

Characteristics of olfactory dysfunction in patients with long-haul COVID-19*

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Abstract

Background: A subset of individuals suffering from Coronavirus Disease 2019 (COVID-19) will experience ongoing symptoms that last longer than three months (i.e., long-haul COVID). This includes olfactory dysfunction (OD), which is currently estimated to occur in 1-63.5% of patients at one-year post-infection. However, OD in individuals with long-haul COVID-19 is poorly understood, and there is little information regarding how initial SARS-CoV-2 variants correlate with long-haul symptoms. In this study, we investigated the prevalence and severity of OD in patients with long-haul COVID-19 and investigated how OD severity varied with SARS-CoV-2 variants.

Methods: Patients were recruited from the University of North Carolina-Chapel Hill COVID Recovery Clinic. Each patient completed the University of Pennsylvania Smell Identification Test (UPSIT). The dominant strain at the time of infection was determined using the date of COVID-19 diagnosis, and Centers for Disease Control and Prevention, World Health Organization, and North Carolina Department of Health and Human Services databases.

Results: Nearly 85% of patients with long-haul COVID-19 reported some degree of OD, which persisted in some patients for two or more years from the date of the initial infection. There was no association between the time since COVID-19 infection and severity of OD. No difference was detected between OD in patients with long-haul COVID-19 based on the dominant variant at the time of infection.

Conclusion: A vast majority of patients with long-haul COVID-19 had some degree of ongoing olfactory complications, although the severity of symptoms was not dependent on the dominant SARS-CoV-2 variant at the time of infection.

Key words: Long-haul COVID-19, olfactory dysfunction, variants, COVID-19 symptoms, smell loss

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in 2019 and subsequently developed into a global public-health emergency ⁽¹⁾. Patients with acute COVID-19 experience symptoms ranging from asymptomatic infection and mild upper respiratory tract illness to severe viral pneumonia

with respiratory failure requiring hospitalization and ventilation, which, in some cases, results in death ⁽²⁾. In addition to respiratory symptoms, there have been many reports of acute disease presenting with gastrointestinal symptoms (diarrhea, anorexia, nausea, vomiting) ⁽³⁾, central nervous system symptoms (headache, confusion, brain fog) ⁽⁴⁾, and chemosensory symptoms (alterations or loss of smell and taste) ^(5,6). Early in the pandemic,

olfactory dysfunction (OD) was identified as a strong indicator of acute COVID-19 infection and was prevalent in greater than 80% of patients ^(7,8). Although most patients fully recover from COVID-19 within weeks to months after their initial diagnosis, some patients experience persistent, ongoing symptoms. Long-haul COVID-19, also referred to as post-acute sequelae of SARS-CoV-2 (PASC), is characterized by ongoing symptoms after SARS-CoV-2 infection that persist beyond three months ^(9,10). Long-haul COVID-19 can cause significant disability, with patients frequently reporting fatigue, cognitive impairments, dyspnea, and headache lasting months and even years after acute infection ⁽¹¹⁾. One systematic review reported that more than 50% of COVID-19 survivors experience at least one COVID-19 symptom that lasts for months ⁽¹²⁾. It is unclear if these symptoms eventually resolve or if they have lasting, permanent consequences with the possible emergence of a new chronic disease. Moreover, it is poorly understood why some patients develop long-term sequelae while others do not. OD is a well-established symptom for acute COVID-19 infection, and accumulating evidence suggests it is a persistent concern in patients with long-haul COVID-19 as well. Although the exact incidence is not known, current estimates report anywhere between 1-63.5% of patients experience ongoing OD up to one year following acute infection ⁽¹³⁻¹⁸⁾. More recent studies have reported that between 40-80% of patients subjectively reported full or partial olfactory recovery two years after the initial infection, however, this was not confirmed with objective smell testing ⁽¹⁹⁻²¹⁾. Long-term and ongoing follow up is imperative, since olfactory recovery may spontaneously occur in select patients ⁽²¹⁾. Additionally, psychophysical testing is important to consider because patient reports of olfaction function frequently are discordant with psychophysical testing ^(21,22). Confirming OD with objective testing is likely to give a more accurate representation of OD incidence among this patient population and may help to identify patients that are unaware that they may benefit from treatment. To our knowledge, this study is the one of the very few studies ⁽²³⁾ to report on objective olfactory data in Long-haul COVID-19 patients that were diagnosed with COVID-19 greater than two years ago. In addition, the COVID-19 pandemic is characterized by evolving infectious variants of SARS-CoV-2. Previous studies have reported that more recent strains of SARS-CoV-2, such as the Omicron variant, are more transmissible, but cause less severe infection and are less likely to cause OD compared to the earlier variants ^(25,26). However, the differences in OD prevalence and severity between different variants of SARS-CoV-2 are poorly understood. In this study, we investigated the long-term prevalence of OD in patients with long-haul COVID-19 infection, and studied how the various factors that may predispose patients and contribute to these ongoing symptoms.

