Association between psychophysically measured olfactory dysfunction and mental health status in long COVID patients

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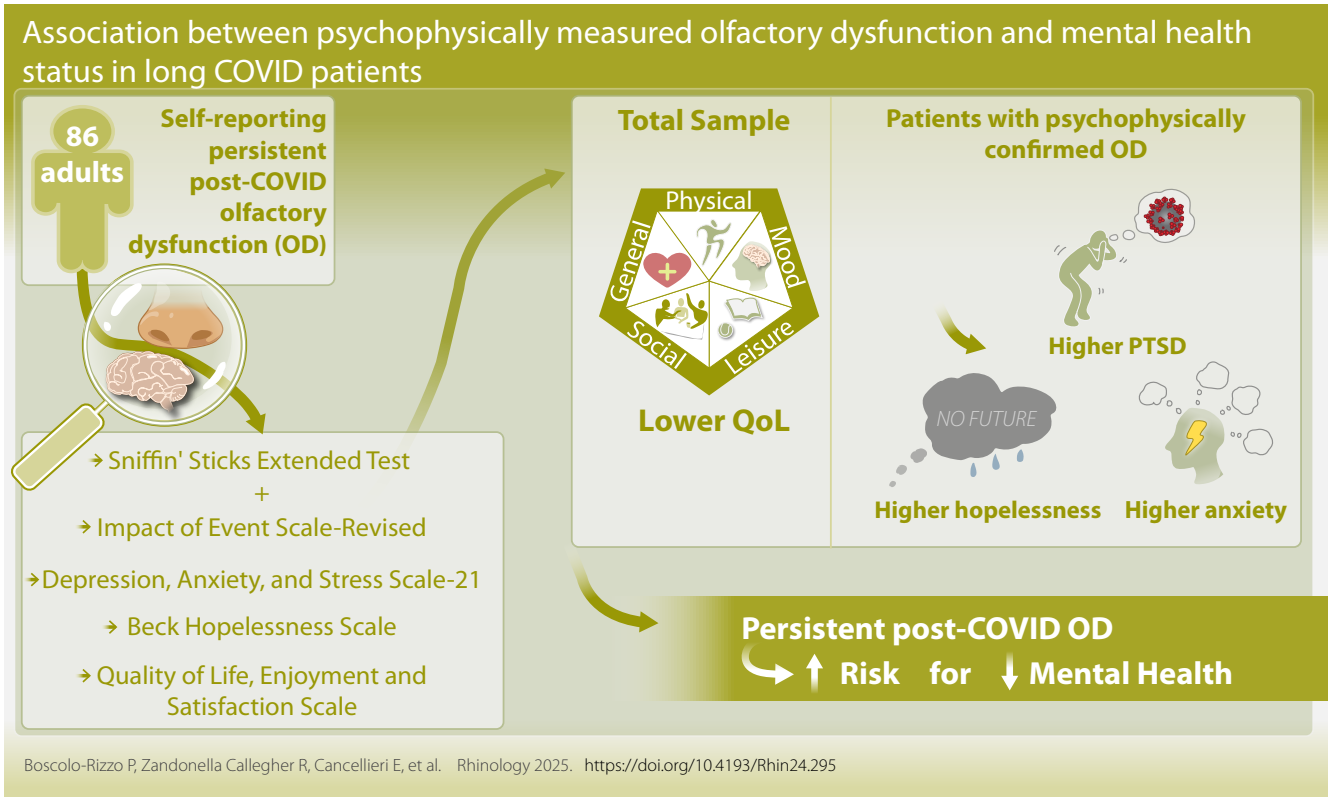

Abstract

Background: Long COVID frequently presents with persistent olfactory dysfunction (OD), affecting both physical and psychological well-being. This study aims to evaluate the mental health consequences of OD in long COVID patients.

