Evaluation and treatment of olfactory dysfunction in chronic upper respiratory tract diseases

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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DECLARATION

I, Dr Alfonso Luca Pendolino, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ABSTRACT

Background

Olfactory dysfunction (OD) represents a common problem in chronic upper respiratory diseases; however, prevalence and treatment options remain poorly understood.

Aims

To evaluate OD in terms of prevalence and severity in three types of chronic upper respiratory disease:

1. Non-steroidal anti-inflammatory drugs (NSAIDs)-exacerbated respiratory disease (N-ERD)
2. Sleep-disordered breathing (SDB)
3. Post-infectious olfactory dysfunction (mainly on patients with COVID-19-related OD – C19OD).

To assess the efficacy and effectiveness of currently available and new treatments in these three diseases including intranasal lysine aspirin (LAS) for N-ERD, radiofrequency of inferior turbinates (RFITs) for SDB and functional septorhinoplasty (fSRP) for C19OD. This is based on the hypothesis that an increase in nasal airflow and/or control of local inflammation can lead to improved olfaction.

Methods

Ten research studies were conducted for this PhD project: 2 retrospective cohort studies, 4 cross-sectional analyses, 2 prospective non-controlled cohort studies and 2 prospective-controlled cohort studies.

Results

OD is highly prevalent amongst N-ERD (81.8%), SDB (23.5%) and C19OD patients (prevalence variable on studies). Long-term use of LAS in N-ERD was associated with

improved olfaction ($p=0.048$), nasal airflow ($p<0.001$) and quality of life (QoL – $p=0.02$) when compared to those not using it. RFITs in SDB subjects significantly improved nasal airways ($p<0.02$) and OD, the latter not significantly. Persistent C19OD significantly affects QoL ($p<0.05$). Corticosteroids plus olfactory training (OT) can significantly improve measured and reported olfaction ($p=0.01$ for both) in medium-term C19OD (~7 months). In patients with long-term (>2years) C19OD, fSRP can significantly restore olfaction ($p<0.05$) when compared to OT.

Conclusion

My research offers new insights in the treatment of OD in N-ERD, SDB and PIOD patients while suggesting new potential therapeutic options through the management of local sinonasal inflammation and/or nasal airways optimisation. My findings will encourage future research and assist in the development of new treatments for smell loss.

IMPACT STATEMENT

Olfaction had long been a forgotten sense. Recently the COVID-19 pandemic brought smell centre stage being olfactory dysfunction (OD) a highly prevalent symptom following SARS-CoV-2 infection. Since then, research on olfaction has flourished, aiming to find the best treatment to restore the sense of smell.

My PhD project is therefore timely since there is a necessity for new research inputs on OD. This is because smell loss severely impacts quality of life (QoL). The majority of my papers have confirmed this strict relationship. My research on N-ERD has suggested that intranasal lysine aspirin can improve sinonasal symptoms, including olfaction, and, as a consequence, patients' QoL. Similarly, my studies on COVID-19-related OD (C19OD) have further emphasized this correlation by also showing how olfactory recovery could contribute to QoL improvement.

My data have also brought further evidence in support of new treatment options to improve sense of smell according to the different pathologies studied. I showed that intranasal lysine aspirin can, not only control nasal polyps and improve nasal airways, but can also increase olfaction in patients with N-ERD whilst being a cost-effective alternative to more expensive biologics. My study on sleep-disordered breathing will support the implementation of radiofrequency of inferior turbinates in the treatment of rhinitis in these patients with positive implications on sense of smell. My research has also demonstrated, in various studies and different pathologies, the strict relationship between nasal airflow and olfaction and how nasal airways optimisation can lead to better olfaction. My contribution in the topic of C19OD has added further data into a rapidly evolving field. My two prospective-controlled studies on C19OD offer good level of evidence in support of the treatments analysed and will drive further research on the topic. More specifically, these explored two of the main topics on which research is

currently focused, including the effect of neuroinflammation and of nasal airflow on the olfactory epithelium. With this in mind, my planned future research will centre on studying the histological changes of the olfactory mucosa in patients with C19OD and on further investigating the role of nasal airway optimisation in improving sense of smell.

The direct impact my articles are having on the scientific community is confirmed by the good number of citations these have already received and the high impact factor of the journals in which these have been published. From a public health perspective, my data will be important to support national funding applications to conduct further research on these topics. In a period in which the National Health Service is trying to keep health costs down, my results could also be used by policymakers when looking at cost-effective treatment solutions. On a personal level, as an ENT surgeon and a researcher, I finally hope my findings will inspire other colleagues to pursue research in this interesting field.

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ACKNOWLEDGEMENT

I would like to start by thanking my PhD supervisors, Professor Peter Andrews and Dr Glenis Scadding for their support throughout my PhD journey.

Prof. Peter Andrews has been my mentor since I moved to London in 2019, providing me with all the unwavering human and professional support anyone could ever ask for. I am incredibly grateful for his insightful feedbacks and the countless opportunities that helped me to reach my goals and develop as a surgeon and researcher. He consistently pushed me beyond my perceived limits and encouraged me during challenging times, especially during the pandemic. His trust and belief in my potential played a crucial role in my professional growth as a clinical scientist and surgeon. He taught me the importance of always considering the broader picture and shaping my research activities to make a meaningful impact on clinical practice and patient's care. Beyond the professional realm, his mentorship has profoundly impacted me personally, fostering my development as an individual. Reflecting on my academic journey from when I first arrived in the UK to this point of completing my PhD, I can only say that I have been truly fortunate to have had Prof. Andrews as my mentor.

Dr Glenis Scadding has been a precious guide since I first started working at the Royal National ENT. She has provided me with an invaluable guidance and continuously encouraged me to explore new avenues and challenge myself intellectually. Her expertise, patience, and passion for research have been a constant source of motivation throughout this challenging journey.

I am deeply indebted to both my supervisors for their incessant support and for creating an environment where I could thrive.

I would also like to express my deepest gratitude to Giancarlo, Bruno, and all the other colleagues I had the opportunity to collaborate with during these years, for their priceless help and expertise.

I especially would like to thank my family for their love and emotional support, which provided me with the strength and resilience to overcome the many obstacles I encountered during these years. Their consistent efforts throughout their lives, coupled with a relentless pursuit of higher standards, have been a profound source of inspiration. Finally, my last thought goes to my uncle, who sadly passed away a few years ago. Although he is no longer with us, his belief in my ability continues to motivate me.

I feel deeply fortunate for the invaluable opportunity to have conducted my doctoral research at the University College London, a prestigious institution renowned for its academic excellence. This experience has not only allowed me to deeply explore my research topic but has also equipped me with a diverse range of critical thinking and analytical skills that will undoubtedly be priceless throughout my future endeavours.

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DECLARATION OF WORD COUNT

The word count is 65,067 words excluding references.

ABBREVIATIONS

ATAD: Aspirin treatment after desensitization
BMI: body mass index
COVID-19: Coronavirus disease-19
C19OD: COVID-19-related olfactory dysfunction
CRS: chronic rhinosinusitis
CRSwNP: chronic rhinosinusitis with nasal polyps
DNS: deviated nasal septum
ESS: endoscopic sinus surgery
fSRP: functional septorhinoplasty
HCWs: health care workers
HRQoL: health-related quality of life
LAS: lysine aspirin
N-ERD: NSAIDs-exacerbated respiratory disease
NSAIDs: Non-steroidal anti-inflammatory drugs
NOSE: Nasal obstruction symptom evaluation
OB: olfactory bulb
OD: olfactory dysfunction
OE: olfactory epithelium
ORN: olfactory receptor neuron
OSA: obstructive sleep apnoea
OT: olfactory training
PhD: doctor of phylosophy
PIOD: post-infectious olfactory dysfunction
PROMs: patient-reported outcome measures
RCT: randomized-controlled trial
RFITs: radio frequency of inferior turbinates
SDB: sleep-disordered breathing
SNOT-22: sinonasal outcome test-22
TDI: threshold, discrimination, and identification
UA: upper airway
URTI: upper respiratory tract infections
VAS: visual analogue scale

CHAPTER 1: INTRODUCTION TO THESIS

1.1. How this PhD came about

I am an Ear, Nose and Throat (ENT) surgeon, who trained in Italy (Padua) and moved to London six years ago to undertake further subspecialty training in Rhinology. Since qualifying from medical school in Rome, I have received parallel clinical and research training while developing a particular interest in rhinology, nasal airways and olfaction. During my time at the Royal National ENT Hospital (previously called the Royal National Throat, Nose and Ear Hospital), which is part of the University College London Hospitals (UCLH) Foundation Trust, I met and learnt from world-leading academics and clinicians aiming to further our understanding on sense of smell and develop treatments for olfactory dysfunction (OD).

To gain further insights in olfaction, I attended the 'Smell and Taste' course in Dresden (Germany) led by Prof. Thomas Hummel, unquestionably the current world leader on olfactory disorders. Inspired by the discussions with scientists, clinicians, and patients but also intrigued by the research questions raised at the course, I decided to focus my research activity for the following years on olfaction. That was when I started planning a PhD project with Prof Andrews and Dr Scadding to better understand causes and mechanisms leading to anosmia or hyposmia (respectively complete or partial loss of sense of smell) in some chronic upper respiratory tract diseases and, more importantly, to look at potential ways to improve or restore olfaction when this is lost. I was enthusiastic to contribute to this area and, building upon the expertise of my supervisors, I decided to concentrate my efforts on three main respiratory disorders for which research on olfaction was lacking or at its early stages. In particular, I started focusing my research on OD in patients with non-steroidal anti-inflammatory drugs (NSAIDs)-

exacerbated respiratory disease (N-ERD), patients with sleep-disordered breathing (SDB) and patient with post-infectious OD (PIOD).

In the previous years, Dr Scadding and her collaborators had collected a huge quantity of data on N-ERD patients trialled on a new treatment for their disease at the Royal National ENT and created one of the largest databases currently available in the literature on this topic. This was a great opportunity to look at sense of smell in these patients but also to evaluate changes in olfaction prospectively. On the other side, Prof Andrews had secured funding for a project that was aiming to look at the effect of radiofrequency to the inferior turbinates in improving nasal function in patients with SDB, in which I became involved. The outbreak of the COVID-19 pandemic in March 2020, almost six months after the official start of my PhD, gave further impetus to my research journey. The spreading news that a high percentage of people infected by the SARS-CoV-2 virus developed a persistent loss of sense of smell, gave me further confirmation of the importance of the study I was undertaking and of how my research might help in the development of treatments to help patients with COVID-19-related olfactory dysfunction (C19OD). OD remains an important symptom of chronic upper respiratory disease, whether it is post-infective or post-inflammatory. However, prevalence and treatment options remain poorly understood.

1.2. Aims of the project

My research project has two aims. Firstly, I will evaluate OD in terms of prevalence, presentation and severity in three types of chronic upper respiratory disease. Secondly, I will assess the efficacy and effectiveness of new treatments in these diseases.

First aim: OD evaluation in terms of prevalence, presentation and severity in three types of chronic upper respiratory disease:

1. Non-steroidal anti-inflammatory drugs (NSAIDs)-exacerbated respiratory disease (N-ERD – a sub phenotype of chronic rhinosinusitis with nasal polyps);
2. Sleep-disordered breathing (SDB);
3. Post-infectious olfactory dysfunction (PIOD – mainly including patients who have experienced OD after SARS-Cov-2 infection).

Second aim: Assess the efficacy and effectiveness of new treatments for OD in these three types of chronic respiratory disease. Specifically, to evaluate:

1. The efficacy of intranasal lysine aspirin (LAS) treatment in patients with N-ERD;
2. The effects of decongestion using radiofrequency to inferior turbinates (RFITs) in patients with SDB;
3. The role of functional septorhinoplasty in improving olfaction in patients with PIOD. However, considering the high incidence of COVID-19-associated olfactory dysfunction (C19OD) which resulted following the recent pandemic, this last part of the project has enrolled only patients with C19OD**.** Nevertheless, since C19OD is a particular form of PIOD, most of the results from these studies could be generalisable to non-COVID PIOD.

1.3. Hypotheses – the focus of my thesis

Efficacy of the three treatments mentioned in the above section, as part of the second goal of my PhD dissertation, is mainly based upon the concept that an increase in the nasal airflow as well as the control of local olfactory mucosa inflammation, if present, can also improve olfaction. Whilst control of local inflammation in sinonasal diseases has been extensively studied over the years, the relationship between nasal airflow and olfaction has been overlooked for long time. This represents a particular focus of my

thesis and it will be further discussed in *Chapter 3*. A deeper knowledge of the strict relationship between nasal airways and olfaction will help in better understanding the works presented in this thesis and how improvement of sense of smell has been achieved following some of the treatments here evaluated. More importantly, it will put my studies into perspective when comparing these with the relevant literature.

CHAPTER 2: OLFACTION – AN OVERVIEW

2.1. Anatomy of the olfactory system

Olfaction is the ability to smell. Anatomically, the olfactory system is positioned at the apex of the nasal cavity, at the level of the cribriform plate. This is a perforated region of the ethmoid bone which acts as a barrier between the frontal lobe of the cerebrum and the nasal cavity. This area, also referred to as the olfactory area, contains the olfactory epithelium (OE), which is distributed across a surface area of 2.5 cm² extending "over the medial aspect of the superior turbinate, the anterior, middle, and superior portion of the middle turbinate, and the posterior region of the septum".[1] The OE is a pseudostratified columnar epithelium comprising olfactory receptor neurons (ORNs) and a diverse array of supporting epithelial cells, including sustentacular cells, microvillar cells, Bowman's glands, and basal cells. *(Figure 2.1.)*

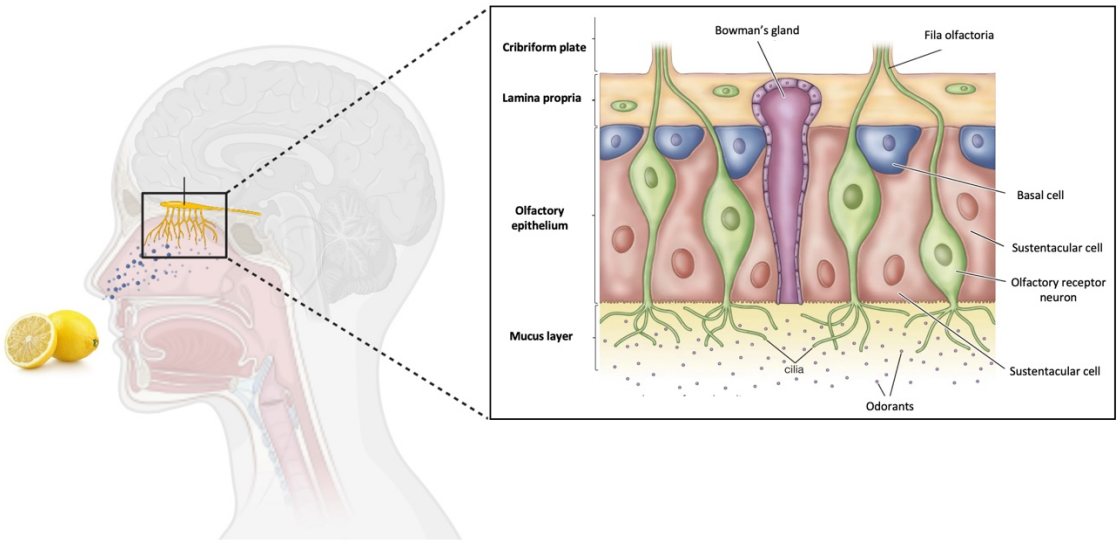

Figure 2.1. Sagittal view of nasal cavity with olfactory area delineated.

It has been reported that humans have roughly 6 to 10 million ORNs per nostril.[2] These are bipolar cells that give off a projection centrally towards the olfactory bulb (OB) while distally they project a single dendrite which contains nonmotile sensory cilia. The

sustentacular cells are supportive elements with protective functions toward ORNs, whereas microvillar cells' function is, thus far, undetermined and could be possibly chemosensory. The Bowman glands, lodged within the olfactory lamina propria, secrete a serous fluid rich in glycoprotein which is important in helping dissolve gaseous odorant particles and for binding odorants for chemoreception, like the odorant-binding proteins (OBPs). Finally, the basal cells, further divided into globose basal cells (GBCs) and horizontal basal cells (HBCs), form the progenitor compartment of the OE.[3,4]

The axons of individual ORNs coalesce to form neurovascular bundles, known as fila olfactoria, which then traverse the small perforations of the cribriform plate (approximately 20 foramina). *(Figure 2.1.)* These bundles subsequently converge with other collections of ORNs' axons to constitute the olfactory nerves. The dura mater which unsheathes the intracranial side of the cribriform plate exhibits continuity with the basal membrane of the OE, extending through the foramina.[5] As a result, the bony cribriform plate constitutes a potential area of damage in case of trauma (shearing stress on olfactory nerves - *see Section 2.4*), but also a possible entry point for pathogens to the intracranial space. The olfactory nerve, which represents the first cranial nerve, is also the shortest cranial nerve in humans. Unlike other cranial nerves, it does not converge with the brainstem. It exclusively comprises afferent sensory nerve fibres and is not myelinated by Schwann cells but ensheathed by specialized olfactory ensheathing cells. Once the olfactory fila have penetrated the cribriform plate and traversed the subarachnoid space, these enter the OBs ventrally.[5] At this level, the ORNs, which were initially organized in bundles (reflecting their point of origin in the OE), defasciculate and reorganise as they target different regions of the OB. On the surface of the OB, the axons of the olfactory nerves establish synaptic connections with the dendrites of mitral and tufted cells within spheroidal structures known as 'glomeruli'.[6] These structures are integral components of the olfactory system, serving a critical role in transducing olfactory information and functioning as a "relay station" for all the impulses conveyed

between the OE and the primary olfactory cortex. Each glomerulus receives converging axons from ORNs that express the same specific protein receptors. Humans are thoughts to have between 1100 and 1200 glomeruli within each OB.[7] The axons of the mitral and tufted cells organize into fascicles that traverse the OB and ascend dorsally, merging to form the olfactory tract. “Each olfactory tract (left and right) extends posteriorly along the olfactory sulcus and terminates in the olfactory trigone, a triangular enlargement of the terminal olfactory tract situated above the anterior clinoid process. At this level the fibres of the olfactory tract diverge to form two main bundles, the medial and lateral olfactory striae.[5] The medial olfactory stria exhibits projections to the ipsilateral anterior olfactory nucleus and, via the anterior commissure, to the contralateral OB, culminating in the septal nuclei from which the medullary stria and the olfacto-hypothalamic-tegmental bundle emanate. The medial olfactory stria plays a pivotal role in mediating autonomic responses associated with olfaction, such as an elevation in salivation, gastric peristalsis and secretion in response to olfactory stimuli”.[5] The lateral olfactory stria, which is larger than the medial stria, projects to the primary olfactory cortex, an area within the temporal lobe in the vicinity of the uncus, which is accountable for most of functional olfactory transmission. The primary olfactory cortex comprises several cortical and limbic structures including the prepiriform cortex, the anterior olfactory nucleus, the olfactory tubercle (a structure which is poorly developed in humans), the periamygdaloid cortex (an area close to the amygdala), the cortical nucleus of the amygdala, and the lateral entorhinal cortex. The primary olfactory cortex is the main centre for processing smell information and has many functions that help integrate sensory information related to smell. [5,8-10] From these regions, the olfactory system projects, via the thalamus, to several additional regions of the cerebral cortex (secondary olfactory areas including orbitofrontal cortex, hippocampus, hypothalamus, cerebellum) where the olfactory information is processed. *(Figure 2.2.)* Here odorants are identified and initiate appropriate motor, visceral, and emotional reactions to olfactory stimuli and

this may provide an explanation for the role of sense of smell in modulating mood and emotion, influencing pleasure sensations, and impacting memory processes.[11]

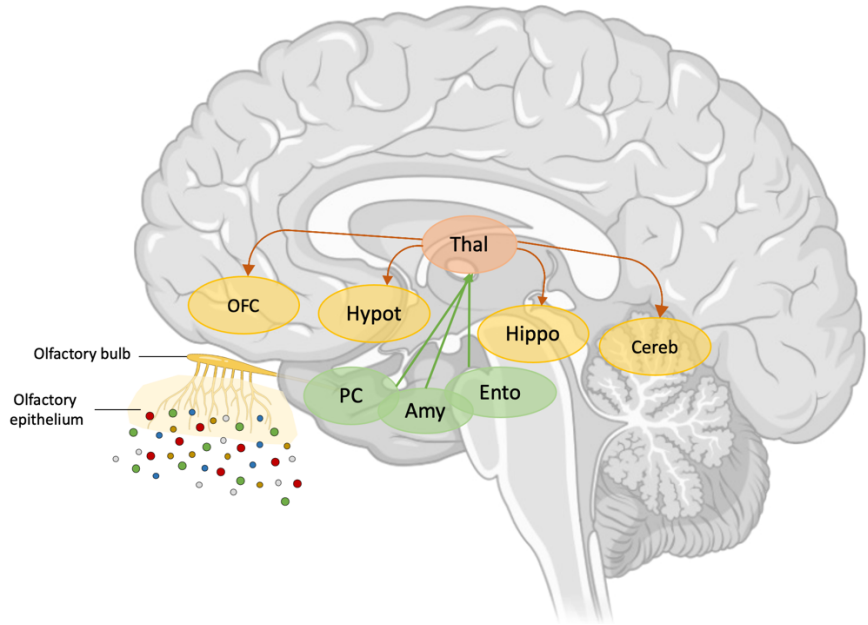

Figure 2.2. A schematic representation of the olfactory system. In green are coloured the primary olfactory regions while in yellow are marked the secondary olfactory regions.

Amy: amygdala; Cereb: cerebellum; Ento: entorhinal cortex; Hippo: hippocampus; Hypot: hypothalamus; OFC: orbitofrontal cortex; PC: piriform cortex; Thal: thalamus.

Consequently, olfaction is subject to modulation by visual, perceptual, and cognitive influences, exhibiting plasticity with a substantial component relying on learnt experience.[12,13] Notably, in contrast to other sensory modalities, there is no thalamic relay for odour-evoked signals to central brain regions.[14] Other distinctive characteristics encompass the truly ipsilateral nature of olfactory projections and the extensive overlap with limbic structures, which may account for the profound capacity of odours to influence emotional processing.[14]

Another olfactory region exists in the nose of humans; however, this is vestigial as confirmed by the fact that its genes have degenerated through evolution.[15] This is called the vomeronasal organ, or Jacobson's organ, and it is situated in the soft tissue of the nasal septum.[16]

2.2. Physiology of the olfactory system

Olfaction can physiologically occur as a result of two distinctive pathways: orthonasally or retronasally. Orthonasal olfaction indicates the perception of odorants via anterior airflow from the nostrils to the olfactory area, as occurs during sniffing or normal respiration. In contrast, retronasal olfaction describes the perception of odours coming from the oral cavity during the processes of eating and drinking, facilitated by airflow to the olfactory area through the nasopharynx during the acts of swallowing or nasal exhalation. Retronasal olfaction contributes to the flavour of foods and drinks and is commonly confused with the sense of taste which explains the common situation of subjects with OD complaining of taste dysfunction in the absence of any real loss of taste sensation.[17] Odorant molecules that arrive in the nasal passages following nasal breathing (orthonasal olfaction) or swallowing (retronasal olfaction) interact with the olfactory receptors located on the primary cilia of ORNs. After diffusion within the mucus layer, odorant molecules are subsequently transported to the OBPs, which are believed to facilitate the transport of the odorants through the mucus layer to their receptors and also to help in the clearance of the olfactory signal.[2,18] *(Figure 2.3.)*

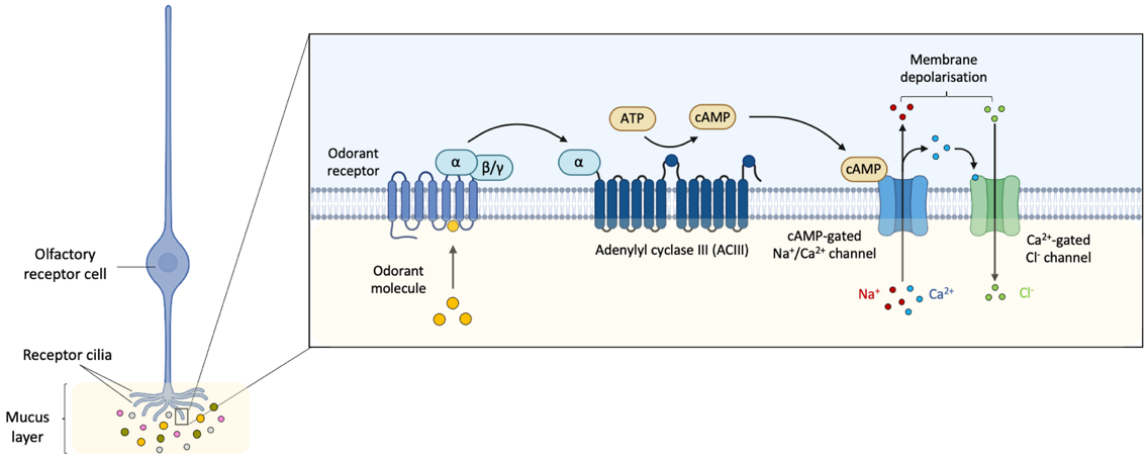

Figure 2.3. Mechanism of signal transmission following odorant stimulation

ATP: adenosine triphosphate; cAMP: cyclic adenosine monophosphate.

In the year 1991, Linda Buck and Richard Axel[19] made a pioneering discovery, identifying the transmembrane proteins believed to function as odour receptors and subsequently characterizing a subset of the genes responsible for their encoding.[20] The olfactory receptors genes include roughly 900 genes which makes them the largest superfamily in the genome and represent approximately 3% of the entire human genome. Although only half of these are functional, this highlights their crucial role in mammalian physiology and evolution.[20] The bond between the odorant molecule and the specific olfactory receptor results in the activation of the G proteins which leads to a depolarization of the ORN. The beginning of the action potential induces the signalling.[2] At the level of the OB, a complex process of signal transduction and encoding of intricate signals occurs prior to the transmission and subsequent processing of this information within other regions of the central nervous system.[21,22]

Each neuron has only one type of receptor on its dendritic extensions,[19] but each odorant can bind to different receptors and, thus, activate multiple neurons. Additionally, each receptor can recognize different odorants.[4] Moreover, most of the odours in the environment are combinations of different components. This results in complex signals that are interpreted by the brain.[2] The combination of different signals through stimulation of different receptors allow for the detection and discrimination of a potentially limitless diversity of odorant molecules.[2] It is interesting to note that the human olfactory system is more sensitive and specific than that in rodents and primates[23], and that humans can promptly differentiate between two distinct odours differing by a single molecule.[24] The individual variability in olfactory performance, as well as sensitivity to a specific odour, may be attributable to several factors, including differential expression patterns of OR gene sets, genetic variability within the OR genes themselves, functional differences in the activity of OR proteins, and/or variations in central olfactory processing mechanisms.[25-27] In addition to this, odorant molecules also create imposed mucosal activity patterns based on their solubility in the mucus lining. For instance, odorants with

high mucus solubility tend to be absorbed quickly, resulting in an uneven distribution across the olfactory mucosa. Conversely, less soluble odorants are more evenly distributed, which might provide the central nervous system with additional cues for odour identification. These imposed patterns, in conjunction with inherent patterns, are believed to contribute to the brain's ability to identify and differentiate between various smells.[28]

Over the years a debate has arisen regarding the initial stage of olfactory reception. The mechanism of odour signalling described above is called the “lock and key” theory. However, the main criticism that has been raised is this theory’s inability to predict odour character and guide rational odorant design due to the vast number of ORs.[29] Furthermore, diverse structures can yield similar odours, and subtle structural changes can drastically alter smell. In 1996, Luca Turin first described the “vibration” theory suggesting that “ORs respond not to the shape of the molecules but to their vibrations”.[30] According to this theory, olfaction is characterized as a spectral sense, with olfactory events being initiated by electron transfer (ET) occurring within an OR.[30] More recently, Liu et al. described the “Donor-Bridge-Acceptor” model, proposing that the “ET process could be viewed as an electron hopping from the Donor molecule to the odorant molecule (Bridge), then hopping off to the Acceptor molecule, making the electronic state of the odorant molecule change along with vibrations (vibronic transition)”.[31] In this model, once an “odorant molecule enters the binding pocket of the OR and docks successfully, the odorant molecule changes its electronic state with an excitation of one or more phonons leading to a combination of vibrational and electronic transitions (vibronic transitions)”.[31] However, so far, the true mechanism leading to odour signalling is still under investigation.

Many substances can stimulate both the olfactory system and also the trigeminal system, which is at the basis of what is called chemosensory function. In fact, the ophthalmic and

maxillary branches of the trigeminal nerve (fifth cranial nerve) innervate the sinonasal mucosa and are responsible for irritant responses. These are activated by irritants such as “air pollutants, ammonia, ethanol and other alcohols, acetic acid, carbon dioxide, menthol, capsaicin”.[2] These axons form synaptic connections within the trigeminal nucleus, which subsequently relays neural impulses to the ventral posteromedial nucleus of the thalamus.[2] From there, these signals are projected to cortical regions specialized in the processing of facial irritation and pain.[2] Responses to these stimuli include pain, sneezing, tearing, irritation, salivation, vasodilation causing nasal congestion, nasal secretion, sweating, but also bronchoconstriction and a decreased respiratory rate.[2]

The ORNs have a half-life of 30 to 40 days[2] and the OE has the unique property of being able to constantly regenerate (neurogenesis). This is extremely important considering that, owing to its direct exposure to the external environment, the OE exhibits an inherent vulnerability to damage induced by toxins, pathogens, and traumatic insults.[32-34] This ability is mainly related to the presence of the basal cells (GBCs and HBCs), multipotent olfactory progenitor cells, exhibiting the capacity to differentiate into both neuronal and non-neuronal cell lineages within the OE. GBCs are believed to be responsible for the turnover of the OE under both physiological and acute pathological conditions while HBCs are believed to initiate differentiation only in response to severe injury.[35-37] In addition, olfactory ensheathing cells, which provide structural and functional support to olfactory axons, play a crucial role in maintaining the normal sense of smell by facilitating the continual turnover and axonal regrowth of ORNs.[38,39] However, aging, but also environmental insults (like toxins, industrial or occupational chemicals, tobacco smoke, or airborne pollutants) or pathophysiologic processes such as viral infection or chronic inflammation, can induce metaplasia within the OE. This process involves the conversion of the OE into respiratory epithelium, resulting in a consequential loss of ORNs.[2,40]

2.3. Classification of olfactory dysfunction

OD is highly prevalent and affects up to 29% of the general population.[41] However, the prevalence could be much higher as epidemiology studies on OD are missing. It is usually divided into quantitative and qualitative disorders of olfaction. Quantitative OD can range from a complete lack of olfaction (anosmia) to a reduced sense of smell (hyposmia). Anosmia affects 5% of the population.[42] Distortions or pathologic alterations in the perception of odours, termed as qualitative OD, are generally categorized under the term "dysosmia". Dysosmia includes parosmia and phantosmia. Parosmia refers to the perception of a typically unpleasant odour in response to an environmental odour. Phantosmia, instead, is the perception of an odour, usually unpleasant, occurring spontaneously in the absence of a trigger. Phantosmia is also usually referred to as chemosensory hallucination. Interestingly, reports suggest that presence of phantosmia is as high as 55% in individuals experiencing transient epileptic amnesia.[43] Furthermore, dysosmia may also present as olfactory agnosia, characterized by the inability to discriminate between distinct olfactory stimuli.[43]

2.4. Causes of olfactory dysfunction

The initial classification of OD was made according to the anatomical location of the presumed pathology/lesion and divided as:

- Conductive dysfunction: caused by blockage of odorants transmission to OE;
- Sensorineural dysfunction: caused by damage/loss of the OE or nerve;
- Central dysfunction: caused by damage to olfactory processing pathways in the central nervous system.

However, with years, it became evident that this classification has got some limitations due to the fact that the majority of the causes leading to OD can actually affect olfaction at more than one levels with varying contribution and their use as such may prevent a comprehensive understanding of the underlying pathophysiological mechanisms. Therefore, although this classification has not been completely abandoned today, OD is now described according to putative underlying aetiology. *(Figure 2.4.)* The commonest cause of OD is chronic rhinosinusitis (CRS) with or without nasal polyps, which accounts for approximately 67% of OD cases among patients presenting to rhinology centres.[44-46] It is also the commonest cause of OD amongst all the sinonasal disease being responsible for 14%-30% of cases.[44-46] OD in CRS with nasal polyps (CRSwNP) has been consistently reported by patients as one of the most distressing aspects of this disease.[47]

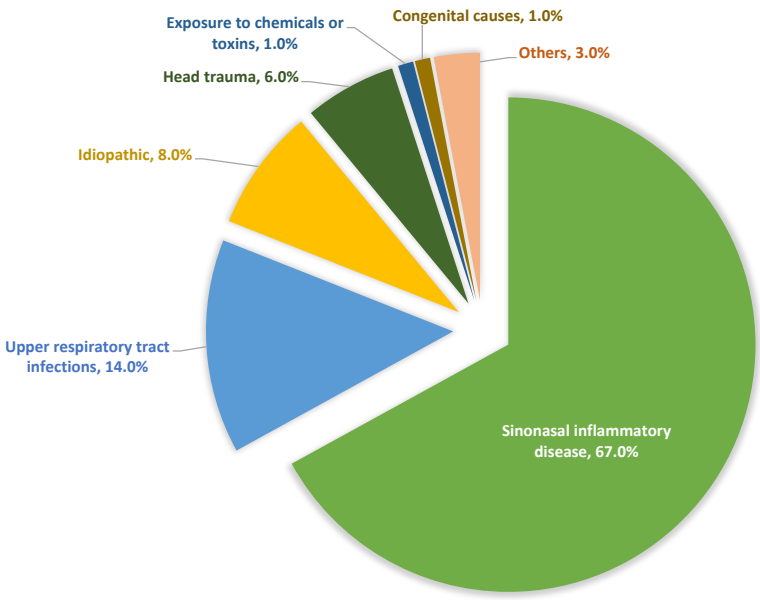

Figure 2.4. Causes of olfactory disorders. Others include: olfactory dysfunction related to drugs, neurological and neurodegenerative disorders or aging.

Despite CRS being the commonest cause of OD, this usually causes a transient and incomplete anosmia due to inflamed nasal mucosa and increased mucus production.[48] Interestingly, parosmia is not a distinctive feature of CRS-related OD.[49] This form of OD

is usually gradual in its onset and responds well to steroid treatment, either topical or systemic.[42] However, in the long-term, the chronic inflammation of the OE in CRS patients can lead to permanent olfactory loss.[42] The pathophysiology of OD in CRS will be further discussed in *Section 4.2*.

Viral upper respiratory tract infections (URTI) represent the second commonest cause (14%).[45] Viral infections can lead to OD following damage to the olfactory neuroepithelium by neurotropic viruses. The onset of this type of OD is usually sudden, often permanent, and it has been shown to represent the most frequent cause of both permanent anosmia and hyposmia.[50] The pathophysiology of post-infectious OD will be further discussed in *Section 5.3*.

Head trauma involving the cribriform plate (6% of all causes),[45] can also cause a sudden-onset olfactory loss due to direct damage to the sinonasal tract or to the OE, shearing forces exerted on olfactory fibres at the level of the cribriform plate, or the occurrence of cerebral contusion or intraparenchymal haemorrhage.[51]

Exposure to chemicals or toxins (1% of all causes)[45] can also be a cause of OD in subjects presenting with idiopathic olfactory disorders.[52] These include metals like cadmium, manganese, arsenic, chromium, mercury, lead, aluminium and nickel, but also organic compounds like “butyl acetate, benzene, and benzyl acetate, industrial agents (paint solvents, toluene or styrene), dusts (cement and hardwood), and non-metal inorganic compounds (methylbromide, chlorine, hydrogen sulfide)”.[53] Cadmium targets the ORNs and the severity of OD directly correlates with the years of exposure.[54] Manganese, instead, has been shown to be absorbed by the ORNs and transported from the OB to the olfactory cortex.[55] Air pollution (like nitrogen dioxide) can similarly impact olfaction by contacting the OE, translocating to the OB and migrating to the olfactory cortex inducing local inflammation and/or leading to direct damage of the tissue.[56] In this

regard, people living in non-polluted regions have been shown to have better olfactory scores than residents of cities exposed to high level of air pollution.[57]

Several medications can also affect olfactory function such as zinc, tetrahydrocannabinol, remifentanil, sildenafil, chemotherapeutic agents, propofol, duloxetine, midodrine, metoprolol, local anaesthetics, and oral antibiotics.[58-63]

Progressive OD can also represent an early sign of neurodegenerative disorders, like Parkinson and Alzheimer disease, and olfactory assessment is now included in the evaluation of neurodegenerative disease.[64,65] Other neurological causes are: schizophrenia,[66] migraine, seizures, and severe vomiting in pregnancy (hyperemesis gravidarum) with a possible common pathophysiological mechanism involving "variations in dopaminergic receptors allele".[67] Hippocampal lesions, psychosis, particularly characterized by olfactory hallucinations, meningiomas arising from the olfactory groove, and other intracranial masses can also cause progressive OD.[68]

Moreover, OD can be congenital, as in [1]Kallmann syndrome, [2]CHARGE syndrome, syndromic ciliopathies, such as [3]Bardet-Biedl,[69] but can also be caused by acquired abnormalities secondary to perinatal toxic insult.[70]

Other causes of OD include: radiation therapy, autoimmune diseases ("Sjögren syndrome, systemic sclerosis, multiple sclerosis, granulomatosis with polyangiitis, systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, neuromyelitis optica, Behçet disease, and Mikulicz disease"), deficiency of vitamins or minerals which

[1] Kallmann syndrome is a condition characterized by hypogonadotropic hypogonadism and anosmia due to bilateral agenesis or hypoplasia of the olfactory bulbs

[2] CHARGE syndrome is a rare genetic disorder characterised by coloboma, heart defects, atresia of choanae, retardation, genital and ear abnormalities.

[3] Bardet-Biedl syndrome is characterised by holoprosencephaly associated with absence of the entire olfactory apparatus

are involved in the regeneration of the OE (such as vitamin A, B and zinc), endocrine disorders (disorders involving the hypothalamus, hypothyroidism, diabetes, Kallman syndrome, Turner syndrome), renal failure (possibly due to accumulation of accumulation of uremic toxins exerting a deleterious effect on olfactory function or leading to polyneuropathy), sinonasal or intracranial tumours (leading to conductive or neurosensory OD), disorders related to extremely high or low BMI, smoking. [69,71,72]

A decline in the smell ability can also simply be the result of aging. It has been reported that prevalence of OD is approximately 2% in adults under 65 years of age but this increases to 75% in subjects over 80 years old.[73] Multiple mechanisms are involved in age-related OD including "ossification of the cribriform plate, a reduction in the size of its foramina and accumulation of damage to olfactory receptors over the course of an individual's lifetime".[74,75]

Finally, whereas the cause of OD cannot be identified despite a comprehensive workup this is then defined as idiopathic (8% of all causes),[45].

2.5. Influence of sex on olfaction

The relationship between olfaction and sex is not clear and anatomical differences of the olfactory system between males and females have not yet fully elucidated. Although many studies seem to suggest a better olfactory performance in the female population with females outperforming males in odour identification,[76-79] other studies did not find an effect of sex on odour identification.[76,80-83] However, no significant differences have been documented based on gender with respect to olfactory discrimination or threshold.[84] (*see next paragraph for threshold, discrimination and identification*). A meta-analysis evaluating gender-related differences in odour identification, confirmed this discrepancy is exclusively observed in patients within the age range of 18 to 50 years,

but not in subjects under 18 years or over 50 years.[76] It has been hypothesized that these changes may be related to three main mechanisms. The first one is the fluctuating gonadal steroid levels (especially in the level of oestrogen). In fact, "gonadal steroid hormones and their receptors have been found in the OE, OBs, and other brain regions" associated with olfactory function.[76,85] Moreover, studies have suggested that androgens may exert a suppressive effect on olfactory performance, whereas oestrogens can enhance it.[76,86] The second mechanism may be related to a sexual dimorphism with evidence showing that the densities of neurons, non-neurons, and total cell count within the OBs are higher in females compared to males.[87] Moreover, the volumes of the orbitofrontal cortex Broadmann areas 10, 11 and 25, and hippocampus are larger in women than in men.[88,89] The third mechanism contributing to gender differences is olfactory processing.[76] Specifically, a "higher cerebral blood flow and cerebral metabolic rate of glucose use have been documented in women compared to men" during olfactory tasks. This observation suggests that the female OB facilitates a greater transmission of olfactory information to cortical regions than men. This may reflect a higher capacity of women to identify and perceive odorants compared to men.[90,91]

2.6. Olfactory dysfunction and quality of life

An intact olfaction is of paramount importance for assessing the safety of food, evaluating impending danger, and recognizing the nuances of social relationships. In fact, whereas odours have powerful impacts in the animal kingdom due to their association with predators, food, and sexual gratification,[14] in humans odours can also modulate human behaviour and social interactions.[2] As a result, OD significantly reduces quality of life (QoL)[92,93] and has recently gained public and press attention after being recognised by Public Health England as a key presenting symptom of SARS-Cov-2 infection and a persisting post-infectious symptom of 'Long COVID'.[94-97] Loss of sense of smell is devastating and remains an invisible disability which is often overlooked. The QoL of

patients with OD is significantly impaired and is comparable to that in heart disease in days off work and reduced productivity. Although more common than other sensory disorders, such as blindness and deafness, there is less known about OD with fewer available effective treatments.

OD increases morbidity as well as mortality, [92,93,98,99] and the reasons for this are multiple. OD results in decreased flavour perception in up to 69% of sufferers, thereby extinguishing the pleasure of eating and drinking.[100] This leads to a less varied diet with a negative impact on health and appetite, with 20% of sufferers eating more and between 20–36% eating less.[101] OD results in a diminished capacity to detect spoiled food, hazardous odours, such as gas leaks, smoke or undetected volatile chemicals, thereby constituting a significant health and safety risk.[102] Patients are unable to perceive their own body odours which leads to social insecurity.[100] As a result, OD patients experience a feeling of anxiety and may lead to social isolation and reduced employment.[103] Consequently, depression is very common in OD ranging from 40% to 76%, with depression scores directly increasing with increased severity of OD.[104] Assuming 10% of anosmia sufferers receive antidepressants, we estimate the annual UK cost would be close to £10 million.

2.7. Objective and subjective assessment of olfactory function

In general, three different types of olfactory testing[44] can be undertaken.

i. Subjective (i.e. patient-reported olfaction)

Subjective assessment of olfactory function can be performed using a visual analogue scale (VAS, ranging from 0 to 10 - 0 represents 'sense of smell absent' and 10 'sense of smell not affected') or Likert questionnaires. For example, the commonly used Sinonasal outcome test-22 items (SNOT-22)[105], a validated patient-reported outcome measure

(PROMs) for CRS, contains one question regarding OD scoring from 0 (“no problems”) to 5 points (“problem as bad as it can be”). Another specific questionnaire for olfaction is the Questionnaire of Olfactory Disorders-Negative Statements (QOD-NS)[106], available also in its short version,[107] quantifies the smell loss symptoms' effect on patients' QoL. However, correlation between subjective and psychophysical measures has been reported to be absent or very low and subjective olfactory assessment tends to be unreliable if performed in isolation.[44]

ii. Psychophysical olfactory tests

Psychophysical tests, while offering greater reliability than subjective self-reporting, necessitate a cooperative subject capable of comprehending, adhering to instructions, and effectively communicating choices to the investigator. In these tests, an olfactory stimulus is presented, and the outcome of the test depends on the patient's response. These tests can assess different aspects of olfaction and are generally categorised into threshold and suprathreshold tests. By definition, odour threshold represents the lowest concentration of an odorant that a person can notice and it is technically the “concentration at which 50% of stimuli are detected and 50% remain undetected”.[44] Suprathreshold olfactory tests, defined as those employing odour stimuli of sufficient concentration to be detectable by an individual with unimpaired olfactory function, are utilized to assess the abilities of odour discrimination and identification.[44] Odour discrimination refers to the capacity to differentiate between distinct olfactory stimuli, while odour identification necessitates not only the recognition of a presented stimulus but also the accurate verbalisation of its identity (i.e., the ability to correctly name the perceived odour).[44] Threshold, discrimination and identification components can assess different causes of OD. “Odour threshold preferentially assesses peripheral causes of olfactory loss (e.g. sinonasal disease), while the suprathreshold tests (i.e. discrimination and identification) better evaluate central or cognitive causes of OD (e.g. dementia)”.[49] Therefore, these tests can provide complimentary information when performed together.

Below a brief description of the main psychophysical olfactory tests currently used and available. *(Table 2.1.)*

- The Smell Identification Test ('SIT/SIT-40', previously also known as 'UPSIT')[73] is a 40-item suprathreshold test which assesses odour identification. This test utilises microencapsulated (scratch & sniff) odours and is as far the only olfactory test on the market that can be self-administered. A brief version of the SIT (the Brief Smell Identification Test, B-SIT) exists and contains 12 items, instead of 40. This is also known as also known as the Cross-Cultural Smell Identification Test.
- Nez-du-Vin test[108] is a six odour multiple choice suprathreshold smell test which assess identification. Although quick, it explores a limited number of odorants.
- The Connecticut Chemosensory Clinical Research Center Test (CCCRCT)[109,110] assesses odour threshold and identification.
- The "Sniffin' Sticks",[111] which assesses the odour threshold, discrimination and identification. Additional information is provided later in this section.

	Olfactory ability investigated	Maximum score	Normosmia	Hyposmia	Anosmia	MCID
Sniffin' Sticks[112]						
TDI	Composite	48	TDI ≥30.75	16<TDI<30.75	TDI ≤16	5.5
Threshold	Threshold	16				2.5
Discrimination	Discrimination	16				3
Identification	Identification	16				3
SIT[113]	Identification	40	≥34 (male) ≥35 (female)	33-19 (male)* 34-19 (female)*	≤18	4
B-SIT[114]	Identification	12	≥8	<8	<8	1
Nez du vin[108]	Identification	6	>3	-	≤3	N/A
CCCRCT[109]	Threshold Identification	7[+]	6-7[+]	5.75-2*,[+]	0-1.75[+]	N/A

Table 2.1. Main olfactory tests used with related scores.

*These are further divided into mild, moderate and severe hyposmia
[+] This score is the arithmetic mean of threshold and identification scores (both having a maximum score of 7)

MCID: Minimal clinically importance difference; TDI: Threshold + Discrimination + Identification; SIT: Smell Identification Test; B-SIT: Brief-Smell Identification Test; CCCRCT: Connecticut Chemosensory Clinical Research Center Test.

Other odour identification tests include: the 4-Item NHANES (U.S. National Health and Nutrition Examination Survey) Pocket Smell Test and the 3-item Quick Smell Identification Test (PCT and Q-SIT - similar to the SIT but containing only 4 or 3 items respectively); the Odour Stick Identification Test; the Scandinavian Odour Identification Test; the San Diego Odour Identification Test; the Barcelona Smell test; the Open Essence test; T&T olfactometer; the Smell Diskettes Test. [115-117] Other odour threshold tests are the Snap & Sniff Olfactory test system, T&T olfactometer, Smell Threshold test, Olfactory Perception Threshold test.[115,116]

The "Sniffin sticks" test

Initially described in 1996 by Kobal and colleagues,[118] it has now become one of the most used tests to assess olfaction both in daily clinical practice as well as scientific research. It uses pen-like odour-dispensing devices and requires the subject to sniff felt-tip pens containing the smell, thus representing a highly practical and cost-effective way to measure olfaction. (*Figure 2.5.)* When opened, the felt tip ensures a consistent presentation of odorants at a constant concentration. Conversely, when closed, the cap provides an effective means of sealing the odorants within the pen, thereby effectively preventing olfactory contamination of the surrounding environment and desiccation of the odorant within the pen.[118] In this test, the odour is presented to the subject for approximately 3 seconds by removing the cap of the pen and placing the pen's tip roughly 2 cm under the nostrils (birhinally). In a clinical setting, Sniffin' Sticks are commonly done birhinally although this test can also be performed monorhinally. To avoid olfactory desensitization, an interval of at least 30 seconds is recommended before presenting a new pen.[119] Sniffin' Sticks has been designed as a re-usable and portable test-kit which, in its "extended version", include three different subtests that allow the assessment of different smell abilities namely odour threshold, discrimination and identification. In the short version, instead, it only includes the identification test (either using 12 or 16

odours). The threshold test is intended to determine the olfactory threshold of a subject (i.e. from which concentration on the subject can perceive a smell) with the help of a graduated concentration of n-butanol. During the test, repeatedly, three pens are presented one after another, with only one containing the odorant (the other two contain water). The patient has to make a statement on which of the three pens contains the odorant.

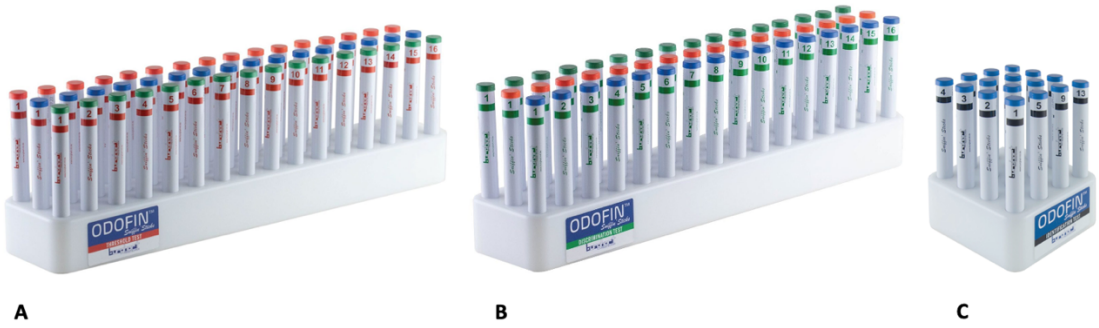

Figure 2.5. Sniffin' Sticks extended test including threshold (a), discrimination (b) and identification (c) tests.

A forced stair-case procedure is used whereby the examiner moves up and down to different n-butanol dilutions and this is repeated for a total of 7 times (turning points). The final threshold score is determined as the mean of the last 4 turning points. Odour discrimination, which assesses the ability to distinguish odours from one another, is based on a comparison between three pens (triplets): two of these have the same odour (non-target) and one has got a different one (target). The subject has to indicate the odour (target) that smells differently in each case. These comparisons are performed for 16 triplets and the score is obtained by summing up the correct answers. To prevent visual detection of the target sticks, both the threshold and discrimination tests are performed with the subject blindfolded. The identification test explores the ability of the subject to identify everyday smells. This is a "multiple-forced-choice" in which, after the odorant is presented to the subject, he has to choose one option amongst the 4 offered. During this test a total of 16 odours are presented and the score is obtained by summing up the correct answers. Each of these tests generates a number of points (maximum of

16 for each one), which is added up to obtain the final TDI score, with a theoretical maximum TDI score of 48. Since its first introduction, the test has been successfully adapted across cultures and validated for different populations,[120-122] including the British one.[123] Normative data have been published both in adults and children. According to the literature, "normosmia is defined by a TDI score of ≥30.75, hyposmia when TDI is >16, but <30.75, and functional anosmia by a TDI ≤ 16".[112] *(Table 2.1.)*

The minimal clinically important difference (MCID)

When assessing sense of smell, especially when reporting the results of longitudinal prognostic studies or when evaluating efficacy of an intervention, an important value to take into account is the minimal clinically important difference (MCID) which indicates the "minimum test score change required to denote a clinical improvement or deterioration". Moreover, the use of the MCID is important when determining the sample size necessary in clinical studies, especially when evaluating effectiveness of a treatment. In fact, a treatment can be considered powered enough when it is able to reveal a difference between groups of at least the MCID threshold or greater.[124] MCID has not been identified for all available tests but it has been reported only for those most commonly used in clinical studies. *(Table 2.1.)* For SIT (also known as UPSIT), MCID has been determined as a change of 4 points or greater.[125,126] For B-SIT (the 12-item version of SIT) this has been reported to be 1 point.[127] For Sniffin' Sticks, instead, this has been defined as 5.5 points for the composite TDI score, 3 points for identification/discrimination and 2.5 points for threshold.[128]

Benefits and limitations of psychophysical olfactory tests

Psychophysical testing can assess olfactory abilities more objectively and, as many patients could experience an olfactory decline without being aware of it (this is often described as a gustatory/flavour impairment), these tests can further confirm whether a patient has an OD or not. Some tests, such as the Nez du Vin or the UPSIT, despite

assessing only one single olfactory ability, are quick inexpensive tests which can represent useful screening tools to exclude gross olfactory impairments. These tests are suprathreshold tests that, however, evaluate only the identification component. On the other side, multicomponent smell tests, (like the Sniffin' Sticks), which include both the olfactory threshold testing but also suprathreshold tests, as the odour identification and discrimination tests, although being more time-consuming, can detect a pattern of olfactory decline, which might help to define the aetiology of the smell loss.[49] For example, diseases that primarily affects the nose exert a negative impact on odour threshold, whereas suprathreshold test results typically remain within normal limits. Conversely, diseases of the central nervous system known to affect olfaction, such as Parkinson's disease, primarily impact performance on suprathreshold tests, while odour threshold is usually unaffected.[49] Odour identification tests are "culturally specific" and some populations may "not be familiar" with certain odours.[116] Therefore, it is important to confirm that the test chosen has been validated for the population under evaluation; if not, alternatively local versions should be preferred. Furthermore, it has been observed that the accuracy of psychophysical tests can be enhanced through the utilization of composite scores.[129] Nevertheless, these tests require a subject who can understand adhere to instructions, and is capable of effectively communicating their choices to the investigator. Consequently, their administration is precluded in subjects who exhibit non-cooperative behaviour.

iii. Electrophysiological studies or magnetic resonance imaging

Electroolfactograms (EOG) record the generator potential of olfactory sensory neurons via an electrode in contact with the OE and are limited to the research setting.[44] Electroencephalography (EEG) is useful in uncooperative patients unable to have psychophysical testing as well as in medico-legal assessment.[116] Functional imaging modalities, including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), "enable the identification of brain activity in response to

olfactory stimuli". These techniques rely on changes in the metabolism and cerebral blood flow, respectively, to map alterations in the brain activity associated with stimulus presentation.[44] However, electrophysiological and imaging studies are typically reserved for research purposes, although EEG-based olfactory testing can possess utility in medico-legal contexts.

CHAPTER 3: NASAL AIRWAYS AND OLFACTION

3.1 The relationship between nasal airflow and olfaction

Airflow through the olfactory cleft is one of the conditions necessary to smell.[130] It has been reported that the airflow reaching the olfactory area during a normal resting breath accounts for only 5% to 15% of the total nasal flow.[131-134] This limited airflow is critical for the sense of smell, as it directs odorant molecules toward the OE,[2] and its reduction can decrease the transport of odorants to the olfactory mucosa by over 700%, especially for chemicals with high solubility and diffusivity.[132]

The nasal cycle, the physiologic alternating partial congestion and decongestion of nasal turbinates and mucosa, plays a significant role in regulating the distribution of airflow through each nostril and directly impacts on olfactory function.[135] During the nasal cycle, one nasal passage experiences a relative increase in airflow (high-flow side) while the other one becomes partially obstructed (low-flow side) due to the engorgement of the nasal mucosa.[136,137] This alternating pattern ensures that each side of the nasal cavity receives varying amounts of air over time, affecting the delivery of odorants to the OE.[136] This phenomenon is known as nostril dominance and influences olfactory threshold between the two nostrils.[138] Sobel et al.[139] showed that when a subject keeps the sniff constant to generate an airflow rate which is equal to the rate at which the high flow rate side can detect the odorant, the accuracy of detecting the odour (olfactory threshold) in the low-flow rate side is 18% lower of the other nostril. In such a situation the olfactory system can compensate for the reduced air-flow rate by either sniffing longer or stronger, thus improving olfactory performance.[139] On the other side, less airflow through one side of the nostril (low-flow side) may provide an opportunity for the olfactory system to reset as it avoids continuous exposure to the same odorant, which could otherwise lead to olfactory desensitisation.[140,141] Moreover, the nasal cycle may have a role in olfactory

spatial perception. The asymmetry in airflow between the two nostrils during the nasal cycle can create a differential detection of odorants, which might help the brain in localising the source of a smell. This was shown in Sobel et al.[142] research study which demonstrated that the difference in airflow between nostrils influences sensitivity to varying odorants in each nostril, relaying a marginally different “olfactory image” to the brain. Nevertheless, the sniff represents a major component in olfaction. To further confirm this, an impairment in sniffing has been pointed as an additional and alternative pathogenetic mechanism of Parkinson disease OD. In this experimental study, Sobel et al.[143] observed that an improvement in patients sniffing (increase of 54% of their initial sniffing volume) was accompanied by a temporary significant improvement in their olfactory performance (increase of 12% in their initial identification score). Whether, on the one side this confirms the strict relationship between olfaction and nasal airflow, on the other side it further highlights the protective role of olfaction in neurodegenerative diseases.

Studies have demonstrated that odorants with different absorptive properties can influence olfaction in different ways. For high-sorption odorants in particular, smaller olfactory responses are generated in case of low airflows.[142] This may be due to the fact that at low airflow rates, high-sorption odorant molecules adhere to the nasal mucosa before traveling far, limiting the activation of the OE and resulting in a weaker overall olfactory response. However, with higher airflow, the odorants spread over a larger area of the mucosa before being absorbed, leading to stronger olfactory responses.[142] These results have been supported by research from Mozell et al.[144] which showed a reduced olfactory function in case of lower nasal airflows.

Interestingly, the characteristics of the airflow, turbulent or laminar, also play an important role in olfaction. Airflow in the nasal cavity is generally laminar, moving in smooth, parallel layers. However, the nasal septum and nasal turbinates generate convoluted flow paths

for both the inhaled and exhaled air. As air navigates through the nasal passages, it may transition from laminar to turbulent flow, especially during activities like sniffing, which increases the velocity of airflow.[145] Our sniffing behaviour, which itself uses short, turbulent bouts of high flow rate inhalation, increases odorant uptake [4]flux to the olfactory mucosa, and had long been thought to increase olfactory perception.[146] In fact, although turbulence can improve odours sensitivity by increasing the amount of air that comes into contact with the OE,[28] it has been found that laminar airflow, instead, facilitates a smooth and direct pathway for odorants to reach the olfactory region thus enhancing olfactory perception.[147] Turbulent airflow occurs in case of nasal obstruction,[148] and this can disrupt the odorant molecules flow to the OE, leading to a reduced sense of smell.[147]

3.2 The relationship between nasal airways surgery and olfaction

Nasal anatomy can play an important role in controlling the access of odorants to the olfactory area and several studies have shown the relationship between variations in the structures of the nasal cavity and olfactory function.[149-155] In 1988, Leopold[150] was the first to identify two regions in the upper nasal cavity – located between the lower middle turbinate and the septum – able to influence the olfactory function. Valsimidis et al.[155] found a significant correlation between odour thresholds and nasal cavity volume (NV) as determined through acoustic rhinometry. Similarly, Masala et al.[152] observed positive correlations between odour threshold and NV, and negative correlations between odour thresholds and minimal cross-sectional areas in both nostrils. Damm and colleagues,[151] using MRI scans, found a correlation between odour threshold scores and volumes of the segment in the upper meatus directly below the cribriform plate and the anterior segment of inferior meatus. Computational fluid dynamics (CFD) studies have unequivocally demonstrated that the airflow directed towards the olfactory cleft region is

[4] Odorant flux refers to the number of odorant molecules absorbed.

critically influenced by anatomical variations within the olfactory cleft itself, and particularly highlighting the importance of the internal nasal valve (INV) region.[132,149] In fact, a small decrease in this area (1.45%) resulted in a large reduction of nasal airflow to the olfactory area (76.9%).[149] Always using the CFD, Wu et al.[131] found that not just the overall nasal airflow is important for olfaction, but that the mean flow, mean velocity, and airflow ratio of the objective parameters of the olfactory cleft were strongly positively correlated with sense of smell. Moreover, Hornung et al.[156] demonstrated an increase in the olfactory threshold following widening of the nasal valve angle after application of nasal dilators to the INV region.

Alterations in nasal structures, like the nasal septum, nasal turbinates, or even the external nasal architecture and nasal vestibule, can determine the pattern of airflow through the nose, alter the velocity through the olfactory cleft region and, as a result, affect the path that the air takes to get to the olfactory receptors as well as olfactory mucosa sensitivity.[150,157,158] This can in turn impact on the supply of odorants to the OE, and ultimately influence olfactory function. Alam et al.[159] used CFD to analyse changes in the nasal airflow field following a virtual middle turbinate (MT) resection, assessing for effects on olfaction. In their study, they found that nasal resistance decreased whilst olfactory flux increased, suggesting that middle turbinate reduction can have a significant impact on the flux of odorants to the olfactory cleft.[159] In support of these results, Soler et al.[160] found that patients who underwent bilateral MT resection during functional endoscopic surgery had improved olfaction compared to those with bilateral MT preservation. In contrast, a study by Friedman et al.[161] showed that MT reduction did not produce a significant improvement in the UPSIT score.

Surgical interventions that aim to restore or improve laminar airflow, such as septoplasty or septorhinoplasty, can lead to improvements in the sense of smell.[153,154,162-169] Previous investigations have demonstrated that a deviated nasal septum (DNS) results in a

diminution of olfactory function on the obstructed side. Furthermore, lateralised olfaction has been observed in a significant proportion of healthy individuals, with reported prevalence reaching up to 23.4%.[170] Pfaar et al.[171] found that DNS results in a decrease in odour thresholds on the obstructed side, whereas Altundag et al.[172] reported a decrease in odour thresholds, discrimination, and identification abilities on the narrower side. Mackers et al.[173] demonstrated worse olfactory function (using the Barcelona Olfactory Test, an 8-item identification test) in the more obstructed side. Mackers et al.[173] reported a significant improvement in the olfactory scores following nasal surgery (septoplasty +/- inferior turbinoplasty or inferior turbinoplasty alone). Similar results were found by Gupta and colleagues[153] using a combination of an odour threshold and an identification tests. Choi et al.[167] found that septoplasty improved birhinal olfaction by reducing lateralized olfaction as measured by butanol threshold tests (BTTs). Aydogdu and colleagues found that at 8 weeks after septoplasty olfaction, measured by means of CCCRCT (*see Section 2.7.* for a better understanding of this test), was significantly improved with no significant difference between patients undergoing closed and open septoplasty. In a study which evaluated the role of endonasal septoplasty with inferior turbinate reduction in improving olfaction the authors found a good correlation between lower nasal obstruction scores (using NOSE score) and better reported olfaction (using sVAS score).[174] However, a poor correlation between the sVAS and UPSIT scores was demonstrated.[174] Overall improvement in sense of smell following septoplasty has been reported to range between 13% and 77% while the chance of reduced olfaction is reported to be around 7%.[153-155,175]

By altering the angle of the INV (e.g., by using spreader grafts) and increasing the nasal cavity volume, functional septorhinoplasty (fSRP) can increase nasal airflow as well as influencing direction to the olfactory area and potentially improve nasal airflow to a greater extent than septoplasty.[151,154] Effectiveness of fSRP and, particularly, the influence of INV dimension and nasal airflow on the olfactory area following fSRP have

been confirmed by several authors.[130,164,176,177] Notably, a study by Whitcroft et al[178] conducted in patients with long-standing OD (either idiopathic or post-infectious) undergoing fSRP found that improvement of sense of smell was significantly correlated with the overall increase in bilateral nasal airflow rather than the symmetry of airflow, suggesting that the improvement in total nasal airflow played a more important role in enhancing olfaction than the correction of septal deviation alone. Other studies have supported these results. Following the increase of nasal airflow, the increased and normalised stimulation of the olfactory receptors may lead to enhanced neural connectivity and OB function, further contributing to the recovery or improvement of olfactory abilities.[179,180] In their functional MRI study, Whitcroft et al[178] demonstrated that the observed improvement in olfactory function was associated with "structural and functional plasticity in critical regions of the central olfactory network, including the anterior cingulate, orbitofrontal cortex, insula, and temporal pole". Taken together, these findings suggest that nasal cavity augmentation (i.e. by means of fSRP) may lead to a larger olfactory surface with more olfactory receptive structures. Interestingly, in a meta-analysis by Pfaff et al.[130] a similar number of studies on fSRP and septoplasty alone reported an improvement in olfaction. The role of fSRP in improving sense of smell will be further discussed in *Section 6.15*.

CHAPTER 4: OLFACTORY DYSFUNCTION IN PATIENTS WITH NSAIDS-EXACERBATED RESPIRATORY DISEASE

4.1. My research questions and hypotheses on OD in N-ERD

OD represents a common complaint amongst patients with N-ERD and can severely affect QoL. As further discussed in this chapter, intranasal administration of lysine aspirin (LAS) represents an alternative way to desensitise N-ERD patients to aspirin and can help in controlling CRSwNP in these patients. Long-term efficacy of intranasal LAS remains unknown and its effects on olfaction have not been evaluated. My aims and hypotheses regarding OD in N-ERD matured during these years are summarised in *Table 4.1*. An introduction to the topic has been included to give a background to the studies conducted.

Research questions
1. What is the prevalence of OD in N-ERD patients?
2. Is OD in N-ERD reversible? If so, can intranasal LAS improve OD?
3. Is QoL worse in N-ERD patients with OD? If so, can intranasal LAS improve QoL?
Hypotheses
1. OD is highly prevalent in N-ERD patients resulting from a combination of nasal obstruction, caused by nasal polyps, and chronic nasal inflammation.
2. Intranasal LAS can control sinonasal inflammation, reduce polyps' size and, therefore, improve nasal airflow. Olfaction would consequently improve as a result of the reduction of olfactory mucosa inflammation but also following an increased odorants delivery to the olfactory cleft.
3. QoL is reduced in patients with N-ERD and worse in those patients with OD. LAS will improve QoL following nasal symptoms control and improved olfaction.

Table 4.1. Research questions and hypotheses leading to my published studies on NSAIDs-exacerbated respiratory disease.

LAS: lysine aspirin; N-ERD: NSAIDs-exacerbated respiratory disease; OD: olfactory dysfunction; QoL: quality of life.

4.2. Introduction – an overview on N-ERD

4.2.1. Clinical aspects

N-ERD, also referred to as Samter's triad, is a clinical syndrome characterized by asthma, CRSwNP, and intolerance to aspirin/NSAIDs.[181] It affects approximately 15% of severe asthmatics, 10% of CRSwNP patients and 9% of patients with CRS.[182,183] N-ERD is characterized by moderate-to-severe asthma, a severe form of CRSwNP, with recalcitrant polyps, and persistent eosinophilic inflammation.[184] In the majority of the patients, N-ERD is diagnosed in their third or fourth decade, rarely in late childhood.[185,186] Women outnumber men in most studies.[187] The onset is with rhinitis progressing to CRSwNP. [188] Lower respiratory symptoms manifest two years, on average, after the upper airway (UA) symptoms and NSAIDs hypersensitivity manifests four years later.[188] All Cox-1 inhibitory drugs can cause symptom exacerbation[189] while Cox-2 inhibitors are usually well-tolerated by the majority of N-ERD subjects, although initial use should be supervised. Respiratory symptoms in N-ERD patients, following ingestion of NSAIDs, can involve the upper and/or lower respiratory tract and can be a combination of nasal congestion, rhinorrhoea, bronchoconstriction, mucus secretion, cough, wheezing or breathlessness.[190] The onset can be rapid with a risk of fatal bronchospasm.[190] N-ERD symptoms will continue to progress despite strict avoidance of NSAIDs in the majority of subjects.[188] Alcohol-induced and high salicylate food-induced upper and lower airway symptoms have also been reported by some N-ERD patients.[191,192]

4.2.2. Pathophysiology

The cause of N-ERD is unknown, although there are genetic susceptibilities[193] and some sufferers report an initiating respiratory tract infection. The pathophysiology of N-ERD

involves an alteration of the arachidonic acid metabolism with a dysregulation of cyclooxygenase (COX) and lipoxygenase (LOX) pathways. Here arachidonic acid is metabolized to “cysteinyl leukotrienes (cysLTs), mostly LTE4 via the 5-lipoxygenase (5-LO) and LTC4 synthase (LTC4S); prostaglandins (PGE2, PGF2, PGI2 and PGD2); and thromboxanes (TBX) A2 by the prostaglandin synthase and TBX synthase”.[194] PGD2 is a pro-inflammatory bronchoconstrictor precursor, induces chemotaxis and activates eosinophils, basophils, Th2 cells and innate lymphoid cells (ILC2), accelerating type 2 airway inflammation.[195,196] Conversely, “PGE2 is anti-inflammatory and bronchoprotective, and reduces recruitment of eosinophils and degranulation of mast cells after binding to E prostanoid 2 (EP2) receptors”.[195,196] “ILC2s and Th2 cells are abundant in polyp tissue, and together with mast cells, produce type 2 cytokines such as interleukin (IL)-4, IL-5, and IL-13. IL-4 and IL-13 signal through the common IL-4Rα,” leading to several effects such as tissue fibrosis and remodelling, mast cell activation and survival, goblet cell hyperplasia and mucus production.[197] IL-5 is required for eosinophil survival and activation.[197] NSAID-induced inhibition of the COX pathway results in a redirection of arachidonic acid metabolism towards the 5-lipoxygenase (5-LO) arm.[198] This metabolic shift leads to an overproduction of CysLTs and PGD2, while concurrently decreasing PGE2 levels.[198] In this context, the reduced PGE2 levels diminish the capacity to suppress 5-LO pathways through IL-10-dependent mechanisms, thereby contributing to an exacerbated production of CysLTs in these patients.[199] *(Figure 4.1.)* Released CysLTs and PGD2 subsequently activate “inflammatory cells (eosinophils, ILC2, mast cells, smooth muscle cells, granulocyte-adherent platelet, and neutrophils)” through receptor-mediated interactions, inducing the release of cytokines, histamine, and additional pro-inflammatory mediators. This cascade of events contributes to airway inflammation and remodelling in the nasal mucosa of N-ERD patients.[199] Elevated levels of both IL-4 and interferon-gamma (IFN-γ) have been detected within the tissue of N-ERD patients. Prior research has shown that IL-4 has a

pivotal role in the upregulation of LTC4S expression by mast cells, whereas IFN-γ drives this process in eosinophils.[200]

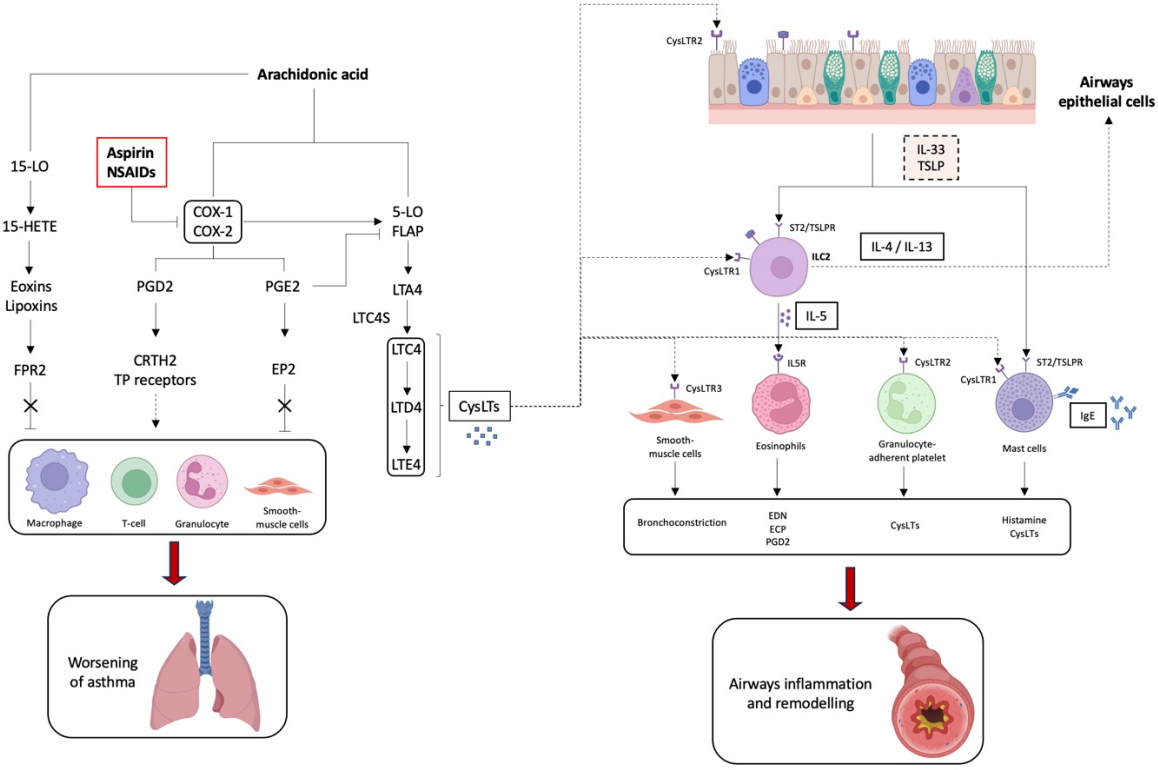

Figure 4.1. Imbalance in the arachidonic acid metabolism in patients with N-ERD.

N-ERD polyps show also overexpression of platelet activation markers and more aggregates of platelets and leucocytes than aspirin-tolerant patients. A disturbance in the intricate interplay between platelets and leukocytes can thus be partially responsible for the respiratory tissue inflammation and the overproduction of CysLTs that are characteristic hallmarks of N-ERD.[201] Moreover, a recent study has provided compelling evidence confirming a significant relationship between levels of IgE in nasal polyps and the rapidity of nasal polyp regrowth in patients with N-ERD. These findings suggest that IgE levels may serve as a valuable marker of disease severity and may represent a plausible driver of sustained mast cell activation and the perpetuation of respiratory tissue inflammation.[202]

4.2.3. Diagnosis

N-ERD remains a diagnostic and therapeutic challenge. A history of adult-onset asthma, bilateral nasal polyposis and one or more episodes of acute onset of respiratory symptoms following ingestion of aspirin or other NSAIDs suggest the diagnosis of N-ERD. A reaction to two different NSAIDs is sufficient to establish the diagnosis.[203] All patients with an unclear history should undergo a provocation (challenge) test if clinically indicated, as a precise diagnosis is relevant in managing their disease.[204] Aspirin challenges can be done via oral, bronchial, nasal or intravenous routes. The last three require a truly soluble form of aspirin and are rarely used in the UK, where LAS, the only soluble form of aspirin, is not routinely available in the UK. Oral challenge is regarded as the gold standard and this should take place in a specialised centre with well-trained staff able to manage severe asthma and anaphylaxis. Some subjects are unsuitable for aspirin challenge.[205] Some centres also practise other routes of challenges such as intranasal or inhalation using LAS (UK) or ketorolac (USA). The oral route claims higher sensitivity but also has a higher rate of adverse reactions; conversely, the intranasal route is both faster and safer.[203,206,207] However, if nasal challenge is negative, in case a high-suspicious of N-ERD exists, an oral challenge should follow. LAS can be used for both nasal challenge and topical nasal desensitisation and is widely available in Europe, but not in the USA or UK. Oral or bronchial challenges usually start at a dose of aspirin at around 30 mg with the dose gradually increased until a reaction is observed.[208] The real disadvantage of these two methods remains that, due to the relatively high doses of aspirin used, they can both lead to severe symptoms in more than 50% of patients, such as asthma requiring emergency treatment and/or hospital admission in some cases.[208] In view of the fact the reaction to aspirin can be delayed, patient is usually admitted overnight after the challenge and thus the whole process requires at least one day.[208]

- Intranasal LAS challenge

First introduced in 1990s, nasal challenge using LAS has been proposed as a quicker and safer alternative to oral and bronchial challenges.[209] On the day of the nasal challenge, the patient remains in the laboratory for an initial acclimatisation period of 15 min. After that, nasal and lower airways measurements are taken alongside patient-reported symptoms. The LAS solution used for the challenge is prepared by dissolving one sachet of LAS (ASPEGIC 500 mg, Sanofi – Aventis, Ditto, France) in 10 mL of normal saline. LAS demonstrates significantly higher water solubility compared to aspirin (40% vs. 0.3%) and exhibits non-irritant properties. Prior to initiating the aspirin provocation test, a single-blind challenge with normal saline is conducted by administering 100 μl of saline solution to each nostril via pipette while the patient assumes a supine position with the head tilted downwards for a duration of one minute. This initial test is done to rule out any nasal hyper-reactivity. This is confirmed if the patient reports a worsening of nasal/respiratory symptoms and/or a 25% decrease in acoustic rhinometry measurements (MCA1 and/or nasal volume) and/or a 40% decrease in peak nasal inspiratory flow (PNIF) after 15 mins from the test. In the case of nasal hyperreactivity, the diagnostic procedure is discontinued as the degree of nasal reactivity precludes the acquisition of accurate diagnostic data. The patient is given appropriate nasal treatment and the challenge is rescheduled for a minimum of one month thereafter. If the saline challenge is negative, a graduated challenge with LAS is then initiated. This involves the administration of initial doses ranging from 5 to 10 mg, applied as 100 μL drops to each nostril, with the patient maintaining a supine position with the head upside-down for a duration of one minute. Symptoms are reassessed after 45 mins, and if no significant changes from baseline nasal measurements (as previously explained) are observed, then a double dose of intranasal LAS is administered with further readings after 45 min. This procedure is repeated until the patient reacts to the dose given. The final nasal dose to be administered is 40 mg, resulting in a cumulative nasal dose typically ranging from

75 to 100 mg. Following this, patients who exhibit no adverse reaction to the nasal provocation are subsequently challenged orally with increasing doses of aspirin administered sublingually, commencing with an initial dose of 100 mg and progressing until a cumulative dose of at least 350 mg of aspirin is reached. In the nasal challenge, patients exhibiting high aspirin sensitivity are expected to react at low LAS doses, predominantly manifesting with nasal symptoms and minimal asthma exacerbation. Conversely, patients displaying lower sensitivity who tolerate the initial nasal doses without experiencing any nasal or respiratory symptoms are unlikely to experience a severe adverse reaction upon receiving a subsequent oral aspirin challenge.[203] If patients do not react to either the nasal and oral challenge, they are considered aspirin tolerant.[203] A nasal challenge usually does not last longer than 4 hours and can be fitted into one day.

4.2.4. Treatment

Treatments for CRSwNP in N-ERD can be distinguished in pharmacological and surgical. Table 4.2. briefly summarise the main treatment options and drugs used.

	Type of drug/treatment
Pharmacological	
Oral ATAD	Aspirin (300 mg/day to 650 mg twice/day)
Intranasal ATAD	Lysin aspirin (75mg to 100 mg daily)
Monoclonal antibodies	Omalizumab (75 mg to 600 mg every 2 or 4 weeks) Dupilumab (300 mg every other week) Mepolizumab (100 mg every four weeks)
Others	Oral or topical corticosteroids (different formulations/protocols) Leukotriene modifying drugs (Montelukast 10mg/day)
Surgical	
FESS	Ranging from polypectomy to full-house FESS and more extended approaches (Draf 2b/Draf 3)

Table 4.2. Treatments currently utilised for CRSwNP in N-ERD.

ATAD: Aspirin Treatment After Desensitisation; FESS: functional endoscopic sinus surgery.

- Pharmacological

Treatments of CRSwNP in N-ERD patients include the use of nasal corticosteroids, nasal douches, inhalers, leukotriene-modifying drugs, aspirin treatment after desensitisation (ATAD) and, more recently, biologics targeting type 2 inflammatory cytokines.[210] ATAD, particularly using intranasal LAS, and monoclonal antibodies will be further discussed below.

