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## COVID-19 related olfactory dysfunction prevalence and natural history in ambulatory patients

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### Abstract

**Background:** Evidence regarding prevalence of COVID-19 related Olfactory dysfunction (OD) among ambulatory patients is highly variable due to heterogeneity in study population and measurement methods. Relatively few studies have longitudinally investigated OD in ambulatory patients with objective methods.

**Methods:** We performed a longitudinal study to investigate OD among COVID-19 ambulatory patients compared to symptomatic controls who test negative. Out of 81 patients enrolled, 45 COVID-19 positive patients and an age- and sex-matched symptomatic control group completed the BSIT and a questionnaire about smell, taste and nasal symptoms. These were repeated at 1 month for all COVID-19 positive patients, and again at 3 months for those who exhibited persistent OD. Analysis was performed by mixed-effects linear and logistic regression.

**Results:** 46.7% of COVID-19 patients compared to 3.8% of symptomatic controls exhibited OD at 1-week post diagnosis ( $p < 0.001$ ). At 1 month, 16.7%, (6 of 36), of COVID-19 patients had persistent OD. Mean improvement in BSIT score in COVID-19 patients between 1-week BSIT and 1 month follow-up was 2.0 (95% CI 1.00 – 3.00,  $p < 0.001$ ). OD did not correlate with nasal congestion ( $r = -0.25$ , 95% CI,  $-0.52$  to  $0.06$ ,  $p = 0.12$ ).

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**Ethics approval and consent to participate:** This study was approved by the Institutional Review Board at UNC (IRB# 20-1992).

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**Conclusions:** Ambulatory COVID-19 patients exhibited OD significantly more frequently than symptomatic controls. Most patients regained normal olfaction by 1 month. The BSIT is a simple validated and objective test to investigate the prevalence of OD in ambulatory patients. OD did not correlate with nasal congestion which suggests a congestion-independent mechanism of OD.

### Keywords

Ambulatory Patients; Anosmia; Hyposmia; Olfactory Disorders; Olfactory Dysfunction; Olfactory Testing; Psychophysical Testing; SARS-CoV-2; Smell Loss

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## INTRODUCTION

SARS-CoV-2 has become ubiquitous throughout the world, infecting more than 130 million people, and prompting the largest public health intervention in history.<sup>(1)</sup> Many containment strategies rely on early identification and isolation of infected individuals. In this regard, COVID-19 related olfactory dysfunction (OD), having been identified as an early indicator of infection by the World Health Organization (WHO) and Center for Disease Control and Prevention (CDC),<sup>(2,3)</sup> represents a red flag that could help clinicians, public health officials and the general public contain the spread of disease.<sup>(4)</sup>

A recent meta-analysis of nearly 30,000 patients reported a prevalence of COVID-19 related OD of 47.9% (95% confidence interval [CI]: 41.2 – 54.5).<sup>(5)</sup> Notably, further systemic review has revealed a wide range in reported prevalence (19 – 73.6%),<sup>(6)</sup> and furthermore prevalence was higher among studies using objective methods (72.1% vs 44.5%).<sup>(5)</sup> Lima et al and Prajapati et al have independently found that 30–40% of patients with objectively measured OD may not actually perceive OD by self-report.<sup>(7,8)</sup> Furthermore, significant heterogeneity ( $I^2$ : >90%) exists, not only between measurement methods, but also between study populations which has limited precise definition of prevalence.<sup>(5)</sup> However, Moein et al. report near universal prevalence of OD (96%) among hospitalized patients using objective psychophysical testing.<sup>(9)</sup>

While knowledge of OD in hospitalized patients is important, understanding its manifestations in ambulatory patients bears more relevance to the pandemic response. This is especially true as these patients are in the community, have milder symptoms or are otherwise asymptomatic, and thus may not isolate themselves to prevent transmission. The reported prevalence of COVID-19 related OD among ambulatory patients has significant variation, which is in part attributable to differing measurement methods: 41.1%<sup>(10)</sup> (Lee et al. survey), 66.3%<sup>(11)</sup> (Boscolo-Rizzo et al. survey) 68%<sup>(12)</sup> (Yan et al. survey), 70%<sup>(13)</sup> (Niklassen et al. objective threshold testing). Evidence regarding resolution of OD in ambulatory patients is mainly from survey data, though some have used threshold and psychophysical testing.<sup>(13–16)</sup> In a predominately outpatient cohort, Gorzkowski et al. used a survey to find that greater than 95% of COVID-19 patients reported improvement in olfaction by 26 days after onset, and the mean time from onset to start of recovery was 11.6 days.<sup>(17)</sup> Studies using threshold testing identified OD in 27% to 37% of patients 1–5 months after onset.<sup>(13,14)</sup>

