American Academy of Otolaryngic Allergy (AAOA)

Since 1941, the American Academy of Otolaryngic Allergy has been a well-known leader in providing the latest training and education on diagnosing and treating allergic conditions of the ear, nose, and throat.

Much has changed over the past 80 years, but the AAOA remains dedicated to education, advocacy, and research that supports otolaryngologists and related healthcare providers in their efforts to offer cost-effective, quality care for their patients.

AAOA Membership

Why you should be an AAOA member:

- Join a prestigious organization with a 80-year history of supporting its members in providing exceptional, practical, and current care
- Receive discounts of up to 50% on cutting-edge CME courses and meetings, both live and online, on new procedures, findings, and best practices
- Stay connected to relevant, timely research through the *International Forum on Allergy and Rhinology* (IFAR), the official journal of the AAOA and its Foundation
- Provide excellent training opportunities for your staff through Allied Health memberships linked to your membership
- Lend your voice to AAOA advocacy efforts, giving us a greater ability to impact patient care in Otolaryngic Allergy
- Support research to advance the field of Otolaryngic Allergy, gain new understanding of allergic conditions, and, ultimately, provide insight that will allow you to better care for your patients
- Be a part of that innovative research with access to AAOA Foundation research grants
- Network with peer AAOA members, who represent a large contingent of general ENTs in private practice, to learn from each other how to navigate today's healthcare and practice challenges

Being a member of the AAOA ensures not only that you stay up to date on the latest advances in the field of Otolaryngology and Allergy, but that your voice is heard in the broader national discussions that impact you and your patients.

For more information

Visit **aaoallergy.org/education** to learn about our CME courses
Contact **membership@aaoallergy.org**,
or **visit aaoallergy.org** to apply today!

AMERICAN ACADEMY OF OTOLARYNGIC ALLERGY

WILEY

Received: 30 December 2022 | Revised: 15 February 2023 | Accepted: 23 February 2023

DOI: 10.1002/alr.23148

IFAR: International Forum of Allergy & Rhinology

ORIGINAL ARTICLE

Psychophysical assessment of olfactory and gustatory function in post-mild COVID-19 patients: A matched case-control study with 2-year follow-up

Paolo Boscolo-Rizzo MD[1] | **Thomas Hummel MD**[2] | **Sara Invitto PhD**[3] | **Giacomo Spinato MD**[4,5] | **Michele Tomasoni MD**[6] | **Enzo Emanuelli MD**[5] | **Margherita Tofanelli MD, PhD**[1] | **Angelo Cavicchia MD**[1] | **Vittorio Grill MSc**[7] | **Luigi Angelo Vaira MD**[8] | **Jerome R Lechien MD, PhD**[9] | **Daniele Borsetto MD**[10] | **Jerry Polesel MD**[11] | **Michele Dibattista PhD**[12] | **Anna Menini PhD**[13] | **Claire Hopkins MA(Oxon), DM**[14] | **Giancarlo Tirelli MD**[1]

[1]Department of Medical, Surgical and Health Sciences, Section of Otolaryngology, University of Trieste, Trieste, Italy

[2]Smell & Taste Clinic, Department of Otorhinolaryngology, Technical University of Dresden, Dresden, Germany

[3]INSPIRE LAB-Laboratory of Cognitive and Psychophysiological Olfactory Processes, DiSTeBA, University of Salento, Lecce, Italy

[4]Department of Neurosciences, Section of Otolaryngology, University of Padova, Treviso, Italy

[5]Unit of Otolaryngology, Azienda Unità Locale Socio Sanitaria 2-Marca Trevigiana, Treviso, Italy

[6]Unit of Otorhinolaryngology–Head and Neck Surgery, ASST Spedali Civili of Brescia, Brescia, Italy

[7]Department of Life Sciences, University of Trieste, Trieste, Italy

[8]Department of Medicine, Surgery and Pharmacy, Maxillofacial Surgery Operative Unit, University of Sassari, Sassari, Italy

[9]Department of Anatomy and Experimental Oncology, Mons School of Medicine, UMONS. Research Institute for Health Sciences and Technology, University of Mons (UMons), Mons, Belgium

[10]Department of ENT, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[11]Unit of Cancer Epidemiology, Centro di Riferimento Oncologico di Aviano (CRO) Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Aviano, Italy

[12]Department of Translational Biomedicine and Neuroscience, University of Bari A. Moro, Bari, Italy

[13]Neurobiology Group, Scuola Internazionale Superiore di Studi Avanzati (SISSA), Trieste, Italy

[14]Ear, Nose and Throat Department, Guy's and St Thomas' Hospitals, London, UK

Correspondence
Paolo Boscolo-Rizzo, Department of Medical, Surgical and Health Sciences, Section of Otolaryngology, University of Trieste, Strada di Fiume 447, 34149 Trieste, Italy.
Email: paolo.boscolorizzo@units.it

Abstract

Background: The aim of this study was to psychophysically evaluate the prevalence of smell and taste dysfunction 2 years after mildly symptomatic severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2) infection compared to that observed at 1-year follow-up and while considering the background of chemosensory dysfunction in the no-coronavirus disease 2019 (COVID-19) population.

Method: This is a prospective case-control study on 93 patients with polymerase chain reaction (PCR)-positive SARS-CoV-2 infection and 93 matched controls. Self-reported olfactory and gustatory dysfunction was assessed by 22-item Sino-Nasal-Outcome Test (SNOT-22), item "Sense of smell or taste." Psychophysical

orthonasal and retronasal olfactory function and gustatory performance were estimated using the extended Sniffin' Sticks test battery, 20 powdered tasteless aromas, and taste strips test, respectively. Nasal trigeminal sensitivity was assessed by sniffing a 70% solution of acetic acid.

Results: The two psychophysical assessments of chemosensory function took place after a median of 409 days (range, 366–461 days) and 765 days (range, 739–800 days) from the first SARS-CoV-2–positive swab, respectively. At 2-year follow-up, cases exhibited a decrease in the prevalence of olfactory (27.9% vs. 42.0%; absolute difference, −14.0%; 95% confidence interval [CI], −21.8% to −2.6%; $p = 0.016$) and gustatory dysfunction (14.0% vs. 25.8%; absolute difference, −11.8%; 95% CI, −24.2% to 0.6%; $p = 0.098$). Subjects with prior COVID-19 were more likely than controls to have an olfactory dysfunction (27.9% vs. 10.8 %; absolute difference, 17.2%; 95% CI, 5.2% to 28.8%) but not gustatory dysfunction (14.0% vs. 9.7%; absolute difference, 4.3%; 95% CI, −5.8% to 14.4% $p = 0.496$) still 2 years after the infection. Overall, 3.2% of cases were still anosmic 2 years after the infection.

Conclusions: Although a proportion of subjects recovered from long-lasting smell/taste dysfunction more than 1 year after COVID-19, cases still exhibited a significant excess of olfactory dysfunction 2 years after SARS-CoV-2 infection when compared to matched controls.

