The COVANOS trial – insight into post-COVID olfactory dysfunction and the role of smell training*

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Abstract

Background: Olfactory dysfunction is a cardinal symptom of COVID-19 infection, however, studies assessing long-term olfactory dysfunction are limited and no randomised-controlled trials (RCTs) of early olfactory training have been conducted.

Methodology: We conducted a prospective, multi-centre study consisting of baseline psychophysical measurements of smell and taste function. Eligible participants were further recruited into a 12-week RCT of olfactory training versus control (safety information). Patient-reported outcomes were measured using an electronic survey and BSIT at baseline and 12 weeks. An additional 1-year follow-up was open to all participants.

Results: 218 individuals with a sudden loss of sense of smell of at least 4-weeks were recruited. Psychophysical smell loss was observed in only 32.1%; 63 participants were recruited into the RCT. The absolute difference in BSIT improvement after 12 weeks was 0.45 higher in the intervention arm. 76 participants completed 1-year follow-up; 10/19 (52.6%) of participants with an abnormal baseline BSIT test scored below the normal threshold at 1-year, and 24/29 (82.8%) had persistent parosmia.

Conclusions: Early olfactory training may be helpful, although our findings are inconclusive. Notably, a number of individuals who completed the 1-year assessment had persistent smell loss and parosmia at 1-year. As such, both should be considered important entities of long-Covid and further studies to improve management are highly warranted.

Key words: COVID-19, anosmia, parosmia, quality of life, olfactory training

Introduction

Shortly after the emergence of SARS-CoV-2, it became evident that sudden loss of sense of smell is a cardinal symptom of COVID-19 and early recognition is key in affected patients and healthcare workers in particular[1-4]. It is typically more common in those with mild disease or who are otherwise asymptomatic[5]. To date, nearly 277 million cases of COVID-19 have been reported (22 December 2021), with 11.7 million in the UK and 51.4 million in the USA[6]. With an incidence of roughly two-thirds, over 150 million individuals, globally, will have lost their sense of smell during this pandemic, including roughly 5 and 29 million in the UK and the USA, respectively[7].

Encouragingly, the vast majority of patients will recover their sense of smell within the first two months, on average; however, olfactory dysfunction has been reported in patients even six-months after initial infection[8-10]. In their assessment of 51 patients with acute smell loss beyond 7 days at 8 months, Renaud et al. demonstrated persistent hyposmia in 2 patients (3.9%) [11]. Comparatively, another study has demonstrated olfactory dysfunction in 46% of patients followed up beyond 1-year, with functional anosmia in 7%[12]. Altogether, the precise burden of long-term olfactory dysfunction remains unknown but is likely substantial.

In the COVID-19 context, both the British Rhinological Society (BRS) and Clinical Olfactory Working Group (COWoG) recommend olfactory training based on existing evidence of its efficacy, particularly for post-viral olfactory dysfunction[13-17]. While the use of oral and topical steroids was very controversial at the beginning of the pandemic, and at the time of the planning of the trial, recent evidence indicates a potential benefit. However, the evidence is not robust[18,19]. In line with this, the BRS further recommend oral steroids, steroid rinses, and omega-3 supplements whilst the COWG acknowledge a potential role for oral and topical steroids and vitamin A drops[16,17]. Both emphasize the need to examine the use of further medical treatment on a case-by-case basis with careful risk assessments undertaken. Here, we aim to obtain long-term follow-up data of individuals with olfactory dysfunction for at least four weeks prior to enrollment during the COVID-19 pandemic and evaluate the efficacy of early olfactory training in a parallel, 2-arm, randomised controlled trial.

Material and Methods

Trial design and recruitment

This study, entitled 'COVID-19 and Anosmia' (acronym: 'COVANOS') was sponsored by University College London and conducted across four NHS trusts: Barts Health NHS Trust, Guy's and St. Thomas', James Paget University Hospitals/Norfolk and Norwich University Hospitals, and Wrightington, Wigan and Leigh NHS Foundation Trusts. Ethical approval was obtained through the UK Health Research Authority Research Ethics Committee (ref. 20/WM/0147). Participants were recruited through trust-wide email and poster advertisements directed primarily toward healthcare workers (HCWs), who were identified via surveys which were conducted across all these NHS Trusts and results published separately[20,21].

Individuals with persistent and sudden loss of sense of smell (at least 4 weeks) were invited to participate in the study. A positive COVID-19 test was not a requirement for participation, as availability of testing was extremely limited at the beginning of the pandemic when the trial was launched. However, information regarding COVID-19 antigen and antibody testing were collected post-hoc from those for who data were readily available. All participants underwent psychophysical smell testing using the Brief Smell Identification Test (Brief Smell Identification Tests™ - Cross-Cultural Smell ID Test, Sensonics Inc., USA) A subgroup of participants also underwent gustatory testing using Taste Strips (Burghart Messtechnik GmbH, Germany). Participants also completed a validated electronic survey [*submitted for publication*], which collected relevant demographic data, details of symptoms experienced, co-morbidities and other COVID-19 related symptoms including olfactory function assessment. This included self-rating of smell and taste function with the corresponding prompts: 'How would you rate your sense of smell today (0 being really bad, 10 being completely normal)?' and 'How would you rate your sense of taste (salt/sweet/sour/bitter/savoury) today (0 being really bad, 10 being completely normal?' As well, participants were asked a series of quality of life (QoL)-related items, which were scored on a 7-point Likert scale. These items were separated into 4 categories: the impact of their smell dysfunction 1) on their social and professional life, 2) with regards to eating habits, 3) on their sense of anxiety and 4) the extent to which it was annoying.

