Persisting chemosensory dysfunction in COVID-19 - a cross-sectional population-based survey*

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Abstract

Background: Chemosensory dysfunction (CD) has been reported as a common symptom of SARS-CoV-2 infection, but it is not well understood whether and for how long changes of smell, taste and chemesthesis persist in infected individuals.

Methodology: Unselected adult residents of the German federal state of Schleswig-Holstein with Polymerase Chain Reaction (PCR)-test-confirmed SARS-CoV-2 infection were invited to participate in this large cross-sectional study. Data on the medical history and subjective chemosensory function of participants were obtained through questionnaires and visual analogue scales (VAS). Olfactory function (OF) was objectified with the Sniffin' Sticks test (SST), including threshold (T), discrimination (D) and identification (I) test as well as summarized TDI score, and compared to that in healthy controls. Gustatory function (GF) was evaluated with the suprathreshold taste strips (TS) test, and trigeminal function was tested with an ampoule containing ammonia.

Results: Between November 2020 and June 2021, 667 infected individuals (mean age: 48.2 years) were examined 9.1 months, on average, after positive PCR testing. Of these, 45.6% had persisting subjective olfactory dysfunction (OD), 36.2% had subjective gustatory dysfunction (GD). Tested OD, tested GD and impaired trigeminal function were observed in 34.6%, 7.3% and 1.8% of participants, respectively. The mean TDI score of participants was significantly lower compared to healthy subjects. Significant associations were observed between subjective OD and GD, and between tested OD and GD.

Conclusion: Nine months after SARS-CoV-2 infection, OD prevalence is significantly increased among infected members of the general population. Therefore, OD should be included in the list of symptoms collectively defining Long-COVID.

Key words: COVID-19, gustatory dysfunction, olfactory dysfunction, smell, taste

Introduction

Coronavirus Disease 2019 (COVID-19) is a novel clinical entity caused by infection with Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2) [1,2]. Common symptoms of COVID-19 include fever, cough, headache, nausea, and fatigue [3]. Concomitantly, viral upper respiratory tract infections including SARS-CoV-2 are known to cause olfactory or gustatory disturbance [4,5].

Emerging signs of impairment of olfactory (OF) and/or gustatory function (GF) have been observed in individuals infected with SARS-CoV-2, even in the absence of other typical respiratory symptoms [6]. Moreover, previous questionnaire-based studies reported that such impairment may well represent the only symptom of COVID-19 and SARS-CoV-2 infection [6–10]. The level of OF and GF impairment in the acute phase of the disease was found to range from 5% to over 85% [7,11,12]. The few studies that also addressed nasal chemesthesis revealed that this biological function can be impaired in COVID-19 as well [13].

Smell and taste result from complex sensory perception. It is currently unknown if and when restitutio ad integrum of OF and GF is achieved after SARS-CoV-2-infection. According to research published so far, improvement of OF and GF occurs in most patients. However, the corresponding assessments were mostly performed weeks, or at most a few months, after the infection and only a few studies have addressed the potential long-term persistence of olfactory and gustatory impairment [14,15]. The primary aim of the present study was thus to determine, in a large representative cohort of infected individuals, the frequency, severity, and extent of these health problems through detailed subjective assessment and psychophysical testing at approximately 9 months after SARS-CoV-2 infection. In addition, the study compared the prevalence of tested olfactory impairment in infected individuals to that in the general, non-infected population.

Materials and methods

Design (ethics, study design)

This study comprises the cross-sectional population-based assessment of CD in SARS-CoV-2-infected individuals approximately 9 months post infection. Data were acquired as part of COVIDOM, a population-based cohort study within the NAPKON (National Pandemic Cohort Network) framework of the German Network University Medicine for COVID-19 Research (NUM). COVIDOM has been registered with the German registry for clinical studies (DRKS00023742) and ClinicalTrials.gov (NCT04679584). The study protocol and procedures were approved by the local ethics committee at Kiel (D537/20). All participants gave written informed consent prior to their inclusion. Further details about COVIDOM have been published previously [16].

Participants (inclusion criteria, recruitment period, drop out)

Unselected SARS-CoV-2-infected individuals were contacted through local health authorities, informed about COVIDOM, and invited to participate in the study irrespective of the severity of their disease. Inclusion criteria comprised a positive PCR test for SARS-CoV-2, primary residency in the German federal state of Schleswig-Holstein, ≥18 years of age at the time of infection and written informed consent to participate. The virus variant was not determined. Acute re-infection with SARS-CoV-2 was an exclusion criterion. The population of Schleswig-Holstein is characterized by low mobility due to the rural character and geographical location of the state between the Danish border in the north, and the North and Baltic Sea to the West and East, respectively. These circumstances facilitated the recruitment of a representative sample of the infected population. Participants were examined between November 2020 and June 2021. All dropouts were documented.

