European Archives of Oto-Rhino-Laryngology (2023) 280:5625–5630
https://doi.org/10.1007/s00405-023-08227-y

SHORT COMMUNICATION

Evaluating long-term smell or taste dysfunction in mildly symptomatic COVID-19 patients: a 3-year follow-up study

Paolo Boscolo-Rizzo[1] · Giacomo Spinato[2] · Claire Hopkins[3] · Riccardo Marzolino[1] · Angelo Cavicchia[2] · Simone Zucchini[1] · Daniele Borsetto[4] · Jerome R. Lechien[5] · Luigi Angelo Vaira[6,7] · Giancarlo Tirelli[1]

Received: 23 May 2023 / Accepted: 31 August 2023 / Published online: 16 September 2023

Abstract

Introduction No studies have reported data on 3-year prevalence and recovery rates of self-reported COVID-19-related olfactory and gustatory dysfunction. The aim of the present study was to estimate the 3-year prevalence and recovery rate of self-reported COVID-19-related chemosensory dysfunction in a cohort of patients with antecedent mild COVID-19.

Methods This is a prospective observational study, measuring the prevalence of altered sense of smell or taste at follow-up and their variation from baseline, on adult patients consecutively assessed at Treviso and Trieste University Hospitals, who tested positive for SARS-CoV-2 RNA by polymerase chain reaction during March 2020.

Results Overall, out of 403 respondents, 267 patients (66.3%) reported an altered sense of smell or taste (SNOT-22 > 0) at baseline, while 56 (13.9%), 29 (7.2%), and 21 (5.2%) reported such alterations at 6–24 months, 2 years, and 3 years, respectively. Among the 267 patients with COVID-19-associated smell or taste dysfunction at baseline, 246 (92.1%) reported complete resolution at 3 years. Of the patients who still experienced smell or taste dysfunction 2 years after COVID-19, 27.6% and 37.9% recovered completely and partially, respectively, at the 3-year follow-up.

Conclusion Among subjects with antecedent mildly symptomatic SARS-CoV-2 infection, the 3-year prevalence and recovery rate of COVID-19-related alteration in sense of smell or taste was 5% and 92%, respectively. In approximately two-thirds of patients experiencing chemosensory dysfunction still 2 years after COVID-19, it is still possible to observe a delayed complete or partial recovery after a period of 3 years, while the remaining one-third of individuals continues to have unchanged persistent chemosensory alteration.

Keywords Anosmia · COVID-19 · Prognosis · SARS-CoV-2 · Smell · Taste · Loss · Anosmia · Otolaryngology

✉ Paolo Boscolo-Rizzo
paolo.boscolorizzo@units.it

1 Department of Medical, Surgical and Health Sciences, Section of Otolaryngology, University of Trieste, Strada Di Fiume 447, 34149 Trieste, Italy

2 Department of Neurosciences, Section of Otolaryngology, University of Padova, Treviso, Italy

3 Guy's and St Thomas' Hospitals, London, UK

4 Department of ENT, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

5 Department of Laryngology, EpiCURA Hospital, Mons School of Medicine, University of Mons, Mons, Belgium

6 Department of Medicine, Surgery and Pharmacy, Maxillofacial Surgery Operative Unit, University of Sassari, Sassari, Italy

7 PhD School of Biomedical Sciences, Department of Biomedical Sciences, University of Sassari, Sassari, Italy

Introduction

During the initial waves of the COVID-19 pandemic, loss of smell and taste were common symptoms of the acute phase of the disease [1–3]. Long-term COVID-19 patients have also experienced these symptoms, with up to 28% still exhibiting olfactory dysfunction even 2 years after being infected with the SARS-CoV-2, when psychophysically evaluated, compared to 11% of matched controls [4]. Thus, long-term chemosensory dysfunction was identified as a hallmark of post-acute sequelae of COVID-19 (PASC).