Recruitment took place either in-person at designated clinics across the NHS trusts or remotely through email and post, the latter due to lockdown measures. Where relevant, all study materials were posted to the participants with additional correspondence by email. Informed consent was obtained for all participants.

Those with a BSIT score of 8 or less (considered abnormal smell, as published previously)[22] were further invited to participate in the smell training trial (RCT), which consisted of randomisation to either undergo 12 weeks of olfactory training using Sniffin' Sticks (Duft-Quartett, Burghart Messtechnik GmbH, Germany; treatment group) or receive safety information only (control group). Eligible participants were randomised 1:1. Both arms were followed up at 12 weeks with regular correspondence by email throughout the duration of the trial to ensure compliance and safety. At the end of the 12-week periods, participants completed a follow-up BSIT and electronic 'End of Study' survey.

All participants enrolled at baseline within the eligible timeframe, for whom a valid email address was available, were

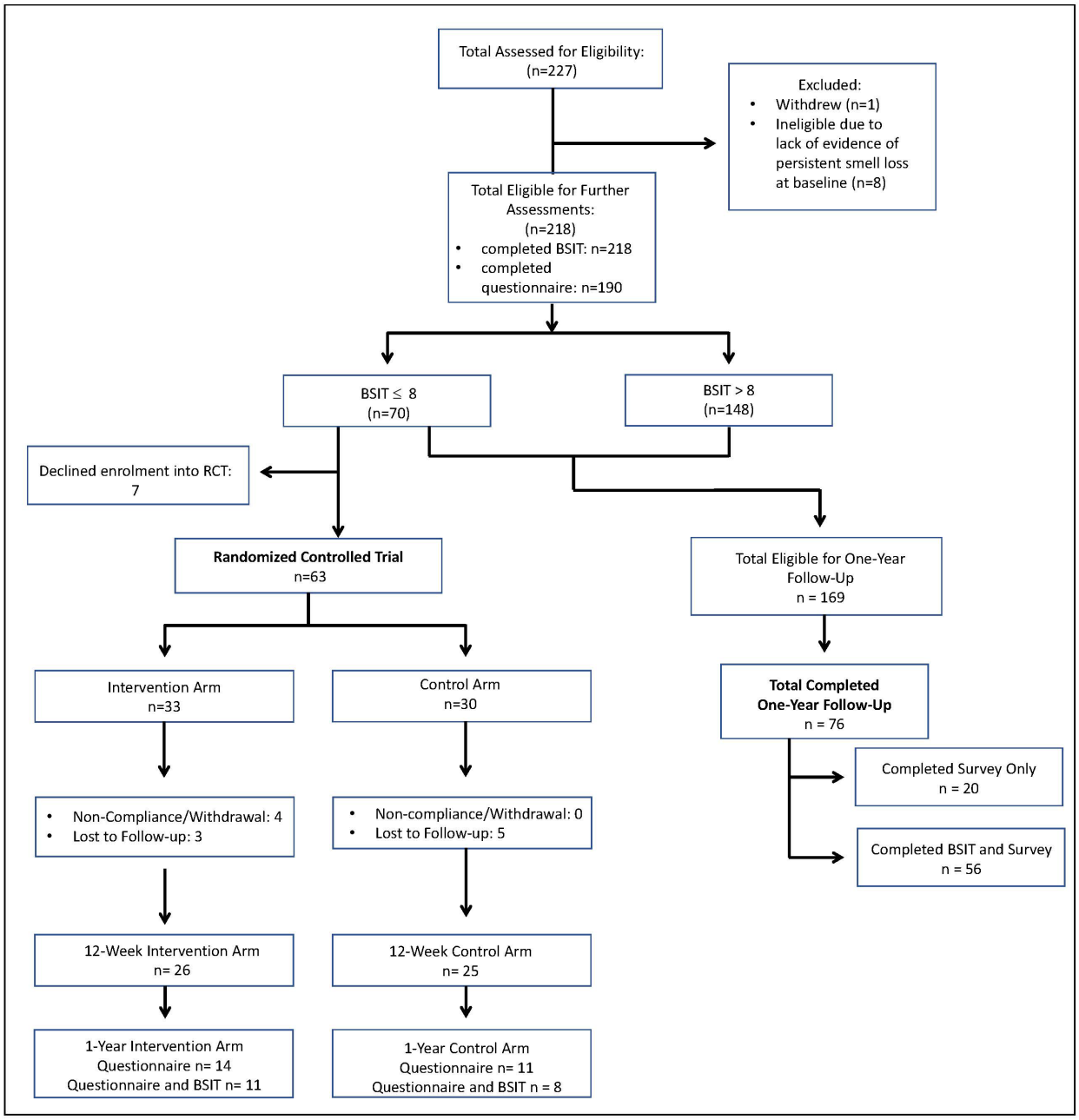

Figure 1. Flow-chart.

invited to participate in 1-year follow-up assessments. This included all participants irrespective of baseline BSIT result and RCT participation. The follow-up included a final electronic survey and BSIT. In addition to questions related to their sense of smell, which were identical to those in the baseline and 12-week follow-up surveys, participants were also asked about any symptoms of long-COVID, including fatigue, brain fog, chest pain, joint pain, amongst others.