Methodology: A cross-sectional study involved 86 adult patients. Participants presented OD for at least three months post-COVID-19 and were evaluated using the extended battery of Sniffin' Sticks test (SST). Psychological assessments included the Impact of Event Scale-Revised (IES-R), Beck Hopelessness Scale (BHS), Depression, Anxiety, and Stress Scale-21 (DASS-21), and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

Results: Significant differences in mental health factors were observed between patients with and without OD: in comparison to normosmic patients, hyposmic patients showed higher IES-R Total, Avoidance, and Hyperarousal scores, along with increased DASS-21 Anxiety scores and BHS total scores.

Conclusions: OD in long COVID patients were significantly associated with increased post-traumatic stress symptoms, anxiety symptoms and hopelessness, and with lower quality of life. Limited sample size, inability to determine causation and exploratory nature of the study may limit the generalizability of results. Comprehensive management addressing both physical and mental health should be assessed in long COVID patients.

Key words: anxiety, COVID-19, mental health, olfaction disorders, post-traumatic stress disorder

Introduction

The COVID-19 pandemic has caused severe global impacts, with the acute effects of SARS-CoV-2 infection being well documented. While most people recover, a significant number of subjects experience prolonged symptoms, known as long COVID. Long COVID, defined by WHO as post-COVID condition [1], refers to the persistence of symptoms long after the acute phase of the infection has resolved [2,3]. Long COVID remains a clinical challenge [4], with an estimated incidence of 10-35% for unvaccinated people not hospitalized and 8-12% for vaccinated individuals [5]. Persistent COVID-specific symptoms that significantly affect quality of life include fatigue, alterations in the sense of smell or taste, and muscle pain [6]. One of the most common and distressing symptoms reported by long COVID patients are the loss of the sense of smell [7–9]. Olfactory dysfunction (OD) has profound implications not only on physical health but also on psychological well-being [10]. The ability to smell influences daily activities, social interactions, enjoyment of food, and can even affect personal safety [11]. Consequently, patients experiencing OD may face unique psychological challenges, which are yet to be fully understood [12].

Evaluating the psychological and psychiatric consequences of OD in long COVID patients is critical for several reasons. Firstly, it provides a deeper understanding of the range of long COVID symptoms and their multidimensional effects on patients' lives. Secondly, assessing the psychological and psychiatric consequences can guide healthcare providers developing comprehensive management plans that address both physical and mental health needs. This is particularly important considering the potential for these psychological effects to exacerbate the burden of the disease, leading to a vicious cycle of deteriorating mental and physical health.

Despite the increasing recognition of long COVID as a public health issue, there remains a significant gap in the literature regarding the effects of OD on mental health in these patients. Most existing studies have focused on the physiological aspects of COVID-19 and its long-term symptoms, with less attention given to the psychological and psychiatric sequelae. Instead, symptoms of depression, anxiety and stress could be present 1 year after infection in 6%, 29% and 10% of previously infected patients respectively [13]. Furthermore, there is a lack of standardized, systematic approaches to evaluate these mental health impact, which hinders the development of effective interventions and support mechanisms.

Olfactory function can be assessed through questionnaires that capture patient self-reports, but it can also be measured and more precisely quantified using psychophysical tests [14]. To date, there is a significant gap in the literature regarding studies that correlate the degree of OD, as psychophysically quantified, with the severity of psychiatric issues.

To address this gap, we conducted an exploratory cross-sectional study. This study, which is the result of a collaboration between specialists in otolaryngology and psychiatry, evaluated psychological and psychiatric outcomes in long COVID patients with persistent self-reporting OD using validated psychological questionnaires and mental health screening tools. These instruments assess various aspects of mental health, including trauma, depression, anxiety, stress, and quality of life. We opted to psychophysically measure olfactory function and evaluate psychiatric symptoms dimensionally. By correlating the degree of OD with psychological outcomes, our study seeks to clarify the specific mental health challenges faced by these patients. We hypothesize that a psychophysically confirmed persistent OD following COVID-19 is associated with increased post-traumatic, depressive and anxiety symptoms, as well as reduced quality of life.