Demographic data

Prior to the on-site examination (for details, see below), a comprehensive health questionnaire was completed by the participants either online, paper-based, or by telephone interview. The questionnaire served to collect data on age, sex, socio-demographic and socio-economic factors, tobacco consumption, pre-existing general or ear-nose-throat (ENT)-specific illnesses, pre-existing traumas, and surgical interventions. Participants also self-reported a COVID-19-specific medical history, including symptoms, course of disease, treatment, and vaccination history.

Subjective assessment of OF, GF and NP

During the visit to the study center nine months post infection, participants were asked to rate their OF, GF and nasal patency (NP) before infection, during acute infection, and at the time of the on-site examination, using a 10-point visual analogue

Table 1. Demographics and basic characteristics of COVIDOM study sample (n=667).

Characteristics	N (%)
Age (in years), mean (SD)	48.2 (15.9)
Total participants	667
Women	376 (56.4)
Men	290 (43.5)
n/a	1 (0.1)
Post-COVID time (T3-T2, in months), mean (SD)	9.1 (2.4)
Self-reported ethnicity	
European/Caucasian	644 (96.6)
African	1 (0.1)
Asian	3 (0.4)
Arab	7 (1.0)
Latin-American	4 (0.6)
mixed	5 (0.7)
other	3 (0.4)
Current smoker (at T3)	68 (10.6)
Pack years[&], mean (SD)	9.7 (12.0)
Symptomatic (at T2)	605/640 (94.5)
OD	400/605 (66.1)
OD initial [$]	82/667 (12.3)
GD	406/605 (67.1)
GD initial [$]	89/667 (13.3)
Symptomatic (at T3, n=601)	338/601 (56.2)
OD	114/338 (33.7)
GD	85/338 (25.1)

Results are given as number (%), unless otherwise indicated.
OD, olfactory dysfunction; GD, gustatory dysfunction; T2, time during acute SARS-CoV-2 infection; T3, time of examination; [$] OD/GD presenting as first symptom of SARS-CoV-II infection. [&] includes current and former smokers (n=291).

scale (VAS; 10: extremely good function, 0: loss of function). The three time points were coded as T1, T2 and T3, respectively. The difference between T2 and T3 will henceforth be referred to as the 'post-COVID time' (PCT). In addition, all participants filled out questionnaires addressing possible qualitative or quantitative changes of OF and GF.

Psychophysical assessment of OF, GF and NP

Participant OF was tested psychophysically by means of the Sniffin' Sticks test (SST, Burghart Messtechnik GmbH, Germany) comprising odor threshold, discrimination, and identification [17]. The scores of these three component tests were summed up to yield the Threshold, Discrimination and Identification (TDI) score. To classify the outcome clinically, terms 'normosmia', 'hyposmia' and 'functional anosmia' were used in line with the relevant literature [17]. In addition, a TDI score ≤30.5 was defined as 'tested olfactory dysfunction' (OD). All tests were performed according to the manufacturer's instructions [17] except for odor threshold, where the 'wide step method' that uses only every second dilution step was employed [18]. Results of the SST were then compared to a healthy control group (n=667) with comparable sex ratio and age distribution, derived from the SST normative data provided by Oleszkiewicz et al. [17].

Participant GF was assessed by whole-mouth suprathreshold testing with Taste Strips in the four qualities of sweet, sour, salty, and bitter (TS, Burghart Messtechnik GmbH, Germany) exerting forced choice, according to Müller et al. and Landis et al. [19,20]. Less than 3 out of 4 correctly identified TS was defined as 'tested gustatory dysfunction (GD)' as previously described for taste sprays [21].

Trigeminal function was tested with AmmoLa ampoules (PZN 6766849) containing ammonia and lavender oil in a watery isopropanol solution. Ampoules were opened and moved towards the participant's nose. The absence of a burning, pungent, or stinging perception was defined as 'trigeminal impairment' [22].

Endoscopy

The oral and nasal cavity were inspected by rigid 30° endoscopy (Karl Storz GmbH, Germany). Anatomy was recorded on video and analyzed asynchronously by a board-certified ENT physician. The Nasal Polyp Score (NPS) was derived according to the Polyp Grading System [23]. Positioning on the Olfactory Cleft Endoscopy Scale (OCES), ranging from 0 to 20, was determined by evaluating the degree of discharge, edema, polyps, crusting, and scarring in the olfactory cleft [24]. The oral cavity was examined for mucosal abnormalities, tumors, scarring, and dental status.

Statistics

IBM SPSS Statistics software (version 22.0.0.2 for Windows, IBM, 2013) was used to calculate descriptive statistics and to perform hypothesis tests. For categorical and dichotomous variables, absolute and relative frequencies will be reported below. Group differences were assessed for statistical significance with a chi-squared test. For metric variables, mean and standard deviation were calculated and a Wilcoxon-Mann-Whitney U-test or a Wilcoxon rank sign test was used for inter-group comparisons, as appropriate. Associations between metric variables were quantified by Spearman correlation coefficients and assessed for statistical significance with a Student t-test of rho-transformed. P values <0.05 were deemed statistically significant.

