Clinical characteristics and associated factors of qualitative olfactory dysfunction*

Tae-Seong Eo[1], Ho Young Lee[1], Hyung-Ju Cho[1,2], Joo-Heon Yoon[1,2,3], Min-Seok Rha[1,4], Chang-Hoon Kim[1,2,3,5]

[1] Department of Otorhinolaryngology, Yonsei University College of Medicine, Seoul, Republic of Korea
[2] The Airway Mucus Institute, Yonsei University College of Medicine, Seoul, Republic of Korea
[3] The Korea Mouse Sensory Phenotyping Center, Yonsei University College of Medicine, Seoul, Republic of Korea
[4] Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul, Republic of Korea
[5] Taste Research Center, Yonsei University College of Medicine, Seoul, Republic of Korea

Rhinology 61: 5, 432- 440, 2023
https://doi.org/10.4193/Rhin23.004

***Received for publication:**
January 7, 2023
Accepted: May 20, 2023

Abstract

Background: Although interest in qualitative olfactory dysfunction (OD), including parosmia and phantosmia, has been increasing since the COVID-19 pandemic, little is known about the clinical characteristics and associated factors of qualitative OD.

Methods: Adult patients with subjective smell disturbance who underwent both the olfactory questionnaire and psychophysical olfactory function test were retrospectively enrolled. Demographic and clinical characteristics were analysed according to the presence or absence of parosmia or phantosmia.

Results: Among a total of 753 patients with self-reported OD, 60 (8%) and 167 (22.2%) patients reported parosmia and phantosmia, respectively. Younger age and female sex were related to both parosmia and phantosmia. The frequency of parosmia was significantly higher in patients with post-viral OD (17.9%) than in patients with the sinonasal disease (5.5%), whereas that of phantosmia was not different according to aetiologies of OD. Patients with COVID-19 had significantly younger ages and higher TDI scores than those with other viral infections. Remarkably, patients with parosmia or phantosmia had significantly higher TDI scores than those without but experienced more disruption in daily life. In the multivariate analysis, younger age and higher TDI score were identified as independent factors associated with both parosmia and phantosmia, while the viral infection was associated with parosmia but not with phantosmia.

Conclusions: Patients with OD who have parosmia or phantosmia have higher odour sensitivity than those who do not, but experience more deterioration in the quality of life. Viral infection is a risk factor for parosmia but not for phantosmia.

Key words: olfaction disorders, smell, quality of life, COVID-19

Introduction

Olfaction is essential for food intake and the detection of dangerous situations. Olfactory dysfunction (OD) causes a decrease in quality of life and is often accompanied by gustatory dysfunction (GD). OD is caused by sinonasal diseases, upper respiratory infections (URIs), head trauma, aging, and neurodegenerative diseases [(1)]. Because OD is a common symptom of coronavirus disease 2019 (COVID-19), a currently ongoing pandemic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, interest in OD has recently increased. A previous meta-analysis has reported that more than 40% of patients with COVID-19 complained of OD [(2,3)].

OD is divided into two types based on its characteristics: quantitative and qualitative. Quantitative OD includes decreased olfactory sensitivity (hyposmia), total loss of olfactory function (anosmia), and excessive olfactory sensitivity (hyperosmia). Meanwhile, qualitative OD is subdivided into parosmia, defined as distorted odour perception, and phantosmia, defined as odour

perception without olfactory stimulus [4].

To date, previous studies have mainly focused on quantitative OD and little attention has been paid to qualitative OD. However, it has been reported that qualitative OD is quite common, occurring in about 46% of all OD patients [5]. Since the outbreak of COVID-19, the prevalence of qualitative OD has increased and the impact of parosmia and phantosmia has been emphasized [6]. It has been hypothesised that parosmia may result from axon regeneration after damage to the olfactory nerve [7]. In this regard, patients with qualitative OD may have distinct pathophysiological and clinical features compared to those without qualitative OD. However, few studies have investigated clinical characteristics and psychophysical test results of patients with qualitative OD. Additionally, little is known about factors associated with qualitative OD.

In the present study, we aimed to investigate demographic and clinical factors associated with parosmia and phantosmia in patients complaining of OD.

Materials and methods

Study design and subjects

The medical records of patients with a major complaint of smell disturbance who visited the Department of Otorhinolaryngology, Severance Hospital, Republic of Korea, from 28 March 2021 to 22 September 2022 were retrospectively reviewed.

The inclusion criteria were as follows: 1) patients aged over 18 years, 2) patients who responded to the olfactory questionnaire regarding the characteristics and severity of OD, and 3) patients who underwent psychophysical olfactory function test. Patients who satisfied all the above criteria were included in the study.

This study was reviewed and approved by the Institutional Review Board (IRB) of Severance Hospital (IRB no. 4-2022-1343). All procedures involving human participants were performed in accordance with the principles of the Declaration of Helsinki.

Olfactory questionnaire and aetiology of OD

The olfactory questionnaire was written in Korean and completed before participants entered the clinic. The questionnaire consisted of three parts: 1) demographic information, including age, sex, and underlying diseases; 2) characteristics of OD, including its duration and severity; and 3) questions about accompanying GD and quality of life (Supplementary Table 1). All of the following questions were translated from the Korean language. The presence or absence of parosmia and phantosmia was investigated through standardized questions [8]: ("Have you ever smelled odours differently compared to previous experiences or certain pleasant odours in an unpleasant way?") and ("Have you ever smelled an unpleasant, weird, or the smell of something burned in the absence of an odour?"), respectively. Patients with parosmia or phantosmia were classified as having a qualitative OD. The severity of smell loss was determined by their answer to the question as follows: hyposmia ("I cannot smell well".) and anosmia ("I cannot smell at all"). Patients with subjective GD were requested to determine which sense of basic taste (salty, sour, sweet, bitter, and umami) was impaired. Disruption in daily life or work (decreased quality of life) was assessed using a binary question: "Is there any ill-being or difficulty due to olfactory dysfunction in daily life or work?"