Table 1. Demographic information and baseline characteristics of the participants in our cohort. The mean age, gender, race, UPSIT scores, smoking status, and subjective olfactory function.

Characteristics	N = 86
Age, mean	50.5
Gender (%)	
Male	26 (30.2%)
Female	60 (69.8%)
Race (%)	
Black	8 (9.3%)
White	69 (80.2%)
Hispanic or Latino	4 (4.7%)
Other/ Unspecified	5 (5.8%)
UPSIT (%)	
Anosmia	10 (11.6%)
Severe hyposmia	6 (7%)
Moderate hyposmia	23 (26.7%)
Mild hyposmia	34 (39.5%)
Normosmia	13 (15.1%)
Smoking Status	
Former Smoker (%)	
Yes	6 (7%)
No	51 (59.3%)
Current Smoker (%)	
Yes	1 (1.2%)
No	60 (69.8%)
Declined to Respond	22 (25.6%)
Do you have smell loss? (%)	
Yes	34 (39.5%)
No	27 (31.4%)
Declined to Response	25 (29.1%)
Time between Initial COVID-19 Diagnosis and Completion of UPSIT (%)	
3 – 6 months	22 (25.6%)
7 – 12 months	21 (24.4%)
13 – 18 months	16 (18.6%)
19 – 24 months	17 (19.8%)
24+ months	10 (11.6%)

Methods

The primary objectives of this study were to 1) investigate the prevalence and severity of OD in patients with long-haul COVID-19 and 2) investigate OD severity based on the dominant SARS-CoV-2 variant at the time of diagnosis.

Study population

Patients with long-haul COVID-19 from the COVID Recovery Cli-

Table 2. Male long-COVID patients. UPSIT mean scores compared to the 50th percentile for that age group based on the UPSIT Manual.

Age range in years	Approximate 50th% score for healthy controls (based on UPSIT manual)	Mean UPSIT scores in long-COVID patients
15-19	37.5	-
20-44	37	31.1
45-49	36	27.5
50-59	35.5	24.2
60-69	34.5	31.5
70-74	29.5	30.3
75-79	33	-
80-84	26	-
>85	23.5	-

nic were included. All patients seen for in-person visits between May 2022 and November 2022 were asked to complete the University of Pennsylvania Smell Identification Test (UPSIT) as part of their intake assessment. All patients seen for in-person visits during the study period were included, regardless of the long-haul COVID-19 symptoms that they were experiencing or for which they were seeking treatment. To be included, adult patients needed to demonstrate a prior positive COVID-19 diagnosis, meet the requirements of long-haul COVID-19 (by experiencing ongoing symptoms lasting more than 3 months) and complete the UPSIT in its entirety. Exclusion criteria included individuals under the age of 18, those who did not have a confirmed COVID-19 test, those who did not meet the requirements for long-haul COVID-19, and those who did not complete the UPSIT in its entirety.

