Multidimensional benefits of olfactory training for chronic COVID-19-related olfactory dysfunction: a systematic review and meta-analysis

Chih-Hao Chen[1,2,3,4,#], Chiu-Fang Shih[1,#], Thomas Hummel[5], Yun-Ting Chao[1,2]

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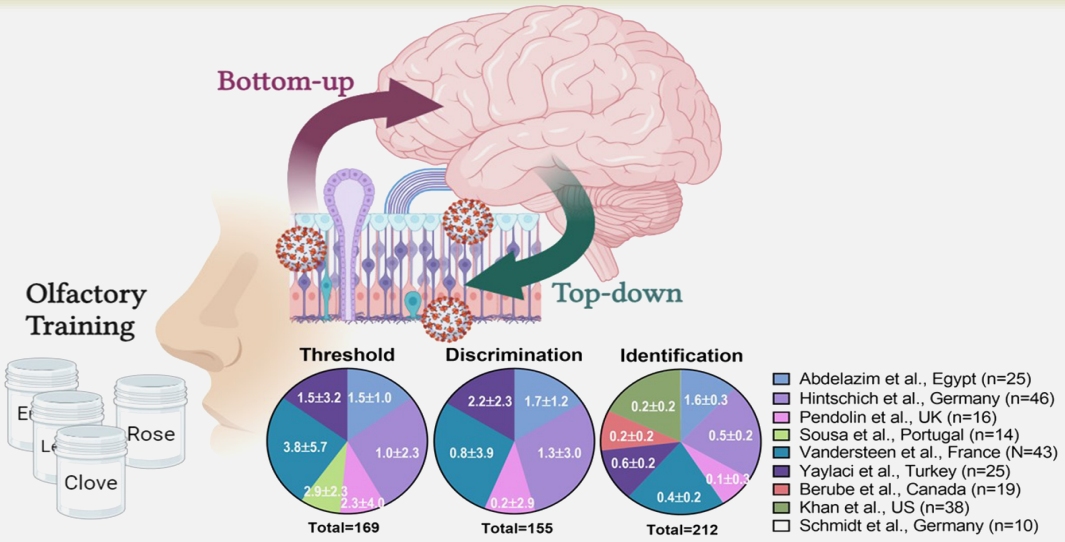

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Abstract

Background: Olfactory dysfunction is commonly observed in patients with COVID-19 infection. Chronic olfactory dysfunction can have a profound effect on one's quality of life. Olfactory training (OT) is a rehabilitation therapy, which has emerged as a viable treatment for COVID-19-related olfactory dysfunction. Our primary objective was to assess the effectiveness of OT for individuals with chronic COVID-19-related olfactory dysfunction.

Methods: A search was performed on the Cochrane Library, Embase, PubMed, Scopus, and Web of Science databases from their inception through Feb 24, 2024. Eligible studies included those with sufficient information for meta-analysis pertaining to the effectiveness of OT performed for more than 8 weeks in treating chronic (duration > 16 weeks) COVID-19-related olfactory dysfunction.

Results: After a systematic review of all relevant articles, 9 studies qualified for inclusion. A total of 179 patients within 7 studies had eligible Sniffin' Sticks test data. The pooled results showed significant post-OT increases in TDI score, threshold, discrimination, and identification. Two studies documented qualified UPSIT scores in 63 patients. Pooled results of all identification tests revealed significant improvement.

Conclusions: OT demonstrates benefits in treating chronic COVID-19-related olfactory dysfunction, as evidenced by multidimensional evaluations. These findings suggest the involvement of both top-down and bottom-up mechanisms in the recovery process.

Key words: COVID-19, olfactory training, meta-analysis, odor detection threshold, odor discrimination, odor identification

Introduction

Olfaction is a fundamental human sense serving a myriad of essential functions, including the ability to seek food, discern flavors, protect the individual against environmental toxins [1], facilitate spatial orientation [2], and recognize emotions [3]. It has also been linked to mate selection [4, 5], memory [6], and other cognitive functions [7]. Many individuals with olfactory dysfunction (OD) report difficulties in preparing meals, a sense of insecurity [8], and feelings of depression and anxiety [9]. Numerous studies have also reported a correlation between anosmia and mortality rates [10, 11].