Materials and methods

Study design and participants

This exploratory cross-sectional study, adhering to the Declaration of Helsinki guidelines, received approval from the Ethics Committee for Clinical Experimentation of the Friuli Venezia Giulia Region (CEUR-2020-Os-156). Informed consent was secured from participants both verbally and in written form. Participants were consecutively recruited at the Department of Medical, Surgical and Health Sciences, Section of Otolaryngology, University of Trieste, Trieste, Italy. Inclusion criteria were adult patients (age ≥ 18); mild symptom during the acute phase of COVID-19; self-reported persistent alteration in the sense of smell ongoing for at least three months at the time of psychophysical evaluation with onset in conjunction with SARS-CoV-2 infection confirmed by positive results on real-time polymerase chain reaction. Subjects were considered to have had mild symptoms during the acute phase of the illness if they exhibited symptoms of COVID-19 without evidence of lower respiratory disease during clinical assessment or imaging and had an oxygen saturation of 94% or greater. Participants were excluded if they had: 1) previous surgery, trauma, or radiotherapy in the oral and nasal cavities, 2) chronic rhinosinusitis or allergic rhinitis, 3) psychiatric or neurological disorders, 4) pre-existing OD preceding COVID-19 diagnosis. Comparisons were made between subjects with psychophysically confirmed OD and those who were normosmic according to psychophysical tests.

Psychophysical evaluation of the orthonasal olfactory function

All enrolled subjects underwent an orthonasal olfactory function evaluation using the extended Sniffin' Sticks test (SST) battery (Burghart messtechnik, Wedel, Germany). This included tests for phenylethyl-alcohol (PEA) odour thresholds (T), odour discrimination (D), and odour identification (I), each with a maximum score of 16. The combined three results provided a total TDI

score ranging from 1 to 48, categorizing olfactory function into functional anosmia (TDI ≤ 16.0), hyposmia (16.25 - 30.50), or normosmia (TDI ≥ 30.75) [15]. The SST is known for its high test-retest reliability and was administered according to a standardized protocol [16].

Mental health status assessment

Impact of Event Scale-Revised (IES-R). The IES-R is a 22-item self-report measure designed to assess current post-traumatic stress symptoms [17]. It includes three subscales: intrusion (8 items), avoidance (8 items), and hyperarousal (6 items). Each item is scored on a 5-point scale ranging from 0 (not at all) to 4 (extremely), with higher scores indicating greater distress [18]. The IES-R is widely used in post-traumatic stress research and is considered reliable and valid for assessing distress related to traumatic events. A cut-off score of ≥ 33 for the total score or 1.5 for mean score indicate probable diagnosis of post-traumatic stress disorder (PTSD) [19]. The IES-R is validated within the Italian population [20].

Beck Hopelessness Scale (BHS). The BHS is a 20-item self-report inventory designed to measure three major aspects of hopelessness: feelings about the future, loss of motivation, and expectations [21]. Respondents answer 'true' or 'false' to each statement, with the total score indicating the level of hopelessness. The total BHS score ranges from 0 to 20, with higher score reflecting higher level of hopelessness, which is an important consideration for patients dealing with chronic conditions like long COVID, a risk factor for depressive symptoms. The score of the Italian version of BHS [22] can be categorized into normality (0–3), mild hopelessness (4–8), moderate hopelessness (9–14) and severe hopelessness (15–20) [23]. A total BHS score ≥ 9 is related to increased risk for suicide [24,25].

Depression Anxiety Stress Scale-21 Items (DASS-21). This scale, a short form of the original DASS [26], is a set of three self-report inventories designed to measure the negative emotional states of depression, anxiety, and stress [27]. The items are scored on a 4-point Likert scale, ranging from 0 (did not apply to me at all) to 3 (applied to me very much, or most of the time). The DASS-21 is a well-validated instrument and helps in differentiating between symptoms of anxiety and depression, which can often overlap. Excellent internal consistency of the three scales of the DASS-21 has been reported [28]. An Italian version of DASS-21 is available with normative data, confirming the validity of the three-factor structure [29]. The total score is calculated by adding the response values of each item, with higher scores indicating more severe levels of depressive, anxiety, and stress symptoms.

