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Improved Nasal Airflow Is Associated With Olfactory Recovery in a Large Population of Patients With COVID-19-Related Olfactory Dysfunction

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ABSTRACT

Objective: Nasal airflow is essential for delivering odorants to the olfactory epithelium. With increasing evidence demonstrating a strong link between nasal airflow and olfaction, we conducted a large multicenter retrospective study to further examine if nasal airflow can influence olfactory recovery in patients with COVID-19-related olfactory dysfunction (C19OD).

Methods: Patients with reported C19OD received Sniffin' Sticks extended set, peak nasal inspiratory flow (PNIF), and VAS for smell (sVAS) at baseline (T_0). Subjects with a confirmed OD at T_0 were offered a second follow-up, averaged at 6 months (T_1). All tests were repeated at T_1 .

Results: Two hundred and five patients (median age 46) with a median length of OD of 1.1 years were seen at T_0 . One hundred and eleven dysosmics at T_0 were seen at T_1 . At T_1 43 patients (38.7%) recovered their sense of smell. A statistically significant improvement was observed for PNIF ($p = 0.001$) and sVAS ($p < 0.001$) in the whole population at T_1 . A statistically significant difference was noted for all the olfactory scores and sVAS ($p < 0.001$ for all) between normosmic and dysosmic subjects at T_1 . When we looked at changes in the scores between T_0 – T_1 , statistically significant correlations were observed between changes (Δ) in PNIF and Δ threshold ($\rho = 0.24$ and $p = 0.015$), Δ PNIF and Δ TDI ($\rho = 0.22$ and $p = 0.021$). An increase in Δ PNIF of 77.4 L/min corresponded to a 65% probability of reaching the normosmic level, with olfactory threshold being the more sensitive to PNIF changes.

Conclusion: Improvement in nasal airflow can have a positive impact on smell recovery and on olfactory threshold in particular, highlighting its importance in persistent C19OD.

Level of Evidence: 3.

1 | Introduction

The relationship between nasal airflow and olfaction is complex. The detection of olfactory stimuli intrinsically depends on the delivery of odorants to the olfactory epithelium (OE), an area located at the apex of the nasal cavity at the level of the

cribriform plate. It has been reported that the airflow reaching the olfactory area during a normal resting breath accounts for only 5% to 15% of the total nasal flow [1–3]. This limited airflow is critical for the sense of smell, as it directs odorant molecules toward the OE [4], and its reduction can decrease the transport of odorants to the olfactory mucosa by over 700%, especially for

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chemicals with high solubility and diffusivity [2]. Sniffing is also another important part of olfactory perception and can affect perception, odorant identification, and intensity [5, 6]. The act of sniffing increases the airflow toward the olfactory cleft, termed olfactory nasal airflow (ONA), and simulations of sniffing versus quiet breathing in the canine nasal cavity have shown an increase of ONA by 2.5-fold when sniffing [6].

Following the COVID-19 pandemic, olfactory dysfunction (OD) has gained considerable notability as it is a common symptom caused by SARS-CoV-2 infection. According to research conducted during the pandemic, from 34% to 86% of subjects experience an acute loss of their sense of smell following SARS-CoV-2 infection [7]. A previous meta-analysis published in the early phase of the pandemic and including 27,492 patients confirmed the prevalence of COVID-19-related olfactory dysfunction (C19OD) to be 47.9% [8]. In particular, the alpha and delta variants of the virus were linked to a higher rate of C19OD when compared to omicron [9]. Long-term prognosis still remains undetermined, although it has been reported that 5.2% of subjects infected during the first wave of the pandemic and 7.9% of those who had a chemosensory dysfunction during the acute phase of the disease still have C19OD after 3 years following the infection [10].

Factors influencing olfactory recovery remain partially unknown. In a previous retrospective study conducted on 100 patients with persistent C19OD, we observed a highly significant positive influence of nasal airflow on smell performance [11]. Similarly, in another study, we found that patients with long-term reduced olfactory function had significantly lower values of nasal airflow when compared to subjects with normal olfactory function [12].

Given the strict relationship between sense of smell and nasal airflow, and in view of the recent findings supporting this close association, we conducted a multicenter study to further investigate the influence of nasal airflow on olfactory recovery in a large population of patients with C19OD.