Considering the importance of chemosensory function both for quality of life and safety [5–7], the above observations as well as the high case rate of COVID-19 make it important to estimate the long-term prevalence of persistent chemosensory alterations. The most recent meta-analysis reported a long-term prevalence of smell and taste loss of

14% and 15%, respectively, after asymptomatic infections [8]. However, prevalence and recovery rate of chemosensory dysfunction 3 years after COVID-19 are still unknown.

We previously described in two independent series the prevalence of self-reported altered sense of smell or taste in mildly symptomatic patients two years after COVID-19 [9, 10]. The aim of the present study was to estimate the 3-year prevalence and recovery rate of smell or taste dysfunction using data pooled from these two series.

Methods

During the first wave of COVID-19 in Italy in March 2020, two cohorts of subjects consecutively testing positive for SARS-CoV-2 infection were recruited from two centers in the Northeast of Italy, the Trieste University Hospital and Treviso General Hospital, Italy. The aim of both studies was to evaluate prevalence, intensity, and evolution of an altered sense of smell or taste in patients with SARS-CoV-2 infection, as well as other respiratory symptoms.

Particularly, adults (aged ≥ 18 years) were included if they tested positive for SARS-CoV-2 RNA by polymerase chain reaction on swabs performed according to World Health Organization recommendation between March 1 and March 22, 2020, and were considered suitable for home management.

The results of these assessments were initially reported independently for the two series of patients. Since the inclusion criteria were the same, and the tools used to estimate symptom prevalence were identical, in the present study we merged the two case-series. In both series, indeed, symptoms were assessed through the same structured questionnaires, including the ARTIQ (Acute Respiratory Tract Infection Questionnaire) and the Sino-nasal Outcome Test 22 (SNOT-22) [11], item "sense of smell or taste" as previously described [1]. The sense of smell and taste was assessed by SNOT-22 both at baseline and during the follow-up interviews at 6–12 months, 2 years, and 3 years to evaluate their persistence and the recovery rate. The SNOT-22 grades symptom severity as none (0), very mild (1), mild or slight (2), moderate (3), severe (4), or as bad as it can be (5) and refers to the presence of self-reported alterations in the sense of smell alone, in the sense of taste alone, or both.

Overall, 517 patients participating at the baseline survey, including 315 subjects recruited at Trieste University Hospital and 202 at Treviso General Hospital. Among those, 437 (84.5%) participated in all follow-up interviews.

Symptom prevalence was expressed as percentage of total patients, and 95% confidence interval (CI) were calculated using Clopper-Pearson method; differences in prevalence were evaluated through Fisher's exact test. Analyses were performed using R 3.6. and statistical significance was claimed for $p < 0.05$ (two-tailed).

These cohort studies were approved by the ethic committee of Treviso and Belluno provinces (ethics committee: 780/CE) and the Friuli Venezia Giulia Region (ethics committee: CEUR-2020-Os-156). Informed consent was obtained verbally for telephone interviews.

Results

Among the 437 patients who participated in all follow-up interviews, 29 patients were excluded from the analysis due to a documented re-infection with SARS-CoV-2, while 5 were excluded due to a late onset (> 3 months) of smell or taste dysfunction that suggests possible re-infection, thus leaving 403 (77.9%) eligible patients (median [range] age, 52 [20–89] years; 234 [56.9%] women). The baseline, 6–12 months, 2-, and 3-year evaluation occurred at a median of 4 (interquartile range [IQR]:4–6), 298 (IQR:180–316), 724 (IQR:706–733), and 1092 days (IQR:1081–1107) from the first SARS-CoV-2-positive swab, respectively.

Among them, 267 patients (66.3%, 95% CI: 61.4–70.8%), 56 (13.9%, 95% CI: 10.7–17.8%), 29 (7.2%, 95% CI: 5.0–10.3%), and 21 (5.2%, 95% CI: 3.3–8.0%) reported an altered sense of smell or taste (SNOT-22 > 0) at baseline, 6–24-months, 2-year, and 3-year, respectively (Fig. 1 and Table 1).