We asked all patients whether they had a history of URI and head trauma, and examined the temporal relationship between these possible aetiologies and OD. All patients underwent nasal endoscopy to identify the possible causes of OD. We classified the aetiology of OD into four groups: sinonasal disease, viral infection, head trauma, and others. Patients with sinonasal diseases, such as chronic rhinosinusitis (CRS), septal deviation, and sinonasal tumours, without a history of head trauma or URI, were included in the 'sinonasal disease' group. CRS was diagnosed based on symptoms and endoscopic findings according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 guideline [9]. Patients with a history of upper respiratory viral infection and subsequent OD were considered the 'viral infection' group. In the case of COVID-19, we asked all patients whether they had a history of COVID-19 confirmed by diagnostic tests (polymerase chain reaction or rapid antigen test), and the patients in the 'viral infection' group were sub-classified into the 'COVID-19' group if SARS-CoV-2 infection was the cause of OD. Patients who exhibited consecutive OD after head trauma were included in the 'head trauma' group. The remaining patients were included in the group referred to as 'others'. The aetiologies of the 'others' group were congenital disorders, neurodegenerative diseases, and idiopathic. If more than one cause was identified, the authors discussed and selected the most influential aetiology. If sinonasal OD was suspected, the 22-item Sino-Nasal Outcome Test (SNOT-22) questionnaire was administered.

Psychophysical olfactory function and gustatory function tests

Olfactory function was evaluated using the YSK olfactory function test (YOF test; Kimex Co., Suwon, Republic of Korea), as described previously [10]. The odour threshold (T), discrimination (D), and identification (I) scores were measured and the total score (TDI score) was calculated as the sum of the T, D, and I scores. A total score of 14.5 or less was defined as anosmia and a score of 21 or less was defined as hyposmia. The gustatory function was assessed using the YSK gustatory function test (RHICO Medical Co., Seoul, Republic of Korea) [11] for each of the five basic taste (salty, sour, sweet, bitter, and umami). A sum score of five or less for the five recognition thresholds was defined as loss of taste (ageusia), and a score of 12 or less was defined as hypogeusia.

Table 1. Characteristics of OD according to the aetiology.

Variables	Total patients (n = 753)	Sinonasal disease (n = 488)	Viral infection (n = 84)	Head trauma (n = 28)	Others (n = 153)
Age (years) †‡§φψ	50.3 ± 16.5	49.96 ± 16.01	42.44 ± 15.56	40.96 ± 15.25	57.42 ± 15.97
Sex †§¶φψ					
Male	373/753 (49.5%)	273/488 (55.9%)	29/84 (34.5%)	13/28 (46.4%)	58/153 (37.9%)
Female	380/753 (50.5%)	215/488 (44.1%)	55/84 (65.5%)	15/28 (53.6%)	95/153 (62.1%)
Qualitative OD	206/753 (27.4%)	122/488 (25%)	28/84 (33.3%)	8/28 (28.6%)	48/153 (31.4%)
Parosmia†	60/753 (8%)	27/488 (5.5%)	15/84 (17.9%)	3/28 (10.7%)	15/153 (9.8%)
Phantosmia	167/753 (22.2%)	105/488 (21.5%)	18/84 (21.4%)	6/28 (21.4%)	38/153 (24.8%)
Quantitative OD	728/753 (96.7%)	474/488 (97.1%)	82/84 (97.6%)	28/28 (100%)	144/153 (94.1%)
Hyposmia (self-reported)‡¶ψ	460/753 (61.1%)	313/488 (64.1%)	57/84 (67.9%)	6/28 (21.4%)	84/153 (54.9%)
Anosmia (self-reported)‡¶ψ	268/753 (35.6%)	161/488 (33%)	25/84 (29.8%)	22/28 (78.6%)	60/153 (39.2%)
Duration of OD					
< 3 months	162/753 (21.5%)	77/488 (15.8%)	48/84 (57.1%)	14/28 (50%)	23/153 (15%)
3 – 12 months	168/753 (22.3%)	90/488 (18.4%)	27/84 (32.1%)	8/28 (28.6%)	43/153 (28.1%)
1 – 4 years	148/753 (19.7%)	96/488 (19.7%)	3/84 (3.6%)	3/28 (10.7%)	46/153 (30.1%)
5 – 9 years	96/753 (12.7%)	76/488 (15.6%)	2/84 (2.4%)	1/28 (3.6%)	17/153 (11.1%)
> 10 years	152/753 (20.2%)	127/488 (26%)	3/84 (3.6%)	2/28 (7.1%)	20/153 (13.1%)
Olfactory function test					
Total score (TDI) †‡¶φψ	15.81 ± 6.75	16.03 ± 6.87	18.38 ± 6.27	10.07 ± 4.88	14.83 ± 6.21
Anosmia (TDI ≤ 14.5)	350/753 (46.5%)	222/488 (45.5%)	24/84 (28.6%)	22/28 (78.6%)	82/153 (53.6%)
Hyposmia (TDI ≤ 21)	186/753 (24.7%)	111/488 (22.7%)	29/84 (34.5%)	6/28 (21.4%)	40/153 (26.1%)
Normosmia (TDI > 21)	217/753 (28.8%)	155/488 (31.8%)	31/84 (36.9%)	0/28 (0%)	31/153 (20.3%)
Self-reported GD	269/753 (35.7%)	130/488 (26.6%)	48/84 (57.1%)	19/28 (67.9%)	72/153 (47.1%)
Gustatory function test*					
Taste Recognition score (TR)	16.83 ± 4.74	16.91 ± 4.72	17.79 ± 3.99	15.14 ± 4.65	16.31 ± 5.14
Ageusia (TR ≤ 5)	7/662 (1.1%)	5/449 (1.1%)	0/68 (0%)	0/21 (0%)	2/124 (1.6%)
Hypogeusia (TR ≤ 12)	81/662 (12.2%)	54/449 (12%)	3/68 (4.4%)	4/21 (19%)	20/124 (16.1%)
Normogeusia (TR > 12)	574/662 (86.7%)	390/449 (86.9%)	65/68 (95.6%)	17/21 (81%)	102/124 (82.3%)
Disruption in daily life or work †§	353/753 (46.9%)	188/488 (38.5%)	61/84 (72.6%)	17/28 (60.7%)	87/153 (56.9%)

Categorical variables - Number of patients (percent). Continuous variables - Mean ± Standard deviation. Multiple comparison tests were performed using the Chi-square test or the Kruskal-Wallis test with Bonferroni correction. Statistically significant differences in the pairwise comparison are presented as follows (P < 0.05). † Sinonasal disease vs. Viral infection; ‡ Sinonasal disease vs. Head trauma; § Sinonasal disease vs. Others; ¶ Viral infection vs. Head trauma; φ Viral infection vs. Others; ψ Head trauma vs. Others. *All 662 patients who gave consent underwent gustatory function tests.