- Aspirin Treatment after desensitisation (ATAD)

ATAD, which involves a gradual exposure of patients to increasing doses of aspirin until a final daily dose is achieved, has emerged as an effective treatment for N-ERD patients with recalcitrant nasal polyposis.[181] Since its initial description in 1980,[211] several studies have constantly confirmed the clinical benefit of ATAD, including "a reduction in sinonasal symptoms (Grade 1A), a decrease in the use of nasal corticosteroid (Grade 2B), a reduction in recurrence of nasal polyps (Grade 2B), and a decrease in the need for revision surgery (Grade 2B)".[181] According to the American Academy of Allergy, Asthma and Immunology, ATAD is a "unique treatment option that should be considered in all eligible patients with AERD as a means to improve clinical outcomes and delay or prevent future sinus surgery".[212] ATAD has emerged as a viable therapeutic option for CRSwNP refractory to conventional medical and surgical interventions, owing to its favourable safety profile and cost-effectiveness.[213-215] The precise mechanisms underlying the efficacy of ATAD remain to be fully elucidated. However, it is established that ATAD "modulates deregulated immune responses in N-ERD through mechanisms including decreased levels of pro-inflammatory leukotrienes and their receptors (like the cysLT receptor),[216] inhibition of Th2 activation, IL-4 production, and mast cell activation".[217] While the majority of patients with N-ERD are expected to benefit from ATAD,[212] a subset may experience intolerance due to associated symptoms affecting the skin, gastrointestinal tract, or respiratory system. Adverse events may include gastritis,

major gastrointestinal bleeding, asthma exacerbation, and severe rash. To mitigate the risk of ATAD-related adverse events, intranasal administration of LAS has been proposed as a potentially safer and faster route compared to oral ATAD.[218] However, the evidence supporting the efficacy and safety of intranasal LAS is currently less robust. Previous clinical trials have confirmed the benefits of long-term intranasal LAS (75 mg) in the management of CRSwNP,[219-224] resulting in a significantly lower recurrence rate of nasal polyps at 2 years when compared to control groups (21% vs 76%). [218]

- ATAD using intranasal LAS

Once the diagnosis of N-ERD has been confirmed by challenge, the patient can start intranasal ATAD. The starting dose is the dose to which the patient has reacted at the nasal challenge plus an additional drop into each nostril. The patient receives instruction to slowly increase the number of drops administered to each nostril on a daily basis, with a gradual escalation of dosage, if asymptomatic, up to a maximum of 9 drops/nostril, corresponding to 45 mg of aspirin, with a subsequent assessment scheduled after 3 months. Subsequently, the number of drops is further increased on a daily basis up to a maximum of 15-20 drops/nostril, equivalent to 75-100 mg of aspirin.[221] This low dose of aspirin has been reported to be cardioprotective, but more importantly does not carry the gastro-intestinal side effects or other complications associated with the higher doses required for oral ATAD (usually of at least 300 mg daily).[225-228] Moreover, based on the principle of direct administration of LAS to the nasal mucosa, a higher intranasal concentration can be achieved without subjecting the gastrointestinal tract or the cardiovascular system to the potential adverse effects associated with high systemic aspirin doses.[221] Nonetheless, a previous randomised-controlled trial (RCT) involving 43 N-ERD patients treated with a lower, alternate-day dose of intranasal LAS (16mg every 48 hours) failed to show a clinically significant benefit, despite demonstrating a reduction in the expression of leukotriene receptors.[229]

- Monoclonal antibodies

Monoclonal antibodies, such as omalizumab, mepolizumab and dupilumab, are showing encouraging results in treating difficult-to-treat CRSwNP in N-ERD. While Omalizumab "blocks the activity of circulating IgE, mepolizumab binds to and blocks circulating IL-5, a key cytokine involved in eosinophil recruitment and activation. In contrast, dupilumab is directed towards the IL-4 receptor alpha subunit (IL-4Rα), a shared component of both IL-4 and IL-13 receptors, thereby inhibiting the activity of both signalling pathways".[230] These molecules have been studied in large placebo-controlled trials in patients with asthma and in CRSwNP, most included subjects with N-ERD; however, a study exclusive to N-ERD subjects is lacking. A Cochrane systematic review of RCTs concluded that all three monoclonals showed some degree of efficacy in treating patients with CRSwNP (with or without asthma), although dupilumab resulted in the most significant improvement in the disease-specific health-related QoL (measured using SNOT-22) compared with the placebo.[231] NSAIDs sensitivity among the study groups was not mentioned. Another systematic review and meta-analysis analysed the comparative efficacy and safety of various monoclonal antibodies and aspirin desensitisation in treating CRSwNP.[232] In a retrospective analysis, N-ERD patients with inadequate response to mepolizumab, reslizumab, and benralizumab significantly improved their upper and lower airway symptoms when switched to dupilumab.[233] The selection of the agent and timing have to be decided carefully and wisely, and published guidance is available.[234] In Europe, both mepolizumab and dupilumab are approved as add-on treatments for CRSwNP. Currently, no monoclonal is licensed in the UK for CRSwNP per se. However, patients with concomitant severe eosinophilic asthma may become eligible to be treated with monoclonal antibodies such as omalizumab, mepolizumab, dupilumab, reslizumab or benralizumab, and those with concomitant severe atopic dermatitis with dupilumab. Despite their high efficacy, these immunomodulatory medications are associated with a substantial cost, and long-term safety and outcome data for many of these agents are currently limited. In view of that, biologics are not recommended as a

first-line treatment and should be reserved following completion of extensive sinus surgery and a trial of aspirin desensitization, thereby enabling a more cost-effective approach to disease management.[235,236]

- Surgical treatment - Functional Endoscopic Sinus Surgery (FESS)

FESS in N-ERD is indicated when CRSwNP is uncontrolled despite optimal medical treatment.[210] In this surgery, polyps are removed and the sinonasal cavities are opened up to allow better access of topical treatments to the sinonasal mucosa in order to prevent polyp recurrence and achieve better disease control. However, recurrence of nasal polyps after sinus surgery is higher in patients with N-ERD compared to patients with CRSwNP without N-ERD.[181,187] Moreover, failure rates of standard FESS in this population have been reported to be as high as 90% at 5 years, while rates of revision surgery can range from 38% to 89% at 10 years.[237,238] Additionally, patients with N-ERD tend to undergo a significantly higher number of revision FESS procedures (up to 10-fold increase) and have a greater probability of requiring long-term treatment with oral corticosteroids for effective disease control.[239] Currently, there exists no consensus among surgeons regarding the optimal FESS extension strategy to adopt in these patients with the aim of minimizing the risk of polyp recurrence. Recent evidence seems to suggest a role for more extended sinus surgery (i.e. large cavity FESS) which include "a combination of complete uncinectomy, wide middle meatal antrostomy, complete ethmoidectomy, wide bilateral sphenoidotomy, and a Draf IIb or Draf III frontal sinus surgery".[240-245] It has been observed that patients with N-ERD who undergo large cavity FESS exhibit superior clinical outcomes compared to those undergoing more conservative FESS, showing a reduction in disease recurrence, a lower rate of revision surgery, and improved QoL scores.[240-245]

4.3. Pathophysiology of OD in N-ERD

OD is a highly prevalent condition amongst patients with N-ERD, affecting over 90% of subjects.[246] The pathogenesis of OD in N-ERD appears to be multifactorial, involving both conductive and inflammatory mechanisms. Contributing factors include the significant burden of nasal polyps and the resultant swelling of the sinonasal mucosa in the olfactory region, which can physically obstruct the passage of odorants to the OE. Additionally, chronic inflammation within the OE itself may play a role in the development of OD in this patient population.[247] Research suggests that elevated levels of IL-2, IL-5, and IL-13 in nasal mucus may contribute to loss of sense of smell in patients with N-ERD.[248,249] OD significantly impact on the quality of life of N-ERD patients. It is well-established that diminished olfaction is associated with various negative consequences, including depression, social isolation, emotional distress, changes in weight, cognitive decline, neurodegeneration, and even increased mortality risk in older adults.[99,250,251] *(Table 4.3.)* In the past, it was believed that CRS-related OD was due to a conduction problem only caused by the obstruction of the olfactory cleft by nasal polyps or nasal mucosa congestion.[252] However, a significant number of patients still have OD despite removal of nasal polyps and increase of nasal airflow.[210]

	Mechanism	Rationale
Nasal polyps	Conductive	Obstruction of the olfactory cleft by nasal polyps or nasal mucosa congestion
Chronic mucosal inflammation	Sensorineural	Long-term local inflammation of the olfactory mucosa causes: 1. Cell death of the olfactory sensory neurons; 2. Changes in the mucus layer that covers the olfactory epithelium; 3. Reduced number of olfactory binding proteins (OBPs) 4. Reduction of olfactory metabolizing enzymes
Abnormalities in olfactory central areas	Central	Sensory deprivation and/or injury of the olfactory sensory neurons decreasing projections to the olfactory bulb

Table 4.3. Relevant mechanisms leading to olfactory dysfunction in N-ERD.

Further studies have shown that the situation is more complex. In addition to a nasal airway obstruction by nasal polyps, a conductive problem may also be related to changes in the mucus layer that covers the OE with alterations and reduced number of OBPs, which plays an important role in olfactory signal transmission, but also of olfactory metabolizing enzymes, that eliminate odorants.[18,253,254] Evidence is now showing that OD in these patients is also caused by a chronic inflammation at the level of the sinonasal mucosa.[252,255-257] CRS presents with two distinct inflammatory phenotypes: “Type 2 (T2) and Type 1/Type 3 (non-T2) inflammation.[210] The specific phenotype is determined by the primary cytokines and effector cells involved in the inflammatory process.[210] T2 inflammation is characterized by the presence of ILC2s and T-helper (Th) 2 cells. These cells produce IL-4, IL-5, and IL-13, leading to the recruitment of eosinophils to the sinonasal mucosa. In contrast, non-T2 inflammation is characterized by the secretion of more general inflammatory cytokines, including IL-8, IFN-γ, and IL-6, as well as IL-17 and IL-22. These cytokines are produced by Th1, Th17, or Th22 cells, respectively. The recruitment of neutrophils to the nasal and sinus mucosa is typically observed in non-T2 inflammation.[258] This inflammatory response leads to the influx of inflammatory cells such as lymphocytes, macrophages and eosinophils in the OE of CRS patients and the resulting chronic inflammation can cause a cell death of the olfactory sensory neurons resulting in OD”.[252]

N-ERD is typically characterised by a T2 inflammatory response. Eosinophils, the “primary effector cells of T2-inflammation endotype, are known to release cytotoxic proteins, including major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil peroxidase (EPO)”, which can damage epithelial tissues.[259-261] A high “eosinophil presence in the lamina propria of the OE, as well as extensive inflammatory responses around nerve bundles”, has been observed in patients with severe CRSwNP.[252] Moreover, studies have shown a correlation between the presence of “eosinophils in superior turbinate biopsies from CRSwNP patients and the severity of

OD".[262] "Elevated levels of galectin-10, a protein produced by eosinophils that forms Charcot-Leyden crystals (a marker of cell death), have been found in the OE mucus and superior turbinate biopsies of CRS patients with OD compared to those without OD".[263] T2 inflammatory cytokines can also contribute to OD. A Chinese study confirmed a positive correlation between "levels of IL-4 and IL-5 in mucus from the middle meatus of CRSwNP patients and the severity of OD".[264] Conversely, the non-T2 inflammation endotype, predominantly seen in CRSsNP, is characterized by a neutrophil-rich sinonasal mucosa.[265] Although limited research exists on OD in CRSsNP patients, the T1-inflammatory cytokine TNF-α, which regulates cell proliferation, differentiation, and apoptosis, appears to be a key mediator. A negative correlation has been observed between the "presence of TNF-α in mucus from the middle meatus of CRSwNP patients and olfactory scores".[264]

A third mechanism that could potentially contribute to OD in N-ERD patients is the alteration of microbial diversity in the sinonasal mucosa (dysbiosis).[264] Dysbiosis has been found to be higher in CRS patients with OD compared to those without.[264] Another mechanism is olfactory metaplasia, which is the substitution of OE with squamous or respiratory epithelium following an injury. This is characteristic of sinonasal diseases when recurrent infection or chronic insults to the OE induce an irreversible damage of the OE resulting in permanent OD.[266,267]

Finally, patients with CRS and OD exhibit structural abnormalities within the central nervous system. These include a reduction in the volume of the OB and a decreased "volume of grey matter in certain regions of the secondary olfactory cortex, such as the orbitofrontal cortex, the right insula, and the left thalamus".[268,269] The precise mechanisms underlying these central olfactory impairments remain unknown. However, it is hypothesized that "sensory deprivation and/or injury to the ORNs may lead to diminished projections to the OB", contributing to these observed structural changes.[268]

8.3.1. Treatment of OD in N-ERD

Treatment options for OD in N-ERD patients are typically the same as in other patients with CRSwNP. *(Table 4.2.)* Due to their anti-inflammatory effect, corticosteroids are considered to be the mainstay therapy of CRS[210] and, according to the most recent position paper on olfaction,[44] “the use of systemic (short courses) and/or intranasal (long-term) corticosteroids is recommended for CRS-related OD”. The effect of topical steroid on sense of smell is controversial and results from studies have been conflicting. Their efficacy is mainly influenced by the administration route. Nasal sprays predominantly deposit in the anterior nasal cavity, whereas drops or high-volume douche devices can reach deeper regions depending on head position.[270] Notably, drops administered in the "Kaiteki" position have demonstrated a high rate of reaching the olfactory cleft, with rates of 96% in decongested noses and 75% in non-decongested noses.[270,271] Systemic corticosteroids have generally been considered more efficacious than topical ones (sprays or drops) for treating CRS-related OD. A previous systematic review encompassing over 400 CRS patients with OD confirmed a “significant subjective improvement in olfaction following a brief course of oral steroids compared to placebo”.[272] Moreover, another study suggested that the “combination of oral and intranasal corticosteroids can significantly improve sense of smell in CRSwNP patients in the short-term” when compared to topical spray alone, although this benefit does not last long-term.[273] The mechanism through which corticosteroids can improve OD in CRSwNP is not completely known. Corticosteroids bind to the glucocorticoid receptor, “triggering the transcription of anti-inflammatory genes”. This action leads to the suppression of inflammatory cells and their mediators.[274] However, no data are available on the human OE.

FESS is the treatment of choice for patients with CRSwNP not responding to optimal medical treatment. A meta-analysis confirmed the role of FESS in improving olfaction in

CRSwNP patients.[179] The mechanisms through which FESS restores olfaction are double and mainly related to polyps' removal. In fact, FESS not only improves odorant conduction to the OE by removing polyps, but also enhances the effectiveness of topical nasal steroids. Additionally, research has shown that FESS can lead to an increase in the volume of the OB and increased activity in "key areas of the central olfactory system, including the orbitofrontal cortex, anterior cingulate cortex, insula, and temporal pole".[275,276]

More recently, biologic treatment (i.e. monoclonal antibodies) have increasingly been used for the treatment of severe and uncontrolled CRS, in patients failing maximal medical and surgical treatment. These medications target specific molecules in the Type 2 inflammatory pathway, effectively blocking the inflammatory cascade. Currently, only "three monoclonal antibodies have been approved by regulatory agencies (European Medicines Agency and Food and Drug Administration) for treating Type 2 CRSwNP.[230] These are: omalizumab (anti-IgE), mepolizumab (anti-IL5) and dupilumab (anti-IL4Rα)".[230] Several studies have shown a significant improvement in the sense of smell following treatment with both dupilumab and omalizumab, but not with mepolizumab.[277-279]

Other treatment options for OD in CRSwNP patients like long-term antibiotics, antifungal or herbal treatment have poor evidence.[180] Similarly, the role of OT for CRS-related OD remains controversial.[180] Comparative studies in relations to their effectiveness in improving OD in N-ERD are limited by data availability as olfaction has not often been included as an outcome measure in these studies.

4.4 Published studies on N-ERD – hypotheses and aims

Sections 4.5. and 4.6. include my own published papers. In the first study[224] I retrospectively analysed a large database of N-ERD patients who started on ATAD with intranasal LAS for the treatment of CRSwNP. This represents the largest database of N-ERD patients on intranasal LAS of the country and currently available in the literature. I particularly focused on nasal airflow and olfactory long-term changes following intranasal LAS treatment. As explained in *Sections 4.1.* and *4.2.*, OD in N-ERD is multifactorial and mainly caused by a combination of both conductive (obstruction created by nasal polyps) and inflammatory mechanisms to the OE. The hypothesis is that intranasal LAS can control sinonasal inflammation, reduce polyps' size and, therefore, improve nasal airflow. Olfaction would consequently improve as a result of the reduction of olfactory mucosa inflammation but also following an increased stimulation of olfactory receptors due to better odours' delivery.

The second study,[280] instead, is a survey which I conducted during the COVID-19 pandemic to follow up our N-ERD patients. In this study, I could only evaluate olfaction and nasal airways using patient-reported outcome measures (PROMs). In this group of N-ERD patients, some subjects had stopped LAS over the years whilst others were still on it. This gave me the opportunity to further assess the benefits of long-term intranasal LAS on patient-reported sinonasal symptoms and olfactory function.

Minor edits to the text in the papers have been made following departmental guidelines to ensure articles fit the overall style of the thesis.

4.5. A retrospective study on long-term efficacy of intranasal lysine-aspirin in controlling N-ERD[224]

4.5.1. Introduction

Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD), also referred to as Samter's triad, remains a diagnostic and therapeutic challenge.[181] Standard treatments include the use of nasal corticosteroids, nasal douches, inhalers, leukotriene-modifying drugs, and biologics targeting type 2 inflammatory cytokines.[210] Endoscopic sinus surgery (ESS) is also used to debulk nasal polyps and improve corticosteroid delivery when CRSwNP is uncontrolled despite optimal medical treatmen.[210] Nevertheless, patients with N-ERD tend to undergo up to 10-times more revision ESS and are more likely to be dependent on oral corticosteroids to control their disease.[239] Aspirin treatment after desensitization (ATAD), whereby a patient is exposed to a gradually increasing dose of aspirin until a final daily dose is reached, has emerged as an effective therapeutic option suitable for N-ERD patients with recalcitrant disease.[181] Since its first description in 1980,[211] several blinded and longitudinal studies have consistently shown the benefit of ATAD including a decrease in sinonasal symptoms (Grade 1A), decrease in intranasal corticosteroid use (Grade 2B), reduction in recurrence of nasal polyps (Grade 2B), and decrease in the need for revision surgery (Grade 2B).[181] According to the American Academy of Allergy, Asthma and Immunology, ATAD is a "unique treatment option that should be considered in all eligible patients with AERD as a means to improve clinical outcomes and delay or prevent future sinus surgery".[212] The majority of N-ERD sufferers would benefit from ATAD.[212] However, there are some patients who cannot tolerate ATAD because of associated symptoms affecting the skin, gut or lungs. To minimise ATAD-related risks, intranasal administration of lysine-aspirin (LAS) has been suggested as a safer and faster route than oral ATAD.[218] However, the evidence for its use is less strong. Previous trials have demonstrated the

beneficial effects of long-term intranasal LAS (75 mg) in the treatment of nasal polyps[219-223] leading to a significantly lower rate of polyp recurrence at 2 years when compared with controls (21% vs 76%).[218] Nevertheless, a previous small randomized-controlled trial (RCT) on 43 patients with N-ERD treated with a lower alternate-day dose of intranasal LAS (16 mg LAS every 48 h) failed to demonstrate a clinical benefit although it showed a decrease in leukotriene receptors.[229]

The long-term effects of ATAD using intranasal LAS (75mg) remain unknown and we aim to perform a long-term cross-sectional analysis of 80 N-ERD patients on intranasal LAS which follows on from our previous short-term evaluation.[221] LAS long-term efficacy will be evaluated using objective outcomes, smell function assessment, polyp recurrence and the need for rescue medicines and surgery. Our secondary aims are to evaluate potential clinical biomarkers to help predict success and determine which patients would be most likely to benefit from intranasal LAS. In addition, we will evaluate the consequences of discontinuing LAS treatment, the long-term side effects of intranasal LAS and potential pulmonary benefits.

4.5.2. Materials and methods

Study design

A retrospective analysis of patients with confirmed or possible N-ERD seen at the Royal National Ear, Nose and Throat Hospital (University College London Hospital, London, UK) between 2012 and 2020 was performed in March 2021. Only those patients who continued the intranasal LAS treatment for a minimum of 3 months were included. This cohort of patients was then followed up at 1, 2 and 3 years. N-ERD patients who stopped intranasal LAS at any point during this time frame but who continued to attend the outpatients' follow-ups were included in order to compare their nasal and pulmonary function measurements with those still on intranasal LAS. The study was conducted in

accordance with the 1996 Helsinki Declaration and approved by the research ethic committee (reference 06/Q0301/6).

Diagnosis of Aspirin Sensitivity

Patients with nasal polyps with a clear history of respiratory reaction to aspirin and at least one other different Cox-1 inhibitor NSAID were considered aspirin sensitive.[281] In patients with one reaction to aspirin/NSAID or no previous ingestion, diagnosis of N-ERD was confirmed with an intranasal graded aspirin challenge, as previously described.[203] Exclusion criteria to aspirin challenge included pregnancy, a history of an immediate anaphylactic or urticarial reaction to aspirin or NSAID, bleeding diatheses, severe gastro-intestinal disease, patients with grade 3 or larger polyps at the pre-challenge endoscopic examination, or patients considered unable to use such medication regularly.[203] All patients were refractory to standard medical therapy (i.e. long-term nasal corticosteroid drops, regular nasal douches with normal saline and corticosteroid inhalers) and gave written informed consent to LAS nasal challenge and to LAS therapy continuation at home after a positive challenge [i.e. increased symptoms (recorded by a visual analogue scale), plus either 25% or greater decrease in the nasal airway as assessed by acoustic rhinometry (reduction of cross-sectional area) or a 40% decrease in PNIF][203].

LAS treatment after positive aspirin challenge

Treatment was started at home on the day after the positive challenge using drops (50µl each) from a freshly prepared 50mg/ml solution of LAS in sodium chloride 0.9%. The starting dose for therapy was the dose to which the patient had responded intra-nasally on the previous day plus an extra one drop into each nostril. The patient was given instructions to increase similarly the number of drops each day, up to a maximum of nine drops in each nostril, equivalent to 45mg of aspirin, until assessment at 3 months (first follow-up). The number of drops was then further increased each day up to a maximum suggested dose of 15–20 drops in each nostril equivalent to 75–100 mg aspirin.[221] This

was chosen as it is also an optimal dose for cardiovascular protection [228] and the nasal administration is followed by swallowing the LAS.

Objective evaluation

At each follow-up upper and lower airway functions were assessed and objective measurements taken were recorded. A portable Youlten peak flow meter (Clement Clark International) was used to obtain the peak nasal inspiratory flow (PNIF), as previously described.[282] The ability to smell was scored using Le Nez du Vin system[108], a 6-item suprathreshold identification test (maximum score 6). The lower respiratory function was evaluated using a spirometer (Maids Moreton, UK).

Data

Population data including demographic, disease onset, number of previous ESS, benefit on anti-leukotrienes and home medications were collected. Skin prick test (grass and tree pollens, house dust mite, cat and dog hair, alternaria, cladosporium, aspergillus) and relevant blood tests (eosinophils count, ANCA positivity, vitamin D3 and aspergillus fumigatus IgG levels) results at baseline were also documented. Details about the aspirin challenge and the dose of intranasal LAS taken at each follow-up were recorded. Objective measurements values, any modification in the patients' home medications as well as number of courses of oral corticosteroid taken and revision ESS received in between each follow-up were also noted.

Statistical analysis

Outcome variables are measured repeatedly on the same cohort of individuals at multiple time-points, with the aim of characterize changes in the individuals' measurements over time and their association with clinical factors. A linear fixed effect model[283] has been fitted to the data with random effects on the patients and, if needed, on time. Significant variables were selected by AIC and for the t-tests the Satterthwaite's method[284] was

used. Ottaviano et al.[285] showed that the relationship between PNIF and covariates is typically not linear and they proposed a square root transform of PNIF, which has been evaluated appropriate also for our data. The residuals analysis of the models suggests that the same transformation is adequate to all the pulmonary variables used here. The Nez du Vin is a discrete quantity thus a generalized linear mixed model with binomial distribution and logic link was fitted. All the analysis has been performed in R (R Core Team, 2021).

4.5.3. Results

Database analysis

Of the 190 patients referred since 2012 with possible N-ERD and who underwent intranasal LAS challenge for diagnosis confirmation, 75 had no notes available for screening at the moment of the analysis while data had not been recorded for 16 patients. A further 19 patients did not show any reaction to the escalating aspirin dose at the challenge and thus were excluded from the study leading to a final population of 80 N-ERD patients who were asked to start on intranasal LAS as part of their treatment. Seven patients never started ATAD with intranasal LAS after the challenge. Sixty patients had at least a 3-month follow-up and they were included in the analysis. *Figure 1* shows the flow chart of study population with the number of N-ERD patients on LAS treatment, those who stopped intranasal LAS and those lost at each follow-up during the study period.

Population characteristics

The total population was composed of 34 men and 26 women (male to female ratio of 1.3:1) with a median age of 46.5 years. The median age of onset for both rhinitis/chronic rhinosinusitis and asthma was 30 years, followed by nasal polyps (33 years). Before LAS challenge, patients had undergone a median number of 2 revision ESSs and sense of

smell was affected in the majority of them (84.6%). The majority of patients (59.6%) had a history of lower airway reaction following aspirin/NSAIDs intake. Detailed characteristics of the population as well as family history of N-ERD and parental ethnicity are reported in *Table 1*.

LAS treatment drop-out rate and side effects

At 3 months a drop-out rate of 25.0% (20/80) was observed while at the following follow-ups (1, 2 and 3 years) it was respectively of 16.7% (10/60), 26.1% (12/46) and 12.9% (4/31). Of those who started LAS but then suspended the treatment over the 3-year follow-up period, 11.3% of patients (9/80) discontinued LAS because of lack of improvement, 3.8% (3/80) for “gut problems”, 2.5% (2/80) because of “worsening of nasal symptoms”, 2.5% (2/80) for an unbearable “nasal burning sensation”, 2.5% (2/80) for the appearance of an urticarial rash, 1.3% (1/80) for the appearance of tinnitus, and 1.3% (1/80) for pregnancy. For those lost to follow-up (26/80) we were not able to record any reasons.

Investigations at baseline

Skin prick test demonstrated that over half of the patients (56.9%) were atopic, with the majority of them (32.8%) reacting to 2 to 4 allergens. ANCA was negative in 95.7% of the subjects and the median values for eosinophils, vitamin D and aspergillus fumigatus were within the normal range in the studied population. (*Table 1*) Aspirin challenge was performed in 55 (91.7%) subjects, of which 50 (83.4%) reacted at the nasal challenge stage while 5 (8.3%) required a further oral challenge. Five patients (8.3%) had a clear history of previous reaction to aspirin or other NSAIDs and the aspirin challenge was not necessary. (*Table 1*)

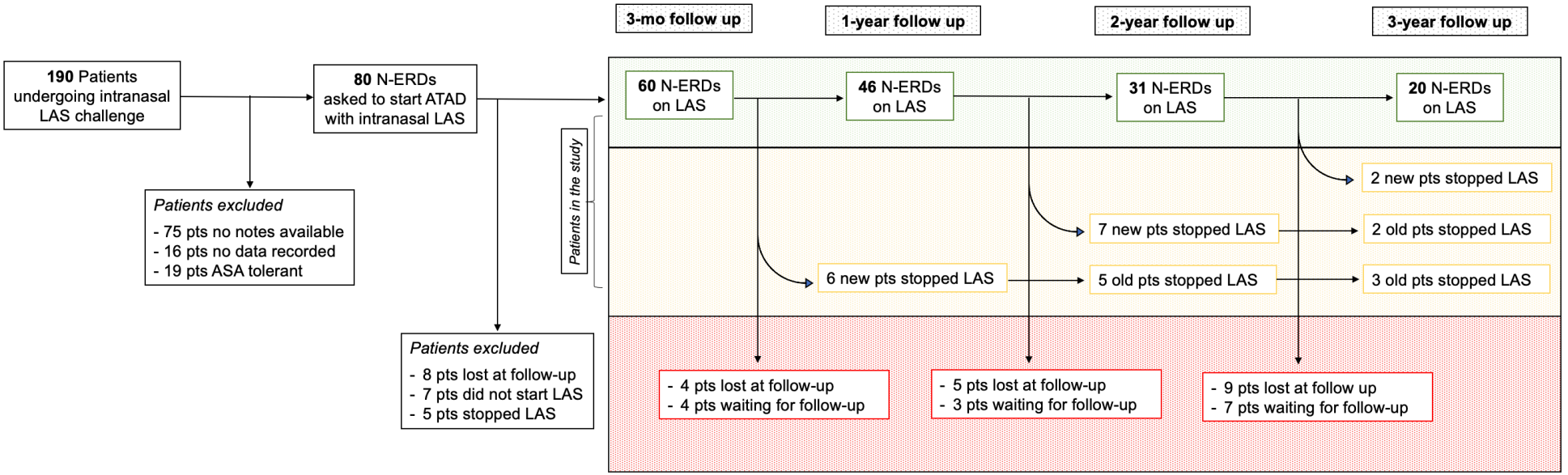

Figure 1. Flow diagram of patients included in the study.

N-ERD: Non-steroidal anti-inflammatory drugs (NSAIDs)-exacerbated respiratory disease; LAS: Lysine Aspirin; PNIF: Peak Nasal Inspiratory Flow;

Subjects (*n* = 60)		Subjects (*n* =60)	
Demographics		Therapy at baseline	
Age, median [P25-P75], r	46.5 [39-58.5]	Long-term nasal corticosteroid drops, *n* (%)	60 (100%)
Sex, *n* (%)		Nasal douche, *n* (%)	60 (100%)
Male	34 (56.7%)	ICS, *n* (%)	16 (30.2%)
Female	26 (43.3%)	LABA, *n* (%)	1 (1.9%)
Father ethnicity, *n* (%)		ICS+LABA, *n* (%)	33 (62.3%)
White	46 (85.2%)	SABA, *n* (%)	23 (43.4%)
Asian/Asian British	5 (9.3%)	Anticholinergic inhaler, *n* (%)	2 (3.8%)
Mixed/Multiple ethnic groups	3 (5.5%)	Long-term macrolides, *n* (%)	4 (7.5%)
Mother ethnicity, *n* (%)		Antileukotrienes, *n* (%)	28 (52.8%)
White	44 (84.7%)	Oral antihistamines, *n* (%)	25 (47.2%)
Asian/Asian British	5 (9.6%)	Investigations	
Mixed/Multiple ethnic groups	2 (3.8%)	Skin prick test positivity, *n* (%)	
Black Caribbean	1 (1.9%)	None	25 (43.1%)
Family history, *n* (%)		One allergen	9 (15.5%)
Aspirin/NSAIDs sensitivity	4 (7.8%)	2-4 allergens	19 (32.8%)
Asthma	26 (52.0%)	More than 5 allergens	5 (8.6%)
Rhinitis/rhinosinusitis	20 (40.0%)	Aspergillus positivity	4 (6.9%)
Nasal polyps	13 (26.0%)	ANCA, *n* (%)	
Rhinitis/CRS onset, median [P25-P75], yr	30 [19.3-39.8]	Positive	2 (4.3%)
Nasal polyps' onset, median [P25-P75], yr	33 [24-40]	Negative	45 (95.7%)
Number of polypectomies, median [P25-P75], yr	2 [2-5]	Eosinophils, median [P25-P75], x10^9/L	0.43 [0.26-0.73]
Sense of smell affected, *n* (%)		Vitamin D3, median [P25-P75], nmol/L	63 [44-77]
Yes	44 (84.6%)	Aspergillus Fumigatus IgG, median [P25-P75], mcg/mL	20.1 [16.9-32.3]
No	8 (15.4%)	Aspirin Challenge, *n* (%)	
Diagnosed asthma, *n* (%)	59 (98.3%)	Intranasal	50 (83.4%)
Asthma onset, median [P25-P75], yr	30 [18.8-40]	Oral	5 (8.3%)
History of aspirin/NSAIDs reaction, *n* (%)		Not performed*	5 (8.3%)
Upper airway	21 (40.4%)	Aspirin dose at challenge, median [P25-P75], mg^{+}	
Lower airway	31 (59.6%)	Intranasal	20 [15-47.5]
Antileukotrienes benefit, *n* (%)	19 (41.3%)	Oral	100 [100-120]

Table 1. Detailed characteristics of the population. Valid percentages, not including missing values.
*Not performed because of a clear history of aspirin sensitivity. + 1 drop ≈ 2.5 mg of lysine aspirin.

NSAIDs non-steroidal anti-inflammatory drugs, ICS inhaled corticosteroids, LABA long-acting β2 adrenergic receptor agonists, SABA short-acting β2 adrenergic receptor agonists

Therapy at baseline and during follow-ups

All subjects were on long-term nasal corticosteroid drops (Fluticasone propionate 400µg), regular nasal douches with normal saline and corticosteroid or corticosteroid plus long-acting beta agonist (LABA) inhalers. Two patients (3.8%) were on anticholinergic inhalers, 4 (7.5%) on long-term macrolides (Clarithromycin 250 mg od), 28 (52.8%) on antileukotrienes (Montelukast 10mg) with benefit and 25 (47.2%) on oral antihistamines. (*Table 1*) At the follow-ups, no relevant changes to patients' medical therapy were noted apart from a significant increase of those taking a combination of inhaled corticosteroids and long-acting β2 adrenergic receptor agonists (p=0.021) and a significant decrease of those taking inhaled corticosteroids only (p=0.01).

Long-term variability of pulmonary and nasal function and effect of LAS treatment

PNIF values remained stable during the study period in patients on long-term LAS treatment, but higher values of PNIF and Nez du Vin scores were found at each follow-up in patients taking LAS when compared to those who discontinued it. A significant positive linear correlation between the dose of LAS taken and nasal airflow (average increase of 0.048 at $\sqrt{\text{PNIF}}$ for each drop of LAS taken) as well as the odour identification were demonstrated. No influence of LAS on pulmonary function measurements was observed in patient on LAS nor on those who ceased taking it. An increase in the number of revision ESSs and courses of oral corticosteroid was observed in those who stopped LAS with a significant negative linear correlation found between the dose of LAS taken and the number of revision ESSs. Conversely, no effect of LAS was found on the number of courses of oral corticosteroid taken. *(Figure 2-4; Table 2-3)*

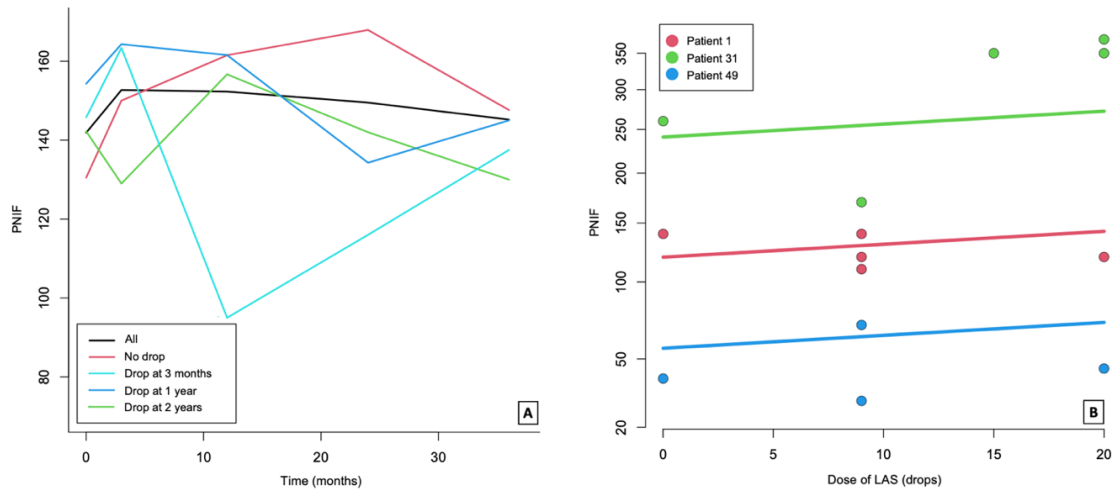

Figure 2. (A) Temporal trend of PNIF mean values in the different groups representing patients who discontinuing the treatment at 3 months, 1 year, 2 years, or not. (B) Relationship between PNIF and the dose of lysine aspirin (LAS) drops in 3 different patients taken as example.

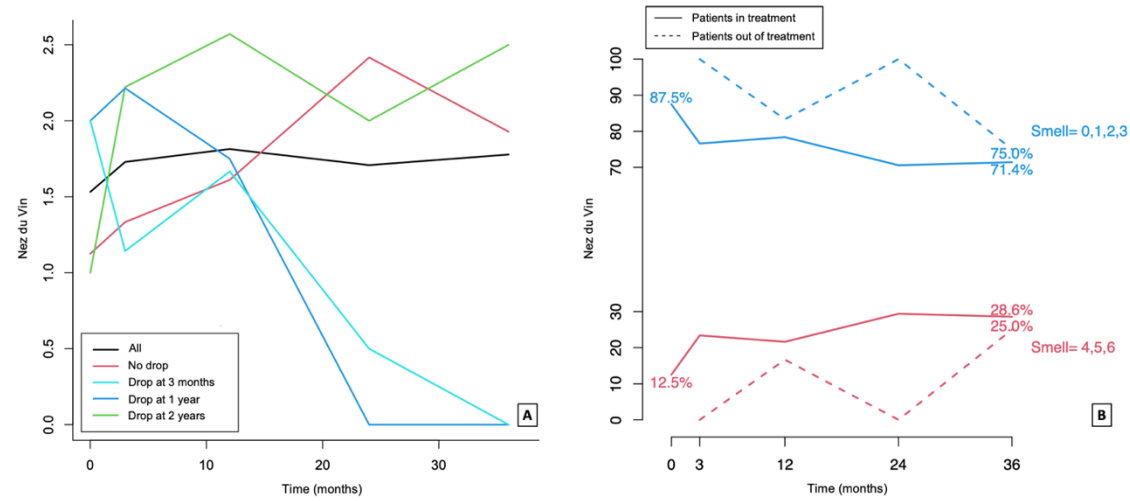

Figure 3. (A) Temporal trend of Nez du Vin mean scores in the different groups representing patients who discontinuing the treatment at 3 months, 1 year, 2 years, or not. (B) Percentage of patients obtaining low (0,1,2,3) and high (4,5,6) scores at Nez du Vin over time according to treatment.

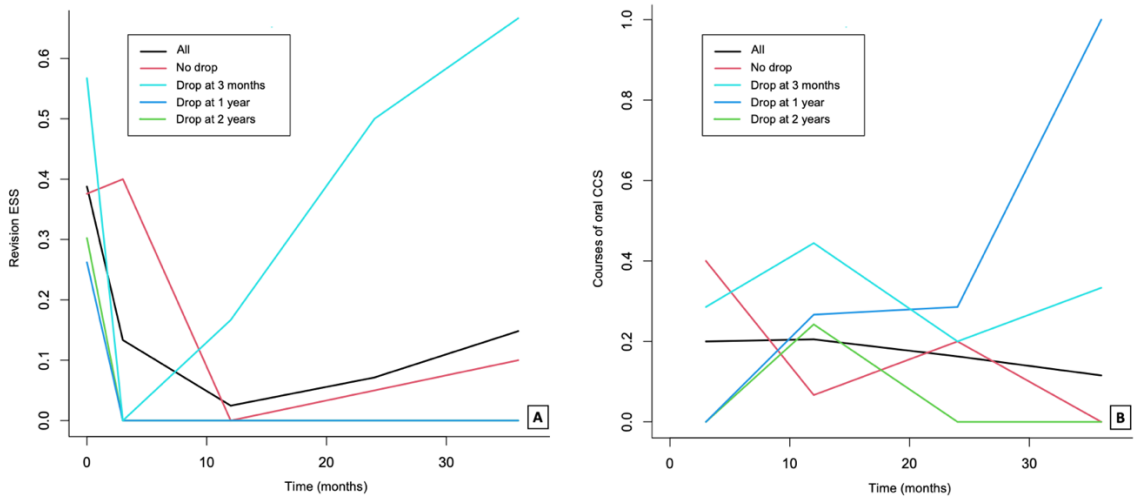

Figure 4. (A) Temporal trend of revision endoscopic sinus surgery (ESS) mean number or (B) of the mean number of oral corticosteroid (CCS) courses taken in the different groups representing patients who discontinuing the treatment at 3 months, 1 year, 2 years, or not.

	Baseline	3-month	1-year		2-year		3-year	
	n = 60	On LAS *n = 60*	On LAS *n = 46*	Stopped *n = 6*	On LAS *n = 31*	Stopped *n = 12*	On LAS *n = 20*	Stopped *n = 7*
LAS drops/nostril*	-	10 [9-15]	14 [10-20]	-	15 [10-20]	-	17.5 [11.5-20]	-
PNIF (L/min)	140 [110-170]	150 [120-190]	150 [130-180]	80 [70-100]	150 [130-160]	130 [77.5-160]	140 [107.5-162.5]	115 [102.5-150]
Nez du Vin	0 [0-3]	1 [0-3]	2 [0-3]	0.5 [0-2.5]	2 [0.5-4]	0 [0-0]	1.5 [0.5-4]	0 [0-0]
FEV_1 (L)	2.7 [2.3-3.6]	2.6 [2.1-3.5]	2.4 [2.1-3.7]	2.9 [2.3-3.4]	2.5 [2.2-3.4]	2.5 [2-3]	2.4 [2-3.7]	2.2 [1.9-2.3]
FVC (L)	3.7 [2.8-4.5]	3.7 [2.7-4.5]	3.4 [2.8-4.6]	3.7 [2.7-4.3]	3.5 [3-4.3]	3.7 [2.5-4.3]	3.6 [2.5-4.7]	2.5 [2.4-3]
FEV_1/FVC (%)	80.2 [72-85.7]	79.2 [70.7-85.1]	79.6 [73.1-86.2]	80.1 [78.1-93.4]	75.1 [68.4-82.5]	72.2 [68.4-79.3]	81.2 [66.8-87.3]	74.3 [71.6-80.5]
Revision ESS	-	2 (3.3%)	0 (0.0%)	1 (16.7%)	1 (3.2%)	2 (16.7%)	2 (10.0%)	2 (28.6%)
Courses of oral corticosteroids	-	3 (5.0%)	6 (13.0%)	2 (33.3%)	4 (12.9%)	3 (25.0%)	0 (0.0%)	3 (42.9%)

Table 2. Variables at baseline and follow-ups. Results shown as median and interquartile ranges for all the variables apart from revision ESS and oral corticosteroids courses where frequencies and percentages were used.
*1 drop ≈ 2.5 mg of lysine aspirin

LAS: Lysine Aspirin; PNIF: Peak Nasal Inspiratory Flow; FEV_1: Forced Expiratory Volume in the first second; FVC: Forced Vital Capacity; ESS: Endoscopic Sinus Surgery.

	Covariates	Partial regression coefficients	*p*-value
$\sqrt{\mathbf{PNIF}}$	LAS drops/nostril	0.048	< 0.001
	Age	-0.036	0.032
	Random effect: Patient variance	1.87	
	Random effect: Time variance	0.002	0.025
Nez du Vin	LAS drops/nostril	0.029	0.048
	Random effect: Patient variance	4.84	
	Random effect: Time variance	0.009	< 0.001
$\sqrt{\mathbf{FEV_1}}$	Sex (male)	0.291	< 0.001
	Age	-0.013	< 0.001
	Eosinophils	-0.156	0.026
	Use of inhalers	-0.312	< 0.001
	Random effect: Patient variance	0.001	
	Random effect: Time variance	0.0004	0.021
$\sqrt{\mathbf{FVC}}$	Sex (male)	0.373	< 0.001
	Age	-0.012	< 0.001
	Eosinophils	-0.151	0.037
	Pre-nasal therapy	-0.379	0.037
	Nasal therapy	0.171	0.017
	Use of inhalers	-0.277	< 0.001
	Random effect: Patient variance	0.001	
	Random effect: Time variance	0.0004	0.039
FEV_1/FVC	Nasal therapy	< 0.001	< 0.001
	Random effect: Patient variance	0.006	<0.001
Revision ESS	LAS drops/nostril	-0.014	< 0.001
	Random effect: Patient variance	0.139	
	Random effect: Time variance	0.0001	0.005

Table 3. Influence of covariates on selected variables. Only significant correlations have been reported where level of significance was greater than p<0.05.

LAS: Lysine Aspirin; PNIF: Peak Nasal Inspiratory Flow; FEV_1: Forced Expiratory Volume in the first second; FVC: Forced Vital Capacity; ESS: Endoscopic Sinus Surgery.

Effect of other available variables on nasal and pulmonary functions and on treatment response

A significant negative linear correlation between age and $\sqrt{\mathrm{PNIF}}$, $\sqrt{\mathrm{FEV_1}}$ and $\sqrt{\mathrm{FVC}}$ (i.e older age is associated with worse nasal airflow and pulmonary function) was observed while a significant correlation with sex (male) was found only for $\sqrt{\mathrm{FEV_1}}$ and $\sqrt{\mathrm{FVC}}$ (i.e male patients have better pulmonary function). The eosinophil count was found to vary

with pulmonary but not nasal function measurements. A significant negative association between the use of inhalers and both $\sqrt{\mathrm{FEV}_1}$ and $\sqrt{\mathrm{FVC}}$ (i.e patients taking inhalers have a worse pulmonary function) and a significant positive association between nasal therapy and $\sqrt{\mathrm{FVC}}$ and FEV_1/FVC (i.e patients on nasal therapy have better pulmonary function) were also demonstrated. *(Table 3)* We did not observe any influence of all the variables studied (sex, age, parental ethnicity, age of disease onset, positivity at skin prick test, eosinophil count, vitamin D3 and aspergillus IgG levels, final aspirin dose at challenge) on the LAS treatment response.

4.5.4. Discussion

To our knowledge, this study represents the first long-term evaluation of intranasal ATAD demonstrating the long-term (3-year follow-up) effectiveness of intranasal LAS in managing CRSwNP in N-ERD using a dose which is also beneficial to the cardiovascular system.[228] Our results corroborate our previous short-term findings on 105 N-ERD patients where we found a significant increase of PNIF, olfaction, exhaled and nasal nitric oxide levels following intranasal treatment with LAS at 12-months follow-up.[221]

We observed that patients on intranasal LAS showed higher scores of PNIF when compared to those who discontinued the treatment ($p<0.001$ at the linear fixed effect model) (*Table 2,3*). Moreover, the median PNIF values of those who continued the treatment remained almost stable during the whole length of the follow-up which suggests the efficacy of LAS in controlling polyp growth (*Table 2*). This reflects previous results obtained with oral ATAD both in the short- and in the long-term despite using a consistently higher dose of daily aspirin (300mg/day to 650mg twice/day)[226,286-288], whereas no significant differences in endoscopic polyp scores have been reported by an RCT in patients on low-dose oral aspirin (100mg/day)[289].

Sense of smell is more impaired in patients with N-ERD when compared to the aspirin-tolerant counterpart[247,281] and odour identification has been found to be the most affected ability as measured by means of a validated reliable olfactory test.[247] In our population we observed a significant improvement in smell function (i.e. identification) in patients on long-term intranasal LAS (p=0.048 at the linear fixed effect model) when compared to those who stopped the treatment. (*Table 2,3*; *Figure 3B*) Similar findings have been reported in patients on high-dose of oral aspirin (300mg/day[247] or 650mg twice/day[290]), but once more, no significant difference in olfaction were observed when using a lower daily oral aspirin dose (100mg/day).[289] Nevertheless, a meta-analysis, which considered also 5 RCTs, did not demonstrate significant changes in smell scores in N-ERD patients receiving a high maintenance dose of oral aspirin (650mg/day).[291]

We also observed a significantly lower rate of revision ESS in patients on long-term intranasal LAS when compared to those who discontinued the treatment (p<0.001 at the linear fixed effect model) (*Table 2,3*) which indirectly confirms the ability of LAS to reduce nasal polyp' growth and recurrence rate. In particular, the median number of operations per year changed from 0.24 (roughly one operation per 4 years) to zero operation in the 3-year follow-up period. Moreover, even if the rate of revision ESS for N-ERDs on LAS increased in the last two years of follow-up this remained considerably lower than that of those who discontinued the treatment. (*Table 1-3*) This mimics previous findings by Stevenson et al in a long-term follow-up study of 65 ASA-sensitive treated with oral ATAD who found a concomitant decline of sinonasal surgery from one operation per 3 years to one operation per 9 years.[288]

Even though the percentage of oral corticosteroid courses taken was higher at each follow-up in the group of N-ERD patients who suspended the treatment (*Table 2*), this difference was not statistically significant. However, a significant reduction in annual oral

corticosteroid requirements was found with oral ATAD (daily dose of aspirin between 325 and 650mg).[215]

We did not observe a significant change in pulmonary function between those on long-term intranasal LAS and those who stopped LAS treatment; however, we did demonstrate that spirometry measurements remained stable over time in our LAS population. (*Table 2*) Even if these results suggest an inability of intranasal LAS to improve breathing, we did demonstrate that LAS intake does not adversely affect lung function in the long-term. Conversely, oral ATAD has been shown its efficacy to be strongest in improving asthma symptoms and pulmonary outcomes.[215,291-293] This incapacity of intranasal LAS to improve pulmonary function may explain the lack of a significant reduction in the number of oral corticosteroid courses taken by those on long-term treatment where this is needed to control asthma exacerbations.

Patient concordance with such a long-term treatment requires continued clinician input and monitoring and strong patient motivation. A higher drop-out rate is expected to happen in the first months because of the initial side effects, poor compliance with the complicated treatment and/or the lack of symptomatic improvement. In our retrospective study, the drop-out rate was of 37.5% at 1 year but this went down in the following 2 years of follow-ups (respectively 26.1% and 12.9%). The majority of N-ERD patients who discontinued intranasal LAS did so because of an absence of improvement (11.3%). However, a lack of clinical benefit has also been reported to be a common reason for treatment suspension in oral ATAD.[215] In order to differentiate potential responders from non-responders to aspirin treatment, many researchers have tried to identify biomarkers able to predict a positive response to ATAD. Female sex, high blood eosinophil count, low sputum neutrophil percentage, severe nasal symptoms, high hydroxyprostaglandin dehydrogenate, and low proteoglycan 2 gene expression have recently been shown to be good predictors for a positive response to oral ATAD (650 mg/day).[294] Patients with

an inflammatory neutrophilic phenotype are unlikely to respond to aspirin treatment[294] and a recent study found that use of anti-leukotrienes reduces the response to LAS nasal challenge[295]. However, we were not able to find any correlation between the variables studied and intranasal LAS treatment response failing to confirm our previous findings of higher PNIF and smell scores in allergic patients and those with later N-ERD onset.[221]

Daily oral administration of high-dose of aspirin represents the gold standard for ATAD[212] but it is affected by a high incidence of side effects (8–46%)[218]. These include naso-ocular reactions (90%), bronchial/laryngeal (43%) or gut (23%) problems and skin reactions (10%).[296] Intranasal administration of LAS is better tolerated and has a lower rate of side effects when compared to oral aspirin.[221] In our current study, only 3.8% of the patients on LAS complained of gut problems, while 2.5% reported a worsening in their nasal symptoms, nasal burning sensation (2.5%) or had an urticarial rash (2.5%). The same rate of gut problems (3.8%) was found in our previous audit on N-ERD patients treated with intranasal LAS, confirming the lower risk of gastrointestinal side-effects linked to intranasal aspirin administration.[221]

A consensus does not exist on the exact daily dose of aspirin which should be offered. Nucera et al used significantly lower doses of intranasal LAS (initial dose of 20μg progressively increased to a maintenance dose of 4mg six times/week) than ours and observed a favourable effect of LAS in nasal polyposis.[219] Sousa et al showed that doses of 16mg of intranasal LAS daily reduced leukotriene receptors but had no clinical effect.[216] Ogata et al using 30mg of intranasal LAS daily did find clinical benefit on PNIF.[297] In our study, the median dose of daily intranasal LAS ranged from 50 mg at 3 months to 87.5mg at 3 years whereas, according to the EAACI position paper, a dose of 75mg/day “may be effective to relieve symptoms of CRS”.[181] A comparable variety in the maintenance oral dose of aspirin has been reported in a recent meta-analysis where this ranged between 100mg and 1300mg daily.[291] For intranasal LAS, we recommend to

reach a final dose of 15 drops of LAS/nostril/day which corresponds to a total of 75mg of LAS/daily. This represents also an ideal cardiovascular protective dose.[228] However, in our experience some patients may benefit from a higher dose of LAS, with some of them taking up to 150 mg of LAS/daily without any nasal discomfort. This is supported by the fact that a linear positive correlation between $\sqrt{\text{PNIF}}$ and the dose of LAS was demonstrated in our study. (*Figure 2B)*

Since nasal polyps represent an obstacle to intranasal LAS activity, a role for ASA desensitization therapy following recovery from ESS has been advocated in the management of N-ERD. [298] Even though we do not routinely perform ESS before starting the intranasal LAS, for the reason above-mentioned patients with a polyp grade of 3 or 4 at the endoscopic examination performed before the LAS challenge are considered ineligible to start LAS desensitization. Conversely, they are treated, either medically with oral and intranasal corticosteroids, or surgically, to reduce polyp size prior to the challenge. [203]

So far, it is not known, once ATAD is started, when it could be suspended without losing the beneficial effects gained. To our knowledge this is the first study to have demonstrated that the suspension of intranasal LAS treatment at any point of the follow-up period is associated with a worsening of the nasal airflow and olfaction as well as an increase in the need for revision ESS. Therefore, we recommended to attempt an initial trial period of 3 months on LAS to determine whether the patient notes a clinical improvement. For patients who respond to treatment, we suggest continuation of intranasal LAS indefinitely.

Study strengths and limitations

The present study has the longest follow-up for intranasal LAS desensitisation with a dose which is beneficial to the cardiovascular system.[228] However, the retrospective

design of our study constitutes a limitation due to the intrinsic limit of data homogeneity and availability in retrospective studies. For instance, we were unable to retrieve patient-reported outcomes measures (PROMs) which represents a lack in our data collection. Even if the drop-out of patients at each follow-up is a further limitation, on the other hand it allowed us to evaluate what happens when a N-ERD patient discontinues intranasal LAS treatment.

4.5.5. Conclusion

Our study demonstrates the long-term clinical effectiveness of intranasal LAS in the treatment of N-ERD in terms of improved nasal airflow, olfaction and a reduced need for rescue surgery. However, treatment discontinuation at any stage is associated with a loss of clinical benefit. Additionally, intranasal LAS is associated with a lower rate of side effects when compared to oral ATAD. New biologics may provide substantial benefit to patients with N-ERD but represent an expensive option. Intranasal LAS can be a highly cost-effective and safe treatment option when compared to revision ESS or biologics and should be offered, if possible, before other treatments are considered.

4.6. Quality of life in NSAID-exacerbated respiratory disease on or off intranasal lysine aspirin therapy[280]

4.6.1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs)-exacerbated respiratory disease (N-ERD) or aspirin exacerbated respiratory disease (AERD) is a clinical syndrome characterized by chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, and intolerance to aspirin/NSAIDs. It affects approximately 15% cases of patients with severe asthma, 10% of those with CRSwNP and 9% of cases with chronic rhinosinusitis (CRS).[182,183] CRS impacts multiple aspects of health-related quality of life (HRQoL) including mental and physical health, sleep, productivity, cognitive and social functioning, and general health status.[299,300] HRQoL is further worsened in patients with CRSwNP who have asthma.[299] Moreover, CRSwNP in N-ERD is usually refractory to conventional medical management and surgery and often requires several courses of systemic steroids for nasal polyposis and multiple endoscopic sinus surgeries (ESS).[301] As a result, patients with N-ERD usually have ongoing and more severe sinonasal symptoms when compared to their non-N-ERD counterpart.[213] Chronic nasal symptoms and poor sense of smell are the major drivers to N-ERD patients' reduced HRQoL. Olfactory dysfunction (OD), in particular, is highly prevalent amongst patients with N-ERD and reported to affect >90% of patients.[246] It is well-documented that a reduced sense of smell is associated with depression, feeling of isolation, emotional distress, changes in weight, cognitive decline, neurodegeneration in the brain and it is an independent risk factor for death among older adults.[99,250,251]

Aspirin treatment after desensitization (ATAD) is an effective therapeutic option for CRSwNP in N-ERD and its safe profile and low cost make it an attractive alternative treatment option in case of failure of maximal medical and surgical treatment.[213-215] The mechanism behind aspirin desensitization is not completely understood. It has been

shown that aspirin desensitization modulates deregulated immune responses in N-ERD through decreased levels of pro-inflammatory leukotrienes and their receptors, inhibition of Th2 activation, IL-4 production, and mast cell activation.[217] A recent systematic review and meta-analysis[214] has confirmed that oral ATAD improves HRQoL when compared to placebo. However, oral ATAD is associated with adverse outcomes severe enough to cause drug discontinuation, including major gastrointestinal bleeding, gastritis, asthma exacerbation, and severe rash.[214,215] Intranasal administration of lysine aspirin (LAS) is a faster and safer route for ATAD when compared to oral daily aspirin and has been shown to be equally effective to oral ATAD.[221,224]

Changes in HRQoL in patients on intranasal LAS have not been documented and in this cross-sectional study we aimed to investigate HRQoL in N-ERD patients on or off nasal ATAD. Additionally, a focus on costs of treatment options currently available for difficult-to-treat CRSwNP in N-ERD patients is also provided.

4.6.2. Materials and methods

Due to pandemic restrictions, in the months of October-November 2020 we reviewed all our challenge-confirmed N-ERD patients who were in follow-up in our rhinology clinic through a remote telephone consultation. As part of that, they were sent an email in which they were asked to fill a SNOT-22 questionnaire, a disease-specific HRQoL questionnaire for use in CRS.[105] This questionnaire has a recall period of 2 weeks (i.e. symptoms are rated as these have been over the last 2 weeks) and evaluates five main domains including sinonasal (8 items), ear/facial (4 items), sleep (4 items), function (3 items), and emotion (3 items) with each item scoring from 0 (“no problems”) to 5 points (“problem as bad as it can be”) leading to a total score ranging from 0 to 110.[105,302] In each case, higher scores represent worse HRQoL. Moreover, patients are asked to tick up to 5 “most important” items that they feel are affecting their QoL the most. To determine the portion of respondents who complained of OD at the time of the survey,

the answer to the item 21 of the SNOT-22, which asks patients to rate their sense of taste/smell, was analysed separately. Patients were also asked to self-assess their olfaction during the last 2 weeks using a visual analogue scale (sVAS – 0 represents 'sense of smell absent' and 10 'sense of smell not affected') and to report which medications they were taking at the moment of which the questionnaire was completed. Other relevant data were retrieved using our hospital medical system. Information on prices of LAS and other consumables used for intranasal ATAD were obtained from our hospital pharmacy to get an estimate of the cost burden. The study was conducted in accordance with the 1996 Helsinki Declaration and approved by the Research Ethic Committee (Ref:06/Q0301/6).

Statistical analysis

Quantitative variables were summarized using median and interquartile range (P25–P75) whereas qualitative variables were described with frequency and percentage. Comparisons of general characteristics and findings between groups were performed using the T-test for quantitative variables, if normally distributed, or the Mann-Whitney U test, if not, while the Pearson chi-square test was used for categorical variables. p-values have been calculated for all tests, and 5% was considered as the critical level of significance. A post-hoc power analysis has been calculated using the SNOT-22 total score as the main outcome and keeping the alpha level at 0.05.

4.6.3. Results

Of the 43 patients on follow-up, 34 were remotely reviewed (79.1% response rate) between the 14th October 2020 and the 29th November 2020 and sent back to us their questionnaires (SNOT-22 and sVAS) along with the other information requested. Of the 34 respondents, 21 patients (61.8%) were on intranasal LAS with a median length of LAS treatment of 44 months (range 10-180 months). The median time from sinus surgery

to LAS initiation was 16 months (range 3-48 months). Four patients initially tried intranasal LAS but then stopped because of no improvement in their nasal symptoms and were included in the group of patients “not on LAS”. The remaining patients refused intranasal LAS and did not start any aspirin desensitisation treatment. Similarly, these patients were included in the group of patients “not on LAS”. Characteristics of the population are reported in *Table 1*.

	Whole n = 34	**On LAS n = 21**	**Not on LAS n = 13**	***p*-value**
General characteristics				
Age, median [P25-P75], yr	49.0 [38.0-56.8]	48.0 [37.0-59.0]	50.0 [38.0-56.0]	0.50
Sex, No (%)				
Female	17 (50.0%)	10 (47.6%)	7 (53.8%)	0.72
Male	17 (50.0%)	11 (52.4%)	6 (46.2%)	
Onset CRSwNP, median [P25-P75], yr	27.0 [18.8-36.8]	25.0 [17.0-35.0]	28.0 [24.0-34.5]	0.39
Onset nasal polyps, median [P25-P75], yr	30.0 [24.0-40.0]	31.0 [24.0-41.0]	30.0 [25.0-38.5]	0.34
Onset asthma, median [P25-P75], yr	30.0 [25.0-40.0]	29.0 [19.5-40.0]	34.5 [28.5-40.0]	0.22
Numbers of previous ESS, median [P25-P75]	3.0 [2.0-4.5]	3.0 [1.5-3.5]	4.0 [2.0-5.5]	0.34
Routine medications				
Long-term nasal CS drops, No (%)	32 (94.1%)	20 (95.2%)	12 (92.3%)	0.75
Nasal douche, No (%)	34 (100%)	21(100%)	13 (100%)	1
ICS, No (%)	12 (35.3%)	5 (23.8%)	7 (53.8%)	0.09
LABA, No (%)	2 (5.9%)	1 (4.8%)	1 (7.7%)	0.75
ICS+LABA, No (%)	19 (55.9%)	14 (66.7%)	5 (38.5%)	0.07
SABA, No (%)	13 (38.2%)	7 (33.3%)	6 (46.2%)	0.52
Anticholinergic inhaler, No (%)	1 (2.9%)	0 (0.0%)	1 (7.7%)	0.21
Long-term macrolides, No (%)	2 (5.9%)	1 (4.8%)	1 (7.7%)	0.75
Antileukotrienes, No (%)	13 (38.2%)	9 (42.9%)	4 (30.8%)	0.41
Oral antihistamines, No (%)	14 (41.2%)	9 (42.9%)	5 (38.5%)	0.71
Laboratory findings and testing				
Eosinophils, median [P25-P75], x10^9/L*	0.5 [0.4-0.7]	0.6 [0.4-0.9]	0.4 [0.3-0.7]	0.28
Missing	11	7	4	
Skin prick test, No (%)				
Negative	10 (41.7%)	4 (19.0%)	6 (46.2%)	0.12
One allergen	3 (12.5%)	1 (4.8%)	2 (15.4%)	
Two allergens	5 (20.8%)	4 (19.0%)	1 (7.7%)	
Multiple allergens	6 (25.0%)	5 (23.8%)	1 (7.7%)	
Missing	10	7	3	

Table 1. Characteristics of the whole population and according to intranasal Lysine Aspirin (LAS) use. Level of significance p≤0.05. Significant p values in bold. *Eosinophils normal range:0.0–0.4 x10^9/L

CRSwNP: Chronic rhinosinusitis with nasal polyps; ESS: endoscopic sinus surgery; CS: corticosteroids; ICS: Inhaled corticosteroids; LABA: long-acting β2-adrenergic; SABA: short-acting β2-adrenergic; ANCA: antineutrophil cytoplasmic antibodies.

The most affected SNOT-22 domain was “rhinologic symptoms” and the question with the highest score (worst symptom) overall was “loss of smell or taste”. “Loss of smell or taste” was also the most frequently ticked “most important item” by respondents (20/34; 58.8%), followed by nasal obstruction (12/34; 35.3%), thick nasal discharge (8/34; 23.5%) and post-nasal discharge (8/34; 23.5%). (*Figure 1*) Only 2 patients, both amongst those using LAS, reported in question 21 of the SNOT-22 that they had “no problem” with their sense of smell while 27 patients (81.8%) confirmed to have at least a moderate problem with their sense of smell. Similarly, 18 patients (52.9%) reported at least a moderate nasal blockage and 12 patients (35.3%) reported this to be one of the most affected items.

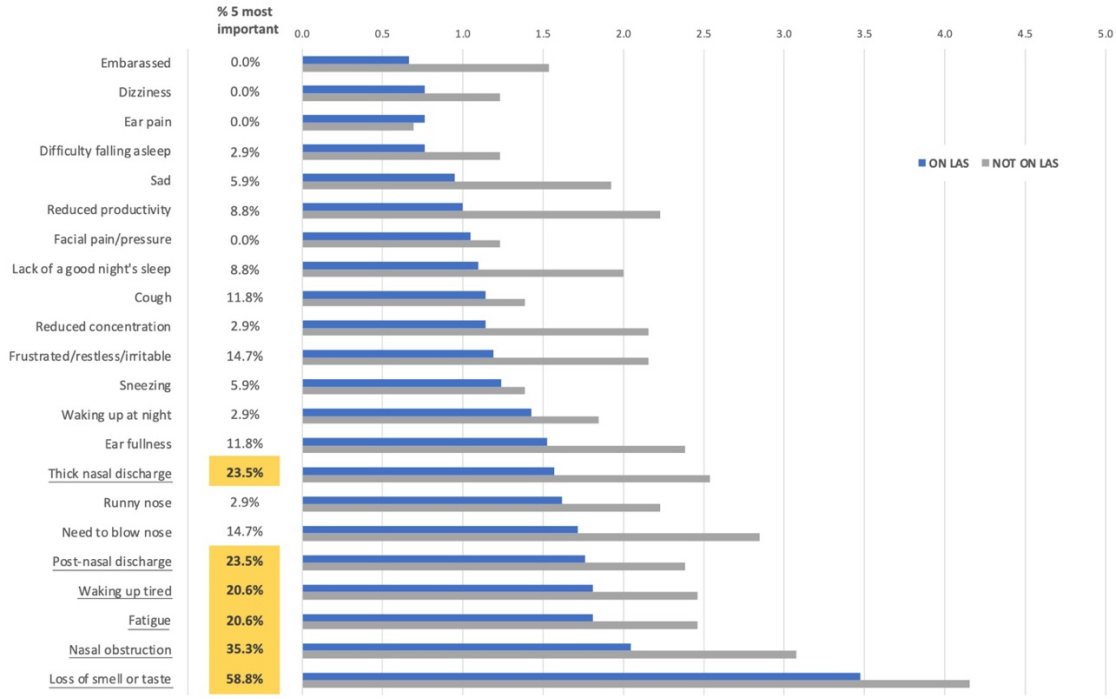

Figure 1. Average score for each SNOT-22 items in patients on or off intranasal lysine aspirin (LAS).
“% 5 most important” represents the percentage of patients who considered each item as one of the 5 most important items. The 5 most frequently reported items in the population are highlighted in ocre and underlined. Please note that due to similar scores in 4 items, we highlighted 6 most important items.

SNOT-22: 22-item Sino-Nasal Outcome Test; LAS: lysine aspirin

No statistically significant differences were noted in terms of general characteristics, laboratory findings or medical treatment when comparing those patients who were on intranasal LAS or not. (*Table 1*) A statistically significant lower score in the total SNOT-22 was found in patients on intranasal LAS (p=0.02). Moreover, when we performed a subanalysis of the SNOT-22 domains (rhinologic symptoms, ear/facial, sleep dysfunction, function and emotion), as previously described,[302] patients on LAS showed statistically significant lower scores in the domains "rhinologic symptoms" (p=0.05), "function" (p=0.02) and "emotion" (p=0.01). (*Figure 2*; *Table 2*)

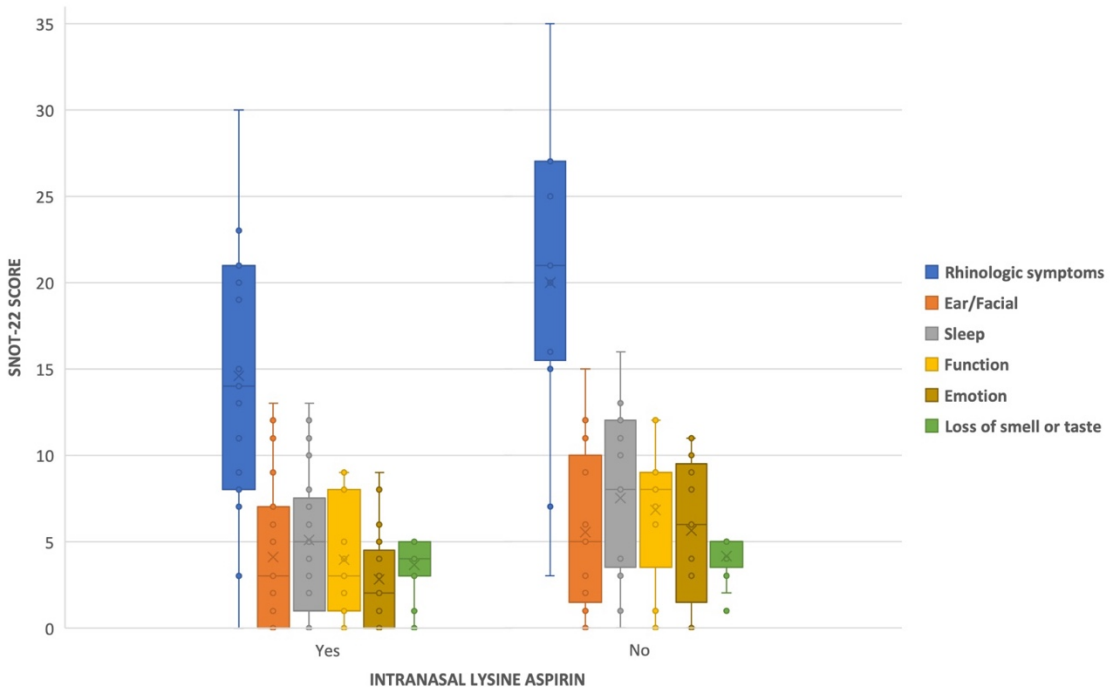

Figure 2. Box plots showing SNOT-22 domains scores in patients on or off intranasal lysine aspirin.

SNOT-22: 22-item Sino-Nasal Outcome Test.

No significant differences were observed when looking at the sVAS or at the SNOT-22 item "decreased sense of smell/taste". (*Table 2*)

	Whole n = 34	On LAS n = 21	Not on LAS n = 13	*p*-value
sVAS, median [P25-P75]	0.0 [0.0-3.0]	0.5 [0.0-3.0]	0.0 [0.0-2.5]	0.67
Missing	3	1	2	
SNOT-22 score, median [P25-P75]				
Rhinologic symptoms	19.0 [11.0-21.0]	14.5 [8.5-21.0]	21.0 [16.0-27.0]	**0.05**
Ear/Facial symptoms	3.0 [1.0-7.0]	3.0 [0.5-7.0]	5.0 [2.0-9.0]	0.22
Sleep dysfunction	5.5 [2.3-10.0]	5.0 [2.0-7.0]	8.0 [4.0-12.0]	0.07
Function status	4.5 [1.0-8.8]	3.0 [1.0-8.0]	8.0 [6.0-9.0]	**0.02**
Emotion status	3.0 [0.3-6.0]	2.0 [0.0-4.0]	6.0 [3.0-9.0]	**0.01**
Decreased sense of smell/taste[+]	5.0 [3.0-5.0]	4.0 [3.0-5.0]	5.0 [4.0-5.0]	0.41
Total SNOT-22 score	36.0 [24.0-51.0]	29.0 [19.5-43.5]	49.0 [29.0-62.0]	**0.02**
Missing	1	1	0	

Table 2. Patient-reported outcome measures (PROMs) in the whole population and according to intranasal Lysine Aspirin (LAS) use. Level of significance p≤0.05. Significant p values in bold. [+]This item is already included in the "rhinologic symptoms" and, thus, has not been considered when calculating the total SNOT-22 score.

sVAS: Visual Analogue Scale for sense of smell; SNOT-22: 22-item Sino-Nasal Outcome Test.

When looking at the prices of intranasal ATAD, the price of a box containing 20 sachets of lysine acetylsalicylate (=20 days treatment) is £8.30 while the price of one box of sodium chloride 0.9% containing 20 ampules (each of 10 mL), used to mix with the LAS sachet to prepare the solution, is £1.60. Other expenses include the use of a reusable glass bottle and a dropper pipette to instil the solution in the nose (one-time expense of ≈ 1£). This brings the cost of 1-year treatment of LAS per person to ≈ £180.7 and a daily cost of ≈ £0.50.

4.6.4. Discussion

The SNOT-22 is a patient-reported outcome measure (PROM) commonly used to assess the impact of CRS on HRQoL and can be a useful tool to evaluate the benefits of a treatment on patients' health.[105,302] In our study, the median SNOT-22 score in N-ERD patients on nasal LAS was 20 points lower than in those off LAS and this was statistically significant (p=0.02). So far, several studies have confirmed an improvement in the reported sinonasal symptoms in patients undergoing oral ATAD, also in the long-term. Swierczynska-Krepa et al.[303] found a statistically significant improvements in the SNOT-

20 score in a placebo-controlled randomized trial of ASA desensitization in ASA tolerant and ASA intolerant asthmatics. Esmaeilzadeh et al.[292] found a statistically significant improvement in SNOT-22 in the desensitization arm at 6 months when comparing 16 ASA desensitization patients to 16 controls. Mortazavi et al.[293] observed a significant improvement in the SNOT-22 score in 19 patients randomized to ASA when compared to 19 receiving placebo. Fruth et al.[289] reported improved QoL scores on the Rhinosinusitis Disability Index in 18 ASA desensitized patients compared to 13 controls at 36 months after sinus surgery. Similar results were found by Rozsasi et al.[226] using modified validated QoL questionnaires. In a previous study, Cooper et al.[286] observed a significant decrease in the SNOT-22 median score of averagely 10 points after 6 months of maintenance therapy. However, to the best of our knowledge, this is the first study evaluating the HRQoL in patients on intranasal ATAD using LAS. Interestingly, the 20 units difference found in the total score of the SNOT-22 in our N-ERD patients on and off nasal LAS was higher to that observed in patients on oral ATAD in a recent metanalysis (difference 10.27 units).[214] The lower SNOT-22 scores found in our patients on intranasal LAS could also be related to a better tolerability of nasal ATAD compared to the oral one. In fact, it is well-known that people on oral ATAD can develop symptoms affecting the skin, gut or lungs and in previous studies conducted by our team, we confirmed a lower rate of side effects in patients using intranasal LAS when compared to those on oral aspirin, including lower risk of gastrointestinal bleeding or urticarial rash.[221,224] Nevertheless, up to 30% of patients may not respond to ATAD.[215] In a previous audit on intranasal LAS,[221] our team found that 18.7% of patients reported no efficacy following intranasal ATAD at their 3-month follow-up. With this in mind, a common issue is to determine how long a patient should be trialled before considering him to be a non-responder to ATAD. In this regard, A total score of 20 at the SNOT-22, has been defined to be the threshold to distinguish responders (SNOT-22 < 20) from non-responders (SNOT-22 $\geq$ 20).[304] Moreover, a recent study from Tripathi et al.[305] found that the SNOT-22 score obtained at 6-month post-desensitization had the greatest predictive value for

long-term outcomes at 24-month post-desensitization, with an OR of 16.5, proposing a 6-month time point of ATAD as a predictor for long-term success. In our practice, we tend to consider a patient a good-responder to the treatment when their SNOT-22 score significantly improves from baseline (SNOT-22 before treatment). In this regard, the minimal clinically important difference (MCID) for the SNOT-22 total score has been reported to be 8.9 points[105] and this is the minimal improvement in the SNOT-22 total score we usually seek for in order to consider a patient a responder to the treatment. In our population, 11.8% (4/34) were deemed to be non-responders to intranasal ATAD (based on our medical records) although this percentage could have been higher considering that the remaining 9 patients never started intranasal LAS.

Assessing domains and item scores of the SNOT-22 separately can provide clinicians with a better understanding of which individual aspect of CRSwNP has the greatest impact on patients HRQoL and, thus, offer valuable information in view of a personalised treatment decision-making. In our study, the domain “rhinologic symptoms” remained the most affected domain across both groups of patients (on or off LAS) with the items “nasal obstruction”, “thick nasal discharge” and “post-nasal discharge” reported to be the most important items from our N-ERD respondents. This corroborates previous results of a recent randomized double-blind placebo-controlled study which included patients with CRSwNP considered hard to treat, including patients with N-ERD.[306] Moreover, in our study patients on LAS had significantly lower scores in the rhinologic domain (p=0.05) when compared to their counterparts not on nasal LAS, suggesting that LAS is effective in controlling nasal polyps and the local inflammatory burden, confirming results from our previous retrospective study[224]. We also observed significant improvements in the domains function (p=0.02) and emotion (p=0.01), which could simply reflect the indirect effect of improved sinonasal symptoms on other aspects of health.

Loss of smell in N-ERD negatively impacts on QoL and has been reported to be more severe as compared to patients with ASA-tolerant CRSwNP.[307] In our population, more than 80% of the patients reported to have at least a moderate problem with their sense of smell at the SNOT-22 and almost 60% of the respondents confirmed this was one of the five most important items affecting their health. This suggests that, from a patient's perspective, OD remains an important marker of disease severity and, thus, a critical outcome measure of treatment efficacy. The cause of OD in N-ERD seems to be multifactorial. Contributing factors include the high nasal polyp burden and swelling of the sinonasal mucosa in the olfactory area which could cause a physical obstruction preventing odorants from reaching the olfactory epithelium. In addition, the long-standing chronic inflammation within the olfactory epithelium may also be a causative mechanism for OD in these patients.[247] In fact, elevated nasal mucous levels of IL-2, IL-5 and IL-13 have been associated with altered olfaction suggesting a potential immunological cause for OD in these patients.[248,249] A previous review looking at studies evaluating olfactory outcomes following oral ASA desensitization demonstrated improvements in patient reported and objective assessments of olfactory function.[226,286,308] Interestingly, in one of these, Sweet et al.[309] compared individuals who were on long-term oral ASA therapy and those who discontinued therapy for a variety of reasons and observed statistically significant improvement in the PROMs while on ASA with a subsequent worsening of symptoms after discontinuation. Although we previously demonstrated improved olfaction in patients on long-term nasal ATAD, as measured by a 6-item identification test (Nez du Vin),[224] in this study there was no statistically significant difference in the patients' reported olfaction (both at the sVAS and at the SNOT-22 item "decreased sense of smell/taste") between those on intranasal LAS or not. This could be because subjective olfaction measures are less sensitive than the objective ones.[310] In this regard, it is interesting to mention that Landis et al.[311] observed that healthy subjects are usually unable to accurately self-report their sense of smell but the accuracy of this self-

assessment improves after undergoing olfactory testing, forcing them to pay conscious attention to their sense of smell.

Despite several studies showing an improvement of HRQoL in N-ERD patients whilst on ATAD, aspirin desensitisation remains an underutilized treatment modality as confirmed by a survey of allergists and fellows conducted in the United States in 2016.[312] More recently, biologics have set their scene on the treatment of severe CRSwNP and, although not specific for N-ERD, they have been shown to be very effective in CRSwNP in N-ERD patients.[313,314] In this regard, dupilumab, an anti-interleukin-4 and -13, has gained increased popularity since its approval as a treatment for severe or refractory CRSwNP in 2019 and several studies have demonstrated effective reduction in both objective and subjective measurements.[278,315,316] So far, dupilumab is the only biologic showing a difference between aspirin-tolerant and aspirin-intolerant CRSwNP patients with N-ERD patients reporting significantly greater improvement in nasal congestion and SNOT-22 scores after treatment.[317] In a previous study Buchheit and colleagues[318] reported a higher improvement in the total SNOT-22 score when using dupilumab if compared to our study (mean change of –34.4 and –34.5 at month 1 and 3, respectively; all $p<0.0001$). Additionally, differently from our results, an improvement in all five SNOT-22 domains at 6 months has also been demonstrated in patients on dupilumab, with the most marked improvements observed for nasal, sleep, and function domains.[306] However, no direct trials with ATAD and biologic therapy in N-ERD patients exist which makes it difficult to choose the best alternative to use when maximal medical and surgical treatments have failed. Only recently, Tuncay and colleagues[319] conducted an observational real-life study including 59 N-ERD patients receiving ATAD or biologics (either omalizumab or mepolizumab) and found no significant difference in the SNOT-22 scores between patients who received ATAD only and/or biologics although SNOT-22 scores were lower in those who received mepolizumab. Biologics have also been demonstrated to significantly improve olfactory function in several studies.[278,320,321]

Moreover, Barroso and colleagues[322] did not show any differences for partial or total improvement in sense of smell when comparing N-ERD (35.7%) and non–N-ERD patients (37%) in patients undergoing long-term treatment with omalizumab, mepolizumab, reslizumab, or benralizumab. However, there remains a need for further studies to demonstrate the effectiveness of biologics more clearly against ATAD for the decision of which biologics are beneficial in patients with both eosinophilia and atopy.

In spite of its superb effects in controlling CRSwNP and improving HRQoL, also in N-ERD patients, dupilumab is over a hundred times more expensive than ATAD which poses questions over appropriate use of healthcare resources. In fact, cost of ATAD is less than $100 per year compared to Th2 biologic therapy which is estimated to be $30.000 to $40.000 per patient per year that corresponds to a multimillion dollars per patient per year for biologic treatment.[317,323] Moreover, a study from Shaker et al.[324] found that ambulatory desensitization for N-ERD could save $6.768 per “quality-adjusted life year” (QALY), and ATAD remained cost-effective with less than $50,000 per QALY saved. Cost of intranasal LAS is slightly higher than oral aspirin being of roughly 180£/year which is mainly related to the fact that LAS has to be imported from France (LAS is currently not sold in the United Kingdom). However, this cost is again derisory if compared to the yearly cost of biologics. Considering its safety profile, its effectiveness and its relatively low costs, ATAD should be the considered as one of the first-line therapies, if no contraindication, in N-ERD patients with uncontrolled CRSwNP. Nonetheless, the role of endoscopic sinus surgery, in particular of large cavity sinus surgery, with post-operative ATAD should be considered when treating CRSwNP in patients with N-ERD.[245,325]

In this regard, a recent cost-effectiveness analysis comparing dupilumab and ATAD for CRSwNP in N-ERD showed that dupilumab treatment can be cost-effective when offered as salvage therapy after failing ATAD after ESS.[236] This offers new insights into when to

recommend biologic therapy in a cost-effectively manner within the available treatment options.

Limitations of the study

Our study is slightly unpowered (post-hoc power of 50.4%) and, therefore, results should be interpreted in view of this limitation. The main reason for this relies on the large data dispersion (i.e. interquartile range) observed in the SNOT-22 total scores for both groups which reflects the high variability in the severity of symptoms reported by our N-ERD patients. Other limitations of the study are those that are intrinsically inherent to the use of self-reporting outcomes (i.e. PROMs) including changing internal standards (recalibration), changing priorities (reprioritization), and changing interpretations (reconceptualization),[326] which are particularly present when assessing efficacy of a treatment and especially in chronic conditions like CRS.[327,328] Moreover, for both the SNOT-22 and sVAS patients were asked to rate their symptoms as these had been over the 2 weeks before questionnaires administration, which inevitably introduced a recall bias. However, it must be considered that all these biases are present when evaluating quality of life using SNOT-22 and/or other PROMs.

4.6.5. Conclusions

N-ERD has significant financial and HRQoL detriment to sufferers. This first study, in which HRQoL was evaluated in patients on long-term intranasal LAS, supports the efficacy of nasal ATAD in the management of N-ERD and suggests that long-term use can lead to QoL improvement. Since nasal LAS has less comorbidities than oral ATAD and is cheaper than monoclonal antibodies we suggest that these results should be confirmed in larger populations. In addition, these results can provide evidence to policymakers looking to support cost-effective treatment options for CRSwNP in N-ERD.

Nevertheless, when choosing the best alternative for uncontrolled CRSwNP amongst the available options, pros and cons of each treatment should be tailored taking into account patient's comorbidities and disease's profile in an attempt to offer a more personalised therapy.

4.7 Published studies on N-ERD – summary of findings and their relevance in the PhD project

In the first study[224] I confirmed a high prevalence of severe OD amongst patients with N-ERD (prevalence 84.6%; median Nez du Vin score at baseline 0/6). I have demonstrated how long-term administration of intranasal LAS can lead to a statistically significant improvement of sense of smell. In my opinion, olfactory improvement in these patients was achieved through a combination of reduced sinonasal inflammation in the OE, reduction in polyps' size and increased airflow through the olfactory cleft. This was corroborated by the evidence of a statistically significant increase of nasal airflow and long-standing nasal airflow improvement during the whole study period in patients on LAS.

The second study, instead, focused more on the health-related quality of life (HRQoL) changes and olfactory impairment in N-ERD patients. In this survey, N-ERD patients on intranasal LAS were compared with patients who stopped LAS. Firstly, I confirmed that reduction of sense of smell was one of the most prevalent and highly-impacting reported symptoms by N-ERD patients. My data revealed that a substantial proportion (80%) of the study participants reported a notable impairment of their olfactory function. Furthermore, approximately 60% of respondents ranked this issue among their top five health priorities. Secondly, I showed how reported OD was less severe, although not statistically significant, in patients on long-term intranasal LAS. Again, this study, whilst demonstrating a high prevalence of OD amongst N-ERD, suggested that intranasal LAS could be beneficial in improving sense of smell.

All the above findings substantiate my initial hypothesis that control of local olfactory mucosa inflammation and, more importantly, airways optimisation achieved using intranasal LAS can lead to improved olfaction in N-ERD patients.

CHAPTER 5: OLFACTORY DYSFUNCTION IN SLEEP-DISORDERED BREATHING

5.1. My research questions and hypotheses on OD in SDB

Olfactory function is not frequently assessed when evaluating treatments' outcomes in SDB patients and, therefore, effects of nasal surgery on olfaction in these patients are not completely known. As further explained in *Section 5.2*., chronic nasal obstruction is common in SDB patients and can consequently lead to a reduction of nasal airflow and odorants delivery to the olfactory cleft. My aims and hypotheses regarding OD in SDB matured during these years are summarised in *Table 5.1*. An introduction to the topic has been included to give a background to the study conducted.

Research questions
1. Is OD present in SDB patients? If so, what is its prevalence?
2. Is OD in SDB patients caused by nasal congestion (i.e. conductive)? If so, can RFITs restore olfaction by increasing nasal airflow?
Hypotheses
1. OD is highly prevalent in SDB patients and mainly caused by nasal congestion.
2. Inferior turbinates decongestion, achieved by means of RFITs, will lead to an improvement in the nasal airflow and nasal airways. The increased nasal airflow will then improve odorants delivery to the olfactory cleft and, consequently, olfaction.

Table 5.1. Research questions and hypotheses leading to my published study on sleep-disordered breathing.

OD: olfactory dysfunction; RFITs: radiofrequency of inferior turbinates; SDB: sleep-disordered breathing.

5.2. Introduction – an overview on SDB

Sleep-disordered breathing (SDB) describes a range of disorders including primary snoring and obstructive sleep apnoea (OSA).

