



## Comparative study of the factors affecting the Microbiota presence in the human nasal cavity after Covid-19 influence

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This study presents a comprehensive comparative analysis of the factors affecting the microbiota presence in the human nasal cavity, particularly post-COVID-19. Our research delves into the multifaceted interactions between environmental exposures, host genetic makeup, medical interventions, and lifestyle choices, such as smoking, in shaping the nasal microbial ecosystem. Utilizing advanced sequencing technologies like Next-Generation Sequencing (NGS), Illumina sequencing, and RT-PCR, we have identified significant changes in the nasal microbiota composition due to various factors, including COVID-19. We observed that post-COVID-19, there is an increased prevalence of *Staphylococcus* species and alterations in other bacterial taxa, highlighting the potential implications of these changes for respiratory health and disease pathogenesis. Our study also explores the age-related transformations in the nasal microbiota and its implications for respiratory and neurodegenerative disorders. Additionally, we investigate the impact of high altitude and its associated environmental factors on nasal microbiota composition. Our findings offer crucial insights into the complex dynamics of the nasal microbiota and its interaction with various factors, paving the way for the development of targeted therapeutic interventions. This research underscores the importance of further exploring the nasal microbiota's role in health and disease, with an aim to harness this knowledge for improved clinical outcomes.

**key words:** microbiota, Actino bacteria, Bacteroidetes, human nasal cavity, Covid-19

### INTRODUCTION

The Nasal is an important organ in the body (K, 2020), and one of the basic organs in the respiratory system. So, making sure that the nasal cavity is clear of any pathogenic bacteria which will cause hardness of breathing (Bhatta et al. 2018, Frank et al. 2010), or inhaling some bacteria in the air can cause diseases if they are found in any other site of the body.

*Staphylococcus aureus* (*S. aureus*), *Staphylococcus epidermidis* (*S. epidermidis*),  $\alpha$ - and  $\gamma$ -streptococci, can cause sinuses (EK et al. 2009), and knowing which bacteria can be found in the nasal cavity will introduce a new way of treating these microorganisms or any other nasal disease (Chen et al. 2019). On the other hand, knowing the normal flora in the human nasal cavity will help to get over any pathogenic and which treatment or medication can be used. The microbiota found in the

normal human nasal cavity commonly are phyla Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria (Kumpitsch et al. 2019). Living in mountains or coastal areas can be a reason to have different strains of bacteria as well as having gender differences, seasonal diseases, and COVID-19 in consideration (Chen et al. 2019, Kumpitsch et al. 2019). This review aims to compare the types of bacteria in the nasal cavity that can be found in different atmospheres. In contrast, identifying the most common bacteria in both locations and how these bacteria can resist in different atmospheres.

### Literature Review

Air pollution has been a major health concern for decades. Motor exhaust emissions are a complex mixture of gases and particulate matter (Kumpitsch et al.

2019). It also said that an improved understanding of competitive bacterial colonization will increase our ability to define predispositions to pathogen carriage at these sites and the subsequent risk of infection (Hardy and Merrel, 2021). Another study discussed that being a source of infection, nasal colonization by bacterial pathobionts is a reservoir for transmission (Brüning et al. 2020). Humans body hosts diverse microbiota (Alharbi, 2020) Distribution of microbial communities between humans and the environment, which can occur through direct surface or airborne release, and transmit pathogens to other individuals and indoor surfaces (Mariani et al. 2020). The human upper respiratory tract (URT) offers a variety of niches for microbial colonization (Gupta, 2022). Human microbiomes are communities of microorganisms that live in symbiotic relationships in human microhabitats (Kumpitsch et al. 2019). However, another article said that the colonization of people with *S. aureus* may be a basic prerequisite of ensuing clinical contamination (Frank et al. 2010). Competition among microorganisms is widespread in habitats that are unfavorable to microbial growth, such as the nasal cavity (Brüning et al. 2020). Numerous investigations contend that aging-related decreases in *S. pneumoniae* loads in the nasal cavity may open up a space for *S. aureus* colonization (EK et al. 2009). The Navier-Stokes Equations are non-linear partial differential equations that explain how airflow and geometry interact (Mariani et al. 2020). An important research goal connected to community health is the investigation of antibiotic-resistant microorganisms among healthy people and patients (Gupta et al. 2022).