Results

A total of 667 SARS-CoV-2-infected residents of the German federal state of Schleswig-Holstein were examined at 9.1 months, on average, post infection (Table 1). Complete data could not be

Table 2. Self-assessment of olfactory function, gustatory function, and nasal patency at different time points of SARS-CoV-2-infection.

	T1	T2	T3	P value
Olfactory Function (OF)				
VAS score				
All	8.05 (1.74)	3.23 (3.34)	6.76 (2.21)	**<0.001**[a]
Women	8.37 (1.62)	3.0 (3.42)	7.01 (2.12)	0.106[b]
Men	7.65 (1.80)	3.52 (3.22)	6.44 (2.28)	
VAS score ≤ 3, n (%)	14/611 (2.3)	364/621 (58.6)	62/639 (9.7)	
Subjective OD, n (%)				
All			277/608 (45.6)	
Women			168/338 (49.7)	
Men			109/270 (40.4)	
Gustatory Function (GF)				
VAS score				
All	8.37 (1.31)	3.65 (3.39)	7.47 (1.84)	**<0.001**[a]
Women	8.57 (1.24)	3.42 (3.51)	7.65 (1.84)	0.393[b]
Men	8.10 (1.36)	3.94 (3.20)	7.24 (1.82)	
VAS score ≤ 3, n (%)	4/643 (0.6)	354/639 (55.4)	27/640 (4.2)	
Subjective GD, n (%)				
All			231/639 (36.2)	
Women			137/359 (38.2)	
Men			94/280 (33.6)	
Nasal Patency				
VAS score	7.87 (1.66)	5.33 (2.58)	7.31 (1.87)	**<0.001**[a]
Subjective NPI, n (%)			182/624 (29.2)	

Results are given as mean (SD), unless otherwise indicated. [a] Wilcoxon test of a difference between the VAS score at T3 and T1. [b] U-test of a sex difference in VAS score at T3. T1, time before SARS-CoV-2 infection; T2, time during acute SARS-CoV-2 infection; T3, time of examination; VAS, Visual Analogue Scale; OD, olfactory dysfunction; GD, gustatory dysfunction; NPI, nasal patency impairment.

acquired for all participants, resulting in variable levels of missingness as indicated below in the respective sections.

Post infection development of OD and GD

No statistically significant association was observed between hospitalization at T2 and the impairment of chemosensory function of participants at T3, neither in terms of OD (χ^2=0.033,1 df, p>0.05), nor GD (χ^2=1.381, 1 df, p>0.05), nor trigeminal dysfunction (χ^2=0.706, 1 df, p>0.05). Moreover, while trigeminal dysfunction at T3 was significantly associated with a necessity for treatment at T2 (χ^2=7.200, 1df, p=0.013), this was not the case for tested OD (χ^2=0.279, 1 df, p>0.05) or tested GD (χ^2=1.627, 1 df, p>0.05).

Endoscopy

Most participants had an NPS of zero (527 of 532 examined, 99.1%, for the right nostril; 563 of 567, 99.3%, for the left nostril) while NPS=1 for the remainder. The mean OCES score was 0.22 (SD: 0.79). Endoscopy of the oral cavity did not reveal any overall morphological changes such as mucosal abnormalities, tumors,

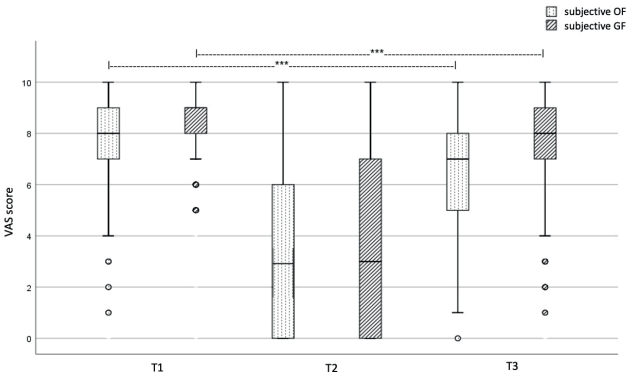

Figure 1. Subjective assessment of olfactory and gustatory function at different time points to SARS-CoV-2 infection. OF, Olfactory Function; GF, Gustatory Function; VAS, Visual Analogue Scale; TI, Time before SARS-CoV-2 Infection; T2, Time during SARS-CoV-2 Infection; T3, Time of examination.

Table 3. Psychophysical assessment of olfactory function at T3, using Sniffin' Sticks test (SST).