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). This questionnaire is a self-reported assessment tool that measures enjoyment and satisfaction experienced in various areas of daily functioning, such as physical health, mood, leisure activities, and social relationships [30]. It is particularly relevant in assessing the quality of life in patients with chronic health conditions like long COVID. Participants rate their satisfaction levels on a scale ranging from 1 (very poor) to 5 (very good), with higher scores reflecting higher levels of satisfaction. Scores are often calculated as percentage values of maximum score to facilitate meaningful comparisons between these areas. The percentage score is calculated as follows: (Raw score – Minimum possible score) / (Maximum possible score – Minimum) x 100 [31]. Rossi et al. [32] conducted an Italian validation study of the Q-LES-Q.

Statistical analysis

Study sample size was calculated to estimate a difference in mental health outcomes between normosmic and hyposmic patients using Cohens d as effect size. Assuming that the rate of hyposmic-to-normosmic patients was 2.5 [33], at least 81 patients had to be enrolled to estimate a Cohen's d of 0.7, fixing the a priori probabilities $\alpha=0.05$ and $\beta=0.20$.

IBM SPSS Statistics 28.0.0.0. program was used for the statistical analysis of the data. Data analysis was conducted to evaluate the prevalence of psychological and/or psychiatric alterations among the participants and correlate the severity of OD, as measured by the Sniffin' Sticks test, with the mental health outcomes derived from the administered questionnaires. Continuous variables were reported as mean values and standard deviation (SD), whereas dichotomous and categorical variables were reported as percentages. Effects size was calculated for each mental health outcomes; for consistency, Cohen's statistics were adopted for all outcomes, taking into consideration their nature (i.e., Cohen's d for continuous variables, Cohen's h for dichotomous variables, Cohen's w for categorical variables) and reported as absolute values. Student's t test was used for test difference in continuous variables between groups. Additionally, the Fisher's exact test was utilized for comparing distributions across different patient groups and focusing on the categorical data from psychological questionnaires and psychophysical test scores. The possible association between severity of OD (TDI score) and mental health outcomes was assessed using Pearson's correlation coefficient.

To account for potential confounding in the association between OD and mental health outcome, an analysis of variance (ANOVA) was further conducted to include sex and age (i.e., <45, 45-54, ≥55 years) as predictors. The significance level assumed was a p-value of < 0.05.

During the administration of the questionnaires, a psychiatrist was present to address any questions and minimize the likelihood of missing data. A predefined protocol was established to manage potential missing values in accordance with the gui-

Table 1. IES-R, DASS-21 and BHS scores according to TDI score.