### Factors Influencing Nasal Microbiota

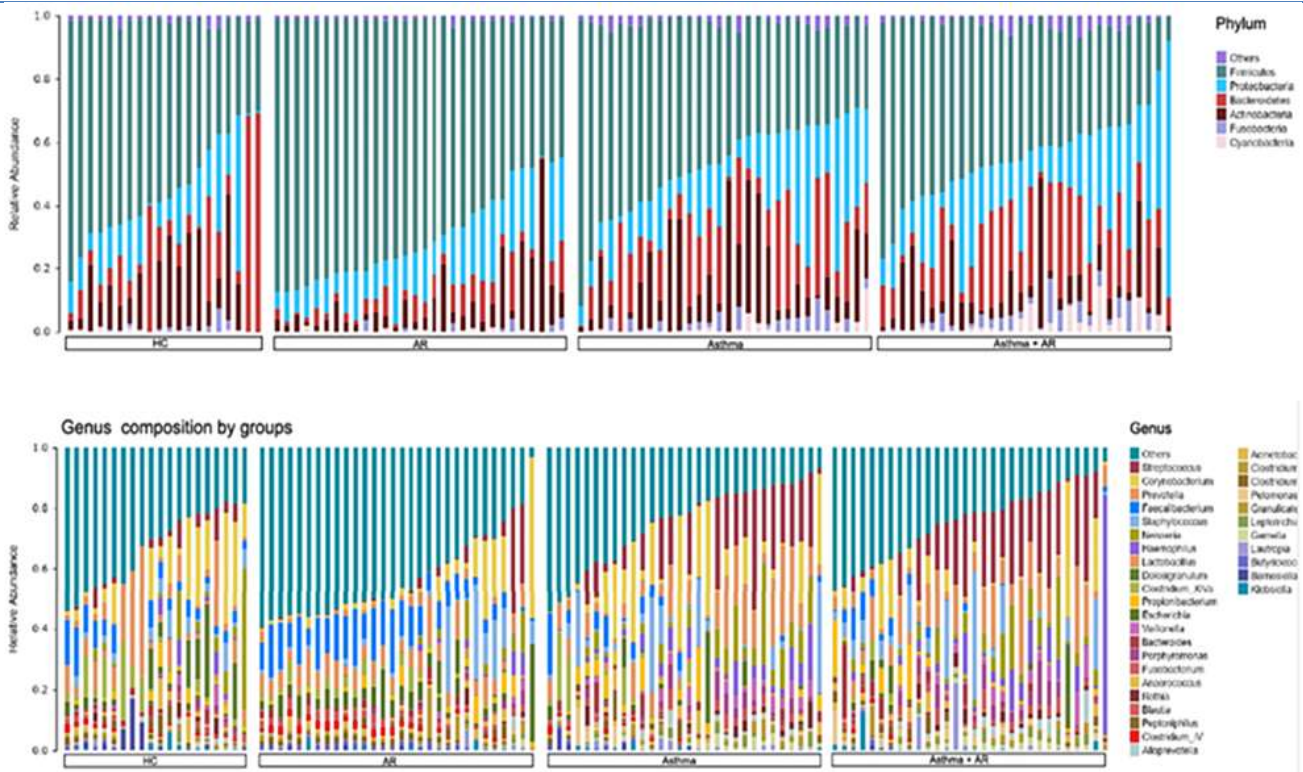
The nasal microbiota represents a complex microbial ecosystem, the composition of which is modulated by an intricate interplay of environmental, host-specific, and medical variables. Environmental perturbations, such as exposure to particulate matter, have been empirically substantiated to induce oxidative stress pathways, thereby engendering significant shifts in microbial diversity within the nasal biogeography (Alharbi, 2020, Mariani et al. 2020, Gupta et al. 2022). Concurrently, abiotic factors like ambient humidity and temperature serve as modulators of microbial community structure, selectively enriching for specific bacterial genera and inducing compositional flux (Gisler et al. 2021, Chen et al. 2019). On the host-specific front, genetic polymorphisms, particularly single nucleotide polymorphisms (SNPs), have been implicated through genome-wide association studies to correlate with the prevalence of specific bacterial taxa within the nasal microbiota (Irizar et al. 2022). Additionally, endocrinological variations associated with the host's