This is a prospective longitudinal cohort study using the Brief Smell Identification Test (BSIT) in ambulatory patients with COVID-19 compared to symptomatic controls. Its findings contribute to the growing body of objectively measured olfactory literature regarding prevalence and recovery of COVID-19 related OD among ambulatory patients. Additionally, this study contributes to prognostic clarity for patients suffering from COVID-19 related OD.

## MATERIALS AND METHODS

### Study Design and Patient Population

This study was approved by the Institutional Review Board at UNC (IRB# 20-1992). The schedule of events is depicted in Figure 1. Patients presenting to a respiratory diagnostic center (RDC) affiliated with the University of North Carolina (UNC) Health system were prospectively enrolled in a longitudinal study. Patients were enrolled between August 3, 2020 and November 19, 2020 within 1–5 days of a SARS-CoV-2 polymerase chain reaction (PCR) test. Inclusion criteria included: age  $\geq$  18 years and presentation to a UNC RDC. Exclusion criteria included: hospitalization, presence of OD at baseline, or non-English speaking. Asymptomatic patients were excluded from the COVID-19 negative control group. The control group was age- and sex-matched ( $\pm$  3 years).

Participants were enrolled during a phone encounter 1–5 days after diagnosis at which point, they were specifically asked about smell loss, and were administered a past medical history questionnaire. One week after a COVID-19 test, participants were provided an enrollment packet including a 12-item Brief Smell Identification Test (BSIT), and a symptom questionnaire inquiring about nasal, olfactory and gustatory symptoms (Supplemental File). All COVID-19 positive patients were sent a follow-up BSIT and symptom questionnaire 1 month after their positive test. COVID-19 positive patients who exhibited OD received an additional BSIT and symptom questionnaire 3 months after their positive test. The age and sex matched control group all presented to a testing center with symptoms of COVID-19 but had a negative SARS-CoV-2 PCR test. They completed the BSIT and symptom questionnaire only at 1-week post diagnosis.

### Olfactory Testing and Questionnaire

The BSIT is a 12-item psychophysical olfactory test that is validated with good test-retest reliability (Sensonics International, Haddon Heights, NJ). Each correctly identified odorant from a list of four multiple choice options confers one point. The BSIT has a minimal clinically important difference (MCID) of 1 question.<sup>(18)</sup> A score  $<9$  indicates OD.<sup>(19)</sup> A score  $<4$  fails to surpass guesswork which may suggest complete anosmia. A score  $<2$  is suggestive of malingering. Nasal, olfactory, and gustatory symptoms were assessed using a 13-question survey on a 5-point Likert scale. The olfactory and gustatory questions were derived from a validated chemosensory questionnaire for patients treated for head and neck cancer.<sup>(20)</sup> Three additional questions were included regarding nasal symptoms such as congestion, pain and drainage. The Likert scale assessed frequency of symptoms, ranging from 1=never, 2=rarely, 3=sometimes, 4=often, to 5=always.

Baseline demographics, presenting symptoms and comorbid conditions were obtained by combination of a pre-specified telephone questionnaire and medical record review. The selection of comorbid conditions was taken directly from the CDC list of high-risk conditions for COVID-19.<sup>(21)</sup> The telephone questionnaire also asked about history of conditions that have potential to impair olfaction at baseline, such as head injury, sinus surgery, or allergic rhinitis.

### Statistical Analysis

Statistical analysis was performed by GraphPad Prism version 9 (GraphPad Software, La Jolla, CA) and SAS version 9.4 (Cary, NC). Descriptive statistics were used to report baseline characteristics, clinical features and comorbid conditions. These were reported as means, percentages, standard deviation (SD), ranges and absolute numbers.

The primary outcomes were the percentage of COVID-19 positive patients with OD at 1-week compared to their matched control group as well as to percentage of COVID-19 positive patients exhibiting persistent OD at 1 month follow-up. Statistical significance was set at  $p < 0.05$ .