KEYWORDS
olfaction, olfactory disorders, olfactory test

1 | INTRODUCTION

Chemosensory dysfunction has emerged as a highly prevalent symptom of severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2) infection during the acute phase of coronavirus disease 2019 (COVID-19).[1–4] Despite smell and taste perception improved within 4 weeks after the onset in most cases,[1] a persistent impairment remained a predominant symptom in post-COVID-19 patients 6 and 12 months after the infection,[5–7] significantly influencing the quality of life.[8,9] Moreover, as it has been suggested that smell loss at 12 months may be permanent,[10] is crucial to perform longer-term studies to inform both patients and health professionals of likelihood of further recovery.

Studies based on self-reported symptoms are easy to perform and, most importantly, have a baseline parameter of comparison that is the subjective perception of smell and taste preceding the onset of COVID-19. However, compared with psychophysical assessment, this approach has been reported to overestimate recovery from olfactory dysfunction (OD).[9,11] Thus, psychophysical evaluation is required to identify those patients unaware of their impaired sense of smell, for example, to identify those at risk of exposure to environmental hazards.

Due to the pressure of the COVID-19 pandemic, several studies have used quick and brief psychophysical tests[12] or have developed olfactory and gustatory function assessments based on commonly available household items.[13–15] Although these tools facilitate a more accurate evaluation than assessments based on self-reported symptoms, they only capture limited aspects of the olfactory and gustatory dysfunction and, regarding the sense of smell, the ability to identify a limited number of volatile substances. Furthermore, it has been observed that SARS-CoV-2 affected mainly odor thresholds, and to a lesser degree odor discrimination, and odor identification. This pattern is consistent with damage of the olfactory neuroepithelium.[9,16]

The lack of pre-COVID-19 baseline olfactory and gustatory assessment for the large majority of patients further complicates estimation of the real prevalence rates of chemosensory changes induced by SARS-CoV-2 infection. According to psychophysical tests, indeed, OD affects approximately 20% of the general population.[17,18] Furthermore, in older adults the prevalence of psychophysical impairment in the sense of smell in the setting of no self-reported deficit is 15%.[19]

The aim of the present investigation was to estimate the prevalence of altered sense of smell and taste 2 years after mildly symptomatic SARS-CoV-2 infection through a comprehensive psychophysical evaluation, while considering the background of chemosensory dysfunction in population that never had COVID-19.

2 | SUBJECTS AND METHODS

2.1 | Study design and population

This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the ethic committees for clinical experimentation of Treviso and Belluno provinces (ethic vote: 780/CE) and Friuli Venezia Giulia Region (CEUR-2020-Os-156). Written informed consent was obtained from the participants. Cases were randomly sampled from home-isolated, mildly symptomatic COVID-19 subjects living in Trieste municipality who tested positive during March and April 2020 as described.[9] Subjects were considered mildly symptomatic if they had symptoms of COVID-19 without evidence of lower respiratory disease during clinical assessment or imaging and the oxygen saturation was ≥94%.[20] Patients did not require hospitalization and therefore were considered suitable for being treated at home.

Controls were recruited from Hospital staff of Trieste University Hospital and Treviso General Hospital who, according to institutional surveillance, were at least biweekly tested for SARS-CoV-2 with polymerase chain reaction (PCR) until the time of the psychophysical evaluation. Controls were enrolled on a voluntary basis among those who consistently tested negative for SARS-CoV-2 infections and matched 1:1 to cases by sex and age (±3 years) at the time of evaluation.

Exclusion criteria for both cases and controls were as follows: (1) previous surgery, trauma, or radiotherapy in the oral and nasal cavities; (2) chronic rhinosinusitis; (3) neurological/psychiatric disorders; and (4) preexisting olfactory/gustatory dysfunction (patients were asked: "Did you have an impairment in the sense of smell or taste preceding COVID-19 diagnosis?"). Both cases and controls underwent nasal fiber optic endoscopy at the time of the enrolment.

2.1.1 | Self-assessment of chemosensory perception

Upon enrolment into the study, 1 year after COVID-19, patients were asked to self-evaluate the alteration in olfactory or gustatory perception during the acute phase of COVID-19 and whether it was still present. More precisely, self-reported chemosensory function during the acute phase of the disease, at the enrolment, and 2 years after the infection, was evaluated by 22-item Sino-Nasal Outcome Test (SNOT-22), item "Sense of smell or taste," scored on a six-point Likert scale.[21]

2.2 | Psychophysical olfactory and gustatory assessment

Psychophysical evaluation was performed 1 and 2 years after SARS-CoV-2 infection in clinical subjects, whereas healthy subjects underwent the same evaluation at the time of enrolment. Orthonasal olfactory function was assessed using the validated extended Sniffin' Sticks test battery (Burghart Messtechnik, Holm, Germany) including phenylethyl-alcohol odor thresholds, odor discrimination, and odor identification.[22] Retronasal olfactory function was tested using 20 powdered tasteless aromas (Givaudan Schweiz AG, Dubendorf, Switzerland) as described by Yoshino et al.[23] The gustatory assessment was performed using the Taste Strips test (Taste Strips; Burghart Messtechnik, Holm, Germany) according to a standardized protocol.[24] Orthonasal function was expressed through a Threshold, Discrimination, and Identification (TDI) score, indicating normosmia (TDI ≥ 30.75), hyposmia (TDI 16.25–30.50) and anosmia (TDI ≤ 16.0). To estimate the overall rate of improvement, an increase of 5.50 points or more in TDI score was considered a minimal clinically significant difference for subjective improvement in olfactory function, as described.[25] By Taste Strips test a Taste Strips Score (TSS) was calculated and used for the identification of hypogeusia (TSS < 9 points) and normogeusia (TSS ≥ 9 points). A compromised orthonasal and retronasal identification ability was defined as score < 12.[26,27] More details on psychophysical evaluation and statistical methods are in the online Supporting Information Methods. At 1-year evaluation, cases self-reporting an OD and all participants showing an OD at psychophysical evaluation were advised starting with olfactory training according to guidelines.[28]

2.2.1 | Nasal trigeminal chemesthesis

To obtain an approximation of nasal trigeminal function, each participant was asked to sniff freshly prepared 70% acetic acid solution and indicate the intensity of the stinging on a Visual Analogue Scale (VAS) with a range score of 0–100 (i.e., 0 as no perception to 100 as extremely strong perception).

2.3 | Statistical analyses

The sample size was calculated as described in our first previous research timeline.[9] Qualitative variables were reported as percentage with corresponding 95% confidence intervals (CIs) according to Clopper-Pearson. Variation in the prevalence of independent samples was calculated as the difference in percentages with corresponding 95% CI. To compare paired proportions, McNemar's test was used. Continuous variables were reported as median values with interquartile range (IQR). Median differences and corresponding 95% CIs around the point estimate were computed using Hodges-Lehmann method. Statistical analysis was conducted with R (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Patients' characteristics

The 1-year and 2-year psychophysical assessments of the olfactory and gustatory function took place after a median of 409 days (range, 366–461 days) and 765 days (range, 739–800 days) from the first SARS-CoV-2 positive swab, respectively. Of 100 patients with mild COVID-19 completing the 1-year follow-up evaluation, 93 (93.0%) responded and completed the 2-year follow-up interview and psychophysical assessment (median [IQR] age, 49 [37–56] years; 38 [40.9%] men). Sociodemographic and clinical characteristics of 93 cases and 93 controls are summarized in Table 1. Eight patients (8.6%) had documented re-infection with SARS-CoV-2 during the period when the Omicron variant was prevalent. None of these reported changes in chemosensory symptoms following re-infection.