age and sex exert a modulatory effect on the microbial community structure [K, 2020, Bomar et al. 2018]. From a medical perspective, pharmacological interventions such as antibiotic administration manifest as potent disruptors of microbial homeostasis, precipitating a marked diminution in microbial diversity and facilitating the overgrowth of antibiotic-resistant phenotypes (Mackenzie et al. 2017). Furthermore, the host's immunological status serves as a determinant of microbial diversity; immunocompromised states are often concomitant with a reduction in microbial diversity, thereby influencing respiratory health outcomes (Kropshofer et al. 2022). These multifactorial interactions elucidate the complexity inherent in the nasal microbiota and underscore its pivotal role in shaping both individual and population-level health outcomes.

### Nasal Microbiome and Chronic Respiratory Diseases

The nasal microbiome serves as a critical determinant in the pathogenesis of asthma, a chronic inflammatory disease of the respiratory tract. Empirical studies have demonstrated a correlation between perturbations in the nasal microbiome and poor disease control, particularly in cases of comorbid asthma and allergic rhinitis (AR) (Chen et al. 2022). Furthermore, the nasal microbiome's interaction with host inflammatory pathways can serve as a double-edged sword, either exacerbating or ameliorating the clinical manifestations of asthma (HM and JH, 2021).

Allergic rhinitis, another prevalent chronic inflammatory disease of the respiratory tract, is also significantly influenced by the nasal microbiome. The nasal cavity functions as a major reservoir for opportunistic pathogens, which can disseminate to other sections of the respiratory tract and contribute to the development of conditions such as allergic rhinitis (Pinheiro et al. 2020). The intricate interplay between the nasal microbiome and host inflammatory pathways is pivotal in this context. Dysbiosis in the nasal microbiome can lead to an imbalance in the local microbial ecosystem, thereby affecting respiratory health and disease (Kumpitsch et al., 2019). This complex relationship between the nasal microbiome and host immune responses is an area that warrants further investigation, particularly for its potential role in modulating inflammation (Mees et al. 2008).



**Figure 1: (A) Phylum: Partial least squares discriminant analysis (PLS-DA) representing grouped microbiome profile among AR, asthma, combined asthma+AR and healthy controls. (B) Genus: Bar plots of the phylum and genus taxonomic levels in AR, asthma, combined asthma+AR and healthy controls. P < 0.05 was considered as statistically significant, \*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001 (Chen et al. 2022).**

**Nasal Microbiota and Ageing**

**Age-Related Transformations**

The composition of the nasal microbiota undergoes a series of complex, age-related transformations. These transformations have been shown to be associated with a decrease in microbiota diversity, particularly in the abundance of phylum Actinobacteria and genus Corynebacterium in aged patients (Chen et al. 2019) These shifts can have profound implications for an individual's susceptibility to a diverse array of diseases and conditions, including but not limited to, respiratory and neurodegenerative disorders (Philip et al. 2019).

**Implications for Respiratory and Neurodegenerative Disorders**

The age-associated shifts in the nasal microbiome have profound implications for both respiratory and neurodegenerative disorders. In the context of respiratory health, older individuals exhibit distinct bacterial compositions in their nasal microbiota compared to younger patients with chronic rhinosinusitis(Thangaleela et al. 2023). Such variations could potentially modulate the host immune response, playing a pivotal role in the nasal bacterial microbiota dynamics of patients with respiratory ailments (Chen et

al. 2023). Concurrently, the nasal microbiota is intricately linked with the progression of neurodegenerative diseases (NDs) during aging, including Parkinson's disease (PD), Alzheimer's disease (AD), and multiple sclerosis (MS) (Chen et al, 2023). Notably, dysbiosis in the nasal microbiota can precipitate olfactory dysfunctions, which frequently manifest as early indicators of NDs (Thangaleela et al. 2023).