From a clinical perspective, olfactory function can be measured in terms of sensitivity (odor detection threshold), the ability to differentiate nonverbally between distinct odors (odor discrimination), and the capacity to name specific odors (odor identification) [12]. The odor detection threshold is more closely linked to peripheral olfactory function, whereas discrimination and identification are more closely linked to higher cognitive functions, such as executive function and semantic memory [13]. These components manifest a range of unique patterns according to the cause of OD [14].

OD has emerged as a pivotal symptom and early indicator of coronavirus disease 2019 (COVID-19) [15]. Two recent meta-analyses have reported a high prevalence of OD among COVID-19 patients, with rates of 47.9% and 52.7%, respectively [16, 17]. COVID-19-related OD typically manifests suddenly, often accompanied by other symptoms [18]. In the majority of cases, OD resolves within a short period, with 95% of patients recovering spontaneously within two weeks and a mean recovery time of nine days [19]. However, a subset of cases experiences chronic long-term effects. The persistence of impaired odor identification suggests a sequela of central damage [20].

In 2009, an innovative approach to rehabilitating the sense of smell was introduced, referred to as olfactory training (OT). This approach was inspired by earlier findings demonstrating that repeated exposure to specific odors could enhance human olfactory sensitivity [21]. The standard OT protocol involves exposing the subject to four distinct odorants – phenyl ethyl alcohol (rose), eucalyptol (eucalyptus), citronellal (lemon), and eugenol (cloves) – twice daily over a period of 12 weeks [22]. Numerous studies have confirmed the effectiveness of OT in restoring olfactory function, particularly in cases of OD attributed to viral infections [23]. It seems that in this group OT affects mainly discrimination and identification functions [24, 25], both of which are associated with increased attention to odors and the cognitive processing of olfactory signals. It has been hypothesized that repeated exposure to odors could modulate regenerative capacity within the olfactory mucosa; however, OT was shown to have less effect on odor detection threshold compared to odor identification or discrimination [26].

During the COVID-19 pandemic, a surge in the number of patients reporting a loss of smell prompted extensive research into mitigation techniques, such as OT [27]. Several studies and meta-analyses have reported on the efficacy of OT in addressing acute and chronic OD resulting from COVID-19 [26, 28, 29]. Note, however, that some of the previous research failed to address the effectiveness of OT in dealing with specific olfactory components. There has been considerable research on acute (≤ 4 weeks), and subacute OD (≤ 12 weeks) which tend to resolve spontaneously; however, there has been relatively little research on chronic OD (> 16 weeks) associated with long COVID [30, 31].

Our primary objective in this single-group pre-post meta-analysis was to evaluate the outcomes of OT in patients who developed chronic OD as a result of confirmed COVID-19 infection. Specifically, we aimed to assess changes in olfactory function following OT by comparing pre- and post-training in both subjective assessments and objective psychophysical tests. For objective psychophysical tests, statistics from different subtests were extracted to evaluate outcomes across multiple dimensions.

Materials and methods

This meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [32].

Eligibility criteria of studies selected

We adopted the "Population, Exposure, Outcome" (PEO) framework to define our research question in this single-group meta-analysis using a pre-post intervention design [33, 34]. Specifically, pre-treatment scores served as the baseline to evaluate whether post-treatment scores following OT demonstrated significant improvements. All studies selected for inclusion focused on patients diagnosed with COVID-19 who exhibited OD lasting more than 16 weeks and who underwent OT for at least 8 weeks. The OT methods were based on the approach proposed by Hummel et al. in 2009 [22], with minor methodological adjustments, such as modifications in odor selection and slight variations in the OT duration. Further inclusion criteria included data sufficient for the quantification of effects applicable to meta-analysis. If a study does not provide information on the duration of OD or the length of OT, it will be excluded. In dealing with studies investigating other therapies that incorporated OT as a positive control, we extracted data exclusively from the pure OT group. However, studies with positive control groups receiving placebo medications, such as therapy plus OT versus placebo plus OT, were excluded to avoid potential confounding from placebo effects. Additionally, articles were excluded if they applied OT to pediatric patients, involved olfactory loss unrelated to COVID-19, were not written in English, or were case reports, case series, conference papers, or reviews.