3.2 | Self-reported chemosensory function

Sixty-two patients (66.7%, 95% CI: 56.1–76.1%), reported an altered sense of smell or taste (SNOT-22 > 0) at baseline, 28 (30.1%, 21.0–40.5%) at 1-year, compared with 18 (19.4%, 11.9–28.9%) at the 2-year visit. Among the 62 patients with COVID-19–associated smell or taste dysfunction during the acute phase of the disease at baseline, 44 (71.0%, 95% CI: 58.1–81.8%) reported complete resolution after 2 years, 13 (21.0%, 11.7–33.2%) reported a decrease in the severity, and 5 (8.1%, 2.7–17.8%) reported the symptom was unchanged or worse.

3.3 | Olfactory function and nasal trigeminal chemesthesis

Cases performed poorly compared with controls, both at 1-year and 2-year follow-up, across all orthonasal olfactory sub-tests including TDI as well as the combined TDI score (Figure 1 and Table S1). Although a significant improvement was seen between 1-year and 2-year evaluation in identification and discrimination capabilities, no improvement was observed concerning threshold. On an individual basis, 19 subjects (20.4%) exhibited improvement of more than 5.5 points in the TDI score from 1-year to 2-year follow-up, whereas 7 (7.5%) subjects exhibited a decrease > 5.5 points. Among cases, the rate of orthonasal OD (TDI $\leq$ 30.50) fell from 42.0% at 1-year evaluation to 27.9% at 2-year follow-up (absolute difference, −14.0%; CI, −21.8% to −2.6%; $p = 0.016$). Two years after the infection, subjects with prior COVID-19 were significantly ($p = 0.005$) more likely than controls to have an altered sense of orthonasal smell (27.9% vs. 10.8%; absolute difference, 17.2%; 95% CI, 5.2% to 28.8%) (Figure 2 and Table S2). Three patients (3.2%) were functionally anosmic at 2-year follow-up compared to 0% of controls (absolute difference, 3.2%; 95% CI, −1.4% to 9.1%). Figure 3 showed the prevalence of anosmic, hyposmic, and normosmic cases at 1-year and 2-year follow-up according to TDI score.

A significant improvement in the orthonasal olfactory identification function was observed between 1-year and 2-year evaluation in cases (40.9% vs. 12.9%; absolute difference, −28.0%; 95% CI, −31.7% to −18.0%; $p < 0.001$), whereas no significant differences ($p = 0.220$) were seen between cases at 2 years and controls (Figure 2 and Table S2). A significant improvement in the retronasal olfactory function was observed between 1-year and 2-year evaluation in cases and no significant differences in retronasal smell were seen between cases at 2 years and controls (Figure 1 and Table S1). On individual basis, a decline in the prevalence of retronasal OD (retronasal score < 12) was observed at 2-year compared to 1-year evaluation (8.6% vs. 16.1%; absolute difference, −7.5%; 95% CI, −18.0% to 2.9%; $p = 0.077$). A nonsignificant ($p = 0.211$) absolute difference of 5.4% (95% CI, −2.2% to 13.5%) was observed between the prevalence of retronasal dysfunction in controls (3.2%) and that observed in cases (8.6%) at 2-year follow-up (Table S2).

The estimation of the trigeminal sensitivity by VAS after sniffing a 70% acetic acid solution revealed significant lower VAS scores in cases compared to controls both at 1-year and 2-year follow-up assessment. No improvement in trigeminal sensitivity was observed in cases between 1-year and 2-year evaluation (Table S1).

TABLE 1 Sociodemographic and clinical characteristics of cases and age and sex-matched controls.

Characteristic	Participants, *n* (%)		Difference (95% CI)
	Cases (*n* = 93)	Controls (*n* = 93)	
Age (years), median (IQR)	49.0 (36.5 to 56.0)	49.0 (36.0 to 56.5)	
Sex, *n* (%)			
Female	55 (59.1)	55 (59.1)	
Male	38 (40.9)	38 (40.9)	
Smoking habits, *n* (%)			
Current	18 (19.4)	23 (24.7)	0.05 (−0.07 to 0.17)
Former	20 (21.5)	15 (16.1)	0.05 (−0.06 to 0.17)
Never	55 (59.1)	55 (59.1)	0.00 (−0.14 to 0.14)
Drinking habits, *n* (%)			0.08 (−0.07 to 0.22)
Current	35 (37.6)	42 (45.2)	
Never	58 (62.4)	51 (54.8)	
Comorbidities (number), *n* (%)			0.06 (−0.06 to 0.19)
0	66 (71.0)	72 (77.4)	
1–2	27 (29.0)	21 (22.6)	
Comorbidity, *n* (%)			
Immune suppression	2 (2.2)	0 (0.0)	0.02 (−0.01 to 0.05)
Diabetes	1 (1.1)	2 (2.2)	0.01 (−0.02 to 0.04)
Obesity (BMI ≥30 kg/m^2)	10 (10.8)	2 (2.2)	0.09 (0.02 to 0.16)
Cardiovascular disease	9 (9.7)	16 (17.2)	0.08 (−0.02 to 0.17)
Cancer	1 (1.1)	0 (0.0)	0.01 (−0.01 to 0.03)
Chronic respiratory disease	6 (6.5)	2 (2.2)	0.04 (−0.02 to 0.10)
Kidney disease	0 (0.0)	0 (0.0)	0.00 (0.00 to 0.00)
Liver disease	2 (1.1)	0 (0.0)	0.01 (−0.01 to 0.03)

Abbreviations: BMI, body mass index; CI, confidence interval; IQR, interquartile range.

3.4 | Gustatory function

Cases performed poorly in TSS compared with controls, both at 1-year and 2-year follow-up (Figure 1 and Table S1). Among cases, the prevalence of gustatory dysfunction (TSS < 9) decreased from 25.8% at 1-year follow-up to 14.0% at 2 years (25.8%; absolute difference, −11.8%; 95% CI, −24.2% to 0.6%; $p = 0.098$). A nonsignificant ($p = 0.496$) absolute difference of 4.3% (95% CI, −5.8% to 14.4%) was observed between the prevalence of gustatory dysfunction in controls (9.7%) and that observed in cases (14.0%) at 2-year follow-up (Figure 2 and Table S2).