Statistical methods

The primary outcome was the absolute difference between the intervention and control arms in BSIT score smell improvement, measured as a change from baseline at 12-weeks. Secondary outcome measures were quality of life in relation to anosmia and COVID-19 infection, compliance, and safety of olfactory training in the intervention arm and the identification of predictive biomarkers for clinical outcome. A total sample size of 200 patients, 100 per arm, was calculated to detect the target standardised effect size of 0.5 at the two-sided 5% significance level with 90% power, after allowing for up to 15% dropout. Descriptive statistical analysis was conducted on participant characteristics and associations were evaluated using Chi-Square and Fisher's Exact tests, where appropriate. Trial arms were compared using linear and logistic regression adjusted for base-

Table 1. Demographic characteristics of overall cohort by baseline BSIT result.

		Normal smell (BSIT > 8) n=148		Abnormal smell (BSIT 8 or less) n=70		Total n=218		p-value
		n	%	n	%	n	%	
Age (median, range)		44.0 (22 – 68) N=128		42.0 (23 – 78) N=61		44.0 (22 – 78) N=190		
Gender	Female	108	85.0	55	88.7	163	86.2	0.654
	Male	19	15.0	7	11.3	26	13.8	
	Missing*	21	NA	8	NA	29	NA	
Education	GSCEs or eq.	15	11.7	3	4.8	18	9.5	0.391
	A-Levels or eq.	6	4.7	4	6.5	10	5.3	
	Degree	36	28.1	25	40.3	61	32.1	
	Higher Ed.	12	9.4	6	9.7	18	9.5	
	Post-Grad	51	39.8	22	35.5	73	38.4	
	Vocational	8	6.3	2	3.2	10	5.3	
	Missing*	20	NA	8	NA	28	NA	
Ethnicity	White	111	86.7	54	87.1	165	86.8	0.193
	Mixed	3	2.3	2	3.2	5	2.6	
	Indian	9	7.0	1	1.6	10	5.3	
	Pakistani	0	0.0	0	0.0	0	0.0	
	Bangladeshi	0	0.0	1	1.6	1	0.5	
	Chinese	0	0.0	0	0.0	0	0.0	
	Black	3	2.3	4	6.5	7	3.7	
	Other	2	1.6	0	0.0	2	1.1	
	Missing*	20	NA	8	NA	28	NA	
Smoking history	Never	93	72.7	44	71.0	137	72.1	0.843
	Former	27	21.1	15	24.2	42	22.1	
	Current	8	6.3	3	4.8	11	5.8	
	Missing*	20	NA	8	NA	28	NA	
Alcohol history	Never	24	18.8	11	17.7	35	18.4	0.986
	1-14 units/week	93	72.7	46	74.2	139	73.2	
	15-21 units/week	8	6.3	4	6.5	12	6.3	
	Over 21 units/week	3	2.3	1	1.6	4	2.1	
	Missing*	20	NA	8	NA	28	NA	

*baseline questionnaires were not available from 28 participants (either incomplete or not returned); as such, only information regarding objective smell testing were available for these.

line score where absolute as well as standardised effect sizes and odds ratios (with 95% confidence intervals and P-values) are presented, respectively. Smell and quality of life scores were compared at different time-points using the paired samples t-test and differences between groups were assessed using the Mann-Whitney U test. All statistical tests were performed on SPSS version 27.

Results

Recruitment and enrolment

A total of 227 participants were recruited into the study and completed the baseline BSIT between 4th May 2020 and 4th January 2021. One participant withdrew at this time. Eight participants were further excluded due to a lack of evidence of persistent smell loss ascertained through the baseline questionnaire. A final cohort of 218 participants was included in subsequent analyses.

Seventy participants scored 8 or below at 4 weeks following onset of the loss of sense of smell and were subsequently invited to participate in the smell training trial. At this point, most participants (67.9%, 148/218) scored within the normal range of the BSIT test at the required 4 weeks and were thus ineligible for

Table 2. Participant medical history and COVID-19 symptomology and associations with baseline BSIT result for overall cohort.

	Normal smell (BSIT > 8) n=148		Abnormal smell (BSIT 8 or less) n=70		Total n=218		p-value
	n	%	n	%	n	%	
Medicial history							
Sinonasal disease	29	22.7	18	29.0	47	24.7	0.372
Diabetes	1	0.8	1	1.6	2	1.1	0.547
COPD	0	0.0	0	0.0	0	0.0	NA
Asthma	16	12.5	8	12.9	24	12.6	1.000
Bronchitis	1	0.8	1	1.6	2	1.1	0.547
Other chronic lung disease	0	0.0	0	0.0	0	0.0	NA
Cancer	2	1.6	2	3.2	4	2.1	0.598
Stroke	0	0.0	0	0.0	0	0.0	NA
Heart Disease	0	0.0	0	0.0	0	0.0	NA
Arthritis	6	4.7	3	4.9	9	3.8	1.000
SLE	1	0.8	0	0.0	1	0.5	1.000
Other autoimmune disease	4	3.1	2	3.2	6	3.2	1.000
High blood pressure	12	9.4	5	8.1	17	8.9	1.000
If high BP, treatment with ACEi/ARBs (n=17)	6	50.0	4	80.0	10	58.8	0.338
Any	53	41.4	25	40.3	78	41.1	1.000
Missing*	20	NA	8	NA	28	NA	
COVID-19 symptoms							
Persistent cough	38	29.7	24	38.7	62	32.6	0.249
Shortness of breath	39	30.5	31	50.0	70	36.8	0.011
Sore throat	33	25.8	24	38.7	57	30.0	0.091
Loss of smell	128	100.0	62	100.0	190	100.0	NA
Loss of taste	93	72.7	51	82.3	144	75.8	0.206
Hoarse voice	7	5.5	9	14.5	16	8.4	0.050
Fever	4	35.2	29	46.8	74	38.9	0.153
Fatigue	86	67.2	48	77.4	134	70.5	0.176
Difficulty breathing	16	12.5	16	25.8	32	16.8	0.037
Nasal congestion	32	25.0	19	30.6	51	26.8	0.485
Burning in nose/mouth	17	13.3	9	14.5	26	13.7	0.824
Aches/pains	60	46.9	41	66.1	101	53.2	0.015
Diarrhoea	29	22.7	10	16.1	39	20.5	0.342
Delirium	2	1.6	2	3.2	4	2.1	0.598
Chest pain	13	10.2	16	25.8	29	15.3	0.009
Abdominal pain	12	9.4	8	12.9	20	10.5	0.459
Metallic taste	16	12.5	11	17.7	27	14.2	0.377
Skipped meals	34	26.8	15	24.2	49	25.9	0.860
Missing	20	NA	8	NA	28	NA	

