The effect of smell training on COVID-19 induced smell loss

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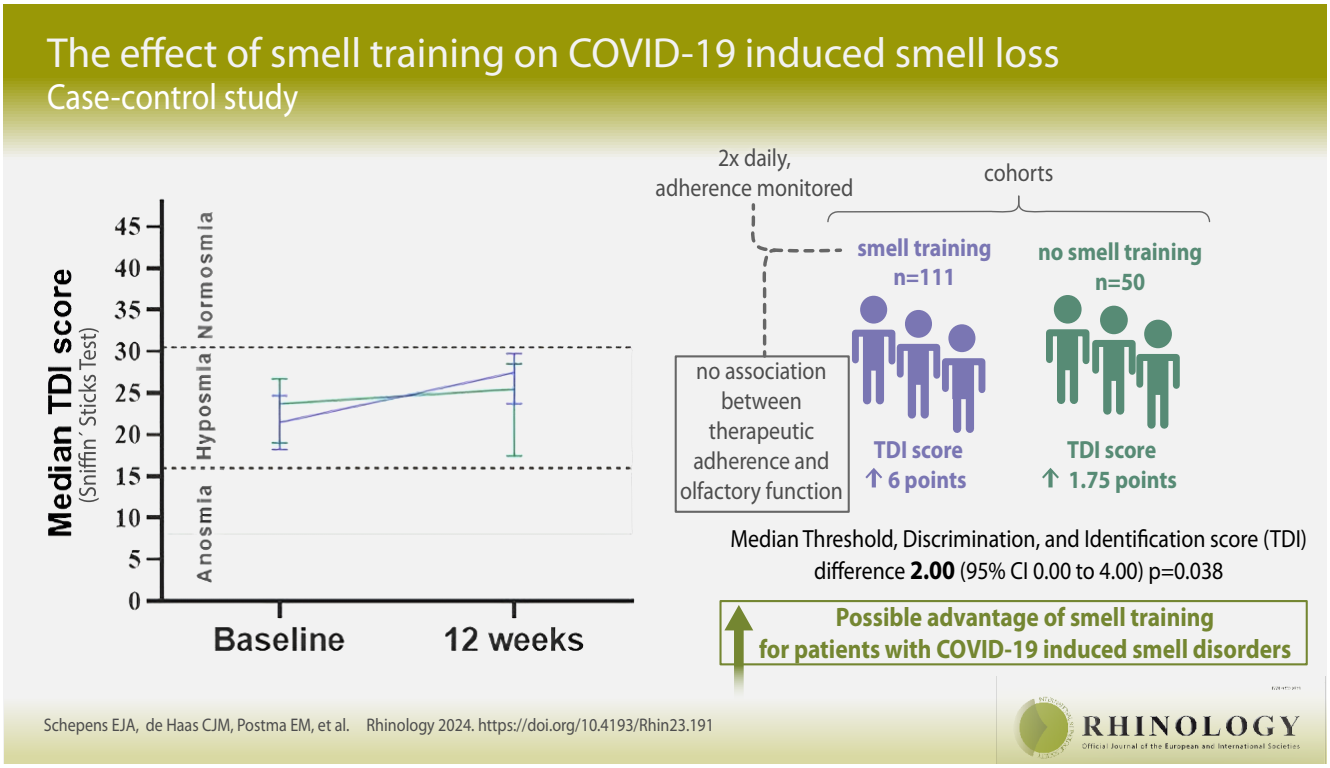

Abstract

Objective: while smell training appears to be effective for post viral smell loss, its effectiveness in COVID-19 induced smell loss is currently not well known. Therefore, we aim to investigate the potential effect of smell training on patients with COVID-19 induced smell loss.

Methods: we conducted a case-control study with two comparable cohorts. One of which (n=111) was instructed to perform smell training twice daily for 12 weeks, therapeutical adherence was monitored on a daily schedule, while the other cohort (n=50) did not perform smell training. The Sniffin' Sticks Test (SST) was used to objectify participants' sense of smell at baseline and after 12 weeks, reported as a Threshold, Discrimination, and Identification (TDI) score. We also determined the association between therapeutical adherence and the TDI scores.