Objective olfactory function testing

The UPSIT is an objective smell test consisting of four 10-page booklets, each page with a different odorant. It is a forced-choice test that participants self-administer by scratching the odor with a pencil to release the odorants, sniffing the scent, and identifying the odor from four multiple-choice options. Scores are classified into five clinical categories of normosmia (≥ 34 for males and ≥ 35 for females), mild hyposmia (30–33 for males and 31–34 for females), moderate hyposmia (26–29 for males and 26–30 for females), severe hyposmia (19–25), and anosmia (≤ 18). The UPSIT has high internal reliability across various populations⁽²⁷⁾. All patients completed the UPSIT between May 2022 and November 2022.

Determination of the major SARS-CoV-2 variant

The date of COVID-19 diagnosis, and Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and

Table 3. Female long-Covid patients. UPSIT mean scores compared to the 50th percentile for that age group based on the UPSIT Manual.

Age range in years	Approximate 50th% score for healthy controls (based on UPSIT manual)	Mean UPSIT scores in long-COVID patients
15-19	37.5	34
20-24	38	30
25-44	37.5	29.9
45-49	37	29
50-54	36.5	30
55-59	37	26.4
60-64	36	30.4
65-69	34.5	28
70-74	32.5	22.3
75-79	32	-
80-84	26	-
>85	23	15

North Carolina Department of Health and Human Services (NCDHHS) databases were used to determine the dominant SARS-CoV-2 strain at the time of infection. Based on these databases, the major variants causing infection in North Carolina were G-strain, Alpha, Delta, and Omicron. G-strain was the major variant of concern from January 2020 to November 2020, the Alpha variant was the major variant of concern from December 2020 to June 2021, the Delta variant was the major variant of concern from July 2021 to October 2021, and the Omicron variant was the major variant of concern from November 2021 to July 2022.

Statistical analysis

Statistical analysis was performed by GraphPad Prism version 9 (GraphPad Software, La Jolla, CA, USA). Descriptive statistics were calculated for demographic data and UPSIT performance. Kruskal-Wallis Test was used to analyze any correlation among SARS-CoV-2 variants and mean UPSIT scores. Multivariate linear regression was performed to assess if COVID-19 strain influenced UPSIT score while controlling for gender and age of the patient.

Results

A total of 86 long-haul COVID-19 patients were included in the study (Table 1). The study population included 60 (69.8%) females (Table 2) and 26 (30.2%) males (Table 3), with the mean age of 50.5 years (range 18-89 and Standard deviation [SD] 13). Based on the time between initial infection and completion of the UPSIT, 22 patients were between 3 to 6 months, 21 patients were between 7 and 12 months, 16 patients were between 13