*baseline questionnaires were not available from 28 participants (either incomplete or not returned); as such, only information regarding objective smell testing were available for these.

the RCT. Of the 70 participants who were eligible, 63 were enrolled into the smell training trial with 7 declining participation. 12-week follow-up data was available from 51 participants: 26 intervention and 25 controls, respectively. Four participants in the treatment arm had withdrawn their participation or were removed from the study due to non-compliance with the olfactory

Table 3a. Summary of BSIT scores at baseline, 12-weeks and 1-year.

		All	RCT	
			Treatment	Control
Baseline score		**N=218**	**N=33**	**N=30**
	Normal, n(%)	148 (67.9)	0 (0.0)	0 (0.0)
	Mild, n(%)	53 (24.4)	25 (75.8)	22 (73.3)
	Moderate, n(%)	17 (7.8)	8 (24.2)	8 (26.7)
	Severe, n(%)	0 (0.0)	0 (0.0)	0 (0.0)
	mean (std. dev.)	9.1 (2.12)	6.5 (1.70)	6.7 (1.51)
12-week score		**N=51**	**N=26**	**N=25**
	Normal, n(%)	21 (41.2)	13 (50.0)	8 (32.0)
	Mild, n(%)	25 (49.0)	11 (42.3)	14 (56.0)
	Moderate, n(%)	4 (7.8)	1 (3.8)	3 (12.0)
	Severe, n(%)	1 (2.0)	1 (3.8)	0 (0.0)
	mean (std. dev.)	7.9 (2.23)	8.0 (2.52)	7.8 (1.92)
Change from baseline	mean (std. dev.)	1.3 (2.07)	1.5 (2.49)	1.0 (1.53)
1-year score		**N=56**	**N=11**	**N=8**
	Normal, n(%)	42 (75.0)	6 (54.5)	3 (37.5)
	Mild, n(%)	13 (23.2)	5 (45.5)	4 (50.0)
	Moderate, n(%)	1 (1.8)	0 (0.0)	1 (12.5)
	Severe, n(%)	0 (0.0)	0 (0.0)	0 (0.0)
	mean (std. dev.)	9.5 (1.71)	8.6 (1.29)	8.0 (2.33)
Change from baseline	mean (std. dev.)	0.2 (1.77)	1.6 (1.97)	0.9 (1.81)

Table 3b. Primary and secondary outcomes for early olfactory training at 12-weeks and at 1-year.

		Treatment vs. Control
12-weeks (n=51)	Difference in BSIT change between arms	0.45 (95% CI: -0.69 to1.59); p = 0.43
	Standardized effect size	0.22 (95% CI: -0.34 to 0.77)
	Odds of having normal smell	OR=2.38 (95% CI: 0.73 to 7.76); p = 0.15
1-Year	Difference in BSIT change between arms	0.65 (95% CI: -1.01 to 2.31); p=0.42
	Standardized effect size	0.31 (95% CI: -0.38 to 1.01); p = 0.36
	Odds of having normal smell	OR=2.33 (95% CI: 0.37 to 14.61); p=0.37

training regimen; a further 3 participants were lost to follow-up. In the control arm, there were no withdrawals nor removals whilst 5 participants were lost to follow-up.

In addition, 169 of the 218 participants in the overall cohort were re-contacted for further assessments after approximately 1-year (8-13 months depending on the time of recruitment). Of these, 76 participants completed the electronic survey and 56 completed an additional BSIT. Figure 1 presents the flow of participants through the study.

Baseline characteristics and potential predictors of baseline BSIT score

Of the 218 participants recruited with a persistent loss of sense of smell and eligible for analysis (self-reported, at least 4 weeks), 190 completed the baseline questionnaire. The median age was 44.0 years (range 22–78), and 85.0% (163/189) were female (see Table 1). 72.1% (137/190) were never-smokers with 22.1% (42/190) having smoked previously and 5.8% (11/190) being current smokers. 73.2% (139/190) of participants consume 1–14 units of alcohol per week, 6.3% (12/190) consuming 15–21 units per week and 2.1% (4/190) consuming over 21 units per week and 18.4% (35/190) having never consumed alcohol.

24.7% (47/190), 12.6% (24/190) and 8.9% (17/190) had a history of sinonasal disease, asthma, and high blood pressure, respectively (Table 2). Of those with a history of high blood pressure, 58.8% (10/17) had been treated with either angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs). There was no evidence of an association between

Table 4. Prevalence of parosmia and phantosmia at baseline and at 1-year.