	Total sample	TDI (1-48)		p-value
		<30.75	≥30.75	
	86	62	24	
IES-R				
Total score (0-88); mean (SD)	22.59 (20.02)	25.42 (20.93)	15.29 (15.58)	0.035*
Mean intrusion score; mean (SD)	1.01 (0.97)	1.12 (1.02)	0.72 (0.79)	0.086
Mean avoidance score; mean (SD)	0.98 (0.89)	1.11 (0.92)	0.65 (0.69)	0.027*
Mean hyperarousal score; mean (SD)	1.11 (1.06)	1.26 (1.11)	0.73 (0.80)	0.038*
% Normal (0-23)	58.1	50.0	79.2	0.098
% Mild psychological impact (24-32)	11.6	14.5	4.2	
% Moderate psychological impact (33-36)	5.8	8.1	0.0	
% Severe psychological impact (≥ 37)	24.4	27.4	16.7	
% Probable PTSD (≥ 33)	30.2	35.5	16.7	0.118
DASS-21				
Total score (0-126); mean (SD)	28.81 (24.38)	31.32 (26.11)	22.33 (18.11)	0.126
Depression score (0-42); mean (SD)	8.45 (10.02)	9.52 (10.89)	5.75 (6.78)	0.058
Anxiety score (0-42); mean (SD)	7.21 (7.74)	8.23 (8.51)	4.58 (4.43)	0.012*
Stress score (0-42); mean (SD)	13.14 (9.24)	13.58 (9.28)	12.00 (9.25)	0.480
% Normal depressive score (0-9)	23.3	19.4	33.3	0.680
% Mild depressive score (10-13)	7.0	6.5	8.3	
% Moderate depressive score (14-20)	15.1	16.1	12.5	
% Severe depressive score (21-27)	12.8	12.9	12.5	
% Extremely severe depressive score (≥ 28)	41.9	45.2	33.3	
% Normal anxiety score (0-7)	15.1	12.9	20.8	0.265
% Mild anxiety score (8-9)	8.1	6.5	12.5	
% Moderate anxiety score (10-14)	12.8	14.5	8.3	
% Severe anxiety score (15-19)	3.5	1.6	8.3	
% Extremely severe anxiety score (≥ 20)	60.5	64.5	50.0	
% Normal stress score (0-14)	36.1	33.9	41.7	0.461
% Mild stress score (15-18)	3.5	1.6	8.3	
% Moderate stress score (19-25)	12.8	12.9	12.5	
% Severe stress score (26-33)	15.1	17.7	8.3	
% Extremely severe stress score (≥ 34)	32.6	33.9	29.2	
BHS				
Total score (0-20); mean (SD)	4.83 (4.32)	5.31 (4.69)	3.58 (2.90)	0.044*
% Normal (0-3)	46.5	41.9	58.3	0.367
% Mild hopelessness (4-8)	38.4	38.7	37.5	
% Moderate hopelessness (9-14)	11.6	14.5	4.2	
% Severe hopelessness (15-20)	3.5	4.8	0.0	
% Increased risk for suicide (≥ 9)	15.1	19.4	4.2	0.100

* = p value statistically relevant.

delines of each questionnaire manual. Specifically, participants would have been excluded from the analyses if they had three or more missing items in any subscale. For subscales with two or fewer missing items, missing values would have been imputed using the median value calculated from the available items within that subscale. Outliers were identified through graphical

Table 2. Q-LES-Q scores according to TDI score.

	Total sample	TDI (1-48)		p-value
		<30.75	≥30.75	
	86	62	24	
Q-LES-Q				
Percentage score of Q-LES-Q areas; mean (SD)				
Physical health/activities %	58.96 (21.97)	58.89 (23.29)	59.11 (18.59)	0.967
Feelings %	72.65 (12.22)	72.49 (17.50)	73.09 (16.82)	0.886
Work %	54.26 (40.07)	54.40 (40.76)	53.91 (39.07)	0.960
Household duties %	69.94 (25.17)	71.12 (26.00)	66.90 (23.15)	0.488
School/course work %	5.99 (18.48)	4.35 (15.85)	10.23 (23.87)	0.274
Leisure time activities %	61.80 (18.01)	61.25 (19.39)	63.23 (14.10)	0.650
Social relations %	74.14 (14.81)	73.27 (15.16)	76.41 (13.92)	0.380
General activities %	63.86 (17.78)	62.99 (19.50)	66.09 (12.34)	0.384
Raw score of Q-LES-Q areas; mean (SD)				
Physical health/activities (13-65)	43.66 (11.43)	43.63 (12.11)	73.75 (9.67)	0.965
Feelings (14-70)	54.67 (9.64)	54.58 (9.81)	54.92 (9.41)	0.886
Work (12-60)	34.14 (24.65)	34.05 (25.12)	34.38 (23.91)	0.956
Household duties (10-50)	37.38 (11.82)	37.79 (12.31)	36.33 (10.63)	0.611
School/course work (10-50)	3.44 (10.36)	2.55 (8.96)	5.75 (13.28)	0.284
Leisure time activities (6-30)	20.86 (4.32)	20.69 (4.65)	21.17 (3.38)	0.651
Social relations (11-55)	43.63 (6.52)	43.24 (6.68)	44.63 (6.12)	0.381
General activities (14-70)	49.76 (9.95)	49.27 (10.92)	51.00 (6.90)	0.386

inspection of the distribution.