Among the 267 patients with COVID-19-associated smell or taste dysfunction at baseline, 246 (92.1%, 95% CI: 88.1–94.9%) reported complete resolution at 3 years, 17 (6.4%, 3.9–10.2%) reported a decrease in the severity, and 4 (1.5%, 0.5–4.0%) reported the symptom was unchanged or worse.

Overall, the complete recovery rate was 79.0% (73.5–83.6%), 89.1% (84.6–92.5%), and 92.1% (88.1–94.9%), at 6–12 months, 2-year, and 3-year, respectively. At 6–12 months, complete recovery was reported by 211 out of 267 patients (recovery rate: 79.0%; 95% CI: 73.5–83.6%). Twenty-seven of the remaining 56 patients recovered between 6–12 months and 2 years follow-up (recovery rate: 48.2%; 95% CI: 34.8–61.8%). Between 2- and 3-year follow-up 8 out of 29 patients completely recovered (recovery rate: 27.6%; 95% CI: 13.4–47.5%), 11 (37.9%; 95% CI: 21.3–57.6%) reported an improvement in chemosensory perception, while 10 (34.5%; 95% CI: 18.6–54.3%) subjects reported no changes in their smell or taste dysfunction.

At 3-year follow-up, the most frequent non-chemosensory symptoms (Fig. 2 and Table 1) were shortness of breath (6.5%, 4.3–9.4%) followed by fatigue (5.5%, 3.5–8.3%).

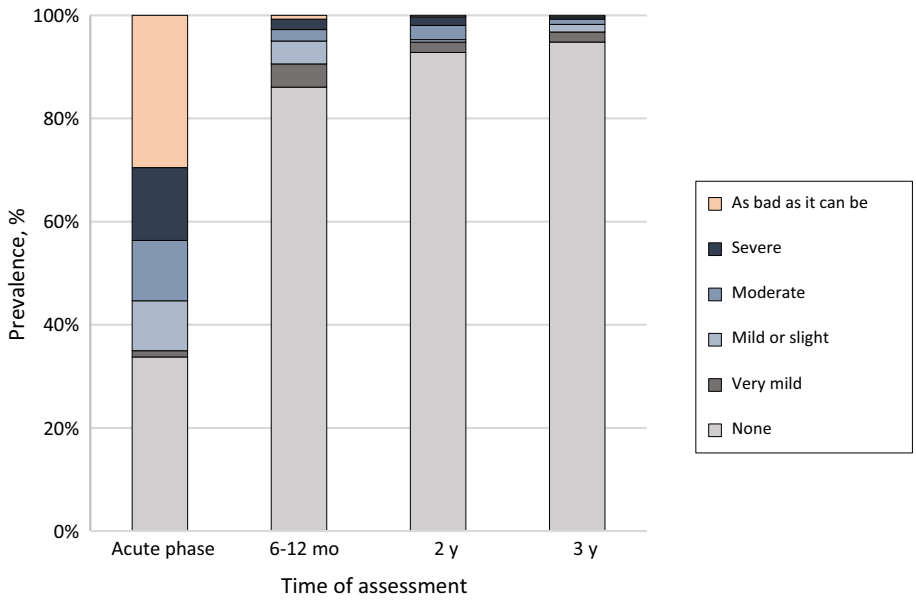

Fig. 1 Prevalence and severity of altered sense of smell or taste from baseline to the 3-year follow-up in 403 patients with COVID-19. Severity of alteration of sense of smell or taste is according to Sino-nasal Outcome Test 22 item "sense of smell or taste."