Results: we found a significant difference in psychophysical smell function between patients with COVID-19 induced smell disorders who performed 12 weeks of smell training and those who did not. Median TDI difference between groups was 2.00 However, there was no association between the therapeutical adherence and olfactory function.

Conclusion: we discovered a significant moderate difference in psychophysical smell function between patients with COVID-19-induced smell disorders who performed smell training and those who did not, implying a possible advantage of training. However, no relationship was found between therapeutical adherence of smell training and olfactory function.

Key words: olfactory training, smell, COVID-19

Introduction

The COVID-19 pandemic has resulted in a significant burden of patients with persistent smell loss [1,2]. Given the limited treatment options for COVID-19 induced olfactory disorders [3–5] and the decreased quality of life experienced by these patients [6], there is a clear need for an effective intervention [7].

The pathophysiologic mechanism underlying COVID-19 induced smell disorders is believed to be damage to sustentacular cells of the olfactory epithelium. These cells support the Olfactory Receptor Neurons (ORNs) in processing odors and the olfactory epithelium in the transduction cascade, both required for a functional olfactory system [8–11]. Therefore, harm to the sustentacular cells indirectly affects the ORNs and the olfactory epithelium, leading to olfactory disorders.

Olfactory training has been proposed as a potential treatment option for COVID-19 induced olfactory disorders [12–19] as it has been shown to promote the regeneration of the number and activity of ORNs through repetitive odor exposure [20,21]. Previous studies have demonstrated the efficacy of olfactory training in other types of olfactory disorders (e.g., post-traumatic and post-infectious olfactory disorders)[20,22–25].

However, current studies investigating the effect of olfactory training in COVID-19 patients have small sample sizes [14–16,26], no generalizable psychophysical measurements [14], lack a control group [15,17,27] [NO_PRINTED_FORM] or monitoring of therapy compliance [12,14,17] which limits the ability to draw conclusions [13,25].

Smell training compliance can be challenging, this could be due to its repetitive nature, the nuanced noticed effect, and a lack of motivation. Autonomous (willingness-based) and controlled (external pressure-based) motivation are crucial for optimal compliance. Healthcare practitioners can enhance autonomous motivation through improved therapy communication [28], while monitoring, such as using a treatment diary, aids-controlled motivation and overall compliance [29].

We observed a different recovery trajectory between two comparable study cohorts within the same project [30], in which one group was stimulated to perform smell training and the other group did not perform smell training. Therefore, we performed a case-control study with psychophysical tests of olfactory function to investigate the efficacy of smell training in comparison to a control group without smell training. In addition, we aim to explore the potential association between the frequency of smell training and its impact on olfactory function. If adherence to the treatment demonstrates a beneficial effect on TDI scores, this could contribute to the instructions we give to patients, e.g. encourage them to strictly perform the smell training consequently and explain the possible consequences of a limited effect when performing the training inconsequent.

Methods

We performed a case-control study in the Netherlands, analyzing two comparable prospective study cohorts of COVID-19 patients. Both studies are part of the national research project 'Sniffing Out COVID', funded by the Dutch Organization for Health Research and Development, project nr 10430102110001. Data from patients who participated in the COCOS study (COrticoisteroids for COVID-19 Induced loss of Smell) [31] and data from patients participating in the COVORTS study (COVid-19 cohORT for Smell loss) were compared [30]. The University Medical Center Utrecht's Institutional Review Board approved the original research protocol for the COCOS trial (21-635/G-D, October 2021). The Medical Ethical Assessment Committee (METC) in the East of the Netherlands approved the COVORTS study (2021-11687, NL77954.091.21).