**Therapeutic Interventions: Age-Associated Shifts and Gut-Nasal Microbiota**

Deciphering the age-associated shifts in the nasal microbiome is pivotal for the development of targeted therapeutic interventions. The intricate crosstalk between the gut and nasal microbiota serves as a cornerstone in this context (Chen et al. 2023). This bidirectional communication is not merely confined to the microbial communities but extends to influence various physiological systems. Specifically, the mucosal regions of both the gut and nasal cavities are intricately connected to olfactory functions, thereby playing a critical role in immune regulation and the homeostasis of the central nervous system (Thangaleela et al. 2023). Understanding this crosstalk is essential for the development of targeted therapies, particularly for age-associated diseases. For instance, modulating the gut microbiota could potentially have downstream effects on



the nasal microbiota (Chen et al. 2022), thereby affecting respiratory health. This opens up avenues for the use of prebiotics, probiotics, or even fecal microbiota transplantation as potential therapeutic strategies for managing age-associated shifts in the nasal microbiota and their subsequent impact on respiratory and neurological health (Thangaleela et al. 2023).

## Nasal Microbiota and Smoking

### Impact on Microbial Composition

Tobacco smoking has been shown to exert a pronounced impact on the composition and diversity of the nasal microbiota. Smokers exhibit a distinct microbial composition when compared to non-smokers, characterized by significant differences in the relative abundance of diverse taxa (Huang et al. 2020). This divergence in microbial composition is not uniformly distributed across the nasal cavity, with some taxa being predominantly found in either the left or right nasopharynx (Yu et al. 2018).

### Implications Future Directions for Smoking-Induced Nasal Microbiota Alterations

The modulation of the nasal microbiota by smoking represents a complex paradigm with far-reaching implications for respiratory health. Smoking-induced alterations in the airway microbiome have been empirically demonstrated to potentiate increased susceptibility to a spectrum of respiratory diseases, most notably chronic obstructive pulmonary disease (COPD) (Pfeiffer et al. 2023, Huang et al. 2020). While the mechanistic underpinnings governing these alterations remain an active area of investigation, preliminary hypotheses postulate that smoking-induced perturbations in the nasal microbiota may serve as contributory factors to a range of pathologies, including periodontitis, asthma, and COPD (Huang et al. 2020).

Given the inherent complexity and heterogeneity of the nasal microbiota, the necessity for large-scale, longitudinal studies becomes paramount. Such studies aim to elucidate the nuanced, smoking-induced shifts in microbial community structure and function (Yu et al. 2018). This is particularly salient for the development of targeted therapeutic interventions aimed at ameliorating conditions that are exacerbated by smoking-induced alterations in the nasal microbiota.

## Nasal Microbiota Composition

### Composition in healthy adults

The nasal microbiota of healthy individuals is generally composed of bacteria of the genera *Staphylococcus*, *Streptococcus*, *Bifidobacterium*, *Dolosigranulum*, *Corynebacterium*, *Propionibacterium*, and *Moraxella* (Bassis et al. 2015). A study was done where swabs of

the nasal microbiome were taken and sequenced to determine different species and their composition. *Staphylococcus* composition ranges from 2.2%-50 %, *Corynebacterium* composition ranged from 1.5%-62.8%, *Propionibacterium* composition ranged from 0.4%-42.4%. *Streptococcus* is not very abundant in the nasal cavity, but is more prevalent in the oral cavity (Bassis et al. 2015).