Statistical analyses

Statistical analyses were performed using the IBM SPSS Statistics for Windows version 26.0 (IBM Corp., Armonk, NY, USA). The independent t-test or Mann–Whitney U test was performed to compare continuous variables between the two groups. Differences between more than two groups were evaluated using a one-way analysis of variance (ANOVA) or the Kruskal-Wallis test. Chi-square or Fisher's exact tests were used to analyse categorical variables. Multiple comparison tests were performed using the Chi-square test with Bonferroni correction or the Kruskal-Wallis test with Dunn's multiple comparisons tests. Statistical significance was set at $P < 0.05$. Variables with significant differences between the groups in the univariate analyses were selected for multivariate binary logistic regression analysis.

Results

Baseline characteristics of total study subjects

The present study included 753 patients with subjective OD. The average age of the study subjects was 50.3 years (range, 19–89 years). The male: female ratio was approximately 1:1. Among all patients with subjective OD, 60 (8%) and 167 (22.2%) patients reported parosmia and phantosmia, respectively, and 21 patients

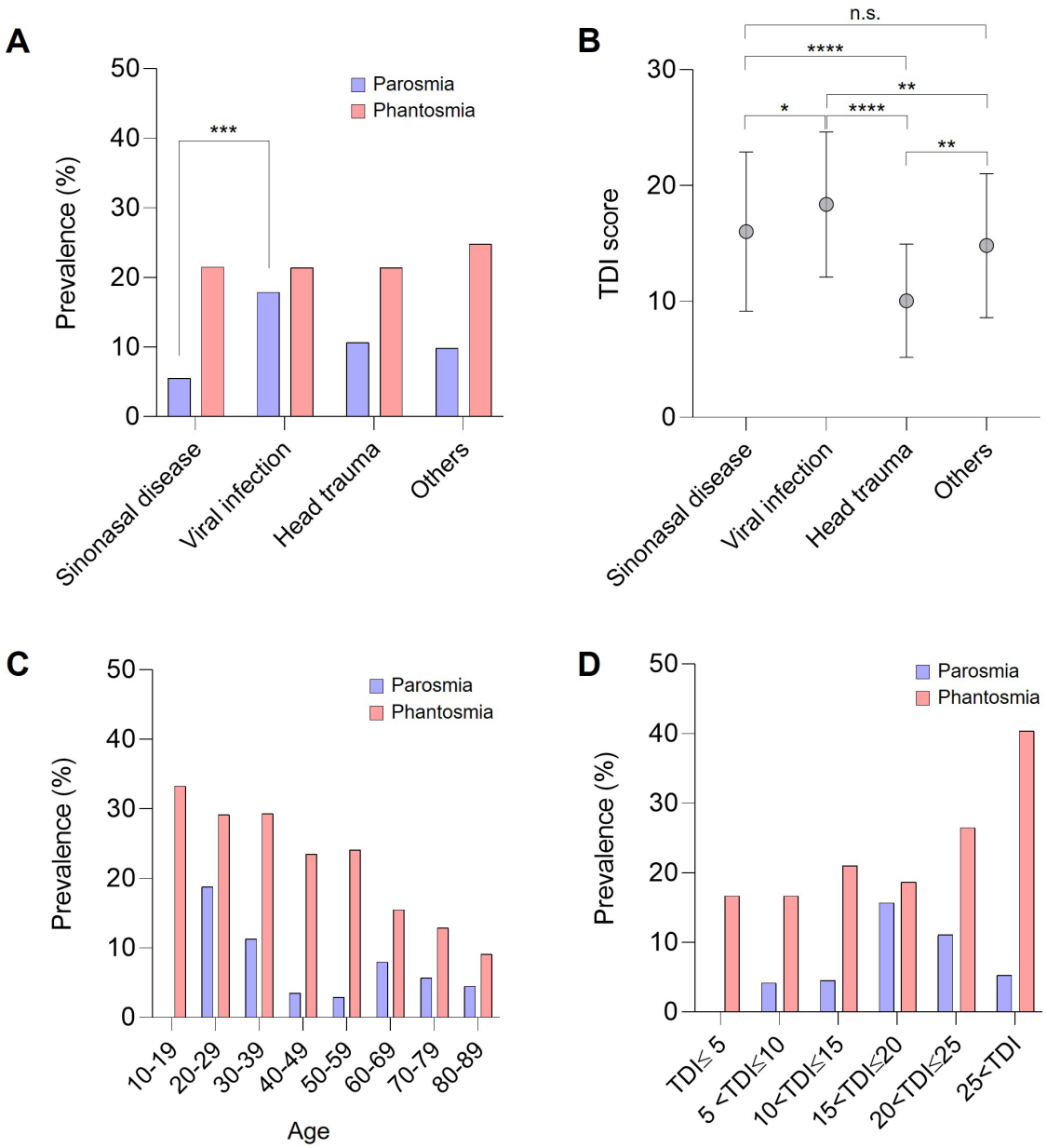


Figure 1. The prevalence of parosmia and phantosmia. (A) The prevalence of parosmia and phantosmia in the 'sinonasal disease' (n = 488), 'viral infection' (n = 84), 'head trauma' (n = 28), and 'others' (n = 153) groups. (B) TDI scores according to the aetiology of OD. (C and D) The prevalence of parosmia and phantosmia according to age (C) and TDI scores (D). Statistical analysis was performed using the Chi-square test with Bonferroni correction (A) or the Kruskal-Wallis test with Dunn's multiple comparisons test (B). n.s., not significant, *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

had both symptoms. In addition, 460 (61.1%) and 268 (35.6%) patients had self-reported hyposmia and anosmia. The duration of OD ranged from less than 3 months to > 10 years, and 27 patients did not know the onset of OD. When we analysed the aetiology of OD, the sinonasal disease was identified in 488 patients (64.8%), viral infection in 84 patients (11.2%), a trauma in 28 patients (3.7%), and the remaining patients were classified into others group (n = 153, 20.3%). In the olfactory function test, the average TDI score of the total study subjects was 15.81 ± 6.75, and 217 (28.8%), 186 (24.7%), and 350 (46.5%) patients showed normosmia, hyposmia, and anosmia, respectively. Self-reported GD was prevalent in 35.7% of the total patients, and umami sensation (31.7%) was the most commonly impaired among the five basic tastes. Among the patients who underwent gustatory function test (n= 662), 81 (12.2%) and seven (1.1%) patients showed hypogeusia and ageusia, respectively. In addition, 353 (46.9%) patients reported a decrease in quality of life due to OD. The demographic and clinical characteristics of the study participants are presented in Table 1.

Table 2. Subgroup analyses of patients with the viral infection.