Table 1 Evolution of symptoms' prevalence from baseline to the 3-year follow-up in 403 patients positive for SARS-CoV-2

Symptom	Acute phase			6–12 months			2 year			3 year		
	n	%	(95% CI[a])	*n*	%	(95% CI[a])	*n*	%	(95% CI[a])	*n*	%	(95% CI[a])
Dry cough	188	46.7	(41.7–51.7)	12	3.0	(1.6–5.3)	12	3.0	(1.6–5.3)	3	0.7	(0.2–2.3)
Coughing up mucus	55	13.6	(10.5–17.5)	5	1.2	(0.5–3.0)	4	1.0	(0.3–2.7)	1	0.2	(0.0–1.6)
Blocked nose	105	26.1	(21.9–30.7)	11	2.7	(1.4–5.0)	12	3.0	(1.6–5.3)	1	0.2	(0.0–1.6)
Fever	272	67.5	(62.6–72.0)	2	0.5	(0.1–2.0)	1	0.2	(0.0–1.6)	0	0.0	(0.0–1.2)
Headache	185	45.9	(41.0–50.9)	11	2.7	(1.4–5.0)	13	3.2	(1.8–5.6)	7	1.7	(0.8–3.7)
Sore throat	105	26.1	(21.9–30.7)	8	2.0	(0.9–4.0)	6	1.5	(0.6–3.4)	0	0.0	(0.0–1.2)
Muscle and joint pain	225	55.8	(50.8–60.7)	35	8.7	(6.2–12.0)	33	8.2	(5.8–11.4)	11	2.7	(1.4–5.0)
Chest pain	82	20.3	(16.6–24.7)	9	2.2	(1.1–4.3)	7	1.7	(0.8–3.7)	0	0.0	(0.0–1.2)
Sinonasal pain	53	13.2	(10.1–16.9)	7	1.7	(0.8–3.7)	9	2.2	(1.1–4.3)	0	0.0	(0.0–1.2)
Loss of appetite	166	41.2	(36.4–46.2)	3	0.7	(0.2–2.3)	3	0.7	(0.2–2.3)	1	0.2	(0.0–1.6)
Problems breathing	89	22.1	(18.2–26.5)	22	5.5	(3.5–8.3)	18	4.5	(2.7–7.1)	10	2.5	(1.3–4.7)
Wheezing	46	11.4	(8.6–15.0)	9	2.2	(1.1–4.3)	7	1.7	(0.8–3.7)	0	0.0	(0.0–1.2)
Shortness of breath	122	30.3	(25.9–35.1)	57	14.1	(11.0–18.0)	45	11.2	(8.3–14.8)	26	6.5	(4.3–9.4)
Felt tired	281	69.7	(64.9–74.1)	98	24.3	(20.3–28.9)	84	20.8	(17.0–25.2)	22	5.5	(3.5–8.3)
Diarrhoea	149	37.0	(32.3–41.9)	5	1.2	(0.5–3.0)	6	1.5	(0.6–3.4)	0	0.0	(0.0–1.2)
Nausea	71	17.6	(14.1–21.8)	3	0.7	(0.2–2.3)	3	0.7	(0.2–2.3)	0	0.0	(0.0–1.2)
Vomit	21	5.2	(3.3–8.0)	0	0.0	(0.0–1.2)	0	0.0	(0.0–1.2)	0	0.0	(0.0–1.2)
Abdominal pain	44	10.9	(8.1–14.5)	1	0.2	(0.0–1.6)	2	0.5	(0.1–2.0)	0	0.0	(0.0–1.2)
Insomnia	67	16.6	(13.2–20.7)	21	5.2	(3.3–8.0)	18	4.5	(2.7–7.1)	2	0.5	(0.1–2.0)
Dizziness	45	11.2	(8.3–14.8)	9	2.2	(1.1–4.3)	8	2.0	(0.9–4.0)	0	0.0	(0.0–1.2)
Altered sense of smell or taste	267	66.3	(61.4–70.8)	56	13.9	(10.7–17.8)	29	7.2	(5.0–10.3)	21	5.2	(3.3–8.0)