4 | DISCUSSION

Two years after SARS-CoV-2 infections, cases scored lower than controls on measures of olfactory and gustatory function, as well as on nasal trigeminal sensitivity subjective perception. Particularly, cases still had a significant excess of psychophysically measured OD compared to control population (28% vs. 11%). Thus, chemosensory impairment seems to be a highly prevalent component of long-COVID-19 in patients with antecedent mild infection. Importantly, these data refer to subjects who contracted the infection during the first wave of the COVID-19 pandemic in Italy when the predominant circulating variant was D614G, which carried a higher prevalence of OD.[29] Recent psychophysical data and case-controls studies based on self-reported symptoms assessing the prevalence of OD during the acute phase of the infection in the different waves sustained by different variants have shown that the impact on chemosensory disorders has significantly diminished with the emergence of the Omicron variant.[30,31]

In line with what observed in the present investigation, four independent studies reported the prevalence and recovery rate of self-reported chemosensory dysfunction 2 years after SARS-CoV-2 infection with figures ranging from 8% to 30%, and from 60% to 87%, respectively.[32–35] However, only one study has evaluated the prevalence of OD 2 years after infection by means of psychophysical evaluation, observing a persistent smell dysfunction in 3% of cases.[33] This much lower rate of OD compared

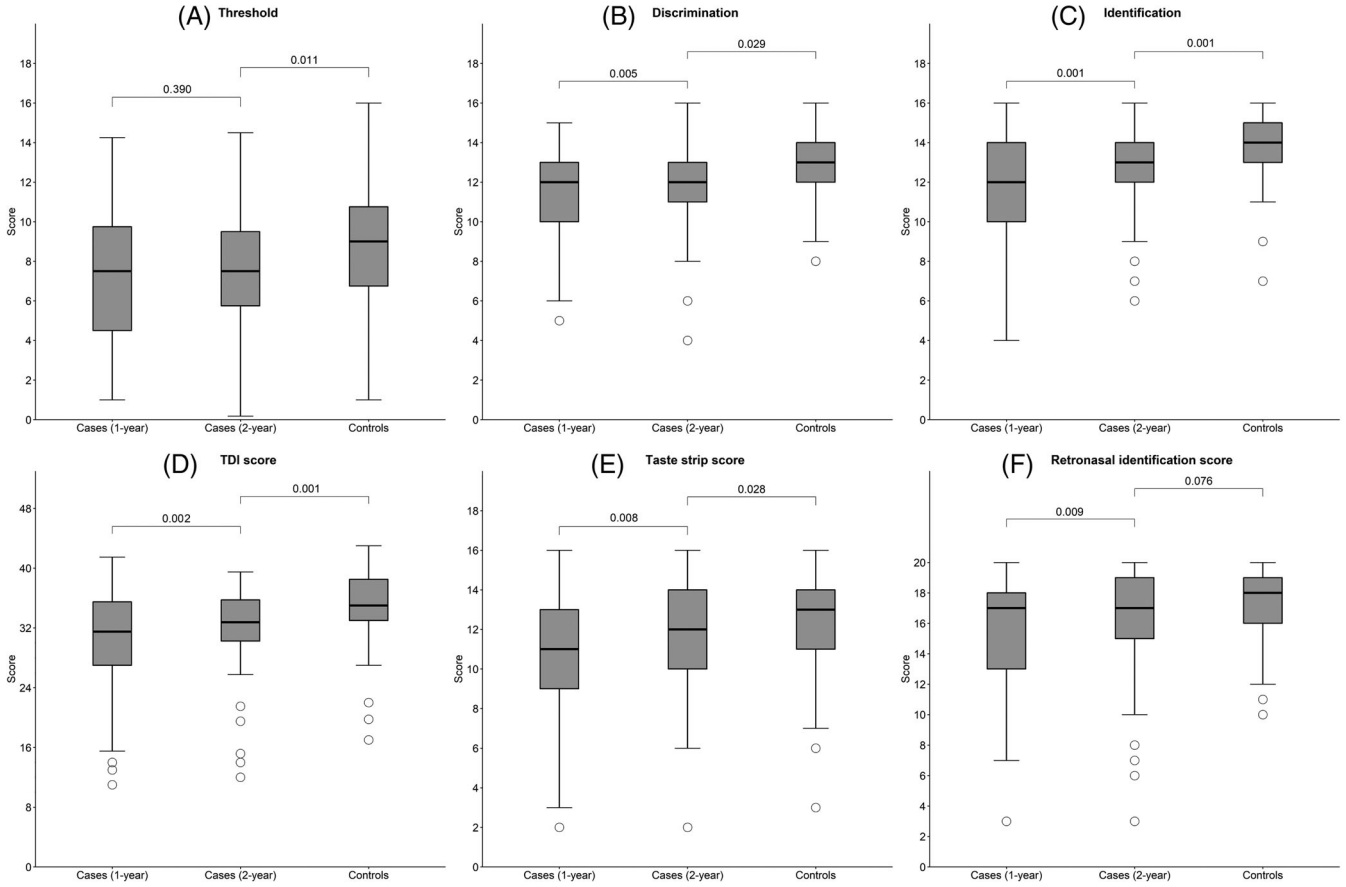

FIGURE 1 Scores for threshold (A), discrimination (B), identification (C), combined TDI score (D), taste (E), and retronasal smell (F) in cases and controls. The top and bottom of the boxes represent the upper and lower quartiles, respectively; the horizontal lines within the boxes indicate the medians; the whiskers show the range and the plotted points represent the outliers. TDI, threshold, discrimination, identification.

to that observed in the present study may at least in part be due to the fact that only an orthonasal odor identification test was performed. In fact, based only on the orthonasal identification test, the prevalence of OD at 2 years in the present study would have been 13%, less than half of what was obtained with a complete evaluation of the orthonasal function. It has already been observed that the most compromised parameter following SARS-CoV-2 infection is the threshold.[9] Moreover, here, we also noted that, although cases significantly improved in discrimination and identification capabilities from 1 to 2 years after the infection, no improvement was seen in threshold performances. Thus, post-COVID-19 patients retaining an OD could be particularly at risk of exposure to environmental hazards.

In the present series, we observed a normalization of olfactory function after more than 1 year after SARS-CoV-2 infection in 14% of subjects and overall, a clinically significant late improvement was observed in 20% of cases. However, we also found that in about 8% of subjects the sense of smell can fluctuate, thus indicating that continuous monitoring of the evolution of the olfactory abilities may be required. These fluctuations could be the consequence of a concomitant nasal congestion causing recurrent conductive problems superimposing on any COVID-19–related sensorineural deficit.[36] However, only limited benefit has been found using intranasal corticosteroids with respect to improved olfactory scores in COVID-19.[37] Although a prospective study[38] found that approximately 20% of confirmed postinfectious OD (PIOD) cases showed significant improvement in olfactory scores following oral steroid course, half of the responders had, however, no findings of nasal inflammation; this suggests that congestion does not fully account for the fluctuations reported.