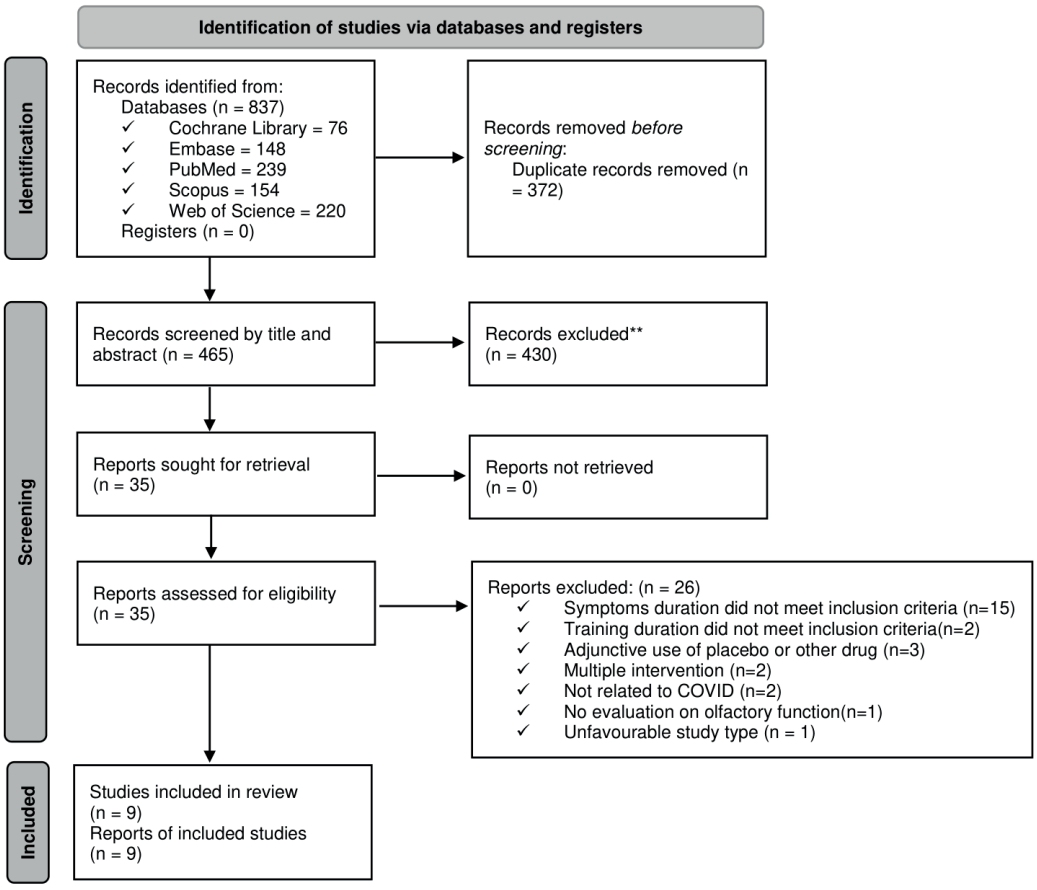

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. After screeing and full-text investigation of all relevant articles, 9 studies qualified for final analysis.