A linear mixed-effects model was used to compare 1-week BSIT scores as continuous variables between the COVID-19 positive group and controls. Fixed effects included time and group, and time by group interaction. A random subject effect was included. The same model was also used to compare the 1-week BSIT in the COVID-19 group to BSIT at 1-month post diagnosis. A mixed effects logistic regression was used to make the same comparisons with OD as a categorical variable (BSIT  $< 9$  represents measurable OD).

Pearson correlation and simple linear regression was performed to assess the relationship between nasal congestion and BSIT scores in the COVID-19 positive group at 1-week. Simple linear regression was used to validate a subjective olfactory composite score derived from the symptoms questionnaire in predicting OD as measured by BSIT.

## RESULTS

81 ambulatory patients with SARS-CoV-2 positive PCR tests and 38 symptomatic but SARS-CoV-2 PCR negative controls were enrolled. Of the enrolled patients, 45 COVID-19 positive patients completed the 1-week BSIT and questionnaire and 36 participants completed a 1-month BSIT. 5 participants who had persistent smell loss at 1 month were sent a 3 month follow up BSIT, and 3 of these 5 participants completed the test. 26 symptomatic controls who presented to a RDC but were SARS-CoV-2 PCR test negative, completed a 1-week BSIT and symptom questionnaire. These results as well as baseline demographics, comorbidities and clinical characteristics are shown in Table 1. Figure 1 depicts the schedule of events. Despite significant attrition, patients completing a BSIT reported very similar rates of smell loss at the time of phone encounter compared to the total enrollment (57.4 vs 57.1%;  $p > 0.999$ , figure 1).

## Comparison of 1-Week BSIT Scores in COVID-19 Positive Patients vs Symptomatic Controls

In the COVID-19 positive cohort, the mean time between COVID-19 test and 1 week time point for BSIT completion was 8.9 days (95% CI 7.4–10.4) compared to 8.2 days (95% CI 7.1–9.2) in the control cohort. At 1 week, 46.7% (21 of 45) of COVID-19 participants had measurable OD (BSIT<9) compared to 3.8% (1 of 26) of controls ( $p<0.001$ ). The mean BSIT score at 1-week in the COVID-19 group was 7.9 out of a total of 12 (95% CI 7.1 – 8.6) compared to 10.7 (95% CI 9.7 – 11.7) in the control group, resulting in a difference of  $-2.9$  (95% CI  $-4.1$  to  $-1.6$ ,  $p<0.001$ ; Figure 2, panel A). As above, previous studies have validated a minimal clinically important difference of 1.0.<sup>(18)</sup> There were no significant differences in sinonasal symptom burden, including frequency of nasal pain, drainage, or congestion, between COVID-19 patients and symptomatic controls (Figure S1).

Stratified BSIT scores among COVID-19 patients and symptomatic controls are shown in figure 2, panel B. Among COVID-19 patients who did exhibit OD ( $n=21$ ), 28.6% ( $n=6$ ) demonstrated scores in the lowest quartile, (0–3). An additional 38.0% ( $n=8$ ) had slightly better scores (4–6), and 33.3% ( $n=7$ ) of patients demonstrated mild OD (7–8). The only patient in the control cohort who exhibited OD had a BSIT score of 8.

## Longitudinal Olfactory Outcome

In the COVID-19 positive cohort, the mean time between the COVID-19 test date and follow-up BSIT completion was 38.4 days (95% CI 35.6–41.1; Figure 3, Panel B). At follow-up, 16.7% (6 of 36) in the COVID-19 cohort had persistent OD. The follow-up BSIT in COVID-19 patients improved by a clinically significant 2.0 (95% CI 1.0 – 3.0,  $p<0.001$ ; Figure 3, Panel A), from 7.9 (95% CI 7.1 – 8.6) to 9.9 (95% CI 9.0 –10.7).