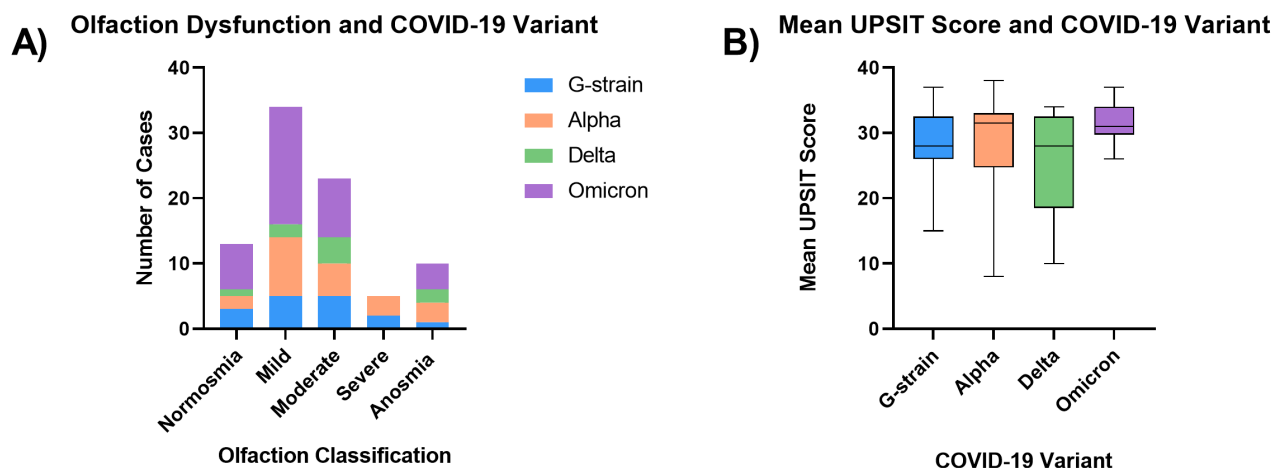


Figure 1. Patients with long-haul COVID-19 exhibited olfactory dysfunction (OD), with no significant difference in mean UPSIT score between SARS-CoV-2 variants. A. Mean UPSIT scores in our cohort of long-haul COVID-19 patients, broken down by SARS-CoV-2 variants: 10 (11.6%) demonstrated anosmia, 6 (7%) demonstrated severe hyposmia, 23 (26.7%) demonstrated moderate hyposmia, 34 (39.5%) demonstrated mild hyposmia, and 12 (15.1%) demonstrated normosmia. B. Mean UPSIT Score among our cohort of patients with long-haul COVID-19. Kruskal-Wallis test was performed to detect differences in olfaction function using UPSIT scores between any of the SARS-CoV-2 variants. $H(3) = 6.346, p = 0.0959$.

and 18 months, 17 patients were between 19 and 24 months, and 10 patients were greater than 24 months from initial COVID-19 diagnosis (Figure 2). All participants were screened for smoking history, with the majority of patients responding that they were neither former nor current smokers. Prior to completing the UPSIT, patients were asked if they were experiencing loss of smell as a consequence of their COVID-19 infection. 40% responded yes, 30% responded no, and 30% declined to respond.

Females were more likely to experience OD compared to males (87.7% vs 80.5%) but did not reach significance. However, both males and females exhibited similar severity of their symptoms, and both exhibited, on average, moderate OD.

Findings also showed that of our long-haul COVID-19 patient cohort, most were > 40 years old (78% > 40 vs 22% ≤ 40) and of our long-haul COVID-19 patient cohort experiencing OD, 79.5% were > 40 vs 20.5% were ≤ 40.

The severity of OD was determined by normative UPSIT scores based on gender and age. The overall prevalence of objective olfactory dysfunction was 84.8%. The mean UPSIT score was 28.36 (95% confidence interval [CI]: 21.2 to 35.54), whereas the normal range in historic controls is 34-38 (27-29). In this cohort of patients, 10 (11.6%) demonstrated anosmia, 6 (7%) demonstrated severe hyposmia, 23 (26.7%) demonstrated moderate hyposmia, 34 (39.5%) demonstrated mild hyposmia, and 13 (15.1%) demonstrated normosmia (Figure 1).

At the time of our analysis, the major SARS-CoV-2 variants causing infection were G-strain, Alpha, Delta, and Omicron. Patients likely infected with the G-strain variant (n=17, 19.8%) exhibited

a mean UPSIT score of 28.65 (95% CI: 23.27 to 34.03). Patients likely infected with Alpha variants (n=22, 25.6%) exhibited a mean UPSIT Score of 28.0 (95% CI: 20.38 to 35.62). Patients likely infected with Delta variants (n=9, 10.5%) exhibited a mean UPSIT Score of 25.78 (95% CI: 17.23 to 34.33). Patients likely infected with Omicron variants (n=38, 44.2%) exhibited a mean UPSIT Score of 29.40 (95% CI: 22.37 to 36.42). Kruskal-Wallis test revealed no statistically significant difference in olfaction function using UPSIT scores among any of the variants $H = 6.346, p = 0.0959$. When controlling for gender and age, there was not a significant correlation.

More than 80% of patients had some degree of ongoing OD after initial infection, ranging from three months, to greater than 24 months since initial infection. However, the prevalence of OD declines over time. At one-year post-infection 44.8% of patients were experiencing OD, and at greater than two years post-infection, nearly 20% still had OD (Figure 2).