	COVIDOM			Controls (n=667)	P value
	All[a]	Women	Men		
Threshold	6.43 (2.09)	6.44 (2.06)	6.41 (2.14)	8.34 (3.11)	**<0.001[b]**
Discrimination	12.35 (2.21)	12.50 (2.21)	12.17 (2.20)	12.05 (2.08)	**0.001[b]**
Identification	12.19 (2.28)	12.26 (2.26)	12.09 (2.30)	12.91 (2.16)	**<0.001[b]**
TDI score	31.44 (4.52)	31.65 (4.56)	31.17 (4.46)	33.40 (5.26)	**<0.001[b]**
Anosmia[d], n (%)	2/570 (0.4)	2/320 (0.6)	0/250 (0)	4/667 (0.6)	0.693[c]
Hyposmia[e], n (%)	195/570 (34.2)	105/320 (33.4)	90/250 (36.0)	174(667 (26.1)	**0.002[c]**
Tested OD, n (%)	197/570 (34.6)	107/320 (33.4)	90/250 (36.0)	189/667 (28.3)	**0.019[c]**
Normosmia[f], n (%)	373/570 (65.4)	213/320 (66.6)	160/250 (64.0)	489/667 (73.3)	**0.003[c]**

Results are given as mean (SD), unless otherwise indicated. [a] n=576 (threshold), n=642 (discrimination), n=656 (identification), n=570 (TDI score). [b] U-test of difference between COVIDOM total and controls. [c] chi-squared test of difference between COVIDOM (all) and controls. [d] functional anosmia; denotes TDI results ≤ 16. [e] denotes TDI results >16 and ≤ 30.5. [f] denotes TDI results > 30.5. TDI, Threshold Discrimination Identification; OD, olfactory dysfunction.

scarring, or abnormal dental status.

Subjective OD

Of 601 participants, 338 (56.2%) reported persistence from T2 to T3 of at least one of 23 pre-given general symptoms of infection (Table 1), and women (215 of 345, 62.3%) reported persistence significantly more often than men (123 of 255, 48.2%; χ^2=11.823, 1 df, p<0.001). Of the 338 symptomatic participants, 114 (33.7%) included OD in their report (women: 62, 28.8%, men: 52, 42.3%; χ^2=6.322, 1 df, p=0.012).

The mean VAS score of self-assessed OF differed significantly between T1 (8.05, SD: 1.74) and T3 (6.76, SD: 2.21; Wilcoxon test z= -14.133, p<0.001), but no significant sex difference was observed (Table 2, Figure 1). Subjective OD, defined as a lower VAS score at T3 than T1, was observed for 277 of 608 participants (45.6%), with a significantly higher proportion of affected women (168 of 338, 49.7%) than men (109 of 270, 40.4%; χ^2=5.272, 1 df, p=0.022).

Out of 547 participants, 156 (28.5%) reported a continuous change of their ability to smell at T3 (women: 96 of 303, 31.7%, men: 60 of 244, 24.6%, χ^2=3.336, 1 df, p>0.05). Of 563 participants providing the respective information, 128 (22.7%) described odors as less intense at T3 than at T1, 127 (22.6%) as altered and 308 (54.7%) as unchanged.

Tested OD

Tested OD at T3, defined as a TDI score <31 (Table 3), was seen in 197 of 570 participants (34.6%; women: 107 of 320, 33.4%, men: 90 of 250, 36.0%; χ^2=0.406, 1 df, p>0.05). The mean scores for threshold (n=576), discrimination (n=642), and identification (n=656) were 6.43 (SD: 2.09), 12.35 (SD: 2.21), and 12.19 (SD: 2.28), respectively, while the mean TDI score (n=570) was 31.44 (SD: 4.52).

Both TDI score (Spearman ρ=-0.192, p=0.002, Table IV) and tested OD (U-test z=-3.311, p<0.001) were found to be negatively correlated with the number of packyears smoked, but not with the presence or absence of any infectious disease 14 days before T3 (U-test z= -0.327, p>0.05).

Participant SST results at T3 were compared to data from healthy controls (n=667). In the latter group, tested OD was present in 189 of 667 individuals (28.3%, Table 3, Figure. 2), and was thus significantly less frequent than in COVIDOM participants (χ^2=5.549, 1 df, p=0.019). All four SST scores were found to differ significantly between COVIDOM participants and controls (Table 3), with mean differences of -1.91 for threshold (U-test z=-11.702, p<0.001), 0.31 for discrimination (z=3.234, p=0.001), -0.71 for identification (z=-6.720, p<0.001), and -1.96 for the summary TDI score (z=-7.384, p<0.001). The proportion of hyposmic individuals was significantly higher (χ^2=9.690, 1 df, p=0.002), and the proportion of normosmic individuals significantly lower (χ^2=9.022, 1 df, p=0.003), among COVIDOM participants than controls. In contrast, the proportion of anosmic individuals did not vary significantly between cohorts (Table 3).