2 | Materials and Methods

A retrospective analysis of patients with reported C19OD was conducted to evaluate the association between nasal airflow and olfactory recovery. All patients were seen in our long-COVID smell clinic at the University College London Hospitals (London, UK) and in the smell clinic at the University Hospital of Trieste (Trieste, Italy) after being referred to us for a reported persistent OD that occurred following a laboratory-confirmed (RT-PCR) SARS-CoV-2 infection. Demographic data, including age, sex, and comorbidities, were also collected for all the participants to investigate any potential influence on smell recovery.

Olfaction was psychophysically measured using the Sniffin' Sticks (S'S) extended set (Burghart, Medisense) to obtain the odor threshold (T), discrimination (D), and identification (I) scores. Normosmia was attributed where TDI score (the sum of T, D, and I individual scores) was ≥ 30.75 , hyposmia where TDI was > 16 , but < 30.75 , and anosmia if TDI ≤ 16 [13]. All patients received a nasal endoscopy to exclude an obstruction/inflammation of the olfactory clefts, signs of rhinitis, or chronic rhinosinusitis (CRS) including the presence of nasal polyps and/or nasal discharge.

Reported olfaction was self-assessed by the patient using a 100 mm visual analog scale (sVAS), ranging from 0 (no sense of smell) to 100 (normal sense of smell) [14]. Nasal airflow was measured using a peak nasal inspiratory flow (PNIF). A portable Youtlen peak flow meter (Clement Clark International) was used for the PNIF measurement. Three satisfactory maximal inspirations were obtained each time at basal condition and in a sitting position, and the highest value of the three was considered as the PNIF value. PNIF was only obtained bilaterally (i.e., without sealing the nostril) after at least 10 min of acclimatization in a room with constant temperature (between 19°C and 22°C) and a relative humidity of 25%–35% [15, 16].

Subjects with a confirmed OD at baseline (T_0) were offered a second follow-up averagely 6 months later (T_1). Olfactory training (OT) was recommended to all of them until follow-up, as previously described [17]. Over the 6-month period, participants were instructed to smell four essential oils (rose, lemon, eucalyptus, and clove) twice daily. Each scent was presented in an amber glass jar and inhaled for 10 s, with a 15-second interval between odors. Adherence to the OT protocol was defined as completing an average of 10 out of the prescribed 14 weekly sessions. All the investigations and measurements were repeated at T_1 again.

This study was conducted in accordance with the 1996 Helsinki Declaration and approved by the Hospital Research Ethics Committees (REC ref 14/SC/1180) and the Ethics Committee for Clinical Experimentation of the Friuli Venezia Giulia Region (CEUR-2020-Os-156). Informed consent was obtained from each subject before starting any study-related procedure.

2.1 | Statistical Analysis

Quantitative variables were presented as median and interquartile range whereas qualitative variables were expressed as the number of observations and percentage. Comparisons of measurements between groups were performed using the Mann-Whitney test for quantitative variables and the proportion test for dichotomic variables while the Mann-Whitney paired test was used to assess changes between T_0 and T_1 . Pearson correlation and Spearman's rank correlation index were used to measure associations between quantitative variables. Multiple linear regression with stepwise selection of variables based on Akaike's information criterion was performed to identify the effects of the available variables on the difference in S'S results and help determine positive and negative influences. For all tests, p -values have been obtained and 5% was considered as the critical level of significance. All the analysis has been performed in R (R Core Team 2021).

3 | Results

3.1 | Population Characteristics

Two hundreds and five patients (135 female; female-to-male ratio approximately 2:1) with a median age of 46 years (range 17–85) were seen between September 2020 and March 2023. All patients had a mild-to-moderate COVID-19, experienced

a complete loss of sense of smell (described as no sense of smell by the patients) following SARS-CoV-2 infection and developed a persistent OD after that episode. The median length of OD (calculated as number of days from the date of smell loss to the day of first consultation) was 1.1 years. The majority of the subjects were non-smokers (177; 86.3%), with no comorbidities (143; 69.8%) and they reported parosmia on the day of the assessment (118; 57.6%). Phantosmia was less frequently reported (77; 37.6%). Twenty-four patients (11.7%) had a history of rhinitis and only three patients (1.5%) had a history of CRS without nasal polyps; however, their sense of smell was not affected by the CRS. Four patients (2.0%) had a history of post-infectious OD (PIOD) but their sense of smell completely recovered after that episode. Similarly, six patients (2.9%) had a previous head trauma and 11 (11.4%) had a nasal operation in the past without any consequences on olfaction. Before coming to our smell clinics, all patients had tried OT without any resolution of their C19OD. Other treatments tried included multivitamins and topical/oral corticosteroids (Table 1).