Discussion

Long-haul COVID-19 can include the persistence of symptoms, such as fatigue, cognitive impairment, dyspnea, headache, and OD. It is unknown why some patients develop long-haul COVID-19, whereas others have no long-term sequelae following acute infection. Currently there is little data on olfactory loss in patients with COVID-19 that extends up to two years after the initial diagnosis. Two recent studies reported that greater than 80% of patients subjectively reported full or partial olfactory recovery two years after the initial infection, however, this was not confirmed with objective smell testing^(19,20). To our knowledge,

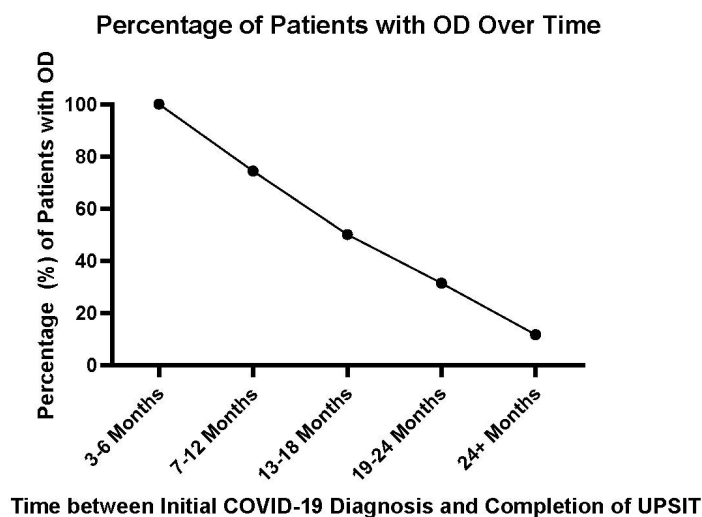


Figure 2. The percentage of patients with long-haul COVID-19 olfactory dysfunction declined over time. 100% had OD at 3-6 months following initial infection, 74.4% had OD at 7-12 months, 50% at 13-18 months, 31.4% at 19-24 months, and 11.6% at greater than 24 months.

this study is one of very few to report on objective olfactory data in patients that were diagnosed with COVID-19 greater than two years ago.

To quantify smell function, we used the UPSIT, which provides a raw score for OD ranging from 0-40 (with a higher score equating to greater olfactory function). Scores equate to classifications indicating normosmia, or mild, moderate, or severe anosmia. These classifications are based on normative data and account for age and gender. These factors are important to consider because olfaction function declines naturally with age and varies between males and females^(30,31).

OD due to COVID-19 infection is usually restored within weeks to months, and some studies even show partial or complete recovery that occurs years after the initial infection (19, 20). In the present study, more than 80% of patients had some degree of ongoing OD after initial infection, ranging from three months, to greater than 24 months since initial infection. However, the prevalence of OD declines over time; 44.8% of patients experiencing OD one year after initial infection, and nearly 20% still have OD at two or more years after initial infection. Of the 20% of patients that have persistent symptoms, the severity of OD was primarily classified as mild and moderate dysfunction. The cross-sectional nature of this study makes it difficult to determine if olfactory function improves over time or if the severity of dysfunction is constant until it suddenly resolves (Figure 2).

Females were more likely to experience OD compared to males (87.7% vs 80.5%) However, both males and females exhibited similar severity of their symptoms, and both exhibited, on average, moderate OD. These findings are congruent with previous studies that found women are more likely to suffer from Long-COVID in general, in addition to OD following COVID-19

⁽³²⁾. However, in a pre-COVID-19 meta-analysis, females typically outperformed males in olfactory testing⁽³¹⁾. This superior olfactory function in females may contribute to the prevalence of long-haul COVID-19 OD symptoms, possibly due to their increased awareness of their sense of smell to begin with or to an underlying physiologic difference that may affect how COVID-19 affects the olfactory cleft in males and females.

Of the long-haul COVID-19 patients who were included in our study, most were > 40 years old (78% > 40 vs 22% ≤ 40), with similar percentages among the long-haul COVID-19 patients experiencing OD (79.5% were > 40 vs 20.5% were ≤ 40). This finding is also consistent with previous studies⁽¹⁹⁾ and is likely due to the inherent decline in olfactory function with age, in addition to older individuals being less likely to withstand the effects of COVID-19.