Study cohorts

The COCOS study (smell training cohort) was a randomized, double-blind, placebo-controlled trial determining the possible benefit of an oral prednisolone treatment (10 days 40mg) on the olfactory function in patients with COVID-19 induced smell disorders. Results showed no difference in olfactory function between patients who received prednisolone and those who received placebo [31]. Consequently, we combined the patients from both groups into a single cohort since there was no distinction between the placebo and prednisolone group. Patients in both placebo and prednisolone group performed olfactory training for 12 weeks, consisting of repeated exposure to four different intense odors; (rose, eucalyptus, lemon, and cloves [20]. To monitor compliance to the training, patients filled in a daily schedule, in which they wrote if they did the training. Therapeutical adherence was registered as frequency. They were recommended to do the training each morning and evening. The maximum achievable score was 168, representing the ideal scenario of performing the training twice a day for a duration of 12 weeks.

The COVORTS study (no smell training cohort) was a prospective cohort study to assess olfactory function and recovery over time, without any interventions [30].

Patients in both studies underwent the same psychophysical Sniffin' Sticks Test (SST) and reported their sense of smell in a Visual Analogue Scale (VAS) at baseline (first visit) and after 12 weeks (second visit).

Patients

Patients were recruited via the Dutch media, the National Institute for Health and the Environment (RIVM), and the National Patients Association 'Reukensmaakstoornis.nl'. All patients

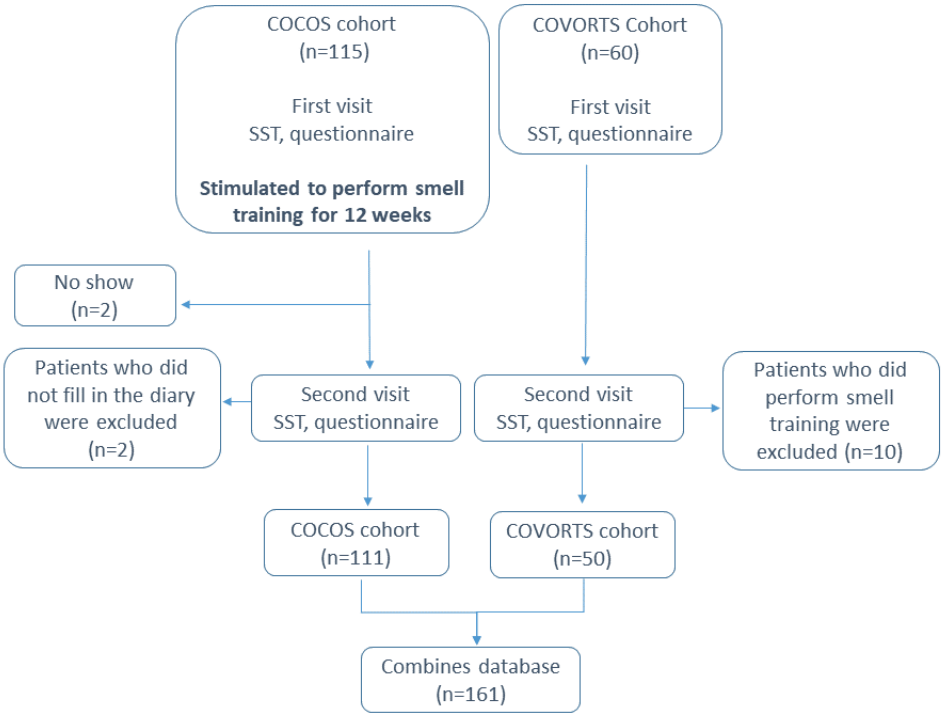

Figure 1. Flow-chart. SST: Sniffin' Sticks Test; TDI score: Threshold, Discrimination, Identification score.

signed informed consent to participate. Inclusion and exclusion criteria for both studies were similar [30,31] apart from a maximum age of 60 years in the COVORTS cohort, whereas there was no maximum age for participation in the COCOS study. Patients in the COCOS study underwent a nasendoscopy at baseline to eliminate other potential causes for their loss of smell. Both studies included patients with at least 4 weeks of COVID-19 induced smell loss objectified by the SST, with a Threshold-Discrimination-Identification (TDI) score of <30.5 at first visit (<12 weeks following a confirmed COVID-19 diagnosis by PCR). So, in both cohorts only patients with a minimum of 4 weeks and a maximum of 12 weeks of COVID-19 induced smell loss were included. The researchers of the COVORTS study made an amendment to include patients with only a positive self-home test as PCR testing had become less common in the Netherlands during their recruitment period. For this study we used one patient with a positive self-home test without confirmed PCR. The Medical Ethical Assessment Committee (METC) in the East of the Netherlands approved the amendment in July 2022. In the COCOS study 115 patients completed their first visit, two patients lost follow-up at second visit. Of these 113 patients, two patients were excluded by not fulfilling the olfactory training diary, resulting in 111 patients for the analysis.
In the COVORTS study, 60 patients finished first visit. Without being encouraged, ten patients performed smell training on their own initiative during the study period. These patients were excluded, resulting in 50 patients for the analysis (Figure 1).