### Composition in Viral Respiratory Tract Infections and Lifespan Variations in Nasal Microbiota

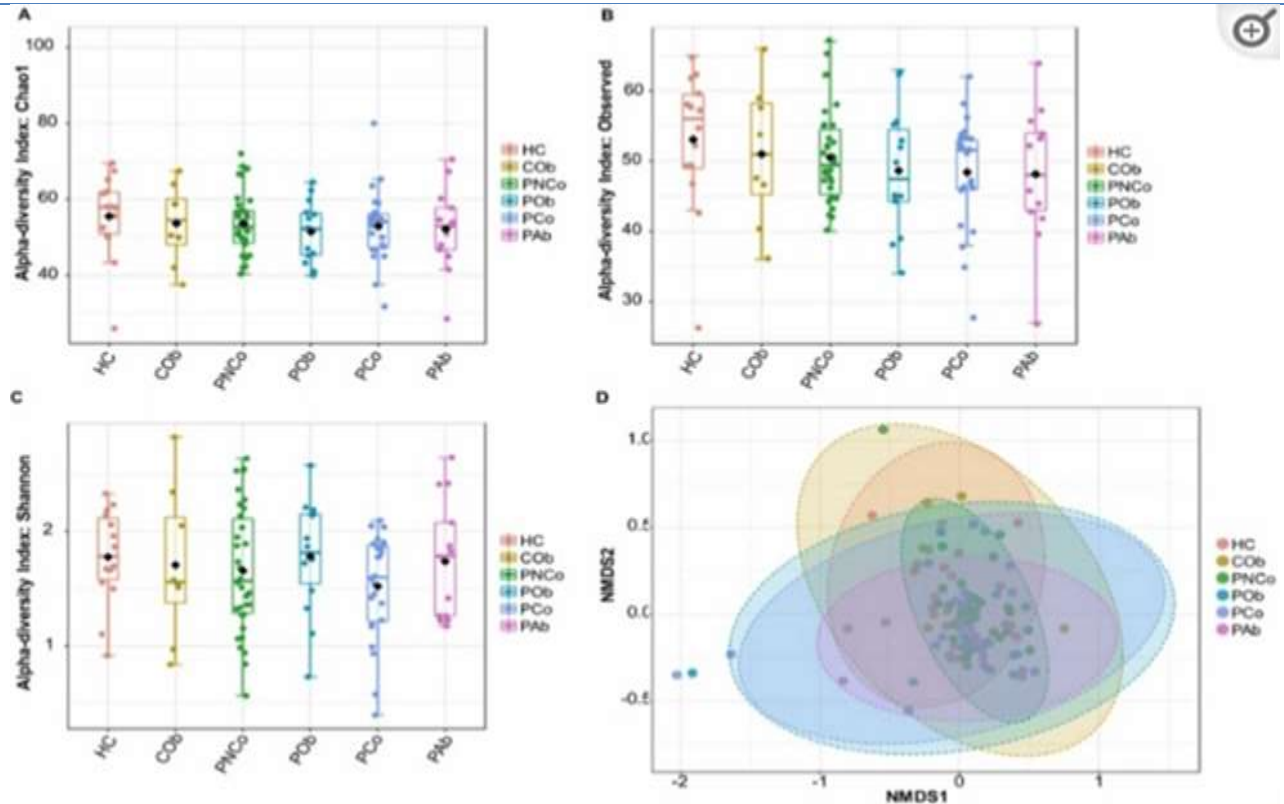
In the context of viral respiratory tract infections, including but not limited to influenza A & B, the nasal microbiota manifests a consistent dominance of three primary bacterial phyla: Proteobacteria, Firmicutes (which notably encompasses the genus *Streptococcus*), and Actinobacteria [Edouard et al. 2018]. Furthermore, eight key respiratory pathogens, such as *S. aureus* and *Haemophilus influenzae*, were identified in patients exhibiting symptomatic respiratory infections. Interestingly, asymptomatic individuals displayed a nasal microbiome composition akin to that of healthy individuals, suggesting a nuanced interplay between microbial communities and symptomatic expression.

When examining the nasal microbiota across the human lifespan, distinct patterns emerge. In pediatric populations, the nasal microbiota undergoes a dynamic evolutionary trajectory, characterized by a gradual decline in pathogenic strains like *S. aureus* and *H. influenzae* (Verhagen et al. 2013). Early-life factors, such as breastfeeding during infancy, have been empirically demonstrated to offer significant protection against respiratory tract infections, thereby influencing the composition of the developing nasal microbiota (Biesbroek et al. 2014, Perez et al. 2023, Ortega-Peña et al. 2023). In contrast, a study involving geriatric populations in Baltimore revealed that the most abundant bacterial phyla in individuals with an average age of 64.4 years closely resembled the microbial community structure observed in younger adults (Mackenzie et al. 2017, Jochems et al. 2022, Yasir et al. 2023). This observation suggests a relative stability in the nasal microbiota across the adult lifespan, albeit with potential variations that merit further scientific scrutiny.

## COVID-19 effects on bacteria in Nasal Microbiota

### General Diversity changes in the Nasal Microbiota and COVID-19

Nasal Microbiota Diversity changes due to different factors like COVID-19 and obesity; figure 2 explains the relationship between them all.



