.6±13.0*†	4.7±4.6†	4.5±6.5*	<0.001
Smoking (%)	13.3	0	7.8	0.416
Self-reported diagnosis (%)				
Allergic rhinitis	66.7	58.3	50.7	0.507
Sinusitis	80.0*	50.0	30.4*	0.001
Sleep apnea	26.7	16.7	11.6	0.317
Nasal obstruction post trauma	13.3	0	7.2	0.416
Nasal obstruction NOS	60.0	25.0	55.1	0.126
Duration post turbinate surgery (yrs)	11.9±12.9*†	3.8±2.2†	3.2±3.1*	<0.001

Abbreviations: ENS, Empty Nose Syndrome; RSI, Reflux Symptom Index; NOS, not otherwise specified

* p value<0.05 on sub-analysis between ENS and high benefit

† p value<0.05 on sub-analysis between ENS and low benefit

‡ p value<0.05 on sub-analysis between low benefit and high benefit

Table 16. Sino-nasal function comparison of ENS, Low benefit and High benefit group

	ENS	Low benefit	High benefit	p-value
n	15	12	70	
RQLQ domains				
Practical problem (0-18)	10.3±4.4*†	4.5±4.8†	3.0±3.6*	<0.001
Nasal symptoms (0-24)	8.3±7.0*	6.8±5.9‡	3.2±3.6*‡	<0.001
Ocular symptoms (0-24)	8.7±9.4*	5.9±7.1	1.9±3.5*	<0.001
Activities (0-18)	13.1±4.5*	9.1±4.4‡	2.2±3.8*‡	<0.001
SNOT-22 (0-110)	63.2±15.9*†	29.2±6.6†‡	12.6±13.9*‡	<0.001

Abbreviations: ENS, Empty Nose Syndrome; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SNOT-22, 22-item Sino Nasal Outcome Test

* p value<0.05 on sub-analysis between ENS and high benefit

† p value<0.05 on sub-analysis between ENS and low benefit

‡ p value<0.05 on sub-analysis between low benefit and high benefit

Table 17. Turbinate pathophysiology comparison of ENS, Low benefit and High benefit group

	ENS	Low benefit	High benefit	p-value
n	15	12	70	
Ray's rules				
Presence of nasal cycling (%)	66.7	45.5	34.4	0.104
Response to decongestant (%)	33.3*	54.5	76.9*	0.007
Postural Congestion (%)	46.7	33.3	29.0	0.413

Abbreviations: ENS, Empty Nose Syndrome

* p value<0.05 on sub-analysis between ENS and high benefit

† p value<0.05 on sub-analysis between ENS and low benefit

‡ p value<0.05 on sub-analysis between low benefit and high benefit

Table 18. Psychogenic function comparison of ENS, Low benefit and high benefit group

	ENS	Low benefit	High benefit	p-value
n	15	12	70	
Hyperventilation syndrome				
Nijmegen (0-64)	29.4±14.0*†	10.6±8.9†	5.4±9.1*	<0.001
Anxiety				
GAD-7 (0-21)	12.1±5.5*†	5.1±4.3†	2.2±3.7*	<0.001
Depression				
PHQ-9 (0-27)	17.3±6.2*†	6.4±4.8†‡	2.0±2.7*‡	<0.001
Somatic symptom disorder				
PHQ-15 (0-30)	12.3±6.4*†	5.1±2.5†	3.9±4.5*	<0.001
SSD-12 (0-48)	33.3±10.9*†	19.5±9.8†‡	5.7±7.1*‡	<0.001

Abbreviations: ENS, Empty Nose Syndrome; GAD-7, 7-item General Anxiety Disorder; PHQ-9, 9-item Patient Health Questionnaire; PHQ-15, 15-item Patient Health Questionnaire; SSD-12, 12-item Somatic Symptom Disorder scale

* p value<0.05 on sub-analysis between ENS and high benefit

† p value<0.05 on sub-analysis between ENS and low benefit

‡ p value<0.05 on sub-analysis between low benefit and high benefit

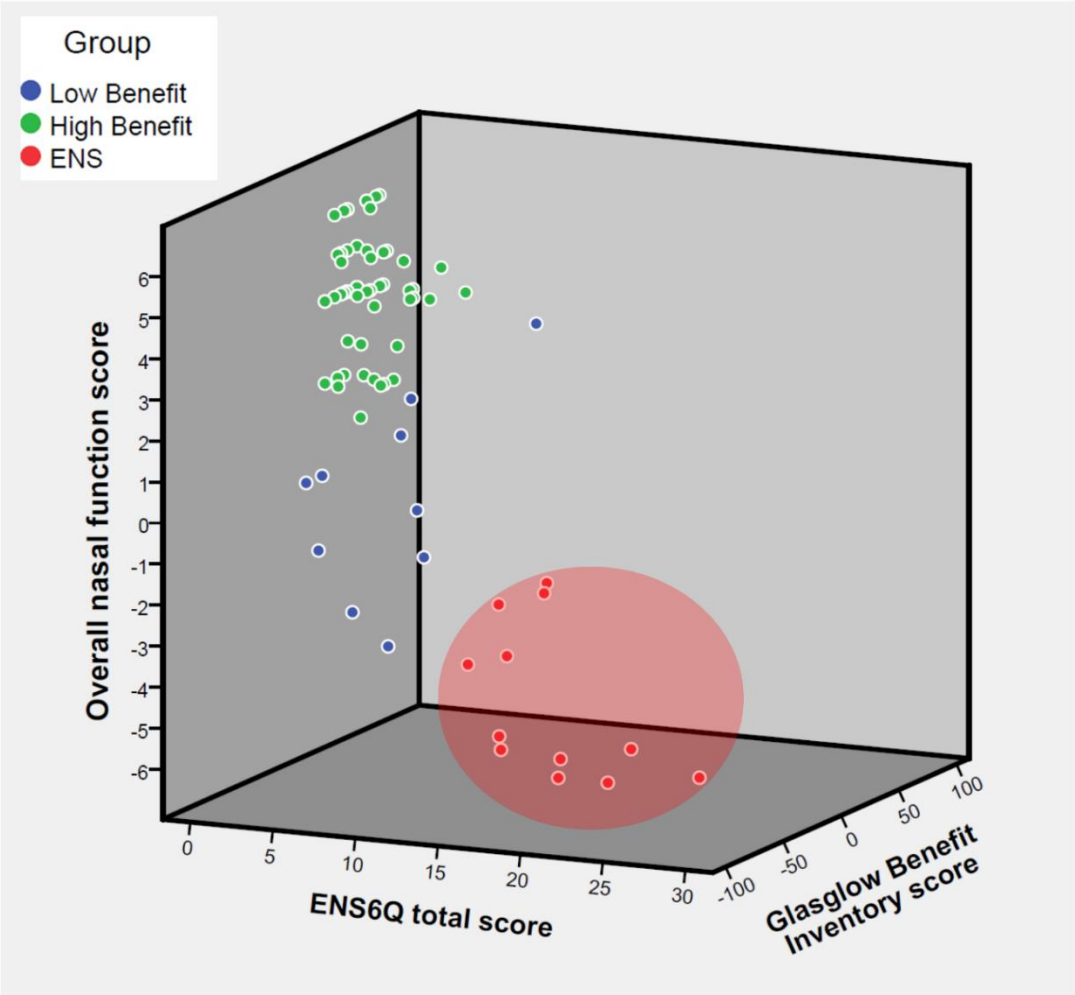


Figure 9. illustrated 3D model of three defining group

Abbreviations: ENS, empty nose syndrome; ENS6Q, 6-item empty nose syndrome questionnaire

Supplementary: Questionnaire

Section 1: Demographic profile

Date of birth ___/____ (MM/YYYY)

Gender
ο Male
ο Female

Race / ethnicity
ο Asian
ο African
ο Caucasian
ο Hispanic
ο Indigenous Australian (Aboriginal or Torres Strait Islander)
ο Native American
ο Pacific Islander
ο Prefer not to answer
ο Other

Year of turbinate surgery _____ (YYYY)

What is your diagnosis?
ο Hayfever/ Allergic rhinitis
ο Sinusitis
ο Sleep apnea
ο nasal obstruction post trauma
ο Nasal obstruction – not otherwise specified

Do you have asthma?
ο Yes
ο No

Do you have Hay fever symptoms? ο Yes

○ No

Have you ever smoked? ○ Yes

○ No

Do you currently smoke (or ceased in last 12mths) ? ○ Yes

○ No

Section 2: Surgery Satisfaction

On the scale below please circle a number to rate your overall nasal function

-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6
TERRIBLE		Bad		Poor		Neither good nor bad		Fair		Good		Excellent

For each question below please rate the change related to your surgical intervention

1. HAS THE RESULT OF THE OPERATION/INTERVENTION AFFECTED THE THINGS YOU DO?

MUCH WORSE (1)	A little or somewhat worse (2)	No change (3)	A little or somewhat better (4)	Much better (5)

2. HAVE THE RESULTS OF THE OPERATION/INTERVENTION MADE YOUR OVERALL LIFE BETTER OR WORSE?

MUCH BETTER (1)	A little or somewhat better (2)	No change (3)	A little or somewhat worse (4)	Much worse (5)

3. SINCE YOUR OPERATION/INTERVENTION, HAVE YOU FELT MORE OR LESS OPTIMISTIC ABOUT THE FUTURE?

MUCH MORE OPTIMISTIC (1)	More optimistic (2)	No change (3)	Less optimistic (4)	Much less optimistic (5)

4. SINCE YOUR OPERATION/INTERVENTION, DO YOU FEEL MORE OR LESS EMBARRASSED WHEN WITH A GROUP OF PEOPLE?

MUCH MORE EMBARRASSED (1)	More embarrassed (2)	No change (3)	Less embarrassed (4)	Much less embarrassed (5)

5. SINCE YOUR OPERATION/INTERVENTION, DO YOU HAVE MORE OR LESS SELF-CONFIDENCE?

MUCH MORE SELF-CONFIDENCE (1)	More self-confidence (2)	No change (3)	Less self-confidence (4)	Much less self-confidence (5)

6. SINCE YOUR OPERATION/INTERVENTION, HAVE YOU FOUND IT EASIER OR HARDER TO DEAL WITH COMPANY?

MUCH EASIER (1)	Easier (2)	No change (3)	Harder (4)	Much harder (5)

7. SINCE YOUR OPERATION/INTERVENTION, DO YOU FEEL THAT YOU HAVE MORE OR LESS SUPPORT FROM YOUR FRIENDS?

MUCH MORE SUPPORT (1)	More support (2)	No change (3)	Less support (4)	Much less support (5)

8. HAVE YOU BEEN TO YOUR FAMILY DOCTOR, FOR ANY REASON, MORE OR LESS OFTEN, SINCE YOUR OPERATION/INTERVENTION?

MUCH MORE OFTEN (1)	More often (2)	No change (3)	Less often (4)	Much less often (5)

9. SINCE YOUR OPERATION/INTERVENTION, DO YOU FEEL MORE OR LESS CONFIDENT ABOUT JOB OPPORTUNITIES?

MUCH MORE CONFIDENT (1)	More confident (2)	No change (3)	Less confident (4)	Much less confident (5)

10. SINCE YOUR OPERATION/INTERVENTION, DO YOU FEEL MORE OR LESS SELF-CONSCIOUS?

MUCH MORE SELF-CONSCIOUS (1)	More self-conscious (2)	No change (3)	Less self-conscious (4)	Much less self-conscious (5)

11. SINCE YOUR OPERATION/INTERVENTION, ARE THERE MORE OR FEWER PEOPLE WHO REALLY CARE ABOUT YOU?

MUCH MORE PEOPLE (1)	More people (2)	No change (3)	Fewer people (4)	Many fewer people (5)

12. SINCE YOU HAD THE OPERATION/INTERVENTION, DO YOU CATCH COLDS OR INFECTIONS MORE OR LESS OFTEN?

MUCH MORE OFTEN (1)	More often (2)	No change (3)	Less often (4)	Much less often (5)

13. HAVE YOU HAD TO TAKE MORE OR LESS MEDICINE FOR ANY REASON, SINCE YOUR OPERATION/INTERVENTION?

MUCH MORE MEDICINE (1)	More medicine (2)	No change (3)	Less medicine (4)	Much less medicine (5)

14. SINCE YOUR OPERATION/INTERVENTION, DO YOU FEEL BETTER OR WORSE ABOUT YOURSELF?

MUCH BETTER (1)	Better (2)	No change (3)	Worse (4)	Much worse (5)

15. SINCE YOUR OPERATION/INTERVENTION, DO YOU FEEL THAT YOU HAVE HAD MORE OR LESS SUPPORT FROM YOUR FAMILY?

MUCH MORE SUPPORT (1)	More support (2)	No change (3)	Less support (4)	Much less support (5)

16. SINCE YOUR OPERATION/INTERVENTION, ARE YOU MORE OR LESS INCONVENIENCED BY YOUR HEALTH PROBLEM?

MUCH MORE INCONVENIENCED (1)	More inconvenienced (2)	No change (3)	Less inconvenienced (4)	Much less inconvenienced (5)

17. SINCE YOUR OPERATION/INTERVENTION, HAVE YOU BEEN ABLE TO PARTICIPATE IN MORE OR FEWER SOCIAL ACTIVITIES?

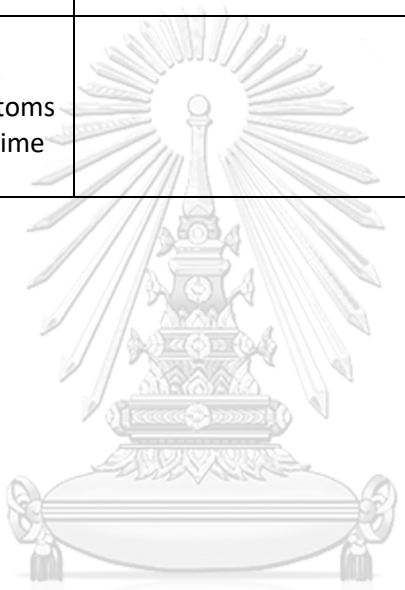
MANY MORE ACTIVITIES (1)	More activities (2)	No change (3)	Fewer activities (4)	Many fewer activities (5)

18. SINCE YOUR OPERATION/INTERVENTION, HAVE YOU BEEN MORE OR LESS INCLINED TO WITHDRAW FROM SOCIAL SITUATIONS?

MUCH MORE INCLINED (1)	More inclined (2)	No change (3)	Less inclined (4)	Much less inclined (5)

Section 3: nasal status

	Yes	No
Do you have good response to nasal decongestant?		
Do you have nasal congestion related to different position, for example, when you lie on your side does one nostril become more block?		
Do you notice of cycling nasal congestion, for example, are your symptoms worse at any particular time of day?		



Please indicate how much you have been troubled by each item, during the last week

Please identify 3 activities that have been limited by nose/eye symptoms during the previous week.

Activity 1 _____

Activity 2 _____

Activity 3 _____

	Not trouble	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
inconvenient of having to carry tissue or handkerchief							
need to rub nose/eyes							
need to blow your nose repeatedly							
stuffy/blocked nose							
runny nose							
Sneezing							
itchy nose							
itchy eyes							
watery eyes							
sore eyes							
swollen eyes							
How trouble have you been by activity 1?							
How trouble have you							

been by activity 2?							
How trouble have you been by activity 3?							

For each problem below, please rate how 'bad' it has been over the last two weeks

	no problem	very mild problem	mild or slight problem	moderate problem	severe problem	problem as bad as it can be
Need to blow the nose						
Postnasal discharge						
Thick nasal discharge						
Ear fullness						
Ear pain						
Facial pressure						
Difficult to smell or taste						
Cough						

For each problem below, please rate how 'bad' it has been over the last two weeks

	No problem	Very mild	Mild	Moderate	Severe	Extremely severe
Dryness						
Lack of air sensation going through your nasal cavities						
Suffocation						

Nose feels too open						
Nasal crusting						
Nasal burning						

Section 4: General health status

For each problem below, please rate how 'bad' it has been over the last two weeks

	no problem	very mild problem	mild or slight problem	moderate problem	severe problem	problem as bad as it can be
Dizziness/dizzy spell						
difficult falling asleep/sleeping too much						
Waking up tired						
Lack of good night's sleep						
Waking up at night						
Reduced productivity						
Reduced concentration						

Please rate how often you have experienced the following symptoms in the past two weeks

	Never	Rarely	Sometimes	Often	Very often
Chest pain					
Palpitations/ feeling your heart pound or race					
Tight feelings in chest					
Faster or deeper breathing					
Short of breath					
Unable to breathe deeply					
Bloated feeling in stomach					
Blurred vision					

Tingling fingers					
Stiff fingers or arms					
Tight feelings around mouth					
Cold hands or feet					
Feeling confused					
Feeling tense					

During the last 4 weeks, how much have you been bothered by any of the following problems?