Participants with VAS-defined subjective OD (i.e. with a VAS score smaller at T3 than at T1) also had a significantly lower mean TDI score (30.79, SD: 4.78) than those without subjective OD (32.12, SD: 4.08; U-test z=-3.125, p=0.002). Similarly, participants with VAS ≤3 at T3 had a lower mean TDI score (27.34, SD: 6.01) than those scoring VAS >3 at T3 (31.97, SD: 4.04, z=-5.797, p<0.001).

There was a weak albeit significant difference in terms of the mean PCT between participants with tested OD (8.85, SD: 2.23) and without tested OD (9.25, SD: 2.37; U-test z=-2.013, p=0.044). Moreover, the TDI score and the PCT of COVIDOM participants were significantly correlated with one another (Spearman

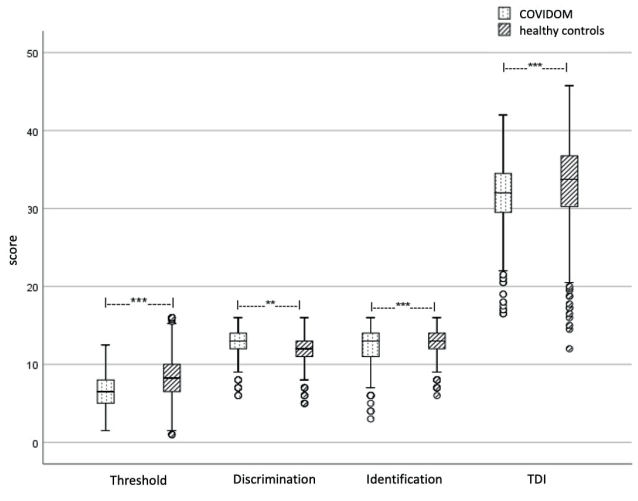

Figure 2. Sniffin' Sticks Test (SST) results in COVIDOM participants and healthy controls. TDI, Threshold, Discrimination, Identification.

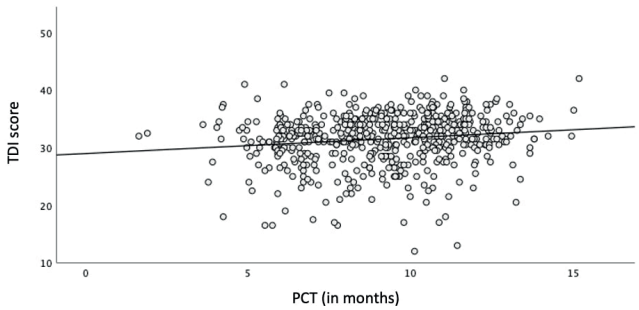

Figure 3. Correlation between post-COVID time (PCT) and TDI (Threshold, Discrimination, Identification) score.

ρ=0.155, p<0.001); Table 4, Figure 3).

Subjective GD

Of the 338 participants reporting at least one persisting symptom at T3 (Table 1), 85 (25.1%) included GD in their report (women: 45 of 215, 20.9%, men: 40 of 123, 32.5%, χ^2=5.583, 1 df, p=0.018).

The mean VAS scores of self-assessed GF differed significantly between T1 (8.37, SD: 1.31) and T3 (7.47, SD: 1.84, Wilcoxon test z= -12.948, p<0.001), but no significant sex differences were noted (Table 2, Figure 1). Subjective GD, defined as a VAS score lower at T3 than at T1, was found in 231 of 639 of participants (36.2%; women: 137 of 359, 38.2%, men: 94 of 280, 33.6%; χ^2=6.322, 1 df, p=0.012).

Continuous changes in their ability to taste was reported at T3 by 122 of 613 of participants (19.9%, women: 72 of 347, 20.7%, men: 50 of 266, 18.8%; χ^2=0.548, 1 df, p>0.05).

Tested GD

A TS test of all four taste qualities was performed by 643 participants (96.4%), and tested GD was detected in 47 of them (7.3%, women: 17 of 342, 4.7%, men: 29 of 283, 10.2%; χ^2=6.324, 1 df, p=0.012). The number of GD cases failing a specific taste was 13 (27.7%) for sweet, 31 (66.0%) for sour, 36 (76.6%) for salty, and 23 (48.9%) for bitter.

There was no significant association between tested GD and VAS-defined subjective GD (i.e. a VAS score lower at T3 than at T1; χ^2=1.363, 1 df, p>0.05). Similarly, the mean number of correctly identified TS was not significantly different in participants who scored GF ≤3 at T3 (3.56, SD: 0.80) than in those who scored GF>3 (3.71, SD: 0.62; U-test z=-1.141, p>0.05). Neither tested GD nor the TS score was significantly associated with PCT (both p>0.05), but the number of packyears smoked was negatively associated with the TS score (Spearman ρ=-0.162; p=0.006, see Table 4). The presence of any infectious disease 14 days before T3 was not significantly associated with the TS score (U-test z=-0.262, p>0.05).