**Figure 2: Alpha and beta diversity analysis of nasopharyngeal bacterial community from the control and COVID-19 patients groups. (A) Chao1 estimate of richness, (B) observed species, (C) Shannon index, and (D) beta diversity analysis using Non-metric Multidimensional Scaling (NMDS). HC, healthy control group; COb, control with obesity; PNCo, COVID-19 patients with no comorbidities; POB, COVID-19 patients with obesity only; PCo, COVID-19 patients with other comorbidities; PAb, COVID-19 patients with antibiotic use. (Yasir et al. 2023)**

**Comprehensive Insights into Nasal Microbiota and COVID-19**

The nasal microbiota landscape undergoes significant alterations in the context of COVID-19, with a marked increase in the prevalence of *Staphylococcus* species compared to healthy individuals (Rueca et al. 2022, Rocafort et al. 2023, Silva-Santana et al. 2022). Specifically, patients with COVID-19 who also have *Staphylococcus aureus* bacteremia exhibit a substantially higher incidence of sepsis, with rates reaching 61.5% as opposed to a mere 7.8% in those without the bacterial infection, suggesting a synergistic exacerbation of disease severity (S. Alibi et al. 2018). In contrast, *Staphylococcus epidermidis*, another member of the *Staphylococcus* genus, has been identified as a potential therapeutic agent.

This bacterium has been shown to inhibit the colonization of other pathogens and could serve as a probiotic to mitigate the inflammatory effects of COVID-19 (S. Alibi et al. 2018).

Furthermore, the role of *Streptococcus pneumoniae* in modulating the immune response to SARS-CoV-2 has been explored. Studies indicate that this bacterium can

negatively impact memory T and B cells specific to SARS-CoV-2 antigens, thereby potentially compromising the host's ability to mount an effective immune response against the virus. These findings collectively underscore the intricate relationships between various bacterial taxa within the nasal microbiota and their potential implications for COVID-19 pathogenesis and treatment (S. Alibi et al. 2018, Nardelli et al. 2023, Kim et al. 2023).

**Comprehensive Insights into Other Bacterial Taxa and COVID-19**

The role of *Corynebacterium* in the nasal microbiota is particularly complex in the context of COVID-19. While *Corynebacterium* is generally known to increase susceptibility to a broad spectrum of human infections, it also presents a unique challenge due to the emergence of antibiotic-resistant strains (Hanada et al. 2019, PalmieriBeniamino, and Maria Vadalà 2022, Kim yeon et al. 2023). Intriguingly, a specific study has shown that the abundance of *Corynebacterium* is significantly reduced in COVID-19 patients compared to healthy controls, suggesting a potential alteration in microbial ecology induced by the virus (Perez et al. 2023).

*Propionibacterium*, another predominant bacterium

in the nasal microbiota of healthy individuals, has been shown to increase in the presence of Human rhinovirus (Ortega-Peña et al. 2023, Jochems et al. 2022). Notably, *Propionibacterium acnes* has been implicated in enhancing innate immunity, which could potentially be leveraged for therapeutic interventions against COVID-19 (Yasir et al. 2023). In contrast, *Moraxella* levels have been observed to plummet by 78.1% in patients post-contraction of COVID-19, indicating a significant disruption in the nasal microbiota composition and its potential implications for disease progression and treatment (Rueca 2022).

## NGS and its application in the Nasal microbiome

### Importance of NGS

Next-Generation Sequencing (NGS) has revolutionized the field of microbiology, enabling researchers to delve deeper into the vast and diverse world of bacterial species residing in the human body. This high-throughput technology allows for the rapid sequencing of millions of DNA/RNA fragments, providing a comprehensive view of the microbial communities present in various human habitats. As well as revealing the composition of the nasal microbiome, which allows us to analyze changes of it due to certain factors. In our case, NGS represents an indispensable tool for taxonomic classification of microbiomes (Gupta et al. 2020, Alharthi et al. 2023).

### Illumina (Molecular Detecting of Microbiota Diversity)

The Illumina sequencing mechanism is only able to sequence short reads (35-300 bases per read). However, the technique Illumina sequencing uses to overcome this obstacle is to attach adapters to the DNA/RNA fragments which fuse them to a glass slide. Then, a process called bridge amplification occurs, where the attached fragments are amplified. After bridge amplification, fluorescent imaging is used to sequence the actual fragment. The sequences of the fragments are put together later in a bioinformatic program (Slatko et al. 2019). Microbiome profiling can be achieved with Illumina by sequencing 16S rRNA regions of the different bacteria and classifying compared to known sequences from databases (Gloor et al. 2011).