	Normal	Abnormal	Total
Parosmia at baseline	*(n=117)*	*(n=61)*	*(n=178)*
Present	43 (36.8%)	30 (49.2%)	73 (41.0%)
Absent	74 (63.2%)	31 (50.8%)	105 (59.0%)
Parosmia at 1-year	*(n=51)*	*(n=25)*	*(n=76)*
Present	17 (33.3%)	16 (64.0%)	33 (43.4%)
Absent	34 (66.7%)	9 (36.0%)	43 (56.6%)
Parosmia for paired samples (1-year/Baseline)	*(n=48)*	*(n=25)*	*(n=73)*
Present / Present	13 (27.1%)	11 (44.0%)	24 (32.9%)
Present / Absent	4 (8.3%)	5 (20.0%)	9 (12.3%)
Absent / Present	4 (8.3%)	1 (4.0%)	5 (6.8%)
Absent / Absent	27 (56.3%)	8 (32.0%)	35 (47.9%)
	Normal	**Abnormal**	**Total**
Phantosmia at baseline	*(n=117)*	*(n=61)*	*(n=178)*
Present	25 (21.4%)	20 (32.8%)	45 (25.3%)
Absent	92 (78.6%)	51 (67.2%)	133 (74.7%)
Phantosmia at 1-year	*(n=51)*	*(n=25)*	*(n=76)*
Present	5 (9.8%)	9 (36.0%)	14 (18.4%)
Absent	46 (90.2%)	16 (64.0%)	62 (81.6%)
Phantosmia for paired samples (1-year/Baseline)	*(n=48)*	*(n=25)*	*(n=73)*
Present / Present	2 (4.2%)	7 (28.0%)	9 (12.3%)
Present / Absent	2 (4.2%)	2 (8.0%)	4 (5.5%)
Absent / Present	6 (12.5%)	3 (12.0%)	9 (12.3%)
Absent / Absent	38 (79.2%)	13 (52.0%)	51 (69.9%)

demographic factors nor medical history with an abnormal BSIT test at baseline.

With regards to COVID-19 status, 50.5% (96/190) had tested positive by PCR test before recruitment at one month post-initial infection, and the remaining 49.5% (94/190) were recruited upon experiencing a sudden-onset smell loss within the last 1-2 months with a suspected COVID-19 infection (PCR testing was not readily available at the beginning of the pandemic, when the isolated symptom of smell loss was not an indication for testing). Post-hoc COVID antibody and antigen testing results were obtained for a subgroup of participants. Of the sixty-five participants for whom antibody testing results were readily available, fifty-three (81.5%) tested positive. For those who had reported a positive COVID-19 antigen result at the time of recruitment, 87.5% (28/32) also had a positive antibody result. For those who had not undergone COVID-19 antigen testing at the time of recruitment, 76.0% (19/25) had a positive antibody result in the time thereafter.

All eligible participants had one or more symptoms in addition to the loss of sense of smell at the time of onset, with 75.8 (144/190) of participants reporting a loss of sense of taste. Other common symptoms were fatigue (70.5%, 134/190), aches and pains (53.2%, 101/190), fever (38.9%, 74/190), shortness of breath (36.8%, 70/190), persistent cough (32.6%, 62/190) and sore throat (30.0%, 57/190). Moreover, 26.8% (51/190) reported nasal congestion, 14.2% (27/190) reported having experienced metallic taste and 13.7% (26/190) reported a burning sensation in the nose or mouth (Table 2). Whilst most symptoms were more common in those with abnormal BSIT test at 4 weeks, there was strong evidence in terms of reporting of shortness of breath (p=0.011), difficulty breathing (p=0.037), aches and pains (p=0.015) and chest pain (p=0.009).

Regarding self-reported qualitative smell dysfunction (Supplemental Table 1), 41.0% (73/178) reported distorted smell, 25.3% (45/178) reported having experienced phantom smells, and 6.7% (12/178) reported a heightened sense of smell. For most participants, the change in smell occurred suddenly (69.7%, 106/172), whilst 23.0% (35/172) reported the change occurring over days. For those who had smell issues, 67.1% (102/152) reported that the issue was consistent throughout the day, 18.4% (28/152) reported that the issue fluctuates, occurring more often than not, and 14.5% (22/152) reported that the issue occurs occasionally throughout the day with the majority of the time being normal.

Table 5. Mean QoL scores at baseline and at 1-year.