We also were interested in evaluating the subjective awareness of patients regarding their OD. To do this, patients were asked if they think they have loss of smell (Y/N) prior to completing the objective UPSIT. We found that 17 out of the 27 patients (63%) that answered “No” actually exhibited some smell deficit, whereas only three out of 34 (9%) patients who answered “Yes” were actually normosmic based on their gender and age. This suggests that most patients with long-haul COVID-19 are likely underestimating their loss of smell.

It is worth considering that SARS-CoV-2 is continuously generating new variants due to mutations in the viral spike proteins. Previous studies have reported that more recent strains, such as the Omicron variant, are more transmissible, but cause less severe infection and are less likely to cause OD compared to earlier variants^(25,26). However, our analysis of patients with long-haul COVID-19 doesn't completely agree with this finding as nearly

44% of patients with OD in our study were those infected with the Omicron variant. Additionally, we did not find that objective OD severity varies significantly among the different variants. Interestingly, those who develop long-haul COVID have no differences in olfactory dysfunction. Olfactory dysfunction may be less prevalent with the new variants, but in those in whom symptoms persist for more than three months it would behave similarly. Further studies are needed to determine how the variant (and therefore the differing spike protein) facilitates target identification, cellular entry, and symptom severity, and how it may play a role in tissue tropism and therefore, the varying degrees of OD.

It is also worth noting that patients may experience a single persistent symptom or a combination of symptoms. The symptoms may be associated with one another and/or may have a cumulative effect on the severity and persistence of symptoms experienced by the patient. For example, previous studies have demonstrated an association between long-haul COVID-19 headache and olfactory dysfunction. They found that cognitive impairment and headache were associated with more severe olfactory loss and hypothesized that this relationship may be due to the neuroinflammatory mechanisms mediating a variety of long-haul COVID-19 symptoms^(33,34). It is important to consider all the symptoms experienced by the patient, as they may be associated with one another and may aid in predicting which patients will have more severe or persistent OD.

This study demonstrated that the initial infectious variant likely does not greatly influence the prevalence or severity of OD in long-haul COVID-19 patients. This may be due to many factors. One explanation for this finding could be because each of the variant groups were compared at different time lapses from the initial infection. However, this is inevitable since by nature, the G strain group will be further from initial infection compared to the Omicron group. Because these patients were not followed over time, the earlier groups have had more time to improve their olfaction compared to the more recently infected groups. This difference in timing may be part of the reason we did not see a significant difference between the groups.

Another explanation, particularly regarding the later variants, such as Omicron, is that vaccination status may play a role in the OD experienced by the patient. Prior studies have demonstrated that being fully or partially vaccinated may have offered some protection against olfactory dysfunction⁽³⁷⁾. Therefore, vaccination status, which was not directly assessed, may contribute to our findings.

Another explanation may be that these patients may have had multiple infections with various strains but were not individually identified. For example, these patients may have been infected with Alpha strain, followed by Omicron but were only evaluated

and completed a confirmatory test once. This possibility creates a limitation to our study, which is discussed below.

The prevalence of OD is of great concern for many reasons. The loss of olfactory function diminishes quality of life and is a safety concern. It places an increasingly large burden on the healthcare system^(35,36). Long-haul COVID-19 is a complex and poorly understood. There is currently no diagnostic test to identify those with long-haul COVID-19 and therefore, diagnosis heavily relies on patient history and presentation of symptoms, which may be due to COVID-19 alone, or more likely, due to a combination of factors. This can make it difficult for healthcare providers to accurately recognize and diagnose long-haul COVID-19.

Limitations to our study include the fact that participant's baseline olfactory function prior to SAR-CoV-2 infection was not assessed and was therefore not available for comparison to determine the degree of olfactory dysfunction from COVID-19 alone. Also, due to the multifactorial nature of OD, it is difficult to determine a single cause of OD. Additionally, patients were not specifically asked about treatments they may have received for OD prior to being seen at the COVID Recovery Clinic. Lastly, the exact variant causing each patient's initial infection was not confirmed, but instead was assumed based on the timing of their initial infection and the dominant variant at that time. Further studies are needed to determine all the factors that play a role in development of long-haul COVID-19 and the persistent OD in these patients.