Association between smell and taste

A significant association was found between subjective OD and subjective GD (χ^2=241.998, 1 df, p<0.001) as well as between tested OD and tested GD (χ^2=9.758, 1df, p=0.002). Furthermore, the TDI score was significantly correlated with the number of correctly identified TS (Spearman ρ=0.136, p=0.001).

Chemesthesis

Some 12 of 657 participants (1.8%) had impaired trigeminal function. Nine of these had performed an SST with a mean TDI score of 28.17 (SD: 5.09), which differed significantly from the mean TDI score of participants without impaired trigeminal function (31.50, SD: 4.50; U-test z=-2.037, p=0.04). However, no significant association was seen between impaired trigeminal function and tested OD, defined as TDI<31 (χ^2= 4.148, 1 df, p>0.05).

A significant difference was observed in terms of the mean number of correctly identified TS between participants with impaired trigeminal function (3.25, SD: 0.75) and without impaired trigeminal function (3.71, SD: 0.63, U-test z=-3.059, p=0.004).

Nasal patency

The mean VAS score of NP at T1 (7.87, SD: 1.66) was significantly different from that at T3 (7.31, SD:1.87; Wilcoxon test z=-10.504, p<0.001). Some 182 of 624 participants (29.2%) perceived subjective impairment of NP (NPI), defined as a VAS score lower at T3 than at T1 (Table 2).

A significant association between NPI and subjective OD (χ^2=42.100, 1 df, p<0.001) as well as between NPI and subjective GD (χ^2=41.286, 1 df, p<0.001) was observed. The VAS-dependent rating of NP was not significantly associated with either the TDI score or the number of correctly identified TS (both p>0.05).

Table 4. Association between participant characteristics and psychophysical test results.

	TDI score	Tested OD	TS score[d]	Tested GD
Infectious diseases	-0.327[a] (p=0.744)	1.375[c] (0.355)	-0.262[a] (p=0.793)	0.859[c] (p=1.0)
PCT	0.155[b] **(p<0.001)**	-2.013[a] **(p=0.044)**	-0.024[b] (p=0.544)	-0.556[a] (p=0.578)
Current smoker (T3)	-0.084[a] (p=0.933)	0.391[c] (p=0.574)	-1.127[a] (p=0.260)	0.118[c] (p=0.809)
Packyears	-0.192[b] **(p=0.002)**	-3.311[a] **(p<0.001)**	-0.162[b] **(p=0.006)**	-1.433[a] (p=0.152)

[a] U-test z value; [b] Spearman correlation coefficient; [c] chi-square value; [d] denotes number of correctly identified Taste Strips; PCT, Post-COVID time; TDI, Threshold Discrimination Identification; OD, olfactory dysfunction; TS, Taste Strips; GD, gustatory dysfunction.

Discussion

OD and GD reportedly are common symptoms of acute SARS-CoV-2-infection [6,25–27], but only few studies so far have assessed the persistence and severity of subjective and tested CD, including chemesthesis, in COVID-19 patients several months after their infection. The present study of a large population-based cohort (n=667), embedded into the German COVIDOM survey of the long-term sequelae of COVID-19 at approximately 9 months post infection, determined the frequency, severity, and extent of the above long-term health problems by way of detailed subjective assessment and psychophysical testing. In addition, the olfactory functional status of affected individuals was compared to that of the general, non-infected part of the population.

General outcome

In terms of their age distribution and sex ratio, COVIDOM participants included in the present study were well representative of the adult infected population of the federal state of Schleswig-Holstein. Since the COVIDOM study protocol involves both the completion of questionnaires and a study site examination, a recruitment bias favoring less severe cases cannot be excluded. However, recruitment for COVIDOM worked by personal invitation confined to cases documented by public health authorities, which is not unlikely to have caused compensatory bias in the other direction.

No association was observed between the presence or absence of infectious diseases during the last 14 days before examination and the outcome of chemosensory testing. One may therefore assume that the participant test results were not influenced by health complications other than COVID-19.

Notably, the number of packyears smoked was found to have had an adverse effect on the tested function of both smell and taste of participants. It may well be that this reflects a general impact of smoking on OF and GF. However, since this relationship has not been clarified yet [28], our results are still compatible with a particular exacerbation of the COVID-19 effect upon chemosensory function by the use of tobacco products.

Finally, the present work is the first to indicate a general lack of major macroscopic changes after COVID-19 in the main nasal and oral cavities, as revealed by in-depth endoscopic examination.

No association with initial disease severity of OD and GD at 9 months post infection

Similar to Bakhshaee et al. [29], no correlation was observed in this study between tested OD or GD and either hospitalization or a necessity for outpatient treatment. Since the latter requirements can be regarded as indicators of disease severity, one may surmise that OD and GD in COVID-19 do not depend upon the actual clinical course of the infection. The few patients with impaired trigeminal function in this study also appeared to have required outpatient treatment more often than the remainder, but this association has not been reported in other studies yet and therefore needs further investigation.

How common are subjective OD and GD at different time points of SARS-CoV-2 infection?