Primary snoring, also known as simple snoring, is characterized by audible vibrations of the UA during sleep. It is generally considered the initial stage of SDB and does not typically have severe medical repercussions for the snorer.[329] By definition, primary snoring involves asymptomatic snoring without apnoeic or hypopnoeic events. The apnoea/hypopnea index (AHI), which measures the number of apnoeic/hypopnoeic events per hour during a polysomnography (PSG), is less than 5 in primary snoring. Daytime sleepiness is not a characteristic feature. Primary snoring is usually caused by a narrowing of the UA, although vibrations of soft tissues can occur even without narrowing.[329]

Obstructive sleep apnoea (OSA), instead, involves cessation of airflow of at least 10 seconds, or a significant decrease in it, occurring in the presence of inspiratory efforts during sleep.[330] OSA is diagnosed when an "AHI or Respiratory Disturbance Index (RDI) of 5 or higher is observed in conjunction with excessive daytime sleepiness, repeated episodes of UA obstruction during sleep, and nocturnal hypoxemia".[330] Prevalence studies estimate that OSA affects between 1% and 4% of the general population.[331] Risk factors associated with OSA include "obesity, craniofacial abnormalities, adenotonsillar hypertrophy (particularly in children and young adults), increased neck circumference, male sex, older age, postmenopausal state, alcohol or sedative use, smoking, hypothyroidism, acromegaly, and stroke".[332] OSA is a potentially disabling condition and associated with other health issues such as cardiovascular and cerebrovascular events.[332] Other consequences of OSA extend beyond excessive sleepiness to include impaired cognitive function and mood disturbances, ultimately impacting overall QoL.[333] Daytime sleepiness poses a significant safety risk, increasing the likelihood of road traffic accidents, workplace injuries, and decreased work performance.

Diagnostic workup in SDB patients include use of full-night PSG, pulse oximetry and Epworth sleepiness scale (a commonly used and validated questionnaire for daytime

sleepiness).[334] PSG, considered the gold standard for OSA diagnosis, involves the simultaneous recording of "electroencephalogram, electrooculogram, chin electromyogram, electrocardiogram, respiratory effort, airflow, oxygenation, ventilation, snoring". However, home sleep studies have been developed during the last decades with the aim to reduce the inconvenience and expense associated with laboratory PSG. According to the guidelines established by the American Academy of Sleep Medicine, a portable monitor must record at least airflow, respiratory effort, and blood oxygenation.[335] This means that home sleep studies should have at least 4–7 channels (type III device), rather than using a type IV device, exemplified by oximeters, which records only pulse rate and oxygen saturation.[335] In fact, type III monitors have the ability to obtain the AHI scores that can help in the diagnosis of OSA.[336]

The severity of OSA is categorized based on the AHI score as follows:[337]

- Mild: AHI ranging from 5 to 15 events per hour.
- Moderate: AHI ranging from 15 to 30 events per hour.
- Severe: AHI exceeding 30 events per hour.

An AHI below 5 events per hour is typically indicative of normal sleep or the presence of primary snoring in individuals exhibiting snoring.

Management of SDB consists of both pharmacological and non-pharmacological treatments. Non-pharmacological measures include diet changes, use of devices (mandibular advancement devices/tongue retaining devices and continuous positive airway pressure [CPAP]) and surgery (such as UA surgery and bariatric surgery for weight loss).[332] CPAP is a non-invasive ventilation device that uses mild positive air pressure to keep UA open and prevent collapse during sleep. It is considered the gold standard for moderate and severe OSA.[338-340] Patients who cannot tolerate CPAP should be offered surgical options. Surgery aims to achieve a permanent increase in UA patency while simultaneously reducing pharyngeal resistance. In selected patients with "mild

OSA who exhibit surgically correctable anatomical abnormalities contributing to UA collapse during sleep", surgical intervention can be considered a first-line therapeutic approach. Several type of surgical procedures can be considered for OSA patients like nasal and tongue surgery, tonsil reduction, soft palate surgery or advancement procedures.[341] Hypoglossal nerve stimulation represents a potential safe and efficacious alternative therapeutic modality for "individuals with moderate-to-severe OSA who experience difficulties adhering to CPAP therapy".[342] However, surgical management of OSA typically requires a multi-stage approach. A comprehensive evaluation of the potential advantages of surgical treatment is imperative, with careful consideration given to the potential for long-term adverse sequelae.

5.3. Pathophysiology of OD in SDB

OD is frequently observed in subjects with SDB.[343,344] Moreover, older adults with SDB have been reported to have a significantly increased risk of impaired odour identification, as evidenced by an odds ratio of 2.13.[345] Previous studies confirm that up to 73% of patients with OSA can show a mild-to-severe OD[344,346-348] and this is more frequent in patients with more severe OSA.[349,350] Conversely, OD seems to be less prevalent amongst simple snorers and, when present, the degree of OD is usually mild,[348] suggesting that long-standing vibration itself is not directly correlated with olfactory function.[349] Pathogenesis is not fully understood and several mechanisms could contribute to OD in these patients. *(Table 5.2.)*

The first mechanism may be attributed to the neurocognitive sequelae of OSA. Recurrent sleep fragmentation, sleep deprivation, and chronic intermittent hypoxemia induce alterations within the primary neural network of the OB and exert an influence on central nervous system pathways involved in chemosensory processing.[345,346,351,352]

	Mechanism	Rationale
Neurocognitive	Central	Sleep fragmentation, sleep deprivation and chronic intermittent hypoxia cause alterations in the main olfactory bulb neural network and affect pathways
Damage of olfactory epithelium	Sensorineural	• Hypoxia of olfactory neurons; • Increase of proinflammatory markers due to hypoxia/reoxygenation episodes; • Poor mucociliary clearance.
Nasal obstruction	Conductive	Physical obstruction for odorants delivery to reach olfactory epithelium

Table 5.2. Relevant mechanisms leading to olfactory dysfunction in SDB.

These regions include the hippocampus and prefrontal cortex, brain structures intimately associated with memory and executive function.[350,353] Previous neuroimaging investigations have confirmed a reduction in cell neurogenesis and density within the hippocampus, frontal cortex, and generalized grey matter in OSA subjects.[354,355] In this context, the observed volumetric reduction within the OBs of OSA patients may be attributed to the same underlying mechanisms.[350,356] The resulting cognitive impairment present in patients with SDB and involving memory, new learning, attention, executive and cognitive functions,[352,357] can then secondarily impact on the olfactory abilities itself. In this regard, OSA patients with OD have been found to have lower scores at global cognition, memory, and executive function.[346,358,359] The interrelationship between olfaction and cognitive impairment is not new and olfactory tests are now used to identify subjects with an elevated risk of cognitive decline and dementia.[360]

A second pathophysiological mechanism could be related to the local effect of OSA on the OE. Nasal obstruction is very common in SDB patients and the prolonged exposure to vibrations and hypoxic conditions, resulting from chronic nasal obstruction, may induce local neuropathy within the OE.[361] Moreover, this resistance in the nasal airflow can impede odorants to reach the olfactory region. As a confirmation of that, acoustic rhinometry studies have demonstrated a significant reduction in the cross-sectional area of the nasal airway in patients with OSA compared to healthy controls.[362] This anatomical

narrowing may impede the efficient transport of odorant molecules to the olfactory region. The intermittent nocturnal hypoxia/reoxygenation episodes, present in OSA patients, can also cause an increase in proinflammatory markers which could potentially damage the OE and/or alter its function.[343] Additionally, patients with OSA have been found to have a poor mucociliary clearance which can interfere in the interaction between odorants and the olfactory receptors at the level of the OE. [347,363]

Another possible pathophysiological mechanism may be attributed to the alterations in cholinergic neurotransmission. Studies have demonstrated a significant reduction in short-latency afferent inhibition in patients with OSA, supporting the potential role for cholinergic dysfunction.[364] Finally, a higher BMI, frequent in SDB patients, could contribute to OD, and previous reports confirmed a decline of TDI with increased BMI.[365]

The link between SDB and OD is also supported by several studies demonstrating a correlation between olfactory and sleep parameters, although results are not always unequivocal. The AHI was shown to have a significant negative correlation with odour threshold and TDI scores,[344,349] but also to discrimination and identification scores according to others.[346,348,350] Such correlations were not found by other authors.[366,367] The AHI had also a significant negative correlation with both right and left OB volumes.[350] Siegel et al.[345] observed that SDB (based on self-reported history and not confirmed by a sleep study) is associated with impaired odour identification but not odour threshold. The average nocturnal SaO_2, another parameter obtained with a sleep study, was shown to significantly and positively correlate with odour threshold,[350] discrimination,[348-350] identification[348] and TDI scores[349] according to different authors. The relationship between olfactory components affected and underlying pathophysiologic mechanisms could be explained as follow. The impairment of cognitive functions may create a deleterious effect on olfactory function, resulting in a decline in odour discrimination and identification abilities. These olfactory functions necessitate the recognition and naming

of common odours and are indicative of more central olfactory processing and cognitive involvement.[368] Conversely, any impairment at the level of the OE, including a reduced odorants stimulation by an alteration of nasal airflow, which is not uncommon in patients with SDB and a contributing factor to OSA,[369] will affect odour threshold.[370,371]

Treatments of OD in SDB patients have not been investigated and research on that is limited. Incidentally, CPAP therapy has been found to improve olfactory function by recent studies, including a systematic review.[340,344,366,367,372,373] The mechanisms through which positive airway pressure may improve olfactory function in OSA patients could be multiple. The increased oxygen saturation achieved with CPAP carries out positive effects on neurocognitive function, including sense of smell,[349,350] helps in normalizing the synthesis of neurotransmitters,[373] and in reducing mucosal inflammation.[374,375] On the other side, CPAP itself can cause an early nasal inflammation due to its "mechanical stimulus" effect on the nasal mucosa,[376] and lead to rhinitis, which could potentially affect the olfactory function.

5.4. Published study on SDB – hypothesis and aim

Section 5.5. includes my own published paper. In this prospective study, I evaluated the efficacy of RFITs in improving nasal airways and sense of smell in SDB patients. In this study, I have also assessed olfactory function (specifically odour identification) at baseline and over a period of 12 months to demonstrate a potential role of RFITs in improving OD in this group of patients. The main hypothesis is that inferior turbinates decongestion, achieved by means of RFITs, will lead to an improvement in the nasal airflow and nasal airways. The increased nasal airflow will then improve odorants delivery to the olfactory cleft and, thus, olfactory function. Minor edits to the manuscript have been made following departmental guidelines to ensure it fits the overall style of the thesis.

5.5. Objective and subjective outcomes following radiofrequency of inferior turbinates in patients with sleep-disordered breathing[377]

5.5.1. Introduction

Sleep-disordered breathing (SDB) describes a spectrum of various clinical entities ranging from primary snoring to severe obstructive sleep apnoea (OSA).[378] Both snoring and OSA exhibit a multilevel phenomenon in which the obstruction can occur at each level of the naso-, oro- and hypopharynx and in different proportions.[379,380] The nose represents the first entry point of the air with nasal obstruction significantly impacting the collapsibility of different segments of the pharyngeal lumen.[378,381] Several large-scale population studies have confirmed that nasal blockage contributes to exacerbate OSA and represents an independent risk factor for OSA.[369,382,383] Moreover, OSA patients with nasal obstruction are at higher risk of continuous positive airway pressure (CPAP) intolerance, which constitutes a significant problem as CPAP treatment is the first-line measure for moderate-to-severe OSA. In addition to that, nasal CPAP itself can lead to alterations in the nasal mucosa, like chronic inflammation and fibrosis,[384] which can exacerbate CPAP intolerance in patients with an already existing congested nose.

For all these reasons, treatment of nasal obstruction in SDB patients becomes crucial for symptom relief and/or to improve CPAP tolerance, especially in cases in which nasal obstruction is the main subjective barrier to its use. From an anatomical point of view, septal deviation, nasal valve dysfunction and/or inferior turbinate (IT) hypertrophy are the most common findings in SDB patients with reported nasal blockage.[385-387] Rhinitis is the main cause of IT hypertrophy, and in this regard, the link between allergic rhinitis (AR), in particular, and sleep impairment is so close that the ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines have categorized the influence of AR on sleep impairment as moderate to severe.[388] Intranasal corticosteroids represent the main treatment of rhinitis, and several studies have confirmed an improvement of sleep study parameters

following the use of nasal cortico-steroids.[389-391] For refractory cases in which patients are not improving with medical treatment, nasal airway surgery can be offered with the aim to improve nasal breathing and, as a result, sleep quality, snoring and daytime fatigue.[392]

The reduction in ITs represents an effective surgical option in cases in which IT hypertrophy is the main driver of nasal obstruction,[393,394] and can improve sleep quality in cases of concomitant rhinitis and nasal obstruction.[392] So far, several techniques have been described, and available options include turbinoplasty, turbinate out-fracturing, microdebrider-assisted inferior turbinoplasty, electrocautery with monopolar or bipolar instruments, coblation and radiofrequency.[395-397] However, no consensus today exists on which surgical technique is most effective in the long term.

Radiofrequency of the IT (RFIT) is a commonly utilized technique for IT reduction and is able to generate a relatively low level of heat in the sub-mucosal layer of the turbinates, thus preserving overlying mucosal integrity and the mucociliary function of the turbinates.[398] Moreover, it has rare complications and can be performed in clinic under local anaesthesia (LA), making it a quick and very attractive option for the surgical management of IT hypertrophy. Although several studies support RFIT effectiveness in managing nasal obstruction secondary to IT hypertrophy,[399-402] few studies have assessed long-term outcomes using disease-specific validated instruments, especially in patients with SDB. Moreover, most studies have focused on subjective outcomes (patient-reported symptoms) of improved breathing and nasal airflow, whereas studies looking at objective measures remain sparce.

In this prospective study, we aimed to evaluate long-term objective and subjective nasal, olfactory and sleep outcomes following RFIT in patients with SDB and IT hypertrophy refractory to medical treatment.

5.5.2. Materials and methods

Study design

A real-life prospective cohort study was conducted to evaluate the efficacy of RFIT in the treatment of IT hypertrophy in patients with SDB. Patients were assessed at baseline (T0), 3 months (T1), 6 months (T2) and 12 months (T3) following RFIT. Patients were asked not to start any nasal steroids during the follow-up period. At the end of T3, patients were discharged to their general practitioners or reassessed in cases of persisting symptoms. Our primary outcome was the improvement of nasal airways following RFIT as measured by peak nasal inspiratory flow (PNIF) and acoustic rhinometry (AR). Secondary outcomes instead were the improvement of sense of smell, sleep symptoms/scores and health-related quality of life (HRQoL) following the procedure.

The study was conducted in accordance with the 1996 Helsinki Declaration. This present study is a retrospective evaluation of service for our department, utilizing anonymized data reviewed in full accordance with national information governance protocols and, thus, did not require separate research ethics committee approval.

Participants' characteristics

We included patients with SDB who underwent RFIT under LA for IT hypertrophy between June 2021 and January 2022 at the Royal National Ear, Nose and Throat Hospital (University College London Hospitals, London, UK). Data were collected on demographics, type of sleep disorder (snoring or OSA only, or both), type of rhinitis (allergic vs. non allergic), smoking status, comorbidities, routine medications taken and history of upper airway surgery. Findings at nasal endoscopy and results of skin prick test for common aeroallergens (grass pollen, birch pollen, mixed tree pollens, house dust mite, cat and dog hair, Alternaria and Aspergillus) were also recorded.

Details of the surgery

All the procedures were performed by the same surgeon (SU). Before treatment, two puffs of co-phenylcaine nasal spray (lidocaine hydrochloride 5% w/v, phenylephrine 0.5% w/v and benzalkonium chloride 0.01%) are sprayed into each nostril. Ten minutes later, under endoscopic vision, a rigid nasal endoscopy is performed, and a cotton pledget soaked in adrenaline 1:10,000 is introduced into each nostril. The head of the IT is later injected with Lignospan Special (lidocaine hydrochloride 2% and adrenaline 1:80,000). After 5 min, under endoscopic vision, the radiofrequency wand at a setting of 15 W is introduced into the submucosal IT tissue for approximately 15 s (the exact duration is based on the auto-stop function, which depends on 3D impedance feedback detected by the machine algorithm). This process is repeated in 3 different sites of each IT (anterior, middle and posterior portion). After treatment, a cotton pledget soaked in adrenaline 1:10,000 is left into each nostril, and the patient is asked to wait in the recovery area for post-operative monitoring of vital parameters. After 15 min, the pledgets are removed and the Naseptin cream (chlorhexidine dihydrochloride 0.1% and neomycin sulfate 0.5%) is applied into each nostril. No nasal pack is inserted unless there is an active nosebleed. Patients are discharged without any limitations in their normal daily activities.

Objective and subjective measurements at baseline and follow-ups

At T0, T1, T2 and T3, patients underwent objective assessment of nasal airways, smell function and HRQoL, and their subjective sinonasal, olfactory and sleep symptoms were evaluated. All patients also received nasal endoscopy, at both baseline and follow-ups, to evaluate signs of chronic rhinosinusitis (CRS)/rhinitis and post-operative outcomes.

All patients received a home-based sleep test (type III – Nox-T3 System, Nox Medical, Reykjavik, Iceland) before being included in the study (same type of device used for all patients), and the diagnosis of simple snoring or OSA was established according to the

apnoea-hypopnoea index (AHI) calculated from the above-mentioned studies as follows: simple snoring, AHI < 5; mild OSA, 5 ≤ AHI < 15; moderate OSA, 15 ≤ AHI < 30; and severe OSA, AHI ≥ 30. The study was also repeated at 6 months following RFIT.

PNIF and AR were tested on the same occasion to objectively assess patients' nasal airways. After baseline measurements, a decongestant test was performed using co-phenylcaine (5% lidocaine and 0.5% phenylephrine) topical nasal spray, and measurements were repeated 15 min after its application to reduce any possible influence of the nasal cycle on nasal airflow measurements.[136,137,403] PNIF was measured using a portable Youlten peak flow meter (Clement Clarke Inter-national, Mountain Ash, UK). Three maximal inspirations were obtained, and the highest of the three measurements was considered.[282] Unilateral PNIF values were also studied by sealing off one nostril at a time with adhesive tape (Micropore™, 3M™, St Paul, US), and the highest values were taken as left PNIF (lPNIF) and right PNIF (rPNIF).[404] AR was tested using an A1 acoustic rhinometer (GM Instruments Ltd., Kilwinning, UK) and conducted while patients held their breath. The minimal cross-sectional area (MCA) and nasal volume (NV) were obtained.[405]

The ability to smell was scored using the Sniffin' Sticks (S'S) 16-item identification test (Burghart, Medisense, Groningen, The Netherlands).[112] Level of hyposmia was defined as a score below 11 as per normative values reported by Oleszkiewicz and colleagues.[112] Subjective olfactory function was recorded using a visual analogue scale for sense of smell (sVAS—0 indicates "sense of smell absent" and 10 indicates "sense of smell not affected")[310] and the short version of the Questionnaire of Olfactory Disorders-Negative Statements (short-QODNS)[107].

Other patient-reported outcome measures (PROMs) included the 36-item Short Form Survey (SF-36) used to assess HRQoL, the Sino-Nasal Outcomes Test-22 (SNOT-22)[406] and the Nasal Obstruction Symptom Evaluation (NOSE) to evaluate sinonasal

symptoms, as well as the Epworth Sleepiness Scale (ESS) as a subjective measure of patients' sleepiness.

Statistical analysis

Quantitative variables were summarized using median and interquartile range (P25–P75), whereas qualitative variables were described with frequency and percentage. Comparisons of measurements between baseline and follow-ups were performed using the paired Wilcoxon test for quantitative variables and the proportion test for dichotomic variables. Ottaviano et al.[285] showed that the relationship between PNIF and covariates is typically not linear and they proposed a square root transform of PNIF, which has been evaluated appropriate also for our data. Mixed effect models have been fitted to the data to evaluate the longitudinal effects of the covariates on the studied variables. A goodness-of-fit analysis for each model has been performed using qqplots to validate their use in our study. p-values were calculated for all tests, and 5% was considered to be the critical level of significance. All the analyses were performed in R (version 4.4.0, R Core Team, Vienna, Austria, 2021).

5.5.3. Results

Breakdown of the population

Seventeen patients were initially included in the study (T0) and underwent RFIT under LA. Thirteen patients attended the 3-month follow-up (T1), fourteen attended the 6-month follow-up (T2) and ten attended the 12-month follow-up (T3).

Demographic data

The median age of the population was 42.0 years, and there was a higher prevalence of male patients (10; 58.8%). The majority of them were non-smokers (15; 88.2%) and had a history of both snoring and OSA (12; 70.6%). All of the patients complained of bilateral nasal blockages and were unsuccessfully treated medically with nasal douches and

steroid sprays (+/− azelastine spray, in cases of allergic rhinitis). Other details of the population, including the patients' history of previous relevant surgeries of the upper airways as well as comorbidities and routinely taken medications, are reported in Table 1.

	n = 17
Demographics	
Age, median [P25-P75], yr	42.0 [35.0-52.0]
Sex, No (%)	
Female	7 (41.2%)
Male	10 (58.8%)
Smoking status, No (%)	
Ex-smoker	1 (5.9%)
Active	1 (5.9%)
No	15 (88.2%)
History of rhinitis, No (%)	
Allergic type	9 (52.9%)
Non-allergic type	8 (47.1%)
Sleep symptoms, No (%)	
Snoring only	5 (29.4%)
OSA only	0 (0.0%)
Both	12 (70.6%)
Comorbidities, No (%)	
None	7 (41.2%)
Asthma	4 (23.5%)
Hypertension	3 (17.6%)
Mental health issues	3 (17.6%)
Other	5 (29.4%)
Medications, No (%)	
Nasal douche	17 (100%)
Steroid spray	8 (47.1%)
Steroid + antihistamine spray	9 (52.9%)
Sartan	2 (11.8%)
Beta-2 agonist inhaler	4 (23.5%)
Other	5 (29.4%)
Previous relevant surgery, No (%)	
Tonsillectomy	3 (17.6%)
Palatoplasty	2 (11.8%)
Rhinoplasty	2 (11.8%)
Septoplasty	1 (5.9%)
Investigations	
Skin prick test, No (%)	
Negative	8 (47.1%)
One allergen	3 (17.6%)
Two allergens	2 (11.8%)
Multiple allergens	4 (23.5%)
Nasal endoscopy findings, No (%)	
Rhinitis	17 (100%)
IT hypertrophy only	9 (52.9%)
Septal deviation + IT hypertrophy	8 (47.1%)

Table 1. General characteristics of the population

OSA: obstructive sleep apnoea; IT: inferior turbinate.

Nasal airflow and olfactory function at baseline

Bilateral and unilateral PNIF values as well as acoustic rhinometry parameters pre- and post-decongestion are reported in *Table 2*. The median identification score at S'S was 13. *(Table 2)*

Other investigations at baseline

The nasal endoscopies confirmed signs of rhinitis and hypertrophy of the IT in all of the cases; in eight patients (47.1%), these were associated with a deviated nasal septum. Skin prick tests confirmed a sensitivity to common aeroallergens in nine patients (52.9%). CT scans of the sinuses showed no concomitant CRS in any of the cases. The majority of the patients were in the moderate OSA category (6; 35.3%) at the time of the pre-operative sleep study with a median oxygen desaturation index (ODI) of 10.5 and a median snore percentage of 24.3%. All of the patients with moderate or severe OSA were using a CPAP machine. The median BMI was 30.1 kg/m^2 with the majority of the patients (5; 35.7%) being overweight (BMI of 25–29.9) (Table 1–3).

Patient-reported outcome measures (PROMs)

Low median scores on the SF-36 were observed in the domains of energy fatigue (50.0%), general health (60.0%) and health changes (50.0%). The median score for the ESS was 8, that for the SNOT-22 was 31.0, that for the NOSE was 14, that for the short-QODNS was 21 and that for sVAS was 7.5 (Table 3).

	Baseline (T_0) n=17	3-month (T_1) n=13	6-month (T_2) n=14	12-month (T_3) n=10	*p*-value (T_0-T_1)	*p*-value (T_0-T_2)	*p*-value (T_0-T_3)
Nasal measurements							
Pre-decongestion							
PNIF, median [P25-P75], L/min							
Bilateral PNIF	130.0 [90.0-160.0]	115.0 [107.5-120.0]	130.0 [120.0-157.5]	135.0 [93.8-147.5]	0.80	0.83	0.83
Right PNIF	95.0 [50.0-140.0]	65.0 [50.0-82.5]	100.0 [60.0-125.0]	75.0 [52.5-98.8]	0.50	0.70	0.68
Left PNIF	80.0 [45.0-120.0]	65.0 [53.8-85.0]	72.5 [60.0-107.5]	77.5 [61.3-88.8]	0.66	0.92	0.76
Acoustic rhinometry, median [P25-P75]							
Right MCA1, cm^2	0.8 [0.4-1.1]	0.6 [0.5-1.0]	0.9 [0.5-1.0]	0.6 [0.6-0.9]	0.50	0.85	0.28
Right Nasal volume (0-5), cm^3	6.1 [4.5-9.5]	7.8 [6.2-12.6]	6.8 [5.9-10.0]	6.2 [5.4-7.8]	**0.03***	0.90	0.49
Left MCA1, cm^2	0.5 [0.4-0.8]	0.7 [0.5-1.0]	0.7 [0.5-0.8]	0.6 [0.5-0.9]	**0.02***	0.19	0.82
Left Nasal volume (0-5), cm^3	6.2 [5.1-8.1]	8.2 [5.8-9.5]	8.3 [5.7-10.5]	6.4 [4.2-8.0]	**0.02***	0.09	0.50
Post-decongestion							
PNIF, median [P25-P75], L/min							
Bilateral PNIF	150.0 [110.0-180.0]	120.0 [110.0-170.0]	150.0 [125.0-200.0]	140.0 [122.5-155.0]	0.58	0.72	0.72
Right PNIF	110.0 [85.0-130.0]	75.0 [60.0-110.0]	80.0 [70.0-135.0]	97.5 [70.0-128.8]	0.69	0.47	0.26
Left PNIF	100.0 [50.0-140.0]	85.0 [65.0-100.0]	85.0 [60.0-110.0]	100.0 [76.3-100.0]	0.72	0.46	1.00
Acoustic rhinometry, median [P25-P75]							
Right MCA1, cm^2	1.0 [0.8-1.5]	0.9 [0.8-1.1]	0.9 [0.8-1.3]	1.1 [0.7-1.3]	0.79	0.54	0.37
Right Nasal volume (0-5), cm^3	9.4 [6.0-11.9]	9.3 [7.7-10.9]	8.2 [7.1-11.2]	8.7 [7.3-10.5]	0.24	0.95	0.84
Left MCA1, cm^2	0.9 [0.6-1.1]	1.0 [0.5-1.2]	1.0 [0.9-1.1]	1.1 [0.9-1.1]	0.19	0.13	0.23
Left Nasal volume (0-5), cm^3	9.5 [6.6-11.6]	9.1 [6.3-12.1]	10.1 [6.2-10.7]	9.9 [8.5-12.0]	0.78	0.79	1.00

Table 2. Nasal measurements at baseline and at 3-, 6- and 12-month following radiofrequency of inferior turbinates. Significant p-values in bold. Levels of significance *p ≤ 0.05.

PNIF; peak nasal inspiratory flow; lPNIF: left PNIF; rPNIF: right PNIF; MCA1: first minimal cross-sectional area.

	Baseline (T_0) n=17	3-month (T_1) n=13	6-month (T_2) n=14	12-month (T_3) n=10	*p*-value (T_0-T_1)	*p*-value (T_0-T_2)	*p*-value (T_0-T_3)
Other measurements							
Sniffin' Sticks Identification, median [P25-P75]	13.0 [11.0-13.0]	12.0 [11.0-14.0]	12.5 [11.3-13.0]	13.0 [11.0-13.0]	0.63	0.93	0.10
Normosmics, n (%)	13 (76.5%)	11 (84.6%)	12 (85.7%)	9 (90.0%)	0.38	0.20	0.10
Hyposmics, n (%)	4 (23.5%)	2 (15.4%)	2 (14.3%)	1 (10.0%)	1.00	0.37	N/A[+]
BMI, median [P25-P75], kg/m^2	30.1 [26.5-32.8]		27.1 [25.5-32.0]			0.47	
Normal range (18.5-24.9), n (%)	2 (14.3%)		3 (23.1%)			0.93	
Overweight, (25-29.9), n (%)	5 (35.7%)		5 (38.5%)			1	
Obese grade I, (30-34.9), n (%)	4 (28.6%)	-	3 (23.1%)	-	-	1	-
Obese grade II, (35-39.9), n (%)	2 (14.3%)		1 (7.7%)			1	
Obese grade III, (≥40), n (%)	1 (7.1%)		1 (7.7%)			1	
Missing	3		4				
Sleep Study							
AHI, median [P25-P75]	12.3 [4.7-17.2]		11.0 [2.8-16.3]			0.42	
Normal (<5), n (%)	5 (29.4%)		5 (33.3%)			1	
Mild OSA (5-14.9), n (%)	5 (29.4%)		5 (33.3%)			1	
Moderate OSA, (15-29.9), n (%)	6 (35.3%)	-	4 (26.7%)	-	-	0.89	-
Severe OSA (≥30), n (%)	1 (5.9%)		1 (6.7%)			1	
ODI, median [P25-P75]	10.5 [3.7-14.6]		9.2 [2.4-14.3]			0.48	
Snore percentage, median [P25-P75]	24.3 [5.6-36.5]		13.8 [2.0-29.7]			0.89	
Missing	0		2				
PROMs							
SF-36, median [P25-P75], %							
Physical functioning	90.0 [80.0-100]	85.0 [60.0-95.0]	90.0 [70.0-100]	90.0 [85.0-100]	0.15	0.94	0.41
Role limitations due to physical health	100 [25.0-100]	100 [62.5-100]	100 [75.0-100]	100 [50.0-100]	0.58	0.34	1.00
Role limitations due to emotional problems	100 [33.3-100]	100 [50.0-100]	100 [100-100]	100 [100-100]	0.79	0.09	0.37
Energy/Fatigue	50.0 [45.0-65.0]	45.0 [42.5-65.0]	45.0 [35.0-70.0]	50.0 [40.0-65.0]	0.73	0.97	0.83
Emotional wellbeing	80.0 [56.0-88.0]	76.0 [62.0-76.0]	76.0 [64.0-84.0]	84.0 [48.0-88.0]	0.93	0.30	0.32
Social functioning	81.3 [50.0-90.6]	75.0 [50.0-75]	75.0 [62.5-100]	87.5 [62.5-100]	0.26	0.55	0.46
Pain	78.8 [45.0-82.5]	77.5 [61.3-95.0]	77.5 [57.5-90.0]	67.5 [67.5-77.5]	0.41	0.76	0.17
General health	60.0 [40.0-70.0]	60.0 [35.0-65.0]	65.0 [55.0-75.0]	65.0 [35.0-70.0]	0.33	0.08	0.80
Health change	50.0 [25.0-75.0]	50.0 [50.0-62.5]	50.0 [50.0-75.0]	50.0 [50.0-75.0]	0.17	0.85	0.42
Epworth sleepiness scale, median [P25-P75]	8.0 [5.0-13.0]	9.0 [4.5-15.0]	4.0 [2.5-10.5]	4.0 [3.0-10.0]	0.55	0.07	0.20
Short-QODNS, median [P25-P75]	21.0 [15.5-21.0]	20.0 [15.0-21.0]	20.0 [15.3-21.0]	18.5 [15.3-21.0]	0.78	0.85	1.00

sVAS, median [P25-P75]	7.5 [7.0-10]	8.0 [7.0-10]	8.0 [7.0-10]	8.0 [6.5-10.0]	0.34	0.68	0.72
SNOT-22, median [P25-P75]	31.0 [24.5-48.5]	36.0 [29.5-48.5]	22.5 [18.8-40.3]	25.0 [20.0-47.0]	0.49	0.42	0.55
NOSE, median [P25-P75]	14.0 [9.3-18.3]	14.0 [9.5-15.0]	7.0 [6.5-9.8]	10.0 [7.0-13.0]	**0.03***	0.09	0.83

Table 3. Other investigations and patients-reported outcome measures (PROMs) at baseline and at 3-, 6- and 12-month following radiofrequency of inferior turbinates. Significant *p*-values in bold.
Levels of significance according to p-values *p ≤ 0.05.
[+]p-value unobtainable considering only 1 hyposmic patient is present at T3.

PROMs: patient-reported outcome measures; BMI: body mass index; OSA: obstructive sleep apnoea; AHI: apnoea-hypopnea index; ODI: oxygen desaturation index; SF-36: 36-item Short Form Survey; sVAS: Visual Analogue Scale for sense of smell; SNOT-22: 22-item SinoNasal Outcome Test; NOSE: Nasal Obstruction and Septoplasty Effectiveness Scale

	Age	**Sex (Male)**	**BMI**	**Septal deviation**	**Non-allergic Rhinitis**	***Random effect (Patient)***
PNIF						
Bilateral						1.60
Right						1.34
Left	-0.10*		-0.22***	-2.42**		
Acoustic Rhinometry						
Right MCA1			-0.03**			
Left MCA1		+0.60***			+0.54***	
Right NV			-0.03**			
Left NV		+2.43*			+2.22*	1.56
AHI					-19.9***	
Epworth sleepiness scale		-1.30		-2.63	-2.41	4.87
SNOT-22		-5.42	+0.92	+1.29	-11.28	13.65
NOSE		-6.94**		+1.01	-4.49	1.30
sVAS						1.39
Sniffin' Sticks (Identification)				-2.25***		

Table 4. Effect of the variables on pre-decongestion nasal airways measurements, patient-reported outcome measures (PROMs) and olfactory test at the multivariate analysis. Level of significance according to p-values: *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001.

PNIF; peak nasal inspiratory flow; MCA1: first minimal cross-sectional area; NV: nasal volume; AHI: apnoea-hypopnea index; SNOT-22: 22-item Sinonasal Outcome Test; NOSE: Nasal Obstruction and Septoplasty Effectiveness Scale; sVAS: Visual Analogue Scale for sense of smell; BMI: body mass index.

Changes at follow-ups

A statistically significant improvement in the patients' right NV (paired test), left NV and MCA1, as well as their NOSE scores, was demonstrated between T0 and T1. Apart from that, no other statistically significant changes were observed in the nasal airway parameters either pre- or post-decongestion, S'S scores, BMI, sleep study parameters or PROMs at any of the follow-ups following RFIT (Figures 1–3; Table 2-3).

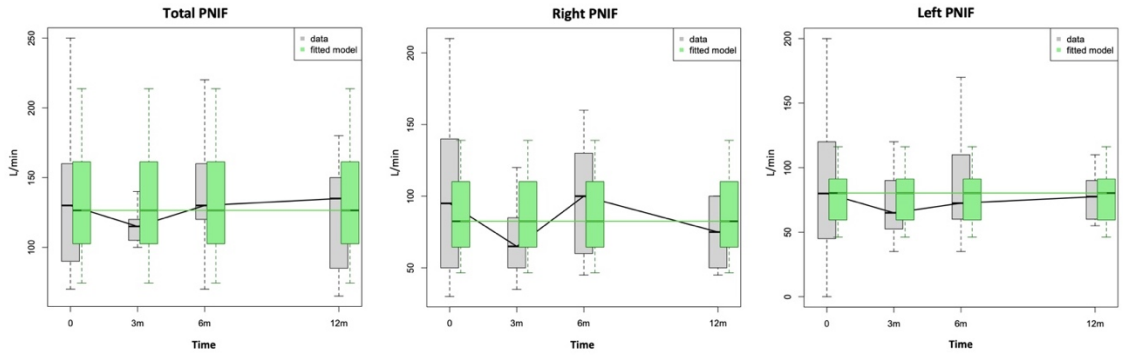

Figure 1: Box-plots showing distribution of total, right and left peak nasal inspiratory flow (PNIF) values at baseline (0) and at 3, 6 and 12 months following radiofrequency of inferior turbinates. The green fitted model was created by taking into account the influence of available variables.

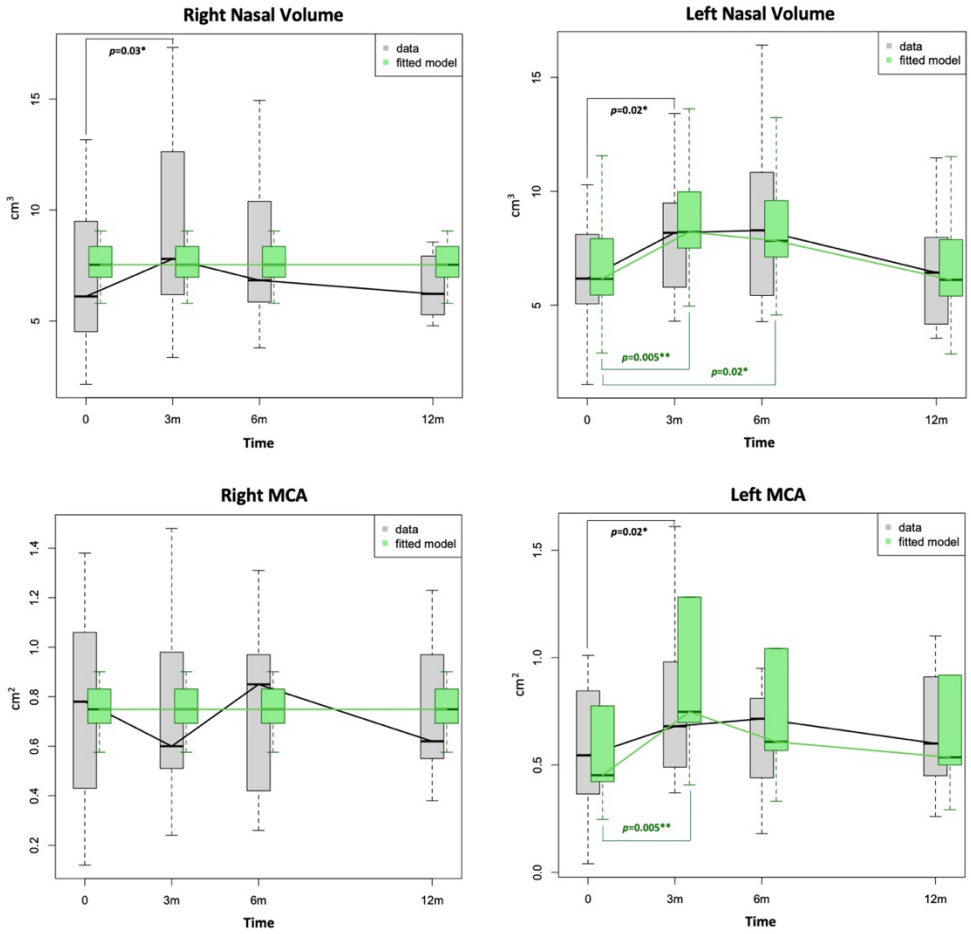

Figure 2: Box-plots showing distribution of right and left nasal volume and right and left minimal cross-sectional area (MCA) values at baseline (0) and at 3 6 and 12 months following radiofrequency of inferior turbinates. The green fitted model was created by taking into account the influence of available variables. Note that differences in grey refer to the data whilst those in green re-fer to the fitted model. Level of significance according to p-values: * $p \leq 0.05$, ** $p \leq 0.01$.

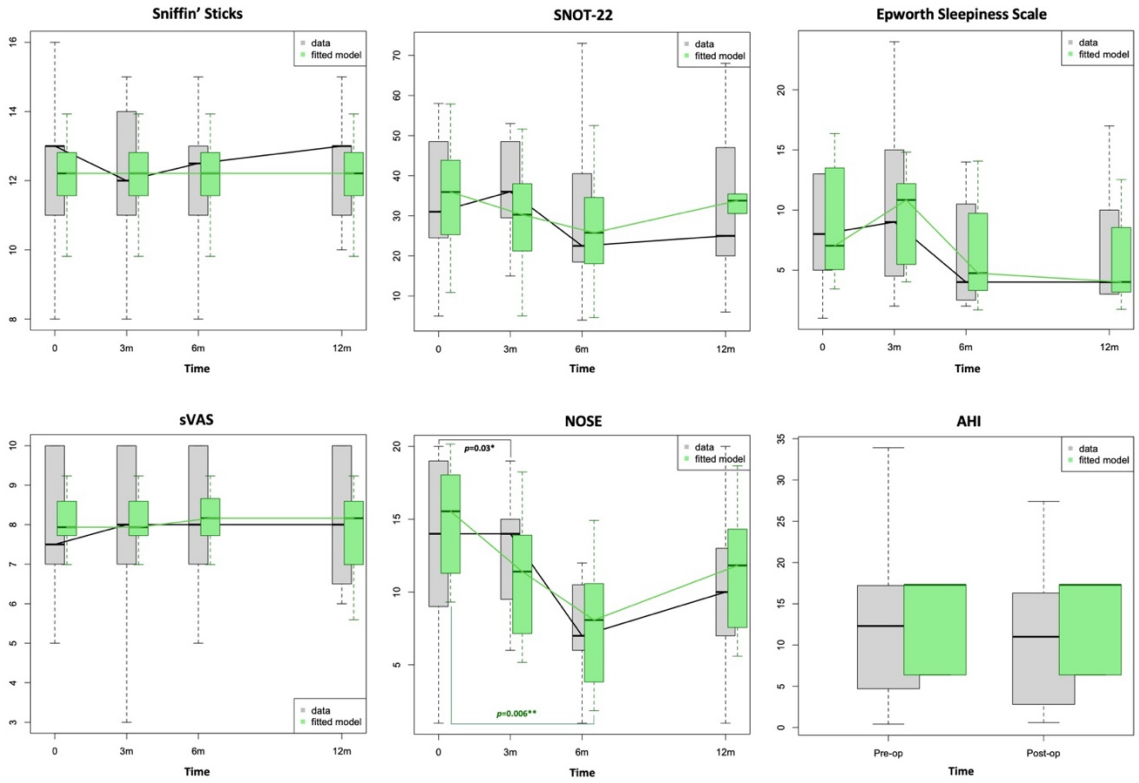

Figure 3: Box-plots showing distribution of patient-reported outcome measures values at baseline (0) and at 3, 6 and 12 months following radiofrequency of inferior turbinates. The green fitted model was created by taking into account the influence of available variables. Note that differences in grey refer to the data whilst those in green refer to the fitted model. Level of significance according to p-values: * $p \leq 0.05$, ** $p \leq 0.01$.

SNOT-22: Sino-Nasal Outcomes Test-22; sVAS: Visual Analogue Scale for Smell; NOSE: Nasal Obstruction Symptom Evaluation; AHI: Apnoea–Hypopnea Index.

Influence of available variables on studied parameters

As seen in the multivariate analysis, left PNIF (pre-decongestion) was significantly negatively influenced by age (older), a higher BMI and the presence of septal deviation. Acoustic rhinometry (pre-decongestion) was significantly negatively influenced by a higher BMI while it was significantly positively influenced by the male sex and the presence of allergic rhinitis. S'S identification was significantly negatively influenced by the presence of septal deviation. The AHI was significantly negatively influenced by the presence of allergic rhinitis, while the NOSE score was significantly negatively influenced by the male sex. The variables influencing the parameters and the strength of these influences are reported in Table 4. The fitted model, which was created by taking into account the influence of all the available variables, demonstrated a statistically significant

improvement of the left NV at 3 and 6 months (p = 0.005 and p = 0.02, respectively) and at 3 months for the MCA (p = 0.005). Similarly, the difference between the baseline and 6-month NOSE scores became statistically significant (p = 0.006) in the fitted model (Figure 3). The qqplots analysis confirmed the goodness of fit for each model.

5.5.4. Discussion

Our prospective study seems to suggest a lack of a significant long-term improvement of nasal airways in patients with SDB following RFIT, with potential benefits, both objective and subjective, limited only to the short-term period (3 and 6 months), as demonstrated by AR and NOSE scores. These findings were further confirmed by our fitted model (Tables 2 and 3; Figures 2 and 3). The role of RFIT in improving nasal airways is well established in non-SDB patients, although results have often been inconsistent.[396] A systematic review conducted in 2009 on the effectiveness of RFIT confirmed a great variability in the methods used for measuring the subjective relief of nasal blockages.[407] The mean patient-reported nasal obstruction scores decreased statistically significantly in all but one study when the effect of RFIT was measured using VAS scores. Cavaliere et al.[408] demonstrated a significant improvement in the nasal airflow using anterior active rhinomanometry and VAS in a cohort of 25 patients (who had IT hypertrophy refractory to medical treatment), but the decongestion effect significantly decreased at 3 months. On one hand, there is enough evidence to support the use of RFIT in non-SDB patients [23–26], but on the other hand, its efficacy becomes less obvious when RFIT is evaluated in SDB patients. Casale et al.[409] found a significant reduction in NOSE and VAS scores roughly 45 days following RFIT in patients with simple snoring. The authors also showed an objective significant improvement in nasal airflow using a video-rhino-hygrometer.[409] Means et al.[402] in a retrospective study on 40 patients who underwent RFIT >14 months (14–30 months), which also included eight SDB patients, reported that their relief from nasal obstruction persisted longer than 14 months post-procedure. However, in the only placebo-controlled, double-blind study

conducted on SDB patients,[410] there was no significant difference in the nasal obstruction outcome as measured by VAS scores, although there was a statistically significant improvement in self-reported CPAP adherence.

The disappointing absence of long-term nasal airways improvement observed in our data is, however, shared by similar studies which evaluated nasal surgery alone in SDB patients.[411-413] In fact, both our data and fitted model, the latter taking into account the effect of the available variables on the studied parameters, demonstrated a statistically significant improvement of nasal airways for AR but only in the short-term (either 3 or 6 months) with these changes found to be non-significant at the 12-month follow-up (Tables 2 and 3; Figures 2 and 3). Similarly, a statistically significant reduction in NOSE scores was demonstrated only in the short-term follow-up at either 3 or 6 months (Figure 3). The NOSE questionnaire is a brief, validated, disease-specific instrument designed to measure nasal obstruction, which has also been confirmed to be a helpful screening tool for OSA.[414] Differently from the SNOT-22, which is more specific for CRS, it does not contain additional questions on otologic, sinus or emotional symptoms. In this regard, the NOSE questionnaire is more specific for nasal obstruction and, thus, able to detect changes in perceived nasal blockage than the SNOT-22. This may suggest that RFIT can actually have a role in improving nasal airways in patients with SDB. Moreover, PNIF may not be the best tool to assess nasal airways in patients with SDB and nasal obstructions, as previously noted,[415] and other factors, mainly an altered pharyngeal morphology,[412] could affect the performance of the test and impact on the values measured. In this regard, Morinaga and colleagues[412] observed that a favourable nasal surgical outcome in SDB patients was seen in individuals who had a high-positioned soft palate and/or in those with a wide retroglossal space.

The influence of nasal surgery on sleep parameters is not clear, and results are conflicting [47–51]. Although we observed a reduction in the median AHI (−1.3

events/hour), ODI (−1.3 events/hour) and snore percentage (−11.5%) 6 months after RFIT, as well as the halving of the patients' post-operative ESS scores at 6 and 12 months, none of these were statistically significant (Table 3). Interestingly, a statistically significant negative influence of the presence of non-allergic rhinitis on the AHI was showed in the multivariate analysis (Table 4). According to findings in the literature, surgical success has been defined as a greater than 50% reduction in the AHI and a final AHI of less than 20.[416] A recent systematic review and meta-analysis on the topic conducted by Schoustra and colleagues,[417] revealed a small overall decrease in AHI of 4.08 events/hour from pre-operative to post-operative sleep study. Equally, a previous meta-analysis by Wu and colleagues[418] looking at the effect of isolated nasal surgery on sleep parameters showed a similar mean improvement in AHI of 4.15 events/hour. Overall, these data suggest that nasal surgery alone has a small effect in lowering the AHI, and our data seem to corroborate this.

Therefore, taking into account that nasal surgery, including RFIT, appears to not significantly improve sleep parameters, most authors seem to agree on the fact that its benefit in OSA patients could rely on the reduction in the CPAP pressure, which translates into a better CPAP adherence.[410,419] However, even for this aspect, results are not univocal.[402] In our cohort, all the patients who were using CPAP pre-operatively, and kept using it in the follow-up period, reported a better adherence to CPAP following RFIT.

Olfactory dysfunction is commonly observed in patients with SDB[343] and older adults with SDB have been reported to be at higher risk to have impaired odour identification (odds ratio 2.13).[345] In our study, 23.5% of patients were found to be hyposmic in the identification test. However, although we observed a reduction in the percentage of hyposmic patients during the follow-up period, this was not statistically significant, and this apparent reduction could have been influenced instead by an attrition bias. Similarly, no statistically significant improvement in the reported smell function was observed when

looking at their sVAS or short-QODNS scores. OD in SDB patients seems to be related to sleep fragmentation and chronic intermittent hypoxia, causing alterations in the main olfactory bulb neural network and affecting pathways in the central nervous system which involve chemosensory processing.[345,346,351] As a confirmation of that, CPAP therapy has been shown to improve olfactory function.[372] Despite its high prevalence in this population, olfactory function is not frequently assessed when evaluating changes following nasal surgery in SDB patients. Anecdotally, the improvement of olfactory function following RFIT has been documented in non-SDB patients [401,420] but studies looking at patients with SDB are scarce.

HRQoL is impaired in patients with SDB[421] and our results confirmed this with lower scores observed for the SF-36 domains of energy/fatigue, pain, general health and health changes when compared to UK normative values.[422] However, no statistically significant changes were noted in any of the SF-36 domains following RFIT during the follow-up period. In the study of Nilsen and colleagues[423] that included, amongst others, patients with SDB, a significant improvement was demonstrated in the general health and vitality domains of the SF-36 following RFIT. However, they observed that patients with sleep apnoea had poorer outcome after surgery than the other patients.[423] To the best of our knowledge, no studies have yet evaluated the general aspects of HRQoL purely in SDB patients undergoing RFIT; therefore, we were unable to compare our results with those from other authors.

Our multivariate analysis confirmed that several patient-related variables can influence objective and subjective outcomes following RFIT, and these should be taken into account in the patient selection process (Table 4). Final nasal airway measurements, in fact, can be negatively influenced by the presence of a septal deviation, a higher BMI and age (older); interestingly, male patients or those with non-allergic rhinitis may have better results.[424] Similarly, these variables can also affect recorded PROMs. Finally, it is

interesting to note that the presence of a septal deviation can also negatively influence olfaction, which is something that has already been confirmed by our research group in previous studies.[178,425,426]

Strengths and limitations

To the best of our knowledge, this is the only study currently available in the literature in which the effectiveness of RFIT has been evaluated in SDB patients only using multiple objective and subjective outcomes, including olfactory performance, which is often overlooked. Our multivariate analysis and fitted model highlighted multiple variables that can potentially influence recorded outcomes; thus, it can help surgeons improve patient selection when offering RFIT to SDB patients. However, our study is limited by a small sample size; as this can cause erroneous inferences, our results should be carefully interpreted in view of this limitation. Moreover, the addition of a control group (no treatment) to compare our results against could have helped in distinguishing the specific effects of RFIT treatment.

5.4.5. Conclusions

Patients with SDB frequently experience nasal obstruction, and RFIT can be considered an option for patients with nasal blockage refractory to medical treatment. Our study confirms that the benefits of RFIT alone in SDB patients are limited potentially only to the short-term period. This could be due to the fact that other patient-related variables, including age, sex, BMI and the presence of septal deviation, as well as anatomical factors, like pharyngeal morphology [43], could impact the final outcome. Nevertheless, our results should be confirmed in future studies conducted in larger populations.

5.6 Published study on SDB – summary of findings and their relevance in the PhD project

In this prospective study[377] I assessed olfactory function (specifically odour identification) at baseline and over a period of 12 months to demonstrate a potential role of RFITs in improving OD in SDB patients.

First of all, I showed that a mild-to-moderate OD is very common amongst SDB patients (23.5% in our population). This is an important finding as prevalence of OD in this category of patients is still unknown and loss of sense of smell is often a symptom not explored when assessing these patients. Considering how OD impacts on quality of life, this highlights the importance of evaluating olfaction in these patients and potential beneficial implications of OD treatment.

Secondly, I evaluated whether an improvement in nasal airways using RFITs could have led to improved olfaction as well. Although I demonstrated a statistically significant improvement of nasal airways (mainly, increase of nasal volume), nasal airflow did not increase following the procedure. Moreover, both measured and reported sense of smell did not improve. Despite the disappointing lack of olfactory improvement following RFITs, this study further supports the strict relationship between nasal airflow and olfaction, and how an increase in the nasal airflow rather than in the nasal volume is more important for olfactory improvement.

CHAPTER 6: POST-INFECTIOUS OLFACTORY DYSFUNCTION

6.1. My research questions and hypotheses on COVID-19-related OD (C19OD)

My PhD took place during the COVID-19 pandemic which put me at the forefront of C19OD evolution. At the very beginning of the COVID-19 pandemic, in line with ongoing worldwide research, I looked into the prevalence and early recovery of C19OD in the UK and Italy as well as objectively measure olfactory changes. As the pandemic progressed, I looked into C19OD prognosis, risk factors and treatments and culminated in devising a new surgical treatment for persistent C19OD. My aims and hypotheses regarding C19OD matured during the pandemic and are summarised in *Table 6.1*. An introduction to the topic has been included to give a background to the studies conducted.

Research questions
1. Is C19OD short-lasting and self-resolving?
2. Is the prevalence of C19OD higher and its severity worst amongst healthcare workers who worked in hospitals during the pandemic?
3. Is prevalence of C19OD different in patients who had severe COVID-19 (i.e. hospitalised)?
4. Is C19OD caused by an end-organ failure? Which olfactory ability is most affected in C19OD? Does this remain impaired long-term?
5. How severely is QoL affected in subjects with persistent C19OD (>1 year)? Can this improve once sense of smell recovers?
6. Are there any clinical factors influencing recovery/persistence of C19OD?
7. Is persistent C19OD reversible, even after 1-2 years?
8. Is ongoing inflammation a pathophysiologic mechanism of C19OD? If so, is the anti-inflammatory effect of corticosteroids effective in C19OD? Is there a benefit over OT or when corticosteroids are given in combination with OT? Does this offer a clinically meaningful improvement (i.e. above MCID)?
9. Is the effect of increased odorant delivery, obtained by increasing nasal airflow to the olfactory area, effective in persistent C19OD? Can fSRP improve C19OD? If so, is this improvement clinically meaningful (i.e. above MCID)?
Hypotheses
1. The majority of subjects with C19OD improves in the short-term and olfactory recovery follows a similar path to previous PIOD.

2. Prevalence of C19OD is expected to be higher amongst healthcare workers due to higher frequency of catching the virus in the pre-vaccination era.
3. Prevalence of C19OD in patients who developed severe COVID-19 is expected to be similar to rest of population.
4. C19OD severely affects QoL but its restoration will also lead to a QoL improvement, confirming the strict relationship between smell loss and QoL.
5. C19OD involves a damage at the level of the OE which will be reflected in a reduced olfactory threshold. This remains impaired long-term and could explain persistent C19OD.
6. Persistent C19OD is supposedly caused by an ongoing inflammation in the OE and, therefore, it would improve on corticosteroids. Corticosteroids effect will further improve OT benefits. If not, then this would imply a non-inflammatory mechanism leading to persistent C19OD.
7. Improvement of nasal airflow in the olfactory cleft leads to an increased odorant delivery to the olfactory mucosa. This increased stimulation leads to improved olfaction. If so, this would imply that olfactory receptor neurons are still present and functioning.

Table 6.1. Research questions and hypotheses leading to my published studies on COVID-19-related olfactory dysfunction.

C19OD: COVID-19-related olfactory dysfunction. MCID: minimally clinical important difference; OE: olfactory epithelium; OT: olfactory training; PIOD: post-infectious olfactory dysfunction; QoL: quality of life;

6.2. Introduction – an overview on PIOD and C19OD

OD following a viral upper respiratory tract infection (URTI) was first described in 1975.[427] In the acute phase PIOD is typically caused by the associated nasal mucosal oedema and, therefore, OD is by definition conductive. Once this resolves, usually within 2 weeks, sense of smell returns; however, in some patients OD may become persistent. URTI can be caused by rhinovirus, accounting for 30%-35%, but also by “adenovirus, coxsackievirus, echovirus, paramyxovirus, respiratory syncytial virus, and enterovirus, which account for 10% to 15%”.[428] The rest remains unidentified. A pre-COVID study investigated the viral presence in nasal discharge of patients with post-URTI OD and confirmed that rhinovirus was the major cause of PIOD.[429] The second commonest cause was Epstein-Barr virus followed by Picornavirus, Parainfluenza virus and Coronavirus.[429] A retrospective study by Konstantinidis et al.[430] found a seasonality of PIOD with two peaks of high incidence during March and May on a retrospective analysis of 6

consecutive years, with probable etiological agents being influenza viruses and parainfluenza viruses (type III), respectively. Nevertheless, the virus linked more commonly to PIOD still remains unknown considering that most people present long after the primary viral insult and, therefore, the source cannot be identified. This, however, was the picture before the COVID-19 pandemic, after which the coronavirus SARS-CoV-2 became the most frequent cause of PIOD.

6.3. Prevalence and associated symptoms

The true prevalence of PIOD remains unknown. This is particularly true if we consider that before COVID-19 there was no public awareness of the relationship between viral infection and OD and, thus, it is expected that some people would not have sought medical attention as a consequence. According to pre-COVID data, prevalence of PIOD amongst those presenting to a smell clinic with a primary complaint of OD ranged between 18.5% and 42.5%,[100,428] and was more common in women, roughly 2-3 times higher, particularly in those over 50 years of age.[428,430] The COVID-19 pandemic has helped us in further understanding PIOD prevalence. According to research conducted during the pandemic, from 34 % to 86 % of subjects experience an acute loss of their sense of smell following SARS-CoV-2 infection.[431-436] A meta-analysis published in the early phase of the pandemic and including 3563 patients reported a median prevalence of self-reported OD of 47% (prevalence ranging from 11–84% in the included case series).[437] Another meta-analysis published a year later and including 27,492 patients confirmed the prevalence of OD following SARS-CoV-2 infection to be 47.9%.[438] In particular, the alpha and delta variants of the virus, were linked to a higher rate of C19OD when compared to the omicron.[439,440] This difference seems to be related first to mutations in the spike protein in the omicron variant, making this more hydrophobic and less soluble in the mucus, thereby diminishing its ability to reach the OE.[440] Secondly, this could be also linked to a different route of cellular entry.[440]

	Date published	Prevalence	Sample size	Method used (OD prevalence %)
Tong et al.[431]	Jul 2020	52.7%	1627	- Non-validated survey (36.64%) - Validated instruments (survey or UPSIT): (86.6%) ○ UPSIT[441]: (98.3%)
Borsetto et al.[437]	Oct 2020	Overall: 47% Mild-to-moderate COVID-19: 67%	3563	Non-validated and validated survey
Soltani et al.[442]	Jan 2021	36.2%	3148	Not reported
Saniasiaya et al.[438]	Apr 2021	47.85%	27,492	- Subjective: (44.53%) - Objective: (72.10%)
Vakili et al.[443]	May 2021	25.34%	6,597	Not reported
Vitalakumar et al.[444]	July 2021	26.4%	83,575	Not reported
Qiu et al.[445]	Jan 2022	47.0%	16,478	Not reported
von Bartheld et al.[440] *(only omicron variant)*	Jan 2023	Overall: 3.7% European ancestry: 11.7% Non-European ancestry: 1.9%-4.9%	626,035	Not reported

Table 6.2. Prevalence of COVID-19-related olfactory dysfunction based on data from meta-analyses and/or systematic reviews.

OD: olfactory dysfunction; UPSIT: University of Pennsylvania Smell Identification Test.

Moreover, genetic/ethnic differences (specifically in the allele at the UGT2A1 locus) can contribute to the differences in OD prevalence.[440] Nonetheless, the true prevalence of C19OD might be different considering that self-reported OD usually underestimate presence of OD. In this regard, Moein et al.[441] found that of the 60 confirmed COVID-19 inpatients 98% had some degree of OD using an identification test (UPSIT) whereas only 35% of them subjectively reported that. Prevalence of C19OD based on data from meta-analyses and systematic reviews and according to the methods used is reported in *Table 6.2*. As further confirmation of what stated above, it is interesting to note from this table that prevalence is higher when C19OD is investigated using objective measures.

In contrast to other viral aetiologies of OD, SARS-CoV-2-induced OD is less frequently accompanied by associated URTI symptoms, such as nasal obstruction or rhinorrhoea.[446,447] In fact, C19OD can precede other symptoms in 23% of cases, it can also be the only symptom (isolated OD) in 17% of mild-to-moderate cases and it is more

frequently associated with milder disease not requiring hospital admission.[437,448-451] However, other studies have found no correlation between severity of OD and severity of illness or viral load.[452,453] An interesting comparison between patients with C19OD and non-C19OD (PIOD patients before the pandemic) found that C19OD patients were younger, even paediatric, whereas it occurred mainly after the fourth decade. Subjects with C19OD had a lower incidence of anosmia or ageusia; conversely, they more often demonstrated distorted sense of smell (i.e. parosmia or phantosmia) and generally exhibited higher TDI scores.[447,454]

Qualitative olfactory disorders are common in PIOD. A study conducted before the pandemic found that the rate of parosmia following PIOD was reported to be of 56%.[455] Conversely, this seems to be slightly higher in patients infected by SARS-CoV-2 and more than two thirds (66.7%) of COVID-19 cases can, in fact, develop a qualitative olfactory disorder.[434-436] This typically occurs 2-3 months after the OD onset and frequently after a period of apparent recovery of their sense of smell, even though some subjects can develop parosmia without an initial loss of olfaction.[456] Parosmia has been reported to be more frequent in PIOD when compared to post-traumatic or sinonasal forms of OD.[457]

6.4. Pathophysiology of OD in PIOD

6.4.1. Pathophysiology of quantitative OD

Our understanding of the pathophysiology of PIOD has improved following the COVID-19 pandemic. Before that, few studies had investigated the mechanisms leading to OD.

Prior investigations have associated PIOD with the degeneration of central olfactory pathways, peripheral destruction of ORNs, or a combination of both.[428] Animal models have shown that the OE and OB are consistently affected by influenza virus, but with

limited histological evidence of degeneration, despite the presence of hemagglutinin, a viral protein crucial for neural cell infection.[458,459]

Similar studies conducted in animals have demonstrated that HSV infection results in cell death of ORNs, mitral cells, and granule cells.[460-462] Furthermore, following infection with parainfluenza virus, ORNs exhibit “diminished calcium signalling in response to odorant binding, suggesting an impairment in cellular depolarization and signal transduction”.[463,464] The neurovirulence of parainfluenza virus appears to be limited to primary ORNs and their surrounding cells within the OE and OB. Notably, when compared to influenza or HSV, parainfluenza virus infection elicits minimal morphological alterations or inflammatory responses within the OE and OB.[463,464]

The recent pandemic has given a new impetus to the research on PIOD and although most of the research on the topic has been conducted on C19OD, findings can be potentially generalised to other forms of PIOD. As previously mentioned, C19OD is less likely to be accompanied by nasal obstruction or rhinorrhoea, and the majority of people have little or no nasal congestion which would point against a conductive pathogenesis of OD.[465] In support of that, the majority of MRI studies conducted in patients with C19OD confirmed a clear olfactory cleft in most of the cases with a selective inflammatory oedema of the olfactory cleft in the absence of any nasal airflow obstruction in a small number of patients.[466-468]

Early in the pandemic, increasing evidence suggested that nasal respiratory epithelial cells and supporting cells within the OE exhibited significant expression of angiotensin-converting enzyme 2 (ACE2) receptors. This finding, coupled with the observation of efficient SARS-CoV-2 utilization of ACE2 for cellular entry, prompted further investigation.[469] Post-mortem analysis of OE tissue from COVID-19 patients confirmed that sustentacular cells serve as the primary target for SARS-CoV-2 infection and

replication, with no evidence of infection of ORNs or of the OB.[470] Other pathological findings included “focal atrophy of the OE, leukocytic infiltration of the lamina propria, and evidence of axonal damage to olfactory nerve fibres”.[471] Although “ORNs themselves do not express ACE2 receptors and are not directly infected by the virus”, the damage to sustentacular cells can lead to diminished ORN sensitivity and ciliary loss, consequently hindering odour transmission.[472] An age-dependent decreased expression of ACE2 receptors has also been observed in the OE which could partially explain why C19OD is less frequent in the elderly.[473] The lack of supporting cell able to sustain the ORNs’ function causes a widespread persistent downregulation of ORNs proteins and of ORNs signalling genes in human ORNs.[474] However, other mechanisms could account for the persistent OD. (*Table 6.3.*)

	Mechanism	Rationale
Damage of OE	Sensorineural	• Damage of sustentacular cells by SARS-CoV-2. • Decreased sensitivity and loss of ORNs cilia due to sustentacular cell damage • Production of pro-inflammatory cytokines by damaged sustentacular cells • Focal atrophy of the OE, leukocytic infiltration of the lamina propria, and axonal damage to olfactory nerve fibres. • Ongoing inflammation causes impairment in regenerative capacity of basal stem cells
Neurocognitive	Central	• Axonal degeneration and microvascular endothelial injury, astrogliosis and microgliosis in the OB leading to decreased volume of the OB • Decreased volume and functional activity of cerebral olfactory processing areas (piriform cortex, insular cortex, orbitofrontal cortex, cerebellum, and limbic regions) and connected white matter.

Table 6.3. Relevant mechanisms leading to COVID-19-related olfactory dysfunction.

OB: olfactory bulb; OE: Olfactory epithelium; ORNs: olfactory receptor neurons.

In 2000 Leopold[475] was the first to point out that an autoimmune process or an inflammatory product released while fighting the URTI could have been responsible for the PIOD. Recent research has focused on the role of macrophages as key immune cells

in olfactory homeostasis and disease, by enhancing tissue regeneration whilst being the first responders to many respiratory and neurotropic pathogens.[459,476] A study conducted in mice has identified two different tissue macrophage populations in the olfactory mucosa and one of these, specialized for neuron interactions and to phagocytose cells and debris, including ORNs, has been found to be decreased in hyposmic patients and further reduced in COVID-19 hyposmic subjects.[477] The production of pro-inflammatory cytokines during the acute and chronic phase of COVID-19 infection by the sustentacular cells is also considered by different authors as a relevant mechanism in the pathogenesis of persistent C19OD.[474,478] These are known to target neural stem cells, thus, attenuating neurogenesis.[474,478-480] This ongoing inflammation in the OE can impair the regenerative capacity of the basal stem cells and could be responsible for the persistent C19OD.[481] Horizontal basal stem cells (HBCs), located in the basal layer of the OE, have regenerative capacity able to replace ORNs and maintain ongoing neurogenesis.

Chronic inflammatory conditions can induce a functional shift within the OE, transitioning it from a neuro-regenerative phenotype to one primarily involved in immune defence.[481] This functional alteration can consequently result in a deficit in the replacement of ORNs.[481] In a murine model, the proinflammatory cytokine tumour necrosis factor (TNF) can be released by the sustentacular cells during a chronic inflammation. Both the TNF and the downstream NF-κB pathways, involved in cell proliferation and immune responses, are enriched in the HBCs during chronic inflammation with the aim to regulate immune cell trafficking (through chemokines) and enhance pathogen removal.[481] On the other side, the prioritization of the immune-related functions rather than ORNs proliferation contributes to the loss of sense of smell.[481] *(Figure 6.1.)* MRI studies have found that the OB volume, as well as the grey matter in the cerebral olfactory processing areas (piriform cortex, insular cortex, orbitofrontal cortex, cerebellum, and limbic regions) and connected white matter, are reduced following PIOD.[482,483]

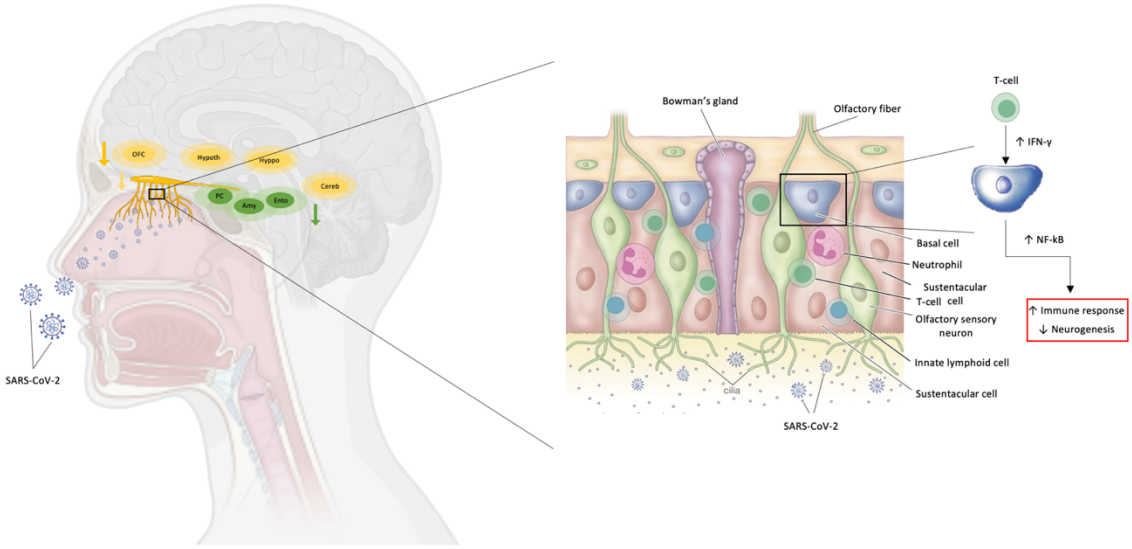

Figure 6.1. Different pathophysiological mechanisms leading to COVID-19 olfactory dysfunction.

Amy: amygdala; Cereb: cerebellum; Ento: entorhinal cortex; Hippo: hippocampus; Hypot: hypothalamus; OFC: orbitofrontal cortex; PC: piriform cortex; Thal: thalamus.

A study conducted by Kim et al.[484] in 2012 revealed that patients with PIOD exhibited a significant reduction in metabolic activity within not only the primary olfactory cortex, including the piriform cortex, but also within secondary olfactory cortical regions, like the bilateral insular cortices and the medial and lateral temporal cortices, when compared to a healthy control group. These changes were more marked in the right hemisphere[484] which could also reflect the right-side predominance in odorant perception.[485,486] Alterations in the central nervous system have also been observed in patients with persistent C19OD. However, these do not seem to be caused by a retrograde transport of SARS-CoV-2 into the OB, that is believed to be highly unlikely in humans.[470,487]

Conversely, it is plausible that the observed changes in the central nervous system may be a consequence of immune system activation and the resulting inflammatory cascade associated with SARS-CoV-2 infection.[488] This hypothesis is corroborated by post-mortem findings, including evidence of axonal degeneration, microvascular endothelial injury found in the OB and olfactory tract tissues in the absence of viral infection,[488] but

also of a pronounced neuroinflammatory response characterized by astrogliosis, microgliosis, and minor infiltration of cytotoxic T lymphocytes within the OB.[489] Additionally, a regenerative deficit within the OB and OE, particularly concerning dopaminergic neurons, which are essential for maintaining olfactory function, has been implicated in the observed neurogenic deficit.[490,491] Interestingly, a recent MRI study comparing patients with C19OD and healthy subjects, revealed a mid-term OB damage in COVID-19 patients, regardless of whether they had persistent OD or recovered from it.[492] As the result of repeated olfactory sensory deprivation, a loss of grey matter in the limbic and olfactory cortical systems as well as a decreased OB volume has been demonstrated by comparing MRI before and after SARS-CoV-2 infection.[493,494] To further support the role of neuroinflammation in persistent C19OD, similarities between C19OD and other central nervous diseases presenting with OD (i.e. multiple sclerosis, Lewy body disease, Parkinson's and/or Alzheimer's disease) have been highlighted.[495]

6.4.2. Pathophysiology of qualitative olfactory disorders

The pathophysiological mechanisms leading to qualitative olfactory disorders are not completely known and, so far, multiple theories have been postulated to explain their occurrence. These mechanisms include: "an aberrant regeneration of ORNs after the acute viral insult" (the so-called 'miswiring' wherein neurons exhibit aberrant responses to inoffensive odorant stimuli);[496] a reduction in the population of functioning ORNs leading to incomplete encoding of odour-induced information;[497] a defect in stimulus processing in demyelinated ORNs;[498,499] and an abnormal level of activity within the central olfactory processing regions.[482,497,500] Yamagishi and colleagues[501] found that parosmia was present in those with mild or moderate impairment of the olfactory mucosa, while it was absent in those with complete destruction of the olfactory mucosa. More recently during the COVID-19 pandemic, Parker et al.[502] hypothesised that parosmia was caused by an incomplete characterization of all constituent odour components, resulting

in the “unopposed detection of unpleasant odour compounds without the counterbalancing detection of more pleasant odour profile aspects”. Pre-pandemic studies using MRI techniques in subjects with parosmia have demonstrated a selective loss of grey matter within key brain regions involved in odour discrimination and memory, namely the anterior insula, anterior insula complex, and hippocampus.[503] An interesting functional MRI study (pre-COVID) revealed “distinct activation patterns in the brains of patients with hyposmia and parosmia in response to odour presentation. Subjects with parosmia exhibited stronger activation within the putamen, a cerebral structure implicated in the recognition of aversive stimuli, as well as the thalamus, a structure considered essential for regulating the direction of attention towards a stimulus”.[500] A further neuroimaging study done in a COVID-19 patient with parosmia using PET/CT and MRI showed a hypometabolism in insula and hippocampus.[504]

6.5. Histopathologic findings

Previous histopathological studies of olfactory biopsies of patients with PIOD found an extensive scarring together with replacement of OE by respiratory epithelium.[505] Moreover, a paucity of dendritic projections reaching the epithelial surface, an absence of sensory cilia within olfactory vesicles, a presence of pathological junctions between olfactory and respiratory epithelium, and a reduction in the number of nerve bundles were also observed.[506] Hyposmic patients showed a less pronounced reduction in the density of ORNs when compared to patients exhibiting anosmia.[506] Furthermore, the remaining ORNs in hyposmic patients displayed a more normal morphological appearance.[506] In a study by Yamagishi and colleagues[501] three different histological patterns of the OE were identified. The first pattern was characterized by a reduction in the number of ORNs while maintaining the overall structural integrity of the OE. The second pattern showed a thinning of the OE with a predominance of supporting and basal cells, and the third, most severe pattern, involved the complete replacement of the

OE by metaplastic squamous epithelium. Ongoing inflammation in the OE is also one of the potential causes of persistent PIOD. Histopathological examination of OE biopsies obtained from seven patients experiencing persistent C19OD demonstrated viral persistence within the OE.[479] This was associated with progressive inflammatory processes, increased IL-6 levels, and presence of cellular apoptosis.[479] A subsequent study evaluating OE biopsies of nine patients with objectively quantified long-term C19OD confirmed persistence of T-cell mediated inflammation in the absence of detectable SARS-CoV-2 RNA or protein.[480]

6.6. Prognosis

Long-term prognosis of PIOD before COVID was barely known. Only few studies had followed up patients long enough to assess long-term recovery. In a study which followed patients for over 1 year, improvement in olfactory function was observed in 90% of patients using the UPSIT test (identification test) with a correlation demonstrated between the amount of improvement and length of follow-up.[507] In a similar study, Lee et al.[508] found that approximately 86% of the patients with PIOD had an improvement in their sense of smell after 1 year (using a Butanol Threshold Test).

The flourishing research on OD during the COVID-19 pandemic has allowed us to better clarify the natural trajectory of C19OD recovery. As previously mentioned, potentially this could be applied to other forms of PIOD. After OD onset following SARS-CoV-2 infection, 44-64% of the subjects recover within 2 weeks.[433,446] At 6 months 27-60% of subjects develop a persistent olfactory loss,[435,465,509-513] 26.5-46% at 1 year[513,514] and 8.3% at 2 years.[515] Recently, it has been reported that 5.2% of subjects infected during the first wave of the pandemic and 7.9% of those who had a chemosensory dysfunction during the acute phase of the disease still have C19OD after 3 years following the infection.[516] Currently, more than 700 million worldwide have been infected by SARS-CoV-2 and,

based on current prevalence and recovery rates, up to 28-30 million people will suffer with persistent C19OD. However, the true long-term prognosis cannot be definitively confirmed.

The reasons why some people recover and others do not, are not completely understood. Age (older)[435,509,512,517] and female sex[518] have been confirmed to be significant predictors of the likelihood of developing persistent loss of smell. On the other side, predictive factors associated with a higher rate of olfactory function recovery included: the absence of coexisting nasal congestion,[508,517] non-smoking status,[519] a higher density of ORNs and the presence of intact nerve bundles in the OE biopsy,[501] lower severity and duration of OD,[501,508,519,520] the "presence of olfactory event-related potentials,[521] and a narrow width of the OB" when measured radiologically.[522] Interestingly, patients with C19OD who also experienced parosmia, particularly younger patients, demonstrated a higher likelihood of recovering their olfactory function compared to those without parosmia.[508,520,523]

6.7. Treatments for C19OD

Table 6.4. summarises the pharmacological and non-pharmacological treatments described for C19OD with their corresponding highest available evidence. However, considering that C19OD is a particular form of PIOD, these findings can be generalised to PIOD as well.

6.7.1. Non-pharmacological treatments

Olfactory training (OT) is regarded worldwide as the gold standard treatment for PIOD and recommended by the major experts on the topic.[44,524] First proposed in 2009 by Hummel and colleagues,[525] several studies, either randomised and not, placebo-

controlled and not, have now confirmed its effectiveness in improving OD following a viral infection.[526-534] In the classic version of the OT, patients use four odorants (lemon, rose, cloves and eucalyptus) and "consciously spend 20 seconds smelling each odour, twice a day, for at least three months".[525] A modified version of OT was suggested in 2015 by Altundag et al.[528] whereas three sets of four different odours are used sequentially every 3 months. Although modified OT can increase patients' compliance and adherence, a recent meta-analysis did not show a superiority over classic OT.[530] Moreover, it has been reported that prolonged OT (assessed up to 56 weeks) is associated with better results than a short-term scheme.[535] The use of odours at higher concentrations has been shown to be more beneficial (better smell improvement in 44% of subjects, p=0.03), as confirmed by a RCT from Damm et al.[527] Conversely, the number of odours used in the OT scheme does not appear to have a significant role.[536] In fact, the use of more than 4 odours in OT can instead reduce adherence amongst patients.[536] As already explained in Chapter 3, the effect of sniffing can also increase uptake of odorants to the olfactory mucosa, as confirmed in an experimental study on patients with Parkinson disease whereas an improvement in patients sniffing was accompanied by a temporary improvement in their olfactory performance.[143] Effectiveness of OT has also been proven in patients with parosmia following PIOD.[537] Despite its potential therapeutic value, OT demonstrates limited efficacy in a substantial proportion of subjects, with an estimated 50% to 85% of individuals exhibiting no significant improvement in olfactory function.[525] Additionally, a considerable subset of patients with PIOD, ranging up to 29% of cases, fails to demonstrate any olfactory improvement even following prolonged courses of OT.[535]

Moreover, evidence seems to suggest that OT is particularly useful when it is started within 12 months after PIOD onset,[527] and therefore, might be less effective in long-standing OD.

	Authors (year published)	Type of study	Control arm(s) (if applicable)	Benefit	Main outcomes
Non-pharmacological					
Olfactory training (OT)	Kattar et al.[530] (2021)	Meta-analysis (2 RCTs, 2 QES)	Placebo / no OT	Yes	OT has 2.77 higher odds of achieving MCID (TDI>5.5)
	Asvapoositkul et al.[531] (2023)	Meta-analysis (5 RCTs)	No OT	Yes	OT leads to +4.68 average TDI increase
	Hwang et al.[534] (2023)	Meta-analysis (3 RCTs, 6 QES)	OT+NCS / OT+PEA-LUT / OT (different odours)	Yes	OT more effective for acute OD (<1 month)
	Delgado-Lima et al.[532] (2024)*	Meta-analysis (6 RCTs, 30 QES)	Placebo / no OT / different OT	Yes	OT increase significantly all the olfactory abilities, with larger effects on D and I, when compared to no OT or placebo
Pharmacological					
Oral corticosteroids (OCS)	Schepens et al.[533] (2022)	DB-RCT	Placebo	No	OCS (prednisolone 40 mg/daily for 10 days) does not improve olfaction
	Asvapoositkul et al.[531] (2023)	Meta-analysis (2 QES)	OCS+OT vs OT	No	Addition of OCS to OT does not improve odour I or TDI
Nasal corticosteroids (NCS)	Kim et al.[538] (2022)	Meta-analysis (4 RCTs, 1 QES)	Placebo / No treatment	Yes	Improvement in the short-term (2-4 weeks). No difference in full olfactory recovery rate
	Asvapoositkul et al.[531] (2023)	Meta-analysis (2 RCT)	NCS+OT vs OT	No	No difference in odour I or reported smell
	Chen et al.[539] (2024)	Meta-analysis (7 RCTs)	Placebo / OT	Yes	Olfactory scores 1.35 points higher in the short-term (4-6 weeks). No difference in recovery time.
Palmitoylethanolamide and luteolin (PEA-LUT)**	De Luca et al.[540] (2022)	RCT	PEA-LUT+OT / PEA-LUT	Yes	PEA-LUT+OT improved significantly odour I vs PEA-LUT
	Capra et al.[541] (2023)	Meta-analysis (3 RCTs)	OT	Yes	PEA-LUT+OT improved significantly olfaction vs OT
Omega-3	Hernandez et al.[542] (2022)	RCT	Omega-3+OT / OT	Yes	Omega-3 (2g BD for 3 months) increase significantly odour T
Alpha-lipoic acid (ALA)	Cantone et al.[543] (2024)	DB-RCT	ALA+OT / OT	No	Addition of ALA (300mg BD for 3 months) to OT does not lead to better odour T and I improvement
Gabapentin	Mahadev et al.[544] (2023)	DB-RCT	Placebo	No	Gabapentin (maximum tolerable dose for 8 weeks) did not improve odour I vs placebo
Systemic Vitamin A (VitA)	Taheri et al.[545] (2024)	DB-RCT	VitA+OT / OT / No treatment	No	Systemic VitA (10,000 units/daily for 3 months) does not lead to better olfactory improvement.
Zinc sulphate	Abdelmaksoud et al.[546] (2021)	RCT	No treatment	Yes	Zinc sulfate (220 mg BD) shortens OD recovery time

Intervention					
Platelet-rich plasma (PRP)	Yan et al.[547] (2023) – injected	RCT	Saline injection	Yes	Significant increase in TDI and odour D vs placebo
	Evman et al.[548] (2023) – injected	RCT	No treatment	Yes	Significant increase in odour T and I
	Duffy et al.[549] (2024) – coated foam	RCT	Saline-coated foam	No	No significant improvement in odour I
Functional septorhinoplasty (fSRP)***	Whitcroft et al.[178] (2023)	Prospective non-controlled study	-	Yes	fSRP leads to statistically and clinically significant improvement in TDI and odour I

Table 6.4. Pharmacological and non-pharmacological treatments for COVID-19-related OD (C19OD). Where multiple studies had been conducted, only the highest available evidence (systematic reviews, meta-analyses or RCT) were included.

BD: bi-daily; CCS: corticosteroids; D: discrimination; DB-RCT: double-blind randomised-controlled trial; I: identification; NC: Nasal corticosteroids; OT: olfactory training; PEA-LUT: Palmitoylethanolamide and luteolin; PRP: Platelet-rich plasma; QES: quasi-experimental studies (prospective controlled or non-controlled studies); RCT: randomised-controlled trial; T: threshold; TDI: threshold + discrimination + identification.

* Including also other causes of OD
** PEA 700mg + luteolin 70 mg daily
*** Although no high evidence studies available, this has been added as important in the context of the present PhD.

The mechanisms through which OT works are not completely known. Some authors suggested OT may work by promoting regeneration of ORNs at the level of the OE through repeated exposure to olfactory stimuli (i.e. odours).[550,551] Others believe that OT exerts a "top-down" effect, characterized by the induction of cortical thickening within olfactory brain regions,[551] further accompanied by a strengthening of olfactory, somatosensory, and integrative neural networks, as well as a volumetric increase in the OB.[552] This theory is further supported by a meta-analysis;[553] however, it is probably a combination of both 'bottom up' and 'top down' regeneration effects. Due to the effects of PIOD on quality of life (*see Section 2.6. on olfactory dysfunction and quality of life*), counselling is fundamental in the management of persistent PIOD with the aim to help in reducing life disruptions linked to the loss of sense of smell.