Procedures

The patients in the COCOS study visited the Outpatient clinic for Ear, Nose, and Throat twice for the assessment of the SST, and to fill out a questionnaire (Figure 1).
The start of recruitment and the assessment of the baseline data started for the COCOS study in November 2021 and ended in February 2022, all second visits were between February 2022 and May 2022. For the COVORTS study, the start of recruitment and the assessment of baseline data used for this study, started as well in October 2021, and ended in November 2022. Second visits were between February 2022 and February 2023. At first visit, all patients received olfactory trainings set, were stimulated to perform smell training twice daily for 12 weeks and were closely monitored by crossing off a treatment diary. At second visit (approximately 12 weeks after first visit), patients administered the same smell tests and VAS questionnaire. Patients who did not fill out the treatment diary were excluded (n=2).
Patients in the COVORTS study were visited at home twice to perform the SST, and to fulfill the same VAS questionnaire (Figure 1). Patients were asked at first and second visit whether they performed olfactory training and were excluded from the analysis if they stated they had (n=10).

Outcome measures

The primary outcome of this study is the comparison of TDI scores reflecting psychophysical olfactory function, obtained from the SST, between the smell training (COCOS) and no smell

Table 1. Baseline characteristics and outcomes.

	Smell training cohort n = 111 (COCOS)	No smell training cohort n = 50 (COVORTS)
Gender		
Male	40 (36.0)	10 (20.0)
Female	71 (64.0)	40 (80.0)
Age, years	49 (41-57)	51 (45-55)
Vaccination status	88 (79.3)	39 (78.0)
Duration between first visit and COVID-19, days	56 (44-69)	88 (71-98.5)
Median frequency of performing smell training	129 (86-151)	-
TDI Score	21.50 (18.25-24.75)	24.0 (19.19-27.31)
Threshold	1.5 (1.0-3.5)	4.5 (1.5-6.5)
Discrimination	9.0 (8.0-11.0)	9.0 (7.8-11.0)
Identification	10.0 (8.0-11.0)	10.0 (7.0-12.0)
Self-reported sense of smell, VAS (0-10)	1.2 (0.4-3.0)	2.1 (0.6-2.9)

Data is reported n (%) or in medians (IQR), unless where otherwise stated. TDI = Threshold Discrimination Identification; VAS = Visual Analogue Scale. Outcome ranges: TDI: 1-48; Threshold: 1-16. Discrimination: 0-16; Identification: 0-16; VAS: 0-10.

Table 2. Primary and secondary outcomes at the second visit. Data is reported in medians (IQR).

	Smell training cohort n = 111 (COCOS)	No smell training cohort n = 50 (COVORTS)	Difference (95% CI)	P-value
TDI Score	27.50 (23.75-29.75)	25.75 (17.88-29.13)	2.00 (0.00-4.00)	0.038
Threshold	4.50 (3.3-5.5)	4.6 (1.8-7.1)	0.25 (-0.50-1.25)	0.387
Discrimination	11 (10-13)	10 (8-12)	2.00 (1.00-2.00)	0.000
Identification	11 (10-13)	10 (8-11.3)	1.00 (1.00-2.00)	0.001
Self-reported sense of smell, VAS	3.2 (1.4-5.9)	4.3 (1.6-6.0)	0.01 (-0.70-1.10)	0.711

TDI = Threshold Discrimination Identification; VAS = Visual Analogue Scale. Outcome ranges: TDI: 1-48; Threshold: 1-16. Discrimination: 0-16; Identification: 0-16; VAS: 0-10.