### RT-PCR

Real-time Polymerase Chain Reaction (RT-PCR), also known as qPCR, works as a DNA/RNA amplification (similar to Illumina) in which you can either quantify the DNA or sequence it. Our interest lies with the second application of RT-PCR, as we need to tell the specific kind of 16S rRNA to identify the bacteria in the microbiome. Heat is applied which denatures the two strands and allows for thermos-resistant polymerase (Taq polymerase usually) to operate on the strand and

add nucleotides. Sequence-specific fluorescent probes are added which bind to very specific oligonucleotide sequences. The certain fluorescence that comes from the probes give us the sequence of the DNA/RNA (Ghannam and Varacallo, 2022, Shawn E. and E. Boone, 2020, Altundag et al. 2013).

### High Altitude Effects on the Nasal Microbiome

It is known that high-altitude trips cause nasal congestion, impaired nasal mucociliary transport rate, and increased nasal resistance due to decreased partial oxygen pressure and dry air. It is also known that olfactory perception is affected by barometric pressure and humidity (C. Cingi et al. 2010).

Headache, hearing disturbances, vestibular disturbances, epistaxis, sleep apnea, coughing, respiratory tract infections, and nasal obstruction are main ear, nose, and throat complaints of individuals traveling to high altitudes (Biesbroek et al. 2014, C. Cingi et al. 2010). Another symptom that climbers experience is epistaxis. This results when the extremely cold air at high altitude dries the nasal mucosa severely, leading to rupture of small vessels (G. Philip et al. 1993).

Exposure to cold dry air induces rhinorrhea and other nasal symptoms in many persons as well as increased nasal secretions (Cingi et al. 2011, Pan et al. 2022). In the nasal cavity, high altitude can cause nasal congestion, impaired nasal mucociliary transport rate, and increased nasal resistance due to decreased partial oxygen pressure and dry air. This can potentially affect the nasal microbiome. (Pan et al. 2022, Alharthi, et al. 2023)

High altitude can cause changes in both the gut and nasal microbiomes. In the gut, high altitude has been found to cause a large compositional shift in the microbiota. This is mainly driven by changes in the bacterial families of *Prevotellaceae*, *Porphyromonadaceae*, and *Streptococcaceae*<sup>1</sup>. The gut microbiome is significantly correlated with metabolic abnormalities of short-chain fatty acids and bile acids in feces. (Cingi et al. 2011)

## CONCLUSIONS

This review paper has successfully unveiled insightful findings regarding the plethora of diverse factors that play pivotal roles in influencing the composition and diversity of the nasal microbiota, with a focus on the notable changes that occur post-COVID-19 infection. We have demonstrated that elements such as environmental exposure, genetic makeup, the aging process, and smoking habits are integral in shaping the microbial ecosystem within the nasal cavity, thereby affecting a range of health outcomes, including respiratory and neurodegenerative diseases. The application of advanced sequencing technologies, such as NGS, Illumina sequencing, and RT-PCR, has been instrumental in deepening our understanding of the

intricate relationships and dynamics within the nasal microbiota. These technologies have allowed us to identify and analyze potential therapeutic targets and strategies, paving the way for innovative interventions. The valuable insights garnered from this review underscore the paramount importance of conducting further research in this interesting field. There is a pressing need to unravel the complexities and nuances of the nasal microbiota to develop targeted and effective therapies that can leverage the potential of this microbial ecosystem for the promotion of optimal health and the prevention of diseases. High altitude, and such things affect the microbial composition of our nose. Our findings lay a solid foundation for future research endeavors aimed at harnessing the knowledge of the nasal microbiota for the development of personalized medicine approaches, with the ultimate goal of improving health outcomes and well-being across diverse and varied populations.

### Supplementary Materials

The supplementary material/supporting information for this article can be found online and downloaded at: <https://www.isisn.org/article/10.3390/antiox12081524/s1>.

### Author Contributions

All authors contributed equally to this study. Each author was involved in designing the experiments, conducting research, analyzing data, and writing and reviewing the manuscript. Their collaborative efforts have culminated in this comprehensive work. All authors have read and approved the final version of the manuscript.

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### Data Availability Statement

All of the data supporting the findings of this study are included within the article and its supplementary materials.

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### Conflict of Interest

The authors declare no conflict of interest in conducting this study.

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