The prevalence of infection-associated OD and GD during acute infection among COVIDOM participants was found to be comparable with previous studies [7,30]. This also conforms the representativeness of the examined COVIDOM cohort despite the fact that the prevalence of subjective OD during COVID-19 varies between 5% and 98% in literature [31].

Subjective OF and GF was determined with VAS, which are frequently used to assess OF and GF [29,32]. The decline of subjective OF and GF seen between T1 and T3 was independent of gender, meaning that subjective loss of smell and taste in COVID-19 is a symptom that affects men and women alike. This lack of sex difference recalls the findings of Biadsee et al. [30] who found no statistically significant sex difference in terms of the recovery of OF among 97 patients examined 7.6 months, on average, after disease onset. Since women generally outperform men in their objective OF [17], however, a sex dependence would have been expected for subjective OF as well. Indeed, a 2021 study of 704 health care workers showed a significant effect of sex on chemosensory self-evaluation (with women being more heavily affected than men) 4.8 months, on average, after SARS-CoV-2 infection. However, it must be taken into account that 84% of

participants in that study were women [33].
When defined through VAS rating, almost half of all participants in the present study had persisting subjective OD and about one third had persisting subjective GD (Table 2). These subjective dysfunctions of OF and GF were found to be dependent upon each other. Similarly, in an 8-month follow-up, Biadsee et al. [30] found 48% of probands to have residual OD and 38.5% to have residual GD, with recovery from subjective OF and GF being positively correlated.
A higher proportion of persisting subjective OD and GD was detected through VAS rating than by asking directly for the presence or absence of OD or GD as persisting symptoms. VAS rating of OF and GF therefore might be more sensitive in detecting OD and GD than simply asking for it, as has been suggested before by Gerkin et al. [32].
Parosmia, meaning an altered perception of odors, was found in 11% of COVID-19 patients by Bussière et al. [33] whereas, in the present cohort, about one fifth of participants reported persisting parosmia. A study by Liu et al. [34] has shown before that parosmia is highly prevalent among patients with post-infectious OD and represents a factor of good prognosis for OD patients following olfactory training. Parosmia therefore may not be a distinct COVID-19-related symptom but rather a symptom accompanying OD, irrespective of its cause, reflecting ongoing changes of the olfactory system.

Psychophysical testing reveals remaining chemosensory dysfunction

The updated Sniffin' Sticks normative data by Oleszkiewicz et al. [17], together with other studies [35], have shown that OD is frequent in the general population. It was therefore obvious to compare the TDI score and its component scores between the COVIDOM cohort and healthy controls, taken from the abovementioned normative data source [17]. For the first time, this comparison revealed significantly reduced scores for TDI, threshold and identification as well as a higher proportion of psychophysically tested OD in COVID-19 patients than in controls (Figure 2).
This notwithstanding, from their study of 83 anosmic or hyposmic patients, Gudziol et al. [36] concluded that only an increase in TDI score by at least 5.5 points may be a good indicator of subjective OF improvement, achieving a positive predictive value in this regard of more than 60%. Measured against this, the mean difference in TDI score of approximately two, as observed between cases and controls in this study, may seem clinically irrelevant. However, the threshold proposed by Gudziol et al. was derived in a test-retest setting so that the two studies are not directly comparable. Since we additionally found lower TDI scores to be associated with a worsening of subjective OF in cases, and because subjective and tested OD clearly are related, one may thus surmise that SARS-CoV-2 infection indeed has a considerable impact upon OF 9 months later. However, since recovery from post-infectious OD is known to take months or even years [37–39], the long-term course of this type of health complication must still be regarded as under-researched.

Interestingly, the component score for discrimination, which requires the ability to memorize two smells, was significantly higher among COVID-19 patients than controls. However, as Lotsch et al. [40] have shown before, the assessment of all three components of the TDI test should form the basis of assessing OF impairment so that the results of a single component test must not be over-interpreted.
In summary, OD was found to be a frequent persisting symptom of COVID-19, and does not seem to be a self-limiting disorder, as proposed by Bakhshaee et al. [29]. This supports our view that COVID-19-associated OD must be included in the list of symptoms collectively defining Long-COVID.
Participants with subjective OD had significantly lower TDI scores in line with findings of a smaller study by Otte et al. [13]. In addition, participants rating their OF as VAS ≤3 achieved lower TDI scores than participants rating their OF >3. Following a similar approach, Gerkin et al. [32] established the ODoR-19-Scale, which is a VAS aimed to indicate the presence of COVID-19 when OF is rated ≤3 on that scale. However, the findings of the present study are at odds with previous non-COVID-19 studies of the relationship between subjective and tested OD, and several authors asserted an underestimation of the actual prevalence of OD in the general population [9,41,42].
The above notwithstanding, the connection between subjective and tested OD observed in our study is evidence that patient-reported OD is a good predictor of tested OD in the context of COVID-19, a link that may have an impact upon both the early and late clinical diagnosis of SARS-CoV-2-related OD in COVID-19 patients.
Tested OD appears to improve over time (Figure 3), a result reminiscent of findings by Prem et al. [43] that may reflect ongoing, but not yet completed, restitutio ad integrum, and should therefore be subject to additional long-term investigations.