We have not included patients with severe forms of COVID-19 and this may influence the prevalence rates of OD because it has been observed that the prevalence of self-reported chemosensory dysfunction is more frequent in subjects with mild to moderate disease.[39] It is very probable that patients suffering from severe forms of COVID-19 either are unable to report any alterations in the sense of taste or smell, or neglect these symptoms, or that these symptoms are not recorded by healthcare professionals. It has been indeed seen how the prevalence of alterations

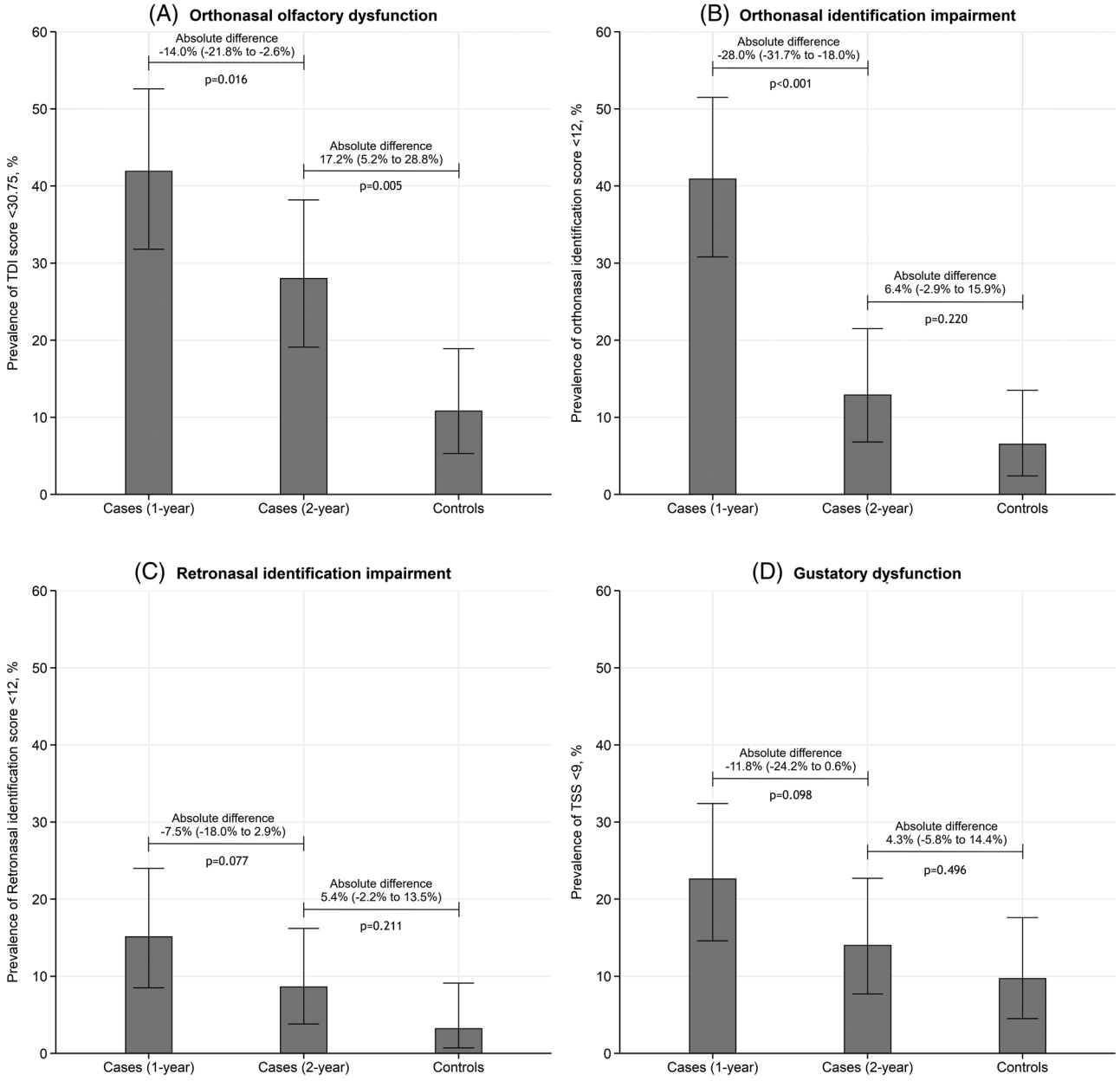

FIGURE 2 Prevalence of psychophysically assessed olfactory and gustatory dysfunction in cases and controls. (A) Prevalence of olfactory dysfunction according to TDI score (defined by Sniffin' Sticks score < 30.75). (B) Prevalence of orthonasal identification impairment based on orthonasal identification score < 12. (C) Prevalence of retronasal identification impairment based on retronasal identification score < 12. (D) Prevalence of gustatory dysfunction based on TSS < 9. Error bars indicate 95% CIs. CI, confidence interval; OD, olfactory dysfunction; TDI, threshold, discrimination, identification; TSS, Taste Strips Score.

of smell in hospitalized patients increase from 33% to 98% depending on whether the evaluation is made by means of interviews or psychophysical tests, respectively.[40]

Although hypogeusia could very often be a consequence of an impairment in the retronasal smell,[41] a fraction of subjects in the present series exhibited a true alteration in the perception of basic tastes with the prevalence at 2 years being, however, lower than that of OD. Several potential mechanisms of the hypogeusia in COVID-19 have been described,[42] including a possible direct infection of the taste buds by SARS-CoV-2.[43] Furthermore, chemosensory interaction after olfactory impairment has been described and could be a reason for the observed lowering in both taste function and nasal trigeminal perception.[44]

Intriguingly, cases exhibited a significantly reduced sensitivity of the intranasal trigeminal system compared to matched controls both at 1-year and 2-year evaluation, without evidence of an improvement, confirming previous self-reported observations showing that chemesthesis is significantly reduced in COVID-19.[45] However, the