3.2 | Olfactory Scores and Nasal Airflow at Baseline (T_0) and Follow-Up (T_1)

At baseline, 41 patients (20.0%) were found to be normosmics at S'S, 136 (66.3%) were hyposmic and the remaining 28 (13.7%) were functionally anosmic. For the analysis, we grouped the hyposmics and anosmics into a single group (dysosmics—TDI < 30.75) to maximize statistical power. The odor threshold score was below the normal value both in the normosmic and dysosmic groups, while the odor discrimination and identification scores were within the normal range in the normosmics [13]. Bilateral PNIF median value was within the normal range for an adult population both in the whole population and in normosmics and dysosmic patients [18]. Reported sense of smell (sVAS) was reduced (40.0) in the whole population (Table 2).

One hundred and eleven dysosmics at T_0 received a second follow-up at T_1 . Eighty-four subjects (75.7%) did the OT for 6 months as recommended, while 23 of them (20.7%) confirmed a poor adherence to that (not every day and/or not twice a day) and 4 of them (3.6%) did not do it. At T_1 43 patients (38.7%) recovered their sense of smell while 67 (60.4%) were still hyposmic and one patient (0.1%) was still functionally anosmic. The median odor threshold score was still below the normal mean value at T_1 in both the whole population and in the normosmic and dysosmic groups. Conversely, the odor discrimination and identification scores were within the normal range in the normosmics [13]. Bilateral PNIF median value was within the normal range for an adult population both in the whole population and in normosmics and dysosmic patients [18]. sVAS at T_1 was reduced only in the whole population (50.0 mm) and in the dysosmics (45.5 mm) (Table 3).

A statistically significant higher percentage of parosmia was observed at T_0 amongst dysosmics ($p = 0.01$). Dysosmic patients also used multivitamins more often than normosmics ($p = 0.01$). A statistically significant difference in the olfactory threshold, discrimination, identification and TDI was observed at T_0

between normosmics and dysosmics ($p < 0.001$ for all) (Tables 1 and 2).

3.3 | Changes at Follow-Up and Correlations Between Olfactory Function and Nasal Airflow

A statistically significant improvement in the median odor threshold, discrimination, identification and TDI score was observed at T_1 in the dysosmic population ($p < 0.001$ for all). A statistically significant improvement was also observed for PNIF ($p = 0.001$) and sVAS ($p < 0.001$) median scores (Table 3). When comparing the normosmic and the dysosmic populations at T_1 a statistically significant difference was noted for all the olfactory scores and sVAS ($p < 0.001$ for all) (Table 3).

No statistically significant correlations were observed between PNIF and olfactory scores at T_0 ($p > 0.05$) (Figure 1, left). Conversely, when we looked at changes in the scores between T_0 – T_1 a weak but statistically significant correlation was observed between changes in PNIF (Δ PNIF) and changes in olfactory threshold (Δ threshold) ($\rho = 0.24$ and $p = 0.015$) and between Δ PNIF and changes in TDI (Δ TDI) ($\rho = 0.22$ and $p = 0.021$). A strong statistically significant correlation was obtained between Δ TDI and Δ threshold ($r = 0.66$ and $p < 0.001$), between Δ TDI and Δ discrimination ($\rho = 0.74$ and $p < 0.001$), and between Δ TDI and Δ identification ($\rho = 0.59$ and $p < 0.001$). A weak but statistically significant correlation was obtained between Δ discrimination and Δ threshold ($\rho = 0.31$ and $p < 0.001$), and between Δ discrimination and Δ identification ($\rho = 0.24$ and $p = 0.013$). A weak but statistically significant correlation was demonstrated between Δ identification and Δ sVAS ($\rho = 0.24$ and $p = 0.013$) (Figure 1, right). The analysis also showed that an increase in Δ PNIF of 77.4 L/min corresponded to a 65% probability of reaching the normosmic level (TDI ≥ 30.75). Smaller Δ PNIF increase was needed for a 65% probability to reach the normal level [13] for olfactory threshold (13.3 L/min for an increase of ≥ 5.75) when compared to olfactory discrimination (31.1 L/min for an increase of ≥ 11) or identification (140.0 L/min for an increase of ≥ 11) (Figure 2).