	Not bothered	Bothered a little	Bothered a lot
Stomach pain			
Back pain			
Pain in your arms, legs, or joints (knees, hips, etc.)			
Feeling tired or having little energy/ fatigue			
Menstrual cramps or other problems with your periods			
Pain or problems during sexual intercourse			
Headaches			
Fainting spells			
Constipation, loose bowels, or diarrhea			
Nausea, gas, or indigestion			

Section 5: Mental health state

For each problem below, please rate how 'bad' it has been over the last two weeks

	no problem	very mild problem	mild or slight problem	moderate problem	severe problem	problem as bad as it can be
Frustation/restlessness / irritability/ become easily annoyed						
Sadness						

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all (0)	Several days (1)	More than half the days (2)	Nearly every day (3)
Little interest or pleasure in doing things				
Feeling down, depressed, or hopeless				
Poor appetite or overeating				
Trouble concentrating on things, such as reading the newspaper or watching television				
Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual				
Thoughts that you would				

be better off dead of or hurting yourself in some way				

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all (0)	Several days (1)	More than half the days (2)	Nearly every day (3)
Feeling nervous anxiety or on edge				
Not being able to stop or control worrying				
Worrying too much about different things				
Being so restless that it is hard to sit still				
Feeling afraid as if something awful might happen				

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Never	Rarely	Sometimes	Often	Very often
I think that my physical symptoms are signs of a serious illness.					
I am very worried about my health.					
My health concerns hinder me in everyday life.					

I am convinced that my symptoms are serious.					
My symptoms scare me.					
My physical complaints occupy me for most of the day.					
Others tell me that my physical problems are not serious.					
I'm worried that my physical complaints will never stop.					
I think that doctors do not take my physical complaints seriously.					
I am worried that my physical symptoms will continue into the future.					

Table 19. Supplementary: Post hoc Bonferroni analysis between three comparisons; ENS vs Low Benefit, ENS vs High Benefit and Low Benefit vs High Benefit

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Duration post turbinate surgery (yrs)	High Benefit	Low Benefit	-.022	1.000	-6.55	6.50
		ENS	-7.826*	.002	-13.06	-2.59
	Low Benefit	High Benefit	.022	1.000	-6.50	6.55
		ENS	-7.804*	.037	-15.26	-.35
	ENS	High Benefit	7.826*	.002	2.59	13.06
		Low Benefit	7.804*	.037	.35	15.26
Glasgow Benefit Inventory score	High Benefit	Low Benefit	27.2433*	.000	12.640	41.846
		ENS	62.9223*	.000	50.952	74.893
	Low Benefit	High Benefit	-27.2433*	.000	-41.846	-12.640
		ENS	35.6790*	.000	18.953	52.406
	ENS	High Benefit	-62.9223*	.000	-74.893	-50.952
		Low Benefit	-35.6790*	.000	-52.406	-18.953
ENS6Q	High Benefit	Low Benefit	-3.5351*	.004	-6.123	-.947
		ENS	-16.0351*	.000	-18.347	-13.724
	Low Benefit	High Benefit	3.5351*	.004	.947	6.123
		ENS	-12.5000*	.000	-15.578	-9.422
	ENS	High Benefit	16.0351*	.000	13.724	18.347
		Low Benefit	12.5000*	.000	9.422	15.578

RSI	High Benefit	Low Benefit	-.7829	1.000	-7.713	6.147
		ENS	-15.2412*	.000	-21.140	-9.342
	Low Benefit	High Benefit	.7829	1.000	-6.147	7.713
		ENS	-14.4583*	.000	-22.589	-6.327
	ENS	High Benefit	15.2412*	.000	9.342	21.140
		Low Benefit	14.4583*	.000	6.327	22.589
RQLQ (practical problem)	High Benefit	Low Benefit	-2.1579	.356	-5.519	1.203
		ENS	-7.4912*	.000	-10.493	-4.489
	Low Benefit	High Benefit	2.1579	.356	-1.203	5.519
		ENS	-5.3333*	.005	-9.331	-1.335
	ENS	High Benefit	7.4912*	.000	4.489	10.493
		Low Benefit	5.3333*	.005	1.335	9.331
RQLQ (nasal symptoms)	High Benefit	Low Benefit	-4.8684*	.011	-8.817	-.919
		ENS	-7.2851*	.000	-10.812	-3.758
	Low Benefit	High Benefit	4.8684*	.011	.919	8.817
		ENS	-2.4167	.628	-7.114	2.281
	ENS	High Benefit	7.2851*	.000	3.758	10.812
		Low Benefit	2.4167	.628	-2.281	7.114
RQLQ (ocular symptoms)	High Benefit	Low Benefit	-5.3480*	.036	-10.433	-.263
		ENS	-6.9868*	.001	-11.529	-2.444
	Low Benefit	High Benefit	5.3480*	.036	.263	10.433
		ENS	-1.6389	1.000	-7.688	4.410
	ENS	High Benefit	6.9868*	.001	2.444	11.529

		Low Benefit	1.6389	1.000	-4.410	7.688
RQLQ (Activities)	High Benefit	Low Benefit	-6.6849*	.000	-10.563	-2.807
		ENS	-11.0539*	.000	-14.191	-7.917
	Low Benefit	High Benefit	6.6849*	.000	2.807	10.563
		ENS	-4.3690	.055	-8.813	.075
	ENS	High Benefit	11.0539*	.000	7.917	14.191
		Low Benefit	4.3690	.055	-.075	8.813
SNOT-22	High Benefit	Low Benefit	-15.8117*	.003	-26.959	-4.664
		ENS	-50.5708*	.000	-60.528	-40.613
	Low Benefit	High Benefit	15.8117*	.003	4.664	26.959
		ENS	-34.7592*	.000	-48.019	-21.499
	ENS	High Benefit	50.5708*	.000	40.613	60.528
		Low Benefit	34.7592*	.000	21.499	48.019
Nijmegen Questionnaire	High Benefit	Low Benefit	-4.7179	.477	-12.875	3.440
		ENS	-24.6679*	.000	-31.950	-17.386
	Low Benefit	High Benefit	4.7179	.477	-3.440	12.875
		ENS	-19.9500*	.000	-29.677	-10.223
	ENS	High Benefit	24.6679*	.000	17.386	31.950
		Low Benefit	19.9500*	.000	10.223	29.677
GAD-7	High Benefit	Low Benefit	-2.2265	.341	-5.645	1.192
		ENS	-10.0571*	.000	-13.109	-7.005
	Low Benefit	High Benefit	2.2265	.341	-1.192	5.645
		ENS	-7.8306*	.000	-11.907	-3.754

	ENS	High Benefit	10.0571*	.000	7.005	13.109
		Low Benefit	7.8306*	.000	3.754	11.907
PHQ-9	High Benefit	Low Benefit	-3.4619*	.044	-6.860	-.064
		ENS	-15.2980*	.000	-18.335	-12.261
	Low Benefit	High Benefit	3.4619*	.044	.064	6.860
		ENS	-11.8361*	.000	-15.868	-7.805
	ENS	High Benefit	15.2980*	.000	12.261	18.335
		Low Benefit	11.8361*	.000	7.805	15.868
PHQ-15	High Benefit	Low Benefit	-1.0298	1.000	-5.035	2.976
		ENS	-8.5132*	.000	-12.091	-4.935
	Low Benefit	High Benefit	1.0298	1.000	-2.976	5.035
		ENS	-7.4833*	.001	-12.248	-2.719
	ENS	High Benefit	8.5132*	.000	4.935	12.091
		Low Benefit	7.4833*	.001	2.719	12.248
SSD-12	High Benefit	Low Benefit	-10.2950*	.001	-17.001	-3.589
		ENS	-28.0181*	.000	-33.821	-22.215
	Low Benefit	High Benefit	10.2950*	.001	3.589	17.001
		ENS	-17.7231*	.000	-25.605	-9.842
	ENS	High Benefit	28.0181*	.000	22.215	33.821
		Low Benefit	17.7231*	.000	9.842	25.605

Abbreviations: ENS6Q, 6-item empty nose syndrome questionnaire; SNOT-22, 22-item Sino Nasal Outcome Test; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; PHQ-9, 9-item Patient Health Questionnaire; PHQ-15, 15-item Patient Health Questionnaire; NQ, Nijmegen Questionnaire; SSD-12, 12-item Somatic Symptom Disorder scale; RSI, Reflux Symptom Index

Chapter 5. Development of questionnaire to identify 'at risk' patients of ENS and poor surgical outcomes

5.1 Introduction

Turbinate hypertrophy is a common finding in patient presented with nasal airway obstruction. Soft tissue swelling from chronic inflammation or irritant is the primary cause. Pharmacological treatment is utilized to decongest turbinate tissue and control the underlying inflammatory process. For whom medical management fails to control the symptoms, turbinate reduction surgery is considered.[189]

While it is generally acknowledged that most turbinate surgery brings about the reduction in symptom severity and nasal airway resistance[230], persistence nasal obstruction has been reported to be as high as 33%.[54-56] The main reason behind this failure is a poor correlation between quantitative nasal airflow measures and patient perception of benefit.[52] This points out the significant role of subjective nasal perception over objective testing. Therefore, subjective symptom improvement is the best evaluation of surgical efficacy.

The nasal perception has been shown to be perceived by cool thermoreceptors in the nasal mucosa. Cooling signal induces depolarization of neurons connected to the brainstem respiratory center and activates specific regions of the cerebral cortex. The cooling signals are interpreted as clear breathing.[2,30,31,64] Menthol provides an excellent example of this mechanism; it creates the impression of enhanced breathing without altering nasal resistance or cross-sectional area.[58,348] Menthol inhalation has also been demonstrated to deactivate the limbic system or emotional processing area. This indicated the influence of psychogenic factors on subjective nasal perception and poor surgical outcome.[2,69,73,241]

Factors associated with poor surgical outcome from turbinate reduction surgery have been studied. (Chapter 4) The post turbinate surgery patients were divided into Empty nose syndrome (ENS) or poor outcome, low benefit and high benefit from the surgery using

satisfaction measurement and empty nose syndrome-specific questionnaire. The poor outcome group reported higher scores in psychogenic function, sinonasal function and gastro-esophageal reflux symptoms than low benefit and high benefit group. Therefore, poor psychogenic function, disproportionate subjective nasal complaint and reflux symptoms are red flags of patients at risk of poor surgical outcome. Avoidance of surgery is the best approach to prevent this disastrous outcome and selection of surgical candidacy is the key to success. This study aims to develop a new questionnaire to identify patients at risk of poor surgical outcome from turbinate surgery.

5.2 Methods

According to previous study on clinical characteristic differences between ENS or poor surgical outcome and patients achieving benefit from turbinate surgery (low and high benefit), a new questionnaire was developed. This new questionnaire will be used to differentiate the two groups and identify patient at risk of poor outcome. This study had ethical approval from Macquarie University and St Vincent's Hospital Human Research Ethics Committee. (2019/ETH13672)

Study population

Participants were adult (Age ≥ 18 years old) patients who has had previous nasal surgery primarily inferior turbinate reduction more than three months. Turbinate surgery is defined as any surgery involving either unilateral or bilateral inferior turbinate. Patients who were unable to provide informed consent or complete the questionnaire because of age, mental illness, dementia, communication difficulties or other reasons were excluded.

Satisfaction measurements and ENS-specific questionnaire were used to diagnose ENS. ENS or poor surgical outcome group was defined as negative score on satisfaction measurement (Glasgow Benefit Inventory[293] and overall nasal function) and score ≥10.5 on Empty Nose 6-item Questionnaire (ENS6Q).[227] Participants who did not meet these criteria were defined as non-ENS group (defined as 'low benefit' or 'high benefit' group from the previous chapter).

Outcome measures

Patient reported outcome measure (PROM) which showed significant differences between ENS and non-ENS (Chapter 4) were included to form a new questionnaire. The included outcome measures assessed sinonasal function, psychological function and gastroesophageal reflux symptoms. Sinonasal function was measured via 22-item Sinonasal Outcome Test (SNOT-22) and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Psychogenic function was measured via 7-item Generalized Anxiety Disorder scale (GAD-7) for anxiety disorder, 9-item Patient Health Questionnaire (PHQ-9) for depressive disorder, 15-item Patient Health Questionnaire (PHQ-15) and 12-item Somatic Symptom Disorder scale (SSD-12) for somatic symptom disorder and Nijmegen questionnaire (NQ) for hyperventilation syndrome and reflux Symptom Index (RSI) was used to evaluate gastroesophageal reflux symptoms.

Item selection

In developing the new questionnaire, two statistical analytic methods were applied to all question items. Univariate logistic regression analysis was performed to assess for predictors of poor surgical outcome. The item that showed statistically significant ($p<0.05$), and with high odds ratio were included for item selection. Cronbach's alpha test was used to evaluate the item-total item correlation and items with acceptable correlation value (≥0.7)[349] were considered for selection. The combination of both statistical results was used as primary screening for item selection. All statistics were computed using SPSS version 24 (IBM Corp., Armonk, NY). After primary selection by statistical methods, secondary screening for item reduction was performed by authors considering practicality and common characteristics of patients with poor surgical outcome based on clinical experience.

Reliability test and cut off value

Internal consistency, defined as the intercorrelation between questionnaire items, was measured using Cronbach's alpha. Receiver operating characteristic (ROC) curves were constructed to determine the ability of the new questionnaire to discriminate ENS from non-ENS patients. The optimal cut-off score which provided the best sensitivity and specificity was then established.

5.3 Results

A total of 97 patients recruited from previous study were analyzed. Mean age was 43.0±13.4 years old and 54.4 percentage was female. Fifteen patients (15.5%) were identified as ENS or poor surgical outcome group and 82 patients (84.5%) in non-ENS (low benefit and high benefit group) according to population definition. Clinical characteristics comparisons between groups were shown in the previous study.(*ref*) A total of 82 question items demonstrated statistically difference between ENS and non-ENS were included for analysis, consisting of 30 items from sinonasal function (SNOT-22 and RQLQ), 43 items from psychogenic function (GAD-7, PHQ-9, PHQ-15, SSD-12 and NQ) and 9 items from RSI.

Logistic regression analysis was performed as the first statistical criteria to identify the predictors of poor surgical outcome. All items predicted poor outcome ($p<0.05$) except for 'back pain', 'menstrual cramps or other problems with periods', 'fainting spells' and 'constipation, loose bowels or diarrhea'. Items with high odds ratios were selected for secondary screening. Thirty-seven items were identified with odds ratios ranging from 3.01 – 22.43. (Table 20)

Cronbach's alpha test was used for second statistical criteria. It was performed to demonstrate inter-correlation between questionnaire items. Question items showing high score of ≥0.8 on item-total correlation were selected for secondary screening. Twenty-three items satisfied the criteria consisting of 13 items derived from psychogenic function (SSD-12, GAD-7 and NQ), 9 items from sinonasal function (SNOT-22), and 1 item from RSI. (Table 21) Primary screening by both statistical methods yielded 42 items. The secondary screening reduced the questionnaire down to 12 question items. Selected items formed '12-item Empty Nose Syndrome Questionnaire for Screening' (ENS12Qs). The ENS12Qs composed of three items from PHQ-9, four items from SSD-12, three items from NQ and 2 items from

SNOT-22. Five-point Likert scale was used according to authors agreement and majority of selected items were originally measured on this scale, ranging from 0 (never) to 4 (very often). (Table 22) Odds ratio on logistic regression analysis and Cronbach's alpha coefficient of selected items were presented in Table 23. The internal consistency was measured using Cronbach's alpha test. The coefficient value for 'ENS12Qs' was 0.95, indicating strong internal consistency. Corrected item- total correlations ranged from 0.63 to 0.87. The removal of any items resulted in lower Cronbach's alpha score, which again reflecting high internal consistency. (Table 25) The ROC curve was performed to illustrate the diagnostic ability of ENS12Qs. ENS12Qs showed a strong ability to differentiate ENS from non-ENS, with area under the curve of 0.98 (95%CI 0.96-1.00). (Figure 10) When analyzing each of the ENS12Qs items individually, "Reduced concentration" was found to be the most predictive symptoms of ENS with AUCs of 0.95 (95% CI 0.91-1.00). (Table 24) The optimal ENS12Qs cut-off score to predict ENS is ≥14 out of a total score of 48. It yielded 100% sensitivity, 91% specificity and positive Likelihood ratio of 11.1.

5.4 Discussion

Although it is assumed that most of the turbinate surgery brings about the desire anatomical outcome, persistent nasal obstruction has consistently been reported in the literature. Physician typically relies on objective test such as rhinomanometry and acoustic rhinometry for surgical decision to measure the outcome. However, the commonly reported discordance between objective and subjective measures shows that the current evaluating tools are unreliable, especially in predicting the success of surgical intervention. The nasal pathophysiologic response, including 'cycling' nasal congestion, postural congestion and subjective response to topical nasal decongestant suggest mucosal pathology or structural obstruction, may guide surgical decision, but the evidence in practical use is still lacking. So far, there is no accurate tool for nasal perception evaluation and surgical candidate selection.

'ENS12Qs' is designed to identify patients at risk of ENS and poor surgical outcome from turbinate surgery. Patient factors associated with poor surgical outcome from previous study provided a list of 85 question items (sinonasal function, psychogenic function and reflux symptoms). Twelve representative items formed 'ENS12Qs' after the item selection and reduction process. The selected items originated from the hyperventilation syndrome, depression and somatic symptom disorder questionnaire.