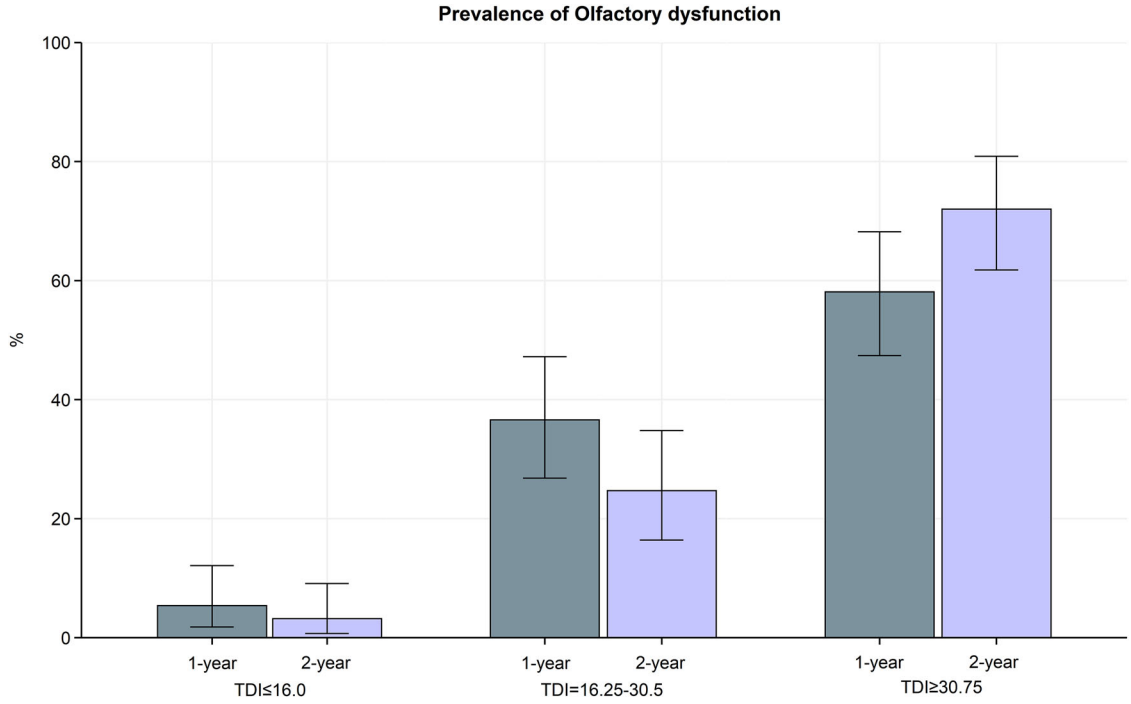

FIGURE 3 Prevalence of anosmic (TDI $\leq$ 16.0), hyposmic (TDI 16.25–30.50), and normosmic cases (TDI $\geq$ 30.75) at 1-year and 2-year follow-up. Error bars indicate 95% CIs. CI, confidence interval; TDI, threshold, discrimination, identification.

mechanisms for trigeminal dysfunction are yet to be elucidated. As a hypothesis, because trigeminal and olfactory afferents share specific brain projection areas, they could amplify each other.[46,47] Thus, a decrease in olfactory input could therefore decrease trigeminal perception. However, a more accurate evaluation of trigeminal function is necessary in order to be able to formulate more detailed hypotheses and study the possible pathogenetic mechanisms of trigeminal dysfunction.

Numerous studies have suggested that acute viral infections (including COVID-19), even in the case of asymptomatic manifestations, could affect cognition both in the short and long term, and may facilitate cognitive decline and the onset of dementia (primarily Alzheimer's disease).[48] This could occur through direct infection of the central nervous system (CNS) or indirectly through neuroinflammation, or epigenetic, immunological, and hypercoagulability changes that cause both structural and functional alterations.[49] Thus, the present findings, in addition to describing the long-term prevalence and recovery rates of smell and taste impairment in subjects who were affected by mild to moderate forms of COVID-19, mirror what has been observed in patients affected by long COVID-19 dominated by the so-called brain fog and characterized by short-term memory loss, confusion, and difficulty concentrating.[50] In fact, neurocognitive disorders have also been reported more frequently in patients who had mild to moderate forms of COVID-19 without hospital admission and were in a substantial fraction of cases associated with OD.[51] Of interest, impairment in cognitive communication and attention and executive functions associated with abnormalities in the medial temporal lobe and gyrus rectus was observed in mildly symptomatic or asymptomatic COVID-19 patients, as well as brain patterns similar to neurodegenerative processes.[39,52–55] These observations provide a rationale for conducting studies to evaluate potential attentional and cognitive deficit in patients with persistent OD. Furthermore, It is known that smell loss is one of the prodromal symptoms of many neurodegenerative diseases including Alzheimer's and Parkinson's diseases[56] and disorders with impaired attentional capacity,[57,58] with mechanisms of OD being yet to be elucidated. Despite there is no evidence yet that patients with post-COVID-19 olfactory loss are at higher risk for neurodegenerative diseases, the existence of a relevant fraction of patients with persistent long-term OD should be enough to consider that hypothesis and design studies to investigate these aspects.

Finally, given that 645 million cases of COVID-19 have been reported worldwide, health leaders, policy makers, and research funders should allocate adequate resources both to support chemosensory research and to sustain health care professionals facing with an unprecedented number of patients with olfactory and gustatory dysfunction.

The main limitation of the present study is the absence of a psychophysical evaluation prior to and during the acute phase of the disease. Also, these data may not apply to subjects with previous severe COVID-19 and patients with recent infections sustained by Omicron variants infections. In order to reduce the burden of assessment, the study of trigeminal sensitivity was carried out using a VAS scale after sniffing a highly concentrated acetic acid solution. We believe that the study of nasal trigeminal sensitivity should be further investigated in such patients using ascending concentrations for threshold determination and/or a trigeminal lateralization test.[59] During the first psychophysical evaluation, all participants with reported or detected OD were recommended to use olfactory training. Unfortunately, we have no information on training compliance and therefore cannot estimate the impact of this treatment on olfactory recovery in cases. The aim of this study was to evaluate the added burden of COVID-19 related OD, and therefore participants with known prior OD were excluded from both groups. In doing so, we likely underestimate the true prevalence of OD, which has been shown to be up to 20% in unselected population studies.[60] Finally, the control group was not re-evaluated 1 year after the first evaluation. However, we believe that within 1 year there are no significant spontaneous changes in chemosensory function.[22,61] Furthermore, given the enormous spread of the infection in the last year, even if not documented, it would have been unlikely that all subjects in the control group were still COVID free at the time of the second evaluation.

5 | CONCLUSION

Two years after SARS-CoV-2 infections, cases scored lower than controls on measures of olfactory, gustatory, and trigeminal nasal sensitivity functions. Although a proportion of subjects recovered from long-lasting smell and taste dysfunction, cases still exhibited a significant excess of OD when compared to matched controls with SARS-CoV-2 infection increasing the prevalence of smell impairment in the population by 2.5-fold. Health systems should be prepared to face with an unprecedented number of patients seeking counseling and care for this disabling morbidity.

AUTHOR CONTRIBUTIONS

Dr Boscolo-Rizzo and Spinato had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Drs Boscolo-Rizzo, Hummel, Invitto, Menini, Hopkins, and Tirelli. Acquisition, analysis and interpretation of data: Drs Boscolo-Rizzo, Hummel, Invitto, Spinato, Tomasoni, Emanuelli, Tofanelli, Cavicchia, Grill, Vaira, Lechien, Borsetto, Polesel, Dibattista, Menini, Hopkins, Tirelli. Drafting of the manuscript: Drs Boscolo-Rizzo, Hummel, Invitto, Hopkins. Critical revision of the manuscript for important intellectual content: Drs Boscolo-Rizzo, Hummel, Invitto, Spinato, Tomasoni, Emanuelli, Tofanelli, Cavicchia, Grill, Vaira, Lechien, Borsetto, Polesel, Dibattista, Menini, Hopkins, Tirelli. Statistical analysis: Drs Tomasoni and Polesel. Supervision: Drs Boscolo-Rizzo, Hummel, Invitto, Menini, Hopkins, Tirelli.