Search strategy and identification of eligible studies

The Cochrane Library, Embase, PubMed, Scopus, and Web of Science databases were searched through Feb. 24, 2024. A combination of Medical Subject Headings (MeSH) and text words was used to establish two search subsets: 1) studies related to COVID-19 infection (e.g., "COVID-19" and "SARS-CoV-2 Infection") and 2) studies related to OT (e.g., "Olfactory Training"). The search strategy is detailed in Table S1. The titles, abstracts, and keywords were screened prior to a review of the full text by the authors. The Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool was employed to assess the methodological quality of the studies included in the analysis [35].

Outcome measure and data management

Estimates of the effect of interest were derived from OT patients who did not receive concurrent treatments, ensuring an unbiased evaluation of OT effectiveness. This was assessed through both subjective and objective measures. Subjective assessments involved self-reported evaluations using the Visual Analogue Scale (VAS), where participants rated their olfactory function on a scale from 0 to 10. Objective assessments employed validated psychophysical tests to provide quantifiable insights into olfactory performance. After a comprehensive search and strict inclusion and exclusion criteria, only studies utilizing the Sniffin' Sticks Test (SST) and the University of Pennsylvania Smell Identification Test (UPSIT) as objective measures were included in the final analysis. SST analysis focused on three subtests: olfactory detection threshold (SST-T), odor discrimination (SST-D), and odor identification (SST-I). The results of the three subtests were combined as a composite threshold/discrimination/identification (TDI) score, which was then used to identify instances of anosmia (≤ 16.5), hyposmia (16.5 - 30.5), and normosmia (> 30.5) [36]. Given that the UPSIT, which scores up to 40, is a specific assessment for odor identification and conceptually resembles the SST-I, the UPSIT and SST-I scores were pooled using the standardized mean difference to harmonize the different psychophysical scales. We also employed VAS ratings, which provided a subjective assessment of olfactory ability on a score from 0 to 10 [37].

Statistical analysis

Random effects models were used to calculate effect sizes under the assumption that a second source of error other than sampling error existed. Mean differences (MD) and standardized

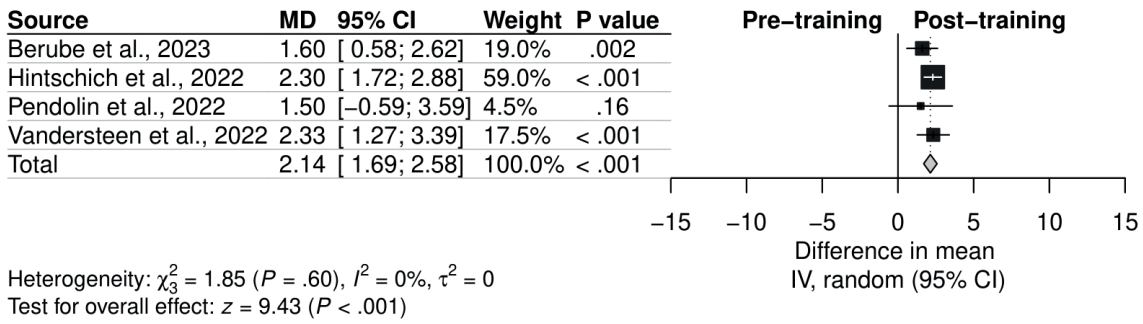

Figure 2. Improvements in subjective outcomes. Pooled results of the visual analog scale (VAS) showing significant improvements after OT. MD indicates difference in mean; CI indicates confidence interval; IV indicates inverse variance method.

mean differences (SMD) were used to evaluate the effect sizes of the interventions. Specifically, for the analysis of VAS and SST, MD and their corresponding 95% confidence intervals were reported to quantify changes before and after OT, as this approach is appropriate when the variables are on a consistent scale and directly comparable. In contrast, for outcomes such as SST-I and UPSIT, SMD were utilized to account for the use of different measurement scales across studies, allowing for standardization of results. A sensitivity analysis was conducted to determine whether excluding a specific study with different characteristics would impact the pooled results. Statistical heterogeneity was assessed using the Cochran Q test and I^2 statistic, wherein heterogeneity was categorized as low (<50%), moderate (50%-74%), or high (≥75%) based on the I^2 values [38]. Influence analysis for comparisons between pre-training and post-training conditions involved the systematic removal of individual studies in which the outcome of interest included more than two studies. In instances where continuous outcomes were initially presented as medians and interquartile ranges, the means and standard deviations were estimated using the methods outlined by Wan et al. in order to render the data amenable for analysis [39, 40]. All meta-analytical computation was conducted using Comprehensive Meta-Analysis software (CMA version 3.0) [41] and the R statistical software version 4.3.2 (R Project for Statistical Computing) in RStudio version 1.3.959 (RStudio).