Conclusions

Nearly all (84.8%) of the patients in our study had some degree of ongoing OD, likely due to long-haul COVID-19, with 10% of patients experiencing OD for longer than 2.5 years. We found that most patients are likely underestimating their loss of smell due to long-haul COVID-19, highlighting the importance of objective olfactory testing in these patients. Additionally, we did not identify a correlation between dominant variants that cause infection and the severity of OD in long-haul COVID-19 patients. Further studies are needed to determine the factors that play a role in the development of long-haul COVID-19 and the persistence of olfaction dysfunction in these patients.

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Authorship contribution

ML, KD, and SR contributed to the conception, design and

acquisition of the work, analysis, and interpretation of the data, drafting the work, and revising. SK, TS, IM, and AD contributed to the design and acquisition of the work, drafting the work, and revising the final manuscript. CKC, CE, JB, BS, and AK contributed to the conception, acquisition, revising, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Ethics approval

Ethical approval for this study was obtained from the University of North Carolina-Chapel Hill (UNC) Institutional Review Board (IRB#: 22-1665).

Consent to participate

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to data being comprised of patient protected health information but are available from the corresponding author on reasonable request.

Conflict of interest

No authors have any financial conflicts of interest.

References

- Nassar M, Nso N, Alfshawy M, et al. Current systematic reviews and meta-analyses of COVID-19. *World J Virol.* 2021;10(4):182-208.
- Çelik I, Öztürk R. From asymptomatic to critical illness: decoding various clinical stages of COVID-19. *Turk J Med Sci.* 2021;51(SI-1):3284-3300.
- Groff A, Kavanaugh M, Ramgobin D, et al. Gastrointestinal manifestations of COVID-19: a review of what we know. *Ochsner J.* 2021;21(2):177-180.
- Khatoun F, Prasad K, Kumar V. COVID-19 associated nervous system manifestations. *Sleep Med.* 2022;91:231-236.
- Santos REA, da Silva MG, do Monte Silva MCB, et al. Onset and duration of symptoms of loss of smell/taste in patients with COVID-19: A systematic review. *Am J Otolaryngol.* 2021;42(2):102889.
- 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.* 2020;163(1):114-120.
- Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. *Int Forum Allergy Rhinol.* 2020;10(8):944-950.
- 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.* 2020;58(5):430-436.
- Pinto MD, Downs CA, Huang Y, et al. A distinct symptom pattern emerges for COVID-19 long-haul: a nationwide study. *Sci Rep.* 2022;12(1):15905.
- Proal AD, VanElzakker MB. Long COVID or Post-acute Sequelae of COVID-19 (PASC): an overview of biological factors that may contribute to persistent Symptoms. *Front Microbiol.* 2021;12:698169.
- Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. Preprint. medRxiv. 2021;2021.01.27.21250617.
- Groff D, Sun A, Ssentongo AE, et al. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: a systematic review. *JAMA Netw Open.* 2021;4(10):e2128568.
- Mendes Paranhos AC, Nazareth Dias AR, Machado da Silva LC, et al. Sociodemographic characteristics and comorbidities of patients with long COVID and persistent olfactory dysfunction. *JAMA Netw Open.* 2022;5(9):e2230637.
- Karamali K, Elliott M, Hopkins C. COVID-19 related olfactory dysfunction. *Curr Opin Otolaryngol Head Neck Surg.* 2022;30(1):19-25.
- Gary JB, Gallagher L, Joseph PV, Reed D, Gudis DA, Overdeest JB. Qualitative olfactory dysfunction and COVID-19: an evidence-based review with recommendations for the clinician. *Am J Rhinol Allergy.* 2023;37(1):95-101.