Results

Between February 2022 and May 2023, 86 patients self-reporting persistent OD following COVID-19 (mean [SD] age, 49 [15.6] years; 63 [73.3%] women) out of 109 consecutive eligible individuals (78.9%) agreed to participate in this study.

Following a comprehensive evaluation of orthonasal olfactory function, the mean (SD) TDI score was 26.3 (5.9), with scores of 5.3 (2.6) for threshold (T), 10.7 (2.3) for discrimination (D), and 10.3 (2.7) for identification (I) subdomains. Based on TDI scores, 3 patients (3.5%) were anosmic, 59 (68.6%) were hyposmic, and 24 (27.9%) were normosmic.

The 86 study participants were categorized into two groups according to their TDI scores: the first group consists of 24 subjects with persistent self-reported OD but a TDI score ≥ 30.75 (mean [SD] TDI score, 33.2 [1.8]), and the second group consists of 62 subjects with persistent self-reported OD and a TDI score < 30.75 (mean [SD] TDI score, 23.6 [4.6]). The mean (SD) duration of OD at the time of evaluation was 15.1 (6.1) months; no differences emerged between normosmic and hyposmic patients (mean OD duration: 15.5 and 14.9, respectively; p=0.752).

The mean psychological questionnaires and mental health screening tools scores of the two groups are reported in Table 1 and Table 2. Considering IES-R scores, significantly higher scores were found in subjects with a TDI score < 30.75 compared to those with a TDI score ≥ 30.75, both in mean IES-R Total score (25.42 ± 20.93 vs 15.29 ± 15.58; Cohen's d=0.55; p=0.035), mean Avoidance score (1.11 ± 0.92 vs 0.65 ± 0.69; d=0.57; p=0.023), and mean Hyperarousal score (1.26 ± 1.11 vs 0.73 ± 0.80; d=0.55; p=0.038), while no significant differences were observed in mean Intrusion score (p=0.086) (Table 1).

Considering DASS-21, the mean Anxiety score was significantly higher in patients with a TDI score < 30.75 (8.23 ± 8.51 vs 4.58 ± 4.43; d=0.54; p=0.012), while only a trend was observed in mean Depression score (p=0.059) and no significant differences were observed in mean Stress score (p=0.480) (Table 1). Considering BHS, the mean total score was higher in subjects with a TDI score < 30.75 (5.31 ± 4.69 vs 3.58 ± 2.90; d=0.44; p=0.044) but BHS ≥ 9 was not significantly more frequent (p=0.100) (Table 1). Finally, no statistically relevant differences in Q-LES-Q scores were observed between groups (Table 2).

After adjusting for potential bias due to sex and age in a multivariable model (ANOVA), scores were significantly different according to OD for IES-R Total score (p=0.038), Avoidance (p=0.032), Hyperarousal (p=0.043), but not for DASS-21 Anxiety

score (p=0.128) and BHS Total score (p=0.174). Finally, we explored the possible association between severity of OD (TDI score) and mental health outcomes, finding no statistically significant correlations (Pearson's coefficient of -0.25 for IES-R Total score, -0.11 for DASS-21 Total score, -0.21 for BHS, -0.02 for Q-LES-Q, all p>0.05).

There were no missing data. No outliers were identified through graphical inspection of the distribution.

Discussion

This study explored whether persistent psychophysically confirmed OD, distinct from the acute phase of COVID-19 and associated with long COVID, may be linked to changes in mental health status.