At the multivariate analysis, none of the available variables influenced improvement in the olfactory scores while presence of rhinitis significantly influenced sVAS improvement at T_1 ($p = 0.048$).

4 | Discussion

The reasons why some people spontaneously recover their sense of smell following COVID-19, whereby others do not, remain poorly understood. Multiple factors are involved in smell recovery, with age (older) [19, 20] and female gender [21] representing significant predictors in developing persistent loss of smell. Alternatively, predictive factors associated with a higher rate of olfactory function recovery include the absence of coexisting nasal congestion [20, 22], non-smoking status [23], lower severity and duration of OD [22–25], presence of parosmia [22, 24, 26], a higher density of the olfactory receptor neurons (ORNs), and the presence of intact nerve bundles in the OE biopsy [25],

TABLE 1 | General characteristics of the whole population and of normosmic and dysosmic patients at baseline.

	Whole population	Normosmics	Dysosmics	<i>p</i>
	<i>n</i> = 205	<i>n</i> = 41	<i>n</i> = 164	
Age, median [P25-P75], yr	46.0 [34.0–56.0]	45.0 [34.0–55.0]	47.0 [33.8–56.0]	0.47
Sex, No (%)				
Female	135 (65.9%)	24 (58.5%)	111 (67.7%)	0.36
Male	70 (34.1%)	17 (41.4%)	53 (32.3%)	
Length of OD, median [P25-P75], yr	1.1 [0.8–1.4]	1.1 [1.1–1.3]	1.1 [0.8–1.5]	0.28
Parosmia, No (%)	118 (57.6%)	21 (51.2%)	97 (59.1%)	0.38
Phantosmia, No (%)	77 (37.6%)	8 (19.5%)	69 (42.1%)	0.01*
Smoking, No (%)				
Yes	28 (13.7%)	7 (17.1%)	21 (12.8%)	0.44
No	177 (86.3%)	34 (82.9%)	143 (87.2%)	
Comorbidity, No (%)				
None	143 (69.8%)	30 (73.2%)	113 (68.9%)	
Yes	62 (30.2%)	11 (26.8%)	51 (31.1%)	
Hypertension	13 (21.0%)	2 (18.2%)	11 (21.6%)	0.85
Hypothyroidism	9 (14.5%)	3 (27.3%)	6 (11.8%)	
Chronic respiratory disease	9 (14.5%)	1 (9.1%)	8 (15.7%)	
Cardiovascular disease	8 (12.9%)	1 (9.1%)	7 (13.7%)	
Diabetes	7 (13.2%)	1 (9.1%)	6 (11.8%)	
Hypercholesterolemia	6 (9.7%)	1 (9.1%)	5 (9.8%)	
Others	21 (33.9%)	5 (45.5%)	16 (31.4%)	
Rhinitis, No (%)	24 (11.7%)	7 (17.1%)	17 (10.4%)	0.27
Chronic rhinosinusitis, No (%)	3 (1.5%)	1 (2.4%)	2 (1.2%)	0.49
History of PIOD, No (%)	4 (2.0%)	0 (0.0%)	4 (2.4%)	0.59
Previous nasal operations, No (%)	11 (5.4%)	0 (0.0%)	11 (6.7%)	0.13
History of head trauma, No (%)	6 (2.9%)	0 (0.0%)	6 (3.7%)	0.60
Previous treatment for OD, No (%)				
None	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
Yes	205 (100%)	41 (100%)	164 (100%)	—
Multivitamins	160 (78.0%)	23 (56.1%)	137 (83.5%)	0.01*
Olfactory training	205 (100%)	41 (100%)	164 (100%)	0.36
Topical corticosteroids	96 (46.8%)	10 (24.4%)	86 (52.4%)	0.33
Oral corticosteroids	57 (27.8%)	5 (12.2%)	52 (31.7%)	1

Abbreviations: OD, olfactory dysfunction; PIOD, post-infectious olfactory dysfunction.