	COVID-19 (n = 55)	other URI (n = 29)	P value
Age (years)	38.7 ± 13.2	49.6 ± 17.4	**0.005**
Sex			
Male	22 (40%)	7 (24.1%)	0.146
Female	33 (60%)	22 (75.9%)	0.146
Qualitative OD	22 (40%)	7 (24.1%)	0.146
Parosmia	12 (21.8%)	3 (10.3%)	0.180
Phantosmia	14 (25.5%)	4 (13.8%)	0.201
Olfactory function test			
Total score (TDI)	20.39 ± 5.38	14.58 ± 6.13	**0.000**
Threshold score (T)	3.01 ± 1.8	1.89 ± 1.46	**0.003**
Discrimination score (D)	7.52 ± 2.26	5.83 ± 2.07	**0.001**
Identification score (I)	10.08 ± 2.48	6.86 ± 3.76	**0.000**
Anosmia (TDI ≤ 14.5)	8 (14.5%)	16 (55.2%)	**0.000**
Hyposmia (TDI ≤ 21)	20 (36.4%)	9 (31%)	**0.000**
Normosmia (TDI > 21)	27 (49.1%)	4 (13.8%)	**0.000**
Disruption in daily life or work	42 (76.4%)	19 (65.5%)	0.289

OD, olfactory dysfunction; URI, upper respiratory infection

Frequency of qualitative OD according to the aetiology of OD

We further analysed the characteristics of OD according to its aetiology (Table 1). The mean age was significantly lower in the 'viral infection' and 'head trauma' groups compared to the 'sinonasal disease' group. In addition, the 'viral infection' group included more females than the other groups. The frequency of parosmia was significantly higher (P = 0.0003) in the 'viral infection' group (17.9%) than in the 'sinonasal disease' group (5.5%), whereas that of phantosmia was not significantly different between the groups (Figure 1A). Conversely, olfactory function test revealed that the proportion of anosmia was lower in the 'viral infection' group (28.6%) compared to the 'sinonasal disease' (45.5%), 'head trauma' (78.6%), and 'others' (53.6%) groups. In line with this, the 'viral infection' group (18.38 ± 6.27) showed a significantly higher TDI score than the 'sinonasal disease' (16.03 ± 6.87), 'head trauma' (10.07 ± 4.88), and 'others' (14.83 ± 6.21) groups (Figure 1B). However, a higher proportion of patients had impaired quality of life in the 'viral infection' (72.6%) and 'others' (56.9%) groups than in the 'sinonasal disease' (38.5%) group. Because COVID-19 has emerged as one of the major causes of OD since its outbreak, we additionally compared the characteristics of the 'COVID-19' group (patients with COVID-19) and the 'other URI' group (patients with URI other than COVID-19). The 'COVID-19' group had significantly younger ages and higher TDI scores than the 'other URI' group (Table 2). The frequencies of parosmia and phantosmia tended to be higher in the 'COVID-19' group than in the 'other URI' group, but the difference was not statistically significant.

Clinical features of patients with parosmia and those with phantosmia

To identify the clinical characteristics of patients with parosmia or phantosmia, we next divided total patients with OD into two groups based on the presence of parosmia ('parosmia' and 'non-parosmia' groups) or phantosmia ('phantosmia' and 'non-phantosmia' groups) (Table 3). The mean age of the 'parosmia' and 'phantosmia' groups was significantly lower than that of the 'non-parosmia' and 'non-phantosmia' groups, respectively. The prevalence of parosmia and phantosmia by age is presented in Figure 1C. In addition, the proportion of females was significantly higher in the 'parosmia' and 'phantosmia' groups than in the 'non-parosmia' and 'non-phantosmia' groups, respectively. In the olfactory function test, the 'parosmia' group showed significantly higher T, D, I, and TDI scores than the 'non-parosmia' group (Supplementary Figure 1A). Accordingly, the frequency of the anosmia was significantly lower in the 'parosmia' group than in the 'non-parosmia' group. The same findings were observed when we compared the results of the olfactory function test between the 'phantosmia' and 'non-phantosmia' groups (Supplementary figure 1B). The prevalence of parosmia and phantosmia according to TDI scores is presented in Figure 1D. In contrast, the percentage of patients who reported an impaired quality of life was significantly higher in the 'parosmia' group than in the 'non-parosmia' group. The 'phantosmia' group also showed a sig-

Table 3. Clinical characteristics of patients with OD according to the presence of parosmia or phantosmia.

Variables	Parosmia (n = 60)	Non-parosmia (n = 693)	P value[a]	Phantosmia (n = 167)	Non-phantosmia (n = 586)	P value[b]
Age (years)	43.42 ± 17.68	50.9 ± 16.3	**0.001**	45.75 ± 15.46	51.6 ± 16.61	**0.000**
Sex						
Male	22 (36.7%)	351 (50.6%)	**0.038**	71 (42.5%)	302 (51.5%)	**0.040**
Female	38 (63.3%)	342 (49.4%)	**0.038**	96 (57.5%)	284 (48.5%)	**0.040**
Olfactory function test						
Total score (TDI)	18.35 ± 5.53	15.61 ± 6.82	**0.001**	17.41 ± 7.00	15.38 ± 6.63	**0.001**
Threshold score (T)	2.75 ± 1.77	2.17 ± 1.6	**0.008**	2.55 ± 1.83	2.12 ± 1.54	**0.006**
Discrimination score (D)	6.73 ± 2.29	6.05 ± 2.63	**0.033**	6.52 ± 2.81	5.99 ± 2.54	**0.021**
Identification score (I)	9.08 ± 2.91	6.73 ± 2.29	**0.000**	8.34 ± 3.47	6.52 ± 2.81	**0.001**
Anosmia (TDI ≤ 14.5)	14 (23.3%)	336 (48.5%)	**0.000**	66 (39.5%)	284 (48.5%)	**0.002**
Hyposmia (TDI ≤ 21)	27 (45%)	159 (22.9%)	**0.000**	35 (21%)	151 (25.8%)	**0.002**
Normosmia (TDI > 21)	19 (31.7%)	198 (28.6%)	**0.000**	66 (39.5%)	151 (25.8%)	**0.002**
Disruption in daily life or work	37 (61.7%)	316 (45.6%)	**0.017**	91 (54.5%)	262 (44.7%)	**0.025**
Self-reported GD	32 (53.3%)	237 (34.2%)	**0.003**	57 (34.1%)	212 (36.2%)	0.626
Gustatory function test						
Taste recognition score (TR)	16.17 ± 5.36	16.89 ± 4.69	0.291	16.75 ± 4.65	16.86 ± 4.78	0.808
Ageusia (TR ≤ 5)	1/53 (1.9%)	6/609 (1.0%)	0.417	2/151 (1.3%)	5/511 (1.0%)	0.701
Hypogeusia (TR ≤ 12)	10/53 (18.9%)	71/609 (11.7%)	0.417	18/151 (11.9%)	63/511 (12.3%)	0.701
Normogeusia (TR > 12)	42/53 (79.2%)	532/609 (87.4%)	0.417	131/151 (86.8%)	443/511 (86.7%)	0.701