6.7.2. Pharmacological treatments

Despite the high number of studies conducted exploring different therapeutic options for PIOD, evidence supporting pharmacological treatments for C19OD remains weak.[554,555] (*Table 6.4.*)

The use of oral corticosteroids (OCS) for PIOD is debated and received only weak support from expert consensus documents and results from previous RCT did not show a superiority of OCS over placebo.[44,69,524,533] Their role in PIOD remains controversial and the majority of the authors recommend these should not be suggested earlier than 4 weeks, considering that spontaneous healing is expected few weeks after recovery from URTI onset.[472] Moreover, considering potential side effects, their use should be offered only after careful discussion of risks and benefits with the patient.[556] (*Table 6.4.*)

Limited evidence is available for nasal corticosteroids (NCS) and a benefit has been shown when these are used in the early phase of C19OD (first 4 weeks).[531,538,539,557,558] However, a systematic review and meta-analysis assessing the effect of NCS on PIOD found no difference in the full olfactory recovery rate between treated and control subjects (placebo or no treatment).[538] This is possibly linked to the fact that NCS may not be able to reach the olfactory cleft when administered nasally using a spray. Conversely, a pre-COVID RCT showed that NCS could be useful when administered as a rinse (budesonide irrigation) and in combination with OT.[557] (*Table 6.4.*)

For several years zinc sulphate has been regarded as a potential effective treatment for PIOD[559,560] but a pre-COVID double-blind placebo-controlled RCT did not show any superiority over placebo in the treatment of taste and smell disorders secondary to a variety of etiological factors.[559,560] Nevertheless, a recent RCT conducted in patients with C19OD demonstrated a shorter recovery time of OD in patients treated with zinc sulphate compared to those not taking it.[546] (*Table 6.4.*)

Supplementation with omega-3[542,561] and alpha-lipoic acid[543,562] has been suggested as a therapeutic option considering their safe profile and infrequent side effects. These fatty acids exhibit potential neuroprotective effects. Omega-3 “increases production of antioxidant and anti-inflammatory amino acids” while alpha-lipoic acid is a potent antioxidant and penetrates the blood-brain barrier enhancing motor-nerve conduction velocity and microcirculation. However, recent RCTs conducted on C19OD suggested a potential role for omega-3[542] but not for alpha-lipoic acid[543].

Intranasal sodium citrate exhibits positive effect on olfaction that lasts minutes to hours, but its long-term efficacy is controversial.[563-565] It has a safe profile and increases sensitivity to odours by “sequestering calcium and reducing free mucosal calcium with subsequent inhibition of negative feedback”. A reduction in patients reporting

phantosmia, but not parosmia, has also been reported.[565] To the best of my knowledge, no studies have been conducted on C19OD to suggest its use in this category of subjects.

Intranasal and systemic vitamin A have been investigated in patients with PIOD in view of vitamin A capacity to stimulate neural regeneration and repair of the peripheral olfactory system. However, efficacy remains controversial. Whilst some studies demonstrated a potential effects of topical intranasal vitamin A when taken in combination with OT,[566] a double-blinded placebo-controlled RCT (intranasal vitamin A vs placebo) conducted pre-COVID did not show any benefit.[567] A two-arm RCT of intranasal vitamin A vs no intervention is currently ongoing in the UK and will be including patients with C19OD as well.[568] Thus, whether evidence supporting intranasal vitamin A is still controversial and under evaluation, the use of systemic vitamin A is not recommended. In this regard, a recent double-blind RCT has confirmed no additional benefit when this is given in combination to OT.[545,554] (*Table 6.4.*)

Positive results have been recently reported with the use of palmitoylethanolamide and luteolin (PEA-LUT) with RCTs and a meta-analysis showing olfactory benefits when PEA-LUT is given in combination to OT.[540,541] PEA-LUT is supposed to "reduce neuroinflammation by modulating microglia and reducing oxidative stress".[540,569] (*Table 6.4.*)

The role of gabapentin in C19OD has also recently been investigated. However, despite initial evidence from a small case series were showing a potential improvement in parosmia,[570] a double-blind RCT did not show any clinically meaningful improvement in olfaction or statistically significant difference between the gabapentin and placebo groups during the study period.[544] (*Table 6.4.*)

Disease-modifying therapy drugs, currently used to treat autoimmune neuroinflammation in multiple sclerosis, have also been proposed to modulate neuroinflammation in COVID-19.[571] However, their effect on C19OD is currently under evaluation.[572] Finally, valproic acid is another drug that has recently gained attention due to its potential neuroregenerative effects and ability to promote differentiation of cultured neural stem cells and neurite outgrowth.[573]

Other treatments investigated before COVID-19 for the management of OD include: intramuscular administration of beta carotene or vitamin A;[574] a regimen comprising a combination of oral vitamin B12, adenosine triphosphate, and betamethasone nasal drip;[501] minocycline;[575] oral or intranasal (saline irrigation) [5]theophylline[576-578] and caroverine.[579-581] However, the available evidence regarding the efficacy of these interventions remains limited and inconclusive.

6.7.3. Interventions

Topical injection of platelet-rich plasma (PRP) in the olfactory cleft has recently gained attention as a potential option for PIOD due to its anti-inflammatory and neuroprotective effects. PRP is an autologous biological product obtained by processing a sample of the patient's own blood. This process results in a product enriched in platelets and a variety of pro-regenerative factors, including “transforming growth factor, vascular endothelial growth factor, epidermal growth factor, and insulin-like growth factor”.[582] These growth factors are known to stimulate tissue repair and regeneration. Studies have been conducted also in patients with C19OD but its efficacy is still under investigation.[547,583] A RCT by Yan et al.[547] showed a significant increase in olfactory function in C19OD patients receiving injected PRP compared to those receiving saline injection. PRP benefits have

[5] Theophylline is a phosphodiesterase inhibitor and increases intracellular cAMP and cGMP levels which promote olfactory signalling and sensory axonal regeneration. It has also anti-inflammatory properties.

also been recently evaluated when this is applied topically as a coated foam.[549] However, a RCT did not show any olfactory improvement when this is compared to saline-coated foam.[549]

More recently Whitcroft et al.[178] showed that fSRP could improve sense of smell in patients with long-standing OD (either idiopathic or post-infectious) confirming a role of nasal airway augmentation in smell restoration. Particularly, the authors found a strict correlation between increase in nasal airflow and olfactory threshold improvement, suggesting that smell restoration resulted from an increased peripheral activity (i.e. increased stimulation of the OE) likely caused by a higher odorants delivery. The role of fSRP in C19OD is the topic of my latest prospective controlled study (*Section 6.15*) and its effectiveness in PIOD will be further analysed in *Section 6.16*.

6.7.4. Long-standing C19OD and the need for clinically meaningful treatments

Although the majority of COVID-19 patients experience symptoms resolution within one year, up to 8.3% of them can still report C19OD after two years[515] and up to 7.9% after three years following SARS-CoV-2 infection.[516] Nevertheless, long-term recovery trajectory of C19OD is still unknown.

Giving the long-term impact of C19OD on quality of life, it is important to find a treatment able to restore sense of smell or at least capable to offer a meaningful improvement of patients' olfactory function. As already explained in *Chapter 2*, this is defined by the minimal clinically importance difference (MCID) which is the minimal improvement in the olfactory function required to denote a noticeable, and clinically important, change relevant to the patient. The concept of MCID becomes even more important when comparing different interventions. In fact, despite a study could have shown a statistically significant improvement in the olfactory score, this increase might have not reached the

MCID level and, therefore, changes obtained may not be meaningful for the patient. Choosing a treatment based on its ability to reach MCID would further support its use as clinically beneficial for the patient. MCID scores are currently available only for the most common olfactory tests, including S'S, SIT and B-SIT (*Table 2.1., Chapter 2*) and this luck of data can prevent comparison between treatments.

Table 6.5. compares changes in S'S olfactory scores according to the different treatments shown to have enough evidence to support their role in C19OD. From this direct comparison, it appears that only OT, PRP and fSRP improved olfaction meaningfully (i.e. reaching MCID threshold for TDI) while demonstrating a benefit over control.[178,533,547,584-587] However, only OT showed to improve olfactory threshold and identification scores above MCID as well.[533,584]

However, the main difference between these three treatments stands upon the length of OD of the patients included in the related studies. In fact, whether the average length of OD was <6 months for studies evaluating OT, this was 8.9 months for injected PRP and 6 years for fSRP. In fact, knowing a priori that a treatment might have different effectiveness depending on the duration of C19OD, may favour a treatment against another one based on the benefits this could offer to our specific category of subjects. Despite several studies have shown that OT is very effective for PIOD and, particularly, for C19OD, studies suggest this might be less effective for long-standing OD.[534] A recent meta-analysis conducted by Hwang et al.[534] confirmed a standard mean difference of 1.78 when comparing improvement of olfactory scores after OT in C19OD patients with an OD shorter vs longer than 1 month (p=0.02). Nevertheless, a recent study by Boscolo-Rizzo et al.[586] has shown benefits of OT in patients with an average length of OD of 9.4 months. To the best of my knowledge, effects of OT in patients with long-term (>1 year) C19OD have not been reported and my studies will bring new insights on this topic.

	Authors	Type of study	Type of control	Duration of OD	Follow-up period	Sniffin' Sticks				Benefit over control
						T	D	I	TDI	
Non-pharmacological										
Olfactory training	Schepens et al.[533] (2022)	DB-RCT	OT+OCS	2 months	3 months	**+3.0**	+2.0	+2.5	**+6.3**	No
	Lechien et al.[584] (2022)	QES	No treatment	4.4 months	18 months	-	-	**+6.9*****	-	Yes
	Yaylaci et al.[585] (2022)	QES	No treatment	5.8 months	3 months	+1.52***	+2.24***	+1.92***	**+5.68*****	Yes (T, D, TDI)
	Boscolo-Rizzo et al.[586] (2024)	QES	Not adherent to OT	9.4 months	4 months	+2.0	+2.4	+1.0	**+6.0**	Yes (TDI)
	Schepens et al.[587] (2024)	QES	No treatment	2 months	3 months	**+3.0**	+2.0	+1.0	**+6.0**	Yes (D, I, TDI)
Pharmacological										
PEA-LUT	De Luca et al.[540] (2022)	RCT	PEA-LUT+OT	8.4 months	3 months	N/A	N/A	N/A	+2.6*	No
	Di Stadio et al.[588] (2023)	RCT	OT	6.8 months	3 months	-	-	+2.9**	-	Yes
	Di Stadio et al.[589] (2023)	RCT (PEA-LUT+OT)	OT	8.8 months	3 months	-	-	+2.9***	-	Yes
Omega-3	Hernandez et al.[542] (2022)	RCT (Omega-3+OT)	OT	9.2 months	3 months	+1.8*	+2.2	+0.6	+4.7	Yes (T)
Intervention										
PRP	Yan et al.[547] (2023)	RCT	Saline	8.9 months	3 months	+1.82**	+2.82***	+1.53*	**+6.25*****	Yes (TDI, D)
fSRP	Whitcroft et al.[178] (2023)	QES		6 years	4 months	+1.78	+2.22	+2.44*	**+6.5***	**-**

Table 6.5. Sniffin' Sticks subtests improvement following treatment with proven efficacy (as per Table 2) for COVID-19-related olfactory dysfunction (C19OD). Only studies conducted on C19OD patients have been included apart from functional septorhinoplasty, which has been added to the table as relevant for this PhD thesis. To allow direct comparison, only studies that used Sniffin' Sticks as olfactory outcome measure have been considered. Where minimal clinically important difference (MCID) has been achieved, the value is marked in bold. For MCID values refer to *Table 2.1, Chapter 2*. Please note that the changes in score are changes withing group (i.e. before and after treatment) and not between groups (i.e. vs control).
Level of significance: * p<0.05; ** p<0.01, ***p<0.001.

D: discrimination; DB-RCT: double-blind randomised-controlled trial; fSRP: functional septorhinoplasty; I: identification; N/A: not available; OCS: oral corticosteroids; OD: olfactory dysfunction; OT: olfactory training; PEA-LUT: Palmitoylethanolamide and luteolin; PRP: platelet-rich plasma; QES: quasi-experimental studies (prospective controlled or non-controlled studies); RCT: randomised-controlled trial; T: threshold; TDI: threshold + discrimination + identification.

When looking at *Table 6.5.*, it could seem that PRP offers similar olfactory scores improvements to OT. However, Yan et al.[547] RCT demonstrated a statistically significant benefit in olfactory discrimination (+2.40 points, p=0.004) and TDI (+3.67 points, p=0.047) when compared to OT. Also, for PRP its effect in long-term C19OD (>1 year) are currently unknown. fSRP is today the only intervention that has been evaluated in patients with long-term OD. The study by Whitcroft et al.[178] included patients with the longest duration of OD (mean duration of 6 years) and showed a similarly high improvement in TDI, and above MCID, to that obtained by OT and PRP. However, it must be said that this study included patients with mixed cause of OD (idiopathic and PIOD) and was conducted before COVID-19; thus, results may not be strictly comparable to those reported in *Table 6.5*. Nevertheless, it is important to put this treatment in comparison with the others as it will give a background for the prospective-controlled study on fSRP I conducted on patients with long-term C19OD (*Section 6.15*).

Finally, the last parameter we should look at when choosing an appropriate treatment for C19OD is the olfactory ability that the intervention is more likely to improve. As it will be discussed and demonstrated in my studies, C19OD is primarily characterised by a peripheral damage of the OE which affects the olfactory threshold, as shown by S'S. Based on *Table 6.5.*, OT seems to be, so far, the only treatment able to achieve a meaningful improvement of olfactory threshold above MCID (≥2.5 points).[533,587] This point will be important when critically reviewing the results of my research.

6.8. Published studies on C19OD – hypotheses and aims

The first study[590] is a multicentre survey I conducted at the beginning of the pandemic in collaboration with the University of Padua. Here I aimed to investigate prevalence and early recovery (2 months) of C19OD in healthcare workers who caught COVID-19 whilst working in their hospitals during the pandemic outbreak. In this study I am also looking

at possible occupational risk factors and demographic differences influencing smell recovery.

The second study,[310] always conducted during the first wave of the pandemic, is a prospective longitudinal study and one of the first available in the literature in which loss of sense of smell had been investigated using psychophysical olfactory tests in addition to patient-reported outcomes. Here I looked at olfactory recovery rate of C19OD over a longer period (6 months). The possibility of running different S'S subtests gave me the opportunity to understand which olfactory ability was the most affected one following SARS-CoV-2 infection.

My third research[591] is a cohort study which looked at prevalence of reported OD in previously hospitalised COVID-19 patients (median time from infection was 9 months). Whilst looking at long-term prevalence of C19OD, this study also investigated QoL changes following loss of smell. Long-term (>1 year) QoL impairment following C19OD was the focus of my fourth study too.[592] This study offered the longest follow-up (14 months) available at that stage at which effects of C19OD on QoL had been measured using extended S'S.

The evidence that a good percentage of people were not recovering their sense of smell following SARS-CoV-2 infection even after 1 year, and developing a persistent C19OD, brought me to look into the clinical factors potentially influencing olfactory recovery. This, in fact, was the focus of my fifth study in which I analysed data collected on 100 patients I reviewed at the long-COVID smell clinic at the Royal National ENT.[425] The identification of clinical factors impacting on smell recovery and the isolation of specific categories of subjects more prone to develop a persistent OD, may have significant implications in terms of disease prevention but, more importantly, can feed future research on treatments options for PIOD.

Finally, I focused my attention on therapies to offer to patients with persistent long-standing C19OD. This led me to review currently available options and explore new promising treatments. As discussed in *Section 6.7.1.*, OT currently remains the only treatment showing strong evidence to suggest its use in PIOD. Corticosteroids represent one of the commonest drugs used to reduce inflammation which, in PIOD, may help in controlling OE local inflammation. Their use in C19OD is still debated as well as it is the best formulation to use (oral vs topical vs combination of both). In my sixth paper, I conducted a multicentre real-life cohort study to assess whether the addition of corticosteroids (oral plus topical) to OT could give a benefit in the treatment of persistent C19OD. The hypothesis is that the addition of corticosteroids to OT could help in reducing the OE inflammation, thus enhancing the effect of OT.

The last paper I wrote on C19OD is exploring a new potential intervention to restore sense of smell in this category of subjects. The evidence that up to 8% of subjects still presented a persistent C19OD at 3 years,[516] led me to look at other ways to improve long-standing OD. A pre-COVID study conducted by our research team, showed that fSRP could improve sense of smell in patients with long-standing OD (either idiopathic or post-infectious).[178] In this study, Whitcroft et al.[178] demonstrated that an improvement in nasal airflow was correlated with an improvement in olfaction, and more importantly in olfactory threshold, which is also the most affected olfactory abilities in C19OD. Therefore, I decided to conduct a prospective controlled study to evaluate olfactory changes in patients with persistent C19OD undergoing fSRP and compared to a control group of C19OD patients on OT with similar baseline characteristics. My hypothesis is that fSRP can increase nasal airflow in the olfactory cleft by augmenting the volume of the INV. This increased stimulation of the OE can then improve olfactory function.

Minor edits to manuscripts have been made following departmental guidelines to ensure these fit the overall style of the thesis. An introduction to the topic will follow to give a background to the studies conducted.

6.9. Olfactory and taste dysfunction among mild-to-moderate symptomatic COVID-19 positive healthcare workers: an international survey[590]

6.9.1. Introduction

Healthcare workers (HCWs) have been identified as a high-risk group to acquire COVID-19.[593] In Europe HCWs account for 10.7% (Italy) to 30.5% [United Kingdom (UK)] of the total number of COVID-19 positive cases.[594,595] A different figure was released by the International Council of Nurses based on data acquired from 30 countries reporting that, on average, 6% of all confirmed cases of COVID-19 were among HCWs.[596] Similarly, an Indian questionnaire-based survey found that only 1.8% (20/1113) of the HCWs tested were positive for the virus.[597] The specific job role of COVID-19 HCWs is also potentially relevant with a higher prevalence in doctors (43.9%) and nurses/health care assistants (HCA) (41%).[598] Particularly, otolaryngologists and intensive care/anesthetists have demonstrated a higher risk of contracting COVID-19 owing to their higher viral load exposure.[599]

The World Health Organization has included 'loss of smell' and 'taste' amongst the less common symptoms of COVID-19 infection.[600] Nonetheless, the estimated prevalence of olfactory and taste dysfunction (OD, TD) amongst COVID-19 subjects in the general population is as high as 38.5% and 30.4% respectively.[601] Because of the work-related risks, HCWs are exposed daily to higher viral load which may lead to a different expression of the chemosensory disorders, both in terms of prevalence, severity and/or recovery rate. In a survey conducted by the American Academy of Otolaryngology–Head and Neck Surgery, 1/3 of COVID-19 positive patients with anosmia were HCWs.[602] Moreover, Lan et al. found that anosmia/ageusia was reported by 15.7% (13/83) of COVID-19 positive HCWs in the US.[603] In a more recent American study a higher percentage of positive HCWs reported anosmia or ageusia, respectively 51% (26/51) and 53% (27/51).[604]

The true prevalence in Europe remains unknown. According to available data between 14.4% (20/139) and 79% (77/97) of the adult COVID-19 positive patients reporting OD and TD were HCWs.[593,598,605] A very recent Belgian study found that almost 40% (62/156) of positive HCWs self-reported loss of sense of smell/taste[605] while a Danish study conducted on a bigger sample found that loss of sense of smell or taste was reported by 32.4% (377/1163) of the tested positive HCWs[606]. Smaller European case series (less than 6 subjects) on OD and TD amongst HCWs are also available but inconclusive.[607-609] In the UK the prevalence of OD and TD amongst COVID-19 positive HCWs is unknown. Moreover, the risk factors and prognosis for OD and TD amongst HCWs are mostly unknown.

The aim of this study is to determine the prevalence of OD and TD amongst COVID-19 positive HCWs in the UK and ascertain risk factors and prognosis in two European hospitals [London (UK) and Padua (Italy)] which have been significantly affected by COVID-19.

6.9.2. Materials and methods

This study was conducted in accordance with the 1996 Helsinki Declaration and approved by the research ethic committee (IRAS project ID: 156511), the UCL joint research office and the Padua Otolaryngology Section's in-house ethical committee. All respondents were invited to take part in this survey via email which included a study information pack and consent form with a cooling off period.

Setting of the survey

Between May 26 and June 10, 2020 an international multicenter survey on sense of smell and taste dysfunction in mild-to-moderate symptomatic COVID-19 positive HCWs, defined as home-managed subjects with symptoms that did not require an intensive care or other hospital admissions, was conducted at the Whittington Hospital (London, UK)

and the Hospital of Padua (Padua, Italy). The survey questionnaire was validated locally and nationally by both ENT and infection clinicians as well as patient advocates to ensure clarity and to exclude ambiguity. In the UK the survey was performed via Survey Monkey (San Mateo, California) and emailed to all COVID-19 positive HCWs. The questionnaire was translated into Italian and equally validated and administered by hand in Padua.

Inclusion criteria were age >18 years old, laboratory confirmation of SARS-CoV2 infection [by reverse transcription polymerase chain reaction (RT-PCR)], good comprehension of the language used in the questionnaire and absence of any clinical impairment to fulfil the questionnaire. Participants with a past history of OD and/or TD or those admitted to hospital at the moment of the survey were excluded from the study. Informed consent was obtained from each participant before starting any study-related procedure.

Population and data collection

The recipients of this survey were mild-to-moderate symptomatic HCWs who tested positive by RT-PCR for SARS-CoV2 and were working at their own hospital during COVID-19 pandemic. Participants were selected using the databases of the Microbiology Laboratory in London and the Infectious Disease Department in Padua. Data were collected anonymously mainly on olfactory and gustatory disorders presentation, type of onset and recovery status, while the presence of other systemic symptoms has not been investigated. Demographic data including age, sex, ethnicity, job role and department of origin were also collected for all the participants in order to investigate any potential influence.

Statistical analysis

Quantitative variables were summarized using median and interquartile range (P25–P75) while qualitative variables were described with frequency and percentage. Missing values (i.e. people who did not answer the question) were not considered in the

calculation of percentages (valid percent). However, unanswered items have been reported in the tables.

Survival analysis was implemented to study recovery time from onset of both sense of smell and taste. Participants that had not recovered at the date of questionnaire administration were considered as censored, with censor time described as the number of days since the onset of the symptom up to the day of the questionnaire. Survival curves have been estimated with Kaplan-Meier estimator, log-rank tests have been performed to compare subpopulations and Cox proportional hazard model has been fitted to model the joint effect of all available variables on the recovery time. The best model has been chosen by stepwise selection based on Akaike Information Criterion (AIC). Likelihood ratio tests have been used to test comparisons between means and proportions, and Pearson chi-square test with Yates correction to compare categorical variables.

6.9.3. Results

Response rate

One hundred and fifty-five HCWs, 119 from London and 36 from Padua received the questionnaire. The different method of questionnaire administration led to a different response rate of 70.6% (84/119) in London and of 100% (36/36) in Padua.

Population characteristics

After further analysis, we excluded 2 participants who did not accept the consent form and 4 participants who did not answer any question, leading to a final population of 114 HCWs who completed the survey. The total population was composed of 28 men and 86 women (male to female ratio approximately of 1:3), ranging from 23 to 65 years, with a median age of 38 years. Most of the HCWs were white (62; 81.6%), worked on COVID-19 wards (59; 53.2%) and were either nurses/HCA (43.7%) or doctors (39.3%). A significant difference in the composition of participants at the two hospitals was observed according to ethnicity ($p<0.00001$) and department of origin ($p=0.00035$) whereas they were similar in terms of age ($p=0.72$), sex ratio ($p=1$) and job role ($p=0.067$). Detailed characteristics of the population at each institution are reported in Table 1.

	Combined *(n=114)*	London *(n=78)*	Padua *(n=36)*	Difference between London and Padua *p*-value
Age, median [P25-P75], yr	38 [29.5-48]	39 [32-47]	39 [27.5-52]	$p = 0.72$
Sex, No (%)				
Female	86 (75.4%)	59 (75.6%)	27 (75.0%)	$p = 1$
Male	28 (24.6%)	19 (24.4%)	9 (25.0%)	
Ethnicity, No (%)†				
White	62 (81.6%)	26 (65.0%)	36 (100.0%)	
Asian	12 (15.8%)	12 (30.0%)	0 (0.0%)	
Black/African/Caribbean	1 (1.3%)	1 (2.5%)	0 (0.0%)	***p < 0.00001****
Mixed/multiple ethnic groups	1 (1.3%)	1 (2.5%)	0 (0.0%)	
Missing	38	38	0	
Role, No (%)†				
Nurse/HCA	49 (43.7%)	32 (41.0%)	17 (50.0%)	
Doctor	44 (39.3%)	29 (37.2%)	15 (44.1%)	p = 0.067
Allied health professional	16 (14.3%)	14 (18.0%)	2 (5.9%)	
Non-clinical role	3 (2.7%)	3 (3.8%)	0 (0.0%)	
Missing	2	0	2	
Department of origin, No (%)†				
COVID-19 ward	59 (53.2%)	51 (65.4%)	8 (24.2%)	
Non-COVID-19 ward	47 (42.3%)	24 (30.8%)	23 (69.7%)	***p = 0.00035****
Office/laboratory	5 (4.5%)	3 (3.8%)	2 (6.1%)	
Missing	3	0	3	
Type of disfunction reported, No (%)				
Olfactory dysfunction	N/A	57 (73.1%)	N/A	N/A
Taste dysfunction		54 (69.2%)		
Both		48 (61.5%)		
OD characteristics, No (%)†				
First symptom	19 (21.6%)	10 (18.9%)	9 (25.7%)	$p = 0.62$
Only symptom‡	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Onset				
Sudden	69 (78.4%)	42 (79.2%)	27 (77.1%)	$p = 1$
Progressive	19 (21.6%)	11 (20.8%)	8 (22.9%)	
Missing	5	4	1	
TD characteristics, No (%)†				
First symptom	14 (16.1%)	6 (11.3%)	8 (23.5%)	$p = 0.23$
Only symptom	1 (1.1%)	1 (1.9%)	0 (0.0%)	-
Onset				
Sudden	65 (74.7%)	42 (79.2%)	23 (67.6%)	
Progressive	22 (25.3%)	11 (20.8%)	11 (32.4%)	$p = 0.34$
Missing	7	5	2	
Dysgeusia§	30 (65.2%)	9 (39.1%)	21 (91.3%)	***p = 0.002****

Table 1. Detailed characteristics of the populations. p-values indicate differences in the distribution between the two Institutions.

* Significant p-values. Level of significance $p < 0.05$. † Valid percent, not including missing values ‡ Please note that in 7 subjects (7.5%) olfactory dysfunction was associated to taste dysfunction alone. §Dysgeusia has been calculated only considering those subjects who reported hypogeusia or ageusia at the moment of questionnaire administration (n=46).

N/A: Not Applicable. Not possible because prevalence not performed in Padua

Olfactory and taste subjective dysfunction characteristics

The prevalence of reported olfactory and taste alteration was 73.1% and 69.2% respectively in London HCWs. Prevalence was not obtained in the Paduan population due to the fact that questionnaire was administered only to HCWs with a reported smell impairment.

In the total study population, among the 93 HCWs who experienced OD, this was the first symptom in 19 participants (21.6%), but none of them reported this to be the only COVID-19 related symptom. Additionally, only 8 of those who reported OD as a first symptom (8/19) also complained of nasal obstruction. In 7 participants (7.5%) it was associated with TD and these were the only symptoms experienced during their COVID-19 illness. The onset of OD was reported to be sudden by 69 participants (78.4%), while it was progressive in 19 of them (21.6%).

Similarly, among the 94 HCWs who had TD during their illness this was the first symptom in 14 of them (16.1%) and was the only one experienced in 1 participant (1.1%). Deterioration of sense of taste was described as sudden by 65 HCWs (74.7%) and as progressive by 22 of them (25.3%). Dysgeusia (distortion of sense of taste) was reported by 30 participants (65.2%). Apart from dysgeusia which was significantly more prevalent among Paduans (p=0.002), no differences were observed in terms of presentation (first symptom, only symptom and type of onset) between the two Hospitals. Detailed characteristics of smell and taste dysfunction amongst healthcare workers according to Institution are reported in Table 1.

Prognosis of smell and taste dysfunction

At 52 days follow-up, 28 HCWs (31.8%) reported that OD had completely recovered while the majority of them (49; 55.7%) reported that their sense of smell had improved but was still lower than before (hyposmia). It was still absent (anosmia) in 11 participants (12.5%) (Table 2). None of the subjects had started any specific treatment for the OD.

With regards to sense of taste, 41 HCWs (47.1%) reported that TD had completely recovered at the time of the questionnaire administration. Thirty-eight participants (43.7%), still reported a lower sense of taste (hypogeusia) while it was still absent (ageusia) in 8 participants (9.2%) (Table 3). No significant differences were noted between the two institutions. The median time for the recovery start as well as the median time to questionnaire administration for both smell and taste are reported in Table 2 and 3.

Influence of available variables on olfactory and taste dysfunction prognosis

Considering the whole population, certain job roles negatively influenced the time to recovery both for sense of smell (doctor p=0.04; nurse/HCA p=0.02) and taste (doctor p=0.02; nurse/HCA p=0.01) (Figure 1; Table 4) In addition, following multiple regression analysis, ethnicity (being white) was shown to positively influence sense of taste recovery time (p=0.036) but not for sense of smell (p=0.5) (Table 4). Conversely, no influence on smell and taste recovery was observed when considering age, sex, department of origin, presentation as first symptom or only symptom and type of onset (Figure 1; Table 4).

Analyzing the results from the two hospitals individually, the prognosis of OD among Paduans was negatively influenced by female sex (p=0.02). Following multiple regression analysis, female sex was shown to negatively influence TD recovery as well. Conversely, in London, job role (Nurse/HCA) influenced OD and TD (p=0.002 and p=0.02 respectively). Following multiple regression analysis, ethnicity (being white) was also shown to positively influence sense of taste recovery time (p=0.022) (Table 4).

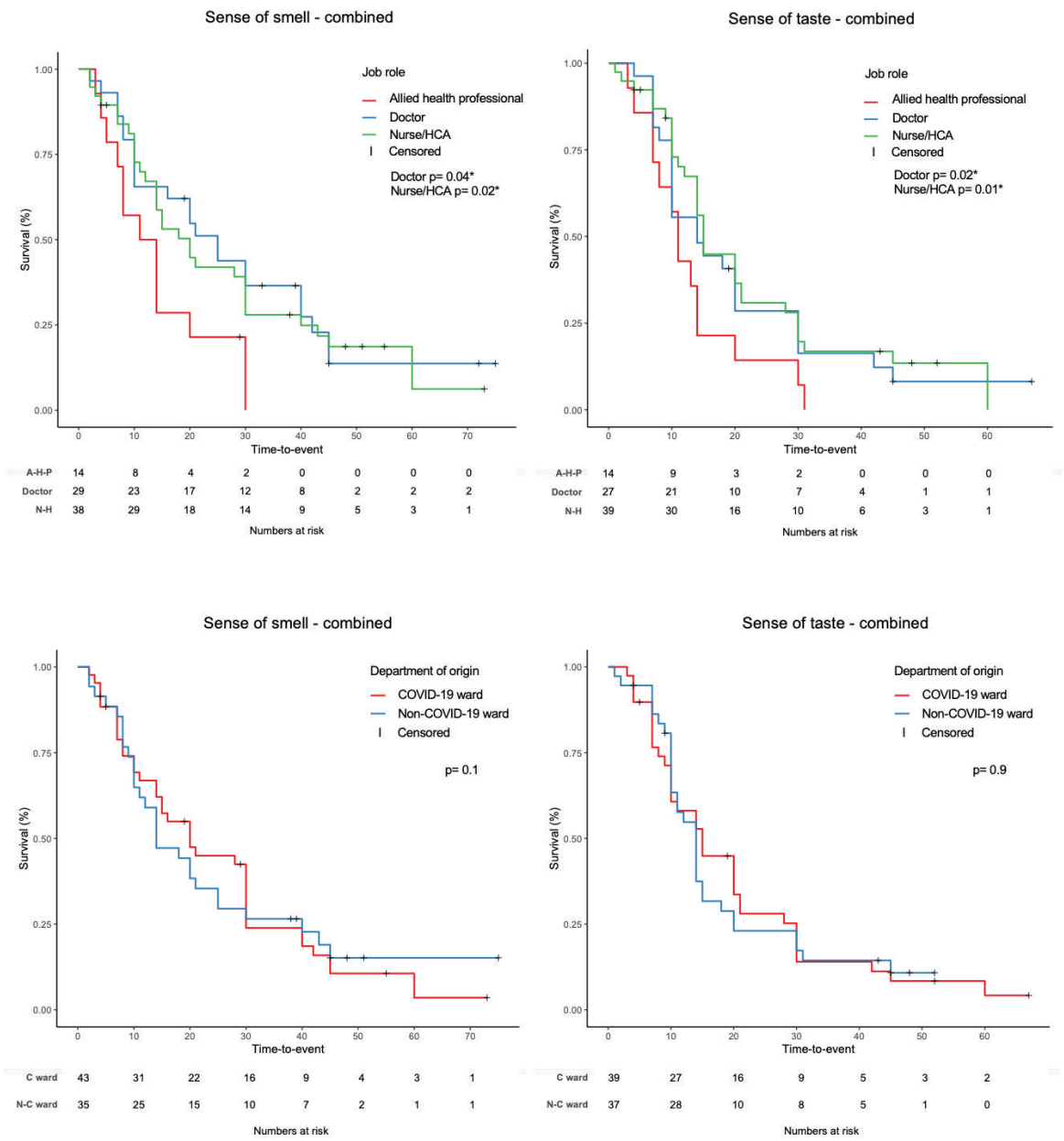

Figure 1. Kaplan-Meier survival curves for smell and taste recovery time according to job role (*upper left and right*) and to department of origin (*lower left and right*).

AHP: allied health professional; NH: nurse/healthcare assistants; HCA: healthcare assistants
C ward: COVID-19 ward; N-C ward: Non-COVID-19 ward

	Sense of Smell											
	N (%)			Time to OD onset Median [P25-P75], days			Time for recovery to start† Median [P25-P75], days			Time to questionnaire administration‡ Median [P25-P75], days		
	Combined	London	Padua	Combined	London	Padua	Combined	London	Padua	Combined	London	Padua
Recovered	28 (31.8%)	22 (41.5%)	6 (17.1%)	4 [2-5]	4 [2-5]	2.5 [1.3-8.3]	10 [7-14.5]	12 [7-14.8]	8 [6-17]	52.5 [47.3-62.8]	53 [49.8-63.8]	24 [13.8-65.3]
Still hyposmia	49 (55.7%)	28 (52.8%)	21 (60.0%)	4 [2-6]	4.5 [3-6.8]	3 [2-5]	20 [10-30]	21 [15.5-40]	10 [7.5-22.5]	51 [35-62]	54 [50-64.3]	35 [22-62.5]
Not recovered	11 (12.5%)	3 (5.7%)	8 (22.9%)	3 [1-5.75]	3 [1-8.5]	3 [1-5]	N/A	N/A	N/A	41 [24.5-54.5]	56 [53-66]	34.5 [12.3-45.5]

Table 2. Time for sense of smell recovery in the three subgroups of subjects who experienced smell dysfunction.
N/A: Not Applicable. Not possible to calculate considering that sense of smell in these subjects has not started to recover.
† Time for the recovery to begin after first symptom onset.
‡ Interval of time between first symptom onset and questionnaire administration.

OD: olfactory dysfunction.

	Sense of Taste											
	N (%)			Time to TD onset Median [P25-P75], days			Time for recovery to start† Median [P25-P75], days			Time to questionnaire administration‡ Median [P25-P75], days		
	Combined	London	Padua	Combined	London	Padua	Combined	London	Padua	Combined	London	Padua
Recovered	41 (47.1%)	30 (56.6%)	11 (32.4%)	4 [2-5]	4 [2-5.3]	2 [1.5-6]	10 [8-18]	12.5 [7.3-15]	10 [9-20]	53 [47-63]	53.5 [48.8-65.3]	47 [24-63]
Still hypogeusia	38 (43.7%)	20 (37.7%)	18 (52.9%)	4.5 [2-6]	5 [2.8-7]	3 [2-5]	15 [10-30]	20 [11-30.5]	14 [9.3-20]	51.5 [34-62]	53 [50-61.5]	34.5 [28.8-64]
Not recovered	8 (9.2%)	3 (5.7%)	5 (14.7%)	3 [2-5]	3 [2-4.5]	3 [2-4.8]	N/A	N/A	N/A	33 [10.3-52.8]	54 [49-62]	11 [9-33]

Table 3. Time for sense of taste recovery in the three subgroups of subjects who experienced taste dysfunction.
N/A: Not Applicable. Not possible to calculate considering that sense of taste in these subjects has not started to recover.
† Time for the recovery to begin after first symptom onset.
‡ Interval of time between first symptom onset and questionnaire administration

TD: taste dysfunction

	Sense of smell prognosis			Sense of taste prognosis		
	Combined	**London**	**Padua**	**Combined**	**London**	**Padua**
Age	p = 0.9	p = 0.5	p = 0.6	p = 0.1	p = 0.4	p = 0.3
Sex	p = 0.9	p = 0.06	***p = 0.02****	p = 0.9	p = 0.3	p = 0.1 (***p = 0.011**** at multiple regression)
Ethnicity	p = 0.5	p = 0.2	..	p = 0.09 (***p = 0.036**** at multiple regression)	p = 0.06 (***p = 0.022**** at multiple regression)	..
Role	***p = 0.04* (Doctor)*** ***p = 0.02* (Nurse/HCA)***	p = 0.0566 (Doctor) ***p = 0.002*(Nurse/HCA)***	p = 0.8 (Doctor) p = 0.6 (Nurse/HCA)	***p = 0.02* (Doctor)*** ***p = 0.01* (Nurse/HCA)***	p = 0.204 (Doctor) ***p = 0.02* (Nurse/HCA)***	p = 0.391 (Doctor) p = 0.733 (Nurse/HCA)
Department	p = 0.1	p = 0.9	p = 0.2	p = 0.9	p = 1	p = 0.7
First Symptom	p = 0.6	p = 0.9	p = 0.7	p = 0.6	p = 0.7	p = 0.9
Only Symptom	p = 0.9	p = 0.9	p = 1	p = 0.4	p = 0.2	p = 0.9
Type of onset	p = 0.9	p = 0.8	p = 0.8	p = 0.2	p = 0.4	p = 0.4

Table 4. Influence of available variables on recovery rate in the population of healthcare workers who experienced smell and/or taste dysfunction.
* Significant p-values. Level of significance p < 0.05.

HCA: healthcare assistants

6.9.4. Discussion

To the best of our knowledge, our study represents the first International multicentric European survey evaluating olfactory and taste dysfunction on COVID-19 positive HCWs with a response rate higher than 70%.

In the UK, the prevalence of both OD and TD amongst our COVID-19 positive HCWs was 73.1% and 69.2% respectively. These rates are significantly higher than those found within the general population (38.5% and 30.4% respectively, according to a recent meta-analysis)[601] and equally considerably higher when compared to HCW prevalence rates in the US[603,604] or in other European countries[605,606]. In addition, a higher rate of dysgeusia was particularly highlighted in our European cohort which had not been previously described. The higher prevalence rates of both olfactory and taste disturbance are unexpected when compared to current published data within the general population. One proposed explanation is that HCWs are more prone to OD and TD because they have a higher exposure to Sars-CoV-2 viral load within their place of work[598]. An alternative explanation for the higher prevalence rates amongst HCWs in our study is a consequence of the higher sensitivity of our survey whereby milder cases of OD and TD are being captured. In addition, all our HCWs were assessed from the time of their diagnosis and then studied longitudinally over a median of 52 days from COVID-19 symptom onset. This enabled us to evaluate the whole of their COVID-19 journey and not just at a single point in time and avoids missing OD and TD before it even started.

Previous studies conducted in Europe on OD and TD amongst COVID-19 HCWs[598,605,606] have focused more on general COVID-19 symptoms with only rudimentary smell and taste dysfunction evaluation and/or not exploring patients with very mild symptoms which may explain why their prevalence rates are lower than ours. Patients with milder OD have been shown to be unaware of their symptoms and therefore less likely to report a problem.[441] A responder bias also needs to be considered. It is possible that those with

OD and TD were more likely to respond to the questionnaire; however, this is unlikely given that our response rate was over 70%.

The presentation of OD and TD, in terms of smell and taste onset (sudden/progressive and first/only), in our population of HCWs seemed to be similar to that seen in the general population. In our study OD and TD occurred suddenly (78.4% and 74.7% respectively) at a median time of 4 days which is similar to the general population.[610-612] Similarly, smell and taste impairment presented as the first symptom in 21.6% and 16.1% respectively, in line with previous surveys on the general population.[448,602,612] None of our respondents described loss of sense of smell as an isolated symptom, but in 7 participants (7.5%) OD and TD were their only COVID-19 symptoms. This percentage is similar to another Italian study.[448] Conversely, a previous survey on 2428 subjects with new-onset anosmia showed that 17% reported OD as an isolated symptom;[451] however, this finding was not confirmed by our results.

Our results also showed a higher prevalence of OD and TD amongst COVID-19 positive doctors and nurses/HCA as compared to other HCWs, which reflects previous Italian findings.[164,598] More importantly, we observed that HCW's job role negatively influenced prognosis and their time to recovery both for sense of smell (doctor p=0.04; nurse/HCA p=0.02) and taste (doctor p=0.02; nurse/HCA p=0.01) (Figure 1, Table 4) with implications to change future behavior in order to mitigate this risk.

Notably, we did not observe that the department of work influenced prognosis of OD (p=0.1) and TD (p=0.9) (Figure 1) which potentially confirms the effectiveness of preventative measures in higher risk departments. In support of our results, Wang et al. also found that the majority of the infected HCWs in Wuhan had worked on the general wards (77.5%), with a lower prevalence in the emergency department (17.5%) and ICU (5%).[613]

According to our findings, ethnicity appears to affect prognosis. We demonstrated that prognosis was significantly more favorable in white HCWs but only for TD (p=0.036) (Table 4) and this novel finding has not been previously described in COVID-19 patients.

However, it corroborates what had been reported by Doty, prior to the COVID-19 pandemic, that being an ethnic minority represents a risk factor for OD.[434] Overall, white and Asian subjects were the most widely affected group amongst our HCW population which is similar to previous reports showing OD and TD being three times more common in Caucasians compared to East Asians.[601]

In our population 75.4% of the HCWs who experienced OD and/or TD were female with a median age of 38 years which confirms previous findings that COVID-19 related OD disproportionately affects the younger generation[434,605,614,615] and the female sex[615]. We also demonstrated that female HCWs in the Paduan population showed a worse prognosis for OD and TD. However, this finding was not confirmed when considering the total study population and therefore it could be related to a bias in the composition of the Paduan sample. Age did not demonstrate an influence on smell or taste recovery time.

The true prognosis of OD and TD amongst COVID-19 HCWs is not known because the follow-up time to date has been too short to draw reasonable conclusions. We have found that the sense of smell and taste started to improve spontaneously on average after a median time of 15 days from onset of symptoms. (Figure 2 left; Table 2,3)

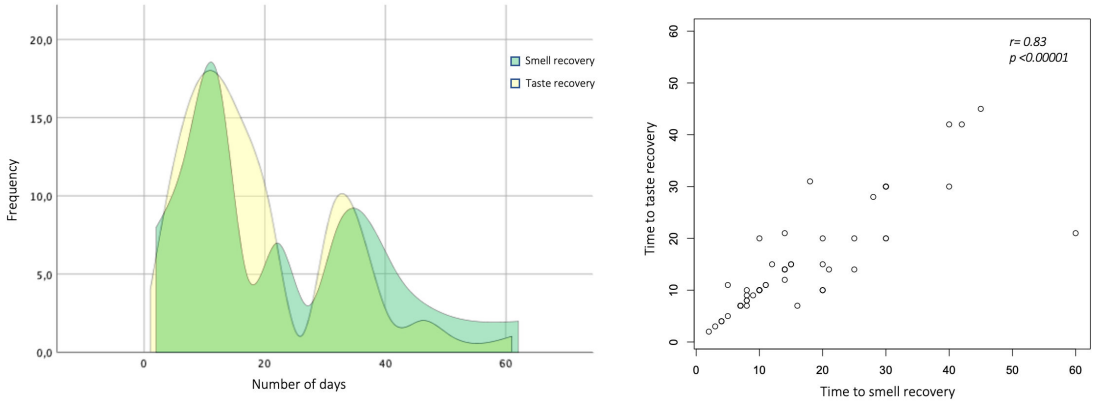

Figure 2. Frequency polygon *(left)* and scatter plot *(right)* showing time to smell and taste recovery.

We observed a bimodal trend in recovery for sense of taste with two identifiable peaks roughly at 15 and 30 days (Figure 2 left – yellow area); conversely, this was not evident

for smell recovery where at least another peak at 22 days was recognized (Figure 2 left – green area). Early spontaneous recovery of sense of smell may indicate a conductive cause for COVID-19 OD, as it has been reported that olfactory disorders may last 3 to 4 weeks after clinical onset, or longer, in case of damage of the olfactory epithelium (i.e. support cell, stem cell and perivascular cell of the olfactory epithelium).[616] Moreover, the infection of basal cells could block or slow down sensory cell turnover which normally lasts 28 to 30 days,[617] justifying the longer recovery period observed in some subjects. On this regard, it has been reported that in non-COVID-19 post-viral anosmia more than 80% of the patients may experience a subjective improvement of OD after a follow-up period of one year whereas only 30% would experience a spontaneous recovery in the same period of time.[508]

Additionally, it must be noted that smell and taste recovery correlated each other in our population ($r=0.83$; $p<0.00001$) confirming that TD is caused by an impairment of the retronasal olfaction, rather than impaired gustation itself (Figure 2 right).[618]

Complete recovery was reported within a median time of 52 days in 31.8% (OD) and 47.1% (TD) of HCWs. Unfortunately, OD and TD was still present in 68.2% and 52.9% of our respective subjects. (Table 2,3) The recovery rates observed in our COVID-19 HCW population are considerably higher when compared to the general population[614,615] and in previous studies of HCWs[593,602]. However, a similar rate of complete resolution of smell or taste impairment (48.7%) has been recently reported by Boscolo-Rizzo et al. at a follow-up of 4 weeks.[619] Therefore, the higher recovery rates we observed can be explained by our larger sample size and longer follow-up period over 52 days.

Considering the huge number of people infected in this pandemic and the significant proportion with long-lasting OD and TD (up to 70%), there will be a need for additional capacity to offer treatment for smell and taste impairment in the post-COVID-19 recovery phase. As a consequence of increased media coverage, the number of patients coming to otolaryngology clinics is also expected to be higher than normal. In addition to current

available therapies for OD,[618] there is a need to embrace new therapies exploring damaged neurons regeneration[38,620].

Strengths and limitations of the study

To our knowledge, this is the first multi-site European study to evaluate risk and prognosis of OD and TD amongst COVID-19 positive HCWs. A study limitation was the inability to calculate OD and TD prevalence in the Paduan population due to the fact that questionnaire was only administered to HCWs with smell impairment. A possible bias in the composition of the samples in terms of sex and ethnicity, may have influenced our findings. Additionally, HCWs have been included within previous studies of the general population. This may have inflated the rates of OD and TD observed in these studies and thus distorted our comparison between healthcare workers, and all other members of the general population. Finally, as most of the currently available studies on COVID-19, OD and TD diagnosis was based on self-reported symptoms which can have added a potential bias considering the low correlation between objective and self-rating olfactory loss.[621] However, even if it were possible that subjects not reporting smell or taste dysfunction may have a degree of impairment, it is also true that those complaining of smell and/or taste loss more than likely will have an impairment in the chemosensory function.

On this regard, our results may have underestimated the real prevalence of OD and TD among HCWs. Validated olfactory and gustatory tests should be encouraged in future studies as soon as the condition will allow it.

6.9.5. Conclusions

This study is the first to demonstrate that the UK prevalence of OD and TD amongst COVID-19 positive HCWs was respectively 73.1% and 69.2% which is unexpectantly

high when compared to previous published results in the general and HCW populations. This study has demonstrated that nurses/HCAs and doctors have a worse prognosis in OD and TD recovery. Interestingly, working on a COVID-19 ward did not influence prognosis confirming preventive measures are effective. Ethnicity (being white) positively influenced only taste recovery. Importantly, up to 68% of the surveyed HCWs continued to experience OD or TD after 52 days and this will require an increase in treatment capacity if spontaneous improvement does not occur in medium to long term.

6.10. Comparison of self-reported symptoms and psychophysical tests in COVID-19 subjects experiencing long-term olfactory dysfunction: a 6-month follow-up study[310]

6.10.1. Introduction

Since the novel severe acute respiratory syndrome coronavirus- 2 (SARS-CoV-2) emerged in Wuhan, China, coronavirus disease 2019 (COVID-19) has rapidly spread worldwide leading to the current pandemic.[622] Olfactory and taste dysfunction (OD, TD) have been included among the most frequent reported symptoms, with a prevalence reported to be 47.85%.[438] Studies published on COVID-19–related OD have mainly assessed smell loss using patient-reported outcome measures (PROMs) such as the visual analogue scale (VAS) and the 22-item Sino-Nasal Outcome Test (SNOT-22).[622] However, self-reported OD poorly correlates with olfactory tests such as Sniffin' Sticks (S'S).[623] The aim of this study is to provide a prospective long-term assessment of COVID-19–related OD using PROMs[609] and S'S[624] and to investigate their correlation.

6.10.2. Methods

Patients with laboratory-confirmed SARS-CoV-2 infection and OD/TD were selected from our Infectious Disease Department database and asked to complete the SNOT- 22 and VAS for smell and taste (sVAS, tVAS: 0 represents "absent" and 10 "not affected"). Exclusion criteria included previous history of OD/TD, head and neck tumours, chemo/radiotherapy, head trauma, chronic rhinosinusitis and neurologic diseases. The study was approved by the Hospital Research Ethics Committee Protocol 056881. After disease recovery, patients who completed the initial screening (T_0) were invited to undergo S'S evaluation (T_1), regardless of their reported olfactory function. SNOT-22 and s/tVAS were repeated. Patients with a confirmed OD at T_1 S'S had a second evaluation

(T_2) roughly 6 months after their first assessment. Paired t-test was used for statistical analysis except for sVAS and tVAS, for which the exact Wilcoxon signed rank test was used. Spearman correlation coefficient was chosen to measure the relationship between the different indicators.

6.10.3. Results

A cohort of 101 consecutive COVID-19 subjects complaining of chemosensory alteration completed the s/tVAS and the SNOT-22 within one week of COVID-19 diagnosis (T_0) (*Table 1*). Eighty-one patients underwent further evaluation with S'S at T_1 (median time 62 days [range, 41–165 days] from diagnosis). Looking at the individual S'S subscores (threshold, discrimination, and identification [TDI]), the percentage of patients below normal were 44%, 41%, 38%, respectively, with the threshold being the most compromised (*Figure 1; Table 1*), whereas the composite TDI S'S score was below normal in 55.6% of patients. At T_1 both sVAS and tVAS showed a significant improvement when compared to T_0 ($p < 0.0001$, for both) and a statistically significant moderate correlation between sVAS and TDI score was demonstrated ($r=0.42$, $p=0.0009$). About 55% (25/45) of the S'S hyposmic patients "self-reported" their olfaction as being recovered, whereas only 72.2% (26/36) of the S'S normosmics reported their smell as normal. Twenty-two patients with a confirmed S'S OD at T_1 received a further smell evaluation 6 months later (T_2 – median time, 230 days [range, 213–252] from diagnosis). Looking at the S'S subscores separately, only the discrimination and identification scores significantly improved when compared to T_1 scores. At T_2, only sVAS demonstrated a significant improvement with respect to T_1 ($p = 0.0394$), whereas neither SNOT-22 nor tVAS changed significantly (*Figure 1; Table 1*). Similarly, a statistically significant correlation was not found between T_2 sVAS and TDI scores ($r = 0.15$, $p = 0.5$). At T_2, 81.8% of normosmics "self-reported" their olfaction as recovered, whereas 72.7% of hyposmics reported smell as recovered.

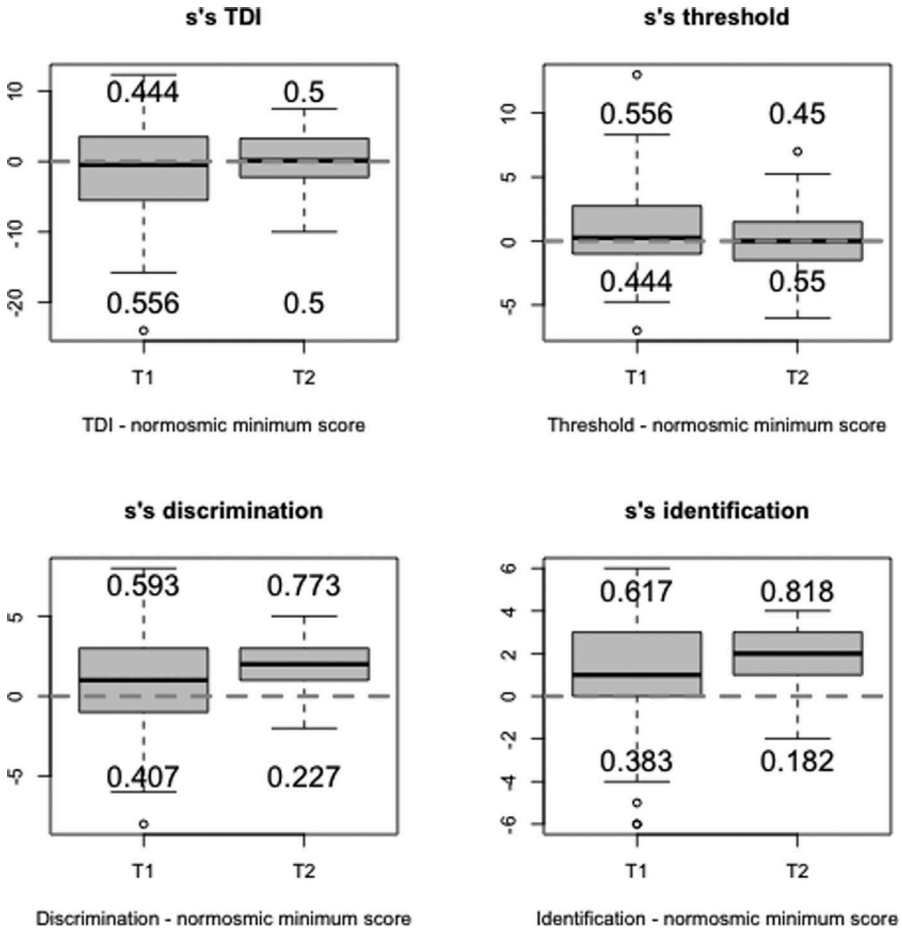

Figure 1. Box-plots showing the distributions of the differences between patients' scores (TDI) and the normosmic minimum score (10th percentile of the distribution of the scores for normosmic)[112] at T_1 and T_2. The numbers indicate the proportion (decimals) of subjects with normal scores (above the dotted line) and with pathological scores (below the dotted line). Dotted line: Normosmic minimum score.

S'S: Sniffin' Sticks; T_1: first psychophysical olfactory test; T_2: second psychophysical olfactory test. TDI, threshold, discrimination, and identification.

Parameter	T_0 ($n = 101$)	T_1 ($n = 83$)	T_2 ($n = 22$)	p T_0 versus T_1[a]	p T_1 versus T_2[a]
sVAS, mean ± SD	2.33 ± 3.18	6.35 ± 3.05	7.20 ± 2.71	**<0.0001**	**0.0394**
tVAS, mean ± SD	3.31 ± 3.46	7.39 ± 2.63	8.30 ± 1.90	**<0.0001**	0.1614
SNOT-22, mean ± SD	41.73 ± 18.24	16.12 ± 13.86	15.09 ± 11.74	**<0.0001**	0.1262
NS SNOT-22, mean ± SD	7.62 ± 5.46	2.76 ± 4.06	2.60 ± 3.99	**<0.0001**	0.1819
Threshold (T), mean ± SD	–	5.90 ± 3.10	5.68 ± 2.71	–	0.0557
Discrimination (D), mean ± SD	–	11.20 ± 2.90	12.18 ± 1.53	–	**0.0009**
Identification (I), mean ± SD	–	11.50 ± 2.40	12.59 ± 1.44	–	**0.0034**
TDI score, mean ± SD	–	28.50 ± 6.50	30.34 ± 4.27	–	**<0.0001**
Normosmic, *n* (%)	–	36 (43.4)	11 (50.0)	–	–
Hyposmic, *n* (%)	–	45 (54.2)	11 (50.0)	–	–
Anosmic, *n* (%)	–	2 (2.4)	0 (0.0)	–	–

Table 1. PROMs, Sniffin' Sticks scores,[112] and percentage of normosmic, hyposmic, and anosmic patients at T_0, T_1, and T_2.

Notes: sVAS/tVAS score range: 0 = the worst thinkable situation, 10 = not affected. NS SNOT-22 items: (1) need to blow nose, (2) sneezing, (3) runny nose, (4) postnasal discharge, (5) thick nasal discharge, and (6) blockage/congestion of nose. TDI score: threshold + discrimination + identification.

NS SNOT-22, SNOT-22 nasal symptoms items without considering those related to smell and taste dysfunctions; PROM, patient-reported outcome measure; SD, standard deviation; SNOT-22, 22-item Sino-Nasal Outcome Test; VAS, visual analogue scale; sVAS, VAS for smell; tVAS, VAS for taste; T_0, subjects' enrollment; T_1, first olfactory evaluation; T_2, second olfactory evaluation.
[a]Significant *p* values are in bold. Level of significance $p < 0.05$.

6.10.4. Discussion

Current evidence shows that OD is an early marker of COVID-19 and one of the best predictors of SARS-CoV-2 infection. Our COVID-19 study provides a prospective long-term evaluation of OD using both PROMs and S'S. At the first olfactory evaluation (T_1), 55.6% of the patients were found to be hypo/anosmic according to the TDI score. Interestingly, when we looked at the S'S subscores separately, we observed that a lower percentage of them showed below-normal scores. This highlights the importance of subanalysis when evaluating smell function using S'S because the sole use of identification tests for screening may underestimate the real prevalence of olfactory loss. Moreover, we found that at T_2 only the discrimination and identification scores improved significantly when compared to T_1, indicating that the odour threshold is affected long-term.

A significant improvement in the self-reported olfactory and taste loss was shown between T_0 and T_1, whereas only sVAS improved significantly at T_2 when compared to T_1. The absence of a T_2 tVAS significant improvement could be explained by the T1 tVAS already being at a normal level, suggesting that TD in these patients is not linked to an impairment of gustation itself but to a retronasal impairment.[625] The correlation between self-rated OD and S'S was moderate ($r = 0.42$) and significant ($p = 0.0009$) at T_1, but not significant at T_2. The lack of correlation observed in the late recovery-phase could be explained by a subject habituation to OD or to the presence of milder smell impairment, which may not be noticeable by the subject. Because threshold represents the main component being affected long-term, this would imply the patient's OD lies with their inability to smell odours at low concentration and a potential end-organ pathogenesis. Our results confirm that psychophysical smell tests remain more sensitive than PROMs[626] and that the latter could be unreliable when used to assess smell recovery in the long-term. Nevertheless, we recognize that PROMs still remain of value in the evaluation of new-onset smell loss given their good discriminative ability.[627] The lag between T_0 and T_1 constitutes a study limitation. Unfortunately, that was mainly related to the patients' need to self-isolate and demonstrate negative swab tests before coming to the clinic in accordance with Italian guidance.

In conclusion, when assessing olfactory performance in patients with COVID-19–related OD we discourage the sole use of PROMs and recommend the use of psychophysical tests with additional subtest analysis. We also showed that in COVID-19–related OD, threshold is the most affected S'S subtest, suggesting an end-organ failure pathogenesis.[628]

6.11. Prevalence of olfactory dysfunction and quality of life impairment in hospitalised patients 1 year after SARS-CoV-2 infection: a cohort study[591]

6.11.1. Introduction

With over 250 million cases and 5 million deaths recorded worldwide so far,[629] the COVID-19 pandemic caused by SARS-CoV-2 is an ongoing global crisis. COVID-19 presentation is highly varied. An estimated 17%–20 of those infected remain asymptomatic,[630,631] while others can develop a mild-to-moderate disease or severe pneumonia.[632] According to WHO, 'loss of smell or taste' is considered a less common symptom of COVID-19. However, findings from many studies conducted worldwide have strongly contradicted this, with several reports depicting high prevalence of olfactory and/or gustatory dysfunction (OD ±GD) among infected subjects.[433,441,590,633-635] So far, the long-term prevalence of OD±GD is unknown, and values determined from the large proportion of studies conducted during the earlier months of the pandemic poorly reflect its persistence and the current proportion of those still affected. Prevalence of OD and GD also vary depending on studied populations between 54.2% and 70.2% of the general population with mild-to-moderate symptoms (mean 11.5±5.7 days),[434] 69.2% and 73.1% in mild-to-moderate symptomatic healthcare workers (median follow-up of 52 days),[590] and 5.1% and 5.6% in acutely hospitalised patients.[636] There also remains conflicting data surrounding associated risk factors. Pre-COVID-19 data show that OD is associated with increased morbidity and mortality,[92,93,100] and population studies have shown that anosmia is an independent risk factor for a shortened life span.[98,637-640] In a study of over 3000 adults, olfactory function was reported to be one of the strongest independent predictors of 5-year mortality, surpassing heart failure, lung disease and even cancer.[99] COVID-19-related OD presentation has been extensively investigated, but its impact on quality of life (QoL) in the context of COVID-19 has not been fully

explored. Therefore, this represents a key area which needs to be addressed to more effectively reduce long-term morbidity.

We conducted a cohort study on previously hospitalised patients with COVID-19 admitted at a central London hospital during the first pandemic wave, to determine the long-term prevalence of OD±GD, potential risk factors and impact on QoL.

6.11.2. Methods

A cohort study of previously hospitalised patients with COVID-19 was performed between 10 December 2020 and 29 January 2021 at the National Hospital for Neurology and Neurosurgery (London, UK).

Study population

Three hundred and fifty-eight patients hospitalised at University College London Hospital with a COVID-19 diagnosis between 10 February 2020 and 22 May 2020 were identified as potentially eligible for this study. Sample size was determined pragmatically based on data available within the medical database at the time of collection. Electronic medical records and laboratory findings were reviewed to verify full adherence to the following inclusion criteria: (1) adults ≥18 years of age, and either (2) laboratory-confirmed SARS-CoV-2 infection, defined as a positive result on reverse transcription PCR analysis of nasopharyngeal swab specimens, or (3) clinically confirmed COVID-19 on the basis of presenting symptoms, in accordance with WHO interim guidance at the time.[641] Considering the lack of widespread testing in the UK during this studied period of the pandemic, both laboratory and clinical diagnostic criteria were initially included to prevent inadvertent exclusion of eligible participants. Prior to commencement of the study, demographic data including age, sex, ethnicity and smoking status were noted to facilitate investigation into any potential associations. Baseline characteristics and

medical status were also recorded to identify ineligible patients (death or patient age <18 years).

Outcomes

Eligible subjects were invited to undertake telephone interviews involving a series of standardised questions from validated questionnaires: the EuroQoL 5-Dimension 5-Level (EQ-5D-5L)[642] and the Sino-Nasal Outcome Test-22 (SNOT-22). Patients reporting decreased sense of smell/taste in the SNOT-22 were subsequently followed up with an additional smell and taste questionnaire (online supplemental figure 1) designed to capture specific details relating to the type(s) of chemosensory dysfunction experienced. All telephone interviews were conducted in English by the same researcher following a standardised procedure in an effort to minimise interobserver bias. Verbal informed consent was obtained from all participants prior to enrolment in the study.

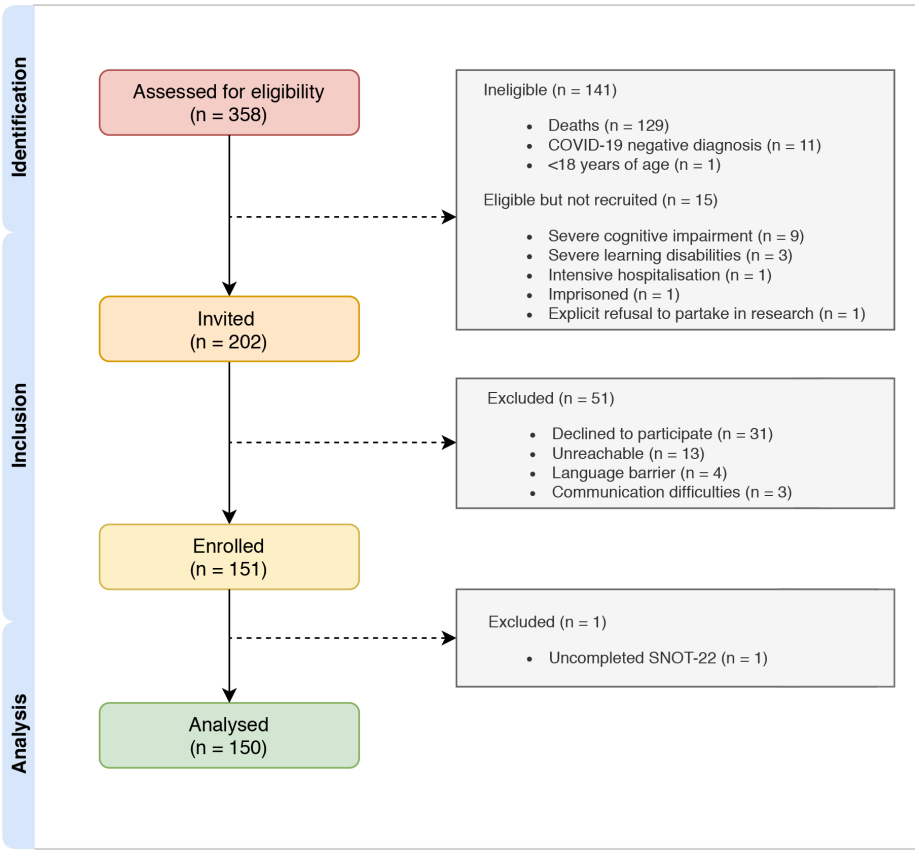

Figure 1. Flowchart depicting stages of patient identification, inclusion and analysis.

SNOT-22: Sino-Nasal Outcome Test-22.

Statistical analysis

All statistical analyses were performed using GraphPad Prism V.9.0.1 for macOS (GraphPad Software, San Diego, California, USA). Qualitative variables were presented as frequency and percentages; quantitative variables were summarised as median and IQR or mean±SD for normally distributed data. Non-parametric variables were compared using the Mann-Whitney test; data following Gaussian distribution were analysed using the unpaired t-test, with Welch's correction applied to adjust for unequal SDs and variances. Fisher's exact test was used to compare associations between variables in patients with OD±GD and patients without OD or GD. Linear regression analysis was performed to explore whether SNOT-22 scores changed over time. The 95% CIs were provided for the reported data where appropriate, and the level of statistical significance was set at a two-sided $p<0.05$.

Patient and public involvement

No patients or members of the public were involved in setting the research question or the outcome measures. They were not involved in the study design or conduct, nor were they invited to contribute to the writing, interpretation, reporting or distribution of the results.

6.11.3. Results

Three hundred and fifty-eight patients previously hospitalised with a COVID-19 diagnosis were identified as potentially eligible for this study. Figure 1 outlines the selection process. Following screening of electronic medical records for all 358 patients, 141 were classed as ineligible and subsequently excluded. This comprised patients who had either died (n=129) or those <18 years of age (n=1), as well as patients with a COVID-19 negative diagnosis (n=11), defined as individuals with presenting complaints initially ascribed to SARS-CoV- 2 infection, but which were later attributed to non-COVID-19

causes. The remaining 217 patients were deemed eligible for this study. However, 15 were not invited to participate due to overarching causes for exclusion. This included patients who were unable to consent, such as those with severe cognitive impairment (n=9), severe learning disabilities (n=3) or patients under intensive hospitalisation (n=1). Additionally, imprisoned individuals (n=1) and those with explicit refusal to partake in research as recorded in the patient notes (n=1) were excluded. Of the 202 patients contacted and invited to participate, 51 were excluded. This included unreachable patients (n=13), defined as those unable to be contacted despite >3 separate attempts (n=5) and those with invalid contact details (n=8). Patients with communication difficulties (n=3) referring to aphonic individuals (n=2) or patients with hearing impairments (n=1) preventing completion of the questionnaires. Responses were received from 151/202 invited participants, thereby resulting in a response rate of 74.8%. One patient who did not provide any answers to the SNOT-22 was excluded.

Demographics and characteristics

A final population of 150 subjects (102 males and 48 females, male:female ratio of approximately 2:1) was obtained. The majority of patients had laboratory-confirmed COVID-19 (n=147) and three patients had a presumptive diagnosis based on clinical criteria. Median time from infection was 264.5 days (range 215–318). Detailed demographics and baseline characteristics of the population are summarised in table 1.

Table 1. Detailed characteristics of the population.

	Total population (n = 150)	Patients without OD or GD (n = 129)	Patients with OD ± GD (n = 19)	P value
Age, (mean ± SD), years	58.0 ± 15.9	57.8 ± 16.4	59.6 ± 11.8	0.5773
Age groups, n (%)				
18 – 30	5 (3.3)	5 (3.9)	0 (0)	
31 – 40	20 (13.3)	18 (14.0)	2 (10.5)	
41 – 50	25 (16.7)	21 (16.3)	3 (15.8)	
51 – 60	23 (15.3)	21 (16.3)	2 (10.5)	
61 – 70	48 (32.0)	37 (28.7)	11 (57.9)	
71 – 80	15 (10.0)	14 (10.9)	0 (0)	
81 – 90	12 (8.0)	11 (8.5)	1 (5.3)	
> 90	2 (1.3)	2 (1.6)	0 (0)	
Sex, n (%)				
Male	102 (68.0)	90 (69.8)	11 (57.9)	0.3032
Female	48 (32.0)	39 (30.2)	8 (42.1)	
Ethnicity, n (%)[a]				
White	80 (58.8)	68 (58.6)	11 (61.1)	
BAME	56 (41.2)	48 (41.4)	7 (38.9)	>0.9999
Missing	14	13	1	
Smoking status, n (%)[a]				
Never smoked	72 (65.5)	64 (66.7)	7 (53.8)	
Have smoked	38 (34.5)	32 (33.3)	6 (46.2)	
Current	10 (9.1)	9 (9.4)	1 (7.7)	0.3699
Quit	28 (25.5)	23 (24.0)	5 (38.5)	
Missing	40	33	6	
Highest CRP value (mean ± SD), mg/L	170.9 ± 135.6	174.5 ± 139.5	158.0 ± 109.5	0.9282
Intubation and ventilation, n (%)[a]				
No	52 (57.8)	44 (55.7)	6 (66.7)	
Yes	38 (42.2)	35 (44.3)	3 (33.3)	0.7263
Missing	60	50	10	
Oxygen supplementation, n (%)[a]				
No	20 (17.2)	18 (17.8)	1 (7.1)	0.4599
Yes	96 (82.8)	83 (82.2)	13 (92.9)	
Missing	34	28	5	

[a] Missing data have been reported but were not used in the calculation of percentages (valid percent).
Percentages may not total 100.0% due to rounding.
CRP: C-reactive protein; BAME: Black, Asian and Minority Ethnic.

Sino-Nasal Outcome Test-22

A total of 150 patients completed the SNOT-22 and the median total score for the whole population was 17.0 (Q1–Q3: 6.0–36.3; 95% CI 13.0 to 22.0). As depicted in figure 2, the five most prevalent SNOT-22 problems were: wake up tired (101/149, 67.8%), fatigue (97/147, 66.0%), lack of a good night's sleep (98/149, 65.8%), reduced productivity (97/148, 65.5%) and wake up at night (94/149, 63.1%). Wake up tired, fatigue and lack

of a good night's sleep were also among the problems most frequently reported to affect patient health the most (Figure 3).

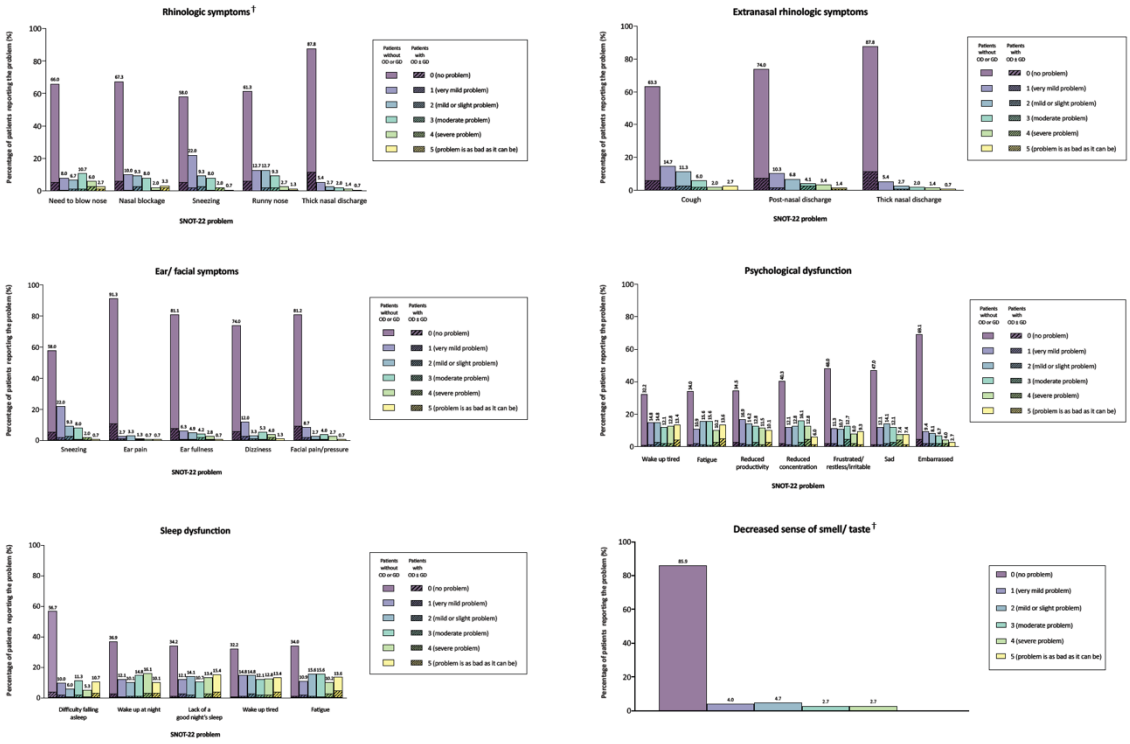

Figure 2. Prevalence of SNOT-22 problems stratified by severity and categorised by domain.
† The item 'decreased sense of smell/taste' was excluded from the rhinologic symptoms domain and presented separately, given OD ± GD status was used as a subgroup in the sub-analysis.

OD±GD, olfactory and/or gustatory dysfunction; SNOT-22, Sino-Nasal Outcome Test-22.

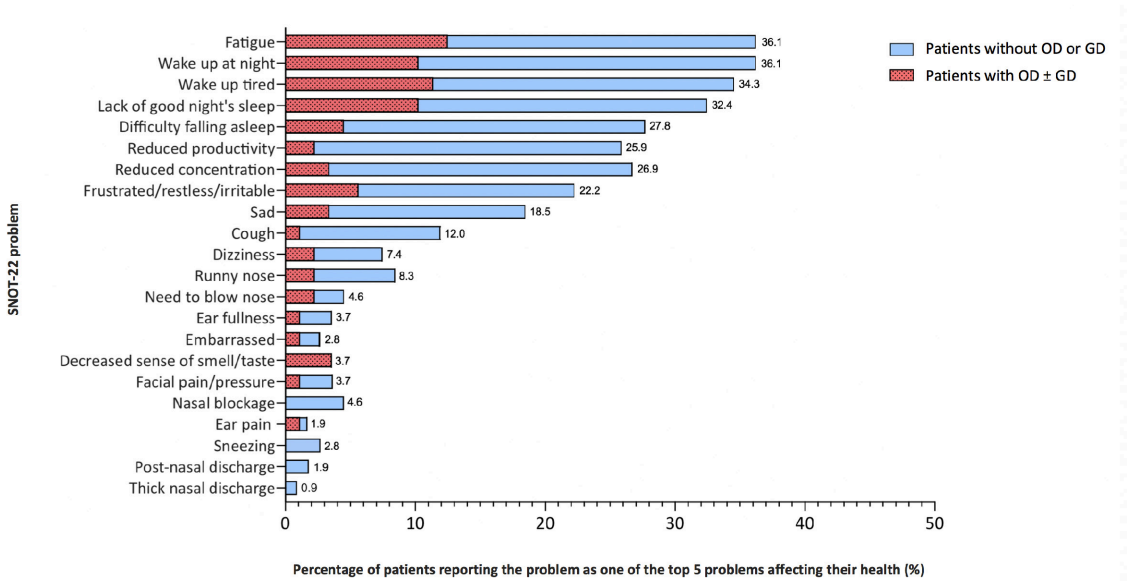

Figure 3. SNOT-22 problems reported to most greatly affect patient health.

OD±GD, olfactory and/or gustatory dysfunction; SNOT-22, Sino-Nasal Outcome Test-22.

14.1% (21/149) of patients reported to have decreased sense of smell/taste in the SNOT-22 (score ≥1 at the corresponding item), of which the severity was very mild in 4.0%, mild in 4.7%, moderate in 2.7% and severe in 2.7%. Two individuals were classed as pre-existing OD±GD based on evidence of iatrogenic causes and age-related olfactory loss predating COVID-19 infection and hospitalisation. This led to a total of 19/149 patients (12.8%) with reported decreased smell/taste in the context of COVID-19. Only 2/18 (11.1%) had sought treatment: one patient did olfactory training and the other patient did not specify. Characteristics of OD and GD are reported in table 2.

Table 2. Prevalence and characteristics of olfactory and gustatory disorders.

	Total responses (n = 149)
Prevalence, n (%)	
Total reporting decreased smell/taste	21 (14.1)
In the context of COVID-19	19 (12.8)
Pre-existing	2 (1.3)
No OD or GD	128 (85.9)
	Analysed population with OD ± GD (n = 19)[a]
Type of dysfunction reported, n (%)	
OD and GD	15 (78.9)
Only OD	4 (21.1)
Only GD	0 (0)
Parosmia[b]	3 (16.7)
Parageusia[b]	5 (27.8)
Phantosmia[b]	2 (11.1)
Phantogeusia[b]	0 (0)
OD ± GD characteristics, n (%)	
Constant[b]	14 (77.8)
Fluctuant[b]	4 (22.2)
Isolated OD[b,c]	1 (5.3)
Isolated GD[b,c]	0 (0)
Treatment, n (%)[b]	
Have not sought treatment	16 (88.9)
Have sought treatment	2 (11.1)

[a] Analyses performed on population following application of exclusion criteria (excludes pre-existing OD ± GD).
[b] Valid percentages calculated based on subjects who provided responses to the question (n = 18). Missing responses were not included in the calculations.
[c] 'Isolated' OD or GD defined as decreased sense of smell/taste in the absence of any other SNOT-22 problem.

Patients with OD±GD demonstrated a statistically significant higher median total SNOT-22 score (46.1; Q1–Q3: 23.0–60.0; 95% CI 23.0 to 60.0) than those without (16.0; Q1–

Q3: 5.0–30.5; 95% CI 12.0 to 18.0) (p=0.0002) and their scores were higher across all SNOT-22 domains[406] except one (extranasal rhinologic symptoms) (Table 3).

Table 3. Subgroup differences in median total SNOT-22 score for each domain.

	Median total SNOT-22 score		
Domain	Patients without OD or GD (n = 129)	Patients with OD ± GD (n = 19)	P value
Rhinologic symptoms	2.0	6.0	***0.0189****
Extranasal rhinologic symptoms	0	1.0	0.0524
Ear/facial symptoms	1.0	3.75	***0.0087****
Psychological dysfunction	7.0	22.0	***0.0004*****
Sleep dysfunction	7.0	16.0	***0.0024****

Significant p values in bold. Level of significance *p < 0.05, **p < 0.01, ***p < 0.001

Total SNOT-22 scores were found to improve over time in patients without OD or GD (p=0.0327), although this was not observed in patients with OD±GD (p=0.4977) (figure 4).

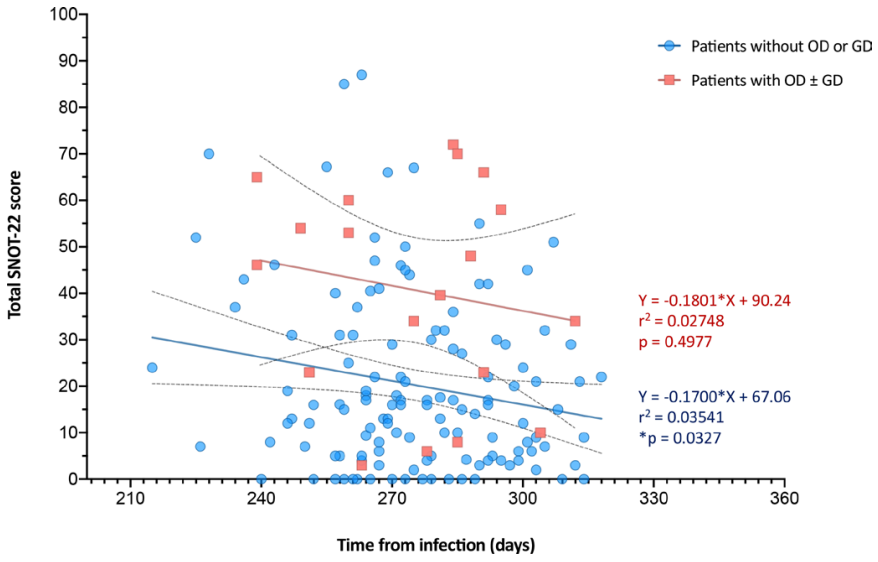

Figure 4 Linear regression analysis of subgroup changes in total SNOT-22 scores over time. Dashed lines denote 95% CI. *Significant p values. Level of significance p<0.05.

OD±GD, olfactory and/or gustatory dysfunction; SNOT-22, Sino-Nasal Outcome Test-22.

Comparisons of the demographics of the two subgroups found no influence of age, sex, ethnicity or smoking status (have smoked vs never smoked) on the development of OD±GD (p>0.05) (table 1). Similarly, no statistically significant association was observed between OD±GD and other characteristics recorded during hospitalisation, such as highest C reactive protein (CRP) value, requirement for intubation and ventilation, or oxygen supplementation (p=0.9282, 0.7263 and 0.4599, respectively).

EQ-5D-5L

A total of 149 patients completed the EQ-5D-5L and the median value for the total population was 0.80 (Q1–Q3: 0.53–0.94; 95% CI 0.73 to 0.86). Patients with OD±GD had a lower median EQ-5D-5L value (0.70; Q1–Q3: 0.38–0.83; 95% CI 0.38 to 0.83) compared with those without OD or GD (0.83; Q1–Q3: 0.61–0.94; 95% CI 0.75 to 0.89); however, the difference was not statistically significant (p=0.0627). Time from infection (the number of days between the date of the patient's first COVID-19 positive swab or their onset of COVID-19 symptoms, and the date at which the questionnaire was administered) was not found to be correlated to EQ-5D-5L value in both patients with OD ±GD (p=0.8693) and those without (p=0.5371) (Figure 5).