## Questionnaire and Self-reported Nasal Congestion

Results of the questionnaire, which can be found in the supplementary file, demonstrated significant differences in smell and taste related symptoms, and notably there were no significant differences in nasal symptoms between COVID-19 group and symptomatic controls (Figures S1–S6). COVID-19 positive patients exhibited no correlation between the 1-week BSIT and the frequency of patient reported nasal congestion ( $r=-0.233$ ,  $p=0.13$ ; slope =  $-0.638$ , 95% CI  $-1.48$  to  $0.203$ ; Figure 4, Panel A). Furthermore, there was no significant difference between the frequency of self-reported congestion in COVID-19 patients compared to controls, while there was a significant difference in self-reported difficulty with smell (1.65,  $p<0.0001$ ; Figure 4, Panel B).

## DISCUSSION

This study prospectively compared olfactory function between ambulatory patients with COVID-19 and symptomatic controls who tested negative. Additionally, we longitudinally followed the COVID-19 positive cohort for 3 months to assess recovery of olfaction.

This study used objective psychophysical testing to investigate the incidence of COVID-19 related OD in ambulatory patients compared to symptomatic patients who test negative

(46.7% vs. 3.8%,  $p < 0.001$ ). Stratified BSIT scores revealed that about one-third of patients with olfactory dysfunction had complete anosmia (score 0–3), and about two-thirds were confined to the lower 2 quartiles of olfactory scores (scores 0–6; Figure 2, Panel B).

Our longitudinal findings indicate that a great majority of COVID-19 ambulatory patients will recover normal olfaction after 1 month (83.3%), and this may be underestimated due to attrition. Recovery of olfaction may represent the clinical consequence of the basic pathophysiologic mechanism of COVID-19-related OD, which is thought to be secondary to SARS-CoV-2 infection of the supporting sustentacular cells, which express ACE2 and TMPRSS2, and not the olfactory neurons directly.<sup>(22)</sup> This mechanism may also explain why we did not find any correlation between BSIT scores and the frequency of nasal congestion; whereas many other pathogens cause transient OD by mechanical obstruction of the olfactory cleft through nasal congestion. Our results clinically support the basic hypothesis that SARS-CoV-2 causes OD independent of nasal congestion (Figure 4).

This study has several limitations. Firstly, it would be ideal to obtain olfactory testing earlier and more frequently following COVID-19 diagnosis. This potentially could have identified patients who had OD but recovered prior to their first BSIT; this also would have more precisely delineated the natural history of OD.

Additionally, there is risk for selection bias for study entry and selection bias by attrition, as patients with smell loss may be more interested in participating than patients without chemosensory complaints. However, this appears to be minimal given similar baseline characteristics between patients who enrolled, and those who were lost to follow-up; most importantly, the rates of self-reported OD at the time of phone encounter in COVID-19 positive patients who completed a BSIT compared to the entire enrollment were very similar, (57.4% vs 57.1%;  $p > 0.999$ , Figure 1).

## CONCLUSIONS

The precise rate of OD among ambulatory patients with COVID-19 is unknown. Incidence of OD is significantly higher than in patients with similar symptoms who test negative for COVID-19. Although our study was not designed to correlate temporality between the onset of OD and infectivity, it is reasonable from these findings to advise ambulatory patients with new onset OD to quarantine and be tested for COVID-19. Additionally, this study provides further prognostic clarity for clinicians to be used in counseling patients that the great majority of ambulatory patients who experience COVID-19 related OD recover during the first month after diagnosis.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Availability of Data and Materials:

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

## Abbreviations

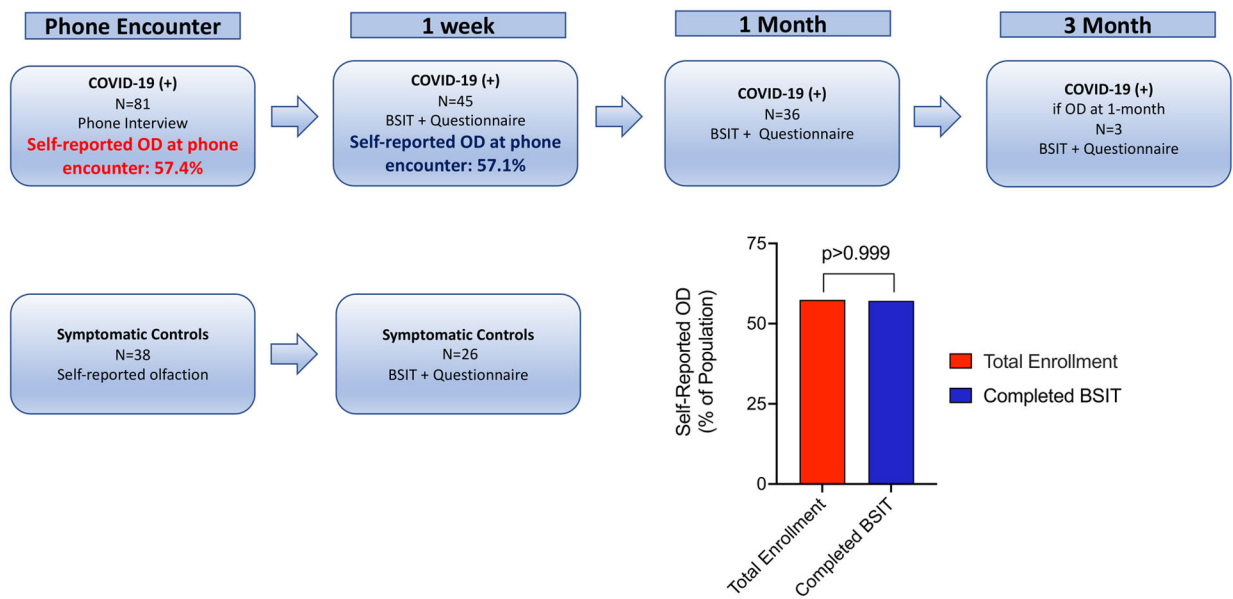
<b>BSIT</b>	Brief Smell Identification Test
<b>CDC</b>	Center for Disease Control and Prevention
<b>CI</b>	Confidence interval
<b>COVID-19</b>	Coronavirus Disease 2019
<b>IRB</b>	Institutional Review Board
<b>MCID</b>	Minimal Clinically Important Difference
<b>OD</b>	Olfactory dysfunction
<b>PCR</b>	Polymerase chain reaction
<b>RDC</b>	Respiratory Diagnostic Center
<b>SARS-CoV-2</b>	Severe Acute Respiratory Syndrome Coronavirus 2
<b>SD</b>	Standard deviation
<b>UNC</b>	University of North Carolina
<b>WHO</b>	World Health Organization