OD, olfactory dysfunction; GD, gustatory dysfunction. Categorical variables - Number of patients (percent). Continuous variables - mean ± standard deviation. [a] Parosmia vs. Non-parosmia. [b] Phantosmia vs. Non-phantosmia.

nificantly higher proportion of patients who reported impaired quality of life compared to the 'non-phantosmia' group. The frequency of subjective GD was significantly higher in the 'parosmia' group than the 'non-parosmia' group, whereas that was not significantly different between the 'phantosmia' and 'non-phantosmia' groups. However, there was no significant difference in the taste recognition scores of the gustatory function test between the 'parosmia' and 'non-parosmia' groups or between the 'phantosmia' and 'non-phantosmia' groups. Among patients with the sinonasal disease who answered the SNOT-22 questionnaire (n = 358), the 'parosmia' (47.91 ± 24.64) and 'phantosmia' (45.11 ± 23.29) groups had a significantly higher SNOT-22 score than the 'non-parosmia' (36.15 ± 21.8) and 'non-phantosmia' (34.42 ± 21.21) groups, respectively.

In comparison between the 'qualitative OD' group (patients with parosmia, phantosmia, or both) and the 'non-qualitative OD' group (patients without parosmia and phantosmia), the qualitative OD group exhibited a younger age distribution, a higher proportion of females, and higher TDI scores than the non-qualitative OD group. Moreover, the qualitative OD group reported greater disruptions in their daily life or work (Supplementary Table 2). We additionally compared the characteristics between patients with both parosmia and phantosmia ('phantosmia & parosmia' group) and those with phantosmia but not parosmia ('phantosmia & non-parosmia' group). The 'phantosmia & parosmia' group had significantly younger age and experienced more deterioration in the quality of life compared to the 'phantosmia & non-parosmia' group. Although TDI score did not differ significantly between the two groups, the frequency of anosmic patients was lower in the 'phantosmia & parosmia' group than in the 'phantosmia & non-parosmia' group (Supplementary Table 3).

Clinical factors associated with qualitative OD in patients with OD

To further identify the clinical factors related to qualitative OD, we performed a binary logistic regression analysis of factors associated with the presence of parosmia and phantosmia in patients with OD (Table 4). Variables with significant differences in the univariate analyses (Table 3) were selected for multivariate binary logistic regression analysis. In multivariate analyses, younger age (P = 0.022), viral infection (P = 0.044), and a higher TDI score (P = 0.035) were identified as independent factors associated with a high frequency of parosmia. In addition, younger age (P = 0.002), female sex (P = 0.021), and a higher TDI score (P = 0.014) were associated with a high frequency of phantosmia.

Table 4. Multivariate logistic regression analysis for the factors associated with the presence of parosmia or phantosmia.

Variables [a]	Parosmia			Phantosmia		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Age	0.978	0.96 to 1	**0.022**	0.982	0.97 to 0.99	**0.002**
Male (Ref = Female)	0.607	0.34 to 1.08	0.091	0.651	0.45 to 0.94	**0.021**
Cause (Ref = Sinonasal disease)						
Viral infection	2.154	1.02 to 4.54	**0.044**			
Head trauma	1.813	0.47 to 7.01	0.388			
Others	1.880	0.92 to 3.82	0.081			
Self-reported GD	1.528	0.85 to 2.73	0.153			
Disruption in daily life or work	1.224	0.67 to 2.23	0.510	1.315	0.92 to 1.89	0.137
TDI score	1.049	1 to 1.1	**0.035**	1.035	1.01 to 1.06	**0.014**

CI, confidence interval; OD, olfactory dysfunction; GD, gustatory dysfunction. [a] Variables with $P < 0.05$ in the univariate analysis were included in the multivariate analysis.

Discussion

Among those who experience smell disturbance, a considerable proportion of individuals experience odour distortion, including parosmia and phantosmia. With the advent of the COVID-19 pandemic, qualitative OD has become a topic of scientific interest. In the present study, we comprehensively investigated the clinical characteristics of patients with parosmia and phantosmia using olfactory questionnaires and psychophysical olfactory function tests. We found that parosmia was associated with younger age and viral infection. In addition, patients with phantosmia were more likely to be young and female but were not associated with any aetiology of OD. Remarkably, our results showed that patients with parosmia or phantosmia paradoxically had worse quality of life despite better olfactory function results, indicating that qualitative OD is a critical determinant of OD-induced discomfort in daily life. These findings imply that not only quantitative OD but also qualitative OD should be carefully evaluated in the diagnosis and management of patients with OD.

The mechanism underlying qualitative OD remains unclear. It has been suggested that aberrant neuronal regeneration occurring during recovery of the olfactory system leads to parosmia [7]. Several studies have described that the presence of parosmia is associated with favourable olfactory recovery [12,13]. In contrast, abnormally active olfactory neurons, loss of inhibitory neurons, or damaged cortical olfactory pathways may underlie phantosmia [14]. In the current study, we found that patients with parosmia or phantosmia showed significantly higher TDI scores than those without parosmia or phantosmia, respectively. Because qualitative OD is hypothesized to occur frequently during recovery or when olfactory sensory neurons are partially damaged, it seems plausible that patients with qualitative OD have a better odour detection ability than patients who are not recovering or those with completely damaged olfactory sensory neurons.

In line with previous studies [5,15], our results showed the highest prevalence of parosmia in post-viral OD among all aetiologies. In addition, multivariate logistic analysis confirmed that viral infection was an independent factor associated with a high frequency of parosmia. As parosmia is suggested to be related to the regeneration of damaged axons, these results indicate that axon regeneration may occur more frequently in post-viral OD than in other aetiologies [16,17]. This hypothesis is supported by the fact that spontaneous recovery was more prevalent [18] and olfactory training was more effective [16] in post-viral OD compared to other aetiologies of OD, particularly post-traumatic OD. In addition, among patients with OD caused by a respiratory virus infection, including COVID-19, those with parosmia had a greater improvement in identification and discrimination scores after olfactory training than those without parosmia [12]. Furthermore, olfactory training is an effective treatment for COVID-19-induced parosmia [19]. Interestingly, we found an increased tendency of the frequencies of parosmia and phantosmia in the 'COVID-19' group compared to the 'other URI' group despite no statistical significance due to the low number of patients. Further studies with larger cohorts are needed to clarify whether qualitative OD is more frequent in COVID-19 by directly comparing COVID-19 with other URIs.