The psychogenic component is primarily involved in the control of respiration and nasal breathing perception. Metabolic and behavioral pathways control the respiratory drive. Historically, it was believed that metabolic activity solely regulates respiration as the level of PaCO2 controls the breathing rate and tidal volume. With the evidence that PaCO2 level is not always related to breathing pattern, the behavioral pathway was proposed.[81,341] Behavioral pathway has an ability to override the metabolic activity and is widely connected with emotional control. The evidence in nasal perception follows the same pattern as respiration. The emotional and psychogenic pathway is involved in the mechanism of nasal perception and can modulate overall perception at higher control centers. (Chapter2)

The current validated tools used in ENS are 'ENS6Q' and 'cotton test'.[226,227] ENS6Q, mainly derived from SNOT-25, incorporated common sinonasal symptoms expressed in ENS patients. The cotton test involves 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. The cotton test's reliability remains debatable with a great chance of placebo effect especially when the result is subjectively measured. The ENS6Q and cotton test were developed in an effort to diagnose ENS after turbinate surgery.

The new 'ENS12Qs' is a screening tool to identify patients at risk of ENS and poor surgical outcome in the pre-operative stage. It was derived from the clinical characteristics of ENS which involved every factor that affect subjective nasal perception. (Chapter 4) ENS12Qs covers a more comprehensive range of factors in subjective nasal perception than the existing tools and predicts outcomes pre- rather than post-operatively. Additionally, since surgery as the cause of ENS is unclear, the use in preoperative stage is reasonable.

ENS12Qs is recommended for screening patients prior to undergoing turbinate surgery. The internal consistency and ability to differentiate ENS and non-ENS is extremely high. A score of ≥ 13 predicts the risk of poor surgical outcome with a high sensitivity and specificity. Thus, surgical decision and planning should be cautiously made. In addition, using ENS12Q in combination with other predictors may further enhance the screening accuracy. The absence of 'Rays rule' (cycling nasal congestion, postural congestion and subjective response to topical nasal decongestant) and discordance between subjective and objective outcome are worth added to the approach. Further instrument reproducibility and validity test is needed. The validation of ENS12Qs will considerably enhance the efficiency of screening for at risk patient of ENS and poor surgical outcome.

5.5 Conclusion

ENS12Qs is a screening questionnaire used to identify patient at risk of ENS and poor surgical outcome from turbinate surgery. These tools provide an opportunity to improve rhinology care by identifying patients who may not benefit from surgical treatment.

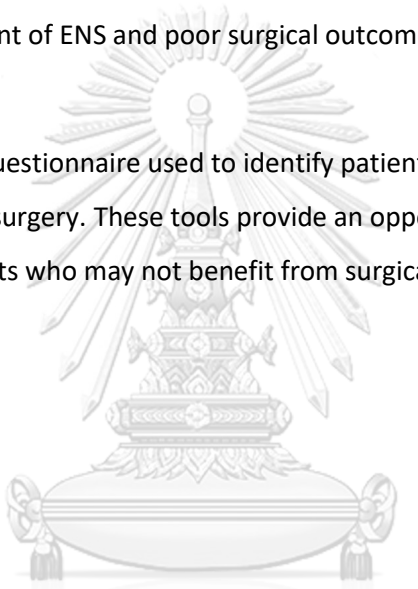


Table 20. Univariate logistic regression analysis of selected items ordered by odd ratio

Question item	**Origin**	**OR (95%CI)**	**P-value**
Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	PHQ-9	22.43 (4.70-107.04)	<0.001
Thoughts that you would be better off dead of or hurting yourself in some way	PHQ-9	11.34 (2.85-45.04)	0.001
Poor appetite or overeating	PHQ-9	6.05 (2.64-13.87)	<0.001
Little interest or pleasure in doing things	PHQ-9	5.73 (2.64-12.43)	<0.001
Lack of good night's sleep	SNOT-22	5.66 (2.17-14.80)	<0.001
Worrying too much about different things	GAD-7	5.27 (2.24-12.36)	<0.001
Faster or deeper breathing	NQ	5.15 (2.29-11.57)	<0.001
I am worried that my physical symptoms will continue into the future.	SSD-12	4.89 (2.30-10.42)	<0.001
My health concerns hinder me in everyday life.	SSD-12	4.37 (2.20-8.67)	<0.001
Unable to breathe deeply	NQ	4.31 (2.15-8.63)	<0.001
I'm worried that my physical complaints will never stop.	SSD-12	4.05 (2.23-7.36)	<0.001

Blurred vision	NQ	4.04 (2.04- 7.99)	<0.001
Waking up at night	SNOT-22	4.02 (1.88-8.60)	<0.001
Frustration/restlessness/irritability	SNOT-22	3.95 (2.08-7.52)	<0.001
I think that doctors do not take my physical complaints seriously.	SSD-12	3.95 (2.15-7.26)	<0.001
Thick nasal discharge	SNOT-22	3.90 (2.08-7.31)	<0.001
Reduced productivity	SNOT-22	3.89 (1.97-7.69)	<0.001
Reduced concentration	SNOT-22	3.85 (2.04-7.26)	<0.001
Stomach pain	PHQ-15	3.77 (1.58-8.99)	0.003
Feeling down, depressed, or hopeless	PHQ-9	3.74 (1.99-7.06)	<0.001
Short of breath	NQ	3.73 (1.97-7.08)	<0.001
Feeling confused	NQ	3.70 (1.80-7.60)	<0.001
difficult falling asleep	SNOT-22	3.63 (1.93-6.81)	<0.001
Feeling tense	NQ	3.55 (1.91-6.60)	<0.001
I am convinced that my symptoms are serious.	SSD-12	3.49 (1.95-6.26)	<0.001
Pain or problems during sexual intercourse	PHQ-15	3.47 (1.02-11.84)	0.047
Waking up tired	SNOT-22	3.47 (1.78-6.75)	<0.001

Feeling afraid as something awful might happen	GAD-7	3.34 (1.68-6.64)	0.001
My symptoms scare me.	SSD-12	3.27 (1.90-5.62)	<0.001
Fatigue	SNOT-22	3.24 (1.75-5.99)	<0.001
Nausea, gas or indigestion	PHQ-15	3.19 (1.26-8.10)	0.015
Not being able to stop or control worrying	GAD-7	3.18 (1.77-5.73)	<0.001
Breathing difficulties or choking episodes	RSI	3.18 (1.85-5.47)	<0.001
I am very worried about my health.	SSD-12	3.14 (1.85-5.32)	<0.001
Postnasal discharge	SNOT-22	3.13 (1.82-5.38)	<0.001
Dizziness/ dizzy spell	SNOT-22	3.01 (1.67-5.45)	<0.001
Pain in your arms legs or joints	PHQ-15	3.01 (1.31-6.91)	0.009

Abbreviations: PHQ-9, 9-item Patient Health Questionnaire; NQ, Nijmegen Questionnaire; SSD-12, 12-item Somatic Symptom Disorder scale; GAD-7, 7-item General Anxiety Disorder; SNOT-22, 22-item Sino Nasal Outcome Test

Table 21. Cronbach's alpha test of selected items ordered by item - total correlation

Question	**Origin**	**Cronbach alpha: item - total correlation**
Reduced concentration	SNOT-22	0.90
Reduced productivity	SNOT-22	0.90
I'm worried that my physical complaints will never stop	SSD-12	0.88
Frustration/restlessness/irritability	SNOT-22	0.87
difficult falling asleep	SNOT-22	0.87
I think that my physical symptoms are signs of a serious illness	SSD-12	0.87
Dizziness	SNOT-22	0.86
My health concerns hinder me in everyday life.	SSD-12	0.86
Feeling tense	NQ	0.85
Palpitations	NQ	0.84
I am worried that my physical symptoms will continue into the future.	SSD-12	0.83
Faster or deeper breathing	NQ	0.83
My physical complaints occupy me for most of the day.	SSD-12	0.83
Breathing difficulties or choking episodes	RSI	0.82
Facial pressure	SNOT-22	0.82
Feeling confused	NQ	0.82
Short of breath	NQ	0.82
I am convinced that my symptoms are serious.	SSD-12	0.81
Lack of good night's sleep	SNOT-22	0.81
Fatigue	SNOT-22	0.81
Waking up tired	SNOT-22	0.80
I am very worried about my health.	SSD-12	0.80

Not being able to stop or control worrying	GAD-7	0.80

Abbreviations: SNOT-22, 22-item Sino Nasal Outcome Test; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; PHQ-15, 15-item Patient Health Questionnaire; RSI, Reflux Symptom Index; Nijmegen Questionnaire; SSD-12, 12-item Somatic Symptom Disorder scale

Please rate how often you have experienced the following symptoms in the past two weeks

	Never	Rarely	Sometimes	Often	Very often
Short of breath					
Faster or deeper breathing					
Unable to breathe deeply					
Reduced concentration					
Dizziness					
My symptoms scare me.					
I think that doctors do not take my physical complaints seriously.					
I am worried that my physical symptoms will continue into the future.					
My health concerns hinder me in everyday life.					
Little interest or pleasure in doing things					
Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual					
Thoughts that you would be better off dead of or hurting yourself in some way					

Table 22. 12-item Empty Nose Syndrome Questionnaire for Screening patient at risk of poor surgical outcome (ENS12Qs)

Table 23. Univariate logistic regression analysis and Cronbach's alpha test of ENS12Qs items

Question item	**Origin**	**Logistic regression analysis**		**Cronbach alpha: item - total correlation**
		OR (95%CI)	**P-value**	
Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	PHQ-9	22.43 (4.70-107.04)	<0.001	0.90
Thoughts that you would be better off dead of or hurting yourself in some way	PHQ-9	11.34 (2.85-45.04)	0.001	0.86
Little interest or pleasure in doing things	PHQ-9	5.73 (2.64-12.43)	<0.001	0.86
Faster or deeper breathing	NQ	5.51 (2.29-11.57)	<0.001	0.83
I am worried that my physical symptoms will continue into the future.	SSD-12	4.89 (2.30-10.42)	<0.001	0.83
My health concerns hinder me in everyday life.	SSD-12	4.37 (2.20-8.67)	<0.001	0.82
Unable to breathe deeply	NQ	4.31 (2.15-8.63)	<0.001	0.79
I think that doctors do not take my physical complaints seriously.	SSD-12	3.95 (2.15-7.26)	<0.001	0.76

Reduced concentration	SNOT-22	3.85 (2.04-7.26)	<0.001	0.75
Short of breath	NQ	3.73 (1.97-7.08)	<0.001	0.70
My symptoms scare me.	SSD-12	3.27 (1.90-5.62)	<0.001	0.68
Dizziness/ dizzy spell	SNOT-22	3.01 (1.67-5.45)	<0.001	0.67

Abbreviations: PHQ-9, 9-item Patient Health Questionnaire; NQ, Nijmegen Questionnaire; SSD-12, 12-item Somatic Symptom Disorder scale; GAD-7, 7-item General Anxiety Disorder; SNOT-22, 22-item Sino Nasal Outcome Test

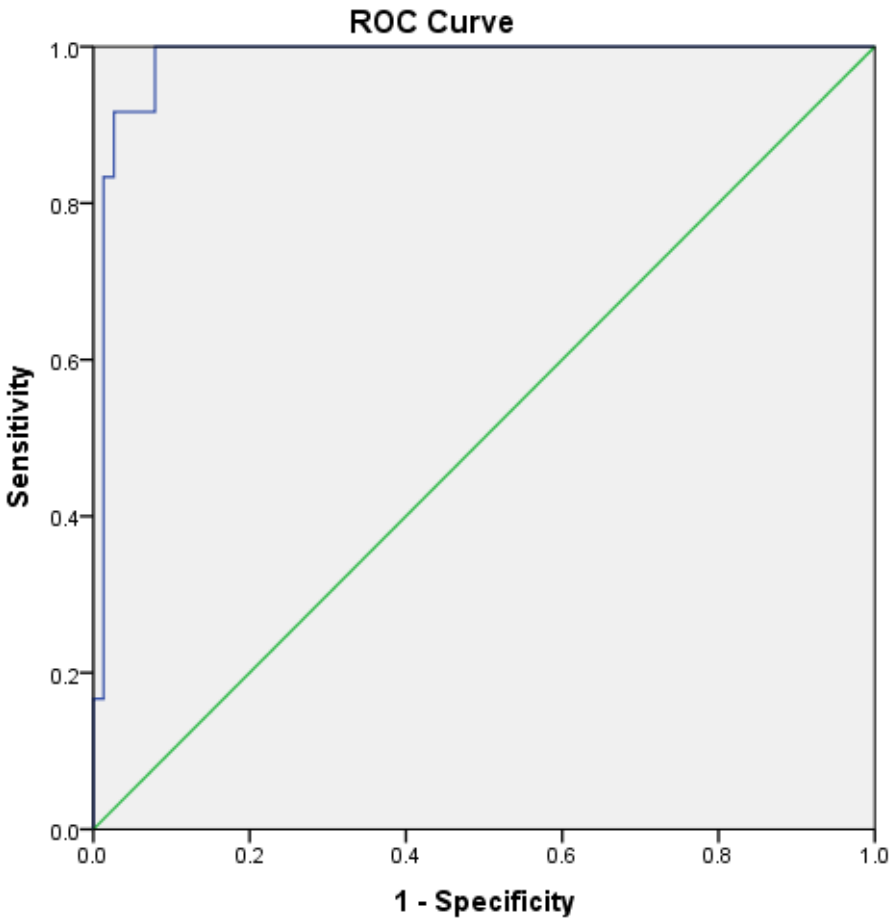


Figure 10. Receiver operating characteristic curves (ROC) analysis of ENS12Qs between patient with ENS vs non-ENS

Table 24. Area Under the Curve of total ENS12Qs and individual item in predicting ENS from non-ENS

	AUC	95% CI
Total ENS12Qs	0.98	0.96-1.00
Short of breath	0.88	0.77-0.99
Faster or deeper breathing	0.91	0.80-1.00
Unable to breathe deeply	0.93	0.88-0.99
Reduced concentration	0.95	0.91-1.00
Dizziness	0.85	0.71-0.99
My symptoms scare me.	0.88	0.77-0.98
I think that doctors do not take my physical complaints seriously.	0.90	0.81-1.00
I am worried that my physical symptoms will continue into the future.	0.93	0.88-0.98
My health concerns hinder me in everyday life.	0.90	0.82-0.97
Little interest or pleasure in doing things	0.94	0.89-0.99
Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0.89	0.77-1.00
Thoughts that you would be better off dead of or hurting yourself in some way	0.81	0.64-0.98

Abbreviations: AUC, Area Under the Curve; ENS, Empty Nose Syndrome; ENS12Qs, ’12-item Empty Nose Syndrome Questionnaire for Screening

Table 25. Supplementary: Internal consistency reliability of ENS12Qs

	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
Short of breath	0.806	0.946
Faster or deeper breathing	0.830	0.945
Unable to breathe deeply	0.747	0.948
Reduced concentration	0.819	0.945
Dizziness	0.712	0.949
My symptoms scare me.	0.791	0.946
I think that doctors do not take my physical complaints seriously.	0.766	0.947
I am worried that my physical symptoms will continue into the future.	0.816	0.946
My health concerns hinder me in everyday life.	0.866	0.944
Little interest or pleasure in doing things	0.796	0.946
Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0.631	0.951
Thoughts that you would be better off dead of or hurting yourself in some way	0.714	0.95

ENS12Qs, ’12-item Empty Nose Syndrome Questionnaire for Screening

Chapter 6. Discussion

Nasal obstruction is one of the most common complaints in rhinology practice. Various factors impact nasal breathing perception, and many instruments are used to measure it. The mechanism of nasal breathing was revealed through the study on 'empty nose syndrome'(ENS). Empty nose syndrome (ENS) is a rare condition characterized by paradoxical nasal obstruction in patients who had received nasal obstruction intervention, such as turbinate surgery. The examination is usually normal except for the evidence of 'empty nasal space'. ENS patients are often led to believe that the surgical procedure is the cause of the current deteriorating situation. A systematic review of the pathophysiologic mechanism of ENS enhances novel knowledge in the nasal breathing perception mechanism. (Chapter 2)

Various subjective and objective assessment has been used to measure nasal patency. Rhinomanometry is the most common objective tool used to measure nasal airflow and pressure, especially for structural obstruction evaluation. The correlations between objective assessments and various subjective tools were studied. (Chapter 3) Moreover, the utility of rhinomanometry in predicting the success of structural surgery was proposed.

The understanding of nasal breathing perception and pathophysiology of ENS can explain the discordance between subjective and objective measures. The comprehensive study of factors contributing to ENS or poor surgical outcome supported the proposed nasal breathing perception mechanism. The clinical characteristics of patient factors were compared between patients with benefit from the surgery and those with ENS or poor outcome. (Chapter 4) The new screening tool was then constructed from the clinical characteristic differences. This new questionnaire will be used to screen for patients at risk of developing poor surgical outcome from turbinate surgery. (Chapter 5) This tool will enhance the accuracy in evaluating the subjective nasal perception which guides proper management.