Table 3. Linear regression of the frequency of smell training associating with TDI score and self-reported sense of smell (COCOS cohort).

	Regression Coefficient (95% CI)	Standard Error	P-value
TDI score	-0.007 (-0.028-0.014)	0.011	0.507
Self-reported sense of smell, VAS	0.004 (-0.008-0.016)	0.006	0.491

TDI = Threshold, Discrimination and Identification; VAS = Visual Analogue Scale

training (COVORTS) cohorts after 12 weeks.The TDI score ranges from 0 to 48, with a higher score indicating a better olfactory function. The TDI score is derived from three tests: Threshold (score range 1-16), Discrimination (score range 0-16), and Identification (score range 0-16) [32], with a clinically relevant difference defined as 5.5 points [33]. We also collected data from the self-reported sense of smell on a Visual Analogue Scale (VAS) ranging from 0-10 [3].

Statistical analyses

All statistical analyses were conducted using IBM SPSS Statistics 26.0.0.1 software. Our data indicated non-normal distribution for all outcomes, so we performed a Mann-Whitney U test for differences on the outcome measures between the COCOS and COVORTS cohort. Median differences between outcomes were calculated using Hodge-Lehmann estimators, and confidence intervals and p-values were reported. An univariable linear regression analysis was conducted on the smell training cohort to explore the potential association of the frequency of smell training on TDI score outcomes at second visit.

Results

Baseline characteristics (first visit)

The smell training cohort had a median age of 49 years (IQR

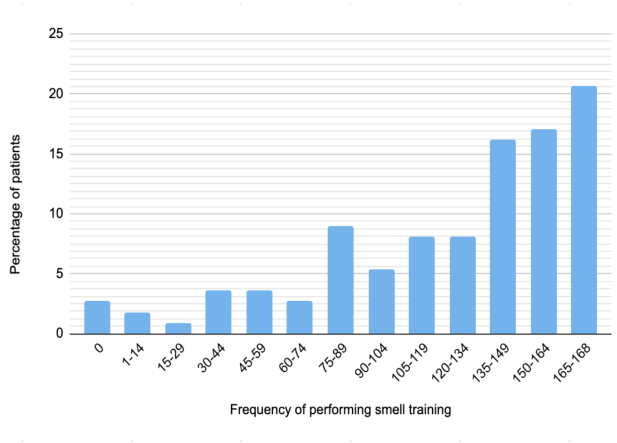

Figure 2. Distribution of performing olfactory training in frequency over 12 weeks.

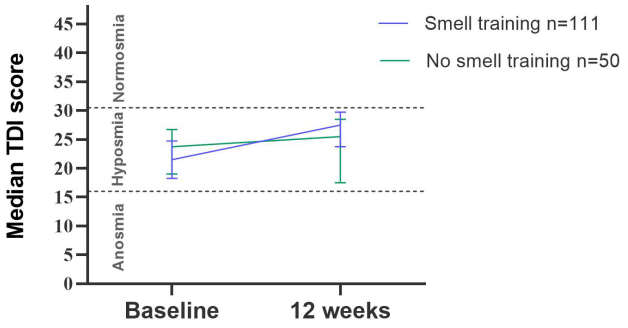

Figure 3. TDI scores over time in smell training cohort (COCOS) and in no smell training cohort (COVORTS). Data is visualized in medians and IQR. TDI = Threshold Discrimination Identification (range 1-48).

41-57), with 40 (36.0%) male patients and 71 (64.0%) female patients. Median duration between COVID-19 infection and first measurements was 56 days (IQR 44-69). Out of 111 patients, 88 patients (79.3%) were vaccinated for COVID-19. Median TDI score on the SST was 21.50 (IQR 18.25-24.75). Patients' median self-reported sense of smell scores on the Visual Analogue Scale (0-10) was 1.2 (IQR 0.4-3.0) (Table 1).