Tested GD was defined here as two or more mis-identified TS, similar to the taste spray assessments made in a study by Niklassen et al. [21]. In combined GF screening of 111 patients with taste sprays and Taste Strips, the authors found 6.5% of participants to have GD at an average 62.9 days after infection, which is in line with our findings in a six times larger study sample. In contrast, a small case series recently reported that patients only presented with normogeusia in a 6-months follow-up [44]. Finally, tested GD showed a significant sex difference in the COVIDOM cohort, with men being affected by GD more often than women not inconsistent with the overall sex-dependency of GF as demonstrated, for example, by Landis [20].

In the present study, taste quality sweet was the one most often identified correctly by participants with tested GD whereas salty and sour were recognized the most rarely, which is in line with previous findings [45]. One possible explanation of this result might be that a higher concentration of Angiotensin II, caused by the degradation of Angiotensin-Converting-Enzyme 2, leads to the suppression of salt taste responses and an enhancement of sweet taste responses through AT1-Receptor [45,46].
In contrast to OD, no correlation was found between subjective and tested GD, in line with a report by Singer-Cornelius et al. [45]. Moreover, no difference in the number of correctly identified Taste Strips was detected between those who rated their GF with a VAS score ≤3 and those with VAS >3.
Finally, no time-dependency was observed for tested GD (Table 4). While Bussière et al. described an effect of time on subjective GD [33], to the best of our knowledge, the effect of time on tested GF has not been investigated yet.

The present study revealed significant correlations between subjective OD and subjective GD as well as between tested OD and tested GD that contrast with previous findings in small case series using olfactory screening tools [45]. Possible explanations for the association between OD and GD include peripheral or central damage affecting both olfactory and gustatory pathways, and a consecutive loss of taste due to olfactory stimuli that are indispensable for gustatory perception and vice versa. In any case, the precise underlying mechanisms in the context of SARS-CoV-2 infection have not been finally understood, despite numerous investigations in this direction [47].

COVID-19-related impairment of chemesthesis has been described occasionally before [13,48]. In the COVIDOM cohort, participants showed impaired trigeminal function in a few cases. Among these, impaired trigeminal function was associated with TDI score and TS score. Similarly, Otte et al. found a correlation of chemesthesis with TDI score and TS score in a study of 65 patients tested 6 months, on average, after onset of disease or positive PCR testing [13]. These findings received additional support from studies claiming an interdependence of OD and impaired trigeminal function, regardless of the underlying etiology [49–51].

The relationship between nasal patency, or nasal congestion, and chemosensory dysfunction in COVID-19 has been addressed in several studies, although with different outcome [13,29]. In the present study, a correlation between NP dysfunction and subjective OD and GD was found. This was in line with observations by Landis et al. [52] that rating of OF is related to rating of nasal airway patency. On the other hand, our study also showed that VAS-rating of NP was not associated with tested OD or GD, which corroborated findings by Otte et al. [13] in COVID-19.

Strengths and limitations

The main strength of the present study is the thorough investigation of OD and GD, using both subjective (questionnaire) and objective methods (psychophysical testing), in a large sample of SARS-CoV-2 infected individuals covering a broad range of initial disease severity. Moreover, the results on tested OD in infected individuals could be compared to the OF status of a healthy control group, thereby adding further to the value of the study. However, the pathophysiology underlying these findings still has to be investigated in more detail in future studies.

Conclusions

Chemosensory dysfunctions are frequent sequelae of SARS-CoV-2 infection, as revealed by the detailed examination of a large cohort of infected individuals with validated tools, undertaken 9 months after positive PCR testing and should therefore be included in the list of symptoms collectively defining Long-COVID as suggested lately by our study group [53]. Even though chemosensory functions tend to improve over time, further investigations of the development of these complication over longer time periods are warranted.

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Authorship contribution

Substantial contribution to the conception or design of the work: SW, AK, BV, MAN, NB, CM, AH, TB, WL, SSc, ML; Acquisition, analysis, or interpretation of the data for the work: SW, AK, BV, MAN, NB, AP, VMH, PS, CM, AH, CB, TB, WL, SSc, MK, ML; Drafting the work: SW, AK, BV, MAN, NB, AP, VMH, PS, CM, AH, CB, TB, WL, SSc, SS, FM, MW, TK, MK, ML; Critical revision for important intellectual content: SW, MK, ML; The underlying data for the current manuscript has been verified by SW, CM, ML, CB, MK. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work. All authors had full access to all the data and accept responsibility to submit the manuscript for publication.

Conflict of interest

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