6.1 Pathophysiology of ENS

While it is acknowledged that most of the patients who underwent turbinate surgery had a successful result, surgery appears to make the symptoms deteriorate in ENS. ENS hugely impacts patient's function and quality of life.[221] The pathophysiology behind ENS has been poorly defined, and there is controversy in this field.[56,223-225] Although there have been reviews on the diagnostic methods of ENS,[228] these diagnostic tools do not advance our understanding of ENS pathophysiology. A systematic review of the literature on investigated pathophysiologic mechanisms in ENS has been conducted. (Chapter2) Eighteen studies were included and with nine pathophysiologic themes identified. The illustrated model of evidence in ENS is shown in Figure 11. The results highlight the major role of psychogenic effect on ENS and nasal perception.

Psychogenic comorbidities, including anxiety, depression and hyperventilation syndrome, were reported in >50% of ENS patients and correlated with ENS symptom severity. As a result, symptom severity is high in ENS and impacts general health.[221,226,227,241] Emotional processing is involved in ENS nasal perception, supported by a f-MRI study demonstrating the deactivation of emotional processing areas after the successful pseudo-decongestant stimulatory effects of menthol in ENS patients.[241] On airflow analysis, similar improvements in nasal airspace, airflow rate and nasal resistance were observed between post turbinate surgery patients with and without ENS. An impairment in trigeminal-thermoreceptor response, demonstrated with menthol detection test, may be presented in some ENS paients.[239,240,248] However, the menthol detection test was subjectively reported without objective test being compared. A discordance between subjective and objective results would still be possible as paradoxical events between subjective and objective outcomes in ENS were observed in several constructs which extended beyond breathing to olfaction and psychogenic influence on nasal perception. (Table 26)

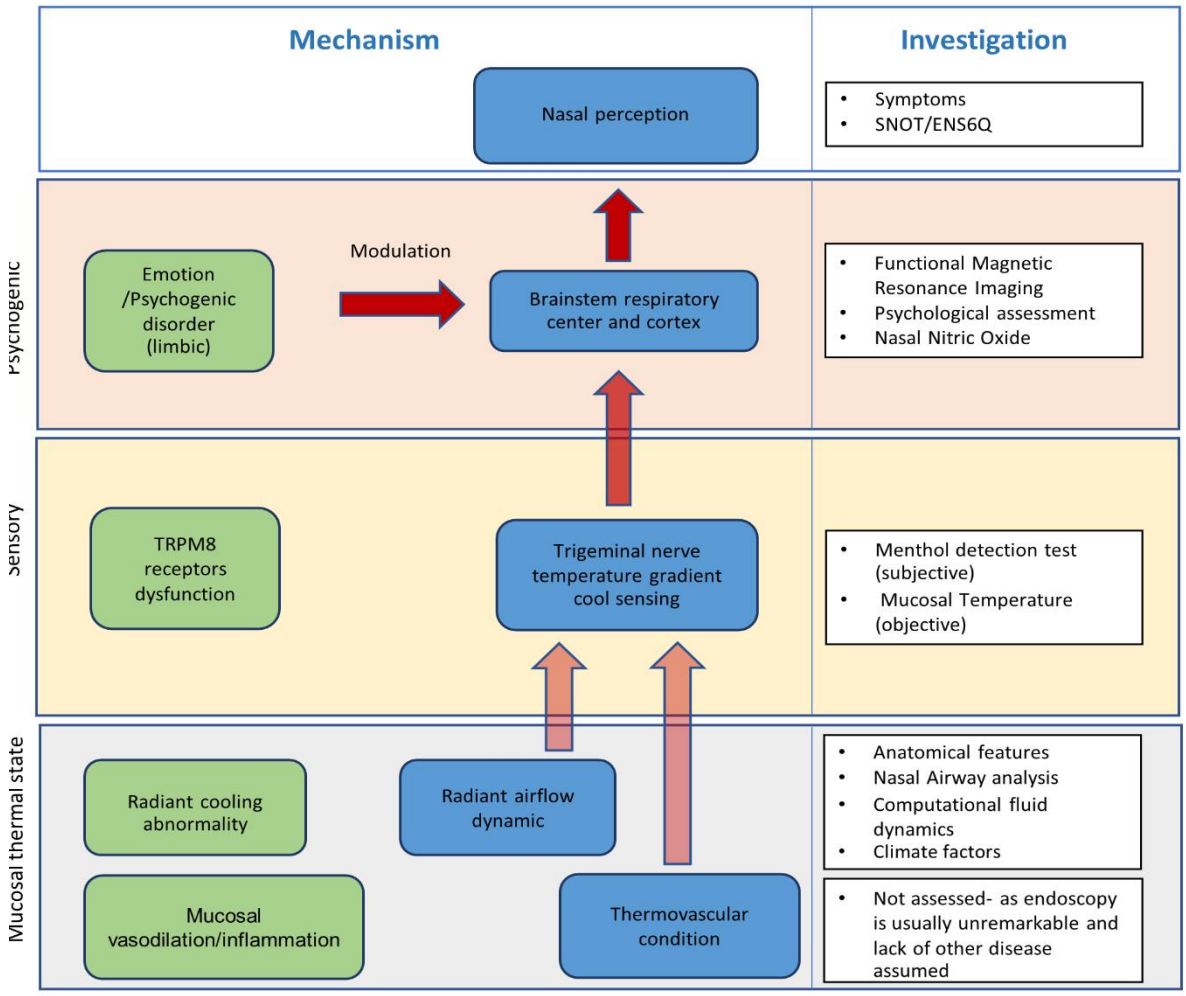


Figure 11. Mechanism of nasal perception and illustrated model of evidence in ENS

Table 26. Comparison between subjective and objective findings on Empty Nose Syndrome constructs

Construct	ENS subjective finding	ENS objective finding
Nasal perception pathway		
Nasal airflow dynamic	'Empty' nasal space is presented in ENS patients. Nasal breathing perception is bad despite wide patency nasal cavity.	Nasal volume and airspace are similar between ITRwENS and ITRsENS patients. There is no described airflow-mechano receptor. Nasal perception and nasal airflow are not correlated. Human airflow assessment demonstrated similar nasal airflow and resistance between ITRwENS and ITRsENS patients.
Nasal airflow related effect	Cotton test subjectively improved nasal breathing perception. Olfactory function rating was impaired in ENS patients.	No objective test was compared. Objective olfactory function (TDI score) was similar between ITRwENS and ITRsENS patients.
Neuro-sensory function	Menthol detection was lower in ENS patients.	No objective test was compared.
Cortex and higher control	ENS patients were associated with anxiety (73%), depression (71%).	Hyperventilation syndrome diagnosed by hyperventilation provocation test and pulmonary function test was reported in 77% of ENS patients. f-MRI demonstrated relation between emotional processing area and nasal breathing perception.
Cause and impact of ENS		
Cause of the event	ENS is an iatrogenic condition following excessive nasal turbinate tissue removal.	Patients initial indication for surgery is often forgotten and surgical failure to improve nasal perception potentially increased perception severity. ENS is possibly a form of functional neurological disorder (conversion disorder), characterized by neurological symptoms incompatible with known neurological pathology. Stressor related to surgical event is considered triggering the event.

Impact of the event	ENS patients self-reported mental health disorder, functional and sleep function impairment.	It is unclear whether these conditions were predisposing, or resultant of the ENS. ENS as a cause of these conditions cannot be inferred. when pre-surgical data were not compared.

Abbreviations: ENS, Empty Nose Syndrome; ITR, Inferior Turbinate Resection; ITRwENS, Inferior Turbinate Resection with Empty Nose Syndrome; ITRsENS, Inferior Turbinate Resection without Empty Nose Syndrome; f-MRI, functional Magnetic Resonance Imaging

6.2 Is surgery the cause of ENS?

It was speculated that ENS is an iatrogenic condition following excessive nasal turbinate tissue removal but the evidence from the systematic review is against the surgery as the cause for ENS. Discordance between subjective and objective measurement in various constructs of ENS is the crucial supporting feature. (Table 26) Studies on anatomical feature, airflow and airflow-related assessment demonstrated a similar finding to post-turbinate surgery patient without ENS. Olfactory test was impaired on subjective assessment, but objective assessment showed a similar response to post turbinate surgery patients without ENS. The 'cotton test', which involves cotton placement in the area where turbinate previously reside, was shown to restore subjective improvement in ENS patients, but the result may be unreliable when objective test was not compared. Furthermore, the discrepancy between subjective and objective measurements indicates that ENS patients depend on subjective 'patient factor' in perceiving nasal perception which influenced by emotional/psychogenic modulation.

Considering the psychogenic component as the primary cause of ENS, an alteration in nasal perception due to psychogenic conditions may exist prior to turbinate surgery. Findings of an 'empty nasal space' in ENS may result from attempts to manage these pre-surgical symptoms. The notion that ENS symptoms exacerbation is directly caused by surgery also remains questionable. Similar event in other specialty has shown that pre-existing psychogenic disorder can lead to poor surgical outcome.[350,351] Stressful and emotional life events, such as a surgical intervention with over-expectation of benefit, may be associated with triggering a conversion disorder.[271,272] Functional neurological disorder or conversion disorder is defined as an abnormal central nervous system functioning of presumed psychogenic etiology, characterized by neurological symptoms incompatible with

known neurological pathology.[352,353] Wide range of manifestations were reported, including non-anatomical sensory loss. Emotional life event stressors could have been a contributing causal factor, [272] including stressors related to surgical intervention triggering this psychogenic event.[271]

6.3 Mechanism of nasal breathing

The result of ENS systematic review enhanced the understanding of the nasal breathing perception mechanism. (Figure 11) The perception of nasal patency is triggered through cool-thermo receptors or Transient Receptor Potential Melastatin 8 (TRPM-8) locate in the nasal mucosa.[31,32,64] TRPM-8 is thermoreceptor respond to a specific temperature range between 8-22°c. In addition to the specific temperature, menthol and a number of cooling agent including icilin, eucalyptol and WS-3 activate TRPM-8.

The high-speed nasal airflow creates evaporation of nasal epithelial water and activates trigeminal TRPM-8 receptors through temperature gradient. The mucosal temperature gradient activation of TRPM-8 is influenced by mucosal vasculature (thermovascular conditions) and the radiant cooling by airflow (radiant airflow dynamics). Thus, allergic rhinitis creates both a high local temperature from vasodilation and secondary poor radiant airflow cooling from nasal congestion. Likewise, septal deviation produces a loss of radiant airflow cooling in otherwise normal nasal mucosa. This temperature gradient induces depolarization of neurons and stimulates the brainstem respiratory center and cerebral cortex and the cool message is interpreted as patent nostrils. [69,73,254]

The nasal cool stimulus activates trigeminal nucleus, brainstem reticular formation and trigger arousal and cerebral cortex activity.[71,72] The specific cortical activation areas include somatosensory cortex regions of the rostral insula, which involve sensory and emotional processing, anterior cingulate cortex area, which relates to decision making, the insula cortex and pre-central gyrus of the frontal lobe, which is the motor cortex. [2,69,73] The involvement of the limbic system or emotional processing area indicates the impact of cognitive function and emotional control on nasal perception. Psychogenic disorders can modulate nasal perception at the control center. Poor psychogenic health status has been linked to poor nasal perception, disproportionate to objective findings and demonstrates emotional regulation deficits. [222,243,269,270]

6.4 The use of an objective test in structural surgery

Rhinomanometry is a gold standard technique for the assessment of nasal patency. It is used to assess the nasal airflow, pressure and nasal airway resistance (NAR) affected by thermovascular condition and airflow radiant cooling.[281,354] Difficulties interpreting rhinomanometry values exist, despite recommendations for use in investigations of candidacy of nasal surgery and interventional outcomes in patients with anatomical obstruction.[115,120]

Correlation analyses between change in nasal airway resistance and a range of subjective measurement tools: Visual analog scale of nasal obstruction (VAS), Nasal Obstruction Symptom Evaluation scale (NOSE), 22-item Sinonasal Outcome Test (SNOT-22), nasal obstruction Likert score, and overall nasal function (12-Likert scale) was performed on patients undergoing turbinate, septal and/or rhinoplasty surgery. (Chapter 3) The results demonstrate that subjective outcome selection is an important factor when assessing nasal obstruction improvements. Symptom severity scores (VAS, nasal obstruction, overall nasal function) are preferred subjective measures as correlations between improvement in NAR and VAS, overall nasal function and nasal obstruction score were shown. While NOSE and SNOT-22 demonstrated no correlation with NAR improvement. The health-related quality of life questionnaires (NOSE, SNOT-22) may not be the most appropriate tools to use alongside rhinomanometric assessment. These tools may poorly reflect the degree of nasal obstruction due to incorporating quality of life related aspects rather than nasal function assessment.

Furthermore, nasal resistance demonstrates higher correlation of the surgical impact with patient reported outcomes on the obstructed side. Previous studies supported the assessment of NAR unilaterally, which demonstrated stronger correlations with patient VAS scores.[93,94,290]

The correlation between NAR and symptom severity improvement reflected the advantage of rhinomanometry assessment in structural obstruction patients. The Minimal clinically important difference (MCID) of NAR was calculated to determine the surgical success in structural surgery. MCID is defined using anchor-based method and distribution-based method. The MCID of 0.1 $Pa/cm^3/s$ for total NAR and t 0.2 $Pa/cm^3/s$ for obstructed

NAR is suggested to serve as the threshold to aid clinicians in the interpretation of successful in controlling 'disease factor' in structural obstruction patients.

The utility of objective airway test is limited to patients with structural obstruction. The routine use of objective airway assessment is not always necessary due to the various factors contributing to nasal breathing perception. (Figure 11) The concordance between the objective test parameter and symptom severity may be a sign to predict the real impact of anatomical obstruction to overall nasal perception. In this situation, structural surgery is suggested and MCID of NAR can be applied to determine surgical success.

6.5 Patient factors associated with poor surgical outcome

Surgical failure can be reported at a level as high as 33%.[54-56] In this surgical failure group, there are patients with uncontrolled rhinitis or rhinosinusitis and structural obstruction (disease factor). Despite achieving the desired outcome in controlling the 'disease factor' by surgery or optimal medical therapy, persistent nasal obstruction also depends on 'patient factor.'

The questionnaire survey conducted in post turbinate surgery patients compared the clinical characteristics of 'patient factor' between ENS or poor surgical outcome to patients reported benefit from the surgery. Satisfactory scales (Glasgow Benefit Inventory (GBI), overall nasal function) and 6-item Empty Nose Syndrome Questionnaire (ENS6Q) were used to define patient groups. The clinical characteristics studied involved all factors affecting the nasal breathing perception pathway including sinonasal function, psychogenic function and nasal pathophysiology. ENS reported higher scores than low benefit and high benefit group on psychogenic function, sinonasal function and gastroesophageal reflux symptoms.

The psychogenic related condition, including hyperventilation syndrome, anxiety, depression and somatic symptom disorder, was reported significantly more often in ENS group as expected. The high incidence report of psychogenic events in ENS and rhinology practice supported the finding. [221,222,247,250,251,292,316] Nasal symptom severity was higher in ENS group than low benefit and high benefit group. This finding is in line with the previous studies in which ENS patients reported higher symptom severity than in other sinonasal diseases. [221,226,227,241,247] Considering 'empty nasal space' described in ENS, the discordance

between this disproportional subjective complaint and objective assessment could predict the possibility of having these deteriorating health conditions. This finding resembles the phenomenon reported in many disorders that are thought to have strong psychogenic etiologies, especially when symptoms are incompatible with observed examination, such as tinnitus, irritable bowel syndrome, fibromyalgia, somatic symptom disorder and body dysmorphic disorder.[261-266]

ENS group also scored higher on reflux score than low benefit and high benefit group. The evidence demonstrated the relation of reflux symptoms with nasal congestion, but this relation was still controversial. The correlation between reflux symptoms and psychogenic disorders in anxiety, depression could further elucidate our finding. Thus, reflux symptom may be one of the predictive symptoms of poor surgical outcome.

In summary, poor psychogenic function, subjective complaints disproportionate to objective measure, poor response to nasal decongestant and reflux symptoms are key features in patents with poor surgical outcome. There is clinical need for the formal screening tools to guide surgical decision and prevent this debilitating event.

6.6 'ENS12Qs'; The screening tools to identify at risk patient with ENS and poor surgical outcome

The best approach to avoid the unpleasant result from ENS is the proper selection of surgical candidate. Despite various tools currently used to evaluate nasal perception, there is no accurate tool for nasal perception evaluation and surgical candidate selection. Discordance between objective and subjective measures shows that the existing tool is unreliable, especially in predicting the success of surgical intervention. The response to nasal pathophysiology includes 'cycling' nasal congestion, postural congestion and subjective response to topical nasal decongestant suggest mucosal pathology or structural obstruction, which may guide a surgical decision, but the evidence in practical use is still lacking.

A new questionnaire was developed according to previous studies on clinical characteristic differences between ENS or poor outcome and patients achieving benefit from the surgery (low and high benefit). This new questionnaire was developed to differentiate the two groups to identify patients at risk of poor outcome from turbinate surgery. Patient factors associated with poor surgical outcome from previous study provided a list of 85

question items (sinonasal function, psychogenic function and reflux symptoms). Twelve representative items formed 'ENS12Qs' after item selection and reduction process. The selected items relate to hyperventilation syndrome, depression and somatic symptom disorder questionnaire.