Previous epidemiological studies have shown that the male sex is an important risk factor for OD [20,21]. In contrast, we found that patients with parosmia or phantosmia were more likely to be females. Similarly, a previous study reported that parosmic patients consisted of more females than non-parosmic patients [5]. Several studies have also reported a female predominance among patients with phantosmia [22,23], whereas one recent study did not [5]. It has been reported that females are significantly more likely to have social and domestic dysfunction related

to olfactory loss and have higher rates of daily life complaints [5,24]. This tendency might be explained by the difference in the subjective patient-perceived burden of disease and the primary determinant of quality of life between the sexes [21,25]. In addition, our results showed a negative correlation between age and qualitative OD. Younger patients may exhibit a higher rate of regeneration of damaged neurons, which in turn may trigger parosmia [7,12,26].

It has been well-described that OD is associated with a decrease in quality of life [27,28]. Intriguingly, factors other than the severity of loss of smell may significantly affect the quality of life. A study analysing a large community sample reported that no significant correlation was observed between the quality of life and results of the Sniffin' Sticks Screening 12 test [29]. Consistent with the results of a previous study [27], we found a significant decrease in the quality of life in patients with parosmia or phantosmia, although the association was not significant in the multivariate analyses. Disruption in quality of life is subjective, difficult to measure, and can manifest as a variety of symptoms. For instance, parosmia can cause discomfort or nausea when eating and induce deterioration of taste due to distorted flavour, consequently leading to disruption in quality of life [30]. Indeed, our results show that the proportion of patients subjectively complaining of GD was significantly higher in parosmic patients than in non-parosmic patients, despite no significant difference in the taste recognition score. Furthermore, a subgroup analysis of the 'sinonasal disease' group revealed that patients with qualitative OD had higher SNOT-22 scores, a high-quality psychometric measure for assessing the quality of life in patients with CRS, than the patient without qualitative OD.

This study has several limitations. First, there might be referral bias because the study was conducted in a tertiary hospital. In this regard, the most common aetiology of OD was a sinonasal disease. Second, we enrolled only patients with subjective smell disturbances. Thus, the number of patients diagnosed with OD using psychophysical tests without subjective symptoms could be underestimated. Third, given that parosmia is considered to appear during the recovery period, the time interval between referral and the first visit may have affected the prevalence of parosmia. Fourth, we did not investigate the treatment outcomes of qualitative OD using a follow-up questionnaire and psychophysical tests in this study. Additional studies are required to identify the prognostic factors of qualitative OD and appropriate treatment strategies for patients with qualitative OD [17,19]. Despite these limitations, our study is the first to directly compare the results of psychophysical tests for both olfactory and gustatory function between patients with and without parosmia or phantosmia across all aetiologies of OD.

Conclusion

We conducted a direct comparison of clinical features, including psychophysical test results, between OD patients with and without parosmia or phantosmia, and investigated factors associated with parosmia or phantosmia. Patients with parosmia or phantosmia were likely to be younger and female. Notably, patients with parosmia or phantosmia had better psychophysical olfactory test results but experienced more deterioration in daily life than those without parosmia or phantosmia, respectively. In addition, younger age and higher TDI score were independent factors associated with both parosmia and phantosmia, whereas viral infection is associated with parosmia but not with phantosmia. Our investigation provides novel insights into the current understanding of qualitative OD, which will aid in the counselling and management of patients with qualitative OD.

Authorship contribution

T-SE, M-SR, and C-HK designed this study. T-SE and HYL collected the data. T-SE, H-JC, J-HY, and M-SR analysed the data. T-SE and M-SR wrote the draft and all authors reviewed and approved the final version of the manuscript. The corresponding author has the final responsibility for the decision to submit for publication.

Acknowledgements

None.

Conflict of interest

None.

Funding

This research was supported by a faculty research grant from Yonsei University College of Medicine (6-2022-0082), the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2021R1I1A1A01047571), and the NRF grants funded by the Korea government (MSIT) (No. 2019R1A2C1089841).