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2

[a]95% CIs were calculated using Clopper-Pearson method

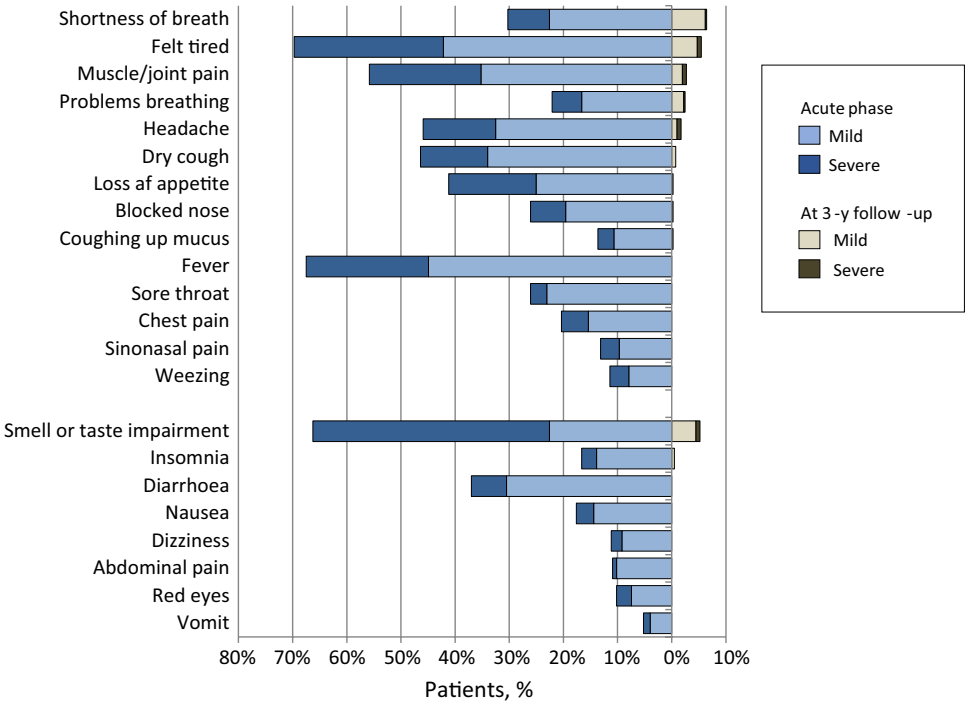

Fig. 2 Evolution of other COVID-19-related symptoms in 403 patients

Discussion

Although the alteration of smell and taste was transient for the majority of patients, a proportion of them still report chemosensory dysfunction 3 years after SARS-CoV-2 infection. Particularly, 5.2% of subjects who contracted the infection during the first wave of COVID-19, and 7.9% of those who had experienced an alteration of smell or taste during the acute phase of the disease, still report such symptoms 3 years after COVID-19.

Given the vast number of people who have contracted COVID-19 globally and considering that the prevalence of olfactory and gustatory impairments associated with COVID-19 significantly declined only with the emergence and predominance of the Omicron variant in early 2022 [12, 13], there is reason to believe that there will continue to be an unprecedented number of individuals with long-term issues related to their sense of smell and taste in the next years.

It should be noted that the magnitude of this burden may vary depending on the geographical area [14]. Ethnic disparities in susceptibility to COVID-19-related chemosensory damage have become evident both during the earlier waves of the pandemic and the more recent Omicron wave, with Western populations exhibiting higher prevalence of olfactory alterations compared to other ethnicities [15]. Polymorphisms in the UGT2A1/UGT2A2 locus codifying for a glycosyltransferase acting as odorant metabolizing enzyme and abundantly expressed in the sustentacular cells of the olfactory neuroepithelium, are associated with elevated risk of COVID-19-related acute loss of smell or taste[16] Interestingly, ethnic differences in the frequency of the risk allele in the UGT2A1/A2 locus were observed with Western populations exhibiting higher frequencies of the risk allele than Asians and Africans less prone to develop olfactory dysfunction following SARS-CoV-2 infection [15].

These data should encourage researchers to investigate innovative therapies aimed at recovering these senses. To date, the most effective therapeutic strategy remains olfactory training [17], which, however, in a significant number of individuals does not allow for recovery of olfactory function [18]. Therefore, health leaders, policy makers, and research funders should allocate adequate resources towards supporting research on chemosensory function and sustaining healthcare professionals to address the ongoing exceptional burden of COVID-19-related chemosensory dysfunction.