Higher rates of symptoms of anxiety, depression, PTSD, psychological distress and stress have already been reported during COVID-19 pandemic [34]. For instance, the persistence of significant PTSD-like symptoms can be related to unremitting exposure to physical symptoms such as OD that could negatively affect mental health and continuously trigger post-traumatic like symptoms. PTSD symptoms have been frequently measured with the Impact of Event Scale-Revised IES-R [23,24], with values higher than 33 and suggestive of PTSD reported in 23.5% of respondents in an Italian general population sample during the first Italian lock-down period [37], and in 31.8% of discharged patients after ICU admission due to acute hypoxemic respiratory failure related to COVID-19 infection [38]. Outside from COVID-19 pandemic, Eid and colleagues [39] reported results from a Norwegian non–clinical sample, with an IES-R mean total score of 15.86, mean intrusion score of 0.91, mean avoidance score of 0.84 and mean Hyperarousal score of 0.36. Results from our outpatient's sample with persistent OD highlighted 30% of responders with an IES-R total score ≥ 33 and therefore suffering from probable PTSD. IES-R scores resulted higher than in non-clinical populations [39] and even greater than individuals from the general population during the COVID-19 pandemic and related lock-down restrictions and stress factors [37]. We found presence of PTSD symptoms at a level comparable to ICU admitted patients [38]. We also found that subjects presenting psychophysically confirmed OD showed significantly higher scores in IES-R mean total score, mean total avoidance score and mean total hyperarousal score when compared to patients without OD.

During COVID-19 pandemic, also higher rates of symptoms of anxiety, depression and stress have been reported [34,40]. In a recent large study conducted by the COvid Mental hEalth Trial (COMET) network [41], 12% of respondents reported severe or extremely severe levels of depressive symptoms, 18% of anxiety symptoms and 42% reported to feel at least moderately stressed by the situation at the DASS-21. The authors found evidence that physical isolation and lockdown represent serious threat for mental health and well-being of the general population; therefore, as an integral part of COVID-19 response, mental health needs should be addressed [41]. Moreover, other studies [37,38] have found that individuals with a history of mental disorders, obsessive-compulsive symptoms, or obsessive-compulsive traits faced greater challenges in adapting to the "new normal" after the lifting of lockdowns. These difficulties were largely mediated by heightened levels of depression, anxiety—including COVID-related anxiety—and stress [42,43] which could contribute to increased morbidity and mortality associated with these conditions [44,45]. Persistent OD, acting as a chronic stressor, may exacerbate or even trigger mental health conditions such as depressive, anxious, or stress-related symptoms. Conversely, compromised mental health could intensify the severity of OD-related complaints. To evaluate the association between OD and mental health status, we chose to use psychophysically confirmed OD to minimize potential confounding factors and ensure the accuracy of symptom reporting, particularly in patients with potentially altered mental health. Our study found elevated DASS-21 scores in outpatients long after COVID-19 infection even if previous psychiatric comorbidities were excluded, with mean values even higher than those reported in a sample of the general Italian population (DASS-21 Total score 28.81±24.38 vs 12.3±8.3, Depression score 8.45±10.02 vs 3.5±3.2, Anxiety score 7.21±7.74 vs 2.4±2.6, Stress score 13.14±9.24 vs 6.4±3.8) [29]. These results suggest higher levels of depressive, anxiety, and stress symptoms in our sample compared to the reference population, suggesting the possible presence of depressive disorders, anxiety disorders and stress-related disorders in individuals with longstanding OD that persisted after SARS-CoV-2 infection. Our analysis also revealed that subjects with psychophysically confirmed OD exhibited significantly higher mean DASS-21 Anxiety scores compared to those without OD. While the difference in mean Depression scores between these groups did not reach statistical significance, we observed a trend towards higher depressive symptoms in hyposmic individuals. These findings underscore an increase in anxiety symptoms and suggest a potential elevation in depressive symptoms among subjects with psychophysically confirmed OD. Future research should further investigate these findings on depressive symptoms to confirm the absence of an association with OD.