ACKNOWLEDGMENTS

The authors would like to thank the patients and healthcare workers whose participation made this study possible. They also thank Emila Cancellieri, MD, Andrea D'Alessandro, MD, Riccardo Marzolino, MD, and Enrico Zanelli, MD for their support during the chemosensory psychophysical assessment. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS APPROVAL

This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the ethic committees for clinical experimentation of Treviso and Belluno provinces (ethic vote: 780/CE) and Friuli Venezia Giulia Region (CEUR-2020-Os-156).

INFORMED CONSENT

Written informed consent was obtained from the participants.

ORCID

Paolo Boscolo-Rizzo MD https://orcid.org/0000-0002-4635-7959

Luigi Angelo Vaira MD https://orcid.org/0000-0002-7789-145X

Claire Hopkins MA(Oxon), DM https://orcid.org/0000-0003-3993-1569

REFERENCES

1. 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*. 2020;146(8):729-732. https://doi.org/10.1001/jamaoto.2020.1379

2. Lechien JR, Chiesa-Estomba CM, Place S, et al. Clinical and epidemiological characteristics of 1,420 European patients with mild-to-moderate coronavirus disease 2019. *J Intern Med*. 2020;288(3):335-344. https://doi.org/10.1111/joim.13089
3. Vaira LA, Deiana G, Fois AG, et al. Objective evaluation of anosmia and ageusia in COVID-19 patients: single-center experience on 72 cases. *Head Neck*. 2020;42(6):1252-1258. https://doi.org/10.1002/hed.26204
4. Iannuzzi L, Salzo AE, Angarano G, et al. Gaining back what is lost: recovering the sense of smell in mild to moderate patients after COVID-19. *Chem Senses*. 2020;45(9):875-881. https://doi.org/10.1093/chemse/bjaa066
5. 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. https://doi.org/10.1093/chemse/bjab006
6. Vaira LA, Salzano G, Le Bon S, 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*. https://doi.org/10.1177/01945998211061511
7. Lechien JR, Journe F, Hans S, et al. Severity of anosmia as an early symptom of COVID-19 infection may predict lasting loss of smell. *Front Med*. 2020;7:582802. https://doi.org/10.3389/fmed.2020.582802
8. 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)*. 2022;12(2):141 https://doi.org/10.3390/life12020141
9. 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*. 2021;59(6):517-527. https://doi.org/10.4193/Rhin21.249
10. Mendes Paranhos AC, Nazareth Dias ÁR, 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. https://doi.org/10.1001/jamanetworkopen.2022.30637
11. 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*. 2020;45(9):865-874. https://doi.org/10.1093/chemse/bjaa064
12. Bagnasco D, Passalacqua G, Braido F, et al. Quick Olfactory Sniffin' Sticks Test (Q-Sticks) for the detection of smell disorders in COVID-19 patients. *World Allergy Organ J*. 2021;14(1):100497. https://doi.org/10.1016/j.waojou.2020.100497
13. Gupta S, Kallogjeri D, Farrell NF, et al. Development and validation of a novel at-home smell assessment. *JAMA Otolaryngol Neck Surg*. 2022;148(3):252-258. https://doi.org/10.1001/jamaoto.2021.3994
14. Sheen F, Tan V, Lim AJ, et al. The COVOSMIA-19 trial: preliminary application of the Singapore smell and taste test to objectively measure smell and taste function with COVID-19. *Food Qual Prefer*. 2022;97:104482. https://doi.org/10.1016/j.foodqual.2021.104482
15. Li Z, Stolper S, Draf J, Haehner A, Hummel T. Smell, taste and trigeminal function: similarities and differences between results from home tests and examinations in the clinic. *Rhinology*. 2022;60(4):293-300. https://doi.org/10.4193/Rhin21.430
16. Le Bon SD, Pisarski N, Verbeke J, et al. Psychophysical evaluation of chemosensory functions 5 weeks after olfactory loss due to COVID-19: a prospective cohort study on 72 patients. *Eur Arch Otorhinolaryngol*. 2021;278(1):101-108. https://doi.org/10.1007/s00405-020-06267-2
17. Landis BN, Hummel T. New evidence for high occurrence of olfactory dysfunctions within the population. *Am J Med*. 2006;119(1):91-92. https://doi.org/10.1016/j.amjmed.2005.07.039
18. Hummel T, Whitcroft KL, Andrews P, et al. Position paper on olfactory dysfunction. *Rhinology*. 2016;56(1):1-30. https://doi.org/10.4193/Rhin16.248
19. Murphy C, Schubert CR, Cruickshanks KJ, Klein BEK, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. *JAMA*. 2002;288(18):2307-2312. https://doi.org/10.1001/jama.288.18.2307
20. Li K, Fang Y, Li W, et al. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). *Eur Radiol*. 2020;30(8):4407-4416. https://doi.org/10.1007/s00330-020-06817-6
21. Spinato G, Fabbris C, Polesel J, et al. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. *JAMA*. 2020;323(20):2089-2090. https://doi.org/10.1001/jama.2020.6771
22. 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*. 1997;22(1):39-52. https://doi.org/10.1093/chemse/22.1.39
23. Yoshino A, Goektas G, Mahmut MK, et al. A new method for assessment of retronasal olfactory function. *Laryngoscope*. 2021;131(2):E324-E330. https://doi.org/10.1002/lary.28698
24. Landis BN, Welge-Luessen A, Brämerson A, et al. "Taste Strips" - a rapid, lateralized, gustatory bedside identification test based on impregnated filter papers. *J Neurol*. 2009;256(2):242-248. https://doi.org/10.1007/s00415-009–0088-y
25. Gudziol V, Lötsch J, Hähner A, Zahnert T, Hummel T. Clinical significance of results from olfactory testing. *Laryngoscope*. 2006;116(10):1858-1863. https://doi.org/10.1097/01.mlg.0000234915.51189.cb
26. Croy I, Hoffmann H, Philpott C, et al. Retronasal testing of olfactory function: an investigation and comparison in seven countries. *Eur Arch Otorhinolaryngol*. 2014;271(5):1087-1095. https://doi.org/10.1007/s00405-013–2684–9
27. Oleszkiewicz A, Schriever VA, Croy I, Hähner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. *Eur Arch Otorhinolaryngol*. 2019;276(3):719-728. https://doi.org/10.1007/s00405-018–5248-1
28. 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*. 2021;147(5):1704-1719. https://doi.org/10.1016/j.jaci.2020.12.641
29. 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*. 2020;11(20):3180-3184. https://doi.org/10.1021/acschemneuro.0c00596