The loss of these senses, in addition to undesirably affecting the ability to detect unpleasant odors, gas or smoke leaks, identify spoiled foods with consequent increasing risk of intoxication and food poisoning, is often accompanied by feelings of depression and anxiety, as well as impairments in social function and quality of life, memory, and sleep quality, eventually compromising the quality of life [19, 20]. This holds particularly true for patients who are aware of their loss of sense of smell, such as those included in our study. Addressing these long-term issues is essential to aiding individuals with chemosensory dysfunction and improving their quality of life.

An encouraging result arising from the data analysis of this study is that about one-third of the subjects who

reported persistent olfactory dysfunction two years after COVID-19 have shown complete recovery after 3 years. These findings confirm the possibility of delayed recovery of olfactory and gustatory sensitivity [9, 10, 21]. This is an important message to convey to patients with long-term chemosensory dysfunction who may feel disheartened and worry that they have permanently lost these senses.

The findings of the current study warrant cautious interpretation. Specifically, it is important to note that the symptoms were self-reported through cross-sectional surveys, which may introduce limitations in terms of sensitivity. Consequently, the prevalence of olfactory dysfunction could potentially be underestimated when compared to psychophysical tests that are not correlated with the severity of patient-reported smell dysfunctions. Moreover, these results are applicable to mildly symptomatic COVID-19 patients who were infected prior to the emergence of the Omicron variant of SARS-CoV-2. Some differences between variants may potentially exist regarding the baseline presentation and the evolution of smell disorders, making the comparison of these patients difficult. [22]

Conclusion

Among subjects with antecedent mildly symptomatic SARS-CoV-2 infection, the 3-year prevalence and recovery rate of COVID-19-related alteration in sense of smell or taste was 5% and 92%, respectively. In approximately two-thirds of patients experiencing chemosensory dysfunction still 2 years after COVID-19, it is still possible to observe a delayed complete or partial recovery after a period of 3 years, while the remaining one-third of individuals continues to have unchanged persistent chemosensory alteration.

Acknowledgements The Authors thank Jerry Polesel, ScD, Unit of Cancer Epidemiology at Centro di Riferimento Oncologico di Aviano (CRO) IRCCS for statistical support.

Author contributions PB-R and GS: had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: PB-R, GS, CH, GT. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: PB-R. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: PB-R. Supervision: PB-R, CH, JRL, LAV, and GT.

Funding None.

Availability of data and materials The authors confirm that the data supporting the findings of this study are available within the article.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval The study was approved by the ethic committee of Treviso and Belluno provinces (ethics committee: 780/CE) and the Friuli Venezia Giulia Region (ethics committee: CEUR-2020-Os-156).