The emotional and psychogenic pathway is involved in the mechanism of nasal perception (Chapter 2) The control of respiratory drive follows a similar basis. The breathing pattern is mainly controlled by acid-based homeostasis, which is detected by brain stem respiratory center. Hyperventilation is induced to restore pCO_2 hemostasis during hypocapnia. But PaCO2 level is not always related to breathing pattern, increased minute ventilation exceeding metabolic control is commonly reported. The behavioral or emotional pathway was proposed with an ability to override the metabolic activity.

The 'ENS6Q' and 'cotton test' are current validated tools used in ENS. These tests were developed in an effort to diagnose ENS after turbinate surgery. The roles of ENS6Q and cotton test in ENS pathophysiology was reviewed in Chapter 2. ENS6Q was mainly derived from SNOT-25, incorporating common sinonasal symptoms expressed in ENS patients. The cotton test measuresd the subjective nasal breathing improvement after placing dry cotton into the region where the turbinate tissue has been removed. However, the reliability of the cotton test remains debatable with a great chance of placebo effect, especially when the result is subjectively measured. Again, the recurring event of subjective and objective measurement mismatch found in many ENS constructs is possible without the objective test being compared. (Table 26)

The new 'ENS12Qs' is a screening tool to identify patients at risk of ENS and poor surgical outcome in the pre-operative stage. It derived from the clinical characteristics of ENS, which involved every aspect affecting subjective nasal perception. (Chapter 4) ENS12Qs covered a more comprehensive range of factors in subjective nasal perception mechanism than existing tools and focused on pre-operative utilized rather than post-operative since surgery as the cause of ENS is unclear.

ENS12Qs is recommended to be included in rhinology workflow to screen patient prior to undergoing turbinate surgery. The internal consistency and ability to differentiate ENS and non-ENS is extremely high. A cut off score of ≥ 13 showed high sensitivity (92%) and

specificity (96%) in the prediction of ENS or poor surgical outcome from surgery. Positive on the screening test indicates that the surgery should be avoided or cautiously performed with consent on the risk of having poor surgical outcome. The absence of 'Rays rule' (cycling nasal congestion, postural congestion and subjective response to topical nasal decongestant), especially poor response to nasal decongestant (Chapter 4) and discordance between subjective and objective outcome (Chapter 2) are other signs that predict poor surgical outcome. The detection of these characteristics in conjunction with ENS12Qs may enhance the screening accuracy and be the best approach.

Overall conclusion

Psychogenic function is strongly involved in determining the subjective perception of nasal breathing evident in both subjective and objective measurement. It can modulate the overall nasal perception and override the effect of other nasal obstruction contributing factors. Psychogenic factor is potentially the true cause of empty nose syndrome and could explain the paradoxical finding between subjective and objective nasal airway test.

The poor psychogenic function found in empty nose syndrome led to the development of subjective measurement tool which provides the comprehensive and reliable subjective nasal perception assessment. The new questionnaire 'ENS12Qs' is beneficial in screening patients at risk of poor surgical outcome from turbinate surgery 'before' it occurs.

References

1. Jessen M, Malm L. Definition, prevalence and development of nasal obstruction. Allergy 1997; 52:3-6.
2. Baraniuk JN. Subjective nasal fullness and objective congestion. Proceedings of the American Thoracic Society 2011; 8:62-9.
3. Osborn JL, Sacks R. Chapter 2: Nasal obstruction. American journal of rhinology & allergy 2013; 27 Suppl 1:S7-8.
4. Wever CC. The Nasal Airway: A Critical Review. Facial plastic surgery : FPS 2016; 32:17-21.
5. Lundbäck B. Epidemiology of rhinitis and asthma. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 1998; 28 Suppl 2:3-10.
6. Stewart M, Ferguson B, Fromer L. Epidemiology and burden of nasal congestion. International journal of general medicine 2010; 3:37-45.
7. Pessey JJ, Reitz C, Los F. [Acute rhinosinusitis in the adult: national survey of general practice management]. Revue de laryngologie - otologie - rhinologie 2000; 121:237-41.
8. Ferrand PA, Mercier CH, Jankowski Ret al. [Acute sinusitus in adults. Management by general practitioners]. Presse medicale (Paris, France : 1983) 2001; 30:1049-54.
9. Tjahjono R, Alvarado R, Kalish Let al. Health Impairment From Nasal Airway Obstruction and Changes in Health Utility Values From Septorhinoplasty. JAMA facial plastic surgery 2019; 21:146-51.
10. Hsiao CJ, Cherry DK, Beatty PC, Rechtsteiner EA. National Ambulatory Medical Care Survey: 2007 summary. National health statistics reports 2010:1-32.
11. Kimmelman CP. The problem of nasal obstruction. Otolaryngologic clinics of North America 1989; 22:253-64.
12. Schuman TA, Senior BA. Treatment Paradigm for Nasal Airway Obstruction. Otolaryngologic clinics of North America 2018; 51:873-82.
13. Chandra RK, Patadia MO, Raviv J. Diagnosis of nasal airway obstruction. Otolaryngologic clinics of North America 2009; 42:207-25, vii.
14. Wittkopf M, Wittkopf J, Ries WR. The diagnosis and treatment of nasal valve collapse. Current opinion in otolaryngology & head and neck surgery 2008; 16:10-3.
15. Bridger GP. Physiology of the nasal valve. Archives of otolaryngology (Chicago, Ill : 1960) 1970; 92:543-53.
16. Ishii LE, Rhee JS. Are diagnostic tests useful for nasal valve compromise? The Laryngoscope 2013; 123:7-8.
17. Rhee JS, Weaver EM, Park SSet al. Clinical consensus statement: Diagnosis and management of nasal valve compromise. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2010; 143:48-59.
18. Fettman N, Sanford T, Sindwani R. Surgical management of the deviated septum: techniques in septoplasty. Otolaryngologic clinics of North America 2009; 42:241-52, viii.
19. Gray LP. Deviated nasal septum. Incidence and etiology. The Annals of otology, rhinology & laryngology Supplement 1978; 87:3-20.
20. Holt GR. Biomechanics of nasal septal trauma. Otolaryngologic clinics of North America 1999; 32:615-9.

21. Costa DJ, Sanford T, Janney C, Cooper M, Sindwani R. Radiographic and anatomic characterization of the nasal septal swell body. Archives of otolaryngology--head & neck surgery 2010; 136:1107-10.
22. Wexler D, Braverman I, Amar M. Histology of the nasal septal swell body (septal turbinate). Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2006; 134:596-600.
23. Hamizan AW, Christensen JM, Ebenzer Jet al. Middle turbinate edema as a diagnostic marker of inhalant allergy. International forum of allergy & rhinology 2017; 7:37-42.
24. Perić A, Sotirović J, Baletić N, Kozomara R, Bijelić D, Rasić D. [Concha bullosa and the nasal middle meatus obstructive syndrome]. Vojnosanitetski pregled 2008; 65:255-8.
25. Rodrigo Tapia JP, Alvarez Alvarez I, Casas Rubio C, Blanco Mercadé A, Díaz Villarig JL. [A giant bilateral concha bullosa causing nasal obstruction]. Acta otorrinolaringologica espanola 1999; 50:490-2.
26. Kimbell JS, Frank DO, Laud P, Garcia GJ, Rhee JS. Changes in nasal airflow and heat transfer correlate with symptom improvement after surgery for nasal obstruction. Journal of biomechanics 2013; 46:2634-43.
27. Hoshino T. In vitro electrophysiologic studies on nasal airway receptors of the rabbit. The Annals of otology, rhinology, and laryngology 1988; 97:294-7.
28. Glebovskiĭ VD, Baev AV. [Stimulation of trigeminal receptors of the nasal mucosa by respiratory airflow]. Fiziologicheskii zhurnal SSSR imeni I M Sechenova 1984; 70:1534-41.
29. Sozansky J, Houser SM. The physiological mechanism for sensing nasal airflow: a literature review. International forum of allergy & rhinology 2014; 4:834-8.
30. Zhao K, Blacker K, Luo Y, Bryant B, Jiang J. Perceiving nasal patency through mucosal cooling rather than air temperature or nasal resistance. PloS one 2011; 6:e24618.
31. Zhao K, Jiang J, Blacker Ket al. Regional peak mucosal cooling predicts the perception of nasal patency. The Laryngoscope 2014; 124:589-95.
32. Willatt DJ, Jones AS. The role of the temperature of the nasal lining in the sensation of nasal patency. Clinical otolaryngology and allied sciences 1996; 21:519-23.
33. Sullivan CD, Garcia GJ, Frank-Ito DO, Kimbell JS, Rhee JS. Perception of better nasal patency correlates with increased mucosal cooling after surgery for nasal obstruction. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2014; 150:139-47.
34. Read RC, Wilson R, Rutman Aet al. Interaction of nontypable Haemophilus influenzae with human respiratory mucosa in vitro. The Journal of infectious diseases 1991; 163:549-58.
35. Lund VJ. Nasal physiology: neurochemical receptors, nasal cycle, and ciliary action. Allergy and asthma proceedings 1996; 17:179-84.
36. Lund VJ, Scadding GK. Objective assessment of endoscopic sinus surgery in the management of chronic rhinosinusitis: an update. The Journal of laryngology and otology 1994; 108:749-53.
37. Scadding GK, Lund VJ, Darby YC. The effect of long-term antibiotic therapy upon ciliary beat frequency in chronic rhinosinusitis. The Journal of laryngology and otology 1995; 109:24-6.

38. Scadding GK, Lund VJ, Holmstrom M, Darby YC. Clinical and physiological effects of fluticasone propionate aqueous nasal spray in the treatment of perennial rhinitis. Rhinology Supplement 1991; 11:37-43.
39. Patel RG. Nasal Anatomy and Function. Facial plastic surgery : FPS 2017; 33:3-8.
40. Dawes JD, Prichard MM. Studies of the vascular arrangements of the nose. Journal of anatomy 1953; 87:311-22.
41. Cauna N. The fine structure of the arteriovenous anastomosis and its nerve supply in the human nasal respiratory mucosa. The Anatomical record 1970; 168:9-21.
42. Lane AP. Nasal anatomy and physiology. Facial plastic surgery clinics of North America 2004; 12:387-95, v.
43. Ogle OE, Weinstock RJ, Friedman E. Surgical anatomy of the nasal cavity and paranasal sinuses. Oral and maxillofacial surgery clinics of North America 2012; 24:155-66, vii.
44. Stafford-Smith M, Bartz R, Wilson K, Baraniuk JN, Schwinn DA. Alpha-adrenergic mRNA subtype expression in the human nasal turbinate. Canadian journal of anaesthesia = Journal canadien d'anesthesie 2007; 54:549-55.
45. Hanif J, Jawad SS, Eccles R. The nasal cycle in health and disease. Clinical otolaryngology and allied sciences 2000; 25:461-7.
46. Beule AG. Physiology and pathophysiology of respiratory mucosa of the nose and the paranasal sinuses. GMS current topics in otorhinolaryngology, head and neck surgery 2010; 9:Doc07.
47. Gilbert AN. Reciprocity versus rhythmicity in spontaneous alternations of nasal airflow. Chronobiology international 1989; 6:251-7.
48. Flanagan P, Eccles R. Spontaneous changes of unilateral nasal airflow in man. A re-examination of the 'nasal cycle'. Acta oto-laryngologica 1997; 117:590-5.
49. Kahana-Zweig R, Geva-Sagiv M, Weissbrod A, Secundo L, Soroker N, Sobel N. Measuring and Characterizing the Human Nasal Cycle. PloS one 2016; 11:e0162918.
50. Fisher EW, Liu M, Lund VJ. The nasal cycle after deprivation of airflow: a study of laryngectomy patients using acoustic rhinometry. Acta oto-laryngologica 1994; 114:443-6.
51. Moore M, Eccles R. Objective evidence for the efficacy of surgical management of the deviated septum as a treatment for chronic nasal obstruction: a systematic review. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2011; 36:106-13.
52. André RF, Vuyk HD, Ahmed A, Graamans K, Nolst Trenité GJ. Correlation between subjective and objective evaluation of the nasal airway. A systematic review of the highest level of evidence. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2009; 34:518-25.
53. Lam DJ, James KT, Weaver EM. Comparison of anatomic, physiological, and subjective measures of the nasal airway. American journal of rhinology 2006; 20:463-70.
54. Courtiss EH, Goldwyn RM. Resection of obstructing inferior nasal turbinates: a 10-year follow-up. Plastic and reconstructive surgery 1990; 86:152-4.
55. Berenholz L, Kessler A, Sarfati S, Eviatar E, Segal S. Chronic sinusitis: a sequela of inferior turbinectomy. American journal of rhinology 1998; 12:257-61.

56. Chhabra N, Houser SM. The diagnosis and management of empty nose syndrome. Otolaryngologic clinics of North America 2009; 42:311-30, ix.
57. Eccles R, Jones AS. The effect of menthol on nasal resistance to air flow. The Journal of laryngology and otology 1983; 97:705-9.
58. Burrow A, Eccles R, Jones AS. The effects of camphor, eucalyptus and menthol vapour on nasal resistance to airflow and nasal sensation. Acta oto-laryngologica 1983; 96:157-61.
59. Lindemann J, Tsakiropoulou E, Scheithauer MO, Konstantinidis I, Wiesmiller KM. Impact of menthol inhalation on nasal mucosal temperature and nasal patency. American journal of rhinology 2008; 22:402-5.
60. Eccles R. Menthol: effects on nasal sensation of airflow and the drive to breathe. Curr Allergy Asthma Rep 2003; 3:210-4.
61. Peier AM, Moqrich A, Hergarden ACet al. A TRP channel that senses cold stimuli and menthol. Cell 2002; 108:705-15.
62. Schäfer K, Braun HA, Isenberg C. Effect of menthol on cold receptor activity. Analysis of receptor processes. The Journal of general physiology 1986; 88:757-76.
63. McKemy DD, Neuhausser WM, Julius D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature 2002; 416:52-8.
64. Baraniuk JN, Merck SJ. New concepts of neural regulation in human nasal mucosa. Acta clinica Croatica 2009; 48:65-73.
65. Abe J, Hosokawa H, Okazawa Met al. TRPM8 protein localization in trigeminal ganglion and taste papillae. Brain research Molecular brain research 2005; 136:91-8.
66. Bautista DM, Siemens J, Glazer JMet al. The menthol receptor TRPM8 is the principal detector of environmental cold. Nature 2007; 448:204-8.
67. Liu SC, Lu HH, Cheng LHet al. Identification of the cold receptor TRPM8 in the nasal mucosa. American journal of rhinology & allergy 2015; 29:e112-6.
68. Liu SC, Lu HH, Fan HCet al. The identification of the TRPM8 channel on primary culture of human nasal epithelial cells and its response to cooling. Medicine 2017; 96:e7640.
69. Albrecht J, Kopietz R, Frasnelli J, Wiesmann M, Hummel T, Lundström JN. The neuronal correlates of intranasal trigeminal function-an ALE meta-analysis of human functional brain imaging data. Brain research reviews 2010; 62:183-96.
70. Peroni DG, Cattazzo E, Chinellato Iet al. Nasal mucosa temperature as a marker of disease in children with allergic rhinitis. American journal of rhinology & allergy 2012; 26:e115-8.
71. Arduini A, Moruzzi G. Olfactory arousal reactions in the cerveau isole cat. Electroencephalography and clinical neurophysiology 1953; 5:243-50.
72. Moruzzi G, Magoun HW. Brain stem reticular formation and activation of the EEG. Electroencephalography and clinical neurophysiology 1949; 1:455-73.
73. Price A, Eccles R. Nasal airflow and brain activity: is there a link? The Journal of laryngology and otology 2016; 130:794-9.
74. Folgering H. The pathophysiology of hyperventilation syndrome. Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace 1999; 54:365-72.
75. Gardner WN. The pathophysiology of hyperventilation disorders. Chest 1996; 109:516-34.
76. Morgan MD. Dysfunctional breathing in asthma: is it common, identifiable and correctable? Thorax 2002; 57 Suppl 2:Ii31-ii35.