		Baseline, All Cases		Paired Analysis				
				Baseline		1-Year		
		N	Mean (Std. Dev.)	N	Mean (Std. Dev.)	Mean (Std. Dev.)	Mean Difference (95% CI: Lower, Upper)	p-value
1	Has the loss of smell affected you socially? (i.e. in your work and personal life)	84	4.3 (1.58)	22	4.9 (1.13)	3.8 (1.47)	-1.0 (-1.60 to -0.49)	0.001
1a	The changes in my sense of smell make me feel isolated.	88	3.1 (1.77)	24	3.8 (1.62)	3.0 (1.49)	-0.8 (-1.62 to -0.05)	0.038
1b	Because of the changes in my sense of smell, I have problems with taking part in activities of daily life.	88	2.6 (1.68)	24	3.2 (1.89)	2.7 (1.49)	-0.5 (-1.29 to 0.21)	0.147
1c	The changes in my sense of smell make me feel angry.	88	4.0 (1.88)	24	4.8 (1.69)	4.4 (1.53)	-0.5 (-1.15 to 0.24)	0.185
2	Has the loss of smell affected your eating habits?	66	4.4 (1.67)	16	4.8 (1.33)	4.7 (1.25)	-0.1 (-0.90 to 0.36)	0.736
2a	Because of the changes in my sense of smell, I cook less often than I used to (or visit restaurants less often than I used to).	88	3.7 (2.07)	24	4.4 (1.98)	4.0 (1.94)	-0.5 (-1.31 to 0.40)	0.278
2b	Because of the changes in my smell, I don't enjoy food or drinks as much as I used to.	88	5.4 (1.86)	24	6.2 (0.88)	4.8 (1.77)	-1.4 (- 2.05 to -0.78)	<0.001
2c	Because of the changes in my sense of smell, I eat less than I used to or more than I used to.	87	3.8 (2.00)	24	4.1 (1.83)	3.2 (1.66)	-1.0 (-0.25 to -1.67)	0.010
3	Has the loss of smell affected your anxiety levels?	64	3.2 (1.67)	15	3.5 (1.46)	3.5 (1.85)	0.0 (-0.73 to 0.73)	1.000
3a	Because of the changes in my sense of smell, I feel more anxious than I used to feel.	87	3.3 (1.78)	24	3.9 (1.82)	3.5 (1.72)	-0.4 (-1.05 to 0.22)	0.187
3b	Because of the changes in my sense of smell, I feel more socially isolated.	88	2.7 (1.67)	24	3.5 (1.64)	3.0 (1.57)	-0.5 (-1.24 to 0.15)	0.120
3c	Because of the changes in my sense of smell, I have to try harder to relax.	88	2.7 (1.72)	24	3.7 (1.76)	3.0 (1.52)	-0.7 (-1.37 to 0.03)	0.061
4	To what degree is the loss of smell annoying to you?	59	5.7 (1.72)	15	6.3 (0.72)	5.3 (1.23)	-1.0 (-1.69 to -0.31)	0.008
4a	I am worried that I will never get used to the changes in my sense of smell.	87	5.3 (1.96)	24	6.3 (1.00)	5.4 (1.17)	-0.9 (-1.51 to -0.32)	0.004
4b	The changes in my sense of smell annoy me when I am eating.	87	5.3 (2.06)	24	6.1 (0.90)	5.3 (1.33)	-0.9 (-1.53 to -0.22)	0.011

Regarding taste function, 30 participants from our first participating centre underwent taste testing. Most participants had normal taste function with regards to sweet (93.3%, 28/30), salty (96.6%, 28/29), sour (86.7%, 26/30) and bitter (96.7%, 29/30). We did not pursue taste testing for the remainder of the cohort due to the remote nature of the study and logistical constraints, and due to the fact that these initial results demonstrated that the underlying impairment was not due to an impaired taste function (sweet, etc.) but rather to do with the perception of flavours, as a result of smell dysfunction, which would not be appropriately captured with this measure.

Regarding smell function, the mean BSIT score at baseline was 9.1 (Std. Dev. = 2.12) (Table 3a). 67.9% (148/218) had normal smell (BSIT 9-12), 24.4% (53/218) had mild anosmia (BSIT 6-8), 7.8% (17/218) had moderate anosmia (BSIT 3-5). No participants scored within the severe anosmia range (BSIT 0-2).

Primary and secondary outcomes for early smell training at 12-weeks and at 1 year

The mean BSIT score for both trial arms at 12-weeks was 7.9 (Std. Dev. 2.23) (Table 3a). Considering the change in BSIT score from baseline to 12-week follow-up, the absolute difference between the trial arms is 0.45 points (95% CI: -0.69 to 1.59, p=0.43), which corresponds to a standardised effect size of 0.22 (95% CI: -0.34 to 0.77), after adjusting for baseline BSIT score. This was a smaller observed effect than the target standardised difference of 0.5, and in a smaller sample than planned (i.e. more uncertainty). Although not significant, the odds were higher in the treatment arm, compared to the control arm, of having normal smell following early olfactory training after 12-weeks (OR=2.38, 95%

CI: 0.73 to 7.76, p=0.15), after adjusting for baseline BSIT score (Table 3b).
Of the participants who responded to the invitation for a 1-year follow-up, 19 participants, who completed the 12-week RCT, responded. At this time-point (control=8, intervention=11), the absolute difference in the change in BSIT score between the trial arms is 0.65 (95% CI: -1.01-2.31, p=0.42), which corresponds to a standardised effect size of 0.31 (95% CI: -0.38-1.01), after adjusting for baseline BSIT score. Similar to at 12-weeks, we observed increased odds of having normal smell at 1 year with olfactory training (OR=2.3, 95% CI: 0.37-14.61, p=0.37), after adjusting for baseline BSIT score, however this was not statistically significant (Table 3b).