Significant *p*-values bold.Level of significance: **p* ≤ 0.05.

the presence of olfactory event-related potentials [27], and a narrow width of the OB when measured radiologically [28]. Notwithstanding, other variables must play a role in influencing spontaneous olfactory recovery in C19OD.

The relationship between nasal airflow and olfaction is well-established. However, it is unclear whether better nasal airflow can also influence olfactory recovery in PIOD. In our study, we did not find a linear correlation between nasal airflow and

TABLE 2 | Measurements of olfaction, nasal airflow and reported olfactory function for the whole population and for the normosmic and dysosmic patients at baseline.

	Whole population	Normosmics	Dysosmics	<i>p</i>
	<i>n</i> = 205	<i>n</i> = 41	<i>n</i> = 164	
Sniffin' Sticks, median [P25-P75]				
Threshold	4.9 [2.5–6.5]	7.5 [6.5–9.3]	4.0 [1.9–5.5]	<0.001***
Discrimination	10.0 [8.0–12.0]	13.0 [12.0–14.0]	10.0 [8.0–11.0]	<0.001***
Identification	10.0 [8.0–12.0]	13.0 [12.0–14.0]	9.0 [7.0–11.0]	<0.001***
TDI score, median [P25-P75]	25.0 [20.0–29.5]	33.5 [31.5–34.3]	23.0 [19.0–27.3]	<0.001***
Normosmic, <i>n</i> (%)	41 (20.0%)	—	—	
Hyposmic, <i>n</i> (%)	136 (66.3%)	—	136 (82.9%)	
Anosmic, <i>n</i> (%)	28 (13.7%)	—	28 (17.1%)	
PNIF, median [P25-P75], L/min	120.0 [90.0–151.3]	130.0 [90.0–150.0]	120.0 [90.0–152.5]	0.71
VAS smell, median [P25-P75], mm	40.0 [20.0–65.0]	77.5 [57.5–85.3]	32.5 [20.0–55.0]	<0.001***

Note: Significant *p*-values in bold.

Abbreviations: PNIF, peak nasal inspiratory flow; TDI, threshold + discrimination + identification; VAS, visual analog scale.

Levels of significance: **p* ≤ 0.05. ***p* ≤ 0.01. ****p* ≤ 0.001.

olfactory scores at T_0 (Figure 1, left), implying that people with higher PNIF can have a similar impaired olfaction despite their better nasal airflow. However, what our research has highlighted for the first time is that a sustained improvement in nasal airflow over time can significantly influence olfactory recovery. In fact, we observed a weak but statistically significant correlation between Δ PNIF and both Δ threshold ($\rho = 0.24$ and $p = 0.015$) and Δ TDI ($\rho = 0.22$ and $p = 0.021$) between T_0 and T_1 (Figure 1, right). Taken together, our findings suggest that the degree of nasal airflow improvement is a more critical factor in predicting olfactory outcomes than the baseline PNIF level. Although the correlation between Δ PNIF and both Δ threshold and Δ TDI is weak but significant, the mean PNIF increase at T_1 is similar in normosmic and dysosmic groups. This indicates that PNIF alone does not account for olfactory recovery. Therefore, nasal airflow should be regarded as one of several factors contributing to recovery, and the observed correlations should be interpreted with caution. Our analysis also indicates that a Δ PNIF of 77.4 L/min corresponds to a 65% probability to become normosmic (i.e., to have a TDI ≥ 30.75) (Figure 2, left). Interestingly, amongst the three olfactory abilities, odor threshold seems to be more sensitive to PNIF changes when compared to odor discrimination and identification, with a smaller Δ PNIF increase needed to achieve a 65% probability to reach the normal level (13.3 L/min for the olfactory threshold) (Figure 2, right). However, despite the strict relationship between olfaction and nasal airflow, the perceived smell improvement (Δ sVAS) did not correlate with Δ PNIF.

The neurophysiological mechanisms by which increased nasal airflow leads to improved olfaction still need to be fully clarified. Intuitively, a higher nasal airflow would allow for better ventilation of the olfactory clefts, enabling more odorants to reach and stimulate the OE. In addition, continuous stimulation of the ORNs is a potential mechanism through which OT improves the sense of smell in PIOD by promoting the regeneration

of ORNs at the OE level, thereby providing a trophic effect on olfactory regeneration [29, 30]. Others believe that OT exerts a “top-down” effect, characterized by the induction of cortical thickening within olfactory brain regions [30], further accompanied by a strengthening of olfactory, somatosensory, and integrative neural networks, as well as a volumetric increase in the OB [31]. While a meta-analysis supports this “top-down” theory [32], the benefits of OT likely arise from a combination of both “bottom-up” (ORN regeneration) and “top-down” (neural network changes) effects. It is plausible that comparable mechanisms underlie the olfactory improvements seen with enhanced nasal airflow.