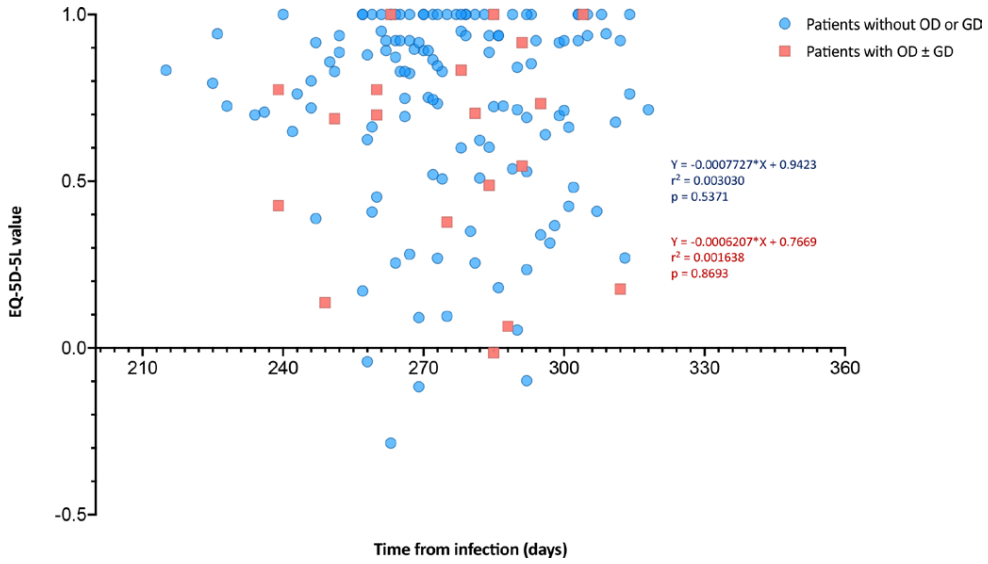

Figure 5. Linear regression analysis of EQ-5D-5L value and time from infection in patients with OD ±GD and patients without OD or GD.

OD±GD, olfactory and/or gustatory dysfunction; EQ-5D-5L, EuroQoL 5-Dimension 5-Level.

6.11.4. Discussion

This is the first study to evaluate the long-term prevalence of OD±GD in a group of previously hospitalised patients with COVID-19. The prevalence of OD±GD in our studied population was 12.8%. This is considerably lower than that of surveys conducted in hospitalised patients in Europe (35.0%–80.6% for OD and 21.0%–90.3% for GD within 1 month),[643-645] and in other countries such as Turkey (42.3% for OD±GD),[646] and Brazil (64.6% and 66.7% for OD and GD, respectively, at follow-up of 15–55 days).[647] The longer follow-up at which our study has been conducted could explain the lower rate of observed chemosensory alteration in our population, whereby recovery of OD/GD is expected to happen over time in some patients. This is supported by a recent French study which found that 24.0% of non-severe COVID-19 subjects reported persistent OD/GD 7 months after symptom onset.[648] Interestingly, our prevalence of 12.8% is similar to that observed by Lee et al[615] (15.3%) in a large Korean cohort of 3191 patients with varying COVID-19 severity at 1 month, but it is relatively higher than that observed by Mao et al[636] in a population of 214 acutely hospitalised patients with COVID-19 (5.1% and 5.6% with OD and GD, respectively). A selection bias could have potentially influenced the observed lower prevalence. Most surveys investigating OD/GD in COVID-19 subjects have been conducted on patients with mild-to-moderate symptoms.[433,434,619,649,650] In this regard, higher prevalence of anosmia has been noted in milder individuals, along with a significantly increased risk of self-reported olfactory loss in outpatients compared with hospitalised patients.[651] This is reflected in the most recent studies on long-term COVID-19-related OD±GD. In one study, 48.0% and 38.5% of non-hospitalised COVID-19 subjects reported persistent OD and GD, respectively, at 8 months follow-up.[652] Similarly, 21.3% of subjects reported OD±GD in another study of mild-to- moderate symptomatic patients at 1 year.[653] These values were notably higher than our described prevalence despite the longer follow-up times, thus suggesting that

selection bias may produce the observed disparities in reported long-term OD±GD prevalence. Additionally, it is important to consider the possible contribution of COVID-19 variants to such disparities due to their potential differing effects on olfaction. Genetic, structural and epidemiological data have shown that a single nucleotide polymorphism from D614 to G614 (D614G mutation) in the spike protein of SARS-CoV-2 may enhance chemosensory impairment, resulting in increased prevalence of COVID-19- related OD±GD.[654,655] With the presence of different viral strains and potentially uncharacterised host and viral variants, such factors may have therefore contributed to the different incidences of OD±GD observed between countries. In our population, OD was associated with GD in most of the cases (78.9%), while none of the subjects reported GD only. This reflects what has extensively been reported in previous studies[449,634,648,656] and confirms that GD is usually linked to an impairment of retronasal olfaction rather than impairment of gustation itself. Nonetheless, although less common, isolated GD has been described in patients with COVID-19.[657] Despite the extensive literature available on quantitative changes in smell and taste, qualitative alterations of smell and taste in COVID-19 have been seldom explored. In our study, 16.7% of patients had parosmia (distortions in smell) while 27.8% had parageusia (distortions in taste). A similar prevalence (15.0%) of parosmia was reported by Gorzkowski et al[658] although a higher rate of 32.4% was previously described by Lechien et al.[433] Prevalence of COVID-19-related parageusia vary widely in the literature, but a recent meta-analysis of 8438 patients with COVID-19 from 13 countries revealed a pooled prevalence of 38.2% (95% CI 24.0% to 53.6%),[659] which is higher than that observed in our study. The differences observed between studies could partly reflect inherent biases in the composition of sampled populations. Additionally, a cultural variability in taste appreciation or perception has been reported to exist in COVID-19 positive subjects with a different cultural background.[625] Phantosmia (the detections of smells not present within the environment) was reported in 11.1% of our study participants. A similar prevalence was reported by Lechien et al[433] and Gorzkowski et al.[658] No cases of phantogeusia (abnormal taste in

the mouth in the absence of any stimulus) were recorded in our population and based on the current published literature, prevalence of phantogeusia in COVID-19 subjects is unknown. In line with previous findings, [433,658] most of our participants (77.8%) reported constant OD±GD, suggesting that the driving mechanism leading to persistent chemosensory dysfunction is sensorineural. No statistically significant association between persistent OD ±GD and age, smoking status, highest CRP value, intubation and ventilation, or oxygen supplementation was found in our study, thus corroborating results from multiple studies.[446,619,647,648,658,660-663] Similarly, sex did not demonstrate any influence on the prevalence of persistent OD±GD in our study, which is in line with previous studies conducted worldwide.[441,619,658,660,664,665] Nonetheless, several authors have observed a significantly higher prevalence of OD±GD in women,[433,446,614,615] with some reports suggesting that being female is a risk factor for prolonged recovery from chemosensory dysfunction.[644,647,661] However, the female predominance observed from such studies may be attributed to the differences in the sampled populations (hospitalised vs mild-to- moderate) or in the gender composition. In fact, previous studies on COVID-19 hospitalised patients have demonstrated a lower prevalence of female patients,[666] which is confirmed by the male:female ratio in our population (2:1). Moreover, women tend to outperform men on olfactory assessment and in their capacity to perceive OD, which could lead to disproportionately increased prevalence seen in females.[90,667] Our study included a more ethnically diverse population in comparison to more geographically limited studies conducted on cohorts of the same ethnic background. Despite this, we found no statistically significant association between ethnicity and OD±GD, in contrast to what was reported by Doty[668] before the pandemic that ethnic minorities are more at risk of developing chemosensory dysfunction. In this study, the majority of patients reporting decreased sense of smell/taste had very mild or mild impairment as opposed to moderate or severe impairment. Decreased sense of smell/taste was also not frequently ranked within the top five of their most important items, suggesting that chemosensory impairment was not of their greatest concern, if

compared with other residual symptoms listed in the SNOT-22. This is an expected finding, considering previous studies which show that hospitalised patients are less likely to report olfactory loss compared with patients with milder course,[651] possibly due to the presence of more prominent symptoms. However, while OD±GD severity was not largely found to be profound in this study, it should be noted that patients with OD±GD had a significantly higher median total SNOT-22 score than those without, with the score only improving over time for the latter subgroup. This corresponds to a greater health burden and subsequent poorer QoL among those affected with chemosensory impairments, as exemplified in a recent study by Chary et al.[446] More importantly, it reflects the ongoing health burden in patients with OD±GD, which has previously been depicted to a similar effect.[664] Analysis of the SNOT-22 items demonstrated intrinsic psychological and sleep dysfunction in our population, where the items wake up tired, fatigue and lack of a good night's sleep were three of the most commonly ticked 'important items' (maximum of five items). While this highlights some of the long-term manifestations of COVID-19, now called 'long-COVID',[634,669] further subanalysis revealed that OD±GD reduced QoL in nearly all domains, especially that of psychological dysfunction, when compared with patients without OD or GD. Recent studies have supported this, with emphasis on both the direct and indirect negative effects of COVID-19-related OD on psychological well-being. In one study, 15.8% of patients with COVID-19 with OD reported depression due to their smell loss,[670] whereas in a separate study, 28.2% had increased anger as a secondary effect.[671] A more recent study reported that chemosensory disturbance in mildly symptomatic patients with COVID-19 was associated with emotional distress and depression, despite over a year since the onset of their COVID-19 infection.[513] Interestingly, long-lasting fatigue has also been found to be significantly associated with persistent OD±GD.[649] Taken together, our findings therefore highlight the negative long-term effects of persistent OD±GD on QoL. Conversely, based on subgroup analysis of EQ-5D-5L values, we did not observe any difference in health-related QoL between those with OD±GD and those without. More importantly, EQ-5D- 5L value did not improve with

time and was not influenced by the presence of a chemosensory alteration. One possible explanation for these results is interpatient variability. Given that the EQ-5D-5L is nonspecific to COVID-19 and captures responses based on overall QoL on the day of questioning, patients' responses could have been influenced by other factors. The questionnaire also may not have been sensitive enough to differentiate the problems experienced by patients with OD±GD. Alternatively, the lack of any significant difference in EQ-5D-5L values between these two subgroups may reflect the residual difficulties of long-COVID which are common to many patients with COVID-19, regardless of anosmia status.

Strengths and limitations

To our knowledge, this represents the first study to have determined the prevalence of OD±GD in a cohort of previously hospitalised patients with COVID-19 at 1 year following infection. We have, therefore, provided a more current insight into both the persistence and the scale of OD and GD from a long-term perspective, and the impact on patients' QoL and well-being. Our cohort of previously hospitalised patients with COVID-19 also adds value by highlighting differences in OD±GD prevalence in different populations, given that current existing studies have predominantly been based on mild-to-moderately affected patients or healthcare workers. The prevalence of OD and GD observed in our study refers to a single-centre population of previously hospitalised patients with COVID-19. Our findings, therefore, may not be directly comparable or generalisable to those reported for mild-to-moderate symptomatic COVID-19 subjects in the general community. There is also the possibility of misdiagnosis, especially with the three clinically confirmed patients with COVID-19, although this is unlikely considering the surging number of COVID-19 cases at the time of their presentation. Without baseline data, we were unable to determine the extent to which the impairments in OD±GD patients were new onset or more chronic, or whether there was any previous improvement of chemosensory function. Lastly, as in other COVID-19 studies, patients

with OD±GD were identified through subjective, self-reported questionnaires. These have a low correlation with psychophysical measurements,[310] and findings derived from these surveys cannot be compared with studies which have used objective tests, such as Sniffin' sticks. However, given that psychophysical testing has not been available or feasible in many countries during the pandemic, we believe that, in an emergency condition, self-rated symptoms remain of value.[627]

Clinical implications of this study

A proportion of previously hospitalised patients with COVID-19 may continue to experience persistent OD±GD long term, especially when this is not treated. With over 9.3 million COVID-19 positive cases in the UK at the time of writing,[672] and with numbers likely to increase including untested asymptomatic individuals and those with milder disease, our study demonstrates the relevance of OD±GD and its place as a key manifestation of long-COVID. OD±GD impacts QoL and can have a potentially substantial long-term burden on patients and healthcare resources. Our study suggests that persistent COVID-19-related chemosensory dysfunction requires increased holistic support. This includes safety counselling, psychological therapy, coping strategies and patient support groups to aid patients in the management of their OD±GD, but concurrent rehabilitation such as olfactory training should also be considered, given the evidence base supporting its effectiveness in post-viral olfactory loss.[116,618,673,674] It should also be noted that there are currently ongoing clinical trials assessing other interventions such as anti-inflammatory agents, nasal/oral steroids and even intranasal photobiomodulation therapy.[675,676] However, while these could play supportive roles in the potential recovery of COVID-19-related OD±GD, further research regarding their safety and efficacy will be needed, alongside additional studies investigating the impact of such modalities on patient QoL.

6.11.5. Conclusions

Up to a year following infection, 12.8% of previously hospitalised patients with COVID-19 in London reported persistent chemosensory dysfunction. COVID-19-related OD±GD reduces both QoL and psychological well-being, and this does not improve over time, creating an important health burden. With the number of patients seeking treatment expected to rise, developing new therapeutic treatments will be important in the future, as well as providing adequate patient support for now.

6.12. Long-term quality-of-life impairment in patients with more than 1-year COVID-19–related olfactory dysfunction[592]

6.12.1. Introduction

Olfactory dysfunction (OD) impacts patients' lives and the causes for this are multiple.[69] It results in decreased flavour perception and the inability to recognise spoiled food, hazardous odours or volatile chemicals poses a health and safety risk. Compared to other causes of olfactory disorders, post-infectious OD is associated with a higher level of quality of life (QoL) impairment. Pre-COVID-19 studies confirmed that QoL is reduced in patients with OD and recent studies showed the impact of COVID-19-related OD on patients' QoL both in the short[671] and medium-term[677]. To date, its long-term consequences on QoL remain partially unexplored. We investigated by means of Sniffin' Sticks (S'S) and validated QoL questionnaires the effects of persistent COVID-19-related OD on QoL in subjects with a history of OD longer than 1 year.

6.12.2. Methods

We conducted a cross-sectional study including patients with a history of mild-to-moderate COVID-19 referred to our long-COVID smell clinic between December 2020 and April 2022 for persistent COVID-19-related OD. Patients with a pre-existing history of OD or other pathologies known to affect olfaction were not included. The study was conducted in accordance with the 1996 Helsinki Declaration and approved by the Research Ethic Committee (Reference 14/SC/1180).

Detailed characteristics of the population are reported in *Table1*. Olfaction was assessed using the S'S extended test while self-assessment of smell was performed using a visual analogue scale(sVAS)[310]. The Medical Outcome Study Short-Form 36(SF-36) was chosen for the measurement of QoL, while the brief version of the Questionnaire

of Olfactory Dysfunction-Negative statements (brief QOD-NS)[107] was used to quantify the smell loss symptoms' effect on patients' QoL. Sinonasal symptoms were evaluated using the Sino-Nasal Outcomes Test-22(SNOT-22).

Variables were compared using the unpaired T-test and Mann-Whitney test. Fisher's exact test was used to investigate associations between variables in normosmic and dysosmic patients. Linear regression analysis was used to explore correlations between TDI scores and questionnaire outcomes.

6.12.3. Results

Sixty patients completed the assessment and were included in the study (*Table1)*. None of the patients had other long-hauler COVID-19 symptoms apart from OD. Subjects were categorised into three groups based on their TDI score: 14 normosmics (subjects who reported OD but showed normal S'S scores - TDI≥30.75), 39 hyposmics (16<TDI< 30.75) and 7 anosmics (TDI≤16). For comparative analysis, patients with hyposmia and anosmia were combined together and classified as 'dysosmics' (n=46).

No differences in the general characteristics and qualitative OD (parosmia/phantosmia) were observed between normosmics and dysmosmics. Dysosmics showed significantly lower scores (worse outcomes) in the SF-36 domains 'energy/fatigue', 'emotional wellbeing', 'social functioning' and 'general health', brief QOD-NS, sVAS and S'S scores, with threshold being the most affected S'S subtest. Similarly, dysosmics had higher scores (worse outcomes) in SNOT-22 subdomains 'psychological dysfunction' and 'loss of smell or taste'. *(Table1; Figure1)* A significant linear correlation was found between the S'S and SF-36 domain 'energy/fatigue' ($p<0.01$ for all but identification, which was not significant) and sVAS ($p=0.03$ for identification and $p<0.01$ for the remaining S'S scores).

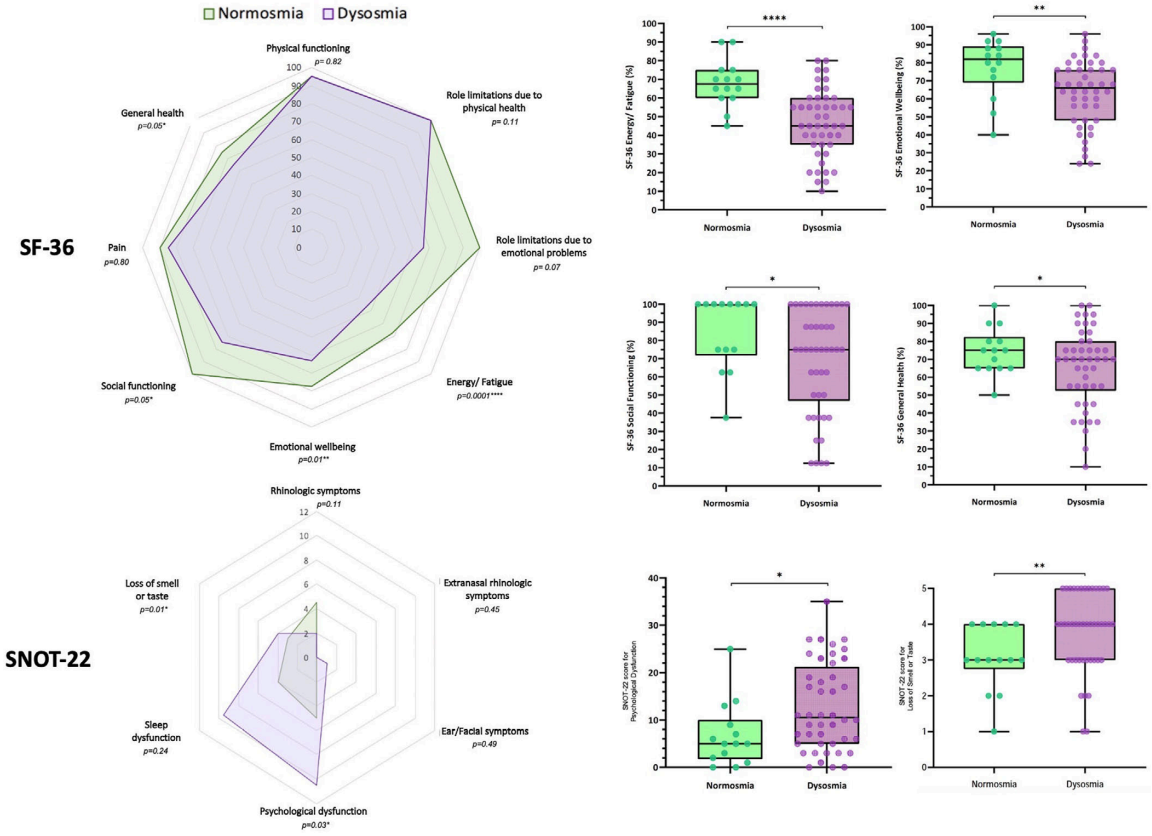

Figure 1. Short-Form 36 (SF-36) and Sino-Nasal Outcome Test-22 (SNOT-22) radar charts (left) showing median scores for normosmic and dysosmic patients and their p-values. Box plots (right) demonstrate SF-36 and SNOT-22 domains with significant differences between the two groups.

TABLE 1. Detailed characteristics and differences in olfaction and questionnaires scores for normosmic and dysosmic patients.

	Normosmia (n = 14)	Dysosmia (n = 46)	*p*-value
General characteristics			
Age, (mean ± SD), yr	44.4 ± 12.3	43.0 ± 13.1	0.71
Sex, n (%)			
Male	7 (50.0)	13 (28.3)	0.19
Female	7 (50.0)	33 (71.7)	
Duration of smell loss, (mean ± SD), days	405.4 ± 151.8	431.1 ± 198.5	0.66
Parosmia, n (%)			
No	2 (14.3)	8 (17.4)	>0.99
Yes	12 (85.7)	38 (82.6)	
Phantosmia, n (%)			
No	10 (71.4)	29 (63.0)	0.75
Yes	4 (28.6)	17 (37.0)	
Smoking status, n (%)			
Never smoked	11 (78.6)	38 (82.6)	
Have smoked	3 (21.4)	8 (17.4)	0.71
Current	1 (7.1)	4 (8.7)	
Quit	2 (14.3)	4 (8.7)	
Comorbidities, n (%)			
None	9 (64.3)	33 (71.7)	
Yes	5 (35.7)	13 (28.3)	0.74
Hypothyroidism	2	2	
Hypertension	1	3	
Hyperlipidaemia	1	2	
Diabetes mellitus	1	2	
Allergic rhinitis	1	1	
Migraine	2	0	
Others	3	15	
Previous nasal operations, n (%)			
No	14 (100.0)	39 (84.8)	0.18
Yes	0 (0)	7 (15.2)	
Rhinitis, n (%)			
No	8 (57.1)	35 (76.1)	0.19
Yes	6 (42.9)	11 (23.9)	
Medication use, n (%)			
None	13 (92.9)	37 (80.4)	
Yes	1 (7.1)	9 (19.6)	0.43
α-blockers	0	0	
Sartans	0	0	
Dicumarolics	0	0	
Antiplatelet drugs	0	2	
Biguanides	0	0	
Antidepressants	0	2	
Others	1	8	
Olfactory test and PROMs			
Sniffin' Sticks score, median [IQR]			
TDI	32.0 [31.4 – 33.6]	23.3 [20.4 – 28.3]	**<0.0001****
Threshold	6.8 [5.8 – 7.6]	4.6 [1.4 – 5.5]	**<0.0001****
Discrimination	14.0 [13.0 – 15.0]	10.0 [8.0 – 12.0]	**<0.0001****
Identification	12.0 [11.0 – 13.0]	10.0 [7.8 – 11.0]	**0.0002*****
SNOT-22, median [IQR]			
Total SNOT-22 Score	16.5 [10.0 – 30.5]	23.0 [12.5 – 46.0]	0.23
Rhinologic Symptoms[+]	4.5 [1.0 – 6.0]	2.0 [0 – 5.0]	0.11
Extranasal Rhinologic Symptoms	0 [0 – 3.0]	0 [0 – 1.0]	0.45
Ear/ Facial Symptoms	0 [0 – 4.3]	1.0 [0 – 4.0]	0.49
Psychological Dysfunction	5.0 [1.8 – 10.0]	10.5 [5.0 – 21.3]	**0.03***

Sleep Dysfunction	4.0 [2.3 – 10.3]	9.5 [1.3 – 16.0]	0.24
Loss of Smell or Taste	3.0 [2.8 – 4.0]	4.0 [3.0 – 5.0]	**0.01****
SF-36, (mean ± SD)/median [IQR] †, (%)			
Physical Functioning	95.0 [85.0 – 100]	95.0 [80.0 – 100]	0.82
Role limitations due to physical health	100 [100 – 100]	100 [43.8 – 100]	0.11
Role limitations due to emotional problems	100 [66.7 – 100]	66.7 [25.0 – 100]	0.07
Energy/ Fatigue	67.9 ± 12.7	46.5 ± 18.1	**0.0001****
Emotional Wellbeing	77.4 ± 16.4	63.2 ± 18.2	**0.01****
Social Functioning	84.8 ± 20.3	68.8 ± 28.6	**0.05***
Pain	90.0 [67.5 – 92.5]	85.0 [67.5 – 100]	0.80
General Health	74.6 ± 12.9	65.2 ± 21.8	**0.05***
QOD-NS, (mean ± SD)	15.1 ± 4.8	8.5 ± 5.5	**0.0001****
sVAS, (mean ± SD)	7.5 ± 0.5	3.3 ± 2.2	**<0.0001****

Significant *p*-values in bold. Levels of significance *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** p ≤ 0.0001.
+ The item 'loss of smell or taste' was excluded from the rhinologic symptoms domain and presented separately
† (mean ± SD) or median [IQR] have been reported according to data distribution (normal vs non-normal distribution).

PROMs: Patient reported outcome measures; SNOT-22, Sino-Nasal Outcome Test-22; SF-36, 36-item Short Form Health Survey; QOD-NS, Brief version of Questionnaire of Olfactory Disorders - Negative Statements; sVAS, Visual Analogue Scale for sense of smell (0 represents "sense of smell absent" and 10 "sense of smell not affected").

6.12.4. Discussion

Our study offers the longest follow-up (14 months) at which effects of COVID-19-related OD on QoL have been measured. Dysosmic patients demonstrated worse QoL scores when compared to normosmics especially in the SF-36 domains 'energy/fatigue', 'emotional wellbeing' and 'social functioning', which confirms the difficulties these patients report in their everyday activities[513]. However, when we looked at the SF-36 scores of those who recovered their sense of smell(normosmics), these were found to be within the normative values for the UK population[678], suggesting how olfactory recovery could contribute to improving QoL.

Our data highlighted a significantly higher psychological dysfunction in dysosmic patients at SNOT-22 when compared to normosmics corroborating previous findings demonstrated both in the medium[679] and long-term[591]. At 14 months from OD onset, dysosmic patients continued to have lower S'S scores with a linear correlation demonstrated with the SF-36 domain 'energy/fatigue' which could reflect the general level of debility commonly reported by dysosmic patients. However, both the identification

and, more significantly, the threshold scores were found to be outside S'S normative values also in the normosmic group. This confirms how threshold remains the most affected task in COVID-19-related OD both in the medium[310] and long-term[513].

Qualitative disorders (parosmia/phantosmia) had been reported to be more associated with severe reduction in QoL than purely quantitative disorders, and the fact that QoL in our normosmic group was within the normal range despite a similar rate of parosmia/phantosmia in the two groups may be due either to a less severe qualitative OD in patients who recovered their sense of smell or the adoption of more efficient compensatory strategies to cope with parosmia.

Dysosmic patients demonstrated lower scores at the brief QOD-NS, confirming its usefulness in discriminating subjects at a higher risk to QoL detriments related to OD.[680] A significant linear correlation between sVAS and S'S(both TDI and S'S subtests scores) was also observed in our analysis replicating previous results.[310]

A limit of the study is the lack of a control group of patients with no history of OD with or without previous COVID-19. However, we could speculate that our normosmic group offers similar characteristics whereas QoL scores were found to be within the normal range. Due to the cross-sectional nature of the study and the fact it included only patients with reported OD, results need to be verified in wider populations.

In conclusion, patients with persistent OD show worse QoL scores than those who recover sense of smell, suggesting how olfactory recovery could contribute to QoL improvement. Threshold remains the most affected task in the long-term which strengthens the hypothesis that SARS-CoV-2 targets the olfactory epithelium.

6.13. Clinical factors influencing olfactory performance in patients with persistent COVID-19 smell loss longer than 1 year[425]

6.13.1. Introduction

Olfactory dysfunction (OD) represents a prevalent symptom in patients infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[590,635] Spontaneous recovery rate of olfaction is very high within the first month following infection and up to 95.7% of subjects fully recover their olfaction within 12 months[472,518,681]. The downside of that is that about 5% of them can develop a persistent OD[518] which has now been recognised as a long-COVID symptom[682].

To date the reasons why some people spontaneously recover their sense of smell soon after the infection while others develop a persistent OD are not fully known. According to recent evidence, SARS-CoV-2 persistence and associated inflammation in the olfactory neuroepithelium and immunological dysfunction may account for prolonged COVID-19-related OD, as demonstrated in olfactory mucosa samples from patients with persistent COVID-19 smell loss[479,683,684]. However, we do not know if associated clinical factors can contribute to the olfactory mucosa inflammation and potentially impede a possible smell recovery.

A metanalysis published in June 2022 and including papers up to October 2021 showed that female patients, subjects with greater initial severity of dysfunction or nasal congestion were less likely to recover their olfaction.[518] More recently, Leung et al.[685] by using an identification test found that presence of phantosmia was associated with a worse evolution in smell recovery. In a survey conducted on 2218 COVID-19 patients, Chudzik et al.[686] found that the risk of developing persistent OD after COVID-19 was greater in younger people with less comorbidities and a higher number of symptoms during the acute phase of COVID-19. In another survey on 798 participants Coelho et

al.[687] showed that age <40 and presence of nasal congestion at time of COVID-19 infection were predictive of improved rates of smell recovery, while difficulty breathing at time of COVID-19 infection, and prior head trauma predicted worsened rates of recovery. A positive influence of age (age <40) on smell recovery was also confirmed by McWilliams and colleagues[688]. In a multicentric study on 147 patients, Menzel et al.[523] using Sniffin' Sticks (S'S) observed a better prognosis in younger patients with parosmia and lower olfactory scores at the first visit. Conversely, Schwab et al.[689] found that parosmia, high severity of OD and female sex were associated with lower rates of recovery.

To date, results from papers evaluating prognostic factors remain difficult to interpret and in some cases these are conflicting. This could have been influenced by the different methods used by the authors to assess olfaction, namely subjective or psychophysical assessment with further differences for the latter one in terms of olfactory abilities assessed (i.e. threshold, discrimination, identification or composite).[310]

We conducted a retrospective analysis of 100 patients seen in a single-centre long-COVID smell clinic for reported persistent COVID-19-related OD who underwent extensive rhinological assessment, patient reported outcome measures (PROMs) and olfactory assessment using S'S extended test. We aim to evaluate the general characteristics, investigations results and PROMs in this population, compare these between patients with normal and altered olfactory scores at assessment, and look at factors influencing persistence of COVID-19-related OD.

6.13.2. Materials and methods

Study design and population

A retrospective analysis of patients with reported persistent COVID-19-related OD was conducted to evaluate the general characteristics, investigations results and PROMs of

the population and compare these between patients with ‘normal’ sense of smell (normosmics) at Sniffin’ Sticks (S’S) and those with a lowered or absent sense of smell (dysosmics). All patients were seen in our long-COVID smell clinic at the University College London Hospitals (London, United Kingdom) and were referred to us for a persistent reported OD occurred after a laboratory confirmed SARS-CoV-2 infection. Informed consent was obtained from each subject before starting any study-related procedure. The study was approved by the Hospital Research Ethic Committees (REC ref 14/SC/1180) and was conducted in accordance with the Declaration of Helsinki.

Investigations

Sense of smell was evaluated using the S'S extended set (Burghart, Medisense) to obtain the odour threshold (T), discrimination (D), and identification (I) scores. Normosmia was attributed where TDI score (the sum of T, D, and I individual scores) was ≥30.75, hyposmia where TDI was >16, but <30.75, and functional anosmia if TDI ≤16.[112] All patients received a nasal endoscopy to exclude signs of chronic rhinosinusitis (CRS) – nasal polyps, nasal discharge, and signs of rhinitis – or an obstruction/inflammation of the olfactory clefts. As part of our rhinology assessment, patients underwent unilateral and bilateral (total) peak nasal inspiratory flow (PNIF) to assess nasal patency.[282] A skin prick test (SPT) was also offered to those patients not on regular antihistamines or oral corticosteroids to rule out any underlying allergen sensitivity to common aeroallergens (house dust mite, grass, tree and birch pollens, cat and dog epithelia, Alternaria). An MRI of the head was arranged to study the olfactory system and exclude any central causes of OD. However, this stopped to be systematically requested for every single patient once new evidence showed that COVID-19-related OD does not affect the central smell regions.[690]

Patient reported outcome measures

The 36-Item Short Form Health Survey (SF-36) was chosen to assess quality of life (QoL), while the short version of the Questionnaire of Olfactory Disorders-Negative Statements (short QOD-NS)[107] was used to quantify the smell loss symptoms' effect on patients' QoL. Self-assessment of olfaction was performed using a visual analogue scale for sense of smell (sVAS—0 represents "sense of smell absent" and 10 "sense of smell not affected")[310] whereas sinonasal symptoms were evaluated using the 22-item Sino-Nasal Outcome Test (SNOT-22)[406]. Qualitative olfactory dysfunction (i.e. parosmia/phantosmia) was investigated by asking the patients if the symptom was present or not at the moment of the examination.

Statistical analysis

Quantitative variables were presented as median and interquartile range whereas qualitative variables were expressed as number of observations and percentage. Comparisons of general characteristics and findings between groups were performed using the Wilcoxon test for quantitative variables and the Pearson chi-square test for categorical variables. Differences between normosmics and dysosmics were evaluated using the Wilcoxon test for quantitative variables or the chi-square test for qualitative variables. Correlation between Sniffin' Sticks, PNIF and PROMs scores was assessed using the Pearson correlation test. Multiple linear regression with selection of variable based on Akaike's information criterion (backward stepwise) was performed to identify the effects of the available variables on the difference in S'S results and help determine positive and negative influences. Cramer V test was used to calculate effect size for qualitative variables while Wilcoxon r test for quantitative ones. *p*-values have been calculated for all tests, and 5% was considered as the critical level of significance. All the analysis has been performed in R (R Core Team, 2021).

6.13.3. Results

General characteristics of the whole population

One hundred patients (66 female; female-to-male ratio 2:1) with a median age of 42 years (range 18-85) were seen between October 2020 and December 2022. All patients had a mild-to-moderate COVID-19, experienced a complete loss of sense of smell (described as no sense of smell by the patients) following SARS-CoV-2 infection and developed a persistent OD after that episode. The median length of OD (calculated as number of days from the date of smell loss to the day of first consultation) was 1.4 years. Sixty-four patients (64.0%) lost their sense of smell during the first wave of the pandemic (between February and June 2020). The majority of the subjects were non-smokers (83; 83.0%), with no comorbidities (62.0%) and they reported parosmia on the day of the assessment (80; 80%). Phantosmia was less frequently reported (31; 31.0%). Only one patient (1.0%) had a history of CRS without nasal polyps but their sense of smell was not affected by the CRS. Four patients (4.0%) had a history of post-infectious OD but their sense of smell completely recovered after that episode. Similarly, 5 patients (5.0%) had a head trauma in the past but olfaction was not affected. Before coming to our smell clinic, 81 patients (81.0%) tried at least one treatment to improve their smell. (*Table 1*)

Olfactory measurements, PROMs and other investigations in the whole population

At presentation, twenty patients (20.0%) were found to be normosmics at S'S, 68 (68.0%) were hyposmics and the remaining 12 (12.0%) were functionally anosmics. For the analysis, we grouped the hyposmics and anosmics into a single group (dysosmics – TDI < 30.75) to maximize statistical power. Total PNIF median value was within the normal range for an adult population[285] while the unilateral PNIF (both right and left) results were reduced[404]. Nasal endoscopy revealed a septal deviation in 32 patients (32.0%) and this was associated with an inferior turbinates hypertrophy in other 14 patients (14.0%). An MRI head was performed in 70 patients (70.0%) and it showed a reduced olfactory bulb volume only in 1 patient (1.4%), using cut-off values as described by Rombaux et al.[691]

	Whole population n = 100	Normosmics n = 20	Dysosmics n = 80	Difference in medians	*p*-value	*Effect size d*
Age, median [P25-P75], yr	42.0 [29.8-53.0]	43.5 [32.0-49.8]	42.0 [30.0-54.0]	1.5	0.69	0.04
Sex, No (%) Female Male	 66 (66.0%) 34 (34.0%)	 11 (55.0%) 9 (45.0%)	 55 (68.8%) 25 (31.2%)		0.69	0.13
Length of OD, median [P25-P75], yr	1.4 [1.0-1.9]	1.1 [1.0-1.9]	1.5 [1.0-1.9]	- 0.4	0.43	
Parosmia, No (%)	80 (80.0%)	16 (80.0%)	64 (80.0%)		0.69	0.02
Phantosmia, No (%)	31 (31.0%)	4 (20.0%)	27 (33.8%)		0.69	0.17
Smoking, No (%) Ex-smoker Yes No	 4 (4.0%) 13 (13.0%) 83 (83.0%)	 1 (5.0%) 2 (10.0%) 17 (85.0%)	 3 (3.8%) 12 (15.0%) 65 (81.2%)		0.69	0.08
Comorbidity, No (%) None Yes Hypothyroidism Asthma Hypercholesterolemia Diabetes Hypertension Others	 62 (62.0%) 38 (38.0%) 9 (23.7%) 6 (15.8%) 5 (13.3%) 5 (13.2%) 4 (10.5%) 18 (47.4%)	 12 (60.0%) 8 (40.0%) 3 (37.5%) 1 (12.5%) 1 (12.5%) 2 (25.0%) 1 (12.5%) 4 (50.0%)	 50 (62.5%) 30 (37.5%) 6 (20.0%) 5 (25.0%) 4 (13.3%) 3 (10.0%) 3 (10.0%) 14 (46.7%)		0.69	0.02
Allergic rhinitis, No (%)	21 (21.0%)	7 (35.0%)	14 (17.5%)		0.06	0.20
Chronic rhinosinusitis, No (%)	1 (1.0%)	0 (0.0%)	1 (1.3%)		1	0.05
Family history Alzheimer/Parkinson, No (%)	12 (12.0%)	2 (10.0%)	10 (12.5%)		1	0.02
History of PIOD, No (%)	4 (4.0%)	0 (0.0%)	4 (5.0%)		1	0.10
Previous nasal operations, No (%)	9 (9.0%)	0 (0.0%)	9 (11.3%)		0.20	0.15

History of head trauma, No (%)	5 (5.0%)	0 (0.0%)	5 (6.3%)	0.58	0.11
Previous treatment for OD, No (%)					
None	19 (19.0%)	7 (35.0%)	12 (15.0%)	0.06	0.22
Yes	81 (81.0%)	13 (65.0%)	68 (85.0%)	0.17	0.17
Olfactory training	66 (81.5%)	9 (69.2%)	57 (83.8%)	0.08	0.20
Topical steroid	48 (59.3%)	8 (61.5%)	40 (58.8%)	0.72	0.06
Multivitamins	44 (54.3%)	7 (53.8%)	37 (54.4%)	0.43	0.09
Oral steroid	11 (13.6%)	1 (7.7%)	10 (14.7%)	0.68	0.08
Others*	7 (8.6%)	1 (7.7%)	6 (8.8%)	1	0.17

Table 1. General characteristics of the whole population and of normosmic and dysosmic patients. Difference between groups medians and level of significance (*p*-value).
*Others: Vitamin A drops, theophylline spray, alpha lipoic acid, sodium citrate, omega-3

OD: olfactory dysfunction; PIOD: post-infectious olfactory dysfunction;

A sensitivity to common aeroallergens was observed in 34 patients (36.9%). Lower scores at the SF-36 were found for the health domains energy/fatigue (55.0%), emotional wellbeing (68.0%), social functioning (75.0%), general health (70.0%) and health change (50.0%). Reduced scores were also observed for sVAS (4.0) and short QOD-NS (9.0) while raised scores were found for the SNOT-22 (23.0). (*Table 2*)

Correlations between Sniffin' Sticks, PNIF and PROMs

A moderate statistically significant positive correlation was observed between sVAS and the TDI (r=0.59; p<0.0001), threshold (r=0.52; p<0.0001), discrimination (r=0.45; p<0.0001) and identification (r=0.46; p<0.0001) scores. A weak statistically significant positive correlation was found between the SF-36 domain energy/fatigue and TDI (r=0.27; p=0.008), threshold (r=0.29; p=0.005) and discrimination (r=0.25; p=0.02). A weak statistically significant negative correlation was shown between SNOT-22 and threshold score only (r=-0.24; p=0.02). (*Figure 1*)

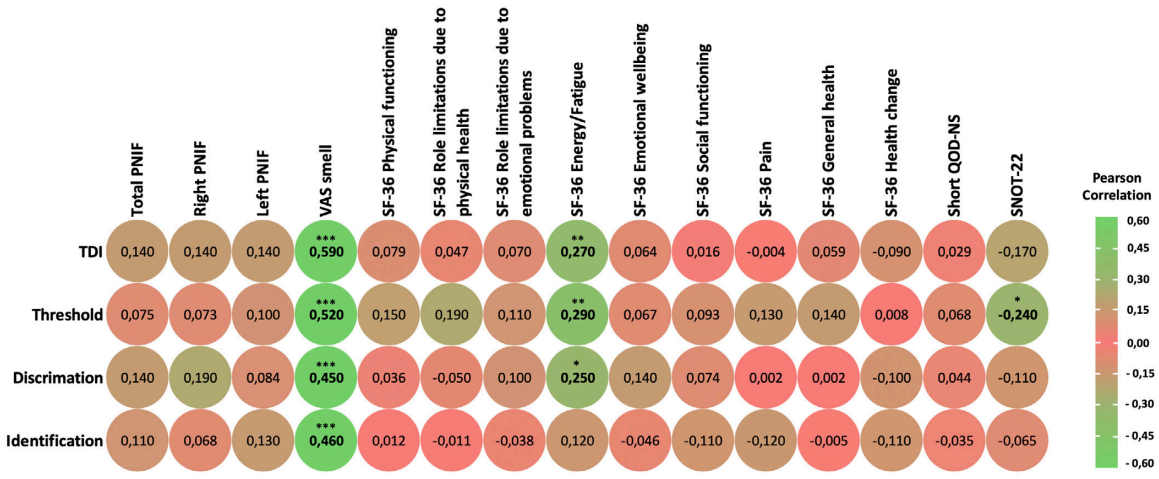

Figure 1. Correlation matrix showing strength of correlations between Sniffin' Sticks, peak nasal inspiratory flow (PNIF) and patient reported outcome measures (PROMs). Levels of significance *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001.

TDI: threshold + discrimination + identification score; VAS: Visual Analogue Scale; SF-36: 36-Item Short Form Health Survey; SNOT-22: 22-item SinoNasal Outcome Test; short QOD-NS: short version of the Questionnaire of Olfactory Disorders-Negative Statements.

	Whole population n = 100	Normosmics n = 20	Dysosmics n = 80	Difference in medians	*p*-value	*Effect size d*
Investigations						
Sniffin' Sticks, median [P25-P75]						
Threshold	4.9 [2.5-5.8]	7.1 [5.8-7.9]	4.5 [2.0-5.5]	2.6	**<0.0001*** **	-0.51
Discrimination	11.0 [9.0-12.0]	13.5 [12.8-14.0]	10.0 [8.0-12.0]	3.5	**<0.0001*** **	-0.50
Identification	10.0 [8.0-12.0]	12.5 [11.0-13.0]	9.5 [7.8-11.0]	3.0	**<0.0001*** **	-0.50
TDI score, median [P25-P75]	25.0 [21.2-29.5]	32.0 [31.5-33.6]	23.5 [19.2-27.8]	8.5	**<0.0001*** **	-0.68
Normosmic, n (%)	20 (20.0%)	20 (20.0%)	-			
Hyposmic, n (%)	68 (68.0%)	-	68 (85.0%)			
Anosmic, n (%)	12 (12.0%)	-	12 (15.0%)			
PNIF, median [P25-P75], L/min						
Bilateral	130.0 [105.0-160.0]	130.0 [117.5-160.0]	127.5 [100.0-160.0]	2.5	0.39	-0.09
rPNIF	80.0 [56.3-100.0]	85.0 [73.8-100.0]	75.0 [50.0-97.5]	10.0	0.17	-0.14
lPNIF	80.0 [60.0-100.0]	92.5 [67.5-105.0]	80.0 [60.0-100.0]	12.5	0.20	-0.13
Nasal endoscopy, No (%)						
Unremarkable	42 (42.0%)	9 (45.0%)	33 (41.3%)			
Septal deviation	32 (32.0%)	7 (35.0%)	25 (31.3%)		0.77	0.11
IT hypertrophy	12 (12.0%)	1 (5.0%)	11 (13.8%)			
Septal deviation + IT hypertrophy	14 (14.0%)	3 (15.0%)	11 (13.8%)			
MRI head, No (%)	70 (70.0%)	8 (40.0%)	62 (77.5%)			
Normal	66 (94.3%)	8 (100%)	58 (93.5%)		0.76	0.09
Incidental findings	3 (4.3%)	0 (0.0%)	3 (4.8%)			
Reduced OB volume	1 (1.4%)	0 (0.0%)	1 (1.6%)			
Skin prick test, No (%)	92 (92.0%)	17 (85.0%)	75 (93.8%)			
Negative	58 (63.0%)	12 (70.6%)	46 (61.3%)			
One allergen	14 (15.2%)	0 (0.0%)	14 (18.7%)		0.25	0.21
Two allergens	5 (5.4%)	1 (5.9%)	4 (5.3%)			
Multiple allergens	15 (16.3%)	4 (23.5%)	11 (14.7%)			
PROMs						
SF-36, median [P25-P75], %						
Physical functioning	95.0 [85.0-100]	95.0 [88.8-100]	95.0 [80.0-100]	0	0.97	0.003
Role limitations due to physical health	100 [25.0-100]	100 [93.8-100]	100 [25.0-100]	0	0.24	-0.12
Role limitations due to emotional problems	100 [33.3-100]	100 [41.7-100]	66.7 [0.0-100]	33.3	0.16	-0.14
Energy/Fatigue	55.0 [35.0-65.0]	65.0 [58.8-71.3]	45.0 [35.0-60.0]	20.0	**0.0004** **	-0.36

Emotional wellbeing	68.0 [56.0-80.0]	76.0 [66.0-85.0]	68.0 [51.0-80.0]	8.0	**0.04***	-0.19
Social functioning	75.0 [62.5-100]	87.5 [62.5-100]	75.0 [50.0-100]	12.0	0.16	-0.14
Pain	90.0 [67.5-100]	90.0 [80.0-95.0]	90.0 [67.5-100]	0	0.73	-0.03
General health	70.0 [55.0-80.0]	75.0 [65.0-81.3]	70.0 [48.8-80.0]	5.0	0.20	-0.13
Health change	50.0 [25.0-50.0]	50.0 [25.0-50.0]	50.0 [25.0-62.5]	0	0.39	0.09
VAS smell, median [P25-P75]	4.0 [2.0-6.0]	7.0 [5.5-7.8]	4.0 [2.0-5.0]	3.0	**0.0008****	-0.34
SNOT-22, median [P25-P75]	23.0 [14.0-40.0]	18.0 [11.5-33.5]	23.0 [14.8-43.8]	- 5.0	0.31	0.10
Short QOD-NS, median [P25-P75]	9.0 [5.0-15.0]	14.0 [5.5-17.0]	8.0 [5.0-12.0]	6.0	0.07	-0.18

Table 2. Investigations and patients reported outcome measures (PROMs) for the whole population and for the normosmic and dysosmic patients. Difference between groups medians and level of significance (*p*-value).
Significant *p*-values in bold. Levels of significance *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001.

TDI: Threshold + Discrimination + Identification; PNIF; peak nasal inspiratory flow; lPNIF: left PNIF; rPNIF: right PNIF; IT: inferior turbinates; VAS: Visual Analogue Scale; SF-36; SNOT-22: 22-item SinoNasal Outcome Test; short version of the Questionnaire of Olfactory Disorders-Negative Statements (short QOD-NS)

Differences between normosmics and dysosmics

No significant differences between normosmics and dysosmics were observed when looking at the general characteristics. (*Table 1*) All the S'S scores were significantly lower in the dysosmic population with a medium effect size. (*Table 2*) In particular, TDI, threshold and identification scores were below the 10th percentile in the dysosmic group while these were all normal in the normosmics. Similarly, significantly lower scores were observed in the dysosmic group in the SF-36 domains energy/fatigue (p=0.0004; d=-0.36), emotional wellbeing (p=0.04; d=-0.19) and in the sVAS (p=0.0008; d=-0.34). (*Table 2; Figure 2*)

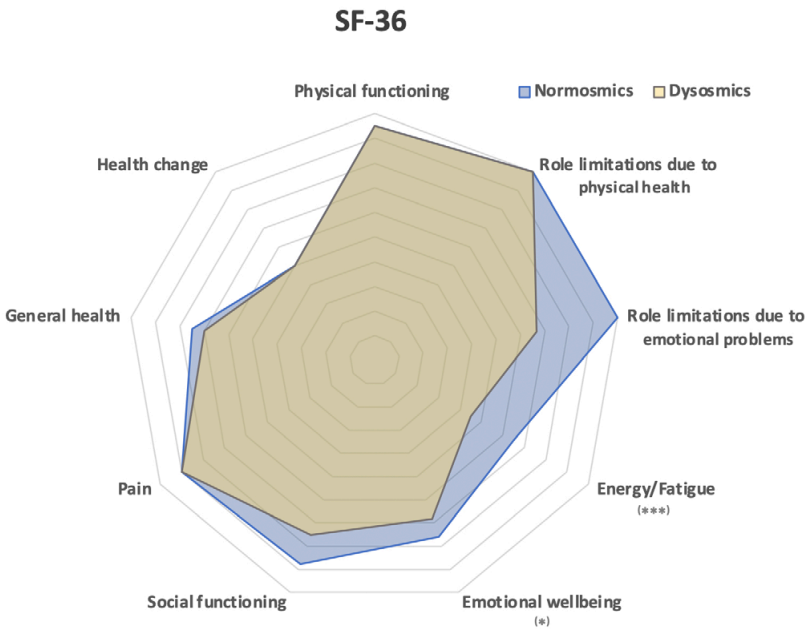

Figure 2. 36-Item Short Form Health Survey (SF-36) radar chart showing median scores for normosmic and dysosmic patients. Levels of significance *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001.

Influence of available variables on olfactory performance (Sniffin'Sticks scores)

At the multivariate analysis a statistically significant positive influence on discrimination for total PNIF (p=0.001), smoking (p=0.03) and presence of comorbidity (p=0.048) and on identification for presence of septal deviation with inferior turbinates hypertrophy (p=0.009). Conversely, a statistically significant negative influence on discrimination was

noted for smell training (p=0.047) and on identification for positivity to common aeroallergens at SPT (p=0.036). (*Figure 3*)

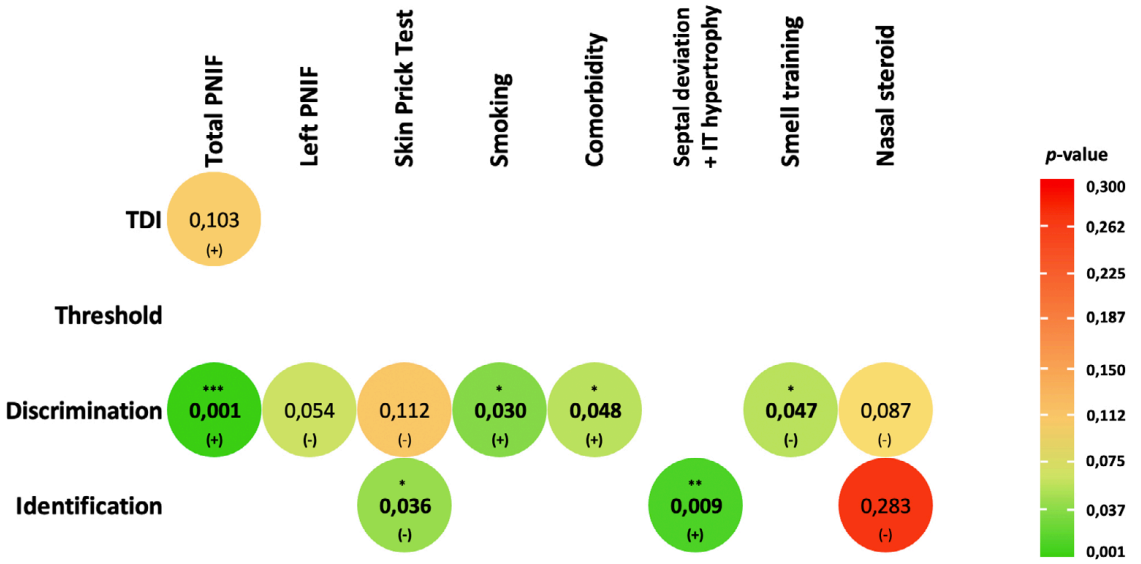

Figure 3. Multivariate analysis showing p-values for the variables influencing Sniffin' Sticks scores and the positive (+) or negative (-) direction of the effect. Levels of significance *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001.

TDI: threshold + discrimination + identification score; PNIF; peak nasal inspiratory flow.

6.13.4. Discussion

Our study highlighted new clinical factors potentially influencing olfactory performance (i.e. quantitative olfactory function) in patients with persistent COVID-19-related OD.

We observed a role of nasal obstruction on smell recovery. In particular, at the multivariate analysis a better nasal airflow, higher scores as measured by means of PNIF, was found to positively and significantly influence odour discrimination (p=0.001). Also, a positive influence of total PNIF on TDI, despite non-significant (p=0.1), was observed. However, a linear correlation between PNIF values and TDI scores was not demonstrated. In support of this finding, Boscolo-Rizzo et al.[513] found that patients with long-term reduced olfactory function (TDI ≤30.5) had significant lower PNIF values when

compared to cases with normal olfactory function. On the other hand, the multivariate analysis also showed a significant positive effect of septal deviation associated with inferior turbinates hypertrophy at nasal endoscopy (p=0.009) on identification scores. Although this result might be difficult to interpret, presence of septal deviation does not necessarily lead to a nasal blockage and, this finding could be simply linked to a sample bias (e.g. high prevalence of patients with non-functionally important septal deviation amongst dysosmics). The relationship between nasal airways and sense of smell is not new. Several studies, in fact, have shown how a surgical improvement of nasal patency is associated with increased olfaction, confirmed not only using PROMs[174,692,693] but also with psychophysical assessment[177,426,693]. This is particularly relevant when the septal deviation impacts on the internal nasal valves[426,694] as this can reduce the airflow onto the olfactory cleft.

Our paper also showed for the first time a potential role of allergic rhinitis on smell performance. In particular, sensitivity to common aeroallergens as shown at SPT, negatively influenced both the discrimination and identification scores at the multivariate analysis, with only the latter being significant (p=0.036). Whether a relationship between olfaction and CRS is well-established,[210] evidence of an impact of allergic rhinitis on sense of smell remains sparce[695,696]. In the past Hinrisdottir and colleagues[697] showed that a pronounced allergic reaction after allergen challenge was accompanied by an elevated olfactory threshold. We hypothesize that allergic rhinitis could impact on smell recovery in two ways: 1) by reducing the nasal airflow and odorants delivery to the olfactory clefts due to an inferior turbinates hypertrophy and increased mucus production; 2) by creating an additional inflammatory component in the olfactory mucosa able to affect the neuroepithelium function. In fact, one of the most credited theories leading to persistent COVID-19-related OD is that of an ongoing inflammation in the olfactory mucosa and a chronic sustentacular cells damage causing olfactory neuron deciliation

and necrosis.[479,684,698] Allergic rhinitis could increase this inflammation in the olfactory mucosa and prolong OD by slowing the regeneration of olfactory neuroepithelium.

So far, many papers have confirmed that both acute loss of sense of smell[590,615] following SARS-CoV-2 infection but also long-term COVID-19-related OD[518,69938] are more frequent in female subjects. In this regard, our study confirms that with two thirds of our patients (64.0%) being female and the majority of them found to be dysosmics at S'S. All our patients experienced a severe smell loss following SARS-CoV-2 infection and this corroborates previous studies suggesting that subjects with greater initial severity of dysfunction are less likely to recover their olfaction[518]. The role of smoking on smell recovery is still controversial.[518,700] A study conducted by Hummel et al.[519] on 894 patients before the COVID-19 pandemic concluded that smoking is a negative predictive factor for recovery by increasing the nasal irritation and causing subsequent nasal obstruction. Conversely, our study showed a positive significant influence of smoking on discrimination scores (p=0.03). Even though this could have been caused by a sample bias in our study, our finding corroborates previous results from Akbari and colleagues[700] who found significant better identification scores in smokers but also previous studies[701,702] which reported that COVID-19 related OD is less frequent in patients with a smoking habit. Prevalence of parosmia in our population (80%) was higher when compared to previous studies, although this varies widely across different studies in the literature and reported to be between 43% at 6 months and 70.9% when evaluated at 1 year.[511,703-705] A higher prevalence of parosmia in our group of patients could be explained either by a longer OD in our population (1.4 years) or by the fact that only patients with a self-reported long-term OD were referred to our long-COVID smell clinic and included in the study. Although past studies have reported a possible influence of parosmia[523,689] and phantosmia[685] on smell recovery our analysis did not confirm that. Similarly, in contrast with previous authors[523,686-688,700] we did not find any effect of age on smell recovery. On the other hand, we found a positive significant effect of presence of

comorbidities on discrimination scores (p=0.048) which in some aspects corroborates previous results from Chudzik and colleagues[686] who concluded that the risk of developing long-COVID smell loss is grater in people with less comorbidities.

Persistent COVID-19-related OD negatively impacts on emotional well-being leading to feelings of loneliness, fear, and depression, as well as difficulties concerning social/sexual relationships.[706] Dysosmic patients were found to have significantly lower scores at the SF-36 health domains for energy/fatigue (p=0.0004; d=-0.36) and emotional wellbeing (p=0.04; d=-0.19) when compared to normosmics, with a small-to-medium effect size. SF-36 scores were all within the normal range[678] in the normosmic group while these were reduced in the dysosmics for the health domains 'role limitation due to emotional problems', 'energy/fatigue', 'emotional wellbeing', 'social functioning' and perceived 'general health'. Moreover, a weak but significant positive correlation was observed between the SF-36 domain 'energy/fatigue' and the S'S scores suggesting that an improvement in the olfactory scores (i.e. olfactory recovery) is associated with an increased level of energy and, thus, a QoL improvement. This further confirms our previous results on a smaller population.[592]

In the dysosmic group both the composite TDI score and all the three subcomponents (threshold, discrimination and identification) were significantly lower (p<0.0001 for each test) when compared to the scores obtained in the normosmic group with a medium effect size in each case (*Table 2*). Moreover, when looking at the normative data for S'S[112], TDI, threshold and identification scores were below the 10th percentile in the dysosmic group whether these were all above the 10th percentile (specifically between the 25th and 50th percentiles) in the normosmics. Whether on the one hand these results demonstrate how both the odour threshold and identification abilities are affected in patients with long-COVID smell loss, on the other hand they also show that these abilities can still go back to a normal level even after more than 1 year from OD onset.

In our study, sVAS was confirmed to be an easy and quick tool to assess olfaction and to discriminate between normal and reduced sense of smell as demonstrated by a moderate correlation with all the S'S scores and a highly significant difference in the sVAS results between normosmics and dysosmics with a small effect size (p=0.0008; d=-0.34).

To date olfactory training remains the only recognised treatment for persistent COVID-19-related OD.[584] Our multivariate analysis showed a significant negative influence of smell training (p=0.047) on discrimination scores. However, we believe that this could be related to the fact that those who tried smell training before were also those in whom sense of smell was more affected.

Strengths and limitations

The present paper is one of the most comprehensive studies currently available in which patients with persistent COVID-19-related OD underwent complete psychophysical smell assessment, a thorough rhinological evaluation and an extensive QoL investigation. It must be stated that this study is not a cohort study including all the subjects who experienced COVID-19-related OD but a cross-sectional study which considered only patients with a persistent reported OD. This means that prognostic factors in our paper were evaluated on a specific sub-group of a wider population of patients who experienced smell loss following SARS-CoV-2 infection, introducing a possible sample bias. In this regard, our findings may not be directly comparable with previous studies. Also, our group of normosmics cannot be strictly considered a group of people with a normal sense of smell as the majority of them were still reporting qualitative OD (80% referring parosmia).

6.13.5. Conclusions

Risk factors affecting long-COVID smell recovery remain partially unknown. In our study, impairment of nasal airflow and sensitivity to common aeroallergens have been shown to influence olfactory performance. The effect of smoking on smell recovery still remains controversial. Nevertheless, these results should be verified in future studies on larger populations and using validated psychophysical tests to assess olfaction. Finally, our study further confirms how long-COVID smell loss deeply affects QoL although recovery of olfaction can bring it back to a normal range.

6.14. A multicentre real-life study to determine the efficacy of corticosteroids and olfactory training in improving persistent COVID-19-related olfactory dysfunction[698]

6.14.1. Introduction

Olfactory dysfunction (OD) represents a highly prevalent symptom in patients infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with up to 85% of mild-to-moderate coronavirus disease 2019 (COVID-19) cases developing loss of sense of smell[590,635]. Spontaneous recovery rate of olfaction is very high within the first month following infection (recovery rate 94.6%) and it becomes 85.7% at 6 months[681] and 93% at 12 months[472]. Persistent post-infectious OD (PIOD) has been recognised as a "long-COVID" symptom, defined as a persistent symptom in individuals who recovered from COVID-19[682] and, unfortunately, no definitive treatments exist to effectively restore function. European guidelines recommend olfactory training (OT) for a minimum of 3 months to maximise the chance of smell improvement[42]. Nonetheless, OT remains ineffective in 50%-85% of subjects[525,707,708] with up to 29% of PIOD cases not improving even after long-term OT (14 months)[535].

Topical and systemic corticosteroids have been considered as a therapeutic option in PIOD but their benefit for non-sinonasal-related OD remain controversial. A systematic review published in 2019[709] suggested that systemic corticosteroids could improve olfactory loss in PIOD (level 4), whereas a more recent one[524] concluded that systemic or topical corticosteroids remain "optional" due to the lack of high-quality studies. The rationale behind the use of corticosteroids to treat PIOD relies on its capacity to reduce a subclinical inflammation which may persist in the nose after an otherwise resolved upper respiratory tract infection. On the other hand, corticosteroids could play a role in the regeneration of the olfactory epithelium of PIOD patients, as already shown in animal

models[710,711]. Studies focusing on corticosteroids as treatment of PIOD did not clarify which formulation, dose and route of administration is better in improving sense of smell and if this is more effective if combined with OT. Another question remains on whether there is a time limit from OD onset at which treatment should be started in order to observe a benefit. Ultimately, in the lack of clear evidence-based guidelines the choice is left to doctor's preferences. To date, most of the authors seem to agree that corticosteroids may have a role when started close to OD onset[712]; however, whether this could have a role in persistent OD remains partially unexplored.

In this study we aim to investigate the role of the combination of corticosteroids plus OT in improving persistent COVID-19-related OD in a cohort of subjects with a history of smell loss longer than 7 months. Patients refusing to take corticosteroids and doing OT alone and those not doing any treatment were used as internal controls.

6.14.2. Materials and methods

Study design

A multicentre real-life cohort study was conducted to assess the efficacy and safety of corticosteroids in combination with OT in the treatment of persistent OD in patients with a history of mild-to-moderate COVID-19. The study was approved by the Hospital Research Ethic Committees (REC ref 14/SC/1180) and was conducted in accordance with the Declaration of Helsinki.

Participants' characteristics

Patients with a reported OD occurred following a laboratory-confirmed SARS-CoV-2 infection referred to our smell clinics at the University College London Hospitals (London, United Kingdom) and the University Hospital of Padua (Padua, Italy) were selected. All participants provided full informed consent prior to their inclusion in the study. Data were collected on demographics, subjective characteristics of OD at onset, smoking status,

comorbidities and medications taken. (*Table 1*) Patients with a chronic or recent short-term oral steroid use, pregnancy, pre-existing history of OD, non-COVID-19-related OD or other pathologies known to affect olfaction (i.e., head and neck tumors, chronic rhinosinusitis, head trauma, radio/chemotherapy of the craniofacial region, psychiatric or neurological disease) were not included in the study.

First assessment (T0) and evaluation of olfactory function

On the first visit, a fully detailed medical history was obtained. Participants were asked to report any medications they used. Factors such as duration of olfactory loss and presence of parosmia, described as the occurrence of distorted olfaction when smelling odour, were also explored. All patients underwent nasal endoscopy to exclude signs of chronic rhinosinusitis (CRS) – nasal polyps, nasal discharge and signs of rhinitis – or an obstruction/inflammation of the olfactory clefts. An MRI of the head was arranged for all patients to study the olfactory system and exclude any central causes of OD. Olfaction was evaluated using Sniffin' Sticks (S'S) - extended set (Burghart, Medisense) to obtain the odour threshold (T), discrimination (D) and identification (I) scores. Normosmia was attributed where TDI score (the sum of T, D and I individual scores) was ≥ 30.75, hyposmia where TDI was >16, but <30.75, and functional anosmia if TDI ≤16[112]. Self-assessment of olfaction was performed using a visual analogue scale (VAS - 0 represents "sense of smell absent" and 10 "sense of smell not affected")[310] while sinonasal symptoms were evaluated using the Sino-Nasal Outcomes Test-22 (SNOT-22)[406].

	Patients with OD (n=44)	*Group A_{S+OT} (n=19)*	*Group B_{OT} (n=16)*	*Group C_{None} (n=9)*	*p-value*
Age, median [P25-P75], yr	40.5 [30.5-53.3]	47.0 [31.0-54.0]	50.0 [33.0-57.0]	32.0 [28.0-35.0]	**0.03***
Sex, No (%)					
Female	28 (63.6%)	11 (57.9%)	11 (68.8%)	6 (66.7%)	0.78
Male	16 (36.4%)	8 (42.1%)	5 (31.2%)	3 (33.3%)	
Comorbidities, No (%)					
Diabetes	1 (2.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0.36
Hypertension	4 (9.1%)	1 (5.3%)	3 (18.8%)	0 (0.0%)	
Hyperlipidaemia	3 (6.8%)	1 (5.3%)	2 (12.5%)	0 (0.0%)	
Hypothyroidism	1 (2.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	
Allergic rhinitis	1 (2.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	
Smoking, No (%)	5 (11.4%)	1 (5.3%)	2 (12.5%)	2 (22.2%)	0.41
Medications, No (%)					
None	35 (79.5%)	13 (68.4%)	13 (81.3%)	9 (100%)	0.28
Yes	9 (20.5%)	6 (31.6%)	3 (18.7%)	0 (0.0%)	
α-blockers	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Sartans	1 (11.1%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	
Dicumarolics	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Antiplatelet drugs	3 (33.3%)	1 (16.7%)	2 (50.0%)	0 (0.0%)	
Biguanides	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Antidepressants	1 (11.1%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	
Others	8 (88.9%)	6 (100%)	2 (50.0%)	0 (0.0%)	
Interval for smell loss onset, median [P25-P75], days	1.0 [0.0-4.3]	2.0 [0.0-7.0]	0.5 [0.0-3.0]	1.0 [0.0-5.0]	0.96
Length of OD [P25-P75], days	224.0 [136.0-383.8]	214.0 [165.5-352.5]	226.5 [126.3-418.0]	235.0 [191.0-383.0]	0.94
Reported level of smell at infection, No (%)					
Anosmia	36 (81.8%)	17 (89.5%)	11 (68.8%)	8 (88.9%)	0.24
Hyposmia	8 (18.2%)	2 (10.5%)	5 (31.2%)	1 (11.1%)	
Previous treatments, No (%)					
Olfactory training	27 (61.4%)	11 (57.9%)	13 (81.3%)	3 (33.3%)	0.06
Oral steroid	2 (4.5%)	2 (10.5%)	0 (0.0%)	0 (0.0%)	0.25
Topical steroid (drops)	2 (4.5%)	2 (10.5%)	0 (0.0%)	0 (0.0%)	0.13
Topical steroid (spray)	8 (18.2%)	6 (31.6%)	1 (6.3%)	1 (11.1%)	0.05
Multivitamins	20 (45.5%)	7 (36.8%)	11 (68.8%)	2 (22.2%)	0.31

Table 1. General characteristics of the whole population of dysosmic patients and according to type of treatment. *Significant p-values. Level of significance p<0.05.

OD: olfactory dysfunction. Others: Anxiety, Migraine, prolapsed discs, Epilepsy, Temporal arteritis, Sleep problem, osteoporosis, Asthma, dermititis, IBS, eosinophilia, Psoriasis, Restless leg syndrome, CAD, osteoarthritis, VITD deficiency, bladder incontinence

Treatment and further follow-up (T1)

Patients with no OD at S'S (TDI ≥30.75) were discharged back to their general practitioner (GP). Conversely, patients with a confirmed OD (TDI<30.75) were offered a steroid treatment consisting in a 2-week course of oral corticosteroids (Prednisolone 40 mg/daily for 5 days, then tapered down over 9 days) followed by intranasal corticosteroids drops for 2 weeks (Betamethasone 0.1%, 2 drops/nostril bidaily) administered in the Kaiteki position[271]. Specific consent to start the previously-mentioned treatment was sought from all patients before giving any related prescription. They were also asked to start OT, as previously described[42], until further follow-up irrespective of whether they had done or not it before. Patients with contraindications to corticosteroids[713] or refusing to take them were asked to start OT. A further follow-up at 6 months was arranged for all patients and patient-reported outcome measures (PROMs) and S'S were repeated on that occasion. Treatment adherence was checked at follow-up by requesting specific questions about treatment (i.e. modalities of topical steroid drops administration, length of time allowed for olfactory training and strict adherence to instructions provided). At follow-up, patients who did not do any treatment during the study period were kept in the analysis and formed an additional control group.

Statistical analysis

Quantitative variables were presented as median and interquartile range while qualitative variables were expressed as number of observations and percentage. Considering the Wilcoxon test, to obtain an increase in the TDI score of 5.5 points, which corresponds to the minimal clinically important difference (MCID),[247] a power (1-β) of 0.8 is obtained with n=17 in each arm, while a sample size of n=15 in each arm gives a power of 0.79, keeping a fix α (uncertainty level) at 5%. Comparisons of general characteristics and findings between groups were performed using the Kruskal-Wallis test for quantitative variables and the Pearson Chi-square test for categorical variables. Differences between T_0 and T_1 were evaluated using the paired Wilcoxon test for quantitative variables while

the chi square test was chosen for parosmia. Multiple linear regression with selection of variable based on Akaike's information criterion (backward stepwise) has also been performed to identify the effects of the available variables on the measurement changes at T_1. P-values have been calculated for all tests, and 5% was considered as the critical level of significance. All the analysis has been performed in R (R Core Team, 2021).

6.14.3. Results

Breakdown of the population

Between December 2020 and April 2022, 67 patients with a reported COVID-19-related OD were seen at our smell clinics. All patients had a history of mild-to-moderate COVID-19 and none of them required hospital admission. Of them, 14 patients were found to be normosmic at S'S and were discharged back to GP care. The remaining 53 subjects (7 anosmics) were advised to start the suggested treatment. Nine patients did not attend their 6-month follow-up leading to a total of 44 patients (28 female; 63.6%), with a median age of 40.5 years, who completed the study period and were considered for data analysis. Of them, 19 patients had the combined treatment (corticosteroids plus OT - group A), 16 patients refused to take corticosteroids and did the OT alone (group B) and 9 patients did not do any treatment despite medical recommendations (group C). *Figure 1* shows the flow chart for the study population.

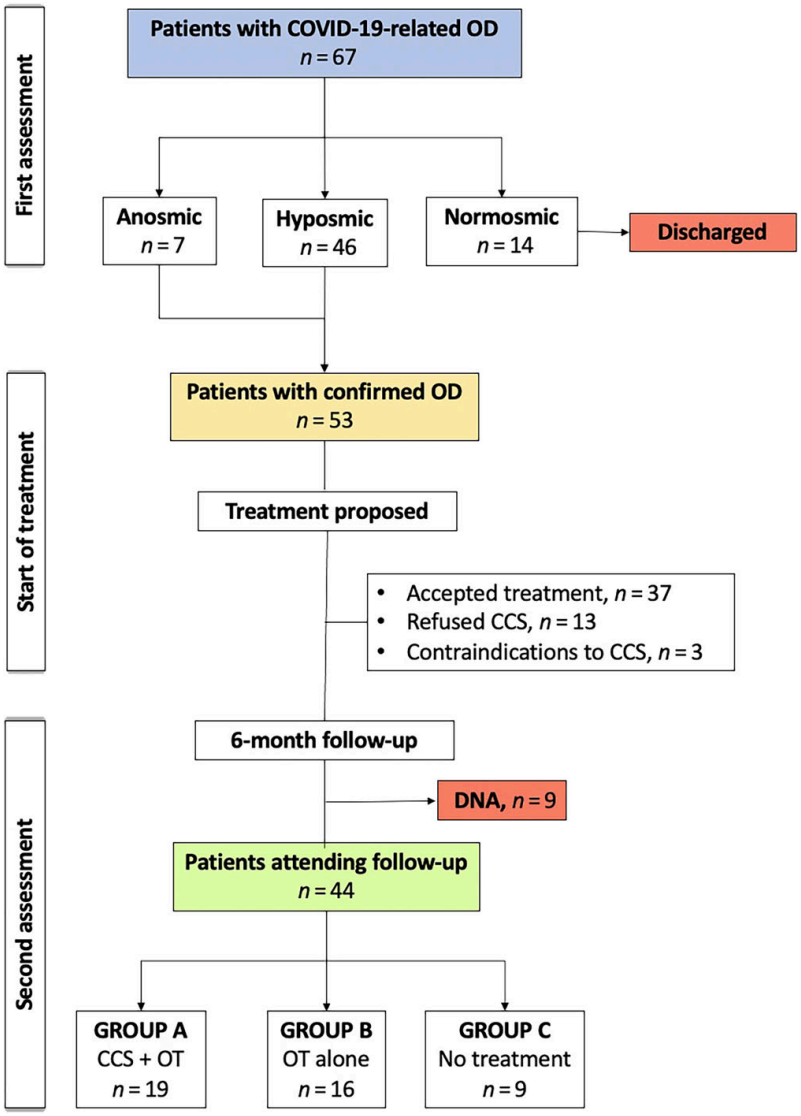

Figure 1. Flow chart of study population.

OD: olfactory dysfunction; CCS: corticosteroids; DNA: did not attend; OT: olfactory training.

General characteristics of the population

Demographics, smoking status, comorbidities, and medications taken are reported in *Table 1*. All patients had a confirmed persistent COVID-19-related OD at S'S with a median length of OD of 224 days (calculated as number of days from the infection date to the day of first consultation). In most of cases this presented as a complete loss of sense of smell (36; 81.8%) and occurred at a median time of 1 day following infection. Most of patients tried OT (27; 61.4%) or oral multivitamins (20; 45.5%) before coming for

their first consultation. None of them received any course of oral steroid for their OD in the past. No side effects were reported after treatment with corticosteroids. Characteristics for each group of patients are reported in *Table 1.* Patients in group C were significantly younger (p=0.03) but, apart from that, no other statistically significant differences were noted in terms of demographics and baseline clinical characteristics among the 3 groups. *(Table 1)*

PROMs, olfactory measurements and other investigations

Nasal endoscopy showed a clear olfactory cleft for all patients. MRI scan of the head was normal in all patients with no radiological sign of CRS or central causes of OD. PROMs scores (VAS and SNOT-22), incidence of parosmia, threshold, discrimination, identification and TDI scores at baseline (T_0) and at follow-up (T_1) for each group of patients are reported in *Table 2.* Apart from a significant lower number of parosmics observed in group B at baseline (p=0.01), no other significant differences were observed in the measurements either at baseline and at follow-up in the three groups. *(Table 2)*

Effects of the therapy on olfaction

A statistically significant improvement in the TDI score was demonstrated at follow-up in patients receiving the combined treatment (p=0.01) and those doing OT alone (p=0.04) while a significant improvement in VAS score was shown only for patients in the former group (p=0.01). No significant changes were noted in group C or in the SNOT-22 score or in the number of parosmics for all groups. *(Table 3)* In 6 patients (31.6%) in group A the TDI improvement was above the MCID of 5.5 points in TDI score[128] when compared to 5 patients (31.3%) in group B and 4 patients (44.4%) in group C. No significant differences were observed when comparing the number of patients reaching the MCID improvement in the three groups (p=0.78).

	Patients with OD (n=44)	***Group A_{S+OT} (n=19)***	***Group B_{OT} (n=16)***	***Group C_{None} (n=9)***	***p-value$_{A-B-C}$***
Findings at first assessment (T_0)					
Sniffin' Sticks, median [P25-P75]					
Threshold	3.5 [1.0-5.5]	4.5 [1.0-5.3]	3.8 [1.0-5.5]	2.5 [2.3-6.0]	0.95
Discrimination	10.0 [9.0-12.0]	10.0 [8.0-11.0]	11.0 [10.0-12.5]	11.0 [10.0-12.0]	0.26
Identification	10.0 [7.5-11.0]	10.0 [7.0-11.0]	11.0 [9.5-12.5]	9.0 [9.0-10.0]	0.26
TDI score, median [P25-P75]	23.5 [20.5-28.4]	22.8 [18.5-27.0]	27.0 [23.5-28.1]	23.3 [20.5-28.3]	0.35
Anosmic, n (%)	7 (15.9%)	4 (21.1%)	2 (12.5%)	1 (11.1%)	
Hyposmic, n (%)	37 (84.1%)	15 (78.9%)	14 (87.5%)	8 (88.9%)	0.75
VAS smell, median [P25-P75]	4.0 [1.0-6.0]	2.5 [0.8-4.0]	5.0 [2.0-7.0]	3.0 [1.8-6.3]	0.35
SNOT-22, median [P25-P75]	22.0 [12.0-38.5]	24.5 [10.0-41.8]	18.0 [15.0-26.0]	32.0 [14.5-60]	0.63
Parosmia, No (%)	31 (70.5%)	16 (84.2%)	7 (43.8%)	8 (89.9%)	**0.01***
Findings at second assessment (T_1)					
Sniffin' Sticks, median [P25-P75]					
Threshold	5.5 [3.3-6.6]	5.0 [2.6-5.8]	5.6 [4.0-7.4]	5.5 [3.8-7.5]	0.52
Discrimination	11.0 [10.0-13.0]	11.0 [9.5-12.0]	11.0 [10.0-13.3]	12.0 [11.0-13.0]	0.33
Identification	10.5 [9.8-12.0]	10.0 [9.0-12.0]	11.5 [10.0-12.0]	10.0 [10.0-10.0]	0.28
TDI score, median [P25-P75]	26.6 [23.0-30.0]	24.8 [22.6-28.8]	27.5 [24.8-32.7]	29.5 [24.5-30.8]	0.27
Anosmic, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Hyposmic, n (%)	33 (75.0%)	16 (84.2%)	11 (68.7%)	6 (66.7%)	0.47
Normosmic, n (%)	11 (25.0%)	3 (15.8%)	5 (31.3%)	3 (33.3%)	
VAS smell, median [P25-P75]	5.0 [3.0-7.0]	5 [3.0-6.0]	5.8 [4.8-8.0]	5.0 [2.0-8.0]	0.27
SNOT-22, median [P25-P75]	18.0 [8.8-26.0]	21.0 [10.5-27.5]	17.0 [9.8-23.0]	8.0 [5.0-26.0]	0.32
Parosmia, No (%)	27 (61.4%)	11 (57.9%)	8 (50.0%)	8 (88.9%)	0.35

Table 2. Measurements at baseline and follow-up. *Significant p-values. Level of significance p<0.05.

TDI: Threshold + Discrimination + Identification; VAS: Visual Analogue Scale; SNOT-22: SinoNasal Outcome Test-22 items.

	Patients with OD (n=44)	***Group A_{S+OT} (n=19)***	***Group B_{OT} (n=16)***	***Group C_{None} (n=9)***	***p-value$_{A-B-C}$***
Sniffin' Sticks, median [IQR]					
Threshold	**+1.25 [3.75] (p=0.004*)**	+0.50 [2.62] (p=0.11)	+2.00 [3.88] (p=0.06)	+2.75 [4.75] (p=0.23)	0.58
Discrimination	**+1.00 [3.00] (p=0.008*)**	+1.00 [3.00] (p=0.06)	+1.00[3.50] (p=0.17)	+2.00 [5.00] (p=0.23)	0.94
Identification	**+1.00 [3.50] (p=0.01*)**	+0.00 [3.50] (p=0.09)	+0.00 [3.50] (p=0.27)	+1.00 [1.00] (p=0.65)	0.85
TDI score, median	**+2.25 [8.25] (p=0.0003*)**	**+2.25 [5.75] (p=0.01*)**	**+2.5 [9.38] (p=0.04*)**	+0.75 [9.75] (p=0.12)	0.99
VAS smell, median [IQR]	**+2.00 [3.00] (p=0.003*)**	**+2.00 [2.62] (p=0.01*)**	+3.00 [5.00] (p=0.22)	+1.00 [2.25] (p=0.09)	0.84
SNOT-22, median [IQR]	-1.00 [13.00] (p=0.59)	-1.50 [12.00] (p=0.57)	0.00 [14.00] (p=0.89)	-8.00 [28.00] (p=0.62)	0.77
Parosmia, No (%)	-4 (0.09%) (p=0.46)	-5 (0.26%) (p=0.51)	+1 (0.06%) (p=1)	0 (0.0%)	0.06

Table 3. Changes between T_0 and T_1 for the available variables and statistical differences. The sign '+' shows an increase in the recorded values while the sign '-' highlights a decrease. Please note that values represent changes either in the median values (Sniffin' Sticks, VAS smell, SNOT-22) or number of observations (Parosmia). *Significant p-values. Level of significance p<0.05.

TDI: Threshold + Discrimination + Identification; VAS: Visual Analogue Scale; SNOT-22: SinoNasal Outcome Test-22 items.

	Patients with OD (n=44)	***Group A_{S+OT} (n=19)***	***Group B_{OT} (n=16)***	***Group C_{None} (n=9)***	***p-value$_{A-B-C}$***
Sniffin' Sticks, median [IQR]					
Threshold	**+1.25 [3.75] (p=0.004*)**	+0.50 [2.62] (p=0.11)	+2.00 [3.88] (p=0.06)	+2.75 [4.75] (p=0.23)	0.58
Discrimination	**+1.00 [3.00] (p=0.008*)**	+1.00 [3.00] (p=0.06)	+1.00[3.50] (p=0.17)	+2.00 [5.00] (p=0.23)	0.94
Identification	**+1.00 [3.50] (p=0.01*)**	+0.00 [3.50] (p=0.09)	+0.00 [3.50] (p=0.27)	+1.00 [1.00] (p=0.65)	0.85
TDI score, median	**+2.25 [8.25] (p=0.0003*)**	**+2.25 [5.75] (p=0.01*)**	**+2.5 [9.38] (p=0.04*)**	+0.75 [9.75] (p=0.12)	0.99
VAS smell, median [IQR]	**+2.00 [3.00] (p=0.003*)**	**+2.00 [2.62] (p=0.01*)**	+3.00 [5.00] (p=0.22)	+1.00 [2.25] (p=0.09)	0.84
SNOT-22, median [IQR]	-1.00 [13.00] (p=0.59)	-1.50 [12.00] (p=0.57)	0.00 [14.00] (p=0.89)	-8.00 [28.00] (p=0.62)	0.77
Parosmia, No (%)	-4 (0.09%) (p=0.46)	-5 (0.26%) (p=0.51)	+1 (0.06%) (p=1)	0 (0.0%)	0.06

Table 4. Influence of the available variables on smell recovery for Group A and Group B. Please note that not all the variables enter the multiple regression model but only those found to be significant at the stepwise selection based on AIC. *Significant p-values. Level of significance p<0.05.

TDI: Threshold + Discrimination + Identification; VAS: Visual Analogue Scale; SNOT-22: SinoNasal Outcome Test-22 items.

Influence of available variables on smell improvement

Presence of comorbidities negatively influenced the TDI and identification scores in group A ($p=0.04$ and $p=0.03$ respectively) and the discrimination and identification scores in group B ($p<0.001$ and $p=0.007$ respectively). Age and sex (male) negatively influenced identification score in group B only ($p<0.001$ for both) while the length of OD negatively influenced threshold and discrimination scores in group A ($p=0.02$ and $p=0.01$ respectively) and the discrimination and identification scores in group B ($p<0.001$ and $p=0.004$ respectively). *(Table 4)* All the other variables were found to not influence smell recovery.