77. Kerr WJ, Gliebe PA, Dalton JW. Physical Phenomena Associated with Anxiety States: The Hyperventilation Syndrome. California and western medicine 1938; 48:12-6.
78. Han JN, Stegen K, Simkens Ket al. Unsteadiness of breathing in patients with hyperventilation syndrome and anxiety disorders. The European respiratory journal 1997; 10:167-76.
79. Prys-Picard CO, Kellett F, Niven RM. Disproportionate breathlessness associated with deep sighing breathing in a patient presenting with difficult-to-treat asthma. Chest 2006; 130:1723-5.
80. Shu BC, Chang YY, Lee FY, Tzeng DS, Lin HY, Lung FW. Parental attachment, premorbid personality, and mental health in young males with hyperventilation syndrome. Psychiatry research 2007; 153:163-70.
81. Howell JB. The hyperventilation syndrome: a syndrome under threat? Thorax 1997; 52 Suppl 3:S30-4.
82. Gardner WN, Meah MS, Bass C. Controlled study of respiratory responses during prolonged measurement in patients with chronic hyperventilation. Lancet (London, England) 1986; 2:826-30.
83. Hornsveld H, Garssen B. Hyperventilation syndrome: an elegant but scientifically untenable concept. The Netherlands journal of medicine 1997; 50:13-20.
84. Hornsveld HK, Garssen B, Dop MJ, van Spiegel PI, de Haes JC. Double-blind placebo-controlled study of the hyperventilation provocation test and the validity of the hyperventilation syndrome. Lancet (London, England) 1996; 348:154-8.
85. Vansteenkiste J, Rochette F, Demedts M. Diagnostic tests of hyperventilation syndrome. The European respiratory journal 1991; 4:393-9.
86. Decuyper M, De Bolle M, Boone E, De Fruyt F. The relevance of personality assessment in patients with hyperventilation symptoms. Health psychology : official journal of the Division of Health Psychology, American Psychological Association 2012; 31:316-22.
87. Fokkens WJ, Lund VJ, Hopkins Cet al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology 2020; 58:1-464.
88. Stewart MG, Smith TL, Weaver EMet al. Outcomes after nasal septoplasty: results from the Nasal Obstruction Septoplasty Effectiveness (NOSE) study. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2004; 130:283-90.
89. Stewart MG, Witsell DL, Smith TL, Weaver EM, Yueh B, Hannley MT. Development and validation of the Nasal Obstruction Symptom Evaluation (NOSE) scale. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2004; 130:157-63.
90. Rhee JS, Sullivan CD, Frank DO, Kimbell JS, Garcia GJ. A systematic review of patient-reported nasal obstruction scores: defining normative and symptomatic ranges in surgical patients. JAMA facial plastic surgery 2014; 16:219-25; quiz 32.
91. Lipan MJ, Most SP. Development of a severity classification system for subjective nasal obstruction. JAMA facial plastic surgery 2013; 15:358-61.
92. Yepes-Nuñez JJ, Bartra J, Muñoz-Cano Ret al. Assessment of nasal obstruction: correlation between subjective and objective techniques. Allergologia et immunopathologia 2013; 41:397-401.
93. Clarke JD, Hopkins ML, Eccles R. Evidence for correlation of objective and subjective measures of nasal airflow in patients with common cold. Clinical otolaryngology :

official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2005; 30:35-8.
94. Sipilä J, Suonpää J, Silvoniemi P, Laippala P. Correlations between subjective sensation of nasal patency and rhinomanometry in both unilateral and total nasal assessment. ORL; journal for oto-rhino-laryngology and its related specialties 1995; 57:260-3.
95. Hirschberg A, Rezek O. Correlation between objective and subjective assessments of nasal patency. ORL; journal for oto-rhino-laryngology and its related specialties 1998; 60:206-11.
96. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 1991; 21:77-83.
97. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2009; 34:447-54.
98. Wise SK, Lin SY, Toskala Eet al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. International forum of allergy & rhinology 2018; 8:108-352.
99. Okuda M, Crawford B, Juniper E, Leahy MJ. [Preparation of Japanese versions of rinoconjunctivitis quality of life questionnaire (RQLQ) and work productivity and activity impairment questionnaire (WPAI-AS)]. Arerugi = [Allergy] 2003; 52 Suppl 1:70-86.
100. Soler R, de la Hoz B, Badia Xet al. [Validation of the Spanish version of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)]. Revista clinica espanola 2004; 204:131-8.
101. Bousquet J, Arnavielhe S, Bedbrook Aet al. MASK 2017: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma multimorbidity using real-world-evidence. Clinical and translational allergy 2018; 8:45.
102. Piccirillo JF, Merritt MG, Jr., Richards ML. Psychometric and clinimetric validity of the 20-Item Sino-Nasal Outcome Test (SNOT-20). Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2002; 126:41-7.
103. Hopkins C, Slack R, Lund V, Brown P, Copley L, Browne J. Long-term outcomes from the English national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. The Laryngoscope 2009; 119:2459-65.
104. de los Santos G, Reyes P, del Castillo R, Fragola C, Royuela A. Cross-cultural adaptation and validation of the sino-nasal outcome test (SNOT-22) for Spanish-speaking patients. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 2015; 272:3335-40.
105. Lü W, Qi F, Gao ZQ, Feng GD, Yuan XD, Jin XF. [Quality of life survey on patients with chronic rhinosinusitis by using Chinese version of the 22-item sinonasal outcome test (SNOT-22)]. Zhonghua er bi yan hou tou jing wai ke za zhi = Chinese journal of otorhinolaryngology head and neck surgery 2008; 43:18-21.

106. Zuo KJ, Fang JQ, Piccirillo JF, Wang H, Xu G. [Development of the Sino-Nasal Outcome Test-20 Chinese version (SNOT-20 CV)]. Zhonghua er bi yan hou tou jing wai ke za zhi = Chinese journal of otorhinolaryngology head and neck surgery 2008; 43:751-6.
107. Alanazy F, Dousary SA, Albosaily A, Aldriweesh T, Alsaleh S, Aldrees T. Psychometric Arabic Sino-Nasal Outcome Test-22: validation and translation in chronic rhinosinusitis patients. Annals of Saudi medicine 2018; 38:22-27.
108. Cakir Cetin A, Kumus O, Keskinoglu P, Sutay S, Ecevit MC. Turkish validation of the Sino-Nasal Outcome Test-22. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2019; 44:557-64.
109. van Oene CM, van Reij EJ, Sprangers MA, Fokkens WJ. Quality-assessment of disease-specific quality of life questionnaires for rhinitis and rhinosinusitis: a systematic review. Allergy 2007; 62:1359-71.
110. Rudmik L, Hopkins C, Peters A, Smith TL, Schlosser RJ, Soler ZM. Patient-reported outcome measures for adult chronic rhinosinusitis: A systematic review and quality assessment. The Journal of allergy and clinical immunology 2015; 136:1532-40.e2.
111. DeConde AS, Mace JC, Bodner Tet al. SNOT-22 quality of life domains differentially predict treatment modality selection in chronic rhinosinusitis. International forum of allergy & rhinology 2014; 4:972-9.
112. Toma S, Hopkins C. Stratification of SNOT-22 scores into mild, moderate or severe and relationship with other subjective instruments. Rhinology 2016; 54:129-33.
113. Phillips KM, Hoehle LP, Caradonna DS, Gray ST, Sedaghat AR. Minimal clinically important difference for the 22-item Sinonasal Outcome Test in medically managed patients with chronic rhinosinusitis. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2018; 43:1328-34.
114. Naito K, Iwata S. Current advances in rhinomanometry. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 1997; 254:309-12.
115. Clement PA. Committee report on standardization of rhinomanometry. Rhinology 1984; 22:151-5.
116. Vogt K, Jalowayski AA, Althaus Wet al. 4-Phase-Rhinomanometry (4PR)--basics and practice 2010. Rhinology Supplement 2010; 21:1-50.
117. Jones AS, Lancer JM, Stevens JC, Beckingham E. Rhinomanometry: do the anterior and posterior methods give equivalent results? Clinical otolaryngology and allied sciences 1987; 12:109-14.
118. Eccles R. A guide to practical aspects of measurement of human nasal airflow by rhinomanometry. Rhinology 2011; 49:2-10.
119. Demirbas D, Cingi C, Cakli H, Kaya E. Use of rhinomanometry in common rhinologic disorders. Expert review of medical devices 2011; 8:769-77.
120. Clement PA, Halewyck S, Gordts F, Michel O. Critical evaluation of different objective techniques of nasal airway assessment: a clinical review. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 2014; 271:2617-25.

121. Lund VJ. Objective assessment of nasal obstruction. Otolaryngologic clinics of North America 1989; 22:279-90.
122. Bermüller C, Kirsche H, Rettinger G, Riechelmann H. Diagnostic accuracy of peak nasal inspiratory flow and rhinomanometry in functional rhinosurgery. The Laryngoscope 2008; 118:605-10.
123. Clement PA, Gordts F. Consensus report on acoustic rhinometry and rhinomanometry. Rhinology 2005; 43:169-79.
124. Hilberg O, Pedersen OF. Acoustic rhinometry: recommendations for technical specifications and standard operating procedures. Rhinology Supplement 2000; 16:3-17.
125. Augé J, Vent J, Agache Iet al. EAACI Position paper on the standardization of nasal allergen challenges. Allergy 2018; 73:1597-608.
126. Valero A, Navarro AM, Del Cuvillo Aet al. Position paper on nasal obstruction: evaluation and treatment. Journal of investigational allergology & clinical immunology 2018; 28:67-90.
127. Hasegawa M. Nasal cycle and postural variations in nasal resistance. The Annals of otology, rhinology, and laryngology 1982; 91:112-4.
128. Hasegawa M, Kern EB. The effect of breath holding, hyperventilation, and exercise on nasal resistance. Rhinology 1978; 16:243-9.
129. Cole P, Forsyth R, Haight JS. Effects of cold air and exercise on nasal patency. The Annals of otology, rhinology, and laryngology 1983; 92:196-8.
130. Ohki M, Naito K, Cole P. Dimensions and resistances of the human nose: racial differences. The Laryngoscope 1991; 101:276-8.
131. Jones AS, Lancer JM, Moir AA, Stevens JC. Effect of aspirin on nasal resistance to airflow. British medical journal (Clinical research ed) 1985; 290:1171-3.
132. Dessi P, Sambuc R, Moulin G, Ledoray V, Cannoni M. Effect of heavy smoking on nasal resistance. Acta oto-laryngologica 1994; 114:305-10.
133. Dastidar P, Numminen J, Heinonen T, Ryymin P, Rautiainen M, Laasonen E. Nasal airway volumetric measurement using segmented HRCT images and acoustic rhinometry. American journal of rhinology 1999; 13:97-103.
134. Grymer LF, Hilberg O, Pedersen OF, Rasmussen TR. Acoustic rhinometry: values from adults with subjective normal nasal patency. Rhinology 1991; 29:35-47.
135. Holmstrom M. The use of objective measures in selecting patients for septal surgery. Rhinology 2010; 48:387-93.
136. Fisher EW, Morris DP, Biemans JM, Palmer CR, Lund VJ. Practical aspects of acoustic rhinometry: problems and solutions. Rhinology 1995; 33:219-23.
137. Parvez L, Erasala G, Noronha A. Novel techniques, standardization tools to enhance reliability of acoustic rhinometry measurements. Rhinology Supplement 2000; 16:18-28.
138. Wilson AM, Fowler SJ, Martin SW, White PS, Gardiner Q, Lipworth BJ. Evaluation of the importance of head and probe stabilisation in acoustic rhinometry. Rhinology 2001; 39:93-7.
139. Lal D, Corey JP. Acoustic rhinometry and its uses in rhinology and diagnosis of nasal obstruction. Facial plastic surgery clinics of North America 2004; 12:397-405, v.
140. Aziz T, Biron VL, Ansari K, Flores-Mir C. Measurement tools for the diagnosis of nasal septal deviation: a systematic review. Journal of otolaryngology - head & neck

surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale 2014; 43:11.
141. Straszek SP, Schlünssen V, Sigsgaard T, Pedersen OF. Reference values for acoustic rhinometry in decongested school children and adults: the most sensitive measurement for change in nasal patency. Rhinology 2007; 45:36-9.
142. Roithmann R, Chapnik J, Zamel N, Barreto SM, Cole P. Acoustic rhinometric assessment of the nasal valve. American journal of rhinology 1997; 11:379-85.
143. Kjaergaard T, Cvancarova M, Steinsvåg SK. Does nasal obstruction mean that the nose is obstructed? The Laryngoscope 2008; 118:1476-81.
144. Terheyden H, Maune S, Mertens J, Hilberg O. Acoustic rhinometry: validation by three-dimensionally reconstructed computer tomographic scans. Journal of applied physiology (Bethesda, Md : 1985) 2000; 89:1013-21.
145. Hilberg O, Jensen FT, Pedersen OF. Nasal airway geometry: comparison between acoustic reflections and magnetic resonance scanning. Journal of applied physiology (Bethesda, Md : 1985) 1993; 75:2811-9.
146. Corey JP, Gungor A, Nelson R, Fredberg J, Lai V. A comparison of the nasal cross-sectional areas and volumes obtained with acoustic rhinometry and magnetic resonance imaging. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 1997; 117:349-54.
147. Corey JP, Nalbone VP, Ng BA. Anatomic correlates of acoustic rhinometry as measured by rigid nasal endoscopy. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 1999; 121:572-6.
148. Min YG, Jang YJ. Measurements of cross-sectional area of the nasal cavity by acoustic rhinometry and CT scanning. The Laryngoscope 1995; 105:757-9.
149. Mamikoglu B, Houser S, Akbar I, Ng B, Corey JP. Acoustic rhinometry and computed tomography scans for the diagnosis of nasal septal deviation, with clinical correlation. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2000; 123:61-8.
150. Scadding GK, Darby YC, Austin CE. Acoustic rhinometry compared with anterior rhinomanometry in the assessment of the response to nasal allergen challenge. Clinical otolaryngology and allied sciences 1994; 19:451-4.
151. Ottaviano G, Scadding GK, Iacono V, Scarpa B, Martini A, Lund VJ. Peak nasal inspiratory flow and peak expiratory flow. Upright and sitting values in an adult population. Rhinology 2016; 54:160-3.
152. Ottaviano G, Scadding GK, Coles S, Lund VJ. Peak nasal inspiratory flow; normal range in adult population. Rhinology 2006; 44:32-5.
153. Chin D, Marcells G, Malek Jet al. Nasal peak inspiratory flow (NPIF) as a diagnostic tool for differentiating decongestable from structural nasal obstruction. Rhinology 2014; 52:116-21.
154. Ottaviano G, Lund VJ, Nardello Eet al. Comparison between unilateral PNIF and rhinomanometry in healthy and obstructed noses. Rhinology 2014; 52:25-30.
155. Cho SI, Hauser R, Christiani DC. Reproducibility of nasal peak inspiratory flow among healthy adults: assessment of epidemiologic utility. Chest 1997; 112:1547-53.
156. Starling-Schwanz R, Peake HL, Salome CMet al. Repeatability of peak nasal inspiratory flow measurements and utility for assessing the severity of rhinitis. Allergy 2005; 60:795-800.

157. Chaves C, Ibiapina Cda C, de Andrade CR, Godinho R, Alvim CG, Cruz Á A. Correlation between peak nasal inspiratory flow and peak expiratory flow in children and adolescents. Rhinology 2012; 50:381-5.
158. van Spronsen E, Ebbens FA, Fokkens WJ. Normal peak nasal inspiratory flow rate values in healthy children aged 6 to 11 years in the Netherlands. Rhinology 2012; 50:22-5.
159. da Cunha Ibiapina C, Ribeiro de Andrade C, Moreira Camargos PA, Goncalves Alvim C, Augusto Cruz A. Reference values for peak nasal inspiratory flow in children and adolescents in Brazil. Rhinology 2011; 49:304-8.
160. Mo S, Gupta SS, Stroud Aet al. Nasal Peak Inspiratory Flow in Healthy and Obstructed Patients: Systematic Review and Meta-Analysis. The Laryngoscope 2020.
161. Timperley D, Srubisky A, Stow N, Marcells GN, Harvey RJ. Minimal clinically important differences in nasal peak inspiratory flow. Rhinology 2011; 49:37-40.
162. Dor-Wojnarowska A, Liebhart J, Rabski M, Fal A, Panaszek B, Samolinski B. Repeatability of peak nasal inspiratory flow rate (PNIF) measurements and its change after administration of 0.05% oxymetazoline. European Respiratory Journal 2012; 40:P2242.
163. !!! INVALID CITATION !!! 72,79-81.
164. Ottaviano G, Lund VJ, Nardello Eet al. Peak nasal inspiratory flow: a useful and handy tool for the diagnosis of nasal obstruction in the elderly. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 2014; 271:2427-31.
165. Poetker DM, Rhee JS, Mocan BO, Michel MA. Computed tomography technique for evaluation of the nasal valve. Archives of facial plastic surgery 2004; 6:240-3.
166. Ardeshirpour F, McCarn KE, McKinney AM, Odland RM, Yueh B, Hilger PA. Computed tomography scan does not correlate with patient experience of nasal obstruction. The Laryngoscope 2016; 126:820-5.
167. Cakmak O, Coşkun M, Celik H, Büyüklü F, Ozlüoğlu LN. Value of acoustic rhinometry for measuring nasal valve area. The Laryngoscope 2003; 113:295-302.
168. Rhee JS, Pawar SS, Garcia GJ, Kimbell JS. Toward personalized nasal surgery using computational fluid dynamics. Archives of facial plastic surgery 2011; 13:305-10.
169. Casey KP, Borojeni AA, Koenig LJ, Rhee JS, Garcia GJ. Correlation between Subjective Nasal Patency and Intranasal Airflow Distribution. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2017; 156:741-50.
170. Gaberino C, Rhee JS, Garcia GJ. Estimates of nasal airflow at the nasal cycle mid-point improve the correlation between objective and subjective measures of nasal patency. Respiratory physiology & neurobiology 2017; 238:23-32.
171. Garcia GJM, Hariri BM, Patel RG, Rhee JS. The relationship between nasal resistance to airflow and the airspace minimal cross-sectional area. Journal of biomechanics 2016; 49:1670-78.
172. Radulesco T, Meister L, Bouchet Get al. Functional relevance of computational fluid dynamics in the field of nasal obstruction: A literature review. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2019; 44:801-09.