Results

Study selection and characteristics

The preliminary search identified 837 records. Following the removal of duplicates and the screening of titles and abstracts, a total of 35 studies remained, 26 of which were excluded after a full-text review (Figure 1). This resulted in 9 studies eligible for final reviews. Most of the studies (n=7) were based on the SST, with the following distribution: composite TDI score plus all subtests (n = 5) [42-46], composite TDI score only (n=1) [47], and SST-T score only (n=1) [48]. Two studies focused on changes in UPSIT scores [49, 50]. Four studies utilized VAS evaluations [42, 44, 45, 50]. The detailed characteristics are listed in Table 1.

Risk of bias assessment

The studies were categorized in terms of the risk of bias, as follows: potential confounding factors (moderately biased; n=1) [48], participant selection (moderately biased; n=3)[42, 48, 49], lack of well-defined interventions (moderately biased; n=3)[42, 45], low compliance and co-interventions (seriously biased; n=1) (moderately biased; n=2)[45, 47, 49], missing data (moderately biased; n=2) [44, 50], and the selection of reported results (moderately biased; n=2)[47]. These assessments are detailed in Figures S1 and S2.

Improvements in subjective outcomes

As shown in Figure 2, pooled analysis of the four studies that reported VAS scores [42, 44, 45, 50] revealed significant post-OT improvements in subjective outcomes (MD, 2.14; 95% CI, 1.69 to 2.58; P<.001; I^2=0%). Influence analysis revealed that all reported results were within the confidence interval, thereby confirming the stability and reliability of the findings (Figure S3).

Improvements in SST scores

As shown in Figure 3A, six studies compared changes in the SST-TDI before and after OT [42-47]. The pooled results showed significant improvements SST-TDI scores after OT (MD, 4.55; 95% CI, 3.35 to 5.75.14; P<.001; I^2=34.0%). Six studies reported significant improvements in SST-T scores after OT (MD, 1.96; 95% CI, 1.16 to 2.77; P<.001; I^2=67.0%) (Figure 3B) [42-46, 48]. Five studies reported significant improvements in SST-D scores after OT (MD, 1.42; 95% CI, 0.85 to 2.00; P<.001; I^2=51.0%) (Figure 3C) [42-46]. Five studies reported significant improvements in SST-I scores after OT (MD, 1.44; 95% CI, 0.80 to 2.07; P<.001; I^2=61.0%) (Figure 3D) [42-46]. We also performed influence analysis involving the systematic removal of studies one by one. Under these conditions, the results remained within the confidence interval of the primary result, and no outliers were identified (Figure S4), thereby confirming the stability and robustness of the findings.

Improvements in odor identification

The outcomes of OT were also evaluated using UPSIT scores (n=2) [49, 50]. These results were combined with those that em-

Table 1. Summary of studies included in the meta-analysis of olfactory training and COVID-19-related olfactory dysfunction.