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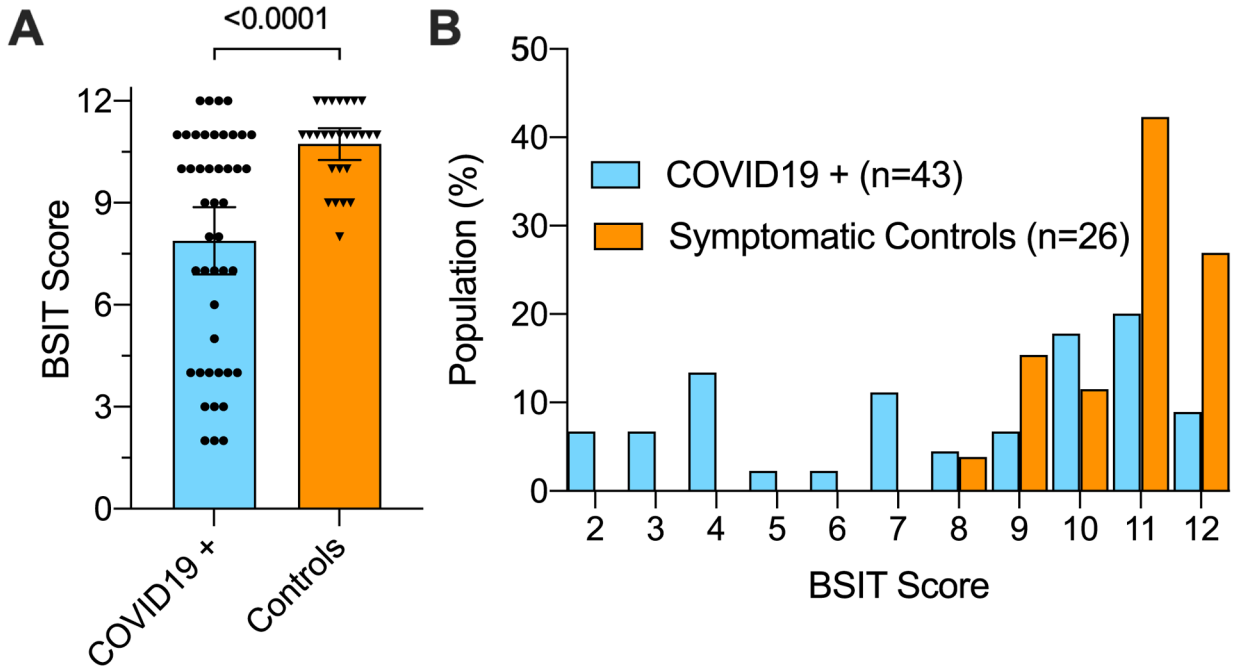
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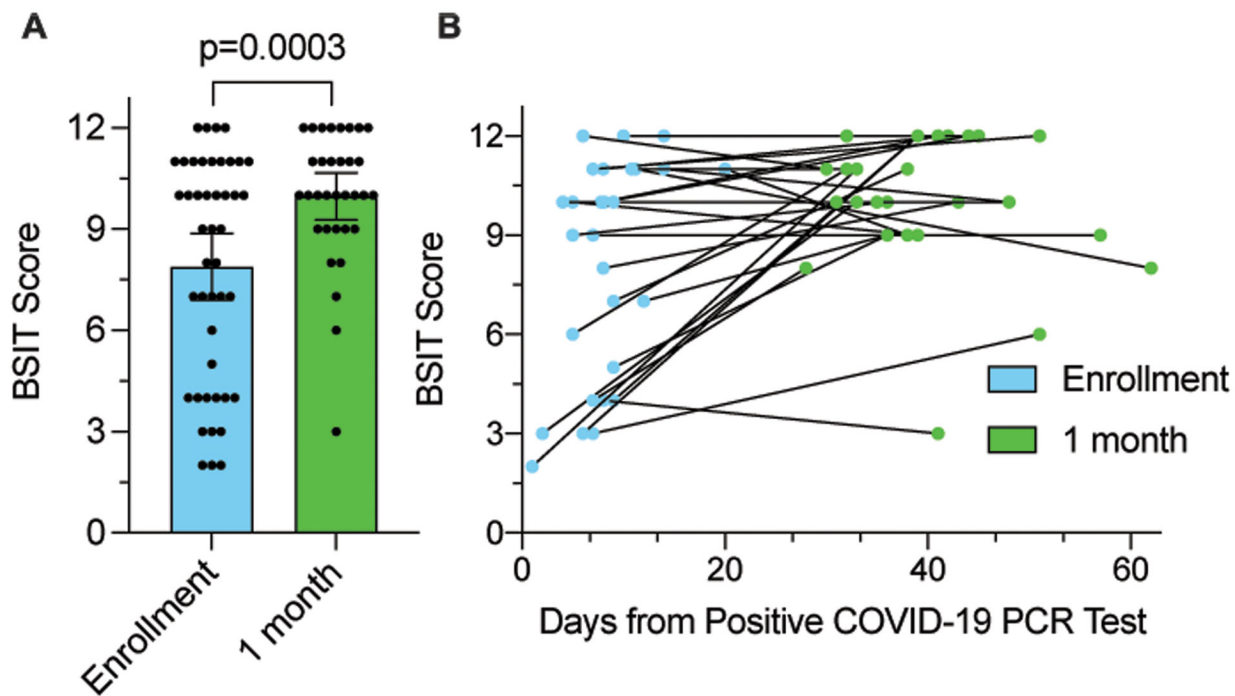