References

1. Goodspeed RB, Gent JF, Catalanotto FA. Chemosensory dysfunction. Clinical evaluation results from a taste and smell clinic. Postgrad Med 1987; 81(1):251-257, 260.
2. Agyeman AA, Chin KL, Landersdorfer CB, Liew D, Ofori-Asenso R. Smell and taste dysfunction in patients with COVID-19: A Systematic Review and Meta-analysis. Mayo Clin Proc 2020; 95(8):1621-1631.
3. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. the prevalence of olfactory and gustatory dysfunction in covid-19 patients: a systematic review and meta-analysis. Otolaryngol Head Neck Surg 2020; 163(1):3-11.
4. Walker A, Kelly C, Pottinger G, Hopkins C. Parosmia-a common consequence of covid-19. Bmj 2022; 377:e069860.
5. Pellegrino R, Mainland JD, Kelly CE, Parker JK, Hummel T. Prevalence and correlates of parosmia and phantosmia among smell disorders. Chem Senses 2021; 46.
6. 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. 2023;85(2):67-71.
7. Hong SC, Holbrook EH, Leopold DA, Hummel T. Distorted olfactory perception: a systematic review. Acta Otolaryngol 2012; 132 Suppl 1:S27-31.
8. Landis BN, Frasnelli J, Croy I, Hummel T. Evaluating the clinical usefulness of structured questions in parosmia assessment. Laryngoscope 2010; 120(8):1707-1713.
9. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology 2020; 58(Suppl S29):1-464.
10. Ha JG, Kim J, Nam JS, et al. Development of a Korean culture-friendly olfactory function test and optimization of a diagnostic cut-off value. Clin Exp Otorhinolaryngol 2020; 13(3):274-284.
11. Hwang CS, Kim JW, Al Sharhan SS, et al. development of a gustatory function test for clinical application in Korean subjects. Yonsei Med J 2018; 59(2):325-330.
12. Liu DT, Sabha M, Damm M, et al. parosmia is associated with relevant olfactory recovery after olfactory training. Laryngoscope 2021; 131(3):618-623.
13. Hummel T, Lötsch J. Prognostic factors of olfactory dysfunction. Arch Otolaryngol Head Neck Surg 2010; 136(4):347-351.
14. Saltagi MZ, Rabbani CC, Ting JY, Higgins TS. Management of long-lasting phantosmia: a systematic review. Int Forum Allergy Rhinol 2018; 8(7):790-796.
15. Reden J, Maroldt H, Fritz A, Zahnert T, Hummel T. A study on the prognostic significance of qualitative olfactory dysfunction. Eur Arch Otorhinolaryngol 2007; 264(2):139-144.
16. Konstantinidis I, Tsakiropoulou E, Bekiaridou P, Kazantzidou C, Constantinidis J. Use of olfactory training in post-traumatic and postinfectious olfactory dysfunction. Laryngoscope 2013; 123(12):E85-90.
17. Kattar N, Do TM, Unis GD, Migneron MR, Thomas AJ, McCoul ED. olfactory training for postviral olfactory dysfunction: systematic review and meta-analysis. Otolaryngol Head Neck Surg 2021; 164(2):244-254.
18. Reden J, Mueller A, Mueller C, et al. Recovery of olfactory function following closed head injury or infections of the upper respiratory tract. Arch Otolaryngol Head Neck Surg 2006; 132(3):265-269.
19. Altundag A, Yilmaz E, Kesimli MC. modified olfactory training is an effective treatment method for COVID-19 induced parosmia. Laryngoscope 2022; 132(7):1433-1438.
20. Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. Jama 2002; 288(18):2307-2312.
21. Yang J, Pinto JM. The Epidemiology of Olfactory Disorders. Curr Otorhinolaryngol Rep 2016; 4(2):130-141.
22. Bainbridge KE, Byrd-Clark D, Leopold D. factors associated with phantom odor perception among US adults: findings from the national health and nutrition examination survey. JAMA Otolaryngol Head Neck Surg 2018; 144(9):807-814.
23. Sjölund S, Larsson M, Olofsson JK, Seubert J, Laukka EJ. Phantom smells: prevalence and correlates in a population-based sample of older adults. Chem Senses 2017; 42(4):309-318.
24. Philpott CM, Boak D. The impact of olfactory disorders in the United Kingdom. Chem Senses 2014; 39(8):711-718.
25. Liu DT, Besser G, Prem B, et al. Self-perceived taste and flavor perception: associations with quality of life in patients with olfactory loss. Otolaryngol Head Neck Surg 2021; 164(6):1330-1336.
26. Ogawa T, Nakamura K, Yamamoto S, Tojima I, Shimizu T. Recovery over time and prognostic factors in treated patients with post-infectious olfactory dysfunction: a retrospective study. Ann Otol Rhinol Laryngol 2020; 129(10):977-982.
27. Frasnelli J, Hummel T. Olfactory dysfunction and daily life. Eur Arch Otorhinolaryngol 2005; 262(3):231-235.
28. Zou LQ, Hummel T, Otte MS, et al. Association between olfactory function and quality of life in patients with olfactory disorders: a multicenter study in over 760 participants. Rhinology 2021; 59(2):164-172.
29. Hinz A, Luck T, Riedel-Heller SG, et al. Olfactory dysfunction: properties of the Sniffin' Sticks Screening 12 test and associations with quality of life. Eur Arch Otorhinolaryngol 2019; 276(2):389-395.
30. Parker JK, Methven L, Pellegrino R, Smith BC, Gane S, Kelly CE. Emerging pattern of post-COVID-19 parosmia and its effect on food perception. Foods 2022; 11(7).

Chang-Hoon Kim, M.D., Ph.D.
Department of Otorhinolaryngology
Yonsei University College of Medicine
Severance Hospital
50-1 Yonsei-ro
Seodaemun-gu
Seoul 03722
Republic of Korea

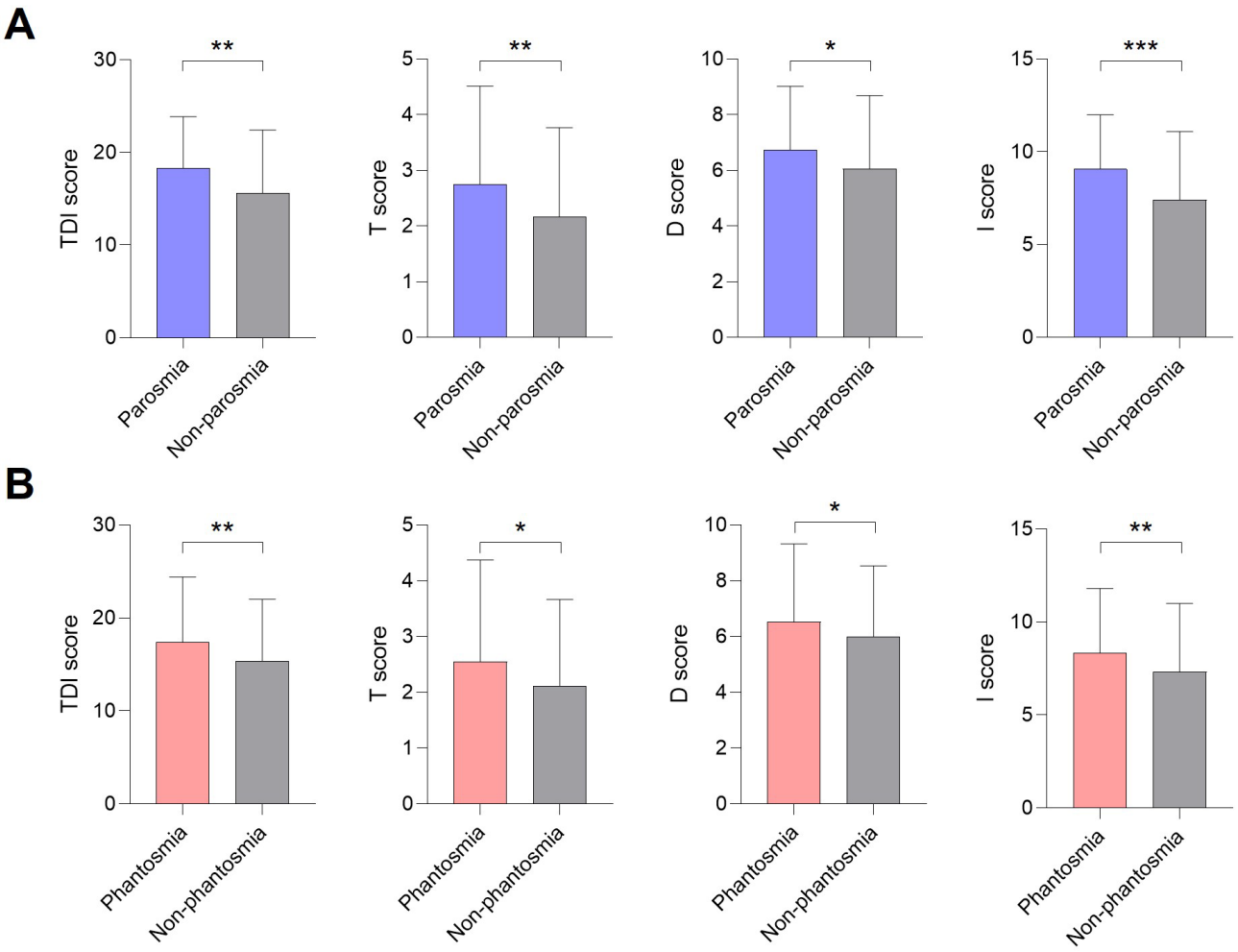
Tel: +82-2-2228-3627
Fax: +82-2-393-0580,
E-mail: entman@yuhs.ac