Informed consent Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

References

1. Spinato G, Fabbris C, Polesel J et al (2020) Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. JAMA 323:2089–2090. https://doi.org/10.1001/jama.2020.6771
2. Lechien JR, Chiesa-Estomba CM, De Siati DR et al (2020) 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 Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg. https://doi.org/10.1007/s00405-020-05965-1
3. Vaira LA, Deiana G, Fois AG et al (2020) Objective evaluation of anosmia and ageusia in COVID-19 patients: single-center experience on 72 cases. Head Neck. https://doi.org/10.1002/hed.26204
4. Boscolo-Rizzo P, Hummel T, Invitto S et al (2023) Psychophysical assessment of olfactory and gustatory function in post-mild COVID-19 patients: a matched case-control study with two-year follow-up. Int Forum Allergy Rhinol. https://doi.org/10.1002/alr.23148
5. Addison AB, Wong B, Ahmed T et al (2021) Clinical Olfactory Working Group consensus statement on the treatment of postinfectious olfactory dysfunction. J Allergy Clin Immunol. https://doi.org/10.1016/j.jaci.2020.12.641
6. Vaira LA, Gessa C, Deiana G et al (2022) The effects of persistent olfactory and gustatory dysfunctions on quality of life in long-COVID-19 patients. Life 12:141. https://doi.org/10.3390/life12020141
7. Croy I, Nordin S, Hummel T (2014) Olfactory disorders and quality of life—an updated review. Chem Senses 39:185–194. https://doi.org/10.1093/chemse/bjt072
8. Ma Y, Deng J, Liu Q et al (2023) Long-term consequences of asymptomatic SARS-CoV-2 infection: a systematic review and meta-analysis. Int J Environ Res Public Health 20:1613. https://doi.org/10.3390/ijerph20021613
9. Boscolo-Rizzo P, Fabbris C, Polesel J et al (2022) Two-year prevalence and recovery rate of altered sense of smell or taste in patients with mildly symptomatic COVID-19. JAMA Otolaryngol Neck Surg. https://doi.org/10.1001/jamaoto.2022.1983
10. Boscolo-Rizzo P, Tofanelli M, Zanelli E et al (2022) COVID-19-related quantitative and qualitative olfactory and gustatory dysfunction: long-term prevalence and recovery rate. ORL J Oto-Rhino-Laryngol Its Relat Spec. https://doi.org/10.1159/000525861
11. Hopkins C, Gillett S, Slack R et al (2009) Psychometric validity of the 22-item sinonasal outcome test. Clin Otolaryngol Off J ENT-UK Off J Neth Soc Oto-Rhino-Laryngol Cervico-Facial Surg 34:447–454. https://doi.org/10.1111/j.1749-4486.2009.01995.x

12. Vaira LA, Lechien JR, Deiana G et al (2022) Prevalence of olfactory dysfunction in D614G, alpha, delta and omicron waves: a psychophysical case-control study. Rhinology. https://doi.org/10.4193/Rhin22.294
13. Boscolo-Rizzo P, Tirelli G, Meloni P et al (2022) 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. https://doi.org/10.1002/alr.22995
14. Butowt R, Bilinska K, Von Bartheld CS (2020) Chemosensory dysfunction in COVID-19: integration of genetic and epidemiological data points to D614G spike protein variant as a contributing factor. ACS Chem Neurosci 11:3180–3184. https://doi.org/10.1021/acschemneuro.0c00596
15. von Bartheld CS, Wang L (2023) Prevalence of olfactory dysfunction with the omicron variant of SARS-CoV-2: a systematic review and meta-analysis. Cells 12:430. https://doi.org/10.3390/cells12030430
16. Shelton JF, Shastri AJ, Fletez-Brant K et al (2022) The UGT2A1/UGT2A2 locus is associated with COVID-19-related loss of smell or taste. Nat Genet 54:121–124. https://doi.org/10.1038/s41588-021-00986-w
17. Hummel T, Rissom K, Reden J et al (2009) Effects of olfactory training in patients with olfactory loss. Laryngoscope 119:496–499. https://doi.org/10.1002/lary.20101
18. Khan AM, Piccirillo J, Kallogjeri D, Piccirillo JF (2023) Efficacy of combined visual-olfactory training with patient-preferred scents as treatment for patients with COVID-19 resultant olfactory loss: a randomized clinical trial. JAMA Otolaryngol Head Neck Surg. 149:141–149. https://doi.org/10.1001/jamaoto.2022.4112
19. Gopinath B, Sue CM, Kifley A, Mitchell P (2012) The association between olfactory impairment and total mortality in older adults. J Gerontol A Biol Sci Med Sci 67:204–209. https://doi.org/10.1093/gerona/glr165
20. Xu L, Liu J, Wroblewski KE et al (2020) Odor sensitivity versus odor identification in older US adults: associations with cognition, age, gender, and race. Chem Senses 45:321–330. https://doi.org/10.1093/chemse/bjaa018
21. Lechien JR, Vaira LA, Saussez S (2023) Prevalence and 24-month recovery of olfactory dysfunction in COVID-19 patients: a multicentre prospective study. J Intern Med 293:82–90. https://doi.org/10.1111/joim.13564
22. Lechien JR, Wajsblat S, Horoi M et al (2023) 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 Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol Head Neck Surg. https://doi.org/10.1007/s00405-023-07923-z