173. Fairley JW, Durham LH, Ell SR. Correlation of subjective sensation of nasal patency with nasal inspiratory peak flow rate. Clinical otolaryngology and allied sciences 1993; 18:19-22.
174. Larsen K, Kristensen S. Peak flow nasal patency indices and self-assessment in septoplasty. Clinical otolaryngology and allied sciences 1990; 15:327-34.
175. Wang DY, Raza MT, Goh DY, Lee BW, Chan YH. Acoustic rhinometry in nasal allergen challenge study: which dimensional measures are meaningful? Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 2004; 34:1093-8.
176. Roithmann R, Cole P, Chapnik J, Barreto SM, Szalai JP, Zamel N. Acoustic rhinometry, rhinomanometry, and the sensation of nasal patency: a correlative study. The Journal of otolaryngology 1994; 23:454-8.
177. Oztürk F, Türktaş I, Asal K, Ileri F, Münevver Pinar N. Effect of intranasal triamcinolone acetonide on bronchial hyper-responsiveness in children with seasonal allergic rhinitis and comparison of perceptional nasal obstruction with acoustic rhinometric assessment. International journal of pediatric otorhinolaryngology 2004; 68:1007-15.
178. Larsson C, Millqvist E, Bende M. Relationship between subjective nasal stuffiness and nasal patency measured by acoustic rhinometry. American journal of rhinology 2001; 15:403-5.
179. Pirilä T, Tikanto J. Unilateral and bilateral effects of nasal septum surgery demonstrated with acoustic rhinometry, rhinomanometry, and subjective assessment. American journal of rhinology 2001; 15:127-33.
180. Jose J, Ell SR. The association of subjective nasal patency with peak inspiratory nasal flow in a large healthy population. Clinical otolaryngology and allied sciences 2003; 28:352-4.
181. Rhee JS. Measuring outcomes in nasal surgery: realities and possibilities. Archives of facial plastic surgery 2009; 11:416-9.
182. Mozzanica F, Gera R, Bulgheroni C, Ambrogi F, Schindler A, Ottaviani F. Correlation between Objective and Subjective Assessment of Nasal Patency. Iranian journal of otorhinolaryngology 2016; 28:313-19.
183. Tomkinson A, Eccles R. Comparison of the Relative Abilities of Acoustic Rhinometry, Rhinomanometry, and the Visual Analogue Scale in Detecting Change in the Nasal Cavity in a Healthy Adult Population. American journal of rhinology 1996; 10:161-66.
184. Andrews PJ, Choudhury N, Takhar A, Poirrier AL, Jacques T, Randhawa PS. The need for an objective measure in septorhinoplasty surgery: are we any closer to finding an answer? Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2015; 40:698-703.
185. Mendes AI, Wandalsen GF, Solé D. Objective and subjective assessments of nasal obstruction in children and adolescents with allergic rhinitis. Jornal de pediatria 2012; 88:389-95.
186. Wallace DV, Dykewicz MS, Bernstein DIet al. The diagnosis and management of rhinitis: an updated practice parameter. The Journal of allergy and clinical immunology 2008; 122:S1-84.
187. Meltzer EO. Allergic Rhinitis: Burden of Illness, Quality of Life, Comorbidities, and Control. Immunology and allergy clinics of North America 2016; 36:235-48.

188. Lunn M, Craig T. Rhinitis and sleep. Sleep medicine reviews 2011; 15:293-9.
189. Seidman MD, Gurgel RK, Lin SYet al. Clinical practice guideline: Allergic rhinitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2015; 152:S1-43.
190. Pearlman DS. Pathophysiology of the inflammatory response. The Journal of allergy and clinical immunology 1999; 104:S132-7.
191. White M. Mediators of inflammation and the inflammatory process. The Journal of allergy and clinical immunology 1999; 103:S378-81.
192. Quraishi SA, Davies MJ, Craig TJ. Inflammatory responses in allergic rhinitis: traditional approaches and novel treatment strategies. The Journal of the American Osteopathic Association 2004; 104:S7-15.
193. Bascom R, Wachs M, Naclerio RM, Pipkorn U, Galli SJ, Lichtenstein LM. Basophil influx occurs after nasal antigen challenge: effects of topical corticosteroid pretreatment. The Journal of allergy and clinical immunology 1988; 81:580-9.
194. Bascom R, Pipkorn U, Lichtenstein LM, Naclerio RM. The influx of inflammatory cells into nasal washings during the late response to antigen challenge. Effect of systemic steroid pretreatment. The American review of respiratory disease 1988; 138:406-12.
195. Bachert C, Wagenmann M, Holtappels G. Cytokines and adhesion molecules in allergic rhinitis. American journal of rhinology 1998; 12:3-8.
196. Gelfand EW. Inflammatory mediators in allergic rhinitis. The Journal of allergy and clinical immunology 2004; 114:S135-8.
197. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. The Journal of allergy and clinical immunology 2001; 108:S2-8.
198. Hastan D, Fokkens WJ, Bachert Cet al. Chronic rhinosinusitis in Europe--an underestimated disease. A GA²LEN study. Allergy 2011; 66:1216-23.
199. Hirsch AG, Stewart WF, Sundaresan ASet al. Nasal and sinus symptoms and chronic rhinosinusitis in a population-based sample. Allergy 2017; 72:274-81.
200. Obaseki D, Potts J, Joos Get al. The relation of airway obstruction to asthma, chronic rhinosinusitis and age: results from a population survey of adults. Allergy 2014; 69:1205-14.
201. Sundaresan AS, Hirsch AG, Storm Met al. Occupational and environmental risk factors for chronic rhinosinusitis: a systematic review. International forum of allergy & rhinology 2015; 5:996-1003.
202. Hoffmans R, Wagemakers A, van Drunen C, Hellings P, Fokkens W. Acute and chronic rhinosinusitis and allergic rhinitis in relation to comorbidity, ethnicity and environment. PloS one 2018; 13:e0192330.
203. Grayson JW, Hopkins C, Mori E, Senior B, Harvey RJ. Contemporary Classification of Chronic Rhinosinusitis Beyond Polyps vs No Polyps: A Review. JAMA Otolaryngol Head Neck Surg 2020; 146:831-38.
204. Cao PP, Wang ZC, Schleimer RP, Liu Z. Pathophysiologic mechanisms of chronic rhinosinusitis and their roles in emerging disease endotypes. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 2019; 122:33-40.
205. Mucida D, Salek-Ardakani S. Regulation of TH17 cells in the mucosal surfaces. The Journal of allergy and clinical immunology 2009; 123:997-1003.

206. Megale SR, Scanavini AB, Andrade EC, Fernandes MI, Anselmo-Lima WT. Gastroesophageal reflux disease: its importance in ear, nose, and throat practice. International journal of pediatric otorhinolaryngology 2006; 70:81-8.
207. Moayyedi P, Axon AT. Review article: gastro-oesophageal reflux disease--the extent of the problem. Alimentary pharmacology & therapeutics 2005; 22 Suppl 1:11-9.
208. DiBaise JK, Huerter JV, Quigley EM. Sinusitis and gastroesophageal reflux disease. Annals of internal medicine 1998; 129:1078.
209. Leason SR, Barham HP, Oakley Get al. Association of gastro-oesophageal reflux and chronic rhinosinusitis: systematic review and meta-analysis. Rhinology 2017; 55:3-16.
210. Bohnhorst I, Jawad S, Lange B, Kjeldsen J, Hansen JM, Kjeldsen AD. Prevalence of chronic rhinosinusitis in a population of patients with gastroesophageal reflux disease. American journal of rhinology & allergy 2015; 29:e70-4.
211. Sella GCP, Tamashiro E, Anselmo-Lima WT, Valera FCP. Relation between chronic rhinosinusitis and gastroesophageal reflux in adults: systematic review. Brazilian journal of otorhinolaryngology 2017; 83:356-63.
212. Loehrl TA, Samuels TL, Poetker DM, Toohill RJ, Blumin JH, Johnston N. The role of extraesophageal reflux in medically and surgically refractory rhinosinusitis. The Laryngoscope 2012; 122:1425-30.
213. Loehrl TA. Sinonasal problems and reflux. Facial plastic surgery clinics of North America 2012; 20:83-6.
214. Morinaka S, Ichimiya M, Nakamura H. Detection of Helicobacter pylori in nasal and maxillary sinus specimens from patients with chronic sinusitis. The Laryngoscope 2003; 113:1557-63.
215. Lin YH, Chang TS, Yao YC, Li YC. Increased Risk of Chronic Sinusitis in Adults With Gastroesophgeal Reflux Disease: A Nationwide Population-Based Cohort Study. Medicine 2015; 94:e1642.
216. Alper J. Ulcers as an infectious disease. Science (New York, NY) 1993; 260:159-60.
217. Lee A, Fox J, Hazell S. Pathogenicity of Helicobacter pylori: a perspective. Infection and immunity 1993; 61:1601-10.
218. Wahid NWB, Shermetaro C. Rhinitis Medicamentosa *StatPearls*. Treasure Island (FL): StatPearls Publishing

219. Moore EJ, Kern EB. Atrophic rhinitis: a review of 242 cases. American journal of rhinology 2001; 15:355-61.
220. Hildenbrand T, Weber RK, Brehmer D. Rhinitis sicca, dry nose and atrophic rhinitis: a review of the literature. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 2011; 268:17-26.
221. Manji J, Nayak JV, Thamboo A. The functional and psychological burden of empty nose syndrome. International Forum of Allergy and Rhinology 2018; 8:707-12.
222. Kim CH, Kim J, Song JA, Choi GS, Kwon JH. The Degree of Stress in Patients With Empty Nose Syndrome, Compared With Chronic Rhinosinusitis and Allergic Rhinitis. Ear, Nose and Throat Journal 2019.
223. Sozansky J, Houser SM. Pathophysiology of empty nose syndrome. The Laryngoscope 2015; 125:70-74.

224. Payne SC. Empty Nose Syndrome: What are We Really Talking About? Otolaryngologic clinics of North America 2009; 42:331-37.
225. Coste A, Dessi P, Serrano E. Empty nose syndrome. European Annals of Otorhinolaryngology, Head and Neck Diseases 2012; 129:93-97.
226. Thamboo A, Velasquez N, Habib ARR, Zarabanda D, Paknezhad H, Nayak JV. Defining surgical criteria for empty nose syndrome: Validation of the office-based cotton test and clinical interpretability of the validated Empty Nose Syndrome 6-Item Questionnaire. The Laryngoscope 2017; 127:1746-52.
227. Velasquez N, Thamboo A, Habib ARR, Huang Z, Nayak JV. The Empty Nose Syndrome 6-Item Questionnaire (ENS6Q): a validated 6-item questionnaire as a diagnostic aid for empty nose syndrome patients. International Forum of Allergy and Rhinology 2017; 7:64-71.
228. Gill AS, Said M, Tollefson TT, Strong EB, Nayak JV, Steele TO. Patient-Reported Outcome Measures and Provocative Testing in the Workup of Empty Nose Syndrome-Advances in Diagnosis: A Systematic Review. American journal of rhinology & allergy 2020; 34:134-40.
229. Scheithauer MO. Surgery of the turbinates and "empty nose" syndrome. GMS current topics in otorhinolaryngology, head and neck surgery 2010; 9:Doc03.
230. Batra PS, Seiden AM, Smith TL. Surgical management of adult inferior turbinate hypertrophy: a systematic review of the evidence. The Laryngoscope 2009; 119:1819-27.
231. Shah K, Guarderas J, Krishnaswamy G. Empty nose syndrome and atrophic rhinitis. Annals of Allergy, Asthma and Immunology 2016; 117:217-20.
232. Hardman J, Ahn J, Nirmalananda A. Assessing symptoms of empty nose syndrome in patients following sinonasal and anterior skull base resection. Australian Journal of Otolaryngology 2018; 1.
233. Wong EH, Orgain CA, Sansoni ERet al. Turbinate loss from non-inflammatory sinonasal surgery does not correlate with poor sinonasal function. American journal of otolaryngology 2020; 41:102316.
234. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine 2009; 6:e1000097.
235. Deeks JJ WS, Davenport C. Chapter4 Guide to the contents of a Cochrane Diagnostic Test Accuracy Protocol In: Deeks JJ, Bossuyt PM, Gatsonis C (editors),Cochrane Handbook for Systematic Reviews of Diagnostic Test AccuracyVersion 1.0.0. The Cochrane Collaboration, 2013.
236. Dekkers OM, Vandenbroucke JP, Cevallos M, Renehan AG, Altman DG, Egger M. COSMOS-E: Guidance on conducting systematic reviews and meta-analyses of observational studies of etiology. PLoS medicine 2019; 16:e1002742.
237. Sterne JA, Hernán MA, Reeves BCet al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ (Clinical research ed) 2016; 355:i4919.
238. Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet (London, England) 2002; 359:248-52.
239. Malik J, Li C, Maza Get al. Computational fluid dynamic analysis of aggressive turbinate reductions: is it a culprit of empty nose syndrome? International Forum of Allergy and Rhinology 2019; 9:891-99.

240. Konstantinidis I, Tsakiropoulou E, Chatziavramidis A, Ikonomidis C, Markou K. Intranasal trigeminal function in patients with empty nose syndrome. The Laryngoscope 2017; 127:1263-67.
241. Freund W, Wunderlich AP, Stocker T, Schmitz BL, Scheithauer MO. Empty nose syndrome: Limbic system activation observed by functional magnetic resonance imaging. Laryngoscope 2011; 121:2019-25.
242. Jang YJ, Kim JH, Song HY. Empty nose syndrome: radiologic findings and treatment outcomes of endonasal microplasty using cartilage implants. The Laryngoscope 2011; 121:1308-12.
243. Hong HR, Jang YJ. Correlation between remnant inferior turbinate volume and symptom severity of empty nose syndrome. The Laryngoscope 2016; 126:1290-95.
244. Thamboo A, Velasquez N, Ayoub N, Nayak JV. Distinguishing computed tomography findings in patients with empty nose syndrome. International Forum of Allergy and Rhinology 2016.
245. Li C, Farag AA, Leach Jet al. Computational fluid dynamics and trigeminal sensory examinations of empty nose syndrome patients. The Laryngoscope 2017; 127:E176-E84.
246. Li C, Farag AA, Maza Get al. Investigation of the abnormal nasal aerodynamics and trigeminal functions among empty nose syndrome patients. International Forum of Allergy and Rhinology 2018; 8:444-52.
247. Fu CH, Wu CL, Huang CC, Chang PH, Chen YW, Lee TJ. Nasal nitric oxide in relation to psychiatric status of patients with empty nose syndrome. Nitric Oxide - Biology and Chemistry 2019; 92:55-59.
248. Maza G, Li C, Krebs JPet al. Computational fluid dynamics after endoscopic endonasal skull base surgery-possible empty nose syndrome in the context of middle turbinate resection. International Forum of Allergy and Rhinology 2019; 9:204-11.
249. Lee TJ, Fu CH, Wu CLet al. Evaluation of depression and anxiety in empty nose syndrome after surgical treatment. Laryngoscope 2016; 126:1284-89.
250. Mangin D, Bequignon E, Zerah-Lancner Fet al. Investigating hyperventilation syndrome in patients suffering from empty nose syndrome. Laryngoscope 2017; 127:1983-88.
251. Huang CC, Wu PW, Fu CH, Chang PH, Wu CL, Lee TJ. What drives depression in empty nose syndrome? A Sinonasal Outcome Test-25 subdomain analysis. Rhinology 2019; 10.
252. Manji J, Patel VS, Nayak JV, Thamboo A. Environmental Triggers Associated With Empty Nose Syndrome Symptoms: A Cross-Sectional Study. Annals of Otology, Rhinology and Laryngology 2019; 128:601-07.
253. Dancey CP RJ. Statistics without Maths for Psychology. Pearson Education, 2007.
254. Peiffer C, Costes N, Hervé P, Garcia-Larrea L. Relief of dyspnea involves a characteristic brain activation and a specific quality of sensation. American journal of respiratory and critical care medicine 2008; 177:440-9.
255. Di MY, Jiang Z, Gao ZQ, Li Z, An YR, Lv W. Numerical simulation of airflow fields in two typical nasal structures of empty nose syndrome: A computational fluid dynamics study. PloS one 2013; 8 (12) (no pagination).
256. Chhabra N, Houser SM. The Diagnosis and Management of Empty Nose Syndrome. Otolaryngologic clinics of North America 2009; 42:311-30.