Min-Seok Rha, M.D., Ph.D.
Department of Otorhinolaryngology
Yonsei University College of Medicine
Severance Hospital
50-1 Yonsei-ro
Seodaemun-gu
Seoul 03722
Republic of Korea

Tel:+82-2-2228-0774
Fax: +82-2-393-0580
E-mail: msrha@yuhs.ac

This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL



Supplementary Figure 1. Olfactory function test results according to the presence of parosmia or phantosmia. (A) TDI, T, D, and I scores in patients with (n = 60) and without (n= 693) parosmia. (B) TDI, T, D, and I scores in patients with (n = 167) and without (n = 586) phantosmia. Statistical analysis was performed using the independent t-test. *P < 0.05, **P < 0.01, ***P < 0.001.

Supplementary Table 1. Olfactory questionnaire.

Olfactory questionnaire				
Sex	☐M ☐F	Age		Date
Duration		☐< 3months, ☐3 - 12months, ☐1 - 4years, ☐5 - 9years, ☐> 10years		
Characteristics	Quantitative olfactory dysfunction and severity	Do you currently have trouble smelling? ☐ Yes, I cannot smell well ☐ Yes, I cannot smell at all ☐ No		
	Qualitative olfactory dysfunction	Parosmia	Have you ever smelled odours differently compared to previous experiences or certain pleasant odours in an unpleasant way? ☐ Yes ☐ No	
		Phantosmia	Have you ever smelled an unpleasant or weird or smelled of something burning in the absence of an odour? ☐ Yes ☐ No	
	Gustatory dysfunction		Are there any changes in the sense of taste? ☐ Yes ☐ No	
			If yes, which sensations have changed? (multiple choices available) ☐salty ☐ sour ☐ sweet ☐ bitter ☐ umami	
	Quality of life		Is there any ill-being or difficulty due to olfactory dysfunction in daily life or work? ☐ Yes ☐ No	

Supplementary Table 2. Characteristics of patients with qualitative OD.

Variables	Qualitative OD (n=206)	Non-qualitative OD (n=547)	P value
Age (years)	45.87 ± 15.95	51.97 ± 16.45	**0.000**
Sex			
Male	87/206 (42.2%)	286/547 (52.3%)	**0.014**
Female	119/206 (57.8%)	261/547 (47.7%)	**0.014**
Olfactory function test			
Total score (TDI)	17.63 ± 6.69	15.15 ± 6.67	**0.000**
Threshold (T)	2.61 ± 1.85	2.06 ± 1.5	**0.000**
Discrimination (D)	6.56 ± 2.69	5.94 ± 2.56	**0.002**
Identification (I)	8.51 ± 3.33	7.18 ± 3.71	**0.000**
Anosmia (TDI ≤ 14.5)	75/206 (36.4%)	275/547 (50.3%)	**0.001**
Hyposmia (TDI ≤ 21)	53/206 (25.7%)	133/547 (24.3%)	**0.001**
Normosmia (TDI > 21)	78/206 (37.9%)	139/547 (25.4%)	**0.001**
Disruption in daily life or work	112/206 (54.4%)	241/547 (44.1%)	**0.011**
Self-reported GD	79/206 (38.3%)	190/547 (34.7%)	0.356
Gustatory function test			
Taste Recognition score (TR)	16.56 ± 4.93	16.94 ± 4.67	0.622
Ageusia (TR ≤ 5)	3/185 (1.6%)	4/477 (0.8%)	0.456
Hypogeusia (TR ≤ 12)	26/185 (14.1%)	55/477 (11.5%)	0.456
Normogeusia (TR > 12)	156/185 (84.3%)	418/477 (87.6%)	0.456

Categorical variables - Number of patients (percent). Continuous variables - Mean ± Standard deviation.

Supplementary Table 3. Characteristics of patients with phantosmia according to the presence of parosmia.

Variables	Phantosmia & parosmia (n=21)	Phantosmia & non-parosmia (n=146)	P value
Age (years)	37.9 ± 15.87	46.88 ± 15.13	**0.007**
Sex			
Male	6/21 (28.6%)	65/146 (44.5%)	0.167
Female	15/21 (71.4%)	81/146 (55.5%)	0.167
Olfactory function test			
Total score (TDI)	17.94 ± 6.34	17.33 ± 7.1	0.826
Threshold (T)	2.46 ± 1.4	2.56 ± 1.88	0.765
Discrimination (D)	6.71 ± 2.61	6.49 ± 2.84	0.799
Identification (I)	8.76 ± 3.53	8.28 ± 3.46	0.586
Anosmia (TDI ≤ 14.5)	5/21 (23.8%)	61/146 (41.8%)	**0.027**
Hyposmia (TDI ≤ 21)	9/21 (42.9%)	26/146 (17.8%)	**0.027**
Normosmia (TDI > 21)	7/21 (33.3%)	59/146 (40.4%)	**0.027**
Disruption in daily life or work	16/21 (76.2%)	75/146 (51.4%)	**0.033**
Self-reported GD	10/21 (47.6%)	47/146 (32.2%)	0.163
Gustatory function test			
Taste Recognition score (TR)	16.95 ± 3.96	16.72 ± 4.75	0.915
Ageusia (TR ≤ 5)	0/19 (0%)	2/132 (1.5%)	1.000
Hypogeusia (TR ≤ 12)	2/19 (10.5%)	16/132 (12.1%)	1.000
Normogeusia (TR > 12)	17/19 (89.5%)	114/132 (86.4%)	1.000

Categorical variables - Number of patients (percent). Continuous variables - Mean ± Standard deviation.