6.14.4. Discussion

Corticosteroids have been considered as a therapeutic option for PIOD with many studies showing promising results[557,714-717]. It has been hypothesised that some patients with persistent PIOD may have an undetectable (not macroscopically evident) ongoing inflammation in the olfactory neuroepithelium[428,718,719] which could explain why some people could respond better than others to steroidal treatment[719,720]. However, in the absence of large randomised-controlled trials, evidence supporting its use in PIOD remains weak. So far, a unanimous consensus has not been reached and clear guidelines do not exist. In January 2021 an experts panel concluded that “oral and topical steroids may still have a role in the management” of PIOD and “may be used in carefully selected patients”[712] while in another international consensus issued a month later on the treatment of COVID-19-related OD the majority of the authors thought that “systemic CCS should not be considered as standard-of-care” although these could “have a potential place” in its treatment[721].

Our results failed to demonstrate a clear superiority of taking corticosteroids in combination with OT over OT alone. In fact, both treatments were found to improve TDI score at follow-up although none was superior to the other (p=0.99). Nevertheless, a higher statistically significant improvement was demonstrated in the group of patients taking the combined treatment (p=0.01 vs p=0.04). When looking at the MCID for the TDI score for single patient in each group, we observed a very similar percentage of patients who reached the MCID in the two treatment groups (31.6% in group A vs 31.3% in group B) with a slightly higher number of patients in group C, although this was not statistically significant (p=0.78). Nonetheless, a statistically significant improvement of the VAS score (p=0.01) was observed only in those having the combined treatment. The lack of statistically significant differences of baseline characteristics between the three groups, helped us to rule out any selection bias in treatment choice. Overall, these results seem to suggest a benefit, at least in the reported OD, of adding a short course of corticosteroids to OT in the management of COVID-19-related OD. In this regard, our data corroborate previous findings by Le bon et al.[716] who found that only patients with combined therapy (10-day course of 32 mg of methylprednisolone once daily combined with OT) significantly improved olfactory function when compared to those who did the OT alone. However, our patients had a considerably longer length of OD (7.5 months on average) compared to Le Bon et al. subjects (5 weeks on average). A recent systematic review by Yuan et al.[717] concluded that “a combination of steroids and OT is more efficient than OT only in managing OD from post-viral OD”. In 2018, Nguyen and Patel[557] found that steroid irrigation (Budesonide respules in a 0.5-mg/2-mL dose) in combination with OT was superior to OT alone in improving olfactory function in patients with anosmia of different causes (46.6% were PIOD). In a retrospective study conducted on 46 adults, Fleiner et al.[707] concluded that OT with a topical nasal steroid (not better described) was more effective than OT alone, especially in the subgroup of patients with PIOD. It must be stated that, in addition to the way of administration, corticosteroid molecules differ in terms of their anti-inflammatory potencies and duration of action[722] which could

eventually influence their potential effect to improve sense of smell. However, to our knowledge, the best corticosteroid molecule to use in COVID-19-related OD, or broadly in post-viral OD, has not yet been identified.

Today, most of the authors agree that, considering the systemic side effects of taking oral corticosteroids, it is not recommended to use them more than 2 weeks for the treatment of COVID-19-related OD[556]. As an option, giving a short course of oral steroids for 3–4 days has been suggested as a diagnostic tool[720], followed then by a full course of steroids completing 2 weeks for those responding. However, this would require an extra follow-up to assess treatment response which could not always be feasible in the context of a stretched national health system.

A strong association between the time of initiation of corticosteroids therapy and smell recovery rate has been confirmed in patients with PIOD. Experts agree that oral corticosteroids could have a role only if administered in the early stage of COVID-19-related OD[712] event though the overall consensus is to not suggest them within the first 3 weeks after OD onset due to the high rate of spontaneous recovery[310,590,721]. However, the question remains whether it is worthwhile trying oral corticosteroids in patients with a persistent OD (longer than 6 months). In this regard, Genetzaki et al.[720] noted a smell improvement also in patients with persistent OD (up to 12 months) receiving oral corticosteroids plus OT. In our study, a significant improvement of the TDI score was observed in group A with patients having an average length of OD of 7.1 months. However, the length of OD did not influence smell recovery in group A while an effect was noted in group B on TDI, threshold and identification scores with a cut-off of 300 days found to be significant for all the three scores. This suggests that an early initiation of the OT (before 10 months) could give a better benefit in terms of olfactory improvement. Interestingly, the lack of influence of the time variable on the olfactory

recovery of patients taking the combined treatment would indicate its effectiveness irrespective of the length of OD.

We also found that patients in both groups who had had previous treatments for OD responded better to the therapy in term of olfactory scores at follow-up. Similarly, the presence of comorbidities significantly correlated with smell recovery in both treatment groups while an impact of age (younger than 50 years) and sex (male) was found to influence identification scores only in those who did the OT alone, as previously noted[590].

The decision over the best way of administering corticosteroids (oral vs topical vs combination) still remains a matter of debate. Despite some studies seem to show no benefit of topical steroid in improving PIOD[723-725], delivery method could influence response to treatment. The majority of the authors agree that nasal corticosteroids sprays are not useful because they cannot reach the olfactory clefts. On the other side, rinsing with a topical steroid irrigation[557] or delivering steroid drops in the Kaiteki position[726] has been reported to be helpful. Given the potential benefits of intranasal steroid drops, we offered a combined treatment of oral and topical steroids for a total length of treatment of 4 weeks.

Finally, our data also highlight the role of OT in persistent PIOD, as demonstrated by the fact that no statistically significant improvement was observed in those who did not do it (group C).

Strengths and limitations

This study is the first one looking at the role of corticosteroids in patients with a persistent COVID-19-related OD. Also, all patients considered in the study had no signs of paranasal inflammation, as demonstrated by a clear MRI head. This allowed us to be more confident that any smell improvement observed in the steroid group would have

not been confounded by treating an underlying sinonasal disease. The main limitation of the study is its non-randomized non-blinded design as treatments suggested were not randomly assigned. However, this represents a real-life study and it was not initially designed as a prospective controlled trial. Group C did not reach the minimal sample size; therefore, we cannot exclude that the results observed regarding this group were affected by a casual effect. Even though it could be considered a controlled study for the presence of two different control groups, their inclusion was not part of the initial study design but was a consequence of patients' own choice to take or not the treatment suggested. As an additional consequence of that, the patients reported outcomes (i.e. VAS and SNOT-22) might have been biased whereas those receiving the combined treatment were more prone to believe they could have achieved an improvement at the end of the treatment. Also, by giving a combination of oral and topical steroid drops to patients in group A, we were not able to conclude whether the observed smell improvement was due to a particular formulation of corticosteroids or to the combination of both.

6.14.5. Conclusions

Our study confirms the importance of OT in the treatment of persistent COVID-19-related OD suggesting that the addition of corticosteroids may also give a benefit in term of patient's perceived olfaction. Topical steroid drops administered in the Kaiteki position may contribute to oral corticosteroids effect by targeting directly the olfactory neuroepithelium. However, benefits of corticosteroids must be considered against their systemic side effects and randomised controlled studies on bigger populations are strongly encouraged to better clarify their role in the treatment of persistent PIOD.

6.15. The effectiveness of functional septorhinoplasty in improving COVID-19-related olfactory dysfunction

6.15.1. Introduction

The recent COVID-19 pandemic has left millions of people with a profound loss of chemosensation due to the high prevalence of olfactory dysfunction (OD) linked to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[310,425,590,592] Although a high recovery rate has been observed during the first months,[69] up to 13% of subjects can show persistent COVID-19 related-OD (C19OD) at 3 years,[727] with severe impact on quality of life (QoL).[425,592]

The olfactory pathophysiology of C19OD is multifactorial. Traditionally, causes of OD have been classidied according to the anatomical location of the presumed pathology/lesion and divided as conductive, sensorineural and central, or a combination of these. SARS-CoV-2 typically damages the olfactory epithelium (OE), thus creating a sensorineural loss of smell, and to a lesser extent affects the central primary and secondary olfactory cortices.[470,684] Although C19OD represents a reversible sensorineural olfactory loss in the majority of cases,[727] the question remains as to why this is not the case for those developing a persistent loss of sense of smell.

Normal nasal airflow through the olfactory cleft is one of the conditions necessary for an intact olfactory sense.[130] Current evidence shows that a moderate-to-severe deviated nasal septum (DNS) results in decreased olfactory function on the obstructed nasal side (lateralised olfaction) and olfaction is normalised following septoplasty.[178] OD caused by a structural obstruction is mainly caused by a conductive loss secondary to a reduction in the access of odorants to the OE and once rectified the sense of smell returns to normal.[155,171-173,728] The relationship between nasal airway improvement following septal

surgery and improved olfaction has been consistently demonstrated.[130,153,165-167,173,174,176,177,426,694,729-731]

Functional septorhinoplasty (fSRP), as well as correcting a DNS, can also increase internal/external nasal valve (INV/ENV) function, which is crucial in regulating airflow to the olfactory region.[149,732] With additional INV and ENV augmentation, there is growing evidence suggesting that fSRP can improve olfaction to a greater extent than septoplasty alone and implying that other mechanisms, in addition to the conductive component, are involved in the smell improvement.[177,178,426,731,733] In this regard, Whitcroft et al.[178] demonstrated that fSRP can improve olfaction in patients with a combination of conductive and sensorineural olfactory loss. The authors hypothesised that the observed olfactory improvement was achieved by an improved OE function caused by an increased nasal airflow to the olfactory niche.[178]

In the post-COVID-19 era, the unmet need is to find a treatment which could achieve a meaningful olfactory increase for patients with long-term (>2 years) C19OD. This noticeable, perceptible for the patient, improvement in the smell function is usually defined as an increase in the smell scores above the minimal clinically important difference (MCID).

Currently only few studies have explored treatments for persistent C19OD lasting longer than one year but MCID in olfactory gain has never been achieved.[734] We conducted a pilot study to evaluate olfactory changes in patients with persistent C19OD undergoing fSRP and compared these to a control group of C19OD patients on OT.

6.15.2. Materials and methods

Participants were recruited from patients seen in the long-COVID smell clinic at the Royal National ENT Hospital hospital between October 2022 and May 2023. Inclusion and exclusion criteria are reported in *Table 1*. This study was approved by the Hospital Research Ethic Committee (ref 14/SC/1180) and was conducted in accordance with the 1996 Declaration of Helsinki. All participants provided full informed written consent prior to participation.

Inclusion	Exclusion
Age ≥18.	Presence of other causes leading/contributing to OD (also confirmed by MRI of the head/sinuses).[+]
Aetiology of OD following a polymerase chain reaction–confirmed diagnosis of SARS-CoV-2 infection.	History of PIOD prior to COVID-19.
OD confirmed at Sniffin' Sticks and longer than 18 months.	Prior nasal/sinonasal/skull base surgery.
OD failing to improve on conservative treatments, including OT and oral/topical corticosteroids.	Bleeding disorders.
Aesthetically unacceptable nasal deformity or reduced nasal airflow caused by a confirmed DNS and/or INV/ENV dysfunction.	Blood thinners assumption.

Table 1. Study inclusion and exclusion criteria.
[+]These include: congenital olfactory loss, post-traumatic olfactory dysfunction, chronic rhinosinusitis, neoplasms, previous chemotherapy or radiotherapy to the head and neck, neurodegenerative diseases

OD: olfactory dysfunction; PIOD: post-infectious olfactory dysfunction; OT: olfactory training; MRI: magnetic resonance imaging; DNS: deviated nasal septum; INV: internal nasal valve; ENV: external nasal valve.

Subjects satisfying eligibility criteria were offered fSRP. Those refusing it but willing to take part in the study, were asked to continue with OT for the entire study period and formed the control arm. Subjects in the treatment group were assessed at baseline (T_0), 3-month (T_1) and 6-month (T_2) from fSRP. Those in the control group, instead, were assessed at T_0 and T_2 only. During the follow-up period, participants were asked to not

start any additional treatment potentially influencing olfaction. Compliance with OT in the control group was assessed at T_2. fSRP was performed using a standardised external approach involving septoplasty with nasal bone realignment to increase airway symmetry, INV and ENV augmentation using autologous spreader grafts and columellar strut respectively. All operations were performed by the same team (yy) and following the same surgical technique.

Sense of smell was evaluated using S'S extended set (Burghart, Medisense) to obtain the odour threshold(T), discrimination(D), and identification(I) scores.[112] Normosmia was attributed where TDI score was ≥30.75, hyposmia where TDI was >16, but <30.75, and functional anosmia if TDI≤16.[112] The MCID was defined as a clinically significant improvement corresponding to 5.5 points increase for TDI (our primary outcome) and 2.5 points for the other S'S scores.[128] Bilateral and unilateral peak nasal inspiratory flow (PNIF) were performed to assess nasal airflow while acoustic rhinometry (AR) was used to obtain unilateral minimal cross-sectional area (MCA) and nasal volume (NV).[282,404,405] QoL was assessed using the 36-Item Short Form Health Survey (SF-36). Self-assessment of olfaction was performed using a visual analogue scale for smell (sVAS – 0 represents "sense of smell absent" and 10 "sense of smell not affected")[310] whereas sinonasal symptoms were evaluated using the 22-item Sino-Nasal Outcome Test (SNOT-22).[406] The Nasal Obstruction Symptom Evaluation (NOSE) scale was used to subjectively assess nasal obstruction.[735] Qualitative olfactory dysfunction (i.e. parosmia/phantosmia) was investigated by asking the participants if the symptom was present or not at the moment of the examination.

Statistical analysis

Quantitative variables were summarized using median and interquartile range whereas qualitative variables were described with frequency and percentage. Comparisons of measurements between baseline and follow-ups were performed using the Mann-

Whitney test for quantitative variables and the proportion test for dichotomic variables. Person correlation index was used to measure associations between quantitative variables. p-values were calculated for all tests, and 5% was considered as the critical level of significance. Sample size was determined using a power analysis of independent Mann-Whitney test (two-sided) assuming a difference between means at the end of the study of 5.5 TDI points (MCID)[128] and an equal standard deviation in the two groups of 4 TDI points. Based on that, a minimum of 10 patients in each group were required to reach a power of 81%, with an alpha error of 0.05.

6.15.3. Results

This study assessed for eligibility 104 subjects. Twenty-five participants were selected with 12 forming the treatment group and 13 entering the control group. Nine patients in the treatment group and 10 in the control arm completed the 6-month follow-up period (6-month drop-out rate of 25.0% and 23.1%, respectively). No complications were recorded following fSRP. Demographics and baseline characteristics for the participants, and comparison between groups, are reported in *Table 2.*

Olfactory scores, nasal measurements and patient-reported outcome measures (PROMs) at baseline

Apart from the median discrimination scores, all S'S subtests scores at baseline were below normative values when compared to those of an adult population of similar age group.[112] Similarly, baseline median bilateral and unilateral PNIF as well as AR parameters were below the reference values for an adult population of similar age group.[285,404,736]

	Treatment group *n* = 12	Control group *n* = 13	*p*-value
Age, median [P25-P75], yr	40.0 [31.5-44.0]	49.0 [30.0-54.0]	0.66
Sex, No (%) Female Male	 9 (75.0%) 3 (25.0%)	 8 (61.5%) 5 (38.5%)	0.77
Length of OD^{+}, median [P25-P75], yr	2.3 [2.0-2.5]	2.4 [1.9-2.8]	0.53
Parosmia, No (%)	10 (83.3%)	10 (76.9%)	1
Phantosmia, No (%)	4 (33.3%)	2 (15.4%)	0.56
Smoking, No (%) Ex-smoker Yes No	 1 (100%) 0 (0.0%) 0 (0.0%)	 0 (0.0%) 2 (100%) 0 (0.0%)	0.50
Comorbidity, No (%) None Yes Hypothyroidism Asthma Others	 8 (66.7%) 4 (33.3%) 1 (25.0%) 1 (25.0%) 4 (100%)	 9 (69.2%) 4 (30.8%) 1 (25.0%) 1 (25.0%) 3 (75.0%)	0.33
Allergic rhinitis, No (%)	2 (16.7%)	0 (0.0%)	0.94
Chronic rhinosinusitis, No (%)	0 (0.0%)	0 (0.0%)	1
Family history Alzheimer/Parkinson, No (%)	3 (25.0%)	1 (7.7%)	1
History of PIOD, No (%)	2 (16.6%)	3 (23.1%)	1
History of previous nasal operations, No (%)	0 (0.0%)	0 (0.0%)	1
History of head trauma, No (%)	1 (8.3%)	0 (0.0%)	0.97

Table 2. General characteristics of the treatment and control groups at baseline. Statistical difference between groups is also shown. Significant p-values in bold. Levels of significance *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001.$^{+}$ Length of OD is calculated as number of days from the infection date to the day of enrolment.

OD: olfactory dysfunction; PIOD: post-infectious olfactory dysfunction.

Lower SF-36 scores were found for the health domains role limitations due to physical health, energy/fatigue, emotional wellbeing, social functioning and general health when compared to normative values for the UK population.[737] Reduced scores were observed for sVAS while raised scores were found for the SNOT-22[105] and NOSE.[738] No statistically significant differences were noted in the olfactory scores, nasal measurements and PROMs at baseline between the two groups.(*Tables 3-4*)

	Treatment group			*Control group*	
	Baseline (T_0) n=12	3-month (T_1) n=10	6-month (T_2) n=9	Baseline (T_0) n=13	6-month (T_2) n=10
Sniffin' Sticks					
TDI, median [P25-P75]	22.3 [20.0-24.8]	26.8 [20.0-24.8]	30.3 [24.5-30.8]	22.0 [18.0-25.0]	21.9 [21.1-31.2]
Threshold, median [P25-P75]	1.8 [1.0-3.8]	4.6 [1.7-7.0]	5.8 [4.0-7.3]	4.0 [2.3-4.5]	4.4 [2.2-5.4]
Discrimination, median [P25-P75]	10.0 [10.0-11.3]	11.5 [10.0-12.0]	12.0 [11.0-13.0]	9.0 [8.0-10.0]	10.5 [8.0-13.0]
Identification, median [P25-P75]	9.0 [8.0-11.3]	10.5 [9.0-12.8]	12.0 [10.0-13.0]	9.0 [7.0-10.0]	10.0 [8.3-10.8]
Normosmics, n (%)	0 (0.0%)	1 (10.0%)	4 (44.4%)	0 (0.0%)	3 (30.0%)
Hyposmics, n (%)	11 (91.7%)	9 (90.0%)	5 (55.6%)	12 (92.3%)	6 (60.0%)
Anosmics, n (%)	1 (8.3%)	0 (23.5%)	0 (0.0%)	1 (7.7%)	1 (10.0%)
Nasal measurements					
PNIF, median [P25-P75], L/min					
Bilateral PNIF	115.0 [87.5-137.5]	137.5 [130.0-157.5]	160.0 [125.0-190.0]	135.0 [110.0-162.5]	-
Right PNIF	62.5 [50.0-82.5]	82.5 [66.3-130.0]	110.0 [70.0-120.0]	82.5 [66.3-98.8]	
Left PNIF	60.0 [48.8-77.5]	90.0 [81.3-107.5]	65.0 [50.0-100.0]	100.0 [68.8-116.3]	
Acoustic rhinometry, median [P25-P75]					
Right MCA1, cm^2	0.5 [0.4-0.7]	0.5 [0.4-0.7]	0.6 [0.4-0.7]	0.6 [0.4-0.9]	
Right Nasal volume (0-5), cm^3	5.7 [5.2-7.3]	8.1 [5.9-10.9]	7.9 [5.8-9.4]	6.9 [6.2-13.1]	-
Left MCA1, cm^2	0.7 [0.4-0.8]	0.7 [0.5-0.8]	0.6 [0.5-0.8]	0.8 [0.6-1.1]	
Left Nasal volume (0-5), cm^3	6.6 [5.7-7.4]	9.5 [7.6-10.7]	8.0 [6.0-9.1]	9.0 [6.1-13.1]	
PROMs					
SF-36, median [P25-P75], %					
Physical functioning	95.0 [83.8-100]	100 [81.3-100]	95.0 [90.0-100]	100 [87.5-100]	100 [91.3-100]
Role limitations due to physical health	62.5 [25.0-100]	75.0 [31.3-100]	75.0 [50.0-100]	100 [75.0-100]	100 [100-100]
Role limitations due to emotional problems	100 [33.3-100]	100 [66.7-100]	100 [100-100]	100 [16.7-100]	100 [50.0-100]
Energy/Fatigue	50.0 [23.8-73.8]	60.0 [37.5-75.0]	55.0 [50.0-80.0]	45.0 [27.5-62.5]	52.5 [38.8-55.5]
Emotional wellbeing	70.0 [67.0-88.0]	72.0 [68.0-88.0]	84.0 [76.0-88.0]	80.0 [58.0-82.0]	72.0 [53.0-90.0]
Social functioning	68.8 [46.9-100]	100 [65.6-100]	100 [81.3-100]	62.5 [50.0-93.8]	81.3 [62.5-96.9]
Pain	78.8 [65.0-90.0]	90.0 [78.1-97.5]	90.0 [73.8-95.0]	90.0 [83.8-100]	95.0 [71.9-100]
General health	65.0 [45.0-72.5]	62.5 [55.0-83.8]	75.0 [50.0-85.0]	65.0 [40.0-77.5]	62.5 [55.0-68.8]
sVAS, median [P25-P75]	4.3 [3.0-5.3]	5.0 [4.0-6.4]	6.0 [4.5-6.0]	4.0 [2.0-5.5]	4.0 [3.5-5.0]

SNOT-22, median [P25-P75]	25.0 [14.3-30.0]	13.0 [9.3-32.5]	11.0 [6.0-15.0]	12.0 [10.0-30.5]	17.5 [15.3-27.8]
NOSE, median [P25-P75]	25.0 [12.5-45.0]	17.5 [7.5-34]	10.0 [10.0-15.0]	20.0 [10.0-52.5]	27.5 [6.5-44]

Table 3. Olfactory and nasal measurements, and patient-reported outcome measures (PROMs) at baseline, 3- and 6-month following functional septorhinoplasty for the treatment group and at baseline and at 6-month for the control group.

TDI: Threshold + Discrimination + Identification; PNIF; peak nasal inspiratory flow; lPNIF: left PNIF; rPNIF: right PNIF; MCA1: first minimal cross-sectional area.
SF-36: 36-item Short Form Survey; EQ-5D-5L: EuroQoL 5-Dimension 5-Level; Short-QODNS: short version of Questionnaire of Olfactory Disorders - Negative Statements; sVAS: Visual Analogue Scale for sense of smell; SNOT-22: 22-item SinoNasal Outcome Test; NOSE: Nasal Obstruction and Septoplasty Effectiveness Scale

	Within group comparisons				Between groups Comparisons†		
	Treatment group			*Control group*			
	T_0-T_1	T_1-T_2	T_0-T_2	T_0-T_2	T_0	T_2	$\lvert\Delta T_0\text{-}T_2\rvert$
Sniffin' Sticks							
TDI	+4.5 (0.15)	+3.5 (0.22)	+8.0 (**0.005**)**	-0.1 (0.39)	+0.3 (0.57)	+8.4 (0.19)	8.1 (0.06)
Threshold	+2.8 (0.08)	+1.2 (0.57)	+4.0 (**0.01**)**	+0.4 (0.53)	-2.2 (0.11)	+1.4 (0.33)	3.6 **(0.05)***
Discrimination	+1.5 (0.46)	+0.5 (0.28)	+2.0 (**0.05**)*	+1.5 (0.51)	+1.0 (0.07)	+1.5 (0.46)	0.5 (0.74)
Identification	+1.5 (0.27)	+1.5 (0.38)	+3.0 (**0.04**)*	+1.0 (0.23)	0.0 (0.32)	+2.0 (0.08)	2.0 (0.07)
Nasal measurements							
PNIF, L/min							
Bilateral PNIF	+22.5 (0.06)	+22.5 (0.84)	+45.0 (**0.04**)*		-20.0 (0.20)		
Right PNIF	+20.0 (0.11)	+27.5 (0.77)	+47.5 (0.07)	-	-20.0 (0.13)	-	-
Left PNIF	+30.0 (**0.03**)*	-25.0 (0.27)	+5.0 (0.40)		-40.0 (0.06)		
Acoustic rhinometry							
Right MCA1, cm^2	0.0 (0.62)	+0.1 (0.29)	+0.1 (0.34)		-0.1 (0.45)		
Right Nasal volume (0-5), cm^3	+2.4 (0.07)	-0.2 (0.66)	+2.2 (**0.03**)*		-1.2 (0.1)		
Left MCA1, cm^2	0.0 (0.72)	-0.1 (0.96)	-0.1 (0.84)	-	-0.1 (0.38)	-	-
Left Nasal volume (0-5), cm^3	+2.9 (0.09)	-1.5 (0.90)	+1.4 (0.11)		-2.4 (0.19)		
PROMs							
SF-36, %							
Physical functioning	+5.0 (0.55)	-5.0 (0.83)	0.0 (0.74)	0.0 (0.78)	-5.0 (0.63)	-5.0 (0.63)	0.0 (0.56)
Role limitations due to physical health	+10.0 (0.68)	0.0 (0.97)	+10.0 (0.61)	0.0 (0.74)	-37.5 (0.14)	-25.0 (0.14)	10 (0.32)
Role limitations due to emotional problems	0.0 (0.85)	0.0 (0.40)	0.0 (0.47)	0.0 (0.64)	0.0 (0.55)	0.0 (0.56)	0.0 (0.33)
Energy/Fatigue	+10.0 (0.69)	-5.0 (0.62)	+5.0 (0.41)	+7.5 (0.59)	+5.0 (0.77)	+2.5 (0.43)	2.5 (0.95)
Emotional wellbeing	+2.0 (0.74)	+12.0 (0.44)	+14.0 (0.43)	-8.0 (1.00)	-10.0 (0.67)	+12.0 (0.29)	22 (0.72)
Social functioning	+31.2 (0.24)	0.0 (0.93)	+31.2 (0.31)	+18.8 (0.73)	+6.3 (0.79)	+18.7 (0.37)	12.4 (0.85)
Pain	+11.2 (0.57)	0.0 (0.65)	+11.2 (0.74)	+5.0 (0.96)	-11.2 (0.28)	-5.0 (0.42)	6.2 (0.27)
General health	-2.5 (0.74)	+12.5 (0.97)	+10.0 (0.50)	-2.5 (1.00)	0.0 (1)	+12.5 (0.32)	12.5 (0.72)
sVAS	+0.7 (0.34)	+1.0 (0.84)	+1.7 (0.17)	0.0 (0.69)	+0.3 (0.78)	+2.0 (0.25)	1.7 (0.82)
SNOT-22	-12.0 (0.27)	-2.0 (0.35)	-14.0 (**0.03**)*	+5.5 (0.53)	+13.0 (0.53)	-6.5 (0.13)	19.5 (0.41)

NOSE	-7.5 (0.48)	-7.5 (0.20)	-15.0 (**0.05**)*	+7.5 (0.84)	+5.0 (0.93)	-17.5 (0.20)	22.5 (0.31)

Table 4. Differences in medians and statistical significance (p-values – in brackets). The sign '+' indicates an improvement while the sign '-' indicates a worsening in the median values. Please note that for the intergroup differences the direction signs have not been used.
Significant p-values in bold. Levels of significance *p ≤ 0.05, **p ≤ 0.01.
† Comparison made with reference to treatment group (i.e. Treatment group – Control group)

TDI: Threshold + Discrimination + Identification; PNIF; peak nasal inspiratory flow; lPNIF: left PNIF; rPNIF: right PNIF; MCA1: first minimal cross-sectional area.
PROMs: patient-reported outcome measures; SF-36: 36-item Short Form Survey; EQ-5D-5L: EuroQoL 5-Dimension 5-Level; Short-QODNS: short version of Questionnaire of Olfactory Disorders - Negative Statements; sVAS: Visual Analogue Scale for sense of smell; SNOT-22: 22-item SinoNasal Outcome Test; NOSE: Nasal Obstruction and Septoplasty Effectiveness Scale

Within and between groups comparisons at follow-ups

An improvement in all S'S scores was observed only in the fSRP group both at T_1 and T_2 but these were statistically significant and all above MCID level (apart from discrimination) only at T_2.(*Figure 1; Tables 3-4*) A statistically significant improvement at T_2 from baseline (T_0-T_2) was noted only in the treatment group in the bilateral PNIF (p=0.04) and right NV (p=0.03), while left PNIF improved significantly only at T_1 from baseline (T_0-T_1, p=0.03).(*Tables 3-4)* A statistically significant reduction in the SNOT-22 and NOSE was demonstrated at T_2 (respectively p=0.03 and p=0.05) only in the treatment group.(*Tables 3-4*) When comparing the gain obtained between T_0 and T_2 between the two groups, a statistically significant difference was noted for the threshold (p=0.05) and a trend towards significance was noted for the TDI (p=0.06) and the identification (p=0.07), all in favour of fSRP.(*Figure 2; Table 4*)

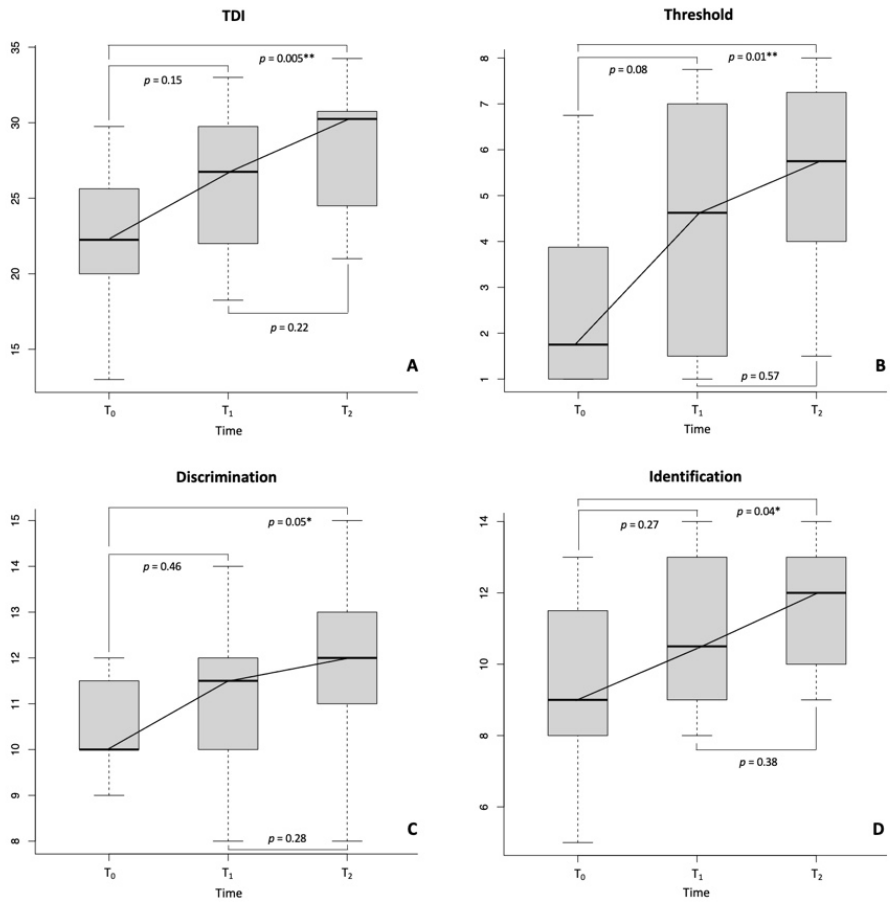

Figure 1. Box plots showing changes in TDI (a), threshold (b), discrimination (c) and identification (d) scores for the fSRP group during the study period. Statistical difference between intervals is also shown. Levels of significance *p ≤ 0.05, **p ≤ 0.01.

TDI: Threshold + Discrimination + Identification.

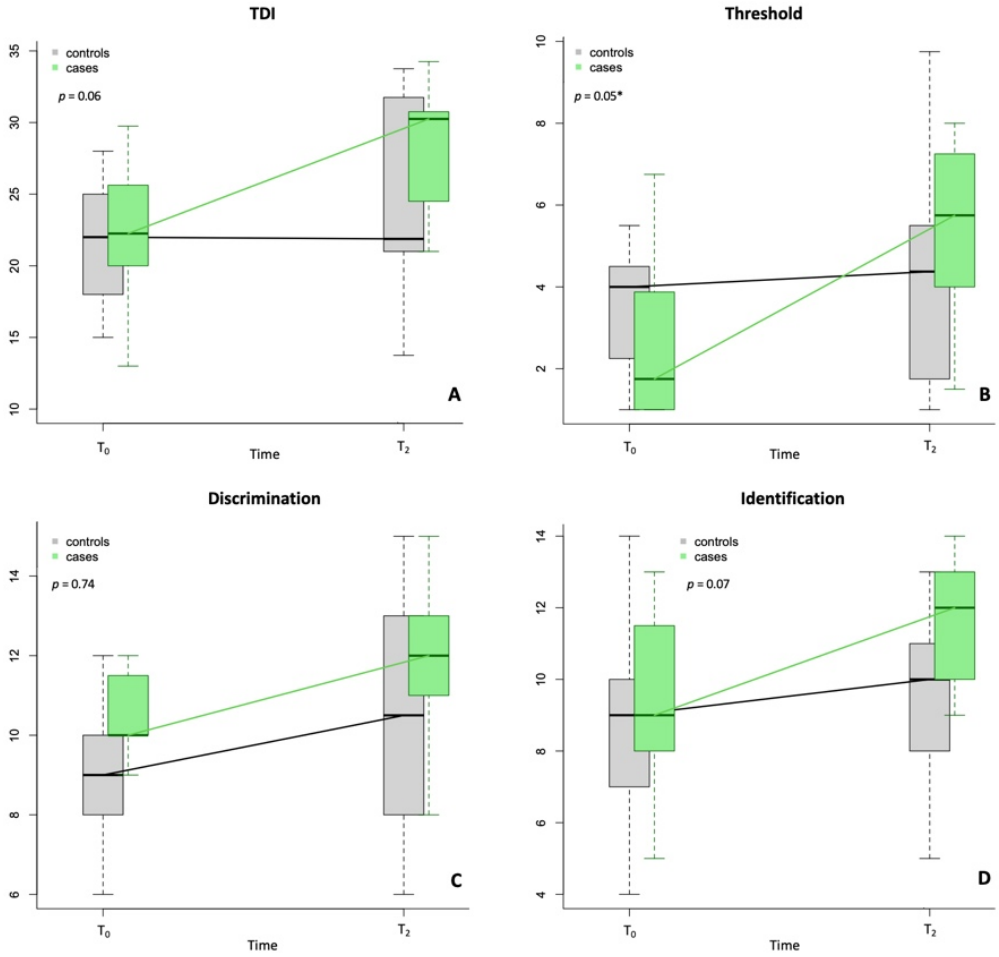

Figure 2. Box plots showing changes in TDI (a), threshold (b), discrimination (c) and identification (d) scores between the treatment (cases) and the control groups between T_0 (baseline) and T_2 (6 months). Statistical difference between intervals is also shown. Levels of significance *p ≤ 0.05.

Correlation between olfactory function and nasal measurements

No correlations were found between S'S scores and nasal measurements when considering all the measurements obtained in the whole population. When we looked at the correlations between the changes in S'S scores and nasal measurements between T_0 and T_2 in the fSRP group, we found strong significant correlations between changes in left PNIF and changes in TDI (r=0.67; p=0.05), between changes in total PNIF and changes in discrimination (r=0.73; p=0.03) and identification (r=-0.67; p=0.05), and between changes in left MCA1 and changes in identification (r=-0.74; p=0.03).*(Figure 3)*

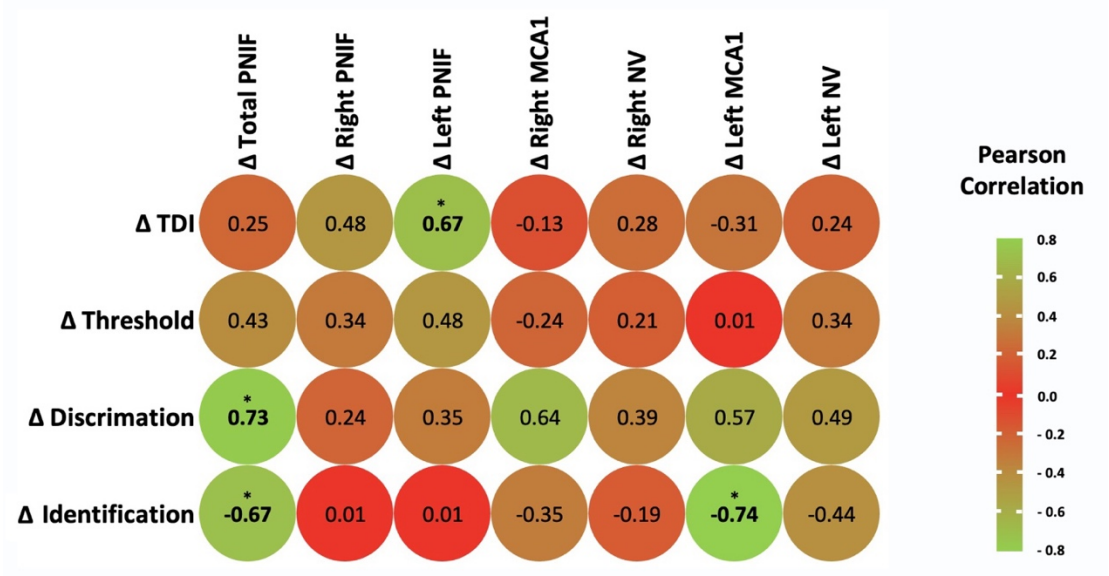

Figure 3. Correlation matrix showing strength of correlations between changes (Δ) in Sniffin' Sticks scores and changes (Δ) in nasal airways parameters in the treatment group. Levels of significance *p ≤ 0.05.

TDI: Threshold + Discrimination + Identification; PNIF; peak nasal inspiratory flow; lPNIF: left PNIF; rPNIF: right PNIF; MCA1: first minimal cross-sectional area; NV: nasal volume.

6.15.4. Discussion

Our pilot study shows that fSRP can significantly improve persistent C19OD in patients who have previously failed other treatment options for post-infectious OD (PIOD). Patients undergoing fSRP demonstrated a statistically significant improvement in their olfactory scores at 6 months, above MCID level for all S'S scores (apart from discrimination),[128] whilst an olfactory improvement was not observed in the control arm (patients on OT). Importantly, at 6 months, we observed a statistically significant improvement in threshold gain following fSRP (+3.6 points, p=0.05). A clear positive trend in TDI gain was also observed but did not reach statistical significance (+8.1 points, p=0.06). *(Table 4)* These olfactory gains represent the olfactory improvement secondary to the intervention minus the control arm, namely the olfactory benefit obtainable with fSRP when compared to OT. Several studies confirm that olfactory threshold reflects the peripheral olfactory apparatus function (i.e. OE).[178,739,740] This suggests that olfactory benefits following fSRP are primarily related to an increased peripheral olfactory

stimulation (i.e. olfactory sensorineural reactivation or sensorineural reversibility) implying that ORNs are still present in patients with persistent C19OD. Our data corroborates previous findings by Whitcroft et al.[178] who showed a statistically significant improvement in the mean TDI (+6.5 points, p=0.03) in patients with long-term OD undergoing fSRP. Similarly, we demonstrated TDI improvement in all our fSRP patients, with six of them (66.7%) reaching MCID,[128] when compared to only 4 (40%) in the control group. Importantly, in the control arm olfaction further decreased in 4 patients (40%) whilst deteroriation was not demonstrated in any of the fSRP patients. Although fSRP patients demonstrated a noticeable improvement in their TDI, statistical significance at T_2 was not reported with patient-reported olfaction (sVAS) and general QoL scores. However, in previous studies we found statistically significant correlations between olfactory scores, sVAS and SF-36,[425,592] and we believe these non-significant improvements obtained in the present study may be related to the small sample size of our cohorts.

The main driving mechanism to the olfactory improvement obtained in the fSRP group is centred around an increase in nasal airflow as confirmed by a strong significant correlation between post-operative changes in S'S scores and PNIF/AR. Following fSRP, patients experienced an objective and subjective increase in the nasal airflow as demonstrated by a significant improvement of bilateral PNIF (p=0.04) and a decrease in NOSE and SNOT-22 (p=0.05 and p=0.03, respectively) at 6 months. In addition to this prevalent mechanism, a previous functional MRI study showed that fSRP can lead to structural and functional plasticity of secondary olfactory cortices, caused by a bottom-up plasticity process.[178] In support of this, we demonstrated a statistically significant improvement of the identification and discrimination scores which have been shown to reflect more complex processing of olfactory information and influenced by cognitive processes.[178,739,740]

The concept of olfactory improvement following nasal surgery is not new.[130,153,165-167,173,176,177,426,694,729-731] However, its efficacy in PIOD, and in particular in C19OD, remains unexplored. Consequentely, in the post-COVID-19 era, in which thousands of people have been left with a debilitating OD unable to improve on other available options, the potential role of fSRP in improving OD is gaining increasing attention from many rhinology surgeons. This notion is supported by recent systematic reviews and meta-analyses showing that fSRP not only constitutes a safe procedure in terms of long-term olfactory function but can also restore smell.[130,733] The majority of studies seem to suggest that an improvement in the nasal airflow in the olfactory area can lead to improved olfaction by enhancing transport of odour molecules to the olfactory cleft.[153,154,163-169] In particular, a growing body of evidence seems to support the critical role of the INV in influencing airflow in the olfactory cleft region.[149-151,156] Spreader grafts are known to increase the INV angle section[741] and, in fact, a positive association between presence of spreader grafts and olfactory outcomes has been reported.[176] Anatomical variation of the ENV can also influence direction of the airflow and play a role in the transportation of odorants to the olfactory cleft.[157,158] Our patients underwent bilateral INV augmentation, by using bilateral spreader grafts, and anatomical variation of the ENV, by means of columellar strut. By increasing the nasal airflow to the olfactory clefts, growing evidence suggests that this increased olfactory stimulation, caused by a greater quantity of odorants reaching the olfactory area, can lead to an improved OE activity. This may contribute to the restoration of the sensorineural deficit (i.e. OE damage) present in C19OD.[178] This increased peripheral input can then lead to a structural and functional plasticity of secondary olfactory cortices through a bottom-up plasticity process.[178]

Although nasal airflow improved following fSRP, all patients were enrolled from our long-COVID smell clinic with a primary diagnosis of persistent C19OD and not nasal blockage. However, all patients had a mild nasal blockage with average NOSE scores less than 25

with mildly reduced PNIF/AR scores. Neevrtheless, it is important to delineate the separate pre-operative diagnoses of C19OD from long-standing mild nasal blockage which appear unrelated in causation prior to COVID. All our patients had reported normal sense of smell prior to COVID-19 (history of OD was an exclusion criteria to the study).

Despite continuous research efforts, treatments for long-term (>1year) C19OD today remain limited and equally have failed to demonstrate a clinically important olfactory improvement (i.e. above MCID). OT is considered the gold standard treatment for C19OD.[44,69,534] However, its benefits can abate when OD becomes long-standing and our study, unfortunately, seems to suggest so. This paints a bleak picture for those untreated patients with persistent C19OD.

Strengths and limitations

To the best of our knowledge, this is the first study to have investigated the role of fSRP, and more widely of nasal airways surgery, in improving sense of smell in patients with C19OD who have failed previous conservative options for PIOD. Moreover, it is the only study that looked into new potential treatments to improve olfaction in patients with a C19OD longer than 2 years, whilst demonstrating significant olfactory improvement above MCID. The main limitation of our study is the small sample size and, although our study was powered enough at baseline and at 3 months, it losts power at the 6-month follow-up due to patients' dropout.

6.15.5. Conclusions

Our pilot study suggests that fSRP can significantly improve sense of smell in patients with persistent C19OD lasting more than 2 years with additional significant olfactory threshold gain when compared to OT. By augmenting the INV angle and optimising nasal airflow to the olfactory cleft, fSRP can improve olfaction by increasing transport of

odorants to the OE. This increased stimulation of the olfactory mucosa leads to a sensorineural improvement of the OE potentially triggering a bottom-up plasticity process in the central olfactory areas. Nevertheless, further studies on larger populations are needed to confirm our preliminary findings.

6.16 Published studies on C19OD – summary of findings and their relevance in the PhD project

Prevalence of C19OD and long-term recovery rate is not completely known. In the multicentre survey on SARS-CoV-2 infected HCWs I found a prevalence of OD amongst HCWs of 73.1% with a complete olfactory recovery rate of 31.8% at 2 months (i.e. prevalence of OD at 2 months of 68.2%).[590] This prevalence is similar to what Borsetto et al.[437] reported in their meta-analysis when looking at mild-to-moderate COVID-19 cases (prevalence of 67%). Interestingly, smell recovery was worse amongst doctors and nurses/health-care assistants. I noted a similar recovery rate of C19OD at 2 months (43.4%) in my second study when assessing sense of smell using S'S, whereas at 6-month C19OD recovery rate was of 50.0%.[310] The second study showed for the first time that olfactory threshold was the most affected ability in C19OD subjects. As explained in the previous chapters, olfactory threshold has been shown to reflect the peripheral olfactory system function and is usually compromised in case of diseases primarily affecting the nose and/or the olfactory mucosa.[49,628] Therefore, I hypothesised that the pathogenesis of C19OD was related to an end-organ failure, namely an alteration of the OE.

In the cohort study on previously hospitalised patients with COVID-19 I found a prevalence of reported OD of 12.8% at median time of 9 months following SARS-CoV-2 infection.[591] This prevalence is lower when compared to those reported in *Table 6.2.* but may confirm a lower prevalence of OD in patients with severe (i.e. hospitalised) COVID-19 when compared to those with a mild-to-moderate disease. This has been discussed in the paper. In this study, I also confirmed a high impact of OD on QoL, with higher sinonasal symptoms (SNOT-22) reported by those with OD compared to those who recovered sense of smell. A high impact of C19OD on QoL was also confirmed in my other two studies on subjects with more than 1-year C19OD.[425,592] Specifically, C19OD

subjects showed difficulties in their everyday activities (affected SF-36 domains were "energy/fatigue," "emotional well-being," and "social functioning") although restoration of sense of smell was also accompanied by normalisation in their QoL scores. One more time, in this study I confirmed that olfactory threshold remained the most affected olfactory abilities in C19OD in the long-term, strengthening the hypothesis that SARS-CoV-2 targets the OE.

Still today clinical factors influencing recovery of C19OD are not known. In my retrospective analysis of 100 patients with persistent C19OD I first showed that an impairment of nasal airflow can negatively affect olfactory performance.[425] This had not been shown in C19OD and it is extremely important because further supports my overarching hypothesis that sense of smell could be improved in C19OD subjects by increasing nasal airflow to the olfactory cleft. Interestingly, in this study total nasal airflow was found to significantly influence olfactory discrimination but not olfactory threshold, as instead previously shown by Whitcroft et al.[178] A positive influence was also demonstrated on TDI.[425]

Although ongoing neuroinflammation in the OE is considered to be a major driving mechanism in persistent C19OD, I showed that corticosteroids (both oral and topical) did not add a clear benefit over OT alone, in terms of objective olfactory function improvement, when given in combination with OT to patients with long-term C19OD (median length of OD was 7.6 months).[698] Only TDI significantly improved in both groups of patients at a very similar rate (+2.25 in the group taking combined treatment and +2.50 in those doing OT alone). Interestingly, olfactory threshold, the most affected ability in C19OD, did not improve. MCID was not reached in any of the S'S subtests and in none of the groups (OT alone, OT+OCS or no treatment). Although disappointing, my results reflect the contradictory role of corticosteroids in PIOD, especially when used for long-term C19OD, as already discussed in *Section 6.7.2*. (*Table 6.4.*) Despite the limitations

of this study, mainly the small sample size and lack of randomisation, the absence of an MCID advantage of OT or OT+OCS when compared to no treatment may also suggest the inability of OT to significantly improve olfactory threshold, discrimination and identification above MCID in patients with a long-standing C19OD. On the other side, the absence of an evident olfactory improvement following corticosteroids administration may suggest either a difficulty of corticosteroids in reaching and treating the local olfactory mucosal inflammation or even an absence of local inflammation in long-term C19OD (7.6 months in my study). This will be matter of further research (*Section 7.2.*).

Finally, my prospective study on fSRP showed for the first time that sense of smell can improve in patients with persistent C19OD (longer than 2 years) following nasal airways augmentation surgery. All the olfactory scores improved following fSRP and all, but discrimination, increased above the MCID level. This olfactory improvement was accompanied by a parallel statistically significant increase in the nasal airflow and nasal airways parameters. Interestingly, the largest improvement was observed in the olfactory threshold in the fSRP group (+4.0 points) with significant additional benefit in olfactory threshold gain when compared to the OT one (+3.6 points). This is also the most affected abilities in C19OD. No previous treatments for C19OD had showed a similarly high increase in olfactory threshold (+4.0 points) and TDI (+8.0 points) suggesting the therapeutic advantage of fSRP in C19OD. (*Table 6.5.*) To the best of my knowledge, fSRP represents the only treatment which showed significant clinically important benefit in patients with long-standing (>2 years) C19OD. Moreover, patients in the control group did not improve on OT. This may further confirm an inefficacy of OT for long-standing OD. On the other side, it corroborates my hypothesis that an improvement in the nasal airways, by means of INV augmentation and airways optimisation, also improves olfactory function. This may be a consequence of the increased nasal airflow in the olfactory cleft with a resulting increased stimulation of the OE due to improved odorants delivery. To a molecular level these findings have multiple implications. The fact that

olfaction, and particularly olfactory threshold, can still improve more than 2 years following OD onset, means that the OE function in C19OD subjects is still preserved. Moreover, this implies that ORNs are still present. This would confirm previous findings reported in pre-COVID studies[501] and suggest that in subjects with long-term C19OD the OE still retains its structure but may have fewer ORNs. The increased odorants delivery, following fSRP, will stimulate more the remaining ORNs, which then translates in the objectively measured olfactory threshold improvement. These more frequent stimuli may affect patterns of neural activity at all levels of the olfactory system, revealed by an improvement of the discrimination and identification scores generally considered to reflect higher brain function. Moreover, the repeated exposure to odorants may modulate regenerative capacity of the olfactory mucosa, as previously shown in animals[742-744] and humans.[525,745,746] Based on a bottom-up mechanism, fSRP would then be able to restore olfaction at multiple levels.

This mechanism would explain the greater advantage that nasal airways augmentation, achieved with fSRP, could offer over nasal airways restoration obtained with septoplasty alone. Pfaar et al.[171] found that septal deviation causes a difference in odour threshold between the two nostrils and that this asymmetry between obstructed and non-obstructed sides disappeared after surgery. However, no differences in TDI were noted before and after surgery. This may suggest that septoplasty can reduce differences in olfaction between nostrils but would not be able to increase overall olfactory function.[171] In fact, whether septoplasty tends to restore nasal airflow in the narrower side by correcting the septal deviation without touching the contralateral airway, fSRP not only restore airway symmetry, by correcting the DNS, but can additionally increase nasal airways volume by working on the internal nasal valve through septal spreader grafts insertion. As explained in previous paragraphs, this will turn into an increased airflow in the olfactory clefts which could translate into improved olfaction. To further support that, our study showed that fSRP can increase all the olfactory scores (including TDI) with a

statistically significant difference in threshold gain (+3.6 points; p=0.05) if compared to OT. This implies a superiority of fSRP for long-term OD, over other treatments currently evaluated for C19OD. (*Table 6.6.*)

Interestingly, in a meta-analysis by Pfaff et al.[130] a similar number of studies on fSRP and septoplasty alone reported an improvement in olfaction. *Table 6.6.* compares olfactory threshold, discrimination, identification and TDI scores improvement following septoplasty and fSRP. For comparison, only studies that used extended Sniffin' Sticks test have been considered. This table shows that MCID level for overall olfaction (TDI) is often not reached (only 1 study reached MCID for TDI) with septoplasty and none of the studies on septoplasty demonstrated an improvement above MCID for the other olfactory subtests. Conversely, fSRP almost consistently reached MCID for TDI and, so far, it is the only treatment that showed an olfactory threshold and identification improvement above MCID. This would suggest that fSRP could achieve greater olfactory improvement than septoplasty. However, since no studies have evaluated the role of septoplasty in patients with a primary diagnosis of OD, a question remains as to whether septoplasty can improve olfaction in patients with a persistent OD (or C19OD) and, if so, whether this improvement is higher than when septoplasty is performed in patients with a reported normal olfactory function (as for the currently available studies on septoplasty). This would create the basis for a future RCT to evaluate superiority of fSRP over septoplasty for OD improvement in patients with long-standing OD (including C19OD).

	Authors	Sample size	Follow-up period	Sniffin' Sticks			
				Threshold	Discrimination	Identification	TDI
Not on PIOD/C19OD							
Septoplasty	Damm et al.[154] (2003)	30	9 weeks	+0.5*	+1.8***	+1.9***	N/A
	Turk et al.[164] (2017)	30	6 weeks	+1.5*	+1.2*	+1.4**	+4.3***
	Valsamidis et al.[155] (2019)	60	6 months	+2.2***	+2.35**	+2.0***	**+5.55*** **
Functional septorhinoplasty	Ulusoy et al.[176] (2015)	35[+]	6 months	+1.4***	+0.5**	+0.5**	N/A
On PIOD/C19OD							
Functional septorhinoplasty	Whitcroft et al.[178] (2023)	9	4 months	+1.08	+2.22	+2.44*	**+6.5***
	Pendolino et al. (PhD paper)	9	6 months	**+4.0****	+2.0*	**+3.0***	**+8.0****

Table 6.6. Changes in Sniffin' Sticks scores following septoplasty and septorhinoplasty conducted on or not in patients with post-infectious olfactory dysfunction (PIOD) or COVID-19-related olfactory dysfunction (C19OD). Where minimal clinically important difference (MCID) has been achieved, the value is marked in bold. For MCID values refer to *Table 2,1., Chapter 2*.
Level of significance: * p<0.05; ** p<0.01, ***p<0.001.

[+] Only patients undergoing fSRP with spreader grafts have been included in the table.

CHAPTER 7: CONCLUSIONS

7.1. Review of my PhD thesis

This thesis demonstrates my literature contribution during the last six years as well as my continuous efforts in looking into new therapeutic options able to improve or restore sense of smell in patients with chronic upper respiratory tract diseases. Although at a first glance these three diseases may not seem linked, they fundamentally share the same underlying causes for their OD: either mucosal inflammation and/or a nasal airflow impairment. As already discussed in the relevant chapters, chronic inflammation in the olfactory clefts can lead, in the long-term, to sensorineural OD and this seems to be a crucial pathophysiologic mechanism for both N-ERD and C19OD patients' smell loss. On the other side all my studies showed a strict relationship between nasal airways/airflow and sense of smell. The influence of nasal airway on olfaction represents a leitmotif that runs through all my works and an impairment of nasal airflow to the olfactory clefts constitutes another critical mechanism which can cause OD in both N-ERD, SDB and C19OD patients.

After retrospectively reviewing a database of 190 N-ERD patients with uncontrolled CRSwNP,[224] I demonstrated how topical LAS can improve nasal airflow and olfaction and lead to QoL improvement in those using it.[280] My study also showed the strict relationship between nasal airflow and olfaction and how these can improve together following intranasal LAS treatment. In fact, whether on the one hand olfaction can improve as a consequence of the achieved reduced inflammation in the olfactory clefts (sensorineural component), on the other side it could also increase as a result of the improved nasal airways and better odorant delivery to the olfactory areas (conductive component). Despite evidence showing biological therapy to be a very effective alternative for the treatment of uncontrolled CRSwNP in N-ERD patients,[316,747] LAS can still find its place

as an effective treatment option in view of its highly cost-effective benefits. Nevertheless, still today a RCT comparing effectiveness of LAS with other treatments available for CRSwNP in N-ERD is lacking. I am confident that my work on this topic will provide further evidence to policymakers looking at supporting cost-effective treatment options for CRSwNP in N-ERD.

My study on the efficacy of RFITs in patients with SDB not only confirmed that RFITs can improve nasal airways in the short/medium-term in patients with SDB but also showed that a higher number of SDB patients suffer from OD, often undiagnosed, and that nasal airway improvement can potentially lead to better olfaction in these subjects.[377] While a reduction in hyposmics was noted over the study period, this finding lacked statistical significance. This could be attributed to the small sample size (due to participant drop-out) or indicate that RFITs are unable to improve the sense of smell. Additionally, the absence of observed smell improvement may correlate with a lack of increase in nasal airflow (PNIF), a relationship that my thesis has consistently shown to be strong. The study limitations raised in the paper, mainly the lack of a control arm, will lay the foundation for a future larger controlled study to further investigate our preliminary results.

Ongoing inflammation in the olfactory cleft following a viral infection (mainly SARS-CoV-2 in this thesis) has been suggested as a relevant mechanism in the pathogenesis of persistent C19OD, and potentially capable to impair the regenerative capacity of the basal stem cells of the OE. Corticosteroids which can affect numerous steps of the inflammatory pathway probably represent the main anti-inflammatory medicines used to reduce sinonasal inflammation.[748-751] In the multicentre real-life study, which looked at the efficacy of corticosteroids and OT in persistent C19OD,[698] I demonstrated benefit in terms of increased olfactory ability and patient's perceived olfaction in the group of subjects receiving both corticosteroids and OT, thus confirming the negative role of

inflammation in persistent C19OD and further supporting corticosteroids use in the early stages of PIOD. Moreover, in another study in which I looked at the clinical factors influencing olfactory performance in patients with persistent C19OD, I demonstrated the presence of a relationship between nasal airflow and measured olfaction.[425] This has become even more evident in my last prospective-controlled study in which I showed how olfaction can improve in patients with persistent C19OD following fSRP when compared to the control group of C19OD patients continuing on OT, but not responding to it. The small sample size and patients' drop-out during the study period have partially flawed these results. Nevertheless, the promising findings observed in this pilot study will pave the way for a future larger controlled study that will further evaluate the role of fSRP, and more widely the influence of nasal airways, in improving OD.

7.2. Future works

I like to compare my PhD to a research journey. However, this is not simply a single, linear, trip bringing me from point A (start of PhD) to point B (thesis submission), but I love to picture it in my mind as if it was a long winding road finally leading to other collateral streets at the end of the path. In my case, these represent new, future, lines of research which naturally open up at the end of this academic degree.

COVID-19 has left millions of people worldwide with a persistent loss of sense of smell unable to improve on the available medical treatments and I believe my future research activity will mainly focus on this field. Current research on the topic is now looking at the histopathological changes in the OE to further develop new therapeutical strategies. As mentioned in *Section 5.3.*, recent evidence is now showing a role of ongoing neuroinflammation in the OE as a potential cause for the basal stem cell regenerative impairment, eventually leading to COVID-19 chronic OD. Reducing or stopping this neuroinflammation can potentially lead to reactivation of basal stem cells able to

encourage ORNs regeneration. However, studies are currently limited by a lack of availability of C19OD human olfactory biopsies. As part of our research project on C19OD, I had the opportunity to take biopsies of human olfactory tissue from our patients undergoing fSRP under general anaesthesia. These are currently stored in our pathology laboratory and we are planning to look at the structural and cellular changes following long-term C19OD.

However, where neuroinflammation is missing, but ORNs and stem cells are still preserved although reduced, increasing the OE stimulation could be another option to stimulate the remaining receptors. As previously discussed, optimisation of nasal airflow to the olfactory clefts could be a potential option to increase odorant delivery to the olfactory areas and stimulation of ORNs. Our study has showed that fSRP is able to achieve that mainly by increasing INV cross-sectional areas. However, as previously reported by Whitcroft et al.,[178] benefits of fSRP could also be related to a bottom-up process that brings to an improved function of brain areas linked with OD (anterior cingulate cortex, insula, orbitofrontal cortex, and temporal poles). As part of my last project on fSRP and C19OD, I have also collected fMRI data on C19OD patients before and after their operation. These may shed some lights on the neuroanatomical correlates of C19OD but also on the mechanisms through which fSRP can improve suprathreshold olfactory functions (i.e. identification and discrimination) in patients with long-term OD.

I like to compare the way fSRP works in PIOD to what a hearing aid does in sensorineural hearing loss (SNHL). In SNHL the function of the cochlea hair cells (the sensory receptors in the auditory organ) is reduced but still preserved and hearing aids work by increasing the volume and intensity of the sounds transmitted to the receptors. In a similar way, the OE in PIOD has a reduced number of ORNs and fSRP may work by increasing the numbers of odorants reaching the OE and stimulating the remaining ORNs. Nevertheless, further research needs to be conducted on the topic to further

confirm this assumption and my aim is to conduct a larger prospective controlled study to evaluate the role of fSRP in improving sense of smell in PIOD. As part of this RCT, comparison should be made with septoplasty (control group) to further confirms preliminary findings showing superiority of nasal airways augmentation (i.e. fSRP) over simple nasal airways restoration (i.e. septoplasty). (See *Section 6.16*) I believe that the skills and surgical abilities developed during these years will help me in realising this interesting project.

Beside the research on PIOD, I would like to further study olfactory impairment in patients with SDB. OSA is becoming a growing problem in our society and mainly related to a change in the dietary and lifestyle habits. Due to the deteriorating impact of OD on mental health and QoL, treatment of OD in SDB patients will become more relevant in the future. Improving nasal congestion, often caused by CPAP machine overnight use, with the application of RFITs could be a new treatment option that could be offered to these patients to improve their nasal airways with potential additional benefits such as increased CPAP tolerance and improved smell function.

7.3. Summary conclusion

OD remains a common finding in chronic upper respiratory tract diseases. My research offers new insights in the treatment of chronic smell loss in N-ERD, SDB and PIOD patients while suggesting new potential therapeutic options for persistent OD through the management of local sinonasal inflammation and nasal airways optimisation. Findings obtained with my works will pave the way for future research in the field and, hopefully, assist in the development of new treatments for loss of sense of smell.

REFERENCES

1. Leopold DA, Hummel T, Schwob JE, Hong SC, Knecht M, Kobal G. Anterior distribution of human olfactory epithelium. *Laryngoscope*. Mar 2000;110(3 Pt 1):417-21. doi:10.1097/00005537-200003000-00016
2. Patel RM, Pinto JM. Olfaction: anatomy, physiology, and disease. *Clin Anat*. Jan 2014;27(1):54-60. doi:10.1002/ca.22338
3. Smith TD, Bhatnagar KP. Anatomy of the olfactory system. *Handb Clin Neurol*. 2019;164:17-28. doi:10.1016/B978-0-444-63855-7.00002-2
4. Hadley K, Orlandi RR, Fong KJ. Basic anatomy and physiology of olfaction and taste. *Otolaryngol Clin North Am*. Dec 2004;37(6):1115-26. doi:10.1016/j.otc.2004.06.009
5. Helwany M, Bordoni B. Neuroanatomy, Cranial Nerve 1 (Olfactory). *StatPearls*. 2024.
6. Shepherd GM. *The synaptic organization of the brain*. 5th ed. Oxford University Press; 2004:xiv, 719 p.
7. Pinching AJ, Powell TP. The neuropil of the glomeruli of the olfactory bulb. *J Cell Sci*. Sep 1971;9(2):347-77. doi:10.1242/jcs.9.2.347
8. Persaud KC. Engineering Aspects of Olfaction. In: Persaud KC, Marco S, Gutierrez-Galvez A, eds. *Neuromorphic Olfaction*. 2013. *Frontiers in Neuroengineering*.
9. Hatt H. Molecular and cellular basis of human olfaction. *Chem Biodivers*. Dec 2004;1(12):1857-69. doi:10.1002/cbdv.200490142
10. Benignus VA, Prah JD. Olfaction: anatomy, physiology and behavior. *Environ Health Perspect*. Apr 1982;44:15-21. doi:10.1289/ehp.824415
11. Doty RL. *Handbook of olfaction and gustation*. 2nd ed. Marcel Dekker; 2003:xiv, 1121 p. 8 p. of plates. http://www.crcnetbase.com/ISBN/9780203911457

12. Dalton P, Doolittle N, Nagata H, Breslin PA. The merging of the senses: integration of subthreshold taste and smell. *Nat Neurosci*. May 2000;3(5):431-2. doi:10.1038/74797

13. Distel H, Hudson R. Judgement of odor intensity is influenced by subjects' knowledge of the odor source. *Chem Senses*. Mar 2001;26(3):247-51. doi:10.1093/chemse/26.3.247

14. Gottfried JA. Smell: central nervous processing. *Adv Otorhinolaryngol*. 2006;63:44-69. doi:10.1159/000093750

15. Witt M, Hummel T. Vomeronasal versus olfactory epithelium: is there a cellular basis for human vomeronasal perception? *Int Rev Cytol*. 2006;248:209-59. doi:10.1016/S0074-7696(06)48004-9

16. Young JM, Massa HF, Hsu L, Trask BJ. Extreme variability among mammalian V1R gene families. *Genome Res*. Jan 2010;20(1):10-8. doi:10.1101/gr.098913.109

17. Rozin P. "Taste-smell confusions" and the duality of the olfactory sense. *Percept Psychophys*. Apr 1982;31(4):397-401. doi:10.3758/bf03202667

18. Soler ZM, Schlosser RJ, Mulligan JK, et al. Olfactory cleft mucus proteome in chronic rhinosinusitis: a case-control pilot study. *Int Forum Allergy Rhinol*. Aug 2021;11(8):1162-1176. doi:10.1002/alr.22743

19. Buck L, Axel R. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. *Cell*. Apr 5 1991;65(1):175-87. doi:10.1016/0092-8674(91)90418-x

20. Miller G. 2004 Nobel Prizes. Axel, Buck share award for deciphering how the nose knows. *Science*. Oct 8 2004;306(5694):207. doi:10.1126/science.306.5694.207

21. Rawson NE. Olfactory loss in aging. *Sci Aging Knowledge Environ*. Feb 8 2006;2006(5):pe6. doi:10.1126/sageke.2006.5.pe6

22. Ma M. Encoding olfactory signals via multiple chemosensory systems. *Crit Rev Biochem Mol Biol*. Nov-Dec 2007;42(6):463-80. doi:10.1080/10409230701693359

23. Laska M, Seibt A. Olfactory sensitivity for aliphatic esters in squirrel monkeys and pigtail macaques. *Behav Brain Res*. Aug 21 2002;134(1-2):165-74. doi:10.1016/s0166-4328(01)00464-8

24. Laska M, Teubner P. Olfactory discrimination ability for homologous series of aliphatic alcohols and aldehydes. *Chem Senses*. Jun 1999;24(3):263-70. doi:10.1093/chemse/24.3.263

25. Cassenaer S, Laurent G. Hebbian STDP in mushroom bodies facilitates the synchronous flow of olfactory information in locusts. *Nature*. Aug 9 2007;448(7154):709-13. doi:10.1038/nature05973

26. Keller A, Zhuang H, Chi Q, Vosshall LB, Matsunami H. Genetic variation in a human odorant receptor alters odour perception. *Nature*. Sep 27 2007;449(7161):468-72. doi:10.1038/nature06162

27. Menashe I, Abaffy T, Hasin Y, et al. Genetic elucidation of human hyperosmia to isovaleric acid. *PLoS Biol*. Oct 30 2007;5(11):e284. doi:10.1371/journal.pbio.0050284

28. Hornung DE. Nasal anatomy and the sense of smell. *Adv Otorhinolaryngol*. 2006;63:1-22. doi:10.1159/000093747

29. Sell CS. On the unpredictability of odor. *Angew Chem Int Ed Engl*. Sep 25 2006;45(38):6254-61. doi:10.1002/anie.200600782

30. Turin L. A spectroscopic mechanism for primary olfactory reception. *Chem Senses*. Dec 1996;21(6):773-91. doi:10.1093/chemse/21.6.773

31. Liu S, Fu R, Li G. Exploring the mechanism of olfactory recognition in the initial stage by modeling the emission spectrum of electron transfer. *PLoS One*. 2020;15(1):e0217665. doi:10.1371/journal.pone.0217665

32. Durante MA, Kurtenbach S, Sargi ZB, et al. Single-cell analysis of olfactory neurogenesis and differentiation in adult humans. *Nat Neurosci*. Mar 2020;23(3):323-326. doi:10.1038/s41593-020-0587-9

33. Schultz EW. Repair of the olfactory mucosa with special reference to regeneration of olfactory cells (sensory neurons). *Am J Pathol*. Jul 1960;37(1):1-19.

34. Schwob JE, Youngentob SL, Mezza RC. Reconstitution of the rat olfactory epithelium after methyl bromide-induced lesion. *J Comp Neurol*. Aug 14 1995;359(1):15-37. doi:10.1002/cne.903590103

35. Leung CT, Coulombe PA, Reed RR. Contribution of olfactory neural stem cells to tissue maintenance and regeneration. *Nat Neurosci*. Jun 2007;10(6):720-6. doi:10.1038/nn1882

36. Schwob JE, Jang W, Holbrook EH, et al. Stem and progenitor cells of the mammalian olfactory epithelium: Taking poietic license. *J Comp Neurol*. Mar 1 2017;525(4):1034-1054. doi:10.1002/cne.24105

37. Child KM, Herrick DB, Schwob JE, Holbrook EH, Jang W. The Neuroregenerative Capacity of Olfactory Stem Cells Is Not Limitless: Implications for Aging. *J Neurosci*. Aug 1 2018;38(31):6806-6824. doi:10.1523/JNEUROSCI.3261-17.2018

38. Smith KE, Whitcroft K, Law S, Andrews P, Choi D, Jagger DJ. Olfactory ensheathing cells from the nasal mucosa and olfactory bulb have distinct membrane properties. *J Neurosci Res*. May 2020;98(5):888-901. doi:10.1002/jnr.24566

39. Chiu SC, Hung HS, Lin SZ, Chiang E, Liu DD. Therapeutic potential of olfactory ensheathing cells in neurodegenerative diseases. *J Mol Med (Berl)*. Dec 2009;87(12):1179-89. doi:10.1007/s00109-009-0528-2

40. Baroody FM, Gungor A, deTineo M, Haney L, Blair C, Naclerio RM. Comparison of the response to histamine challenge of the nose and the maxillary sinus: effect of loratadine. *J Appl Physiol (1985)*. Sep 1999;87(3):1038-47. doi:10.1152/jappl.1999.87.3.1038

41. Desiato VM, Levy DA, Byun YJ, Nguyen SA, Soler ZM, Schlosser RJ. The Prevalence of Olfactory Dysfunction in the General Population: A Systematic

Review and Meta-analysis. *Am J Rhinol Allergy*. Mar 2021;35(2):195-205. doi:10.1177/1945892420946254

42. Hummel T, Whitcroft KL, Andrews P, et al. Position paper on olfactory dysfunction. *Rhinology*. Jan 31 2016;56(1):1-30. doi:10.4193/Rhin16.248
43. Savage SA, Butler CR, Milton F, Han Y, Zeman AZ. On the nose: Olfactory disturbances in patients with transient epileptic amnesia. *Epilepsy Behav*. Jan 2017;66:113-119. doi:10.1016/j.yebeh.2016.09.043
44. Whitcroft KL, Altundag A, Balungwe P, et al. Position paper on olfactory dysfunction: 2023. *Rhinology*. Jul 16 2023;doi:10.4193/Rhin22.483
45. Damm M, Schmitl L, Muller CA, Welge-Lussen A, Hummel T. [Diagnostics and treatment of olfactory dysfunction]. *HNO*. Apr 2019;67(4):274-281. Diagnostik und Therapie von Riechstorungen. doi:10.1007/s00106-019-0614-x
46. Rombaux P, Huart C, Levie P, Cingi C, Hummel T. Olfaction in Chronic Rhinosinusitis. *Curr Allergy Asthma Rep*. May 2016;16(5):41. doi:10.1007/s11882-016-0617-6
47. Mullol J, Marino-Sanchez F, Valls M, Alobid I, Marin C. The sense of smell in chronic rhinosinusitis. *J Allergy Clin Immunol*. Mar 2020;145(3):773-776. doi:10.1016/j.jaci.2020.01.024
48. Raviv JR, Kern RC. Chronic sinusitis and olfactory dysfunction. *Otolaryngol Clin North Am*. Dec 2004;37(6):1143-57, v-vi. doi:10.1016/j.otc.2004.06.003
49. Whitcroft KL, Cuevas M, Haehner A, Hummel T. Patterns of olfactory impairment reflect underlying disease etiology. *Laryngoscope*. Feb 2017;127(2):291-295. doi:10.1002/lary.26229
50. Betchen SA, Doty RL. Bilateral detection thresholds in dextrals and sinistrals reflect the more sensitive side of the nose, which is not lateralized. *Chem Senses*. Aug 1998;23(4):453-7. doi:10.1093/chemse/23.4.453

51. Reiter ER, DiNardo LJ, Costanzo RM. Effects of head injury on olfaction and taste. *Otolaryngol Clin North Am*. Dec 2004;37(6):1167-84. doi:10.1016/j.otc.2004.06.005

52. Gobba F. Olfactory toxicity: long-term effects of occupational exposures. *Int Arch Occup Environ Health*. Apr 2006;79(4):322-31. doi:10.1007/s00420-005-0043-x

53. Upadhyay UD, Holbrook EH. Olfactory loss as a result of toxic exposure. *Otolaryngol Clin North Am*. Dec 2004;37(6):1185-207. doi:10.1016/j.otc.2004.05.003

54. Mascagni P, Consonni D, Bregante G, Chiappino G, Toffoletto F. Olfactory function in workers exposed to moderate airborne cadmium levels. *Neurotoxicology*. Aug 2003;24(4-5):717-24. doi:10.1016/S0161-813X(03)00024-X

55. Henriksson J, Tallkvist J, Tjalve H. Transport of manganese via the olfactory pathway in rats: dosage dependency of the uptake and subcellular distribution of the metal in the olfactory epithelium and the brain. *Toxicol Appl Pharmacol*. Apr 15 1999;156(2):119-28. doi:10.1006/taap.1999.8639

56. Ajmani GS, Suh HH, Pinto JM. Effects of Ambient Air Pollution Exposure on Olfaction: A Review. *Environ Health Perspect*. Nov 2016;124(11):1683-1693. doi:10.1289/EHP136

57. Calderon-Garciduenas L, Franco-Lira M, Henriquez-Roldan C, et al. Urban air pollution: influences on olfactory function and pathology in exposed children and young adults. *Exp Toxicol Pathol*. Jan 2010;62(1):91-102. doi:10.1016/j.etp.2009.02.117

58. Walter C, Oertel BG, Ludyga D, Ultsch A, Hummel T, Lotsch J. Effects of 20 mg oral Delta(9) -tetrahydrocannabinol on the olfactory function of healthy volunteers. *Br J Clin Pharmacol*. Nov 2014;78(5):961-9. doi:10.1111/bcp.12415

59. Lotsch J, Darimont J, Skarke C, Zimmermann M, Hummel T, Geisslinger G. Effects of the opioid remifentanil on olfactory function in healthy volunteers. *Life Sci*. Sep 28 2001;69(19):2279-85. doi:10.1016/s0024-3205(01)01305-4

60. Gudziol V, Muck-Weymann M, Seizinger O, Rauh R, Siffert W, Hummel T. Sildenafil affects olfactory function. *J Urol*. Jan 2007;177(1):258-61; discussion 261. doi:10.1016/j.juro.2006.08.060

61. Steinbach S, Hummel T, Bohner C, et al. Qualitative and quantitative assessment of taste and smell changes in patients undergoing chemotherapy for breast cancer or gynecologic malignancies. *J Clin Oncol*. Apr 10 2009;27(11):1899-905. doi:10.1200/JCO.2008.19.2690

62. Schiffman SS. Influence of medications on taste and smell. *World J Otorhinolaryngol Head Neck Surg*. Mar 2018;4(1):84-91. doi:10.1016/j.wjorl.2018.02.005

63. Lotsch J, Knothe C, Lippmann C, Ultsch A, Hummel T, Walter C. Olfactory drug effects approached from human-derived data. *Drug Discov Today*. Nov 2015;20(11):1398-406. doi:10.1016/j.drudis.2015.06.012

64. Huttenbrink KB, Hummel T, Berg D, Gasser T, Hahner A. Olfactory dysfunction: common in later life and early warning of neurodegenerative disease. *Dtsch Arztebl Int*. Jan 2013;110(1-2):1-7, e1. doi:10.3238/arztebl.2013.0001

65. Hawkes C. Olfaction in neurodegenerative disorder. *Mov Disord*. Apr 2003;18(4):364-72. doi:10.1002/mds.10379

66. Kiparizoska S, Ikuta T. Disrupted Olfactory Integration in Schizophrenia: Functional Connectivity Study. *Int J Neuropsychopharmacol*. Sep 1 2017;20(9):740-746. doi:10.1093/ijnp/pyx045

67. Heinrichs L. Linking olfaction with nausea and vomiting of pregnancy, recurrent abortion, hyperemesis gravidarum, and migraine headache. *Am J Obstet Gynecol*. May 2002;186(5 Suppl Understanding):S215-9. doi:10.1067/mob.2002.123053

68. Jang WY, Jung S, Jung TY, Moon KS, Kim IY. Preservation of olfaction in surgery of olfactory groove meningiomas. *Clin Neurol Neurosurg*. Aug 2013;115(8):1288-92. doi:10.1016/j.clineuro.2012.12.004

69. Patel ZM, Holbrook EH, Turner JH, et al. International consensus statement on allergy and rhinology: Olfaction. *Int Forum Allergy Rhinol*. Apr 2022;12(4):327-680. doi:10.1002/alr.22929

70. Shetty S, Kapoor N, John RA, Paul TV. Olfactory Agenesis in Kallmann Syndrome (KS). *J Clin Diagn Res*. Apr 2015;9(4):OJ01. doi:10.7860/JCDR/2015/11761.5777

71. Bramerson A, Nyman J, Nordin S, Bende M. Olfactory loss after head and neck cancer radiation therapy. *Rhinology*. Sep 2013;51(3):206-209. doi:10.4193/Rhino12.120

72. Sivakumar R, White J, Villwock J. Olfactory dysfunction in type II diabetes: Therapeutic options and lessons learned from other etiologies - A scoping review. *Prim Care Diabetes*. Aug 2022;16(4):543-548. doi:10.1016/j.pcd.2022.05.003

73. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav*. Mar 1984;32(3):489-502. doi:10.1016/0031-9384(84)90269-5

74. Kalmey JK, Thewissen JG, Dluzen DE. Age-related size reduction of foramina in the cribriform plate. *Anat Rec*. Jul 1998;251(3):326-9. doi:10.1002/(SICI)1097-0185(199807)251:3<326::AID-AR7>3.0.CO;2-T

75. Attems J, Walker L, Jellinger KA. Olfaction and Aging: A Mini-Review. *Gerontology*. 2015;61(6):485-90. doi:10.1159/000381619

76. Wang X, Zhang C, Xia X, Yang Y, Zhou C. Effect of gender on odor identification at different life stages: a meta-analysis. *Rhinology*. Oct 1 2019;57(5):322-330. doi:10.4193/Rhin19.005

77. Cardesin A, Alobid I, Benitez P, et al. Barcelona Smell Test - 24 (BAST-24): validation and smell characteristics in the healthy Spanish population. *Rhinology*. Mar 2006;44(1):83-9.

78. Boesveldt S, Lindau ST, McClintock MK, Hummel T, Lundstrom JN. Gustatory and olfactory dysfunction in older adults: a national probability study. *Rhinology*. Aug 2011;49(3):324-30. doi:10.4193/Rhino10.155

79. Masala C, Cavazzana A, Sanna F, et al. Correlation between olfactory function, age, sex, and cognitive reserve index in the Italian population. *Eur Arch Otorhinolaryngol*. Oct 2022;279(10):4943-4952. doi:10.1007/s00405-022-07311-z

80. Kamath V, Turetsky BI, Moberg PJ. Identification of pleasant, neutral, and unpleasant odors in schizophrenia. *Psychiatry Res*. May 15 2011;187(1-2):30-5. doi:10.1016/j.psychres.2010.12.011

81. Larsson M, Finkel D, Pedersen NL. Odor identification: influences of age, gender, cognition, and personality. *J Gerontol B Psychol Sci Soc Sci*. Sep 2000;55(5):P304-10. doi:10.1093/geronb/55.5.p304

82. Novakova L, Varella Valentova J, Havlicek J. Olfactory performance is predicted by individual sex-atypicality, but not sexual orientation. *PLoS One*. 2013;8(11):e80234. doi:10.1371/journal.pone.0080234

83. Stuck BA, Frey S, Freiburg C, Hormann K, Zahnert T, Hummel T. Chemosensory event-related potentials in relation to side of stimulation, age, sex, and stimulus concentration. *Clin Neurophysiol*. Jun 2006;117(6):1367-75. doi:10.1016/j.clinph.2006.03.004

84. San T, Muluk NB, Saylisoy S, et al. Cultural adaptation of an olfactory test: the odour in bottle test. [corrected]. *Rhinology*. Jun 2014;52(2):172-7. doi:10.4193/Rhino13.055

85. Guo XZ, Su JD, Sun QW, Jiao BH. Expression of estrogen receptor (ER) -alpha and -beta transcripts in the neonatal and adult rat cerebral cortex, cerebellum, and olfactory bulb. *Cell Res*. Dec 2001;11(4):321-4. doi:10.1038/sj.cr.7290103

86. Schneider RA, Costiloe JP, Howard RP, Wolf S. Olfactory perception thresholds in hypogonadal women: changes accompanying administration of androgen and estrogen. *J Clin Endocrinol Metab*. Apr 1958;18(4):379-90. doi:10.1210/jcem-18-4-379

87. Oliveira-Pinto AV, Santos RM, Coutinho RA, et al. Sexual dimorphism in the human olfactory bulb: females have more neurons and glial cells than males. *PLoS One*. 2014;9(11):e111733. doi:10.1371/journal.pone.0111733

88. Gur RC, Turetsky BI, Matsui M, et al. Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. *J Neurosci*. May 15 1999;19(10):4065-72. doi:10.1523/JNEUROSCI.19-10-04065.1999

89. Luders E, Narr KL, Thompson PM, et al. Mapping cortical gray matter in the young adult brain: effects of gender. *Neuroimage*. Jun 2005;26(2):493-501. doi:10.1016/j.neuroimage.2005.02.010

90. Doty RL, Cameron EL. Sex differences and reproductive hormone influences on human odor perception. *Physiol Behav*. May 25 2009;97(2):213-28. doi:10.1016/j.physbeh.2009.02.032

91. Brand G, Millot JL. Sex differences in human olfaction: between evidence and enigma. *Q J Exp Psychol B*. Aug 2001;54(3):259-70. doi:10.1080/02724990143000045

92. Landis BN, Konnerth CG, Hummel T. A study on the frequency of olfactory dysfunction. *Laryngoscope*. Oct 2004;114(10):1764-9. doi:10.1097/00005537-200410000-00017

93. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life--an updated review. *Chem Senses*. Mar 2014;39(3):185-94. doi:10.1093/chemse/bjt072

94. Public Health England. Coronavirus (COVID-19): long-term health effects. Accessed 04 August 2021, https://www.gov.uk/government/publications/covid-19-long-term-health-effects/covid-19-long-term-health-effects

95. University College London Hospitals. Anosmia clinic. Accessed 04 August 2021, https://www.uclh.nhs.uk/our-services/find-service/covid19-clinics/anosmia-clinic

96. Payne-Frank MSN, Evangelou K, Phillips C. Inside a long Covid clinic: 'I look normal, but my body is breaking down' – video. Accessed 04 August 2021,

https://www.theguardian.com/society/video/2021/mar/23/inside-a-long-covid-clinic-i-look-normal-but-my-body-is-breaking-down-video

97. Cox D. Anosmia: how Covid brought loss of smell centre stage. The Guardian. Accessed 04 August 2021, https://www.theguardian.com/science/2020/dec/05/anosmia-how-covid-brought-loss-of-smell-centre-stage

98. Devanand DP, Lee S, Manly J, et al. Olfactory identification deficits and increased mortality in the community. *Ann Neurol*. Sep 2015;78(3):401-11. doi:10.1002/ana.24447

99. Pinto JM, Wroblewski KE, Kern DW, Schumm LP, McClintock MK. Olfactory dysfunction predicts 5-year mortality in older adults. *PLoS One*. 2014;9(10):e107541. doi:10.1371/journal.pone.0107541

100. Nordin S, Bramerson A. Complaints of olfactory disorders: epidemiology, assessment and clinical implications. *Curr Opin Allergy Clin Immunol*. Feb 2008;8(1):10-5. doi:10.1097/ACI.0b013e3282f3f473

101. Gopinath B, Russell J, Sue CM, Flood VM, Burlutsky G, Mitchell P. Olfactory impairment in older adults is associated with poorer diet quality over 5 years. *Eur J Nutr*. Apr 2016;55(3):1081-7. doi:10.1007/s00394-015-0921-2

102. Hoffman HJ, Rawal S, Li CM, Duffy VB. New chemosensory component in the U.S. National Health and Nutrition Examination Survey (NHANES): first-year results for measured olfactory dysfunction. *Rev Endocr Metab Disord*. Jun 2016;17(2):221-40. doi:10.1007/s11154-016-9364-1

103. Erskine SE, Philpott CM. An unmet need: Patients with smell and taste disorders. *Clin Otolaryngol*. Mar 2020;45(2):197-203. doi:10.1111/coa.13484

104. Jung YG, Lee JS, Park GC. Does post-infectious olfactory loss affect mood more severely than chronic sinusitis with olfactory loss? *Laryngoscope*. Nov 2014;124(11):2456-60. doi:10.1002/lary.24691

105. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol*. Oct 2009;34(5):447-54. doi:10.1111/j.1749-4486.2009.01995.x

106. Simopoulos E, Katotomichelakis M, Gouveris H, Tripsianis G, Livaditis M, Danielides V. Olfaction-associated quality of life in chronic rhinosinusitis: adaptation and validation of an olfaction-specific questionnaire. *Laryngoscope*. Jul 2012;122(7):1450-4. doi:10.1002/lary.23349

107. Mattos JL, Edwards C, Schlosser RJ, et al. A brief version of the questionnaire of olfactory disorders in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol*. Oct 2019;9(10):1144-1150. doi:10.1002/alr.22392

108. McMahon C, Scadding GK. Le Nez du Vin--a quick test of olfaction. *Clin Otolaryngol Allied Sci*. Jun 1996;21(3):278-80. doi:10.1111/j.1365-2273.1996.tb01741.x

109. Cain WS, Gent JF, Goodspeed RB, Leonard G. Evaluation of olfactory dysfunction in the Connecticut Chemosensory Clinical Research Center. *Laryngoscope*. Jan 1988;98(1):83-8. doi:10.1288/00005537-198801000-00017

110. Veyseller B, Ozucer B, Karaaltin AB, et al. Connecticut (CCCRC) Olfactory Test: Normative Values in 426 Healthy Volunteers. *Indian J Otolaryngol Head Neck Surg*. Jan 2014;66(1):31-4. doi:10.1007/s12070-013-0632-z

111. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chem Senses*. Feb 1997;22(1):39-52. doi:10.1093/chemse/22.1.39

112. Oleszkiewicz A, Schriever VA, Croy I, Hahner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. *Eur Arch Otorhinolaryngol*. Mar 2019;276(3):719-728. doi:10.1007/s00405-018-5248-1

113. Brumm MC, Pierz KA, Lafontant DE, et al. Updated Percentiles for the University of Pennsylvania Smell Identification Test in Adults 50 Years of Age and Older.