**Figure 1.**

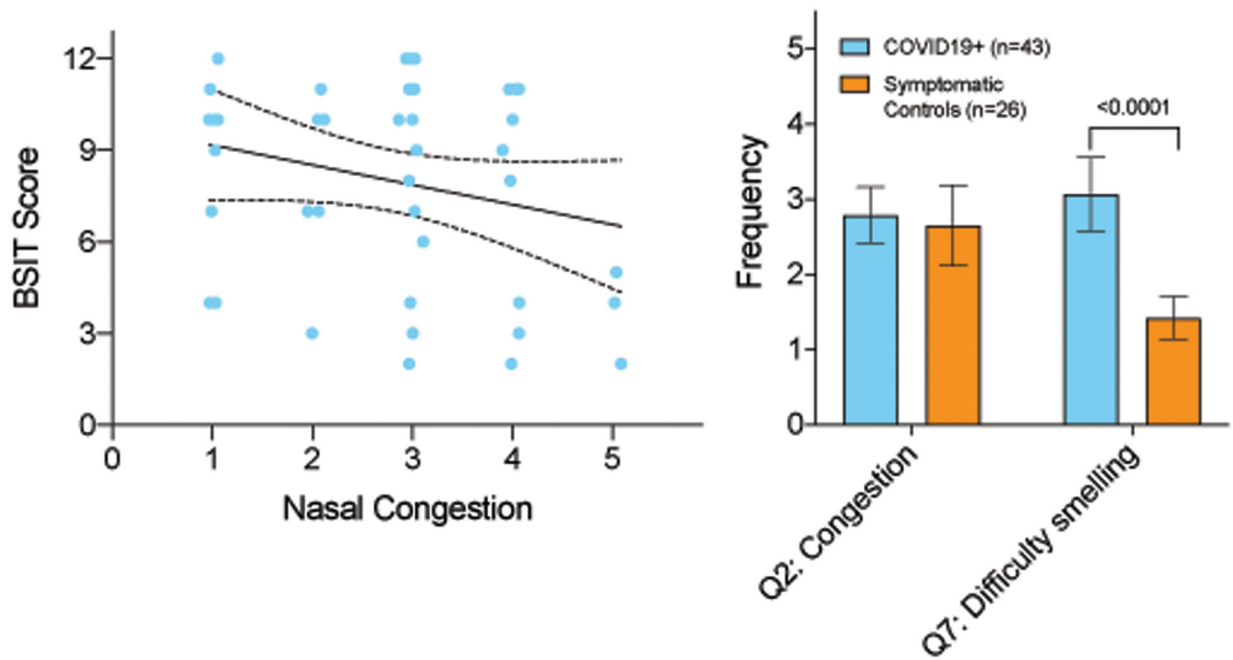
Schedule of Events for COVID-19 Positive and Symptomatic Control Group. Patients were enrolled by phone encounter and were asked about smell loss 1–5 days after a SARS-CoV-2 test. A cohort of COVID-19 patients and age- and sex-matched symptomatic controls were sent a BSIT and questionnaire 1-week post-diagnosis. All COVID-19 positive patients were sent a BSIT and questionnaire at 1 month, and those with persistent olfactory dysfunction (OD) at 1 month (n=5), received a third BSIT and questionnaire at 3 months. The bar graph shows self-reported OD at the time of phone encounter for the total enrollment (57.4%) in red compared to those who ultimately completed a BSIT (57.1%) in blue suggesting patients who completed a BSIT were similar to those who did not at the time of phone encounter.



**Figure 2.** COVID-19 Positive Patients Have Significantly Lower BSIT Scores than Symptomatic Controls. A) The mean BSIT score at 1-week in the COVID- 19 group (blue) was 7.9 (95% CI 7.1 – 8.6) compared to 10.7 (95% CI 9.7 – 11.7) in the control group (orange), resulting in a difference of -2.9 (95% CI -4.1 to -1.6, p<0.001). Each participant score is represented by a dot. Error bars represent 95% confidence intervals. B) The same BSIT scores are plotted as a percentage of the population. Among abnormal BSIT scores in the COVID-19 group (n=21), 28.6% (n=6) were in the lowest quartile (score of 0–3), with an additional 38.0% (n=8) in the second to lowest quartile (score of 4–6). An additional 33.3% (n=7) exhibited mild OD (score of 7–8).



**Figure 3.** BSIT Score improved significantly in COVID-19 patients between 1 week and 1 month. A) BSIT Score improved by 2.0 (95% CI 1.0 – 3.0) from 7.9 (95% CI 7.1 – 8.6) to 9.9 (95% CI 9.0 – 10.7) in COVID-19 patients at baseline (blue) compared to 1 month later (green). B) Shows improvement in BSIT score (y-axis) from baseline (blue) to one month (green) with days from COVID-19 test on the x-axis. A score <9 indicates OD. The average time between COVID-19 test and 1-week BSIT was 8.9 days (95% CI 7.4 – 10.4). The average time from COVID-19 test to follow-up BSIT was 38.4 days (95% CI 35.6 – 41.1).