As discussed above, amongst the three different olfactory abilities, Δ threshold achieved the greater correlation with Δ PNIF but was also the most sensitive to Δ PNIF increase. Odor threshold preferentially assesses the peripheral function of the olfactory system while the suprathreshold tests (i.e., discrimination and identification) better evaluate central or cognitive functions related to the sense of smell [33]. As a result, by increasing nasal airflow and thereby increasing odorant stimulation of the OE, we would expect a higher increase in the olfactory threshold scores. Furthermore, C19OD typically affects odor threshold reflecting the fact that the OE is targeted in SARS-CoV-2 infection. Consequently, this reinforces the significant impact of improved nasal airflow on olfactory recovery in C19OD and its potential benefits for those with PIOD in general.

The reasons for the nasal airflow improvement observed in our population nearly 18 months after infection are unclear. Nasal congestion following an acute viral rhinosinusitis typically resolves within 10 days and can persist for up to 3 months in acute post-viral rhinosinusitis [34]. This has also been confirmed in C19OD patients, where nasal congestion usually resolves within 2 weeks and remains stable in the following period [35]. We could argue that nasal airflow improvement

TABLE 3 | Measurements of olfaction, nasal airflow and reported olfactory function in the dysosmic group at T₀ and at T₁.

	Baseline (T ₀)		6-month follow-up (T ₁)				
	Dysosmics	Whole	Normosmics		Dysosmics	p-value (T ₀ -T ₁)	p-value (N vs D T ₁)
	n = 111	n = 111	n = 43	n = 68			
Sniffin' Sticks, median [P25-P75]							
Threshold	3.9 [1.5-6.0]	6.0 [4.0-8.0]	7.8 [6.8-8.6]	4.5 [3.1-6.0]	<0.001***	<0.001***	<0.001***
Discrimination	9.0 [8.0-11.0]	12.0 [10.0-13.0]	13.0 [13.0-14.0]	11.0 [9.0-11.0]	<0.001***	<0.001***	<0.001***
Identification	9.0 [7.0-11.0]	11.0 [10.0-13.0]	13.0 [12.0-14.0]	10.0 [9.0-11.3]	<0.001***	<0.001***	<0.001***
TDI score, median [P25-P75]	22.6 [18.6-27.0]	28.0 [24.6-32.9]	33.5 [32.4-35.5]	26.0 [22.9-28.0]	<0.001***	<0.001***	<0.001***
Normosmic, n (%)	—	43 (38.7%)	—	—			
Hyposmic, n (%)	90 (81.1%)	67 (60.4%)	—	67 (98.5%)			
Anosmic, n (%)	21 (18.9%)	1 (0.9%)	—	1 (1.5%)			
PNIF, median [P25-P75], L/min	120.0 [90.0-150.5]	130.0 [100.0-167.5]	130.0 [110.0-180.0]	130.0 [100.0-160.0]	0.001***	0.20	
VAS smell, median [P25-P75], mm	30.0 [15.3-56.5]	50.0 [30.0-74.0]	73.0 [49.5-80.0]	45.5 [16.3-60.0]	<0.001***	<0.001***	<0.001***

Note: Please note that only dysosmic patients with a T₁ follow-up have been included in the population of dysosmics at T₁. Significant p-values in bold. Abbreviations: PNIF, peak nasal inspiratory flow; TDI, threshold + discrimination + identification; VAS, visual analog scale. Levels of significance: *p ≤ 0.05. **p ≤ 0.01. ***p ≤ 0.001.