30. Boscolo-Rizzo P, Tirelli G, Meloni P, et al. COVID-19-related smell and taste impairment with widespread diffusion of SARS-CoV-2 Omicron variant. *Int Forum Allergy Rhinol*. 2022;12(10):1273-1281. https://doi.org/10.1002/alr.22995
31. 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*. 2023;61(1):32-38. https://doi.org/10.4193/Rhin22.294
32. 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 Neck Surg*. 2022; 148(9):889-891. https://doi.org/10.1001/jamaoto.2022.1983
33. Lechien JR, Vaira LA, Saussez S. Prevalence and 24-month recovery of olfactory dysfunction in COVID-19 patients: a multicentre prospective study. *J Intern Med*. 2023;293(1):82-90. https://doi.org/10.1111/joim.13564
34. Schambeck SE, Mateyka LM, Burrell T, et al. Two-year follow-up on chemosensory dysfunction and adaptive immune response after infection with SARS-CoV-2 in a cohort of 44 healthcare workers. *Life Basel Switz*. 2022;12(10):1556. https://doi.org/10.3390/life12101556
35. Boscolo-Rizzo P, Tofanelli M, Zanelli E, Gardenal N, Tirelli G. COVID-19-related quantitative and qualitative olfactory and gustatory dysfunction: long-term prevalence and recovery rate. *ORL J Otorhinolaryngol Relat Spec*. 2022; Sep 5; 1-5. https://doi.org/10.1159/000525861
36. Hsieh JW, Daskalou D, Detroux V, et al. Olfactory fluctuation revisited. *Laryngoscope*. 2020;130(10):2442-2447. https://doi.org/10.1002/lary.28918
37. 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*. 2022;47(4):509-515. https://doi.org/10.1111/coa.13933
38. 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. https://doi.org/10.1159/000516316
39. 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. https://doi.org/10.4193/Rhin20.185
40. Moein ST, Hashemian SMR, 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. https://doi.org/10.1002/alr.22587
41. Boscolo-Rizzo P, Hummel T, Hopkins C, et al. Comprehensive chemosensory psychophysical evaluation of self-reported gustatory dysfunction in patients with long-term COVID-19 a cross-sectional study. *JAMA Otolaryngol Head Neck Surg*. 2022;148(3):281-282. https://doi.org/10.1001/jamaoto.2021.3993
42. Hintschich CA, Niv MY, Hummel T. The taste of the pandemic-contemporary review on the current state of research on gustation in coronavirus disease 2019 (COVID-19). *Int Forum Allergy Rhinol*. 2022;12(2):210-216. https://doi.org/10.1002/alr.22902
43. Doyle ME, Appleton A, Liu QR, Yao Q, Mazucanti CH, Egan JM. Human type II taste cells express ACE2 and are infected by SARS-CoV-2. *Am J Pathol*. 2021:191(9):1511-1519. https://doi.org/10.1016/j.ajpath.2021.05.010
44. Migneault-Bouchard C, Hsieh JW, Hugentobler M, Frasnelli J, Landis BN. Chemosensory decrease in different forms of olfactory dysfunction. *J Neurol*. 2020;267(1):138-143. https://doi.org/10.1007/s00415-019-09564-x
45. Parma V, Ohla K, Veldhuizen MG, et al. More than smell-COVID-19 is associated with severe impairment of smell, taste, and chemesthesis. *Chem Senses*. 2020;45(7):609-622. https://doi.org/10.1093/chemse/bjaa041
46. Badran BW, Gruber EM, O'Leary GH, et al. Electrical stimulation of the trigeminal nerve improves olfaction in healthy individuals: a randomized, double-blind, sham-controlled trial. *Brain Stimulat*. 2022;15(3):761-768. https://doi.org/10.1016/j.brs.2022.05.005
47. Frasnelli J, Schuster B, Hummel T. Interactions between olfaction and the trigeminal system: what can be learned from olfactory loss. *Cereb Cortex*. 2007;17(10):2268-2275. https://doi.org/10.1093/cercor/bhl135
48. Xydakis MS, Albers MW, Holbrook EH, et al. Post-viral effects of COVID-19 in the olfactory system and their implications. *Lancet Neurol*. 2021;20(9):753-761. https://doi.org/10.1016/S1474-4422(21)00182-4
49. Hosseini S, Wilk E, Michaelsen-Preusse K, et al. Long-Term neuroinflammation induced by influenza a virus infection and the impact on hippocampal neuron morphology and function. *J Neurosci*. 2018;38(12):3060-3080. https://doi.org/10.1523/JNEUROSCI.1740-17.2018
50. Ali N. Brain fog as a long-term sequela of COVID-19. *SN Compr Clin Med*. 2023;5(1):9. https://doi.org/10.1007/s42399-022-01352-5
51. Graham EL, Clark JR, Orban ZS, et al. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 "long haulers". *Ann Clin Transl Neurol*. 2021;8(5):1073-1085. https://doi.org/10.1002/acn3.51350
52. Ramage AE. Potential for cognitive communication impairment in COVID-19 survivors: a call to action for speech-language pathologists. *Am J Speech Lang Pathol*. 2020;29(4):1821-1832. https://doi.org/10.1044/2020_AJSLP-20-00147
53. Aghagoli G, Gallo Marin B, Katchur NJ, Chaves-Sell F, Asaad WF, Murphy SA. Neurological involvement in COVID-19 and potential mechanisms: a review. *Neurocrit Care*. 2021;34(3):1062-1071. https://doi.org/10.1007/s12028-020-01049-4
54. Ardila A, Lahiri D. Executive dysfunction in COVID-19 patients. *Diabetes Metab Syndr*. 2020;14(5):1377-1378. https://doi.org/10.1016/j.dsx.2020.07.032
55. Appelhans BM, Thomas AS, Roisman GI, Booth-LaForce C, Bleil ME. Preexisting executive function deficits and change in health behaviors during the COVID-19 pandemic. *Int J Behav Med*. 2021;28(6):813-819. https://doi.org/10.1007/s12529-021-09974-0
56. Petekkaya E, Kuş B, Doğan S, et al. Possible role of endocannabinoids in olfactory and taste dysfunctions in Alzheimer's and Parkinson's patients and volumetric changes in the brain. *J Clin Neurosci*. 2022;100:52-58. https://doi.org/10.1016/j.jocn.2022.03.047
57. Invitto S, Piraino G, Ciccarese V, et al. Potential role of OERP as early marker of mild cognitive impairment. *Front Aging Neurosci*. 2018;10:272. https://doi.org/10.3389/fnagi.2018.00272

58. Invitto S, Calcagnì A, Piraino G, et al. Obstructive sleep apnea syndrome and olfactory perception: an OERP study. *Respir Physiol Neurobiol*. 2019;259:37-44. https://doi.org/10.1016/j.resp.2018.07.002
59. Hummel T, Frasnelli J. The intranasal trigeminal system. *Handb Clin Neurol*. 2019;164:119-134. https://doi.org/10.1016/B978-0–444-63855-7.00008-3
60. Mullol J, Alobid I, Mariño-Sánchez F, et al. Furthering the understanding of olfaction, prevalence of loss of smell and risk factors: a population-based survey (OLFACAT study). *BMJ Open*. 2012;2(6):e001256. https://doi.org/10.1136/bmjopen-2012-001256
61. Keller A, Hempstead M, Gomez IA, Gilbert AN, Vosshall LB. An olfactory demography of a diverse metropolitan population. *BMC Neurosci*. 2012;13:122. https://doi.org/10.1186/1471–2202–13-122

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: 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;1-12. https://doi.org/10.1002/alr.23148