- Boscolo-Rizzo P, Menegaldo A, Fabbris C, et al. Six-month psychophysical evaluation of olfactory dysfunction in patients with COVID-19. *Chem Senses.* 2021;46:bjab006.
- 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.* 2022;279(1):515-520.
- Renaud M, Thibault C, Le Normand F, et al. Clinical outcomes for patients with anosmia 1 year after COVID-19 diagnosis. *JAMA Netw Open.* 2021;4(6):e2115352.
- McWilliams MP, Coelho DH, Reiter ER, Costanzo RM. Recovery from COVID-19 smell loss: two-years of follow up. *Am J Otolaryngol.* 2022;43(5):103607.
- 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.* 2022;148(9):889-891.
- Vaira LA, De Riu G, Salzano G, Maglitter F, Boscolo-Rizzo P, Lechien JR. COVID-19 related persistent olfactory disorders represent an unprecedented challenge. *Am J Otolaryngol.* 2023;44(1):103667.
- Boscolo-Rizzo P, Hummel T, Invitto S, et al. Psychophysical assessment of olfactory and gustatory function in post-mild COVID-19 patients: a matched case-control study with 2-year follow-up. *Int Forum Allergy Rhinol.* 2023.
- Landis BN, Hummel T, Hugentobler M, Giger R, Lacroix JS. Ratings of overall olfactory function. *Chem Senses.* 2003;28(8):691-694.
- Lechien JR, Saussez S, Maniaci A, Vaira LA. The study of recovery rates of COVID-19 olfactory and gustatory dysfunctions requires psychophysical evaluations. *Am J Otolaryngol.* 2021;42(6):103168.
- Boscolo-Rizzo P, Tirelli G, Meloni P, et al. Coronavirus disease 2019 (COVID-19)-related smell and taste impairment with widespread diffusion of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) Omicron variant. *Int Forum Allergy Rhinol.* 2022;12(10):1273-1281.
- Coelho DH, Reiter ER, French E, Costanzo RM. decreasing incidence of chemosensory changes by COVID-19 variant. *Otolaryngol Head Neck Surg.* 2023;168(4):704-706.
- Doty RL, Frye RE, Agrawal U. Internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test. *Percept Psychophys.* May 1989;45(5):381-384.
- Viguera C, Wang J, Mosmiller E, Cerezo A, Maragakis NJ. Olfactory dysfunction in amyotrophic lateral sclerosis. *Ann Clin Transl Neurol.* 2018;5(8):976-981.
- Kertelge L, Brüggemann N, Schmidt A, et al. Impaired sense of smell and color discrimination in monogenic and idiopathic Parkinson's disease. *Mov Disord.* 2010;25(15):2665-2669.
- Boyce JM, Shone GR. Effects of ageing on smell and taste. *Postgrad Med J.* 2006;82(966):239-241.
- Sorokowski P, Karwowski M, Misiak M, et al. Sex differences in human olfaction: a meta-analysis. *Front Psychol.* 2019;10:242.

32. Makaronidis J, Firman C, Magee CG, et al. Distorted chemosensory perception and female sex associate with persistent smell and/or taste loss in people with SARS-CoV-2 antibodies: a community based cohort study investigating clinical course and resolution of acute smell and/or taste loss in people with and without SARS-CoV-2 antibodies in London, UK. *BMC Infect Dis.* 2021;21(1):221.
33. Di Stadio A, Brenner MJ, De Luca P, et al. olfactory dysfunction, headache, and mental clouding in adults with long-COVID-19: what is the link between cognition and olfaction? a cross-sectional study. *Brain Sci.* 2022;12(2):154.
34. Tana C, Bentivegna E, Cho SJ, et al. Long COVID headache. *J Headache Pain.* 2022;23(1):93.
35. Saniasiaya J, Prepageran N. Impact of olfactory dysfunction on quality of life in coronavirus disease 2019 patients: a systematic review. *J Laryngol Otol.* 2021;135(11):947-952.
36. Menges D, Ballouz T, Anagnostopoulos A, et al. Burden of post-COVID-19 syndrome and implications for healthcare service planning: A population-based cohort study. *PLoS One.* 2021;16(7):e0254523.

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