The no smell training cohort had a median age of 51 years (IQR 45-55), with 10 (20.0%) male patients and 40 (80.0%) female patients. Median duration between COVID-19 infection and first measurements was 88 days (IQR 71-98.5)

Median TDI score on the SST was 24.0 (IQR 19.20-27.31). Patients rated their sense of smell on the Visual Analogue Scale (0-10) as 2.1 (IQR 0.6-2.9) (Table 1).

Outcomes after 12 weeks (second visit)

Median duration between first and second visit was 12 weeks (IQR 11-13). Median frequency of performing smell training was 129 times (IQR 86-151), with a maximum of 168 times. The distribution of the frequency of performing olfactory training is shown in Figure 2.

The smell training cohort scored a median TDI score of 27.5 (IQR 23.75-29.75). They rated their sense of smell on the Visual Analogue Scale (0-10) as 3.2 (IQR 1.4-5.9) (Table 2).

The no smell training cohort had a median TDI score of 25.75 (IQR 17.88-29.13). They rated their sense of smell on the Visual Analogue Scale (0-10) as 4.3 (IQR 1.6-6.0) (Table 2).

Median TDI difference between groups was 2.00 (95% CI 0.00-4.00, p = 0.038). Median difference in self-reported sense of smell was 0.01 (95% CI -0.70-1.10, p = 0.711) (Table 2). Compared to baseline the smell training cohort showed an improvement in TDI score of 6 points. The improvement of TDI score in the no smell training cohort was 1.75 points (Figure 3).

Frequency of smell training

Table 3 shows an univariable linear regression analysis performed on the smell training (COCOS) cohort. No statistically significant association between the frequency of performed smell training and the TDI score, or self-reported sense of smell (VAS) was found.

Discussion

This case-control study investigated the efficacy of stimulated and monitored smell training in patients with COVID-19 induced smell loss, compared to those who did not perform smell training. The median difference of the smell training cohort on TDI score in 12 weeks is 6 points, which is a clinically relevant improvement. The median difference on TDI score of the no smell training cohort was 1.75 points, which is not a clinically relevant improvement. We want to emphasize that the main outcome of our study is the difference between the groups, not the difference between the pre and post measurement. The difference between the two types of methodology is not too difficult to explain. What we aimed to do here is to assess the differences between using two types of therapies. The best way to do that is by comparing two groups, ideally in a randomized controlled trial. We took the second best, a comparative study of two groups. Assessing the pre-and post-measurement alone will leave us with more known and unknown confounders than using the comparative design. Therefore, the main outcome of our study is the difference between the TDI scores between the groups. There is a significant difference in TDI score between the groups after 12 weeks, however, both in the hyposmic range and with a moderate difference. Furthermore, we determined the association between frequency of smell training and TDI scores at the second visit to inform patients better about the possible effect of optimal therapeutical adherence. The reason for using the association at second visit is because using Delta

as an outcome would lead to bias due to regression to the mean [34]. However, the frequency of smell training was not associated with smell function. We must acknowledge that this study was not suitable for fully assessing this question, because almost all our patients were compliant with the smell training. Thus, the regression cannot truly be discriminative, as the distribution of frequency of performing smell training is not evenly distributed. Therefore, we failed to provide patients with comprehensive information about the significance of treatment compliance or the enhancement of the treatment.

We aimed to addresses limitations of current literature by utilizing a large sample size, conducting thorough psychophysical and subjective measurements, and monitoring therapeutical adherence. Additionally, we included a control group to address the potential confounding effect of spontaneous recovery over time, enabling a more accurate evaluation of the difference between olfactory training and non-intervention. Moreover, we only included patients who had a confirmed COVID-19 diagnosis.