Long COVID and proportion of patients with persistent anosmia and/or parosmia at 1-year

The median number of months between the 1-year follow-up and baseline enrolment was 10 months (range 8-13). For all participants, who participated in the 1-year follow-up, the mean BSIT score was 9.5 (Std. Dev. 1.71). 75.0% (42/56) scored with the normal range, while 23.2 (13/56) and 1.8% (1/56) had mild and moderate anosmia, respectively (Table 4a). The change in BSIT score from baseline was 0.2 (Std. Dev. 1.77). When considering the RCT participants only (n=19), there were slight improvements in BSIT scores in both the treatment (n=11) and control arms (n=8) at 1-year compared to baseline (Table 4a). However, for both arms combined, only 47.4% (9/19) scored within the normal smell range at 1-year.
In an exploratory analysis of potential predictors of psychophysical long-term smell loss, neither gender, smoking/alcohol history, nor medical history were associated with an abnormal BSIT test at 1-year in the responding cohort (Supplemental Tables 2 and 3). However, evidence of associations between the experience of certain COVID-19 symptoms at baseline and an abnormal BSIT result at 1-year was observed: aches and pains (p=0.030) and/or diarrhoea (p=0.011) (Supplemental Table 4).
Regarding subjective measures of olfactory dysfunction, the mean change in participants' sense of smell self-rating, from baseline to 1-year, was 1.39 (Std. Dev. 2.29). This did not correlate with the change in BSIT result (Spearman's correlation coefficient = 0.11, p=0.465).
The overall rate of parosmia in the responding cohort at 1-year was 43.4% (33/76). 24 of the 29 participants, who reported parosmia at baseline, continued to experience this symptom at 1 year (Table 4). In addition, experience of parosmia at 1-year was more likely in those with abnormal BSIT scores at baseline (OR=3.56, 95% CI: 1.30-9.69, p=0.013) Additionally, we observed a correlation between parosmia at 1-year and an abnormal BSIT score at 1-year, which approached significance (p = 0.055).
Regarding phantosmia, 9 of the 18 participants in the responding cohort, who reported the symptom at baseline continued to experience it at 1-year. Experience of phantosmia at 1-year was more likely in those with abnormal BSIT scores at baseline (OR=5.18, 95% CI: 1.51-17.7, p=0.009) and significantly correlated with an abnormal BSIT score at 1-year (p = 0.011).
Considering all participants, who completed the 1-year survey irrespective of RCT enrolment, 65.8% (50/76) reported experiencing at least one symptom of long COVID, with extreme tiredness/fatigue (39.6%, 30/76) brain fog (25.0%, 19/76), joint pain (21.1%, 16/76), insomnia (17.1%, 13/76) and heart palpitations (14.5%, 11/76) being the most common. For the participants for whom a 1-year BSIT and survey result were available (n=56), brain fog significantly correlated with an abnormal BSIT result at 1-year (p = 0.037) (Supplemental Table 5).

Changes in Quality-of-Life measures at baseline and after 1-Year

When comparing QoL scores at 1-year and at baseline, improvements (i.e., negative change) were seen for most items (Table 5). The evidence for these improvements was most robust for items 1 (mean difference -1.0, 95% CI: -1.60 to -0.49, p=0.001), 1a (mean difference -0.8, 95% CI: -1.62 to -0.05, p=0.038), 2b (mean difference -1.4, 95% CI: -2.05 to -0.78, p<0.001), 2c (mean difference -1.0, 95% CI: -0.25 to -1.67, p=0.010), 4 (mean difference -1.0, 95% CI: -1.69 to -0.31, p=0.008), 4a (mean difference -0.9, 95% CI: -1.51 to -0.32, p=0.004) and 4b (mean difference -0.9, 95% CI: -1.53 to -0.22, p=0.011).
In an exploratory analysis of differences in the mean scores between those who experience both anosmia and parosmia at baseline, compared to anosmia only, only two items were significantly different: item 2b, "Because of the changes in my smell, I don't enjoy food or drinks as much as I used to" (p=0.045) and 4b, "The changes in my sense of smell annoy me when I am eating" (p=0.023) (Supplemental Table 6).

Discussion

Crucially, our study confirms that most individuals who experience olfactory dysfunction secondary to proven and/or presumed COVID-19 infection will recover their sense of smell within the first four weeks. Indeed, two-thirds of our participants scored within the 'normal' range of the BSIT at enrollment. As such, while the target for the study was to recruit 200 participants, we found that this would be infeasible within the timeframe of the study due to the high recovery rate within the first four weeks. This is in line with previous studies, which have reported 60-70% of COVID-19 patients recovering their sense of smell within the first month[23-25]. However, there remains a subset of individuals who will experience persistent anosmia, as demonstrated in our study. In those who responded to the 1-year follow-up, most of those with persistent anosmia at baseline, i.e. at least 4 weeks, exhibited some degree of hyposmia even after 1 year. Furthermore, 52.6% of the 19 RCT participants (both arms combined),

who responded at 1-year, saw no improvement in their sense of smell.

Regarding early olfactory training without steroids, valid conclusions cannot be drawn regarding a potential benefit after 12 weeks due to the small number of participants who were ultimately eligible and enrolled in the RCT. Although some benefit may be gained, observed effect sizes were lower than those targeted in the study design and respective power analysis. With regards to the minimal clinically important difference (MCID) between the two groups, there has been no formal study assessing this in the context of anosmia/parosmia. Whilst a previously reported MCID of at least 1.0 for the BSIT appeared to be useful in evaluating chronic rhinosinusitis before and after endoscopic sinus surgery, it is unclear whether this is applicable for the current study[26]. Altogether, further investigation is needed to determine the efficacy of this treatment.

Evaluating 10-weeks of olfactory training either on its own or in conjunction with oral corticosteroids, others have reported that only those in the latter group saw a clinically significant improvement in their olfactory score[27]. This finding suggests that the addition of steroids to early olfactory training may significantly improve the sense of smell, as shown with 6-month olfactory training at 1 year[28]. At the start of the pandemic when this trial was planned and registered there was significant concern regarding the use of both oral and intranasal steroids in SARS-CoV-2 infection. However, evidence now suggests that olfactory training together with topical corticosteroids, including nasal lavage may be the best approach. Further prospective trials are warranted to determine the efficacy of these approaches and re-evaluate some of the consensus guidelines, as corticosteroids appear to be effective for other types of post-viral olfactory loss[16,29,30].