Neurology. Apr 18 2023;100(16):e1691-e1701. doi:10.1212/WNL.0000000000207077

114. Doty RL, Marcus A, Lee WW. Development of the 12-item Cross-Cultural Smell Identification Test (CC-SIT). *Laryngoscope*. Mar 1996;106(3 Pt 1):353-6. doi:10.1097/00005537-199603000-00021
115. Doty RL, Wylie C, Potter M, Beston R, Cope B, Majam K. Clinical validation of the olfactory detection threshold module of the Snap & Sniff(R) olfactory test system. *Int Forum Allergy Rhinol*. Sep 2019;9(9):986-992. doi:10.1002/alr.22377
116. Hummel T, Whitcroft KL, Andrews P, et al. Position paper on olfactory dysfunction. *Rhinol Suppl*. Mar 2017;54(26):1-30. doi:10.4193/Rhino16.248
117. Doty RL. Psychophysical testing of smell and taste function. *Handb Clin Neurol*. 2019;164:229-246. doi:10.1016/B978-0-444-63855-7.00015-0
118. Kobal G, Hummel T, Sekinger B, Barz S, Roscher S, Wolf S. "Sniffin' sticks": screening of olfactory performance. *Rhinology*. Dec 1996;34(4):222-6.
119. Hummel T, Knecht M, Kobal G. Peripherally obtained electrophysiological responses to olfactory stimulation in man: electro-olfactograms exhibit a smaller degree of desensitization compared with subjective intensity estimates. *Brain Res*. Apr 22 1996;717(1-2):160-4. doi:10.1016/0006-8993(96)00094-7
120. Tekeli H, Altundag A, Salihoglu M, Cayonu M, Kendirli MT. The applicability of the "Sniffin' Sticks" olfactory test in a Turkish population. *Med Sci Monit*. Dec 30 2013;19:1221-6. doi:10.12659/MSM.889838
121. Oleszkiewicz A, Taut M, Sorokowska A, Radwan A, Kamel R, Hummel T. Development of the Arabic version of the "Sniffin' Sticks" odor identification test. *Eur Arch Otorhinolaryngol*. May 2016;273(5):1179-84. doi:10.1007/s00405-015-3718-2
122. Silveira-Moriyama L, Sirisena D, Gamage P, Gamage R, de Silva R, Lees AJ. Adapting the Sniffin' Sticks to diagnose Parkinson's disease in Sri Lanka. *Mov Disord*. Jun 15 2009;24(8):1229-33. doi:10.1002/mds.22545

123. Neumann C, Tsioulos K, Merkonidis C, Salam M, Clark A, Philpott C. Validation study of the "Sniffin' Sticks" olfactory test in a British population: a preliminary communication. *Clin Otolaryngol*. Feb 2012;37(1):23-7. doi:10.1111/j.1749-4486.2012.02431.x

124. Kallogjeri D, Spitznagel EL, Jr., Piccirillo JF. Importance of Defining and Interpreting a Clinically Meaningful Difference in Clinical Research. *JAMA Otolaryngol Head Neck Surg*. Feb 1 2020;146(2):101-102. doi:10.1001/jamaoto.2019.3744

125. Doty RL, Yousem DM, Pham LT, Kreshak AA, Geckle R, Lee WW. Olfactory dysfunction in patients with head trauma. *Arch Neurol*. Sep 1997;54(9):1131-40. doi:10.1001/archneur.1997.00550210061014

126. Mahadev A, Kallogjeri D, Piccirillo JF. Validation of Minimal Clinically Important Difference (MCID) for University of Pennsylvania Smell Identification Test (UPSIT). *Am J Rhinol Allergy*. Mar 2024;38(2):123-132. doi:10.1177/19458924231218037

127. Levy JM, Mace JC, Bodner TE, Alt JA, Smith TL. Defining the minimal clinically important difference for olfactory outcomes in the surgical treatment of chronic rhinosinusitis. *Int Forum Allergy Rhinol*. Aug 2017;7(8):821-826. doi:10.1002/alr.21964

128. Gudziol V, Lotsch J, Hahner A, Zahnert T, Hummel T. Clinical significance of results from olfactory testing. *Laryngoscope*. Oct 2006;116(10):1858-63. doi:10.1097/01.mlg.0000234915.51189.cb

129. Lotsch J, Reichmann H, Hummel T. Different odor tests contribute differently to the evaluation of olfactory loss. *Chem Senses*. Jan 2008;33(1):17-21. doi:10.1093/chemse/bjm058

130. Pfaff MJ, Bertrand AA, Lipman KJ, et al. The Effect of Functional Nasal Surgery on Olfactory Function. *Plast Reconstr Surg*. Mar 1 2021;147(3):707-718. doi:10.1097/PRS.0000000000007667

131. Wu S, Wang P, Xie D, Jian F. Correlation analysis of flow parameters in the olfactory cleft and olfactory function. *Sci Rep*. Dec 2 2022;12(1):20819. doi:10.1038/s41598-022-25282-3

132. Zhao K, Dalton P. The way the wind blows: implications of modeling nasal airflow. *Curr Allergy Asthma Rep*. May 2007;7(2):117-25. doi:10.1007/s11882-007-0009-z

133. Kelly JT, Prasad AK, Wexler AS. Detailed flow patterns in the nasal cavity. *J Appl Physiol (1985)*. Jul 2000;89(1):323-37. doi:10.1152/jappl.2000.89.1.323

134. Hahn I, Scherer PW, Mozell MM. Velocity profiles measured for airflow through a large-scale model of the human nasal cavity. *J Appl Physiol (1985)*. Nov 1993;75(5):2273-87. doi:10.1152/jappl.1993.75.5.2273

135. Hasegawa M, Kern EB. The human nasal cycle. *Mayo Clin Proc*. Jan 1977;52(1):28-34.

136. Pendolino AL, Nardello E, Lund VJ, et al. Comparison between unilateral PNIF and rhinomanometry in the evaluation of nasal cycle. *Rhinology*. Jun 1 2018;56(2):122-126. doi:10.4193/Rhin17.168

137. Pendolino AL, Lund VJ, Nardello E, Ottaviano G. The nasal cycle: a comprehensive review. *Rhinology Online*. 2018;1:67-76. doi:10.4193/RHINOL/18.021

138. 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(10):e0162918. doi:10.1371/journal.pone.0162918

139. Sobel N, Khan RM, Hartley CA, Sullivan EV, Gabrieli JD. Sniffing longer rather than stronger to maintain olfactory detection threshold. *Chem Senses*. Feb 2000;25(1):1-8. doi:10.1093/chemse/25.1.1

140. Stuck BA, Fadel V, Hummel T, Sommer JU. Subjective olfactory desensitization and recovery in humans. *Chem Senses*. Feb 2014;39(2):151-7. doi:10.1093/chemse/bjt064

141. Sharma A, Kumar R, Aier I, Semwal R, Tyagi P, Varadwaj P. Sense of Smell: Structural, Functional, Mechanistic Advancements and Challenges in Human

Olfactory Research. *Curr Neuropharmacol*. 2019;17(9):891-911. doi:10.2174/1570159X17666181206095626

142. Sobel N, Khan RM, Saltman A, Sullivan EV, Gabrieli JD. The world smells different to each nostril. *Nature*. Nov 4 1999;402(6757):35. doi:10.1038/46944
143. Sobel N, Thomason ME, Stappen I, et al. An impairment in sniffing contributes to the olfactory impairment in Parkinson's disease. *Proc Natl Acad Sci U S A*. Mar 27 2001;98(7):4154-9. doi:10.1073/pnas.071061598
144. Mozell MM, Kent PF, Murphy SJ. The effect of flow rate upon the magnitude of the olfactory response differs for different odorants. *Chemical Senses*. 1991;16:631-649.
145. Calhoun KH, House W, Hokanson JA, Quinn FB. Normal nasal airway resistance in noses of different sizes and shapes. *Otolaryngol Head Neck Surg*. Oct 1990;103(4):605-9. doi:10.1177/019459989010300413
146. Keyhani K, Scherer PW, Mozell MM. A numerical model of nasal odorant transport for the analysis of human olfaction. *J Theor Biol*. Jun 7 1997;186(3):279-301. doi:10.1006/jtbi.1996.0347
147. Zhao K, Dalton P, Yang GC, Scherer PW. Numerical modeling of turbulent and laminar airflow and odorant transport during sniffing in the human and rat nose. *Chem Senses*. Feb 2006;31(2):107-18. doi:10.1093/chemse/bjj008
148. Chen XB, Lee HP, Chong VF, Wang de Y. Assessment of septal deviation effects on nasal air flow: a computational fluid dynamics model. *Laryngoscope*. Sep 2009;119(9):1730-6. doi:10.1002/lary.20585
149. Zhao K, Scherer PW, Hajiloo SA, Dalton P. Effect of anatomy on human nasal air flow and odorant transport patterns: implications for olfaction. *Chem Senses*. Jun 2004;29(5):365-79. doi:10.1093/chemse/bjh033
150. Leopold DA. The relationship between nasal anatomy and human olfaction. *Laryngoscope*. Nov 1988;98(11):1232-8. doi:10.1288/00005537-198811000-00015

151. Damm M, Vent J, Schmidt M, et al. Intranasal volume and olfactory function. *Chem Senses*. Nov 2002;27(9):831-9. doi:10.1093/chemse/27.9.831

152. Masala C, Kaehling C, Fall F, Hummel T. Correlation between olfactory function, trigeminal sensitivity, and nasal anatomy in healthy subjects. *Eur Arch Otorhinolaryngol*. Jun 2019;276(6):1649-1654. doi:10.1007/s00405-019-05367-y

153. Gupta N, Singh PP, Bagla RK. Will Septal Correction Surgery for Deviated Nasal Septum Improve the Sense of Smell? A Prospective Study. *Surg Res Pract*. 2015;2015:496542. doi:10.1155/2015/496542

154. Damm M, Eckel HE, Jungehulsing M, Hummel T. Olfactory changes at threshold and suprathreshold levels following septoplasty with partial inferior turbinectomy. *Ann Otol Rhinol Laryngol*. Jan 2003;112(1):91-7. doi:10.1177/000348940311200117

155. Valsamidis K, Printza A, Titelis K, Constantinidis J, Triaridis S. Olfaction and quality of life in patients with nasal septal deviation treated with septoplasty. *Am J Otolaryngol*. Sep-Oct 2019;40(5):747-754. doi:10.1016/j.amjoto.2019.07.008

156. Hornung DE, Smith DJ, Kurtz DB, White T, Leopold DA. Effect of nasal dilators on nasal structures, sniffing strategies, and olfactory ability. *Rhinology*. Jun 2001;39(2):84-7.

157. Ramprasad VH, Frank-Ito DO. A computational analysis of nasal vestibule morphologic variabilities on nasal function. *J Biomech*. Feb 8 2016;49(3):450-7. doi:10.1016/j.jbiomech.2016.01.009

158. Sicard RM, Frank-Ito DO. Role of nasal vestibule morphological variations on olfactory airflow dynamics. *Clin Biomech (Bristol, Avon)*. Feb 2021;82:105282. doi:10.1016/j.clinbiomech.2021.105282

159. Alam S, Li C, Bradburn KH, Zhao K, Lee TS. Impact of Middle Turbinectomy on Airflow to the Olfactory Cleft: A Computational Fluid Dynamics Study. *Am J Rhinol Allergy*. May 2019;33(3):263-268. doi:10.1177/1945892418816841

160. Soler ZM, Hwang PH, Mace J, Smith TL. Outcomes after middle turbinate resection: revisiting a controversial topic. *Laryngoscope*. Apr 2010;120(4):832-7. doi:10.1002/lary.20812

161. Friedman M, Caldarelli DD, Venkatesan TK, Pandit R, Lee Y. Endoscopic sinus surgery with partial middle turbinate resection: effects on olfaction. *Laryngoscope*. Aug 1996;106(8):977-81. doi:10.1097/00005537-199608000-00012

162. Courtiss EH, Goldwyn RM. The effects of nasal surgery on airflow. *Plast Reconstr Surg*. Jul 1983;72(1):9-21. doi:10.1097/00006534-198307000-00003

163. Aydogdu I, Atar Y, Aydogdu Z, et al. Comparison of Olfactory Function and Quality of Life With Different Surgical Techniques for Nasal Septum Deviation. *J Craniofac Surg*. Mar/Apr 2019;30(2):433-436. doi:10.1097/SCS.0000000000005109

164. Turk B, Akpinar M, Altundag A, Kirik MO, Unsal O, Coskun BU. The Effect of External Approach Septoplasty on Olfactory Function. *J Craniofac Surg*. Oct 2017;28(7):1675-1678. doi:10.1097/SCS.0000000000003626

165. Dalgic A, Is A, Dinc ME, Ulusoy S, Avincsal MO, Kulekci M. The Effects of Nasal Packing and Transseptal Suturing After Septoplasty on Olfactory Function, Patient Comfort, and Mucociliary Clearance. *J Craniofac Surg*. Jul 2016;27(5):e487-90. doi:10.1097/SCS.0000000000002805

166. Kilicaslan A, Acar GO, Tekin M, Ozdamar OI. Assessment the long-term effects of septoplasty surgery on olfactory function. *Acta Otolaryngol*. Oct 2016;136(10):1079-84. doi:10.1080/00016489.2016.1183168

167. Choi YS, Ryu YJ, Rhee J, et al. Clinical Implications of Septal Deviation in Lateralized Olfaction. *Clin Exp Otorhinolaryngol*. Mar 2016;9(1):39-43. doi:10.21053/ceo.2016.9.1.39

168. Berkiten G, Kumral TL, Salturk Z, et al. Effect of Deviated Nasal Septum Type on Nasal Mucociliary Clearance, Olfactory Function, Quality of Life, and Efficiency of Nasal Surgery. *J Craniofac Surg*. Jul 2016;27(5):1151-5. doi:10.1097/SCS.0000000000002696

169. Philpott CM, Rimal D, Tassone P, Prinsley PR, Premachandra DJ. A study of olfactory testing in patients with rhinological pathology in the ENT clinic. *Rhinology*. Mar 2008;46(1):34-9.

170. Gudziol V, Paech I, Hummel T. Unilateral reduced sense of smell is an early indicator for global olfactory loss. *J Neurol*. Jun 2010;257(6):959-63. doi:10.1007/s00415-009-5445-3

171. Pfaar O, Huttenbrink KB, Hummel T. Assessment of olfactory function after septoplasty: a longitudinal study. *Rhinology*. Dec 2004;42(4):195-9.

172. Altundag A, Salihoglu M, Tekeli H, Saglam M, Cayonu M, Hummel T. Lateralized differences in olfactory function and olfactory bulb volume relate to nasal septum deviation. *J Craniofac Surg*. Mar 2014;25(2):359-62. doi:10.1097/SCS.0000000000000617

173. Mackers P, Rojas-Lechuga MJ, Langdon C, Nogu ASA, Mullol J, Alobid I. Septoplasty and/or inferior turbinoplasty produce significant improvements of the sense of smell. *Rhinology*. Oct 1 2023;61(5):421-431. doi:10.4193/Rhin22.461

174. Gillman GS, Bakeman AE, Soose RJ, et al. Will nasal airway surgery improve my sense of smell? A prospective observational study. *Int Forum Allergy Rhinol*. Nov 22 2022;doi:10.1002/alr.23115

175. Pade J, Hummel T. Olfactory function following nasal surgery. *Laryngoscope*. Jul 2008;118(7):1260-4. doi:10.1097/MLG.0b013e318170b5cb

176. Ulusoy S, Dinc ME, Dalgic A, Dizdar D, Avincsal MO, Kulekci M. Effects of Spreader Grafts on Olfactory Function in Septorhinoplasty. *Aesthetic Plast Surg*. Feb 2016;40(1):106-13. doi:10.1007/s00266-015-0597-2

177. Dengiz R, Haytoglu S, Gorgulu O, Dogru M, Arikan OK. Effect of Septorhinoplasty on Olfactory Function: Assessment Using the Brief Smell Identification Test. *Turk Arch Otorhinolaryngol*. Mar 2015;53(1):4-9. doi:10.5152/tao.2015.694

178. Whitcroft KL, Mancini L, Yousry T, Hummel T, Andrews PJ. Functional septorhinoplasty alters brain structure and function: Neuroanatomical correlates of

olfactory dysfunction. *Front Allergy*. 2023;4:1079945. doi:10.3389/falgy.2023.1079945

179. Kohli P, Naik AN, Farhood Z, et al. Olfactory Outcomes after Endoscopic Sinus Surgery for Chronic Rhinosinusitis: A Meta-analysis. *Otolaryngol Head Neck Surg*. Dec 2016;155(6):936-948. doi:10.1177/0194599816664879
180. Dekeyser A, Huart C, Hummel T, Hox V. Olfactory Loss in Rhinosinusitis: Mechanisms of Loss and Recovery. *Int J Mol Sci*. Apr 18 2024;25(8)doi:10.3390/ijms25084460
181. Kowalski ML, Agache I, Bavbek S, et al. Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD)-a EAACI position paper. *Allergy*. Jan 2019;74(1):28-39. doi:10.1111/all.13599
182. Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: A meta-analysis of the literature. *J Allergy Clin Immunol*. Mar 2015;135(3):676-81 e1. doi:10.1016/j.jaci.2014.08.020
183. Li KL, Lee AY, Abuzeid WM. Aspirin Exacerbated Respiratory Disease: Epidemiology, Pathophysiology, and Management. *Med Sci (Basel)*. Mar 17 2019;7(3)doi:10.3390/medsci7030045
184. Taniguchi M, Mitsui C, Hayashi H, et al. Aspirin-exacerbated respiratory disease (AERD): Current understanding of AERD. *Allergol Int*. Jul 2019;68(3):289-295. doi:10.1016/j.alit.2019.05.001
185. Berges-Gimeno MP, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. Nov 2002;89(5):474-8. doi:10.1016/S1081-1206(10)62084-4
186. Tuttle KL, Schneider TR, Henrickson SE, et al. Aspirin-exacerbated respiratory disease: not always "adult-onset". *J Allergy Clin Immunol Pract*. Jul-Aug 2016;4(4):756-8. doi:10.1016/j.jaip.2016.05.016

187. Stevens WW, Peters AT, Hirsch AG, et al. Clinical Characteristics of Patients with Chronic Rhinosinusitis with Nasal Polyps, Asthma, and Aspirin-Exacerbated Respiratory Disease. *J Allergy Clin Immunol Pract*. Jul - Aug 2017;5(4):1061-1070 e3. doi:10.1016/j.jaip.2016.12.027

188. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *Eur Respir J*. Sep 2000;16(3):432-6. doi:10.1034/j.1399-3003.2000.016003432.x

189. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis. *J Allergy Clin Immunol*. Nov 1977;60(5):276-84. doi:10.1016/0091-6749(77)90106-3

190. Yoshimine F, Hasegawa T, Suzuki E, et al. Contribution of aspirin-intolerant asthma to near fatal asthma based on a questionnaire survey in Niigata Prefecture, Japan. *Respirology*. Sep 2005;10(4):477-84. doi:10.1111/j.1440-1843.2005.00740.x

191. Cardet JC, White AA, Barrett NA, et al. Alcohol-induced respiratory symptoms are common in patients with aspirin exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. Mar-Apr 2014;2(2):208-13. doi:10.1016/j.jaip.2013.12.003

192. Glicksman JT, Parasher AK, Doghramji L, et al. Alcohol-induced respiratory symptoms improve after aspirin desensitization in patients with aspirin-exacerbated respiratory disease. *Int Forum Allergy Rhinol*. Oct 2018;8(10):1093-1097. doi:10.1002/alr.22168

193. Hybar H, Saki N, Maleknia M, Moghaddasi M, Bordbar A, Naghavi M. Aspirin exacerbated respiratory disease (AERD): molecular and cellular diagnostic & prognostic approaches. *Mol Biol Rep*. Mar 2021;48(3):2703-2711. doi:10.1007/s11033-021-06240-0

194. Szczeklik A. The cyclooxygenase theory of aspirin-induced asthma. *Eur Respir J*. May 1990;3(5):588-93.

195. Hirai H, Tanaka K, Yoshie O, et al. Prostaglandin D2 selectively induces chemotaxis in T helper type 2 cells, eosinophils, and basophils via seven-transmembrane receptor CRTH2. *J Exp Med*. Jan 15 2001;193(2):255-61. doi:10.1084/jem.193.2.255

196. Chang JE, Doherty TA, Baum R, Broide D. Prostaglandin D2 regulates human type 2 innate lymphoid cell chemotaxis. *J Allergy Clin Immunol*. Mar 2014;133(3):899-901 e3. doi:10.1016/j.jaci.2013.09.020

197. White AA, Stevenson DD. Aspirin-Exacerbated Respiratory Disease. *N Engl J Med*. Sep 13 2018;379(11):1060-1070. doi:10.1056/NEJMra1712125

198. Dominas C, Gadkaree S, Maxfield AZ, Gray ST, Bergmark RW. Aspirin-exacerbated respiratory disease: A review. *Laryngoscope Investig Otolaryngol*. Jun 2020;5(3):360-367. doi:10.1002/lio2.387

199. Woo SD, Luu QQ, Park HS. NSAID-Exacerbated Respiratory Disease (NERD): From Pathogenesis to Improved Care. *Front Pharmacol*. 2020;11:1147. doi:10.3389/fphar.2020.01147

200. Steinke JW, Payne SC, Borish L. Eosinophils and Mast Cells in Aspirin-Exacerbated Respiratory Disease. *Immunol Allergy Clin North Am*. Nov 2016;36(4):719-734. doi:10.1016/j.iac.2016.06.008

201. Laidlaw TM, Kidder MS, Bhattacharyya N, et al. Cysteinyl leukotriene overproduction in aspirin-exacerbated respiratory disease is driven by platelet-adherent leukocytes. *Blood*. Apr 19 2012;119(16):3790-8. doi:10.1182/blood-2011-10-384826

202. Buchheit KM, Dwyer DF, Ordovas-Montanes J, et al. IL-5Ralpha marks nasal polyp IgG4- and IgE-expressing cells in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. Jun 2020;145(6):1574-1584. doi:10.1016/j.jaci.2020.02.035

203. Miller B, Mirakian R, Gane S, et al. Nasal lysine aspirin challenge in the diagnosis of aspirin - exacerbated respiratory disease: asthma and rhinitis. *Clin Exp Allergy*. Aug 2013;43(8):874-80. doi:10.1111/cea.12110

204. Macy E, Bernstein JA, Castells MC, et al. Aspirin challenge and desensitization for aspirin-exacerbated respiratory disease: a practice paper. *Ann Allergy Asthma Immunol*. Feb 2007;98(2):172-4. doi:10.1016/S1081-1206(10)60692-8

205. Stevenson DD, Simon RA. Selection of patients for aspirin desensitization treatment. *J Allergy Clin Immunol*. Oct 2006;118(4):801-4. doi:10.1016/j.jaci.2006.06.019

206. Nizankowska E, Bestynska-Krypel A, Cmiel A, Szczeklik A. Oral and bronchial provocation tests with aspirin for diagnosis of aspirin-induced asthma. *Eur Respir J*. May 2000;15(5):863-9. doi:10.1034/j.1399-3003.2000.15e09.x

207. White A, Bigby T, Stevenson D. Intranasal ketorolac challenge for the diagnosis of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. Aug 2006;97(2):190-5. doi:10.1016/S1081-1206(10)60012-9

208. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy*. Oct 2007;62(10):1111-8. doi:10.1111/j.1398-9995.2007.01409.x

209. Milewski M, Mastalerz L, Nizankowska E, Szczeklik A. Nasal provocation test with lysine-aspirin for diagnosis of aspirin-sensitive asthma. *J Allergy Clin Immunol*. May 1998;101(5):581-6. doi:10.1016/S0091-6749(98)70163-0

210. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology*. Feb 20 2020;58(Suppl S29):1-464. doi:10.4193/Rhin20.600

211. Stevenson DD, Simon RA, Mathison DA. Aspirin-sensitive asthma: tolerance to aspirin after positive oral aspirin challenges. *J Allergy Clin Immunol*. Jul 1980;66(1):82-8. doi:10.1016/0091-6749(80)90143-8

212. Stevens WW, Jerschow E, Baptist AP, et al. The role of aspirin desensitization followed by oral aspirin therapy in managing patients with aspirin-exacerbated respiratory disease: A Work Group Report from the Rhinitis, Rhinosinusitis and Ocular Allergy Committee of the American Academy of Allergy, Asthma &

Immunology. *J Allergy Clin Immunol*. Mar 2021;147(3):827-844. doi:10.1016/j.jaci.2020.10.043

213. Chang JE, White A, Simon RA, Stevenson DD. Aspirin-exacerbated respiratory disease: burden of disease. *Allergy Asthma Proc*. Mar-Apr 2012;33(2):117-21. doi:10.2500/aap.2012.33.3541
214. Chu DK, Lee DJ, Lee KM, Schunemann HJ, Szczeklik W, Lee JM. Benefits and harms of aspirin desensitization for aspirin-exacerbated respiratory disease: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. Dec 2019;9(12):1409-1419. doi:10.1002/alr.22428
215. Walters KM, Waldram JD, Woessner KM, White AA. Long-term Clinical Outcomes of Aspirin Desensitization With Continuous Daily Aspirin Therapy in Aspirin-exacerbated Respiratory Disease. *Am J Rhinol Allergy*. Jul 2018;32(4):280-286. doi:10.1177/1945892418770260
216. Sousa AR, Parikh A, Scadding G, Corrigan CJ, Lee TH. Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. *N Engl J Med*. Nov 7 2002;347(19):1493-9. doi:10.1056/NEJMoa013508
217. Esmaeilzadeh H, Zare M, Alyasin S, Nabavizadeh H, Mortazavi N, Kanannejad Z. A Review of Aspirin-exacerbated Respiratory Diseases and Immunological Efficacy of Aspirin Desensitization. *Iran J Allergy Asthma Immunol*. Oct 26 2022;21(5):512-523. doi:10.18502/ijaai.v21i5.11039
218. Patriarca G, Bellioni P, Nucera E, et al. Intranasal treatment with lysine acetylsalicylate in patients with nasal polyposis. *Ann Allergy*. Dec 1991;67(6):588-92.
219. Nucera E, Schiavino D, Milani A, et al. Effects of lysine-acetylsalicylate (LAS) treatment in nasal polyposis: two controlled long term prospective follow up studies. *Thorax*. Oct 2000;55 Suppl 2:S75-8. doi:10.1136/thorax.55.suppl_2.s75

220. Patriarca G, Schiavino D, Nucera E, Papa G, Schinco G, Fais G. Prevention of relapse in nasal polyposis. *Lancet*. Jun 15 1991;337(8755):1488. doi:10.1016/0140-6736(91)93185-c

221. Howe R, Mirakian RM, Pillai P, Gane S, Darby YC, Scadding GK. Audit of nasal lysine aspirin therapy in recalcitrant aspirin exacerbated respiratory disease. *World Allergy Organ J*. 2014;7(1):18. doi:10.1186/1939-4551-7-18

222. Parikh A, Scadding GK. Topical nasal lysine aspirin in aspirin-sensitive and aspirin-tolerant chronic rhinosinusitis with nasal polyposis. *Expert Rev Clin Immunol*. May 2014;10(5):657-65. doi:10.1586/1744666X.2014.901889

223. Scadding GK, Hassab M, Darby YC, Lund VJ, Freedman A. Intranasal lysine aspirin in recurrent nasal polyposis. *Clin Otolaryngol Allied Sci*. Dec 1995;20(6):561-3. doi:10.1111/j.1365-2273.1995.tb01603.x

224. Pendolino AL, Scadding GK, Scarpa B, Andrews PJ. A retrospective study on long-term efficacy of intranasal lysine-aspirin in controlling NSAID-exacerbated respiratory disease. *Eur Arch Otorhinolaryngol*. May 2022;279(5):2473-2484. doi:10.1007/s00405-021-07063-2

225. Lee RU, Stevenson DD. Aspirin-exacerbated respiratory disease: evaluation and management. *Allergy Asthma Immunol Res*. Jan 2011;3(1):3-10. doi:10.4168/aair.2011.3.1.3

226. Rozsasi A, Polzehl D, Deutschle T, et al. Long-term treatment with aspirin desensitization: a prospective clinical trial comparing 100 and 300 mg aspirin daily. *Allergy*. Sep 2008;63(9):1228-34. doi:10.1111/j.1398-9995.2008.01658.x

227. Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. Jan 2003;111(1):180-6. doi:10.1067/mai.2003.7

228. Steinhubl SR, Bhatt DL, Brennan DM, et al. Aspirin to prevent cardiovascular disease: the association of aspirin dose and clopidogrel with thrombosis and

bleeding. *Ann Intern Med*. Mar 17 2009;150(6):379-86. doi:10.7326/0003-4819-150-6-200903170-00006

229. Parikh AA, Scadding GK. Intranasal lysine-aspirin in aspirin-sensitive nasal polyposis: a controlled trial. *Laryngoscope*. Aug 2005;115(8):1385-90. doi:10.1097/01.MLG.0000166702.38850.1B
230. Fokkens WJ, Viskens AS, Backer V, et al. EPOS/EUFOREA update on indication and evaluation of Biologics in Chronic Rhinosinusitis with Nasal Polyps 2023. *Rhinology*. Jun 1 2023;61(3):194-202. doi:10.4193/Rhin22.489
231. Chong LY, Piromchai P, Sharp S, et al. Biologics for chronic rhinosinusitis. *Cochrane Database Syst Rev*. Mar 12 2021;3(3):CD013513. doi:10.1002/14651858.CD013513.pub3
232. Oykhman P, Paramo FA, Bousquet J, Kennedy DW, Brignardello-Petersen R, Chu DK. Comparative efficacy and safety of monoclonal antibodies and aspirin desensitization for chronic rhinosinusitis with nasal polyposis: A systematic review and network meta-analysis. *J Allergy Clin Immunol*. Apr 2022;149(4):1286-1295. doi:10.1016/j.jaci.2021.09.009
233. Bavaro N, Gakpo D, Mittal A, Bensko JC, Laidlaw TM, Buchheit KM. Efficacy of dupilumab in patients with aspirin-exacerbated respiratory disease and previous inadequate response to anti-IL-5 or anti-IL-5Ralpha in a real-world setting. *J Allergy Clin Immunol Pract*. Jul 2021;9(7):2910-2912 e1. doi:10.1016/j.jaip.2021.02.020
234. Fokkens WJ, Lund V, Bachert C, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. *Allergy*. Dec 2019;74(12):2312-2319. doi:10.1111/all.13875
235. Buchheit KM, Laidlaw TM, Levy JM. Immunology-based recommendations for available and upcoming biologics in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. Aug 2021;148(2):348-350. doi:10.1016/j.jaci.2021.06.019
236. Yong M, Wu YQ, Howlett J, Ballreich J, Walgama E, Thamboo A. Cost-effectiveness analysis comparing dupilumab and aspirin desensitization therapy

for chronic rhinosinusitis with nasal polyposis in aspirin-exacerbated respiratory disease. *Int Forum Allergy Rhinol*. Dec 2021;11(12):1626-1636. doi:10.1002/alr.22865

237. Amar YG, Frenkiel S, Sobol SE. Outcome analysis of endoscopic sinus surgery for chronic sinusitis in patients having Samter's triad. *J Otolaryngol*. Feb 2000;29(1):7-12.
238. Mendelsohn D, Jeremic G, Wright ED, Rotenberg BW. Revision rates after endoscopic sinus surgery: a recurrence analysis. *Ann Otol Rhinol Laryngol*. Mar 2011;120(3):162-6. doi:10.1177/000348941112000304
239. Walgama ES, Hwang PH. Aspirin-Exacerbated Respiratory Disease. *Otolaryngol Clin North Am*. Feb 2017;50(1):83-94. doi:10.1016/j.otc.2016.08.007
240. Shih LC, Patel VS, Choby GW, Nakayama T, Hwang PH. Evolution of the endoscopic modified Lothrop procedure: A systematic review and meta-analysis. *Laryngoscope*. Feb 2018;128(2):317-326. doi:10.1002/lary.26794
241. Morrissey DK, Bassiouni A, Psaltis AJ, Naidoo Y, Wormald PJ. Outcomes of modified endoscopic Lothrop in aspirin-exacerbated respiratory disease with nasal polyposis. *Int Forum Allergy Rhinol*. Aug 2016;6(8):820-5. doi:10.1002/alr.21739
242. DeConde AS, Suh JD, Mace JC, Alt JA, Smith TL. Outcomes of complete vs targeted approaches to endoscopic sinus surgery. *Int Forum Allergy Rhinol*. Aug 2015;5(8):691-700. doi:10.1002/alr.21541
243. Adappa ND, Ranasinghe VJ, Trope M, et al. Outcomes after complete endoscopic sinus surgery and aspirin desensitization in aspirin-exacerbated respiratory disease. *Int Forum Allergy Rhinol*. Jan 2018;8(1):49-53. doi:10.1002/alr.22036
244. Naidoo Y, Bassiouni A, Keen M, Wormald PJ. Risk factors and outcomes for primary, revision, and modified Lothrop (Draf III) frontal sinus surgery. *Int Forum Allergy Rhinol*. May 2013;3(5):412-7. doi:10.1002/alr.21109
245. Pendolino AL, Bandino F, Navaratnam A, et al. The role of large cavity sinus surgery in the management of chronic rhinosinusitis in non-steroidal anti-

inflammatory drug exacerbated respiratory disease: a single-centre experience and long-term outcomes. *J Laryngol Otol*. Aug 2023;137(8):883-889. doi:10.1017/S0022215122002468

246. Ta V, White AA. Survey-Defined Patient Experiences With Aspirin-Exacerbated Respiratory Disease. *J Allergy Clin Immunol Pract*. Sep-Oct 2015;3(5):711-8. doi:10.1016/j.jaip.2015.03.001
247. Gudziol V, Michel M, Sonnefeld C, Koschel D, Hummel T. Olfaction and sinonasal symptoms in patients with CRSwNP and AERD and without AERD: a cross-sectional and longitudinal study. *Eur Arch Otorhinolaryngol*. Mar 2017;274(3):1487-1493. doi:10.1007/s00405-016-4366-x
248. Morse JC, Shilts MH, Ely KA, et al. Patterns of olfactory dysfunction in chronic rhinosinusitis identified by hierarchical cluster analysis and machine learning algorithms. *Int Forum Allergy Rhinol*. Mar 2019;9(3):255-264. doi:10.1002/alr.22249
249. Wu J, Chandra RK, Li P, Hull BP, Turner JH. Olfactory and middle meatal cytokine levels correlate with olfactory function in chronic rhinosinusitis. *Laryngoscope*. Sep 2018;128(9):E304-E310. doi:10.1002/lary.27112
250. Dintica CS, Marseglia A, Rizzuto D, et al. Impaired olfaction is associated with cognitive decline and neurodegeneration in the brain. *Neurology*. Feb 12 2019;92(7):e700-e709. doi:10.1212/WNL.0000000000006919
251. Neuland C, Bitter T, Marschner H, Gudziol H, Guntinas-Lichius O. Health-related and specific olfaction-related quality of life in patients with chronic functional anosmia or severe hyposmia. *Laryngoscope*. Apr 2011;121(4):867-72. doi:10.1002/lary.21387
252. Kern RC. Chronic sinusitis and anosmia: pathologic changes in the olfactory mucosa. *Laryngoscope*. Jul 2000;110(7):1071-7. doi:10.1097/00005537-200007000-00001

253. Nagashima A, Touhara K. Enzymatic conversion of odorants in nasal mucus affects olfactory glomerular activation patterns and odor perception. *J Neurosci*. Dec 1 2010;30(48):16391-8. doi:10.1523/JNEUROSCI.2527-10.2010

254. Robert-Hazotte A, Faure P, Neiers F, et al. Nasal mucus glutathione transferase activity and impact on olfactory perception and neonatal behavior. *Sci Rep*. Feb 28 2019;9(1):3104. doi:10.1038/s41598-019-39495-6

255. Han X, He X, Zhan X, et al. Disturbed microbiota-metabolites-immune interaction network is associated with olfactory dysfunction in patients with chronic rhinosinusitis. *Front Immunol*. 2023;14:1159112. doi:10.3389/fimmu.2023.1159112

256. Soler ZM, Yoo F, Schlosser RJ, et al. Correlation of mucus inflammatory proteins and olfaction in chronic rhinosinusitis. *Int Forum Allergy Rhinol*. Mar 2020;10(3):343-355. doi:10.1002/alr.22499

257. Stevens WW, Peters AT, Tan BK, et al. Associations Between Inflammatory Endotypes and Clinical Presentations in Chronic Rhinosinusitis. *J Allergy Clin Immunol Pract*. Nov-Dec 2019;7(8):2812-2820 e3. doi:10.1016/j.jaip.2019.05.009

258. Macchi A, Giorli A, Cantone E, et al. Sense of smell in chronic rhinosinusitis: A multicentric study on 811 patients. *Front Allergy*. 2023;4:1083964. doi:10.3389/falgy.2023.1083964

259. Delemarre T, Bochner BS, Simon HU, Bachert C. Rethinking neutrophils and eosinophils in chronic rhinosinusitis. *J Allergy Clin Immunol*. Aug 2021;148(2):327-335. doi:10.1016/j.jaci.2021.03.024

260. Harlin SL, Ansel DG, Lane SR, Myers J, Kephart GM, Gleich GJ. A clinical and pathologic study of chronic sinusitis: the role of the eosinophil. *J Allergy Clin Immunol*. May 1988;81(5 Pt 1):867-75. doi:10.1016/0091-6749(88)90944-x

261. Frigas E, Motojima S, Gleich GJ. The eosinophilic injury to the mucosa of the airways in the pathogenesis of bronchial asthma. *Eur Respir J Suppl*. Apr 1991;13:123s-135s.

262. Lavin J, Min JY, Lidder AK, et al. Superior turbinate eosinophilia correlates with olfactory deficit in chronic rhinosinusitis patients. *Laryngoscope*. Oct 2017;127(10):2210-2218. doi:10.1002/lary.26555

263. Liu Z, Hong J, Huang X, Wu D. Olfactory cleft mucus galectin-10 predicts olfactory loss in chronic rhinosinusitis. *Ann Allergy Asthma Immunol*. Mar 2023;130(3):317-324 e1. doi:10.1016/j.anai.2022.07.014

264. Han X, Wu D, Sun Z, et al. Type 1/type 2 inflammatory cytokines correlate with olfactory function in patients with chronic rhinosinusitis. *Am J Otolaryngol*. Sep-Oct 2020;41(5):102587. doi:10.1016/j.amjoto.2020.102587

265. Cho SH, Kim DW, Gevaert P. Chronic Rhinosinusitis without Nasal Polyps. *J Allergy Clin Immunol Pract*. Jul-Aug 2016;4(4):575-82. doi:10.1016/j.jaip.2016.04.015

266. Jafek BW, Murrow B, Michaels R, Restrepo D, Linschoten M. Biopsies of human olfactory epithelium. *Chem Senses*. Sep 2002;27(7):623-8. doi:10.1093/chemse/27.7.623

267. Yee KK, Pribitkin EA, Cowart BJ, et al. Neuropathology of the olfactory mucosa in chronic rhinosinusitis. *Am J Rhinol Allergy*. Mar-Apr 2010;24(2):110-20. doi:10.2500/ajra.2010.24.3435

268. Rombaux P, Potier H, Bertrand B, Duprez T, Hummel T. Olfactory bulb volume in patients with sinonasal disease. *Am J Rhinol*. Nov-Dec 2008;22(6):598-601. doi:10.2500/ajr.2008.22.3237

269. Han P, Whitcroft KL, Fischer J, et al. Olfactory brain gray matter volume reduction in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol*. Jun 2017;7(6):551-556. doi:10.1002/alr.21922

270. Espehana A, Lee L, Garden EM, et al. Delivery of Topical Drugs to the Olfactory Cleft. *J Clin Med.* Nov 29 2023;12(23)doi:10.3390/jcm12237387

271. Mori E, Merkonidis C, Cuevas M, Gudziol V, Matsuwaki Y, Hummel T. The administration of nasal drops in the "Kaiteki" position allows for delivery of the drug

to the olfactory cleft: a pilot study in healthy subjects. *Eur Arch Otorhinolaryngol*. Apr 2016;273(4):939-43. doi:10.1007/s00405-015-3701-y

272. Banglawala SM, Oyer SL, Lohia S, Psaltis AJ, Soler ZM, Schlosser RJ. Olfactory outcomes in chronic rhinosinusitis with nasal polyposis after medical treatments: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. Dec 2014;4(12):986-94. doi:10.1002/alr.21373
273. Papadakis CE, Chimona TS, Chaidas K, Ladias A, Zisoglou M, Proimos EK. Effect of oral steroids on olfactory function in chronic rhinosinusitis with nasal polyps. *Eur Ann Otorhinolaryngol Head Neck Dis*. Oct 2021;138(5):343-348. doi:10.1016/j.anorl.2020.06.028
274. Barnes PJ. Mechanisms and resistance in glucocorticoid control of inflammation. *J Steroid Biochem Mol Biol*. May 31 2010;120(2-3):76-85. doi:10.1016/j.jsbmb.2010.02.018
275. Gudziol V, Buschhuter D, Abolmaali N, Gerber J, Rombaux P, Hummel T. Increasing olfactory bulb volume due to treatment of chronic rhinosinusitis--a longitudinal study. *Brain*. Nov 2009;132(Pt 11):3096-101. doi:10.1093/brain/awp243
276. Whitcroft KL, Noltus J, Andrews P, Hummel T. Sinonasal surgery alters brain structure and function: Neuroanatomical correlates of olfactory dysfunction. *J Neurosci Res*. Sep 2021;99(9):2156-2171. doi:10.1002/jnr.24897
277. Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol*. Sep 2020;146(3):595-605. doi:10.1016/j.jaci.2020.05.032
278. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. Nov 2 2019;394(10209):1638-1650. doi:10.1016/S0140-6736(19)31881-1

279. Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. Oct 2021;9(10):1141-1153. doi:10.1016/S2213-2600(21)00097-7

280. Pendolino AL, Ferreira J, Scadding GK, Andrews PJ. Quality of Life in NSAIDs-Exacerbated Respiratory Disease on or off Intranasal Lysine Aspirin Therapy. *Applied Sciences*. 2024;14(3):1162.

281. Dursun AB, Woessner KA, Simon RA, Karasoy D, Stevenson DD. Predicting outcomes of oral aspirin challenges in patients with asthma, nasal polyps, and chronic sinusitis. *Ann Allergy Asthma Immunol*. May 2008;100(5):420-5. doi:10.1016/S1081-1206(10)60465-6

282. Ottaviano G, Pendolino AL, Nardello E, et al. Peak nasal inspiratory flow measurement and visual analogue scale in a large adult population. *Clin Otolaryngol*. Jul 2019;44(4):541-548. doi:10.1111/coa.13329

283. Pinheiro JC, Bates DM. *Mixed-Effects Models in S and S-PLUS*. Springer-Verlag; 2000.

284. Fai AH, Cornelius PL. Approximate F-Tests of Multiple Degree of Freedom Hypotheses in Generalised Least Squares Analyses of Unbalanced Split-Plot Experiments. *Journal of Statistical Computation and Simulation*. 1996;54(4):363–378. doi:10.1080/00949659608811740

285. Ottaviano G, Scadding GK, Coles S, Lund VJ. Peak nasal inspiratory flow; normal range in adult population. *Rhinology*. Mar 2006;44(1):32-5.

286. Cooper T, Greig SR, Zhang H, et al. Objective and subjective sinonasal and pulmonary outcomes in aspirin desensitization therapy: A prospective cohort study. *Auris Nasus Larynx*. Aug 2019;46(4):526-532. doi:10.1016/j.anl.2018.12.002

287. Havel M, Ertl L, Braunschweig F, et al. Sinonasal outcome under aspirin desensitization following functional endoscopic sinus surgery in patients with

aspirin triad. *Eur Arch Otorhinolaryngol*. Feb 2013;270(2):571-8. doi:10.1007/s00405-012-2048-x

288. Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA. Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. *J Allergy Clin Immunol*. Oct 1996;98(4):751-8. doi:10.1016/s0091-6749(96)70123-9
289. Fruth K, Pogorzelski B, Schmidtmann I, et al. Low-dose aspirin desensitization in individuals with aspirin-exacerbated respiratory disease. *Allergy*. 2013;68(5):659-65. doi:10.1111/all.12131
290. Berges-Gimeno MP, Simon RA, Stevenson DD. Early effects of aspirin desensitization treatment in asthmatic patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. Mar 2003;90(3):338-41. doi:10.1016/S1081-1206(10)61803-0
291. Chaaban MR, Moffatt D, Wright AE, Cowthran JA, Hsu ES, Kuo YF. Meta-analysis Exploring Sinopulmonary Outcomes of Aspirin Desensitization in Aspirin-Exacerbated Respiratory Disease. *Otolaryngol Head Neck Surg*. Jan 2021;164(1):11-18. doi:10.1177/0194599820932137
292. Esmaeilzadeh H, Nabavi M, Aryan Z, et al. Aspirin desensitization for patients with aspirin-exacerbated respiratory disease: A randomized double-blind placebo-controlled trial. *Clin Immunol*. Oct 2015;160(2):349-57. doi:10.1016/j.clim.2015.05.012
293. Mortazavi N, Esmaeilzadeh H, Abbasinazari M, et al. Clinical and Immunological Efficacy of Aspirin Desensitization in Nasal Polyp Patients with Aspirin-Exacerbated Respiratory Disease. *Iran J Pharm Res*. Fall 2017;16(4):1639-1647.
294. Tyrak KE, Pajdzik K, Jakiela B, et al. Biomarkers for predicting response to aspirin therapy in aspirin-exacerbated respiratory disease. *Clin Exp Allergy*. Apr 27 2021;doi:10.1111/cea.13886

295. Ramirez-Jimenez F, Vazquez-Corona A, Sanchez-de la Vega Reynoso P, et al. Effect of LTRA in L-ASA Challenge for Aspirin-Exacerbated Respiratory Disease Diagnosis. *J Allergy Clin Immunol Pract*. Apr 2021;9(4):1554-1561. doi:10.1016/j.jaip.2020.10.041

296. Williams AN, Simon RA, Woessner KM, Stevenson DD. The relationship between historical aspirin-induced asthma and severity of asthma induced during oral aspirin challenges. *J Allergy Clin Immunol*. Aug 2007;120(2):273-7. doi:10.1016/j.jaci.2007.03.020

297. Ogata N, Darby Y, Scadding G. Intranasal lysine-aspirin administration decreases polyp volume in patients with aspirin-intolerant asthma. *J Laryngol Otol*. Dec 2007;121(12):1156-60. doi:10.1017/S0022215107000515

298. Levy JM, Rudmik L, Peters AT, Wise SK, Rotenberg BW, Smith TL. Contemporary management of chronic rhinosinusitis with nasal polyposis in aspirin-exacerbated respiratory disease: an evidence-based review with recommendations. *Int Forum Allergy Rhinol*. Dec 2016;6(12):1273-1283. doi:10.1002/alr.21826

299. Khan A, Huynh TMT, Vandeplas G, et al. The GALEN rhinosinusitis cohort: chronic rhinosinusitis with nasal polyps affects health-related quality of life. *Rhinology*. Oct 1 2019;57(5):343-351. doi:10.4193/Rhin19.158

300. Zhou S, Hur K, Shen J, Wrobel B. Impact of sinonasal disease on depression, sleep duration, and productivity among adults in the United States. *Laryngoscope Investig Otolaryngol*. Oct 2017;2(5):288-294. doi:10.1002/lio2.87

301. Cho KS, Soudry E, Psaltis AJ, et al. Long-term sinonasal outcomes of aspirin desensitization in aspirin exacerbated respiratory disease. *Otolaryngol Head Neck Surg*. Oct 2014;151(4):575-81. doi:10.1177/0194599814545750

302. Khan AH, Reaney M, Guillemin I, et al. Development of Sinonasal Outcome Test (SNOT-22) Domains in Chronic Rhinosinusitis With Nasal Polyps. *Laryngoscope*. May 2022;132(5):933-941. doi:10.1002/lary.29766

303. Swierczynska-Krepa M, Sanak M, Bochenek G, et al. Aspirin desensitization in patients with aspirin-induced and aspirin-tolerant asthma: a double-blind study. *J Allergy Clin Immunol*. Oct 2014;134(4):883-90. doi:10.1016/j.jaci.2014.02.041

304. Toma S, Hopkins C. Stratification of SNOT-22 scores into mild, moderate or severe and relationship with other subjective instruments. *Rhinology*. Jun 2016;54(2):129-33. doi:10.4193/Rhino15.072

305. Tripathi SH, Corr A, Kumar A, et al. SNOT-22 scores after 6 months of aspirin therapy are predictive of long-term quality of life in AERD. *Allergy Asthma Proc*. Jan 1 2023;44(1):78-80. doi:10.2500/aap.2023.44.220091

306. Lee SE, Hopkins C, Mullol J, et al. Dupilumab improves health related quality of life: Results from the phase 3 SINUS studies. *Allergy*. Jul 2022;77(7):2211-2221. doi:10.1111/all.15222

307. Tchekmedyian R, Lundberg M, Buchheit KM, et al. Loss of smell in patients with aspirin-exacerbated respiratory disease impacts mental health and quality of life. *Clin Exp Allergy*. Dec 2022;52(12):1414-1421. doi:10.1111/cea.14157

308. Spielman DB, Overdevest J, Gudis DA. Olfactory outcomes in the management of aspirin exacerbated respiratory disease related chronic rhinosinusitis. *World J Otorhinolaryngol Head Neck Surg*. Dec 2020;6(4):207-213. doi:10.1016/j.wjorl.2020.07.001

309. Sweet JM, Stevenson DD, Simon RA, Mathison DA. Long-term effects of aspirin desensitization--treatment for aspirin-sensitive rhinosinusitis-asthma. *J Allergy Clin Immunol*. Jan 1990;85(1 Pt 1):59-65. doi:10.1016/0091-6749(90)90222-p

310. Bordin A, Mucignat-Caretta C, Gaudioso P, et al. Comparison of self-reported symptoms and psychophysical tests in coronavirus disease 2019 (COVID-19) subjects experiencing long-term olfactory dysfunction: a 6-month follow-up study. *Int Forum Allergy Rhinol*. Nov 2021;11(11):1592-1595. doi:10.1002/alr.22828

311. Landis BN, Hummel T, Hugentobler M, Giger R, Lacroix JS. Ratings of overall olfactory function. *Chem Senses*. Oct 2003;28(8):691-4. doi:10.1093/chemse/bjg061

312. Waldram JD, White AA. A survey of aspirin desensitization practices among allergists and fellows in training in the United States. *J Allergy Clin Immunol Pract*. Nov-Dec 2016;4(6):1253-1255. doi:10.1016/j.jaip.2016.06.016

313. Yalcin AD, Ucar S, Gumuslu S, Strauss LG. Effects of omalizumab on eosinophil cationic peptide, 25-hydroxyvitamin-D, IL-1beta and sCD200 in cases of Samter's syndrome: 36 months follow-up. *Immunopharmacol Immunotoxicol*. Aug 2013;35(4):524-7. doi:10.3109/08923973.2013.811598

314. Laidlaw TM, Chu DK, Stevens WW, White AA. Controversies in Allergy: Aspirin Desensitization or Biologics for Aspirin-Exacerbated Respiratory Disease-How to Choose. *J Allergy Clin Immunol Pract*. Jun 2022;10(6):1462-1467. doi:10.1016/j.jaip.2021.12.030

315. Orlandi RR, Kingdom TT, Smith TL, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. *Int Forum Allergy Rhinol*. Mar 2021;11(3):213-739. doi:10.1002/alr.22741

316. Ottaviano G, Saccardo T, Roccuzzo G, et al. Effectiveness of Dupilumab in the Treatment of Patients with Uncontrolled Severe CRSwNP: A "Real-Life" Observational Study in Naive and Post-Surgical Patients. *J Pers Med*. Sep 17 2022;12(9)doi:10.3390/jpm12091526

317. Van Broeck D, Steelant B, Scadding G, Hellings PW. Monoclonal antibody or aspirin desensitization in NSAID-exacerbated respiratory disease (N-ERD)? *Front Allergy*. 2023;4:1080951. doi:10.3389/falgy.2023.1080951

318. Buchheit KM, Sohail A, Hacker J, et al. Rapid and sustained effect of dupilumab on clinical and mechanistic outcomes in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. Aug 2022;150(2):415-424. doi:10.1016/j.jaci.2022.04.007

319. Tuncay G, Damadoglu E, Cihanbeylerden M, et al. Comparison of the clinical outcomes of patients with NSAID-exacerbated respiratory disease receiving aspirin or biologicals. *J Asthma*. Oct 2023;60(10):1885-1894. doi:10.1080/02770903.2023.2196567

320. Hayashi H, Mitsui C, Nakatani E, et al. Omalizumab reduces cysteinyl leukotriene and 9alpha,11beta-prostaglandin F2 overproduction in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. May 2016;137(5):1585-1587 e4. doi:10.1016/j.jaci.2015.09.034

321. Laidlaw TM, Mullol J, Fan C, et al. Dupilumab improves nasal polyp burden and asthma control in patients with CRSwNP and AERD. *J Allergy Clin Immunol Pract*. Sep-Oct 2019;7(7):2462-2465 e1. doi:10.1016/j.jaip.2019.03.044

322. Barroso B, Valverde-Monge M, Alobid I, et al. Improvement in Olfaction in Patients With CRSwNP and Severe Asthma Taking Anti-IgE and Anti-IL-5 Biologics: A Real-Life Study. *J Investig Allergol Clin Immunol*. Feb 17 2023;33(1):37-44. doi:10.18176/jiaci.0812

323. Bosso JV. Aspirin desensitization for aspirin-exacerbated respiratory disease in the era of biologics: Clinical perspective. *Int Forum Allergy Rhinol*. Apr 2021;11(4):822-823. doi:10.1002/alr.22709

324. Shaker M, Lobb A, Jenkins P, et al. An economic analysis of aspirin desensitization in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. Jan 2008;121(1):81-7. doi:10.1016/j.jaci.2007.06.047

325. Bassiouni A, Naidoo Y, Wormald PJ. When FESS fails: the inflammatory load hypothesis in refractory chronic rhinosinusitis. *Laryngoscope*. Feb 2012;122(2):460-6. doi:10.1002/lary.22461

326. Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med*. Jun 1999;48(11):1507-15. doi:10.1016/s0277-9536(99)00045-3

327. DeConde AS, Bodner TE, Mace JC, Smith TL. Response shift in quality of life after endoscopic sinus surgery for chronic rhinosinusitis. *JAMA Otolaryngol Head Neck Surg*. Aug 2014;140(8):712-9. doi:10.1001/jamaoto.2014.1045

328. Ring L, Hofer S, Heuston F, Harris D, O'Boyle CA. Response shift masks the treatment impact on patient reported outcomes (PROs): the example of individual quality of life in edentulous patients. *Health Qual Life Outcomes*. Sep 7 2005;3:55. doi:10.1186/1477-7525-3-55

329. De Meyer MMD, Jacquet W, Vanderveken OM, Marks LAM. Systematic review of the different aspects of primary snoring. *Sleep Med Rev*. Jun 2019;45:88-94. doi:10.1016/j.smrv.2019.03.001

330. Panahi L, Udeani G, Ho S, Knox B, Maille J. Review of the Management of Obstructive Sleep Apnea and Pharmacological Symptom Management. *Medicina (Kaunas)*. Oct 28 2021;57(11)doi:10.3390/medicina57111173

331. Stowhas AC, Lichtblau M, Bloch KE. [Obstructive Sleep Apnea Syndrome]. *Praxis (Bern 1994)*. Jan 2019;108(2):111-117. Obstruktives Schlafapnoe-Syndrom. doi:10.1024/1661-8157/a003198

332. Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea: A Review. *JAMA*. Apr 14 2020;323(14):1389-1400. doi:10.1001/jama.2020.3514

333. Osorio RS, Gumb T, Pirraglia E, et al. Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology*. May 12 2015;84(19):1964-71. doi:10.1212/WNL.0000000000001566

334. Kushida CA, Littner MR, Morgenthaler T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep*. Apr 2005;28(4):499-521. doi:10.1093/sleep/28.4.499

335. Collop NA, Anderson WM, Boehlecke B, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. Dec 15 2007;3(7):737-47.

336. Qaseem A, Dallas P, Owens DK, et al. Diagnosis of obstructive sleep apnea in adults: a clinical practice guideline from theAmerican College of Physicians. *Ann Intern Med*. Aug 5 2014;161(3):210-20. doi:10.7326/M12-3187

337. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med*. Mar 15 2017;13(3):479-504. doi:10.5664/jcsm.6506

338. Indications and standards for use of nasal continuous positive airway pressure (CPAP) in sleep apnea syndromes. American Thoracic Society. Official statement adopted March 1944. *Am J Respir Crit Care Med*. Dec 1994;150(6 Pt 1):1738-45. doi:10.1164/ajrccm.150.6.7952642

339. Kuhn E, Schwarz EI, Bratton DJ, Rossi VA, Kohler M. Effects of CPAP and Mandibular Advancement Devices on Health-Related Quality of Life in OSA: A Systematic Review and Meta-analysis. *Chest*. Apr 2017;151(4):786-794. doi:10.1016/j.chest.2017.01.020

340. Loube DI, Gay PC, Strohl KP, Pack AI, White DP, Collop NA. Indications for positive airway pressure treatment of adult obstructive sleep apnea patients: a consensus statement. *Chest*. Mar 1999;115(3):863-6. doi:10.1378/chest.115.3.863

341. Jacobowitz O. Palatal and tongue base surgery for surgical treatment of obstructive sleep apnea: a prospective study. *Otolaryngol Head Neck Surg*. Aug 2006;135(2):258-264. doi:10.1016/j.otohns.2006.03.029

342. Lim DC, Pack AI. Obstructive Sleep Apnea: Update and Future. *Annu Rev Med*. Jan 14 2017;68:99-112. doi:10.1146/annurev-med-042915-102623

343. Iannella G, Magliulo G, Maniaci A, et al. Olfactory function in patients with obstructive sleep apnea: a meta-analysis study. *Eur Arch Otorhinolaryngol*. Mar 2021;278(3):883-891. doi:10.1007/s00405-020-06316-w

344. Binar M, Gokgoz MC. Olfactory function in patients with obstructive sleep apnea and the effect of positive airway pressure treatment: a systematic review and meta-

analysis. *Sleep Breath*. Dec 2021;25(4):1791-1802. doi:10.1007/s11325-021-02349-5

345. Siegel JK, Yuan X, Wroblewski KE, McClintock MK, Pinto JM. Sleep-Disordered Breathing Is Associated With Impaired Odor Identification in Older U.S. Adults. *J Gerontol A Biol Sci Med Sci*. Feb 25 2021;76(3):528-533. doi:10.1093/gerona/glaa276
346. Dong J, Zhan X, Sun H, Fang F, Wei Y. Olfactory dysfunction is associated with cognitive impairment in patients with obstructive sleep apnea: a cross-sectional study. *Eur Arch Otorhinolaryngol*. Apr 2022;279(4):1979-1987. doi:10.1007/s00405-021-07194-6
347. Magliulo G, De Vincentiis M, Iannella G, et al. Olfactory evaluation in obstructive sleep apnoea patients. *Acta Otorhinolaryngol Ital*. Aug 2018;38(4):338-345. doi:10.14639/0392-100X-1981
348. Liu Y, Fang F, Zhan X, Yao L, Wei Y. The impact of obstructive apnea sleep syndrome on chemical function. *Sleep Breath*. Dec 2020;24(4):1549-1555. doi:10.1007/s11325-020-02022-3
349. Shin DH, Ahn SH, Yang Y, et al. The Effect of Sleep Disordered Breathing on Olfactory Functions: Analysis by Apnea-Hypopnea Index. *Clin Exp Otorhinolaryngol*. Mar 2017;10(1):71-76. doi:10.21053/ceo.2015.01438
350. Salihoglu M, Kendirli MT, Altundag A, et al. The effect of obstructive sleep apnea on olfactory functions. *Laryngoscope*. Sep 2014;124(9):2190-4. doi:10.1002/lary.24565
351. Karakurt SE, Karakus MF, Colak M, et al. Evaluation of olfactory function in patients with obstructive sleep apnea syndrome. *Sleep Breath*. Sep 2020;24(3):1137-1142. doi:10.1007/s11325-019-01996-z
352. Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime

cognitive and behavioral deficits. *J Sleep Res*. Mar 2002;11(1):1-16. doi:10.1046/j.1365-2869.2002.00289.x

353. Daurat A, Foret J, Bret-Dibat JL, Fureix C, Tiberge M. Spatial and temporal memories are affected by sleep fragmentation in obstructive sleep apnea syndrome. *J Clin Exp Neuropsychol*. Jan 2008;30(1):91-101. doi:10.1080/13803390701236116
354. Torelli F, Moscufo N, Garreffa G, et al. Cognitive profile and brain morphological changes in obstructive sleep apnea. *Neuroimage*. Jan 15 2011;54(2):787-93. doi:10.1016/j.neuroimage.2010.09.065
355. Zimmerman ME, Aloia MS. A review of neuroimaging in obstructive sleep apnea. *J Clin Sleep Med*. Oct 15 2006;2(4):461-71.
356. Dogan A, Bayar Muluk N, Sahin H. Olfactory Bulb Volume and Olfactory Sulcus Depth in Patients With OSA: An MRI Evaluation. *Ear Nose Throat J*. Aug 2020;99(7):442-447. doi:10.1177/0145561319881571
357. Kang IG, Jung JH, Kim ST. The effect of obstructive sleep apnea on DNA damage and oxidative stress. *Clin Exp Otorhinolaryngol*. Jun 2013;6(2):68-72. doi:10.3342/ceo.2013.6.2.68
358. Roberts RO, Christianson TJ, Kremers WK, et al. Association Between Olfactory Dysfunction and Amnestic Mild Cognitive Impairment and Alzheimer Disease Dementia. *JAMA Neurol*. Jan 2016;73(1):93-101. doi:10.1001/jamaneurol.2015.2952
359. Kirkpatrick MA, Combest W, Newton M, et al. Combining olfaction and cognition measures to screen for mild cognitive impairment. *Neuropsychiatr Dis Treat*. Dec 2006;2(4):565-70. doi:10.2147/nedt.2006.2.4.565
360. Lafaille-Magnan ME, Poirier J, Etienne P, et al. Odor identification as a biomarker of preclinical AD in older adults at risk. *Neurology*. Jul 25 2017;89(4):327-335. doi:10.1212/WNL.0000000000004159

361. Krakow B, Foley-Shea M, Ulibarri VA, McIver ND, Honsinger R. Prevalence of potential nonallergic rhinitis at a community-based sleep medical center. *Sleep Breath*. Sep 2016;20(3):987-93. doi:10.1007/s11325-016-1322-3

362. Banabilh SM, Suzina AH, Mohamad H, Dinsuhaimi S, Samsudin AR, Singh GD. Assessment of 3-D nasal airway morphology in Southeast Asian adults with obstructive sleep apnea using acoustic rhinometry. *Clin Oral Investig*. Oct 2010;14(5):491-8. doi:10.1007/s00784-009-0342-9

363. Deniz M, Gultekin E, Ciftci Z, et al. Nasal mucociliary clearance in obstructive sleep apnea syndrome patients. *Am J Rhinol Allergy*. Sep-Oct 2014;28(5):178-80. doi:10.2500/ajra.2014.28.4094

364. Versace V, Langthaler PB, Sebastianelli L, et al. Cholinergic neurotransmission and olfactory function in obstructive sleep apnea syndrome: a TMS study. *Sleep Med*. Sep 2017;37:113-118. doi:10.1016/j.sleep.2017.06.021

365. Peng M, Coutts D, Wang T, Cakmak YO. Systematic review of olfactory shifts related to obesity. *Obes Rev*. Feb 2019;20(2):325-338. doi:10.1111/obr.12800

366. Kaya KS, Akpinar M, Turk B, Seyhun N, Cankaya M, Coskun BU. Olfactory Function in Patients With Obstructive Sleep Apnea Using Positive Airway Pressure. *Ear Nose Throat J*. May 2020;99(4):239-244. doi:10.1177/0145561319878949

367. Koseoglu S, Derin S, Yilmaz M, Kutlu G, Sahan M. Does positive airway pressure therapy improve olfactory function? *Int Forum Allergy Rhinol*. Jun 2017;7(6):557-560. doi:10.1002/alr.21923

368. Schumm LP, McClintock M, Williams S, et al. Assessment of sensory function in the National Social Life, Health, and Aging Project. *J Gerontol B Psychol Sci Soc Sci*. Nov 2009;64 Suppl 1(Suppl 1):i76-85. doi:10.1093/geronb/gbp048

369. Young T, Finn L, Kim H. Nasal obstruction as a risk factor for sleep-disordered breathing. The University of Wisconsin Sleep and Respiratory Research Group. *J Allergy Clin Immunol*. Feb 1997;99(2):S757-62. doi:10.1016/s0091-6749(97)70124-6

370. Dulay MF, Gesteland RC, Shear PK, Ritchey PN, Frank RA. Assessment of the influence of cognition and cognitive processing speed on three tests of olfaction. *J Clin Exp Neuropsychol*. Apr 2008;30(3):327-37. doi:10.1080/13803390701415892

371. Fu D, Pinto JM, Wang L, Chen G, Zhan X, Wei Y. The effect of nasal structure on olfactory function in patients with OSA. *Eur Arch Otorhinolaryngol*. Feb 2015;272(2):357-62. doi:10.1007/s00405-014-3096-1

372. Walliczek-Dworschak U, Cassel W, Mittendorf L, et al. Continuous positive air pressure improves orthonasal olfactory function of patients with obstructive sleep apnea. *Sleep Med*. Jun 2017;34:24-29. doi:10.1016/j.sleep.2017.02.018

373. Boerner B, Tini GM, Fachinger P, Graber SM, Irani S. Significant improvement of olfactory performance in sleep apnea patients after three months of nasal CPAP therapy - Observational study and randomized trial. *PLoS One*. 2017;12(2):e0171087. doi:10.1371/journal.pone.0171087

374. Borges VM, Vandivier RW, McPhillips KA, et al. TNFalpha inhibits apoptotic cell clearance in the lung, exacerbating acute inflammation. *Am J Physiol Lung Cell Mol Physiol*. Oct 2009;297(4):L586-95. doi:10.1152/ajplung.90569.2008

375. Wang Y, Hu K, Liu K, et al. Obstructive sleep apnea exacerbates airway inflammation in patients with chronic obstructive pulmonary disease. *Sleep Med*. Sep 2015;16(9):1123-30. doi:10.1016/j.sleep.2015.04.019

376. Almendros I, Acerbi I, Vilaseca I, Montserrat JM, Navajas D, Farre R. Continuous positive airway pressure (CPAP) induces early nasal inflammation. *Sleep*. Jan 2008;31(1):127-31. doi:10.1093/sleep/31.1.127

377. Pendolino AL, Unadkat S, Cheong RCT, et al. Objective and Subjective Outcomes Following Radiofrequency of Inferior Turbinates in Patients with Sleep-Disordered Breathing. *Diagnostics (Basel)*. Aug 21 2024;14(16)doi:10.3390/diagnostics14161820

378. Kotecha B. The nose, snoring and obstructive sleep apnoea. *Rhinology*. Aug 2011;49(3):259-63. doi:10.4193/Rhino10.165

379. Kotecha BT, Hannan SA, Khalil HM, Georgalas C, Bailey P. Sleep nasendoscopy: a 10-year retrospective audit study. *Eur Arch Otorhinolaryngol*. Nov 2007;264(11):1361-7. doi:10.1007/s00405-007-0366-1

380. Skatvedt O. Continuous pressure measurements during sleep to localize obstructions in the upper airways in heavy snorers and patients with obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*. 1995;252(1):11-4. doi:10.1007/BF00171432

381. Cole P, Haight JS. Mechanisms of nasal obstruction in sleep. *Laryngoscope*. Dec 1984;94(12 Pt 1):1557-9.

382. Friedman M, Maley A, Kelley K, et al. Impact of nasal obstruction on obstructive sleep apnea. *Otolaryngol Head Neck Surg*. Jun 2011;144(6):1000-4. doi:10.1177/0194599811400977

383. Morris LG, Burschtin O, Lebowitz RA, Jacobs JB, Lee KC. Nasal obstruction and sleep-disordered breathing: a study using acoustic rhinometry. *Am J Rhinol*. Jan-Feb 2005;19(1):33-9.

384. Saka C, Vuralkan E, Firat IH, et al. The effects of CPAP treatment on nasal mucosa in patients with obstructive sleep apnea. *Eur Arch Otorhinolaryngol*. Sep 2012;269(9):2065-7. doi:10.1007/s00405-011-1906-2

385. Lenders H, Schaefer J, Pirsig W. Turbinate hypertrophy in habitual snorers and patients with obstructive sleep apnea: findings of acoustic rhinometry. *Laryngoscope*. Jun 1991;101(6 Pt 1):614-8. doi:10.1288/00005537-199106000-00007

386. Silvoniemi P, Suonpaa J, Sipila J, Grenman R, Erkinjuntti M. Sleep disorders in patients with severe nasal obstruction due to septal deviation. *Acta Otolaryngol Suppl*. 1997;529:199-201. doi:10.3109/00016489709124121

387. Leitzen KP, Brietzke SE, Lindsay RW. Correlation between nasal anatomy and objective obstructive sleep apnea severity. *Otolaryngol Head Neck Surg*. Feb 2014;150(2):325-31. doi:10.1177/0194599813515838

388. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. Apr 2008;63 Suppl 86:8-160. doi:10.1111/j.1398-9995.2007.01620.x

389. Kiely JL, Nolan P, McNicholas WT. Intranasal corticosteroid therapy for obstructive sleep apnoea in patients with co-existing rhinitis. *Thorax*. Jan 2004;59(1):50-5.

390. Lavigne F, Petrof BJ, Johnson JR, et al. Effect of topical corticosteroids on allergic airway inflammation and disease severity in obstructive sleep apnoea. *Clin Exp Allergy*. Oct 2013;43(10):1124-33. doi:10.1111/cea.12158

391. Craig TJ, Teets S, Lehman EB, Chinchilli VM, Zwillich C. Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids. *J Allergy Clin Immunol*. May 1998;101(5):633-7. doi:10.1016/s0091-6749(98)70171-x

392. Pagel JML, Mattos JL. Allergic Rhinitis and Its Effect on Sleep. *Otolaryngol Clin North Am*. Oct 20 2023;doi:10.1016/j.otc.2023.09.003

393. Batra PS, Seiden AM, Smith TL. Surgical management of adult inferior turbinate hypertrophy: a systematic review of the evidence. *Laryngoscope*. Sep 2009;119(9):1819-27. doi:10.1002/lary.20544

394. Bhandarkar ND, Smith TL. Outcomes of surgery for inferior turbinate hypertrophy. *Curr Opin Otolaryngol Head Neck Surg*. Feb 2010;18(1):49-53. doi:10.1097/MOO.0b013e328334d974

395. Jackson LE, Koch RJ. Controversies in the management of inferior turbinate hypertrophy: a comprehensive review. *Plast Reconstr Surg*. Jan 1999;103(1):300-12. doi:10.1097/00006534-199901000-00049

396. Utley DS, Goode RL, Hakim I. Radiofrequency energy tissue ablation for the treatment of nasal obstruction secondary to turbinate hypertrophy. *Laryngoscope*. May 1999;109(5):683-6. doi:10.1097/00005537-199905000-00001

397. Singh S, Ramli RR, Wan Mohammad Z, Abdullah B. Coblation versus microdebrider-assisted turbinoplasty for endoscopic inferior turbinates reduction. *Auris Nasus Larynx*. Aug 2020;47(4):593-601. doi:10.1016/j.anl.2020.02.003

398. Harrill WC, Pillsbury HC, 3rd, McGuirt WF, Stewart MG. Radiofrequency turbinate reduction: a NOSE evaluation. *Laryngoscope*. Nov 2007;117(11):1912-9. doi:10.1097/MLG.0b013e3181271414

399. Porter MW, Hales NW, Nease CJ, Krempl GA. Long-term results of inferior turbinate hypertrophy with radiofrequency treatment: a new standard of care? *Laryngoscope*. Apr 2006;116(4):554-7. doi:10.1097/01.MLG.0000201986.82035.6F

400. Nease CJ, Krempl GA. Radiofrequency treatment of turbinate hypertrophy: a randomized, blinded, placebo-controlled clinical trial. *Otolaryngol Head Neck Surg*. Mar 2004;130(3):291-9. doi:10.1016/j.otohns.2003.11.003

401. Garzaro M, Pezzoli M, Landolfo V, Defilippi S, Giordano C, Pecorari G. Radiofrequency inferior turbinate reduction: long-term olfactory and functional outcomes. *Otolaryngol Head Neck Surg*. Jan 2012;146(1):146-50. doi:10.1177/0194599811423008

402. Means C, Camacho M, Capasso R. Long-Term Outcomes of Radiofrequency Ablation of the Inferior Turbinates. *Indian J Otolaryngol Head Neck Surg*. Dec 2016;68(4):424-428. doi:10.1007/s12070-015-0912-x

403. Pendolino AL, Scarpa B, Ottaviano G. Relationship Between Nasal Cycle, Nasal Symptoms and Nasal Cytology. *Am J Rhinol Allergy*. Nov 2019;33(6):644-649. doi:10.1177/1945892419858582

404. Ottaviano G, Scadding GK, Scarpa B, Accordi D, Staffieri A, Lund VJ. Unilateral peak nasal inspiratory flow, normal values in adult population. *Rhinology*. Dec 2012;50(4):386-92. doi:10.4193/Rhino.12.071

405. Ottaviano G, Fokkens WJ. Measurements of nasal airflow and patency: a critical review with emphasis on the use of peak nasal inspiratory flow in daily practice. *Allergy*. Feb 2016;71(2):162-74. doi:10.1111/all.12778

406. DeConde AS, Mace JC, Bodner T, et al. SNOT-22 quality of life domains differentially predict treatment modality selection in chronic rhinosinusitis. *Int Forum Allergy Rhinol*. Dec 2014;4(12):972-9. doi:10.1002/alr.21408

407. Hytonen ML, Back LJ, Malmivaara AV, Roine RP. Radiofrequency thermal ablation for patients with nasal symptoms: a systematic review of effectiveness and complications. *Eur Arch Otorhinolaryngol*. Aug 2009;266(8):1257-66. doi:10.1007/s00405-009-0914-y

408. Cavaliere M, Mottola G, Iemma M. Comparison of the effectiveness and safety of radiofrequency turbinoplasty and traditional surgical technique in treatment of inferior turbinate hypertrophy. *Otolaryngol Head Neck Surg*. Dec 2005;133(6):972-8. doi:10.1016/j.otohns.2005.08.006

409. Casale M, Bottaro V, Sabatino L, et al. The efficacy of radiofrequency volumetric tissue reduction of hypertrophied inferior turbinate in simple snoring. *Eur Rev Med Pharmacol Sci*. 2014;18(15):2160-8.

410. Powell NB, Zonato AI, Weaver EM, et al. Radiofrequency treatment of turbinate hypertrophy in subjects using continuous positive airway pressure: a randomized, double-blind, placebo-controlled clinical pilot trial. *Laryngoscope*. Oct 2001;111(10):1783-90. doi:10.1097/00005537-200110000-00023

411. Verse T, Maurer JT, Pirsig W. Effect of nasal surgery on sleep-related breathing disorders. *Laryngoscope*. Jan 2002;112(1):64-8. doi:10.1097/00005537-200201000-00012

412. Morinaga M, Nakata S, Yasuma F, et al. Pharyngeal morphology: a determinant of successful nasal surgery for sleep apnea. *Laryngoscope*. May 2009;119(5):1011-6. doi:10.1002/lary.20175

413. Koutsourelakis I, Georgoulopoulos G, Perraki E, Vagiakis E, Roussos C, Zakynthinos SG. Randomised trial of nasal surgery for fixed nasal obstruction in obstructive sleep apnoea. *Eur Respir J*. Jan 2008;31(1):110-7. doi:10.1183/09031936.00087607

414. Ishii L, Godoy A, Ishman SL, Gourin CG, Ishii M. The nasal obstruction symptom evaluation survey as a screening tool for obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg*. Feb 2011;137(2):119-23. doi:10.1001/archoto.2010.251

415. Ottaviano G, Pendolino AL, Nardello E, Pollis M, Scarpa B, Marchese-Ragona R. The role of peak nasal and oral inspiratory flow in the evaluation of patients with sleep-related breathing disorders. *Rhinology*. Oct 1 2020;58(5):465-470. doi:10.4193/Rhin19.417

416. Holty JE, Guilleminault C. Surgical options for the treatment of obstructive sleep apnea. *Med Clin North Am*. May 2010;94(3):479-515. doi:10.1016/j.mcna.2010.02.001

417. Schoustra E, van Maanen P, den Haan C, Ravesloot MJL, de Vries N. The Role of Isolated Nasal Surgery in Obstructive Sleep Apnea Therapy-A Systematic Review. *Brain Sci*. Oct 26 2022;12(11)doi:10.3390/brainsci12111446

418. Wu J, Zhao G, Li Y, et al. Apnea-hypopnea index decreased significantly after nasal surgery for obstructive sleep apnea: A meta-analysis. *Medicine (Baltimore)*. Feb 2017;96(5):e6008. doi:10.1097/MD.0000000000006008

419. Cai Y, Goldberg AN, Chang JL. The Nose and Nasal Breathing in Sleep Apnea. *Otolaryngol Clin North Am*. Jun 2020;53(3):385-395. doi:10.1016/j.otc.2020.02.002

420. Assanasen P, Choochurn P, Banhiran W, Bunnag C. Radiofrequency inferior turbinate reduction improves smell ability of patients with chronic rhinitis and inferior turbinate hypertrophy. *Allergy Rhinol (Providence)*. Mar 2014;5(1):12-6. doi:10.2500/ar.2014.5.0077

421. Migueis DP, Thuler LC, Lemes LN, Moreira CS, Joffily L, Araujo-Melo MH. Systematic review: the influence of nasal obstruction on sleep apnea. *Braz J Otorhinolaryngol*. Mar-Apr 2016;82(2):223-31. doi:10.1016/j.bjorl.2015.05.018

422. Jenkinson C, Stewart-Brown S, Petersen S, Paice C. Assessment of the SF-36 version 2 in the United Kingdom. *J Epidemiol Community Health*. Jan 1999;53(1):46-50. doi:10.1136/jech.53.1.46

423. Nilsen AH, Helvik AS, Thorstensen WM, Bugten V. A comparison of symptoms and quality of life before and after nasal septoplasty and radiofrequency therapy of the inferior turbinate. *BMC Ear Nose Throat Disord*. 2018;18:2. doi:10.1186/s12901-017-0050-z

424. Li HY, Lee LA, Wang PC, Fang TJ, Chen NH. Can nasal surgery improve obstructive sleep apnea: subjective or objective? *Am J Rhinol Allergy*. Nov-Dec 2009;23(6):e51-5. doi:10.2500/ajra.2009.23.3358

425. Pendolino AL, Ottaviano G, Navaratnam AV, Scarpa B, Andrews PJ. Clinical factors influencing olfactory performance in patients with persistent COVID-19 smell loss longer than 1 year. *Laryngoscope Investig Otolaryngol*. Dec 2023;8(6):1449-1458. doi:10.1002/lio2.1160

426. Randhawa PS, Watson N, Lechner M, Ritchie L, Choudhury N, Andrews PJ. The outcome of septorhinoplasty surgery on olfactory function. *Clin Otolaryngol*. Feb 2016;41(1):15-20. doi:10.1111/coa.12463

427. Henkin RI, Larson AL, Powell RD. Hypogeusia, dysgeusia, hyposmia, and dysosmia following influenza-like infection. *Ann Otol Rhinol Laryngol*. Sep-Oct 1975;84(5 Pt 1):672-82. doi:10.1177/000348947508400519

428. Seiden AM. Postviral olfactory loss. *Otolaryngol Clin North Am*. Dec 2004;37(6):1159-66. doi:10.1016/j.otc.2004.06.007

429. Suzuki M, Saito K, Min WP, et al. Identification of viruses in patients with postviral olfactory dysfunction. *Laryngoscope*. Feb 2007;117(2):272-7. doi:10.1097/01.mlg.0000249922.37381.1e

430. Konstantinidis I, Haehner A, Frasnelli J, et al. Post-infectious olfactory dysfunction exhibits a seasonal pattern. *Rhinology*. Jun 2006;44(2):135-9.

431. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The Prevalence of Olfactory and Gustatory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis. *Otolaryngol Head Neck Surg*. Jul 2020;163(1):3-11. doi:10.1177/0194599820926473

432. Giacomelli A, Pezzati L, Conti F, et al. Self-reported Olfactory and Taste Disorders in Patients With Severe Acute Respiratory Coronavirus 2 Infection: A Cross-sectional Study. *Clin Infect Dis*. Jul 28 2020;71(15):889-890. doi:10.1093/cid/ciaa330

433. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol*. Aug 2020;277(8):2251-2261. doi:10.1007/s00405-020-05965-1

434. Lechien JR, Chiesa-Estomba CM, Place S, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. *J Intern Med*. Sep 2020;288(3):335-344. doi:10.1111/joim.13089

435. Lechien JR, Chiesa-Estomba CM, Beckers E, et al. Prevalence and 6-month recovery of olfactory dysfunction: a multicentre study of 1363 COVID-19 patients. *J Intern Med*. Jan 5 2021;doi:10.1111/joim.13209

436. Lerner DK, Garvey KL, Arrighi-Allisan AE, et al. Clinical Features of Parosmia Associated With COVID-19 Infection. *Laryngoscope*. Dec 6 2021;doi:10.1002/lary.29982

437. Borsetto D, Hopkins C, Philips V, et al. Self-reported alteration of sense of smell or taste in patients with COVID-19: a systematic review and meta-analysis on 3563 patients. *Rhinology*. Oct 1 2020;58(5):430-436. doi:10.4193/Rhin20.185

438. Saniasiaya J, Islam MA, Abdullah B. Prevalence of Olfactory Dysfunction in Coronavirus Disease 2019 (COVID-19): A Meta-analysis of 27,492 Patients. *Laryngoscope*. Apr 2021;131(4):865-878. doi:10.1002/lary.29286

439. Vaira LA, Lechien JR, Deiana G, et al. Prevalence of olfactory dysfunction in D614G, alpha, delta and omicron waves: a psychophysical case-control study. *Rhinology*. Feb 1 2023;61(1):32-38. doi:10.4193/Rhin22.294

440. von Bartheld CS, Wang L. Prevalence of Olfactory Dysfunction with the Omicron Variant of SARS-CoV-2: A Systematic Review and Meta-Analysis. *Cells*. Jan 28 2023;12(3)doi:10.3390/cells12030430

441. Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. *Int Forum Allergy Rhinol*. Aug 2020;10(8):944-950. doi:10.1002/alr.22587

442. Soltani S, Tabibzadeh A, Zakeri A, et al. COVID-19 associated central nervous system manifestations, mental and neurological symptoms: a systematic review and meta-analysis. *Rev Neurosci*. Apr 27 2021;32(3):351-361. doi:10.1515/revneuro-2020-0108

443. Vakili K, Fathi M, Hajiesmaeili M, et al. Neurological Symptoms, Comorbidities, and Complications of COVID-19: A Literature Review and Meta-Analysis of Observational Studies. *Eur Neurol*. 2021;84(5):307-324. doi:10.1159/000516258

444. Vitalakumar D, Sharma A, Kumar A, Flora SJS. Neurological Manifestations in COVID-19 Patients: A Meta-Analysis. *ACS Chemical Neuroscience*. 2021/08/04 2021;12(15):2776-2797. doi:10.1021/acschemneuro.1c00353

445. Qiu J, Yang X, Liu L, et al. Prevalence and prognosis of otorhinolaryngological symptoms in patients with COVID-19: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol*. Jan 2022;279(1):49-60. doi:10.1007/s00405-021-06900-8

446. Chary E, Carsuzaa F, Trijolet JP, et al. Prevalence and Recovery From Olfactory and Gustatory Dysfunctions in Covid-19 Infection: A Prospective Multicenter Study. *Am J Rhinol Allergy*. Sep 2020;34(5):686-693. doi:10.1177/1945892420930954

447. Landis BN, Hsieh JW, Konstantinidis I, et al. What Is Different in COVID-19-Associated Olfactory Loss from Classical Postinfectious Olfactory Impairment? *ORL J Otorhinolaryngol Relat Spec*. 2023;85(5):245-247. doi:10.1159/000533228

448. Spinato G, Fabbris C, Polesel J, et al. Alterations in Smell or Taste in Mildly Symptomatic Outpatients With SARS-CoV-2 Infection. *JAMA*. May 26 2020;323(20):2089-2090. doi:10.1001/jama.2020.6771

449. Klopfenstein T, Kadiane-Oussou NJ, Toko L, et al. Features of anosmia in COVID-19. *Med Mal Infect*. Aug 2020;50(5):436-439. doi:10.1016/j.medmal.2020.04.006

450. Yan CH, Faraji F, Prajapati DP, Ostrander BT, DeConde AS. Self-reported olfactory loss associates with outpatient clinical course in COVID-19. *Int Forum Allergy Rhinol*. Jul 2020;10(7):821-831. doi:10.1002/alr.22592

451. Hopkins C, Surda P, Kumar N. Presentation of new onset anosmia during the COVID-19 pandemic. *Rhinology*. Jun 1 2020;58(3):295-298. doi:10.4193/Rhin20.116

452. Vaira LA, Hopkins C, Petrocelli M, et al. Do olfactory and gustatory psychophysical scores have prognostic value in COVID-19 patients? A prospective study of 106 patients. *J Otolaryngol Head Neck Surg*. Aug 6 2020;49(1):56. doi:10.1186/s40463-020-00449-y

453. Amadu AM, Vaira LA, Lechien JR, et al. Analysis of the correlations between the severity of lung involvement and olfactory psychophysical scores in coronavirus disease 2019 (COVID-19) patients. *Int Forum Allergy Rhinol*. Jan 2022;12(1):103-107. doi:10.1002/alr.22869

454. Stankevice D, Fjaeldstad AW, Agergaard J, Ovesen T. Long-Term COVID-19 Smell and Taste Disorders Differ Significantly from Other Post-Infectious Cases. *Laryngoscope*. Jan 2023;133(1):169-174. doi:10.1002/lary.30453

455. Reden J, Maroldt H, Fritz A, Zahnert T, Hummel T. A study on the prognostic significance of qualitative olfactory dysfunction. *Eur Arch Otorhinolaryngol*. Feb 2007;264(2):139-44. doi:10.1007/s00405-006-0157-0

456. Duyan M, Ozturan IU, Altas M. Delayed Parosmia Following SARS-CoV-2 Infection: a Rare Late Complication of COVID-19. *SN Compr Clin Med*. 2021;3(5):1200-1202. doi:10.1007/s42399-021-00876-6

457. Seiden AM, Duncan HJ. The diagnosis of a conductive olfactory loss. *Laryngoscope*. Jan 2001;111(1):9-14. doi:10.1097/00005537-200101000-00002

458. Schrauwen EJ, Herfst S, Leijten LM, et al. The multibasic cleavage site in H5N1 virus is critical for systemic spread along the olfactory and hematogenous routes in ferrets. *J Virol*. Apr 2012;86(7):3975-84. doi:10.1128/JVI.06828-11

459. Mori I, Goshima F, Imai Y, et al. Olfactory receptor neurons prevent dissemination of neurovirulent influenza A virus into the brain by undergoing virus-induced apoptosis. *J Gen Virol*. Sep 2002;83(Pt 9):2109-2116. doi:10.1099/0022-1317-83-9-2109

460. Armien AG, Hu S, Little MR, et al. Chronic cortical and subcortical pathology with associated neurological deficits ensuing experimental herpes encephalitis. *Brain Pathol*. Jul 2010;20(4):738-50. doi:10.1111/j.1750-3639.2009.00354.x

461. Jennische E, Eriksson CE, Lange S, Trybala E, Bergstrom T. The anterior commissure is a pathway for contralateral spread of herpes simplex virus type 1 after olfactory tract infection. *J Neurovirol*. Apr 2015;21(2):129-47. doi:10.1007/s13365-014-0312-0

462. Beers DR, Henkel JS, Schaefer DC, Rose JW, Stroop WG. Neuropathology of herpes simplex virus encephalitis in a rat seizure model. *J Neuropathol Exp Neurol*. May 1993;52(3):241-52. doi:10.1097/00005072-199305000-00008

463. Tian J, Pinto JM, Cui X, et al. Sendai Virus Induces Persistent Olfactory Dysfunction in a Murine Model of PVOD via Effects on Apoptosis, Cell Proliferation, and Response to Odorants. *PLoS One*. 2016;11(7):e0159033. doi:10.1371/journal.pone.0159033

464. Myers LJ, Nusbaum KE, Swango LJ, Hanrahan LN, Sartin E. Dysfunction of sense of smell caused by canine parainfluenza virus infection in dogs. *Am J Vet Res*. Feb 1988;49(2):188-90.

465. Boscolo-Rizzo P, Menegaldo A, Fabbris C, et al. Six-Month Psychophysical Evaluation of Olfactory Dysfunction in Patients with COVID-19. *Chem Senses*. Jan 1 2021;46doi:10.1093/chemse/bjab006

466. Eliezer M, Hamel AL, Houdart E, et al. Loss of smell in patients with COVID-19: MRI data reveal a transient edema of the olfactory clefts. *Neurology*. Dec 8 2020;95(23):e3145-e3152. doi:10.1212/WNL.0000000000010806

467. Eliezer M, Hautefort C. MRI Evaluation of the Olfactory Clefts in Patients with SARS-CoV-2 Infection Revealed an Unexpected Mechanism for Olfactory Function Loss. *Acad Radiol*. Aug 2020;27(8):1191. doi:10.1016/j.acra.2020.05.013

468. Niesen M, Trotta N, Noel A, et al. Structural and metabolic brain abnormalities in COVID-19 patients with sudden loss of smell. *Eur J Nucl Med Mol Imaging*. Jun 2021;48(6):1890-1901. doi:10.1007/s00259-020-05154-6

469. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-Cell RNA Expression Profiling of ACE2, the Receptor of SARS-CoV-2. *Am J Respir Crit Care Med*. Sep 1 2020;202(5):756-759. doi:10.1164/rccm.202001-0179LE

470. Khan M, Yoo SJ, Clijsters M, et al. Visualizing in deceased COVID-19 patients how SARS-CoV-2 attacks the respiratory and olfactory mucosae but spares the olfactory bulb. *Cell*. Nov 24 2021;184(24):5932-5949 e15. doi:10.1016/j.cell.2021.10.027

471. Kirschenbaum D, Imbach LL, Ulrich S, et al. Inflammatory olfactory neuropathy in two patients with COVID-19. *Lancet*. Jul 18 2020;396(10245):166. doi:10.1016/S0140-6736(20)31525-7

472. Karamali K, Elliott M, Hopkins C. COVID-19 related olfactory dysfunction. *Curr Opin Otolaryngol Head Neck Surg*. Feb 1 2022;30(1):19-25. doi:10.1097/MOO.0000000000000783

473. Yoon HE, Kim EN, Kim MY, et al. Age-Associated Changes in the Vascular Renin-Angiotensin System in Mice. *Oxid Med Cell Longev*. 2016;2016:6731093. doi:10.1155/2016/6731093

474. Zazhytska M, Kodra A, Hoagland DA, et al. Non-cell-autonomous disruption of nuclear architecture as a potential cause of COVID-19-induced anosmia. *Cell*. Mar 17 2022;185(6):1052-1064 e12. doi:10.1016/j.cell.2022.01.024

475. Leopold D. A Perplexing Olfactory Loss. *Arch Otolaryngol Head Neck Surg*. Jun 2000;126(6):803. doi:10.1001/archotol.126.6.803

476. Herbert RP, Harris J, Chong KP, Chapman J, West AK, Chuah MI. Cytokines and olfactory bulb microglia in response to bacterial challenge in the compromised primary olfactory pathway. *J Neuroinflammation*. May 29 2012;9:109. doi:10.1186/1742-2094-9-109

477. Wellford SA, Chen CW, Vukovic M, et al. Distinct olfactory mucosal macrophage populations mediate neuronal maintenance and pathogen defense. *Mucosal Immunol*. Jul 27 2024;doi:10.1016/j.mucimm.2024.07.009

478. Karimian A, Behjati M, Karimian M. Molecular mechanisms involved in anosmia induced by SARS-CoV-2, with a focus on the transmembrane serine protease TMPRSS2. *Arch Virol*. Oct 2022;167(10):1931-1946. doi:10.1007/s00705-022-05545-0

479. de Melo GD, Lazarini F, Levallois S, et al. COVID-19-related anosmia is associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters. *Sci Transl Med*. Jun 2 2021;13(596)doi:10.1126/scitranslmed.abf8396

480. Finlay JB, Brann DH, Abi Hachem R, et al. Persistent post-COVID-19 smell loss is associated with immune cell infiltration and altered gene expression in olfactory epithelium. *Sci Transl Med*. Dec 21 2022;14(676):eadd0484. doi:10.1126/scitranslmed.add0484

481. Chen M, Reed RR, Lane AP. Chronic Inflammation Directs an Olfactory Stem Cell Functional Switch from Neuroregeneration to Immune Defense. *Cell Stem Cell*. Oct 3 2019;25(4):501-513 e5. doi:10.1016/j.stem.2019.08.011

482. Rombaux P, Mouraux A, Bertrand B, Nicolas G, Duprez T, Hummel T. Olfactory function and olfactory bulb volume in patients with postinfectious olfactory loss. *Laryngoscope*. Mar 2006;116(3):436-9. doi:10.1097/01.MLG.0000195291.36641.1E

483. Bitter T, Gudziol H, Burmeister HP, Mentzel HJ, Guntinas-Lichius O, Gaser C. Anosmia leads to a loss of gray matter in cortical brain areas. *Chem Senses*. Jun 2010;35(5):407-15. doi:10.1093/chemse/bjq028

484. Kim YK, Hong SL, Yoon EJ, Kim SE, Kim JW. Central presentation of postviral olfactory loss evaluated by positron emission tomography scan: a pilot study. *Am J Rhinol Allergy*. May-Jun 2012;26(3):204-8. doi:10.2500/ajra.2012.26.3759

485. Zatorre RJ, Jones-Gotman M, Evans AC, Meyer E. Functional localization and lateralization of human olfactory cortex. *Nature*. Nov 26 1992;360(6402):339-40. doi:10.1038/360339a0

486. Sobel N, Prabhakaran V, Desmond JE, et al. Sniffing and smelling: separate subsystems in the human olfactory cortex. *Nature*. Mar 19 1998;392(6673):282-6. doi:10.1038/32654

487. Butowt R, Meunier N, Bryche B, von Bartheld CS. The olfactory nerve is not a likely route to brain infection in COVID-19: a critical review of data from humans and animal models. *Acta Neuropathol*. Jun 2021;141(6):809-822. doi:10.1007/s00401-021-02314-2

488. Ho CY, Salimian M, Hegert J, et al. Postmortem Assessment of Olfactory Tissue Degeneration and Microvasculopathy in Patients With COVID-19. *JAMA Neurol*. Jun 1 2022;79(6):544-553. doi:10.1001/jamaneurol.2022.0154

489. Matschke J, Lutgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol*. Nov 2020;19(11):919-929. doi:10.1016/S1474-4422(20)30308-2

490. Rethinavel HS, Ravichandran S, Radhakrishnan RK, Kandasamy M. COVID-19 and Parkinson's disease: Defects in neurogenesis as the potential cause of olfactory system impairments and anosmia. *J Chem Neuroanat*. Sep 2021;115:101965. doi:10.1016/j.jchemneu.2021.101965

491. Marin C, Laxe S, Langdon C, et al. Olfactory Training Prevents Olfactory Dysfunction Induced by Bulbar Excitotoxic Lesions: Role of Neurogenesis and Dopaminergic Interneurons. *Mol Neurobiol*. Dec 2019;56(12):8063-8075. doi:10.1007/s12035-019-1639-6

492. Morra F, Minerva M, Valeggia S, et al. Late olfactory bulb involvement in COVID19. *Chem Senses*. Nov 7 2024;doi:10.1093/chemse/bjae040

493. Douaud G, Lee S, Alfaro-Almagro F, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature*. Apr 2022;604(7907):697-707. doi:10.1038/s41586-022-04569-5

494. Altunisik E, Baykan AH, Sahin S, Aydin E, Erturk SM. Quantitative Analysis of the Olfactory System in COVID-19: An MR Imaging Study. *AJNR Am J Neuroradiol*. Dec 2021;42(12):2207-2214. doi:10.3174/ajnr.A7278

495. Vanderheiden A, Klein RS. Neuroinflammation and COVID-19. *Curr Opin Neurobiol*. Oct 2022;76:102608. doi:10.1016/j.conb.2022.102608

496. Doty RL. A review of olfactory dysfunctions in man. *Am J Otolaryngol*. Fall 1979;1(1):57-79. doi:10.1016/s0196-0709(79)80010-1

497. Leopold D. Distortion of olfactory perception: diagnosis and treatment. *Chem Senses*. Sep 2002;27(7):611-5. doi:10.1093/chemse/27.7.611

498. Hawkes C. Parosmia: treatment, mechanism, and types. *BMJ*. Dec 8 2020;371:m4739. doi:10.1136/bmj.m4739

499. Holbrook EH, Leopold DA, Schwob JE. Abnormalities of axon growth in human olfactory mucosa. *Laryngoscope*. Dec 2005;115(12):2144-54. doi:10.1097/01.MLG.0000181493.83661.CE

500. Iannilli E, Leopold DA, Hornung DE, Hummel T. Advances in Understanding Parosmia: An fMRI Study. *ORL J Otorhinolaryngol Relat Spec*. 2019;81(4):185-192. doi:10.1159/000500558

501. Yamagishi M, Fujiwara M, Nakamura H. Olfactory mucosal findings and clinical course in patients with olfactory disorders following upper respiratory viral infection. *Rhinology*. Sep 1994;32(3):113-8.

502. Parker JK, Kelly CE, Gane SB. Insights into the molecular triggers of parosmia based on gas chromatography olfactometry. *Commun Med (Lond)*. 2022;2:58. doi:10.1038/s43856-022-00112-9

503. Bitter T, Siegert F, Gudziol H, et al. Gray matter alterations in parosmia. *Neuroscience*. Mar 17 2011;177:177-82. doi:10.1016/j.neuroscience.2011.01.016

504. Yousefi-Koma A, Haseli S, Bakhshayeshkaram M, Raad N, Karimi-Galougahi M. Multimodality Imaging With PET/CT and MRI Reveals Hypometabolism in Tertiary Olfactory Cortex in Parosmia of COVID-19. *Acad Radiol*. May 2021;28(5):749-751. doi:10.1016/j.acra.2021.01.031

505. Douek E, Bannister LH, Dodson HC. Recent advances in the pathology of olfaction. *Proc R Soc Med*. Aug 1975;68(8):467-70.

506. Moran DT, Jafek BW, Eller PM, Rowley JC, 3rd. Ultrastructural histopathology of human olfactory dysfunction. *Microsc Res Tech*. Oct 15 1992;23(2):103-10. doi:10.1002/jemt.1070230202

507. Duncan HJ, Seiden AM. Long-term follow-up of olfactory loss secondary to head trauma and upper respiratory tract infection. *Arch Otolaryngol Head Neck Surg*. Oct 1995;121(10):1183-7. doi:10.1001/archotol.1995.01890100087015

508. Lee DY, Lee WH, Wee JH, Kim JW. Prognosis of postviral olfactory loss: follow-up study for longer than one year. *Am J Rhinol Allergy*. Sep-Oct 2014;28(5):419-22. doi:10.2500/ajra.2014.28.4102

509. Petrocelli M, Cutrupi S, Salzano G, et al. Six-month smell and taste recovery rates in coronavirus disease 2019 patients: a prospective psychophysical study. *J Laryngol Otol*. May 2021;135(5):436-441. doi:10.1017/S002221512100116X

510. Niklassen AS, Draf J, Huart C, et al. COVID-19: Recovery from Chemosensory Dysfunction. A Multicentre study on Smell and Taste. *Laryngoscope*. May 2021;131(5):1095-1100. doi:10.1002/lary.29383

511. Hopkins C, Surda P, Vaira LA, et al. Six month follow-up of self-reported loss of smell during the COVID-19 pandemic. *Rhinology*. Feb 1 2021;59(1):26-31. doi:10.4193/Rhin20.544

512. Khan AM, Lee J, Rammaha T, et al. Natural trajectory of recovery of COVID-19 associated olfactory loss. *Am J Otolaryngol*. Sep-Oct 2022;43(5):103572. doi:10.1016/j.amjoto.2022.103572

513. Boscolo-Rizzo P, Hummel T, Hopkins C, et al. High prevalence of long-term olfactory, gustatory, and chemesthesis dysfunction in post-COVID-19 patients: a matched case-control study with one-year follow-up using a comprehensive psychophysical evaluation. *Rhinology*. Dec 1 2021;59(6):517-527. doi:10.4193/Rhin21.249

514. Vaira LA, Salzano G, Le Bon SD, et al. Prevalence of Persistent Olfactory Disorders in Patients With COVID-19: A Psychophysical Case-Control Study With 1-Year Follow-up. *Otolaryngol Head Neck Surg*. Jul 2022;167(1):183-186. doi:10.1177/01945998211061511

515. Boscolo-Rizzo P, Fabbris C, Polesel J, et al. Two-Year Prevalence and Recovery Rate of Altered Sense of Smell or Taste in Patients With Mildly Symptomatic COVID-19. *JAMA Otolaryngol Head Neck Surg*. Sep 1 2022;148(9):889-891. doi:10.1001/jamaoto.2022.1983

516. Boscolo-Rizzo P, Spinato G, Hopkins C, et al. Evaluating long-term smell or taste dysfunction in mildly symptomatic COVID-19 patients: a 3-year follow-up study. *Eur Arch Otorhinolaryngol*. Dec 2023;280(12):5625-5630. doi:10.1007/s00405-023-08227-y

517. Reden J, Mueller A, Mueller C, et al. Recovery of olfactory function following closed head injury or infections of the upper respiratory tract. *Arch Otolaryngol Head Neck Surg*. Mar 2006;132(3):265-9. doi:10.1001/archotol.132.3.265

518. Tan BKJ, Han R, Zhao JJ, et al. Prognosis and persistence of smell and taste dysfunction in patients with covid-19: meta-analysis with parametric cure modelling of recovery curves. *BMJ*. Jul 27 2022;378:e069503. doi:10.1136/bmj-2021-069503

519. Hummel T, Lotsch J. Prognostic factors of olfactory dysfunction. *Arch Otolaryngol Head Neck Surg*. Apr 2010;136(4):347-51. doi:10.1001/archoto.2010.27

520. London B, Nabet B, Fisher AR, White B, Sammel MD, Doty RL. Predictors of prognosis in patients with olfactory disturbance. *Ann Neurol*. Feb 2008;63(2):159-66. doi:10.1002/ana.21293

521. Rombaux P, Huart C, Collet S, Eloy P, Negoias S, Hummel T. Presence of olfactory event-related potentials predicts recovery in patients with olfactory loss following upper respiratory tract infection. *Laryngoscope*. Oct 2010;120(10):2115-8. doi:10.1002/lary.21109

522. Altundag A, Temirbekov D, Haci C, Yildirim D, Cayonu M. Olfactory Cleft Width and Volume: Possible Risk Factors for Postinfectious Olfactory Dysfunction. *Laryngoscope*. Jan 2021;131(1):5-9. doi:10.1002/lary.28524

523. Menzel S, Haehner A, Woosch D, et al. Parosmia as a predictor of a better olfactory function in COVID-19: a multicentric longitudinal study for upper respiratory tract infections. *Eur Arch Otorhinolaryngol*. Dec 22 2022:1-10. doi:10.1007/s00405-022-07781-1

524. Hura N, Xie DX, Choby GW, et al. Treatment of post-viral olfactory dysfunction: an evidence-based review with recommendations. *Int Forum Allergy Rhinol*. Sep 2020;10(9):1065-1086. doi:10.1002/alr.22624

525. Hummel T, Rissom K, Reden J, Hahner A, Weidenbecher M, Huttenbrink KB. Effects of olfactory training in patients with olfactory loss. *Laryngoscope*. Mar 2009;119(3):496-9. doi:10.1002/lary.20101

526. Vandersteen C, Payne M, Dumas LE, et al. Olfactory Training in Post-COVID-19 Persistent Olfactory Disorders: Value Normalization for Threshold but Not Identification. *J Clin Med*. Jun 8 2022;11(12)doi:10.3390/jcm11123275

527. Damm M, Pikart LK, Reimann H, et al. Olfactory training is helpful in postinfectious olfactory loss: a randomized, controlled, multicenter study. *Laryngoscope*. Apr 2014;124(4):826-31. doi:10.1002/lary.24340

528. Altundag A, Cayonu M, Kayabasoglu G, et al. Modified olfactory training in patients with postinfectious olfactory loss. *Laryngoscope*. Aug 2015;125(8):1763-6. doi:10.1002/lary.25245

529. Konstantinidis I, Tsakiropoulou E, Bekiaridou P, Kazantzidou C, Constantinidis J. Use of olfactory training in post-traumatic and postinfectious olfactory dysfunction. *Laryngoscope*. Dec 2013;123(12):E85-90. doi:10.1002/lary.24390

530. Kattar N, Do TM, Unis GD, Migneron MR, Thomas AJ, McCoul ED. Olfactory Training for Postviral Olfactory Dysfunction: Systematic Review and Meta-analysis. *Otolaryngol Head Neck Surg*. Feb 2021;164(2):244-254. doi:10.1177/0194599820943550

531. Asvapoositkul V, Samuthpongtorn J, Aeumjaturapat S, et al. Therapeutic options of post-COVID-19 related olfactory dysfunction: a systematic review and meta-analysis. *Rhinology*. Feb 1 2023;61(1):2-11. doi:10.4193/Rhin22.221

532. Delgado-Lima AH, Bouhaben J, Delgado-Losada ML. The efficacy of olfactory training in improving olfactory function: a meta-analysis. *Eur Arch Otorhinolaryngol*. Oct 2024;281(10):5267-5284. doi:10.1007/s00405-024-08733-7

533. Schepens EJA, Blijleven EE, Boek WM, et al. Prednisolone does not improve olfactory function after COVID-19: a randomized, double-blind, placebo-controlled trial. *BMC Med*. Nov 16 2022;20(1):445. doi:10.1186/s12916-022-02625-5

534. Hwang SH, Kim SW, Basurrah MA, Kim DH. The Efficacy of Olfactory Training as a Treatment for Olfactory Disorders Caused by Coronavirus Disease-2019: A Systematic Review and Meta-Analysis. *Am J Rhinol Allergy*. Jul 2023;37(4):495-501. doi:10.1177/19458924221150977

535. Konstantinidis I, Tsakiropoulou E, Constantinidis J. Long term effects of olfactory training in patients with post-infectious olfactory loss. *Rhinology*. Jun 2016;54(2):170-5. doi:10.4193/Rhino15.264

536. Genetzaki S, Nikolaidis V, Markou K, Konstantinidis I. Olfactory training with four and eight odors: comparison with clinical testing and olfactory bulb volumetrics. *Eur Arch Otorhinolaryngol*. Jan 2024;281(1):497-502. doi:10.1007/s00405-023-08283-4

537. Liu DT, Sabha M, Damm M, et al. Parosmia is Associated with Relevant Olfactory Recovery After Olfactory Training. *Laryngoscope*. Mar 2021;131(3):618-623. doi:10.1002/lary.29277

538. Kim DH, Kim SW, Kang M, Hwang SH. Efficacy of topical steroids for the treatment of olfactory disorders caused by COVID-19: A systematic review and meta-analysis. *Clin Otolaryngol*. Jul 2022;47(4):509-515. doi:10.1111/coa.13933

539. Chen RD, Yang CW, Chen XB, et al. Therapeutic Efficacy of Nasal Corticosteroids in COVID-19-Related Olfactory Dysfunction: A Comprehensive Systematic Review and Meta-analysis. *Otolaryngol Head Neck Surg*. Apr 2024;170(4):999-1008. doi:10.1002/ohn.621

540. De Luca P, Camaioni A, Marra P, et al. Effect of Ultra-Micronized Palmitoylethanolamide and Luteolin on Olfaction and Memory in Patients with Long COVID: Results of a Longitudinal Study. *Cells*. Aug 17 2022;11(16)doi:10.3390/cells11162552

541. Capra AP, Ardizzone A, Crupi L, et al. Efficacy of Palmitoylethanolamide and Luteolin Association on Post-Covid Olfactory Dysfunction: A Systematic Review and Meta-Analysis of Clinical Studies. *Biomedicines*. Aug 3 2023;11(8)doi:10.3390/biomedicines11082189

542. Hernandez AK, Woosch D, Haehner A, Hummel T. Omega-3 supplementation in postviral olfactory dysfunction: a pilot study. *Rhinology*. Apr 1 2022;60(2):139-144. doi:10.4193/Rhin21.378

543. Cantone E, D'Ascanio L, De Luca P, et al. Persistent COVID-19 parosmia and olfactory loss post olfactory training: randomized clinical trial comparing central and peripheral-acting therapeutics. *Eur Arch Otorhinolaryngol*. Jul 2024;281(7):3671-3678. doi:10.1007/s00405-024-08548-6

544. Mahadev A, Hentati F, Miller B, et al. Efficacy of Gabapentin For Post-COVID-19 Olfactory Dysfunction: The GRACE Randomized Clinical Trial. *JAMA Otolaryngol Head Neck Surg*. Dec 1 2023;149(12):1111-1119. doi:10.1001/jamaoto.2023.2958

545. Taheri A, Naderi M, Jonaidi Jafari N, Emadi Koochak H, Saberi Esfeedvajani M, Abolghasemi R. Therapeutic effects of olfactory training and systemic vitamin A in patients with COVID-19-related olfactory dysfunction: a double-blinded randomized controlled clinical trial. *Braz J Otorhinolaryngol*. Sep-Oct 2024;90(5):101451. doi:10.1016/j.bjorl.2024.101451

546. Abdelmaksoud AA, Ghweil AA, Hassan MH, et al. Olfactory Disturbances as Presenting Manifestation Among Egyptian Patients with COVID-19: Possible Role of Zinc. *Biol Trace Elem Res*. Nov 2021;199(11):4101-4108. doi:10.1007/s12011-020-02546-5

547. Yan CH, Jang SS, Lin HC, et al. Use of platelet-rich plasma for COVID-19-related olfactory loss: a randomized controlled trial. *Int Forum Allergy Rhinol*. Jun 2023;13(6):989-997. doi:10.1002/alr.23116

548. Evman MD, Cetin ZE. Effectiveness of platelet-rich plasma on post-COVID chronic olfactory dysfunction. *Rev Assoc Med Bras (1992)*. 2023;69(11):e20230666. doi:10.1590/1806-9282.20230666

549. Duffy A, Naimi B, Garvey E, et al. Topical platelet-rich plasma as a possible treatment for olfactory dysfunction-A randomized controlled trial. *Int Forum Allergy Rhinol*. Sep 2024;14(9):1455-1464. doi:10.1002/alr.23363

550. Hummel T, Stupka G, Haehner A, Poletti SC. Olfactory training changes electrophysiological responses at the level of the olfactory epithelium. *Rhinology*. Dec 1 2018;56(4):330-335. doi:10.4193/Rhin17.163

551. Al Ain S, Poupon D, Hetu S, Mercier N, Steffener J, Frasnelli J. Smell training improves olfactory function and alters brain structure. *Neuroimage*. Apr 1 2019;189:45-54. doi:10.1016/j.neuroimage.2019.01.008

552. Negoias S, Pietsch K, Hummel T. Changes in olfactory bulb volume following lateralized olfactory training. *Brain Imaging Behav*. Aug 2017;11(4):998-1005. doi:10.1007/s11682-016-9567-9

553. Sorokowska A, Drechsler E, Karwowski M, Hummel T. Effects of olfactory training: a meta-analysis. *Rhinology*. Mar 1 2017;55(1):17-26. doi:10.4193/Rhino16.195

554. Liu ZY, Vaira LA, Boscolo-Rizzo P, Walker A, Hopkins C. Post-viral olfactory loss and parosmia. *BMJ Med*. 2023;2(1):e000382. doi:10.1136/bmjmed-2022-000382

555. Klimek L, Hagemann J, Doge J, et al. Olfactory and gustatory disorders in COVID-19. *Allergo J Int*. 2022;31(7):243-250. doi:10.1007/s40629-022-00216-7

556. Hopkins C, Alanin M, Philpott C, et al. Management of new onset loss of sense of smell during the COVID-19 pandemic - BRS Consensus Guidelines. *Clin Otolaryngol*. Jan 2021;46(1):16-22. doi:10.1111/coa.13636

557. Nguyen TP, Patel ZM. Budesonide irrigation with olfactory training improves outcomes compared with olfactory training alone in patients with olfactory loss. *Int Forum Allergy Rhinol*. Sep 2018;8(9):977-981. doi:10.1002/alr.22140

558. Blomqvist EH, Lundblad L, Bergstedt H, Stjarne P. Placebo-controlled, randomized, double-blind study evaluating the efficacy of fluticasone propionate nasal spray for the treatment of patients with hyposmia/anosmia. *Acta Otolaryngol*. Sep 2003;123(7):862-8. doi:10.1080/00016480310002140

559. Henkin RI, Schecter PJ, Friedewald WT, Demets DL, Raff M. A double blind study of the effects of zinc sulfate on taste and smell dysfunction. *Am J Med Sci*. Nov-Dec 1976;272(3):285-99. doi:10.1097/00000441-197611000-00006

560. Aiba T, Sugiura M, Mori J, et al. Effect of zinc sulfate on sensorineural olfactory disorder. *Acta Otolaryngol Suppl*. 1998;538:202-4. doi:10.1080/00016489850182936

561. Yan CH, Rathor A, Krook K, et al. Effect of Omega-3 Supplementation in Patients With Smell Dysfunction Following Endoscopic Sellar and Parasellar Tumor Resection: A Multicenter Prospective Randomized Controlled Trial. *Neurosurgery*. Aug 1 2020;87(2):E91-E98. doi:10.1093/neuros/nyz559

562. Hummel T, Heilmann S, Huttenbriuk KB. Lipoic acid in the treatment of smell dysfunction following viral infection of the upper respiratory tract. *Laryngoscope*. Nov 2002;112(11):2076-80. doi:10.1097/00005537-200211000-00031

563. Philpott CM, Erskine SE, Clark A, et al. A randomised controlled trial of sodium citrate spray for non-conductive olfactory disorders. *Clin Otolaryngol*. Dec 2017;42(6):1295-1302. doi:10.1111/coa.12878

564. Whitcroft KL, Ezzat M, Cuevas M, Andrews P, Hummel T. The effect of intranasal sodium citrate on olfaction in post-infectious loss: results from a prospective, placebo-controlled trial in 49 patients. *Clin Otolaryngol*. Jun 2017;42(3):557-563. doi:10.1111/coa.12789

565. Whitcroft KL, Gunder N, Cuevas M, et al. Intranasal sodium citrate in quantitative and qualitative olfactory dysfunction: results from a prospective, controlled trial of prolonged use in 60 patients. *Eur Arch Otorhinolaryngol*. Aug 2021;278(8):2891-2897. doi:10.1007/s00405-020-06567-7

566. Hummel T, Whitcroft KL, Rueter G, Haehner A. Intranasal vitamin A is beneficial in post-infectious olfactory loss. *Eur Arch Otorhinolaryngol*. Jul 2017;274(7):2819-2825. doi:10.1007/s00405-017-4576-x

567. Reden J, Lill K, Zahnert T, Haehner A, Hummel T. Olfactory function in patients with postinfectious and posttraumatic smell disorders before and after treatment with vitamin A: a double-blind, placebo-controlled, randomized clinical trial. *Laryngoscope*. Sep 2012;122(9):1906-9. doi:10.1002/lary.23405

568. Kumaresan K, Bengtsson S, Sami S, et al. A double-blinded randomised controlled trial of vitamin A drops to treat post-viral olfactory loss: study protocol for a proof-of-concept study for vitamin A nasal drops in post-viral olfactory loss (APOLLO). *Pilot Feasibility Stud*. Oct 12 2023;9(1):174. doi:10.1186/s40814-023-01402-2

569. Di Stadio A, D'Ascanio L, Vaira LA, et al. Ultramicronized Palmitoylethanolamide and Luteolin Supplement Combined with Olfactory Training to Treat Post-COVID-19 Olfactory Impairment: A Multi-Center Double-Blinded Randomized Placebo-Controlled Clinical Trial. *Curr Neuropharmacol*. 2022;20(10):2001-2012. doi:10.2174/1570159X20666220420113513

570. Garcia JAP, Miller E, Norwood TG, et al. Gabapentin improves parosmia after COVID-19 infection. *Int Forum Allergy Rhinol*. Jun 2023;13(6):1034-1036. doi:10.1002/alr.23117

571. Berger JR, Brandstadter R, Bar-Or A. COVID-19 and MS disease-modifying therapies. *Neurol Neuroimmunol Neuroinflamm*. Jul 2020;7(4)doi:10.1212/NXI.0000000000000761

572. Di Stadio A, Bernitsas E, La Mantia I, et al. Targeting Neuroinflammation to Alleviate Chronic Olfactory Dysfunction in Long COVID: A Role for Investigating Disease-Modifying Therapy (DMT)? *Life (Basel)*. Jan 13 2023;13(1)doi:10.3390/life13010226

573. Ogawa T, Matsumoto K, Tojima I, Kikuoka H, Hira D, Shimizu T. Therapeutic Potential of Valproic Acid for Postviral Olfactory Dysfunction: A Single-Arm Pilot

Study. *Ann Otol Rhinol Laryngol*. Jun 2023;132(6):709-714. doi:10.1177/00034894221111245

574. Duncan RB, Briggs M. Treatment of uncomplicated anosmia by vitamin A. *Arch Otolaryngol*. Feb 1962;75:116-24. doi:10.1001/archotol.1962.00740040122008
575. Reden J, Herting B, Lill K, Kern R, Hummel T. Treatment of postinfectious olfactory disorders with minocycline: a double-blind, placebo-controlled study. *Laryngoscope*. Mar 2011;121(3):679-82. doi:10.1002/lary.21401
576. Henkin RI, Velicu I, Schmidt L. An open-label controlled trial of theophylline for treatment of patients with hyposmia. *Am J Med Sci*. Jun 2009;337(6):396-406. doi:10.1097/MAJ.0b013e3181914a97
577. Henkin RI, Hosein S, Stateman WA, Knoppel AB, Abdelmeguid M. Improved smell function with increased nasal mucus sonic hedgehog in hyposmic patients after treatment with oral theophylline. *Am J Otolaryngol*. Mar-Apr 2017;38(2):143-147. doi:10.1016/j.amjoto.2016.11.010
578. Lee JJ, Peterson AM, Kallogjeri D, et al. Smell Changes and Efficacy of Nasal Theophylline (SCENT) irrigation: A randomized controlled trial for treatment of post-viral olfactory dysfunction. *Am J Otolaryngol*. Mar-Apr 2022;43(2):103299. doi:10.1016/j.amjoto.2021.103299
579. Quint C, Temmel AF, Hummel T, Ehrenberger K. The quinoxaline derivative caroverine in the treatment of sensorineural smell disorders: a proof-of-concept study. *Acta Otolaryngol*. Dec 2002;122(8):877-81.
580. Harless L, Liang J. Pharmacologic treatment for postviral olfactory dysfunction: a systematic review. *Int Forum Allergy Rhinol*. Jul 2016;6(7):760-7. doi:10.1002/alr.21727
581. Miwa T, Ikeda K, Ishibashi T, et al. Clinical practice guidelines for the management of olfactory dysfunction - Secondary publication. *Auris Nasus Larynx*. Oct 2019;46(5):653-662. doi:10.1016/j.anl.2019.04.002

582. Yan CH, Mundy DC, Patel ZM. The use of platelet-rich plasma in treatment of olfactory dysfunction: A pilot study. *Laryngoscope Investig Otolaryngol*. Apr 2020;5(2):187-193. doi:10.1002/lio2.357

583. Lechien JR, Saussez S, Vaira LA, et al. Effectiveness of Platelet-Rich Plasma for COVID-19-Related Olfactory Dysfunction: A Controlled Study. *Otolaryngol Head Neck Surg*. Jan 2024;170(1):84-91. doi:10.1002/ohn.460

584. Lechien JR, Vaira LA, Saussez S. Effectiveness of olfactory training in COVID-19 patients with olfactory dysfunction: a prospective study. *Eur Arch Otorhinolaryngol*. Mar 2023;280(3):1255-1263. doi:10.1007/s00405-022-07665-4

585. Yaylaci A, Azak E, Onal A, Akturk DR, Karadenizli A. Effects of classical olfactory training in patients with COVID-19-related persistent loss of smell. *Eur Arch Otorhinolaryngol*. Feb 2023;280(2):757-763. doi:10.1007/s00405-022-07570-w

586. Boscolo-Rizzo P, Hummel T, Menini A, et al. Adherence to olfactory training improves orthonasal and retronasal olfaction in post-COVID-19 olfactory loss. *Rhinology*. Aug 19 2024;doi:10.4193/Rhin24.233

587. Schepens EJA, de Haas CJM, Postma EM, et al. The effect of smell training on COVID-19 induced smell loss. *Rhinology*. Aug 1 2024;62(4):386-393. doi:10.4193/Rhin23.191

588. Di Stadio A, Gallina S, Cocuzza S, et al. Treatment of COVID-19 olfactory dysfunction with olfactory training, palmitoylethanolamide with luteolin, or combined therapy: a blinded controlled multicenter randomized trial. *Eur Arch Otorhinolaryngol*. Nov 2023;280(11):4949-4961. doi:10.1007/s00405-023-08085-8

589. Di Stadio A, Cantone E, De Luca P, et al. Parosmia COVID-19 Related Treated by a Combination of Olfactory Training and Ultramicronized PEA-LUT: A Prospective Randomized Controlled Trial. *Biomedicines*. Apr 6 2023;11(4)doi:10.3390/biomedicines11041109

590. Andrews PJ, Pendolino AL, Ottaviano G, et al. Olfactory and taste dysfunction among mild-to-moderate symptomatic COVID-19 positive health care workers: An

international survey. *Laryngoscope Investig Otolaryngol*. Dec 2020;5(6):1019-1028. doi:10.1002/lio2.507

591. Tan HQM, Pendolino AL, Andrews PJ, Choi D. Prevalence of olfactory dysfunction and quality of life in hospitalised patients 1 year after SARS-CoV-2 infection: a cohort study. *BMJ Open*. Jan 25 2022;12(1):e054598. doi:10.1136/bmjopen-2021-054598
592. Pendolino AL, Tan HQM, Choi D, Ottaviano G, Andrews PJ. Long-term quality-of-life impairment in patients with more than 1-year COVID-19-related olfactory dysfunction. *Int Forum Allergy Rhinol*. Feb 2023;13(2):160-164. doi:10.1002/alr.23071
593. Renaud M, Leon A, Trau G, et al. Acute smell and taste loss in outpatients: all infected with SARS-CoV-2? *Rhinology*. Aug 1 2020;58(4):406-409. doi:10.4193/Rhin20.199
594. Italian National Institute of Health (ISS). COVID-19 integrated surveillance: key national data. COVID-19 epidemic. 16 April 2020 national update. Accessed July 3, 2020. https://www.epicentro.iss.it/coronavirus/sars-cov-2-sorveglianza-dati
595. CEBM. Accessed July 3, 2020. https://www.cebm.net/covid-19/covid-19-how-many-healthcare-workers-are-infected/
596. Euronews. Accessed July 3, 2020. https://www.euronews.com/2020/05/06/at-least-90-000-healthcare-workers-infected-by-covid-19-says-nursing-group
597. Jha S, Soni A, Siddiqui S, et al. Prevalence of Flu-like Symptoms and COVID-19 in Healthcare Workers from India. *J Assoc Physicians India*. Jul 2020;68(7):27-29.
598. Lombardi A, Consonni D, Carugno M, et al. Characteristics of 1573 healthcare workers who underwent nasopharyngeal swab testing for SARS-CoV-2 in Milan, Lombardy, Italy. *Clin Microbiol Infect*. Oct 2020;26(10):1413 e9-1413 e13. doi:10.1016/j.cmi.2020.06.013

599. Vukkadala N, Qian ZJ, Holsinger FC, Patel ZM, Rosenthal E. COVID-19 and the Otolaryngologist: Preliminary Evidence-Based Review. *Laryngoscope*. Nov 2020;130(11):2537-2543. doi:10.1002/lary.28672

600. WHO. July 3, 2020. https://www.who.int/health-topics/coronavirus#tab=tab_3

601. von Bartheld CS, Hagen MM, Butowt R. Prevalence of Chemosensory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis Reveals Significant Ethnic Differences. *ACS Chem Neurosci*. Oct 7 2020;11(19):2944-2961. doi:10.1021/acschemneuro.0c00460

602. Kaye R, Chang CWD, Kazahaya K, Brereton J, Denneny JC, 3rd. COVID-19 Anosmia Reporting Tool: Initial Findings. *Otolaryngol Head Neck Surg*. Jul 2020;163(1):132-134. doi:10.1177/0194599820922992

603. Lan FY, Filler R, Mathew S, et al. COVID-19 symptoms predictive of healthcare workers' SARS-CoV-2 PCR results. *PLoS One*. 2020;15(6):e0235460. doi:10.1371/journal.pone.0235460

604. Kempker RR, Kempker JA, Peters M, et al. Loss of Smell and Taste Among Healthcare Personnel Screened for Coronavirus 2019. *Clin Infect Dis*. Apr 8 2021;72(7):1244-1246. doi:10.1093/cid/ciaa877

605. Van Loon N, Verbrugghe M, Cartuyvels R, Ramaekers D. Diagnosis of COVID-19 Based on Symptomatic Analysis of Hospital Healthcare Workers in Belgium: Observational Study in a Large Belgian Tertiary Care Center During Early COVID-19 Outbreak. *J Occup Environ Med*. Jan 1 2021;63(1):27-31. doi:10.1097/JOM.0000000000002015

606. Iversen K, Bundgaard H, Hasselbalch RB, et al. Risk of COVID-19 in health-care workers in Denmark: an observational cohort study. *Lancet Infect Dis*. Dec 2020;20(12):1401-1408. doi:10.1016/S1473-3099(20)30589-2

607. Ollarves-Carrero MF, Rodriguez-Morales AG, Bonilla-Aldana DK, Rodriguez-Morales AJ. Anosmia in a healthcare worker with COVID-19 in Madrid, Spain. *Travel Med Infect Dis*. May-Jun 2020;35:101666. doi:10.1016/j.tmaid.2020.101666

608. Lechner M, Chandrasekharan D, Jumani K, et al. Anosmia as a presenting symptom of SARS-CoV-2 infection in healthcare workers - A systematic review of the literature, case series, and recommendations for clinical assessment and management. *Rhinology*. Aug 1 2020;58(4):394-399. doi:10.4193/Rhin20.189

609. Ottaviano G, Carecchio M, Scarpa B, Marchese-Ragona R. Olfactory and rhinological evaluations in SARS-CoV-2 patients complaining of olfactory loss. *Rhinology*. Aug 1 2020;58(4):400-401. doi:10.4193/Rhin20.136

610. Gane SB, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? *Rhinology*. Jun 1 2020;58(3):299-301. doi:10.4193/Rhin20.114

611. Haehner A, Draf J, Drager S, de With K, Hummel T. Predictive Value of Sudden Olfactory Loss in the Diagnosis of COVID-19. *ORL J Otorhinolaryngol Relat Spec*. 2020;82(4):175-180. doi:10.1159/000509143

612. Speth MM, Singer-Cornelius T, Oberle M, Gengler I, Brockmeier SJ, Sedaghat AR. Olfactory Dysfunction and Sinonasal Symptomatology in COVID-19: Prevalence, Severity, Timing, and Associated Characteristics. *Otolaryngol Head Neck Surg*. Jul 2020;163(1):114-120. doi:10.1177/0194599820929185

613. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. Mar 17 2020;323(11):1061-1069. doi:10.1001/jama.2020.1585

614. Hopkins C, Surda P, Whitehead E, Kumar BN. Early recovery following new onset anosmia during the COVID-19 pandemic - an observational cohort study. *J Otolaryngol Head Neck Surg*. May 4 2020;49(1):26. doi:10.1186/s40463-020-00423-8

615. Lee Y, Min P, Lee S, Kim SW. Prevalence and Duration of Acute Loss of Smell or Taste in COVID-19 Patients. *J Korean Med Sci*. May 11 2020;35(18):e174. doi:10.3346/jkms.2020.35.e174

616. Brann DH, Tsukahara T, Weinreb C, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *Sci Adv*. Jul 31 2020;6(31)doi:10.1126/sciadv.abc5801

617. Graziadei PP, Graziadei GA. Neurogenesis and neuron regeneration in the olfactory system of mammals. I. Morphological aspects of differentiation and structural organization of the olfactory sensory neurons. *J Neurocytol*. Feb 1979;8(1):1-18. doi:10.1007/BF01206454

618. Whitcroft KL, Hummel T. Olfactory Dysfunction in COVID-19: Diagnosis and Management. *JAMA*. Jun 23 2020;323(24):2512-2514. doi:10.1001/jama.2020.8391

619. Boscolo-Rizzo P, Borsetto D, Fabbris C, et al. Evolution of Altered Sense of Smell or Taste in Patients With Mildly Symptomatic COVID-19. *JAMA Otolaryngol Head Neck Surg*. Aug 1 2020;146(8):729-732. doi:10.1001/jamaoto.2020.1379

620. Hamilton NJI, Hynds RE, Gowers KHC, et al. Using a Three-Dimensional Collagen Matrix to Deliver Respiratory Progenitor Cells to Decellularized Trachea In Vivo. *Tissue Eng Part C Methods*. Feb 2019;25(2):93-102. doi:10.1089/ten.TEC.2018.0241

621. Soter A, Kim J, Jackman A, Tourbier I, Kaul A, Doty RL. Accuracy of self-report in detecting taste dysfunction. *Laryngoscope*. Apr 2008;118(4):611-7. doi:10.1097/MLG.0b013e318161e53a

622. Marchese-Ragona R, Restivo DA, De Corso E, Vianello A, Nicolai P, Ottaviano G. Loss of smell in COVID-19 patients: a critical review with emphasis on the use of olfactory tests. *Acta Otorhinolaryngol Ital*. Aug 2020;40(4):241-247. doi:10.14639/0392-100X-N0862

623. Ta NH, Gao J, Philpott C. A systematic review to examine the relationship between objective and patient-reported outcome measures in sinonasal disorders: recommendations for use in research and clinical practice. *Int Forum Allergy Rhinol*. May 2021;11(5):910-923. doi:10.1002/alr.22744

624. Ottaviano G, Cantone E, D'Errico A, et al. Sniffin' Sticks and olfactory system imaging in patients with Kallmann syndrome. *Int Forum Allergy Rhinol*. Sep 2015;5(9):855-61. doi:10.1002/alr.21550

625. Pendolino AL, Ottaviano G, Scarpa B, Cattelan A, Andrews JA, Andrews PJ. Characteristics of taste dysfunction in COVID-19 subjects coming from two different countries. *J Neurovirol*. Jun 2021;27(3):482-485. doi:10.1007/s13365-021-00942-8

626. Hannum ME, Ramirez VA, Lipson SJ, et al. Objective Sensory Testing Methods Reveal a Higher Prevalence of Olfactory Loss in COVID-19-Positive Patients Compared to Subjective Methods: A Systematic Review and Meta-Analysis. *Chem Senses*. Dec 5 2020;45(9):865-874. doi:10.1093/chemse/bjaa064

627. Prajapati DP, Shahrvini B, MacDonald BV, et al. Association of subjective olfactory dysfunction and 12-item odor identification testing in ambulatory COVID-19 patients. *Int Forum Allergy Rhinol*. Sep 10 2020;doi:10.1002/alr.22688

628. Ottaviano G, Zuccarello D, Frasson G, et al. Olfactory sensitivity and sexual desire in young adult and elderly men: an introductory investigation. *Am J Rhinol Allergy*. May-Jun 2013;27(3):157-61. doi:10.2500/ajra.2013.27.3879

629. World Health Organization. WHO Coronavirus (COVID-19) Dashboard [Internet] 2021. Accessed 10 November, 2021. https://covid19.who.int

630. Buitrago-Garcia D, Ipekci AM, Heron L, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: Update of a living systematic review and meta-analysis. *PLoS Med*. May 2022;19(5):e1003987. doi:10.1371/journal.pmed.1003987

631. Byambasuren O, Cardona M, Bell K, Clark J, McLaws ML, Glasziou P. Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: Systematic review and meta-analysis. *J Assoc Med Microbiol Infect Dis Can*. Dec 2020;5(4):223-234. doi:10.3138/jammi-2020-0030

632. Struyf T, Deeks JJ, Dinnes J, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19. *Cochrane Database Syst Rev*. Feb 23 2021;2(2):CD013665. doi:10.1002/14651858.CD013665.pub2

633. Qiu C, Cui C, Hautefort C, et al. Olfactory and Gustatory Dysfunction as an Early Identifier of COVID-19 in Adults and Children: An International Multicenter Study. *Otolaryngol Head Neck Surg*. Oct 2020;163(4):714-721. doi:10.1177/0194599820934376

634. Samaranayake LP, Fakhruddin KS, Mohammad OE, Panduwawala C, Bandara N, Ngo HC. Attributes of dysgeusia and anosmia of coronavirus disease 2019 (COVID-19) in hospitalized patients. *Oral Dis*. Apr 2022;28 Suppl 1:891-898. doi:10.1111/odi.13713

635. Chiesa-Estomba CM, Lechien JR, Radulesco T, et al. Patterns of smell recovery in 751 patients affected by the COVID-19 outbreak. *Eur J Neurol*. Nov 2020;27(11):2318-2321. doi:10.1111/ene.14440

636. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. Jun 1 2020;77(6):683-690. doi:10.1001/jamaneurol.2020.1127

637. Schubert CR, Fischer ME, Pinto AA, et al. Sensory Impairments and Risk of Mortality in Older Adults. *J Gerontol A Biol Sci Med Sci*. May 1 2017;72(5):710-715. doi:10.1093/gerona/glw036

638. Liu B, Luo Z, Pinto JM, et al. Relationship Between Poor Olfaction and Mortality Among Community-Dwelling Older Adults: A Cohort Study. *Ann Intern Med*. May 21 2019;170(10):673-681. doi:10.7326/M18-0775

639. Laudisio A, Navarini L, Margiotta DPE, et al. The Association of Olfactory Dysfunction, Frailty, and Mortality Is Mediated by Inflammation: Results from the InCHIANTI Study. *J Immunol Res*. 2019;2019:3128231. doi:10.1155/2019/3128231

640. Ekstrom I, Sjolund S, Nordin S, et al. Smell Loss Predicts Mortality Risk Regardless of Dementia Conversion. *J Am Geriatr Soc*. Jun 2017;65(6):1238-1243. doi:10.1111/jgs.14770

641. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 2020. Accessed 13 March, 202. https://apps.who.int/iris/handle/10665/331446

642. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. Dec 1990;16(3):199-208. doi:10.1016/0168-8510(90)90421-9

643. Vacchiano V, Riguzzi P, Volpi L, et al. Early neurological manifestations of hospitalized COVID-19 patients. *Neurol Sci*. Aug 2020;41(8):2029-2031. doi:10.1007/s10072-020-04525-z

644. Meini S, Suardi LR, Busoni M, Roberts AT, Fortini A. Olfactory and gustatory dysfunctions in 100 patients hospitalized for COVID-19: sex differences and recovery time in real-life. *Eur Arch Otorhinolaryngol*. Dec 2020;277(12):3519-3523. doi:10.1007/s00405-020-06102-8

645. Beltran-Corbellini A, Chico-Garcia JL, Martinez-Poles J, et al. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicentre polymerase chain reaction based case-control study. *Eur J Neurol*. Sep 2020;27(9):1738-1741. doi:10.1111/ene.14273

646. Sayin P, Altinay M, Cinar AS, Ozdemir HM. Taste and Smell Impairment in Critically Ill Patients With COVID-19: An Intensive Care Unit Study. *Ear Nose Throat J*. Apr 2021;100(2_suppl):174S-179S. doi:10.1177/0145561320977464

647. Brandao Neto D, Fornazieri MA, Dib C, et al. Chemosensory Dysfunction in COVID-19: Prevalences, Recovery Rates, and Clinical Associations on a Large Brazilian Sample. *Otolaryngol Head Neck Surg*. Mar 2021;164(3):512-518. doi:10.1177/0194599820954825

648. Nguyen NN, Hoang VT, Dao TL, et al. Long-Term Persistence of Olfactory and Gustatory Disorders in COVID-19 Patients. *Front Med (Lausanne)*. 2022;9:794550. doi:10.3389/fmed.2022.794550

649. Boscolo-Rizzo P, Polesel J, Spinato G, et al. Predominance of an altered sense of smell or taste among long-lasting symptoms in patients with mildly symptomatic COVID-19. *Rhinology*. Oct 1 2020;58(5):524-525. doi:10.4193/Rhin20.263

650. Klein H, Asseo K, Karni N, et al. Onset, duration and unresolved symptoms, including smell and taste changes, in mild COVID-19 infection: a cohort study in Israeli patients. *Clin Microbiol Infect*. Feb 16 2021;27(5):769-74. doi:10.1016/j.cmi.2021.02.008

651. D'Ascanio L, Pandolfini M, Cingolani C, et al. Olfactory Dysfunction in COVID-19 Patients: Prevalence and Prognosis for Recovering Sense of Smell. *Otolaryngol Head Neck Surg*. Jan 2021;164(1):82-86. doi:10.1177/0194599820943530

652. Biadsee A, Dagan O, Ormianer Z, Kassem F, Masarwa S, Biadsee A. Eight-month follow-up of olfactory and gustatory dysfunctions in recovered COVID-19 patients. *Am J Otolaryngol*. Jul-Aug 2021;42(4):103065. doi:10.1016/j.amjoto.2021.103065

653. Boscolo-Rizzo P, Guida F, Polesel J, et al. Self-reported smell and taste recovery in coronavirus disease 2019 patients: a one-year prospective study. *Eur Arch Otorhinolaryngol*. Jan 2022;279(1):515-520. doi:10.1007/s00405-021-06839-w

654. Butowt R, Bilinska K, Von Bartheld CS. Chemosensory Dysfunction in COVID-19: Integration of Genetic and Epidemiological Data Points to D614G Spike Protein Variant as a Contributing Factor. *ACS Chem Neurosci*. Oct 21 2020;11(20):3180-3184. doi:10.1021/acschemneuro.0c00596

655. von Bartheld CS, Hagen MM, Butowt R. The D614G Virus Mutation Enhances Anosmia in COVID-19 Patients: Evidence from a Systematic Review and Meta-analysis of Studies from South Asia. *ACS Chem Neurosci*. Oct 6 2021;12(19):3535-3549. doi:10.1021/acschemneuro.1c00542

656. Abalo-Lojo JM, Pouso-Diz JM, Gonzalez F. Taste and Smell Dysfunction in COVID-19 Patients. *Ann Otol Rhinol Laryngol*. Oct 2020;129(10):1041-1042. doi:10.1177/0003489420932617

657. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. Feb 24 2020;12(1):8. doi:10.1038/s41368-020-0074-x

658. Gorzkowski V, Bevilacqua S, Charmillon A, et al. Evolution of Olfactory Disorders in COVID-19 Patients. *Laryngoscope*. Nov 2020;130(11):2667-2673. doi:10.1002/lary.28957

659. Agyeman AA, Chin KL, Landersdorfer CB, Liew D, Ofori-Asenso R. Smell and Taste Dysfunction in Patients With COVID-19: A Systematic Review and Meta-analysis. *Mayo Clin Proc*. Aug 2020;95(8):1621-1631. doi:10.1016/j.mayocp.2020.05.030

660. Otte MS, Klussmann JP, Luers JC. Persisting olfactory dysfunction in patients after recovering from COVID-19. *J Infect*. Sep 2020;81(3):e58. doi:10.1016/j.jinf.2020.06.054

661. Paderno A, Mattavelli D, Rampinelli V, et al. Olfactory and Gustatory Outcomes in COVID-19: A Prospective Evaluation in Nonhospitalized Subjects. *Otolaryngol Head Neck Surg*. Dec 2020;163(6):1144-1149. doi:10.1177/0194599820939538

662. Ugurlu BN, Akdogan O, Yilmaz YA, et al. Quantitative evaluation and progress of olfactory dysfunction in COVID-19. *Eur Arch Otorhinolaryngol*. Jul 2021;278(7):2363-2369. doi:10.1007/s00405-020-06516-4

663. Sakalli E, Temirbekov D, Bayri E, Alis EE, Erdurak SC, Bayraktaroglu M. Ear nose throat-related symptoms with a focus on loss of smell and/or taste in COVID-19 patients. *Am J Otolaryngol*. Nov-Dec 2020;41(6):102622. doi:10.1016/j.amjoto.2020.102622

664. Otte MS, Eckel HNC, Poluschkin L, Klussmann JP, Luers JC. Olfactory dysfunction in patients after recovering from COVID-19. *Acta Otolaryngol*. Dec 2020;140(12):1032-1035. doi:10.1080/00016489.2020.1811999

665. Vaira LA, Hopkins C, Petrocelli M, et al. Smell and taste recovery in coronavirus disease 2019 patients: a 60-day objective and prospective study. *J Laryngol Otol*. Aug 2020;134(8):703-709. doi:10.1017/S0022215120001826

666. Peckham H, de Gruijter NM, Raine C, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. *Nat Commun*. Dec 9 2020;11(1):6317. doi:10.1038/s41467-020-19741-6

667. Kosugi EM, Lavinsky J, Romano FR, et al. Incomplete and late recovery of sudden olfactory dysfunction in COVID-19. *Braz J Otorhinolaryngol*. Jul-Aug 2020;86(4):490-496. doi:10.1016/j.bjorl.2020.05.001

668. Doty RL. Epidemiology of smell and taste dysfunction. *Handb Clin Neurol*. 2019;164:3-13. doi:10.1016/B978-0-444-63855-7.00001-0

669. Mandal S, Barnett J, Brill SE, et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax*. Apr 2021;76(4):396-398. doi:10.1136/thoraxjnl-2020-215818

670. Elkholi SMA, Abdelwahab MK, Abdelhafeez M. Impact of the smell loss on the quality of life and adopted coping strategies in COVID-19 patients. *Eur Arch Otorhinolaryngol*. Sep 2021;278(9):3307-3314. doi:10.1007/s00405-020-06575-7

671. AlShakhs A, Almomen A, AlYaeesh I, et al. The Association of Smell and Taste Dysfunction with COVID19, And Their Functional Impacts. *Indian J Otolaryngol Head Neck Surg*. Jan 23 2021:1-6. doi:10.1007/s12070-020-02330-w

672. Cases in the UK. Coronavirus in the UK. Accessed 10 November, 2021. https://coronavirus.data.gov.uk/details/cases

673. Levy JM. Treatment Recommendations for Persistent Smell and Taste Dysfunction Following COVID-19-The Coming Deluge. *JAMA Otolaryngol Head Neck Surg*. Aug 1 2020;146(8):733. doi:10.1001/jamaoto.2020.1378

674. Whitcroft KL, Hummel T. Clinical Diagnosis and Current Management Strategies for Olfactory Dysfunction: A Review. *JAMA Otolaryngol Head Neck Surg*. Sep 1 2019;145(9):846-853. doi:10.1001/jamaoto.2019.1728

675. D'Ascanio L, Vitelli F, Cingolani C, Maranzano M, Brenner MJ, Di Stadio A. Randomized clinical trial "olfactory dysfunction after COVID-19: olfactory rehabilitation therapy vs. intervention treatment with Palmitoylethanolamide and Luteolin": preliminary results. *Eur Rev Med Pharmacol Sci*. Jun 2021;25(11):4156-4162. doi:10.26355/eurrev_202106_26059

676. Soares LES, Guirado MMG, Berlingieri G, et al. Intranasal photobiomodulation therapy for COVID-19-related olfactory dysfunction: A Brazilian multicenter case series. *Photodiagnosis Photodyn Ther*. Dec 2021;36:102574. doi:10.1016/j.pdpdt.2021.102574

677. Otte MS, Haehner A, Bork ML, Klussmann JP, Luers JC, Hummel T. Impact of COVID-19-Mediated Olfactory Loss on Quality of Life. *ORL J Otorhinolaryngol Relat Spec*. Apr 12 2022:1-6. doi:10.1159/000523893

678. Lloyd A. Assessment of the SF-36 version 2 in the United Kingdom. *J Epidemiol Community Health*. Oct 1999;53(10):651-2. doi:10.1136/jech.53.10.651

679. Vaira LA, Gessa C, Deiana G, et al. The Effects of Persistent Olfactory and Gustatory Dysfunctions on Quality of Life in Long-COVID-19 Patients. *Life (Basel)*. Jan 19 2022;12(2)doi:10.3390/life12020141

680. Liu DT, Prem B, Sharma G, Kaiser J, Besser G, Mueller CA. Depression Symptoms and Olfactory-related Quality of Life. *Laryngoscope*. Mar 30 2022;doi:10.1002/lary.30122

681. Jafar A, Lasso A, Shorr R, Hutton B, Kilty S. Olfactory recovery following infection with COVID-19: A systematic review. *PLoS One*. 2021;16(11):e0259321. doi:10.1371/journal.pone.0259321

682. Halpin S, O'Connor R, Sivan M. Long COVID and chronic COVID syndromes. *J Med Virol*. Mar 2021;93(3):1242-1243. doi:10.1002/jmv.26587

683. Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. *Infect Dis (Lond)*. Oct 2021;53(10):737-754. doi:10.1080/23744235.2021.1924397

684. Liang F, Wang Y. COVID-19 Anosmia: High Prevalence, Plural Neuropathogenic Mechanisms, and Scarce Neurotropism of SARS-CoV-2? *Viruses*. Nov 4 2021;13(11)doi:10.3390/v13112225

685. Leung JS, Cordano VP, Fuentes-Lopez E, et al. Phantosmia May Predict Long-Term Measurable Olfactory Dysfunction After COVID-19. *Laryngoscope*. Dec 2022;132(12):2445-2452. doi:10.1002/lary.30391

686. Chudzik M, Babicki M, Mastalerz-Migas A, Kapusta J. Persisting Smell and Taste Disorders in Patients Who Recovered from SARS-CoV-2 Virus Infection-Data from the Polish PoLoCOV-CVD Study. *Viruses*. Aug 12 2022;14(8)doi:10.3390/v14081763

687. Coelho DH, Reiter ER, Budd SG, Shin Y, Kons ZA, Costanzo RM. Predictors of smell recovery in a nationwide prospective cohort of patients with COVID-19. *Am J Otolaryngol*. Jan-Feb 2022;43(1):103239. doi:10.1016/j.amjoto.2021.103239

688. McWilliams MP, Coelho DH, Reiter ER, Costanzo RM. Recovery from Covid-19 smell loss: Two-years of follow up. *Am J Otolaryngol*. Sep-Oct 2022;43(5):103607. doi:10.1016/j.amjoto.2022.103607

689. Schwab J, Fjaeldstad AW. Recovery rates and parosmia in olfactory loss during the COVID-19 era. *Dan Med J*. Aug 9 2022;69(9)

690. Burulday V, Sayar MS, Bayar Muluk N. Peripheral and central smell regions in COVID-19 positive patients: an MRI evaluation. *Acta Radiol*. Sep 2022;63(9):1233-1242. doi:10.1177/02841851211034043

691. Rombaux P, Duprez T, Hummel T. Olfactory bulb volume in the clinical assessment of olfactory dysfunction. *Rhinology*. Mar 2009;47(1):3-9.

692. Kokubo LCP, Carvalho TBO, Fornazieri MA, Gomes EMC, Alves CMF, Sampaio ALL. Effects of septorhinoplasty on smell perception. *Eur Arch Otorhinolaryngol*. Apr 2019;276(4):1247-1250. doi:10.1007/s00405-019-05356-1

693. Grabosky A, Mackers P, Langdon C, Alobid I. Change in olfactory function after septoplasty. A systematic review and meta-analysis. *Rhinology*. Apr 1 2021;59(2):144-150. doi:10.4193/Rhin20.252

694. Haytoglu S, Dengiz R, Muluk NB, Kuran G, Arikan OK. Effects of septoplasty on olfactory function evaluated by the Brief Smell Identification Test: A study of 116 patients. *Ear Nose Throat J*. Oct-Nov 2017;96(10-11):433-438. doi:10.1177/0145561317096010-1123

695. Doty RL, Mishra A. Olfaction and its alteration by nasal obstruction, rhinitis, and rhinosinusitis. *Laryngoscope*. Mar 2001;111(3):409-23. doi:10.1097/00005537-200103000-00008

696. Hilberg O. Effect of terfenadine and budesonide on nasal symptoms, olfaction, and nasal airway patency following allergen challenge. *Allergy*. Aug 1995;50(8):683-8. doi:10.1111/j.1398-9995.1995.tb02586.x

697. Hinriksdottir I, Murphy C, Bende M. Olfactory threshold after nasal allergen challenge. *ORL J Otorhinolaryngol Relat Spec*. Jan-Feb 1997;59(1):36-8. doi:10.1159/000276902

698. Pendolino AL, Ottaviano G, Nijim J, et al. A multicenter real-life study to determine the efficacy of corticosteroids and olfactory training in improving persistent COVID-19-related olfactory dysfunction. *Laryngoscope Investig Otolaryngol*. Dec 2 2022;doi:10.1002/lio2.989

699. Fornazieri MA, Silva J, Gameiro JG, et al. Chemosensory Dysfunction 3-Months After COVID-19, Medications and Factors Associated with Complete Recovery. *Ann Otol Rhinol Laryngol*. Dec 8 2022:34894221138485. doi:10.1177/00034894221138485

700. Akbari M, Jalali MM, Akbarpour M, Alavi Foumani A, Sharifnia S. Olfactory function trends in COVID-19 patients: a prospective cohort study. *Acta Otolaryngol*. Jun 2022;142(6):515-519. doi:10.1080/00016489.2022.2085326

701. Thakur K, Sagayaraj A, Prasad KC, Gupta A. Olfactory Dysfunction in COVID-19 Patients: Findings from a Tertiary Rural Centre. *Indian J Otolaryngol Head Neck Surg*. Oct 2022;74(Suppl 2):2840-2846. doi:10.1007/s12070-021-02364-8

702. Printza A, Katotomichelakis M, Valsamidis K, et al. Smell and Taste Loss Recovery Time in COVID-19 Patients and Disease Severity. *J Clin Med*. Mar 2 2021;10(5)doi:10.3390/jcm10050966

703. Ohla K, Veldhuizen MG, Green T, et al. A follow-up on quantitative and qualitative olfactory dysfunction and other symptoms in patients recovering from COVID-19 smell loss. *Rhinology*. Jun 1 2022;60(3):207-217. doi:10.4193/Rhin21.415

704. Lechien JR, Wajsblat S, Horoi M, et al. Comparison of prevalence and evolution of COVID-19 olfactory disorders in patients infected by D614 (wild) and B.1.1.7. Alpha variant: a brief report. *Eur Arch Otorhinolaryngol*. Jul 2023;280(7):3461-3467. doi:10.1007/s00405-023-07923-z

705. Garcia-Melendez DD, Morales-Casado MI, Quintana Castro P, Marsal Alonso C. Persistent olfactory dysfunction in mild COVID-19 patients: A descriptive study of the characteristics and association with other symptoms. *Med Clin (Engl Ed)*. Apr 21 2023;160(8):347-351. doi:10.1016/j.medcle.2022.11.016

706. Dudine L, Canaletti C, Giudici F, et al. Investigation on the Loss of Taste and Smell and Consequent Psychological Effects: A Cross-Sectional Study on Healthcare Workers Who Contracted the COVID-19 Infection. *Front Public Health*. 2021;9:666442. doi:10.3389/fpubh.2021.666442

707. Fleiner F, Lau L, Goktas O. Active olfactory training for the treatment of smelling disorders. *Ear Nose Throat J*. May 2012;91(5):198-203, 215. doi:10.1177/014556131209100508

708. Patel ZM, Wise SK, DelGaudio JM. Randomized Controlled Trial Demonstrating Cost-Effective Method of Olfactory Training in Clinical Practice: Essential Oils at Uncontrolled Concentration. *Laryngoscope Investig Otolaryngol*. Apr 2017;2(2):53-56. doi:10.1002/lio2.62

709. Yan CH, Overdevest JB, Patel ZM. Therapeutic use of steroids in non-chronic rhinosinusitis olfactory dysfunction: a systematic evidence-based review with recommendations. *Int Forum Allergy Rhinol*. Feb 2019;9(2):165-176. doi:10.1002/alr.22240

710. Nishimura T, Teranishi S, Kawashima A, Ishimaru T, Miwa T, Furukawa M. Glucocorticoid enhances Na(+)/K(+) ATPase mRNA expression in rat olfactory mucosa during regeneration: a possible mechanism for recovery from olfactory disturbance. *Chem Senses*. Jan 2002;27(1):13-21. doi:10.1093/chemse/27.1.13

711. Takanosawa M, Nishino H, Ohta Y, Ichimura K. Glucocorticoids enhance regeneration of murine olfactory epithelium. *Acta Otolaryngol*. Sep 2009;129(9):1002-9. doi:10.1080/00016480802530663

712. Addison AB, Wong B, Ahmed T, et al. Clinical Olfactory Working Group consensus statement on the treatment of postinfectious olfactory dysfunction. *J Allergy Clin Immunol*. May 2021;147(5):1704-1719. doi:10.1016/j.jaci.2020.12.641

713. Hodgens A, Sharman T. Corticosteroids. *StatPearls*. 2021.

714. Kim DH, Kim SW, Hwang SH, et al. Prognosis of Olfactory Dysfunction according to Etiology and Timing of Treatment. *Otolaryngol Head Neck Surg*. Feb 2017;156(2):371-377. doi:10.1177/0194599816679952

715. Heilmann S, Huettenbrink KB, Hummel T. Local and systemic administration of corticosteroids in the treatment of olfactory loss. *Am J Rhinol*. Jan-Feb 2004;18(1):29-33.

716. Le Bon SD, Konopnicki D, Pisarski N, Prunier L, Lechien JR, Horoi M. Efficacy and safety of oral corticosteroids and olfactory training in the management of COVID-19-related loss of smell. *Eur Arch Otorhinolaryngol*. Aug 2021;278(8):3113-3117. doi:10.1007/s00405-020-06520-8

717. Yuan F, Huang T, Wei Y, Wu D. Steroids and Olfactory Training for Postviral Olfactory Dysfunction: A Systematic Review. *Front Neurosci*. 2021;15:708510. doi:10.3389/fnins.2021.708510

718. Vaira LA, Hopkins C, Sandison A, et al. Olfactory epithelium histopathological findings in long-term coronavirus disease 2019 related anosmia. *J Laryngol Otol*. Dec 2020;134(12):1123-1127. doi:10.1017/S0022215120002455

719. Schriever VA, Merkonidis C, Gupta N, Hummel C, Hummel T. Treatment of smell loss with systemic methylprednisolone. *Rhinology*. Sep 2012;50(3):284-9. doi:10.4193/Rhino.11.207

720. Genetzaki S, Tsakiropoulou E, Nikolaidis V, Markou K, Konstantinidis I. Postinfectious Olfactory Dysfunction: Oral Steroids and Olfactory Training versus Olfactory Training Alone: Is There any Benefit from Steroids? *ORL J Otorhinolaryngol Relat Spec*. 2021;83(6):387-394. doi:10.1159/000516316

721. Huart C, Philpott CM, Altundag A, et al. Systemic corticosteroids in coronavirus disease 2019 (COVID-19)-related smell dysfunction: an international view. *Int Forum Allergy Rhinol*. Jul 2021;11(7):1041-1046. doi:10.1002/alr.22788

722. Samuel S, Nguyen T, Choi HA. Pharmacologic Characteristics of Corticosteroids. *J Neurocrit Care*. 12 2017;10(2):53-59. doi:10.18700/jnc.170035

723. Abdelalim AA, Mohamady AA, Elsayed RA, Elawady MA, Ghallab AF. Corticosteroid nasal spray for recovery of smell sensation in COVID-19 patients: A randomized controlled trial. *Am J Otolaryngol*. Mar-Apr 2021;42(2):102884. doi:10.1016/j.amjoto.2020.102884

724. Kasiri H, Rouhani N, Salehifar E, Ghazaeian M, Fallah S. Mometasone furoate nasal spray in the treatment of patients with COVID-19 olfactory dysfunction: A

randomized, double blind clinical trial. *Int Immunopharmacol*. Sep 2021;98:107871. doi:10.1016/j.intimp.2021.107871

725. Rashid RA, Zgair A, Al-Ani RM. Effect of nasal corticosteroid in the treatment of anosmia due to COVID-19: A randomised double-blind placebo-controlled study. *Am J Otolaryngol*. Sep-Oct 2021;42(5):103033. doi:10.1016/j.amjoto.2021.103033
726. Fukazawa K. A local steroid injection method for olfactory loss due to upper respiratory infection. *Chem Senses*. Jan 2005;30 Suppl 1:i212-3. doi:10.1093/chemse/bjh189
727. Boscolo-Rizzo P, Hummel T, Spinato G, et al. Olfactory and Gustatory Function 3 Years After Mild COVID-19-A Cohort Psychophysical Study. *JAMA Otolaryngol Head Neck Surg*. Jan 1 2024;150(1):79-81. doi:10.1001/jamaoto.2023.3603
728. Fyrmpas G, Tsalighopoulos M, Constantinidis J. Lateralized olfactory difference in patients with a nasal septal deviation before and after septoplasty*. *Hippokratia*. Apr 2012;16(2):166-9.
729. Elbistanli MS, Kocak HE, Celik M, et al. Significance of Medial Osteotomy on the Olfactory Function in Patients Who Underwent Septorhinoplasty. *J Craniofac Surg*. Mar/Apr 2019;30(2):e106-e109. doi:10.1097/SCS.0000000000004953
730. Shemshadi H, Azimian M, Onsori MA, Azizabadi Farahani M. Olfactory function following open rhinoplasty: A 6-month follow-up study. *BMC Ear Nose Throat Disord*. Oct 3 2008;8:6. doi:10.1186/1472-6815-8-6
731. Stevens CN, Stevens MH. Quantitative effects of nasal surgery on olfaction. *Am J Otolaryngol*. Jul-Aug 1985;6(4):264-7. doi:10.1016/s0196-0709(85)80053-3
732. Pendolino AL, Randhawa P, Unadkat S, Andrews PJ. Septoplasty for nasal obstruction. *Lancet*. Feb 15 2020;395(10223):493. doi:10.1016/S0140-6736(19)33013-2
733. Sousa FA, Santos M, Correia JT, Pinto AN, Meireles L, Ferreira M. Septorhinoplasty and the Late Impact on Olfactory Function: A Review and Meta-analysis. *Facial Plast Surg*. Feb 2023;39(1):69-76. doi:10.1055/a-1979-8636

734. O'Byrne L, Webster KE, MacKeith S, Philpott C, Hopkins C, Burton MJ. Interventions for the treatment of persistent post-COVID-19 olfactory dysfunction. *Cochrane Database Syst Rev*. Sep 5 2022;9(9):CD013876. doi:10.1002/14651858.CD013876.pub3

735. Stewart MG, Witsell DL, Smith TL, Weaver EM, Yueh B, Hannley MT. Development and validation of the Nasal Obstruction Symptom Evaluation (NOSE) scale. *Otolaryngol Head Neck Surg*. Feb 2004;130(2):157-63. doi:10.1016/j.otohns.2003.09.016

736. Straszek SP, Schlunssen 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*. Mar 2007;45(1):36-9.

737. Bowling A, Bond M, Jenkinson C, Lamping DL. Short Form 36 (SF-36) Health Survey questionnaire: which normative data should be used? Comparisons between the norms provided by the Omnibus Survey in Britain, the Health Survey for England and the Oxford Healthy Life Survey. *J Public Health Med*. Sep 1999;21(3):255-70. doi:10.1093/pubmed/21.3.255

738. Shastri K, Gao Y, Davis SJ, et al. Normative Values of the Nasal Obstruction Symptom Evaluation Scale. *Facial Plast Surg Aesthet Med*. Jan-Feb 2023;25(1):35-39. doi:10.1089/fpsam.2021.0303

739. Hornung DE, Leopold DA. Relationship between uninasal anatomy and uninasal olfactory ability. *Arch Otolaryngol Head Neck Surg*. Jan 1999;125(1):53-8. doi:10.1001/archotol.125.1.53

740. Hedner M, Larsson M, Arnold N, Zucco GM, Hummel T. Cognitive factors in odor detection, odor discrimination, and odor identification tasks. *J Clin Exp Neuropsychol*. Dec 2010;32(10):1062-7. doi:10.1080/13803391003683070

741. Unadkat SN, Pendolino AL, Auer D, et al. The Evidence Base for the Benefits of Functional Septorhinoplasty and its Future Post COVID-19. *Facial Plast Surg*. Oct 2021;37(5):625-631. doi:10.1055/s-0041-1725162

742. Hudson R, Distel H. Induced peripheral sensitivity in the developing vertebrate olfactory system. *Ann N Y Acad Sci*. Nov 30 1998;855:109-15. doi:10.1111/j.1749-6632.1998.tb10552.x

743. Youngentob SL, Kent PF. Enhancement of odorant-induced mucosal activity patterns in rats trained on an odorant identification task. *Brain Res*. Jan 23 1995;670(1):82-8. doi:10.1016/0006-8993(94)01275-m

744. Wang HW, Wysocki CJ, Gold GH. Induction of olfactory receptor sensitivity in mice. *Science*. May 14 1993;260(5110):998-1000. doi:10.1126/science.8493539

745. Wang L, Chen L, Jacob T. Evidence for peripheral plasticity in human odour response. *J Physiol*. Jan 1 2004;554(Pt 1):236-44. doi:10.1113/jphysiol.2003.054726

746. Livermore A, Laing DG. Influence of training and experience on the perception of multicomponent odor mixtures. *J Exp Psychol Hum Percept Perform*. Apr 1996;22(2):267-77. doi:10.1037//0096-1523.22.2.267

747. Foerster-Ruhrmann U, Jurkov M, Szczepek AJ, Bergmann KC, Fluhr JW, Olze H. Biologics Reduce Symptoms of Alcohol Intolerance Better than Aspirin Desensitization in Patients with N-ERD and Nasal Polyps. *Biomedicines*. May 7 2024;12(5)doi:10.3390/biomedicines12051025

748. Derendorf H, Nave R, Drollmann A, Cerasoli F, Wurst W. Relevance of pharmacokinetics and pharmacodynamics of inhaled corticosteroids to asthma. *Eur Respir J*. Nov 2006;28(5):1042-50. doi:10.1183/09031936.00074905

749. Raissy HH, Kelly HW, Harkins M, Szefler SJ. Inhaled corticosteroids in lung diseases. *Am J Respir Crit Care Med*. Apr 15 2013;187(8):798-803. doi:10.1164/rccm.201210-1853PP

750. Barnes PJ, Adcock IM. How do corticosteroids work in asthma? *Ann Intern Med*. Sep 2 2003;139(5 Pt 1):359-70. doi:10.7326/0003-4819-139-5_part_1-200309020-00012

751. Ericson-Neilsen W, Kaye AD. Steroids: pharmacology, complications, and practice delivery issues. *Ochsner J*. Summer 2014;14(2):203-7.