Considering the impact of depressive symptoms, we also looked for the incidence of hopelessness using the BHS questionnaire [24], which score is associated with increased risk for suicide [25]. Saricali and colleagues [46] reported BHS mean score of 6.62 (SD±4.63) in a cross-sectional online survey in a Turkish general population sample. Our results reported a mean BHS score of 4.83 (SD±4.32) and showed that 15% of responders have a BHS ≥ 9. These findings have important implications as 15% of our sample could be at risk of suicidal behaviours, and particularly the hyposmia group with a percentage of 19% of subjects at

risk (even if no statistically meaningful difference was found between groups for BHS ≥ 9).

Finally, our results highlighted a reduction in perceived quality of life for patients experiencing continuous OD comparing to general population as measured with Q-LES-Q. In the Italian setting, Pallanti et al. [47] reported an evaluation in a group of healthy volunteers, where Q-LES-Q mean percentual score was reported as ranging between 83% and 71% in those areas applicable to all subjects, with mean "general activities" score of 71%. Considering the overall sample, the mean scores across all domains of the Q-LES-Q were observed to be lower than the normative data derived from the Italian population [47].

Taken together, our study underlines the clinical utility of self-report screening for post-traumatic, depressive and anxious symptoms in patients with persistent OD following COVID-19. Our findings suggest that, in clinical practice, particular attention should be given to patients with psychophysically confirmed OD, as they may experience more severe post-traumatic and anxiety symptoms. For these individuals, a targeted psychiatric evaluation could prove beneficial. Our results could be extended only to subjects suffering from persistent OD related to mild to moderate COVID-19 presentation.

A key limitation of this study is its cross-sectional design, which restricts the ability to establish causal relationships, as the findings may represent a snapshot influenced by general psychological stress from the pandemic and uncontrolled environmental factors acting as potential confounders. A longitudinal approach would offer a more comprehensive understanding of symptom progression and help reduce potential bias. Other limitations include the relatively small sample size, which may limit the generalizability of the findings to the broader long COVID patient population, the recruitment of participants from a single outpatient clinic, and the fact that these findings are specifically applicable to individuals with persistent OD related to mild cases of COVID-19, further constraining external validity. Unmeasured factors, such as the influence of social or environmental conditions, previously unrecognized mental health disorders, and varying degrees of COVID-19 severity, may have impacted the outcomes. However, we focused on a homogeneous cohort of long COVID patients with OD to minimize confounding factors from other OD etiologies. Thus, research questions remain: the causality relationship between long COVID related OD and mental health status, the generability of our findings, the impact of unmeasured factors, and the influence of OD secondary to other etiologies on mental health.

Conclusion

Persistent OD after COVID-19 was found to be associated with psychiatric symptoms, in accordance with previous studies [48–50]. Subjects with psychophysically confirmed OD demonstrated significantly higher post-traumatic symptomatology, higher anxiety symptoms and higher hopelessness compared with patients who had normosmia. The perceived quality of life was generally lower than the general population. Individuals with persistent OD following SARS-CoV-2 infection should be screened for possible presence of psychiatric symptomatology, and especially those with psychophysically confirmed OD, in a preventive and personalized medical approach.

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Authors' contributions

PBR: conceptualization analysis and interpretation of data, drafts of the manuscript, revisions during the writing process for important intellectual content, final approval of the article before submission. RZC: acquisition, analysis and interpretation of data, drafts of the manuscript, final approval of the article before submission. EC: acquisition, analysis and interpretation of data, drafts of the manuscript, final approval of the article before submission. LP: acquisition, analysis and interpretation of data, drafts of the manuscript, final approval of the article before submission. GT: acquisition, analysis and interpretation of data, revisions during the writing process for important intellectual content, final approval of the article before submission. UA: conceptualization, analysis and interpretation of data, drafts of the manuscript, revisions during the writing process for important intellectual content, final approval of the article before submission

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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