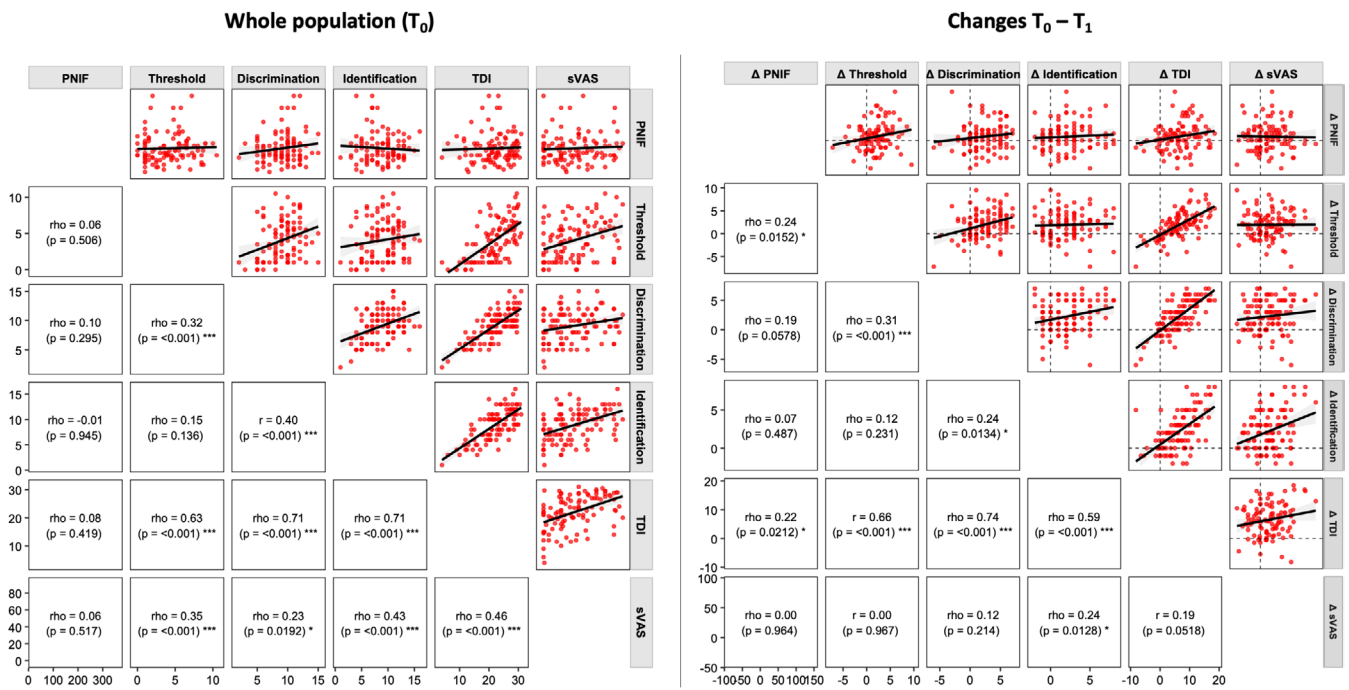


FIGURE 1 | Correlation matrix showing correlation between PNIF values, olfactory scores, and reported olfaction (sVAS) in the whole population (left) and in changes in the same variables between T_0 and T_1 (right). p -values in brackets. Significant p -values in bold. Levels of significance * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$. PNIF, peak nasal inspiratory flow; sVAS, visual analog scale for smell; TDI, threshold + discrimination + identification.