A large proportion of the participants who responded at one year reported experiencing parosmia and, to a lesser extent, phantosmia. This is in line, albeit higher than a previous report, which observed a 43.1% prevalence of parosmia after 6 months[31]. Importantly, parosmia is emerging as a key symptom of long-COVID and our study suggests its increasing prevalence at one year which we further show correlates significantly with an abnormal baseline and 1-year BSIT test which correlates with the long-term COVID symptom of brain fog. This underscores the neurological insult that occurs in a subgroup of patients which then causes a persistent central nervous symptom complex.

It is apparent that there is a significant number of individuals who may suffer from persistent symptoms of parosmia which can be debilitating. Whilst certain strategies are currently used in standard practice, such as sodium valproate or similar, these largely rely on anecdotal evidence with a lack of randomised, controlled trials. This poses as a crucial gap in the management of long-term olfactory dysfunction. Furthermore, the mechanism of parosmia has yet to be elucidated in the context of COVID-19 and why late-onset parosmia occurs is unknown. While some researchers have explored the neuroinvasive capacity of the virus, other research indicates that the infection of sustentacular cells or the presence of viral products in the microenvironment may cause the observed neurological sequelae[32-35]. It is likely that the cause for the symptoms is multifactorial and further investigations are highly warranted.

Regarding quality of life, there were some improvements over the 1-year period for all participant assessed, however, the scores for several items were similar, which may be due to the persistent negative impact of smell dysfunction on these aspects of life, particularly regarding feelings of anxiety as well as the impact on eating. Crucially, considering the proportion of our participants who reported experiencing parosmia at the 1-year assessment, it is important to note the specific way this condition impacts quality of life in comparison to anosmia/hyposmia. A number of our participants have reported, anecdotally (free text option, Supplemental Table 7), the challenges they have faced psychologically and emotionally due to parosmia, which can be seen in the differences in QoL scores between those who experienced parosmia and anosmia, compared to anosmia only. However, these findings may be confounded by other aspects of COVID-19 infection and the ongoing pandemic that we were unable to account for in this study. Indeed, items related to the impact of smell dysfunction socially may be confounded by the changes in societal restrictions as part of the COVID-19 pandemic response and less to do with objective and/or qualitative smell loss.

Our RCT is limited by its sample size, as we were unable to recruit our intended target due to the extremely high rates of smell recovery prior to 4-weeks post-onset. Furthermore, due to the fact that COVID-19 testing was not readily available at the start of the pandemic, not all subjects had formal proof of having had COVID-19 infection. As well, relatively high drop-out rates were observed (13 participants did not complete the RCT or were lost to follow-up). Potential non-compliance is also a limitation, which was largely due to the need to conduct the study remotely, in general, to comply with local safety guidelines. Most of the participants completed the BSIT remotely and unsupervised; this may by influenced by external factors, such as a family member providing help. As such, careful instructions were provided to the participants to mitigate these and results should be considered within the study context. Non-compliance may also be an issue with regards to the olfactory training RCT. Regarding the control group, there may be a chance that these participants conducted 'at-home' olfactory training in any case, with this information so readily available on the internet and through support organisations. We attempted to mitigate these by providing clear instructions, communication with the participant during the study and the subsequent exclusion of

those determined to be non-compliant, making these potential biases less likely. Another potential limitation was the use of the BSIT, itself, as our primary measure of olfactory function. While it is easy to use for the participant and suitable for the remote nature of the study, we acknowledge that this tool is not as sensitive as other more extensive tests (e.g. the University of Pennsylvania Smell Identification Test). Furthermore, a major component of the study was the electronic survey, which was completed by participants at baseline, 12 weeks and at one year. Findings from these data may be subject to recall and response bias although this is likely limited as participants were mainly asked to report their condition at the time of the survey. Lastly, while the majority of participants were invited to complete the 1-year follow-up (169 of 218) a smaller-than-expected proportion responded. The remaining 50 participants were recruited at a stage that was too late to be included within the timeframe of the 1-year follow-up analysis. Hence, a response bias cannot be excluded. However, when comparing the demographic details between responders and non-responders and baseline BSIT scores, we did not observe a substantial difference (Supplemental Table 8). Therefore, response bias is likely minimal.

Conclusion

In summary, early olfactory training may be helpful, although the findings of this trial are inconclusive. For those who responded to the 1-year follow-up, we observed that those with persistent smell loss beyond 4 weeks are unlikely to recover at 1 year with a high proportion of these participants also experiencing long-term parosmia in addition to other symptoms of long COVID-19. As such, both anosmia and parosmia should be considered important entities of long-COVID and further studies to improve on their long-term management are highly warranted.

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Authorship contribution

ML, VJL (Co-CIs) and SJ, CP, CH, NK (local PIs) planned the study and led on the study. All the above authors and CY, SP, NEL, TT, JM and JL and NC were also involved in the planning/conduction of the study and/or analysis and interpretation of the data. ML, JL, DC, RG, JR, CW, AT, JW, RB supported the acquisition of the data. ML, JL, and VJL wrote up the manuscript draft with the help and input of all authors.

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Conflict of interest

CP is a trustee of the charity Fifth Sense. All other authors declare no relevant conflict of interest.

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