257. Houser SM. Surgical treatment for empty nose syndrome. Archives of Otolaryngology - Head and Neck Surgery 2007; 133:858-63.
258. Siu J, Inthavong K, Shang Y, Vahaji S, Douglas RG. Aerodynamic impact of total inferior turbinectomy versus inferior turbinoplasty - a computational fluid dynamics study. Rhinology 2020.
259. Buday T, Brozmanova M, Biringerova Zet al. Modulation of cough response by sensory inputs from the nose - role of trigeminal TRPA1 versus TRPM8 channels. Cough (London, England) 2012; 8:11.
260. Meusel T, Negoias S, Scheibe M, Hummel T. Topographical differences in distribution and responsiveness of trigeminal sensitivity within the human nasal mucosa. Pain 2010; 151:516-21.
261. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis and rheumatism 2002; 46:1333-43.
262. Mertz H, Morgan V, Tanner Get al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. Gastroenterology 2000; 118:842-8.
263. Clauw DJ. Fibromyalgia: a clinical review. Jama 2014; 311:1547-55.
264. Baguley D, McFerran D, Hall D. Tinnitus. Lancet (London, England) 2013; 382:1600-7.
265. Andersson G, Westin V. Understanding tinnitus distress: introducing the concepts of moderators and mediators. International journal of audiology 2008; 47 Suppl 2:S106-11.
266. Ford AC, Lacy BE, Talley NJ. Irritable Bowel Syndrome. The New England journal of medicine 2017; 376:2566-78.
267. Lemogne C, Consoli SM, Limosin F, Bonfils P. Treating empty nose syndrome as a somatic symptom disorder. General Hospital Psychiatry 2015; 37:273.e9-73.e10.
268. American Psychiatric Association. Somatic Symptom and Related Disorders *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC, 2013.
269. Strazdins E, Nie YF, Ramli Ret al. Association of Mental Health Status With Perception of Nasal Function. JAMA facial plastic surgery 2017; 19:369-77.
270. Berking M, Wupperman P. Emotion regulation and mental health: recent findings, current challenges, and future directions. Current opinion in psychiatry 2012; 25:128-34.
271. Hsieh MK, Chang CN, Hsiao MC, Chen WJ, Chen LH. Conversion paralysis after surgery for lumbar disc herniation. Spine 2010; 35:E308-10.
272. Ludwig L, Pasman JA, Nicholson Tet al. Stressful life events and maltreatment in conversion (functional neurological) disorder: systematic review and meta-analysis of case-control studies. The lancet Psychiatry 2018; 5:307-20.
273. Rhee JS, Book DT, Burzynski M, Smith TL. Quality of life assessment in nasal airway obstruction. The Laryngoscope 2003; 113:1118-22.
274. Hopkins C. Re: Correlation between subjective and objective evaluation of the nasal airway. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2010; 35:147-8; author reply 48.
275. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. Jama 1995; 273:59-65.

276. Clarke JD, Hopkins ML, Eccles R. How good are patients at determining which side of the nose is more obstructed? A study on the limits of discrimination of the subjective assessment of unilateral nasal obstruction. American journal of rhinology 2006; 20:20-4.
277. Wyrwich KW, Tierney WM, Wolinsky FD. Further evidence supporting an SEM-based criterion for identifying meaningful intra-individual changes in health-related quality of life. Journal of clinical epidemiology 1999; 52:861-73.
278. Thulesius HL, Cervin A, Jessen M. Can we always trust rhinomanometry? Rhinology 2011; 49:46-52.
279. Ciprandi G, Cirillo I, Vizzaccaro A, Pallestrini E, Tosca MA. Decongestion test in patients with allergic rhinitis: functional evaluation of nasal airflow. American journal of rhinology 2006; 20:224-6.
280. Barham HP, Knisely A, Christensen J, Sacks R, Marcells GN, Harvey RJ. Costal Cartilage Lateral Crural Strut Graft vs Cephalic Crural Turn-in for Correction of External Valve Dysfunction. JAMA facial plastic surgery 2015; 17:340-5.
281. Pirilä T, Tikanto J. Acoustic rhinometry and rhinomanometry in the preoperative screening of septal surgery patients. American journal of rhinology & allergy 2009; 23:605-9.
282. Hsu HC, Tan CD, Chang CWet al. Evaluation of nasal patency by visual analogue scale/nasal obstruction symptom evaluation questionnaires and anterior active rhinomanometry after septoplasty: a retrospective one-year follow-up cohort study. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2017; 42:53-59.
283. Nivatvongs W, Earnshaw J, Roberts D, Hopkins C. Re: Correlation between subjective and objective evaluation of the nasal airway. A systematic review of the highest level of evidence. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2011; 36:181-2.
284. Vogt K, Wernecke KD, Behrbohm H, Gubisch W, Argale M. Four-phase rhinomanometry: a multicentric retrospective analysis of 36,563 clinical measurements. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 2016; 273:1185-98.
285. Numminen J, Ahtinen M, Huhtala H, Rautiainen M. Comparison of rhinometric measurements methods in intranasal pathology. Rhinology 2003; 41:65-8.
286. Simola M, Malmberg H. Sensation of nasal airflow compared with nasal airway resistance in patients with rhinitis. Clinical otolaryngology and allied sciences 1997; 22:260-2.
287. Gungor A, Moinuddin R, Nelson RH, Corey JP. Detection of the nasal cycle with acoustic rhinometry: techniques and applications. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 1999; 120:238-47.
288. Reber M, Rahm F, Monnier P. The role of acoustic rhinometry in the pre- and postoperative evaluation of surgery for nasal obstruction. Rhinology 1998; 36:184-7.
289. Jones AS, Willatt DJ, Durham LM. Nasal airflow: resistance and sensation. The Journal of laryngology and otology 1989; 103:909-11.

290. Thulesius HL, Cervin A, Jessen M. The importance of side difference in nasal obstruction and rhinomanometry: a retrospective correlation of symptoms and rhinomanometry in 1000 patients. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2012; 37:17-22.
291. Houser SM. Empty nose syndrome associated with middle turbinate resection. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2006; 135:972-3.
292. Lee TJ, Fu CH, Wu CLet al. Evaluation of depression and anxiety in empty nose syndrome after surgical treatment. The Laryngoscope 2016; 126:1284-9.
293. Robinson K, Gatehouse S, Browning GG. Measuring patient benefit from otorhinolaryngological surgery and therapy. The Annals of otology, rhinology, and laryngology 1996; 105:415-22.
294. Jiang C, Wong F, Chen K, Shi R. Assessment of surgical results in patients with empty nose syndrome using the 25-item Sino-Nasal Outcome Test Evaluation. JAMA Otolaryngol Head Neck Surg 2014; 140:453-8.
295. Andrews TM, Orobello N. Histologic versus pH probe results in pediatric laryngopharyngeal reflux. International journal of pediatric otorhinolaryngology 2013; 77:813-6.
296. Lou Z, Lou ZH. Laryngopharyngeal reflux is a potential cause of nasal congestion and obstructive sleep apnea syndrome. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 2018; 275:2409-11.
297. Dagli E, Yüksel A, Kaya M, Ugur KS, Turkay FC. Association of Oral Antireflux Medication With Laryngopharyngeal Reflux and Nasal Resistance. JAMA Otolaryngol Head Neck Surg 2017; 143:478-83.
298. Hanna BC, Wormald PJ. Gastroesophageal reflux and chronic rhinosinusitis. Current opinion in otolaryngology & head and neck surgery 2012; 20:15-8.
299. Alharethy S, Baqays A, Mesallam TAet al. Correlation between Allergic Rhinitis and Laryngopharyngeal Reflux. BioMed research international 2018; 2018:2951928.
300. Gray ST, Sedaghat AR. Treatment of Laryngopharyngeal Reflux May Decrease Subjective Symptoms of Nasal Congestion and Objective Measures of Nasal Resistance. JAMA Otolaryngol Head Neck Surg 2017; 143:483-84.
301. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). Journal of voice : official journal of the Voice Foundation 2002; 16:274-7.
302. Mokkink LB, Terwee CB, Patrick DLet al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2010; 19:539-49.
303. Devillier P, Bousquet PJ, Grassin-Delyle Set al. Comparison of outcome measures in allergic rhinitis in children, adolescents and adults. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 2016; 27:375-81.
304. Gómez-Hervás J, García-Valdecasas Bernal J, Fernández-Prada M, Palomeque-Vera JM, García-Ramos A, Fernández-Castanys BF. Effects of oxymetazoline on nasal flow

and maximum aerobic exercise performance in patients with inferior turbinate hypertrophy. The Laryngoscope 2015; 125:1301-6.
305. Smith DH, Brook CD, Virani S, Platt MP. The inferior turbinate: An autonomic organ. American journal of otolaryngology 2018; 39:771-75.
306. Hasegawa M, Kern EB. The human nasal cycle. Mayo Clinic proceedings 1977; 52:28-34.
307. Davis SS, Eccles R. Nasal congestion: mechanisms, measurement and medications. Core information for the clinician. Clinical otolaryngology and allied sciences 2004; 29:659-66.
308. Hasegawa M. Posture-induced nasal obstruction in patients with allergic rhinitis. Clinical otolaryngology and allied sciences 1994; 19:135-7.
309. Kroenke K. Patients presenting with somatic complaints: epidemiology, psychiatric comorbidity and management. International journal of methods in psychiatric research 2003; 12:34-43.
310. Kroenke K, Rosmalen JG. Symptoms, syndromes, and the value of psychiatric diagnostics in patients who have functional somatic disorders. The Medical clinics of North America 2006; 90:603-26.
311. Kroenke K, Spitzer RL, Williams JBet al. Physical symptoms in primary care. Predictors of psychiatric disorders and functional impairment. Archives of family medicine 1994; 3:774-9.
312. Löwe B, Spitzer RL, Williams JB, Mussell M, Schellberg D, Kroenke K. Depression, anxiety and somatization in primary care: syndrome overlap and functional impairment. Gen Hosp Psychiatry 2008; 30:191-9.
313. Simon GE, VonKorff M, Piccinelli M, Fullerton C, Ormel J. An international study of the relation between somatic symptoms and depression. The New England journal of medicine 1999; 341:1329-35.
314. Clarke DM, Piterman L, Byrne CJ, Austin DW. Somatic symptoms, hypochondriasis and psychological distress: a study of somatisation in Australian general practice. The Medical journal of Australia 2008; 189:560-4.
315. Hanel G, Henningsen P, Herzog Wet al. Depression, anxiety, and somatoform disorders: vague or distinct categories in primary care? Results from a large cross-sectional study. Journal of psychosomatic research 2009; 67:189-97.
316. Alam ES, Musselman DL, Chyou Det al. Somatization, Depression, and Anxiety Disorders in a Rhinology Practice. American journal of rhinology & allergy 2019; 33:470-77.
317. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of internal medicine 2006; 166:1092-7.
318. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Löwe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Annals of internal medicine 2007; 146:317-25.
319. Katon WJ, Simon G, Russo Jet al. Quality of depression care in a population-based sample of patients with diabetes and major depression. Medical care 2004; 42:1222-9.
320. Bair MJ, Wu J, Damush TM, Sutherland JM, Kroenke K. Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. Psychosomatic medicine 2008; 70:890-7.

321. Sherbourne CD, Asch SM, Shugarman LRet al. Early identification of co-occurring pain, depression and anxiety. Journal of general internal medicine 2009; 24:620-5.
322. Kroenke K, Bair MJ, Damush TMet al. Optimized antidepressant therapy and pain self-management in primary care patients with depression and musculoskeletal pain: a randomized controlled trial. Jama 2009; 301:2099-110.
323. Callahan CM, Boustani MA, Unverzagt FWet al. Effectiveness of collaborative care for older adults with Alzheimer disease in primary care: a randomized controlled trial. Jama 2006; 295:2148-57.
324. Thombs BD, de Jonge P, Coyne JCet al. Depression screening and patient outcomes in cardiovascular care: a systematic review. Jama 2008; 300:2161-71.
325. Okuyama T, Akechi T, Mackenzie L, Furukawa TA. Psychotherapy for depression among advanced, incurable cancer patients: A systematic review and meta-analysis. Cancer treatment reviews 2017; 56:16-27.
326. Leithner K, Assem-Hilger E, Fischer-Kern M, Loeffler-Stastka H, Sam C, Ponocny-Seliger E. Psychiatric morbidity in gynecological and otorhinolaryngological outpatients: a comparative study. Gen Hosp Psychiatry 2009; 31:233-9.
327. Khoo K, Man REK, Rees G, Gupta P, Lamoureux EL, Fenwick EK. The relationship between diabetic retinopathy and psychosocial functioning: a systematic review. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2019; 28:2017-39.
328. Kendrick T, Dowrick C, McBride Aet al. Management of depression in UK general practice in relation to scores on depression severity questionnaires: analysis of medical record data. BMJ (Clinical research ed) 2009; 338:b750.
329. Duffy FF, Chung H, Trivedi M, Rae DS, Regier DA, Katzelnick DJ. Systematic use of patient-rated depression severity monitoring: is it helpful and feasible in clinical psychiatry? Psychiatric services (Washington, DC) 2008; 59:1148-54.
330. Zijlema WL, Stolk RP, Löwe B, Rief W, White PD, Rosmalen JG. How to assess common somatic symptoms in large-scale studies: a systematic review of questionnaires. Journal of psychosomatic research 2013; 74:459-68.
331. Kroenke K, Spitzer RL, Williams JB. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosomatic medicine 2002; 64:258-66.
332. Sha MC, Callahan CM, Counsell SR, Westmoreland GR, Stump TE, Kroenke K. Physical symptoms as a predictor of health care use and mortality among older adults. The American journal of medicine 2005; 118:301-6.
333. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. The New England journal of medicine 2008; 358:453-63.
334. Harris AM, Orav EJ, Bates DW, Barsky AJ. Somatization increases disability independent of comorbidity. Journal of general internal medicine 2009; 24:155-61.
335. Rief W, Martin A. How to use the new DSM-5 somatic symptom disorder diagnosis in research and practice: a critical evaluation and a proposal for modifications. Annual review of clinical psychology 2014; 10:339-67.
336. Voigt K, Nagel A, Meyer B, Langs G, Braukhaus C, Löwe B. Towards positive diagnostic criteria: a systematic review of somatoform disorder diagnoses and suggestions for future classification. Journal of psychosomatic research 2010; 68:403-14.

337. Toussaint A, Murray AM, Voigt Ket al. Development and Validation of the Somatic Symptom Disorder-B Criteria Scale (SSD-12). Psychosomatic medicine 2016; 78:5-12.
338. Löwe B, Decker O, Müller Set al. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. Medical care 2008; 46:266-74.
339. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. Journal of general internal medicine 2001; 16:606-13.
340. Toussaint A, Hüsing P, Kohlmann S, Löwe B. Detecting DSM-5 somatic symptom disorder: criterion validity of the Patient Health Questionnaire-15 (PHQ-15) and the Somatic Symptom Scale-8 (SSS-8) in combination with the Somatic Symptom Disorder - B Criteria Scale (SSD-12). Psychological medicine 2020; 50:324-33.
341. Boulding R, Stacey R, Niven R, Fowler SJ. Dysfunctional breathing: a review of the literature and proposal for classification. European respiratory review : an official journal of the European Respiratory Society 2016; 25:287-94.
342. Ogata N, Bapat U, Darby Y, Scadding G. Prevalence of hyperventilation syndrome in an allergy clinic, compared with a routine ENT clinic. The Journal of laryngology and otology 2006; 120:924-6.
343. Hanna BC, Woodman P, Adair R. Assessing the role of chronic hyperventilation in patients with nasal congestion: our experience in 118 patients. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2012; 37:155-8.
344. Bartley J. Nasal congestion and hyperventilation syndrome. American journal of rhinology 2005; 19:607-11.
345. van Dixhoorn J, Duivenvoorden HJ. Efficacy of Nijmegen Questionnaire in recognition of the hyperventilation syndrome. Journal of psychosomatic research 1985; 29:199-206.
346. Novis SJ, Akkina SR, Lynn S, Kern HE, Keshavarzi NR, Pynnonen MA. A diagnostic dilemma: chronic sinusitis diagnosed by non-otolaryngologists. International forum of allergy & rhinology 2016; 6:486-90.
347. Choi JM, Yang JI, Kang SJet al. Association Between Anxiety and Depression and Gastroesophageal Reflux Disease: Results From a Large Cross-sectional Study. Journal of neurogastroenterology and motility 2018; 24:593-602.
348. Eccles R, Griffiths DH, Newton CG, Tolley NS. The effects of menthol isomers on nasal sensation of airflow. Clinical otolaryngology and allied sciences 1988; 13:25-9.
349. Cortina JM. What is coefficient alpha? An examination of theory and applications. Journal of Applied Psychology 1993; 78:98-104.
350. Chaichana KL, Mukherjee D, Adogwa O, Cheng JS, McGirt MJ. Correlation of preoperative depression and somatic perception scales with postoperative disability and quality of life after lumbar discectomy. Journal of neurosurgery Spine 2011; 14:261-7.
351. Nickel R, Egle UT, Rompe J, Eysel P, Hoffmann SO. Somatisation predicts the outcome of treatment in patients with low back pain. The Journal of bone and joint surgery British volume 2002; 84:189-95.
352. Espay AJ, Aybek S, Carson Aet al. Current Concepts in Diagnosis and Treatment of Functional Neurological Disorders. JAMA neurology 2018; 75:1132-41.
353. Girouard E, Savoie I, Witkowski LC. Functional Neurological Symptom Disorder: A Diagnostic Algorithm. Behavioural neurology 2019; 2019:3154849.

354. Barham HP, Knisely A, Christensen J, Sacks R, Marcells GN, Harvey RJ. Costal Cartilage Lateral Crural Strut Graft vs Cephalic Crural Turn-in for Correction of External Valve Dysfunction. JAMA facial plastic surgery 2015.

REFERENCES

VITA

NAME	Dichapong Kanjanawasee
DATE OF BIRTH	03 November 1986
PLACE OF BIRTH	Thailand
HOME ADDRESS	1914 Bkk-Nonthaburi 46 Bang-sue Bangkok 10800