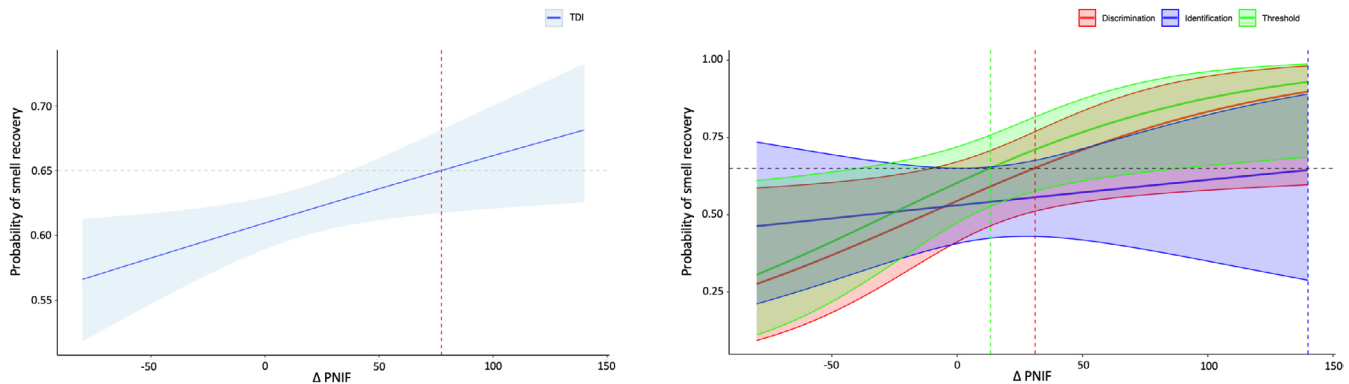


FIGURE 2 | Probability of TDI (left), olfactory threshold, olfactory discrimination, and olfactory identification normalization (right) in relation to changes in nasal airflow (Δ PNIF). Sniffin Sticks normative data from Oleszkiewicz et al. [13]. PNIF, peak nasal inspiratory flow; TDI, threshold + discrimination + identification.

was procedural and due to measurement bias, with patients performing better on the second assessment. However, several factors mitigate against this, including that measurements were performed by the same operators in the two centers, PNIF was taken three times at each appointment, and the advantages of our large sample size. Furthermore, the initial assessment occurring over a year after infection likely minimized any lingering effects of acute COVID-19 that could have impaired respiratory function.

One hypothesis is that repeated OT, which the majority of our population undertook (96.4%), required repeated nasal sniffing, which may have contributed to improved nasal function and airflow by strengthening nasal muscles crucial for the internal and external nasal valves (INV, ENV), such as the nasalis, dilator

nasaris anterior, and levator labii superioris alaeque nasi [36]. Nasal anatomy, in fact, can play an important role in controlling the access of odorants to the olfactory area. Several studies have shown the relationship between variations in the structures of the nasal cavity and olfactory function [37–43]. Moreover, the practice of sniffing is reinforced during OT, with PNIF representing the maximum sniffing measurement [44].

The INV region has been found to be a critical area in influencing the ONA [2, 37]. In a recent prospective-controlled study [45], functional septorhinoplasty significantly improved olfaction in C19OD patients. In these patients, additional olfactory nasal airway improvement was achieved through INV augmentation. Through this additional increase in ONA, an olfactory improvement was demonstrated. Notably, while all olfactory

abilities improved post-surgery, olfactory threshold showed the most significant gain. This further confirms the strong relationship between nasal airflow and the sense of smell, particularly olfactory threshold, and the mechanism of action would be most likely similar to OT.

The relationship between semi-objective (psychophysically measured) and subjective olfactory function remains debated. While individuals are generally aware of an olfactory impairment, they may be less sensitive at noticing subtle smell changes once these occur [11, 45]. Our findings appear to support this. At T_0 , we observed a moderate but highly significant correlation between sVAS and all semi-objective olfactory scores. This confirms sVAS as a simple and rapid tool for assessing olfaction and distinguishing between normal and reduced smell. However, Δ sVAS did not correlate with Δ TDI, implying that changes in semi-objective olfactory function were not consistently perceived by patients as an improvement in their reported sense of smell. Interestingly, we found a weak but statistically significant correlation between Δ sVAS and Δ identification ($\rho = 0.24$, $p = 0.013$). This suggests that an improvement in the ability to identify odorants can be perceived by subjects as an improved sense of smell. This is an intriguing finding, implying that what people perceive as an increase in their olfaction is primarily linked to their ability to detect more surrounding odors rather than changes in their olfactory threshold or discrimination.

4.1 | Strength and Limitations

This is the first study that looked at the relationship between changes in nasal airflow and olfactory function by assessing all three olfactory abilities by means of Sniffin' Sticks extended test. The multicenter design and large sample size are notable strengths. The main limitation of this study remains its retrospective setting and the lack of availability of other patient-reported outcome measures, rather than sVAS, for both centers.

5 | Conclusions

Our multicenter study confirms the direct relationship between the nasal airway and olfaction. Our observations in a large population of C19OD patients indicate that changes in nasal airflow can play a role in spontaneous olfactory recovery. Notably, improved nasal airflow appears to have a positive impact on olfactory threshold, which is frequently the most affected olfactory ability following SARS-CoV-2 infection, thus highlighting its importance in C19OD. Further research is needed to better understand the benefits of enhanced nasal airflow at the level of the OE.

Acknowledgments

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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