There are however limitations in this study to acknowledge. Firstly, the gold standard for assessing the effect of an intervention is a randomized controlled trial (RCT), since RCTs minimize the effect of confounding factors. In the present paper we describe a secondary outcome of both the COCOS and the COVORTS study, therefore we did not assess this topic in an RCT. However, the largest issue with non-RCTs when assessing the effect of an intervention is confounding by indication, in which the confounding is caused by the presence of an indication for the exposure. That confounding by indication might have been the case in our study because individuals who responded to participate in either the COCOS or in the COVORTS cohort, might have had different characteristics. The difference in treatment between the two cohorts could initially have attracted patients who suffered from a higher degree of smell loss to participate in the smell training (COCOS) study. The smell training cohort had a lower starting point on TDI score, and therefore more to gain. They also experienced less days of smell loss at baseline (56 days) in comparison to the no smell training cohort (88 days). Nonetheless, both cohorts shared the same inclusion and exclusion criteria, the same recruitment and testing period, and the same virus variants and vaccines available. Secondly, patients may have exhibited socially desired behavior when filling out the training diary, making the frequency of performed smell training sessions uncertain.
Another noteworthy distinction between the compared cohorts is the likelihood that patients in the smell training cohort exhibited more attention towards their sense of smell due to receiving treatment and performing smell training. However, the SST is a validated psychophysical test, which is used to assess the most objective smell function possible. Therefore, it is unlikely that patients in the COCOS trial might have displayed a positive placebo effect that could have influenced the results in comparison to patients from the COVORTS trial.

Extending the period of smell training could potentially result in further improvement of smell function, as earlier recommended by previous studies ranging from 6 to 12 months [17,22].
We recommend conducting a randomized controlled trial with a prolonged follow-up period to gain more insight on the long-term effects of smell training. Though there are ethical considerations by withholding a control group from olfactory training and there is a challenge ensuring therapeutical adherence for an extended period. By incorporating both stimulation and monitoring (e.g. keeping a treatment diary or using a smartphone application) individuals are more likely to remain motivated and committed to the therapy [28,29]. Although our study reveals a significant moderate difference between the two groups after 12 weeks, there is no association between smell training frequency and olfactory function. There are two explanations for this outcome: first the distribution of the smell training was disbalanced in the cohort, the majority of patients performed the training to a limited extent. A RCT, designed to objectify the significance of frequency, could have led to a more balanced distribution of participants across different frequencies. However, it is worth considering that in real-world clinical settings, patients perform smell training with a wide range of frequencies. Besides, our primary objective was not to focus on the frequency, but to examine the differences between a group that received a training set and explicit instructions to perform smell training, and a group that was not provided any instruction or stimulation for smell training and was even excluded if they engaged in smell training on their own initiative. The other explanation might be that it is not the frequency of the therapy but the awareness of focusing on smell, that has the most effect.
Nevertheless, based on our findings and previous research indicating possible benefits [12–17,25], we highly encourage patients with smell loss following COVID-19 to perform olfactory training.

Conclusions

We found a statistically significant difference in smell function between patients with COVID-19-induced smell disorders who performed smell training and those who did not, implying a possible advantage of smell training. However, no association was found between the frequency of smell training and olfactory function. A randomized controlled trial with an extended follow-up period would be desirable to obtain more conclusive and validated results.

List of abbreviations

COCOS: COrticosteroids for COVID-19 induced Smell loss;

COVORTS: COVid-19 cohORT for Smell loss; PCR: Polymerase Chain Reaction; TDI: Threshold-Discrimination-Identification; SST: Sniffin' Sticks Test; VAS: Visual-Analogue-Scale; IBM SPSS: IBM software for Statistical Package for the Social Sciences; IQR: Interquartile Range; CI: Confidence Interval

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Authorship contribution

DK, IS, CH and ES were responsible for the trial design and DK, IS, SB and EP for the funding acquisition. DK and SB supervised the trial. ES, CH, DK, IS, EP, SB and BD had complete access to the data and were accountable for its integrity. IS, CH and ES were responsible for the statistical analysis, ensured the accuracy of the data analysis and interpreted the data. ES was executive investigator. ES, CH, EP and BD conducted the measurements. All authors have reviewed and approved the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

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Availability of data and materials

Participant data are available under reasonable request.

Ethics approval and consent to participate

The University Medical Center Utrecht's Institutional Review Board approved the original research protocol for the COCOS trial (21-635/G-D, October 2021). The Medical Ethical Assessment Committee (METC) in the East of the Netherlands approved the COVORTS study (2021-11687, NL77954.091.21).

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