**Figure 4.**

BSIT Scores do not correlate with congestion COVID-19 patients suggesting a congestion independent mechanism of OD. A) There was no significant correlation between BSIT scores in COVID-19 patients and self-reported nasal congestion ( $r=-0.233$ ,  $p=0.13$ ). The simple linear regression (solid line) is plotted with 95% confidence interval bands (dotted lines), (slope =  $-0.638$ , 95% CI  $-1.48$  to  $0.203$ ). Simulated noise was performed to display overlapping points. B) There was no significant difference between self-reported congestion in COVID-19 patients vs symptomatic controls ( $0.137$ ,  $p=0.66$ ). COVID-19 patients had self-reported increased difficulty smelling ( $-1.65$ ,  $p<0.001$ ). Error bars represent 95% confidence intervals. The questionnaire used a 5-point Likert scale (1=never, 2=rarely, 3=sometimes, 4=often, 5=always). Q2: I have had nasal congestion. Q7: It has been hard for me to smell.

**Table 1.**

## Baseline Demographics, Clinical Characteristics and Comorbidities

	COVID-19 (+) Phone Encounter	COVID-19 (+) 1 week <sup>a</sup>	COVID-19 (+) 1 Month	Symptomatic Controls Phone encounter	Symptomatic Control 1 week
Sample size	81	45	36	38	26
Mean age, years (SD; range)	38.21 (19;18–81)	39.87 (18; 18–81)	39.68 (18; 18–70)	38.45 (15;18–71)	39.38 (14;19–71)
Sex	52F/29M	32F/13M	25F/11M	26F/12M	20F/6M
Race/Ethnicity, n (%)					
Black	7 (8.6)	2 (4.4)	2 (6.1)	1 (2.6)	0
Caucasian	43 (53.1)	31 (68.9)	25 (69.4)	30 (78.9)	23 (88.5)
Hispanic	8 (9.9)	3 (6.7)	2 (5.6)	1 (2.6)	1 (3.8)
Unknown	23 (28.4)	9 (20.0)	7 (19.4)	6 (15.7)	2 (7.7)
Self-reported olfactory dysfunction during phone encounter <sup>b</sup>	39 (57.4)	24 (57.1)	15 (50)	1 (2.6)	1 (4)
Smoking history	10 (12.7)	4 (8.9)	5 (13.9)	2 (4.8)	0
Prior history of smell loss <sup>c</sup>	7 (9.5)	5 (11)	3 (8.3)	5 (13.5)	5 (20)
Prior history of taste loss <sup>c</sup>	6 (8.0)	4 (8.9)	3 (8.3)	4 (10.5)	4 (15.3)
Medical/Surgical History					
Sinusitis	24 (29.6)	14 (31.8)	14 (38.9)	17 (44.7)	14 (53.8)
Allergic rhinitis	34 (42.0)	20 (44.4)	18 (50)	23 (60.5)	19 (73.1)
Head trauma	10 (12.3)	7 (15.5)	6 (16.7)	9 (23.6)	9 (34.6)
Nose trauma	3 (3.7)	1 (2.2)	1 (2.8)	3 (7.9)	2 (7.7)
Sinus Surgery	3 (3.7)	2 (4.4)	1 (2.8)	2 (5.3)	2 (7.7)
Hypertension	12 (14.8)	7 (15.5)	7 (19.4)	2 (5.3)	1 (3.8)
Diabetes	4 (4.9)	2 (4.4)	0	0	0
Cardiovascular disease	4 (4.9)	2 (4.4)	3 (8.3)	0	0
Asthma	8 (9.9)	4 (8.9)	4 (11.1)	2 (5.3)	2 (7.7)
COPD	2 (2.5)	2 (4.4)	0	0	0
Pulmonary fibrosis	0	0	0	1 (2.6)	0
Cystic fibrosis	0	0	0	0	0
Pregnancy	1 (1.2)	0	0	0	0

<sup>a</sup>1-week sample size refers to the number of patients who completed a BSIT at 1-week.

<sup>b</sup>Participants were asked at enrollment during phone encounter if they experienced smell loss at any point since the onset of symptoms.

<sup>c</sup>Prior history of smell or taste loss was determined by telephone prior to enrollment. Smell loss had to be resolved prior to onset of acute symptoms, and any patient with baseline smell loss was excluded.

Values may not add to 100% due to sporadic missingness.

COVID-19 = Coronavirus Disease 2019.

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