Study	Country	Study type	Patients (M/F)	Mean age (years, SD)	Training method	Olfactory training period (weeks)	Psychophysical test	Subjective evaluations	Main result	OD duration (weeks)
Pendolino et al., 2022 [43]	UK	Nonrandomized, controlled trials	16 (5/11)	46.7 (19.5)	Rose, eucalyptus, lemon, cloves. 4 odors for 10 s. Twice a day.	24	Sniffin' Sticks test (T, D, I)	VAS	Addition of corticosteroids may be beneficial.	37
Khan et al., 2022 [50]	US	Randomized controlled trial*	38 (2/36)	46 (12)	Rose, eucalyptus, lemon, cloves. 4 odors for 10 s. Twice a day.	12	UPSIT	ODOR score	OT failed to show benefit for patients (measured by UPSIT).	24
Yaylaci et al., 2022 [44]	Turkey	Nonrandomized, controlled trials	25 (10/15)	28 (14)	Rose, eucalyptus, lemon, cloves. 4 odors for 10 s. Twice a day.	12	Sniffin' Sticks test (T,D,I)	NA	OT significantly increased olfactory sensitivity.	23
Hintschich et al., 2022 [45]	Germany	Randomized controlled trial*	46 (19/27)	45.7 (14.9)	Rose, eucalyptus, lemon, cloves. 4 odors for 20 s. Twice a day.	12	Sniffin' Sticks test (T,D,I)	VAS	Addition of topical corticosteroid to OT was not beneficial.	29
Vandersteen et al., 2022 [46]	France	Nonrandomized, controlled trials	43 (17/26)	41 (13)	Rose, eucalyptus, citronella, cloves. 2 odors. Twice a day.	14	Sniffin' Sticks test (T,D,I)	VAS, QOD-NS, SF36	TDI score was significantly better after OT.	23
Sousa et al., 2022 [49]	Portugal	Nonrandomized, controlled trials	14		Rose, eucalyptus, lemon, cloves. 4 odors for 15 s. Three times a day.	12	Sniffin' Sticks test (T)	VAS**	Adjuvant therapy with OT exhibited better improvements than OT alone	33
Schmidt et al., 2023 [48]	Germany	Randomized controlled trial*	10 (2/8)	38 (13)	Rose, eucalyptus, lime, cloves. 4 odors for 10 s. Twice a day.	8	Sniffin' Sticks test (composite TDI score)	NA	Early and consistent OT for patients with dysosmia due to COVID-19 was recommended.	21
Bérubé et al., 2023 [51]	Canada	Randomized controlled trial	25 (9/16)	44.9 (7.4)	Rose, eucalyptus, orange, cloves. 4 odors for 10 s. Twice a day.	12	UPSIT	VAS, QOD score	OT improved subjective olfactory function and reduced rate of parosmia	39
Abdelazim et al., 2023 [47]	Egypt	Randomized controlled trial*	25 (10/15)	40.37 (8.58)	Rose, eucalyptus, orange, cloves. 4 odors for 10 s. Twice a day.	12	Sniffin' Sticks test (T,D,I)	NA	OT was associated with improved T, D, and I score	24

OT: olfactory training, QOD: olfactory disorders questionnaire, sQOD-NS: short version of Questionnaire of Olfactory Disorders-Negative Statements; T: threshold; D: discrimination; I: identification; UPSIT: University of Pennsylvania Smell Identification Test; VAS: visual analogue scale; NA: not available.
* "OT only" group from RCTs aiming for other therapy. **No available data for OT alone group.

ployed SST-I (n=5)[42-46]. The pooled results revealed significant improvements after OT (SMD, 0.46; 95% CI, 0.15 to 0.78; P=.002; I^2=71.0%) (Figure 4). During influence analysis, the results remained within the confidence interval of the primary result, and no outliers were identified (Figure S5), thereby confirming the stability and robustness of the findings.

Sensitivity analysis

A sensitivity analysis was conducted to evaluate the robustness of the pooled results by removing the study by Schmidt et al., 2023, due to its differing characteristics in training duration. The analysis revealed that the overall effect size remained statistically significant, indicating that the exclusion of this study did not alter the main findings (Figure S6).

Discussion

This meta-analysis demonstrated that OT could enhance olfactory function in individuals with chronic COVID-19-related OD across subjective outcomes as well as measured values. Previous studies have reported that OT is effective in addres-

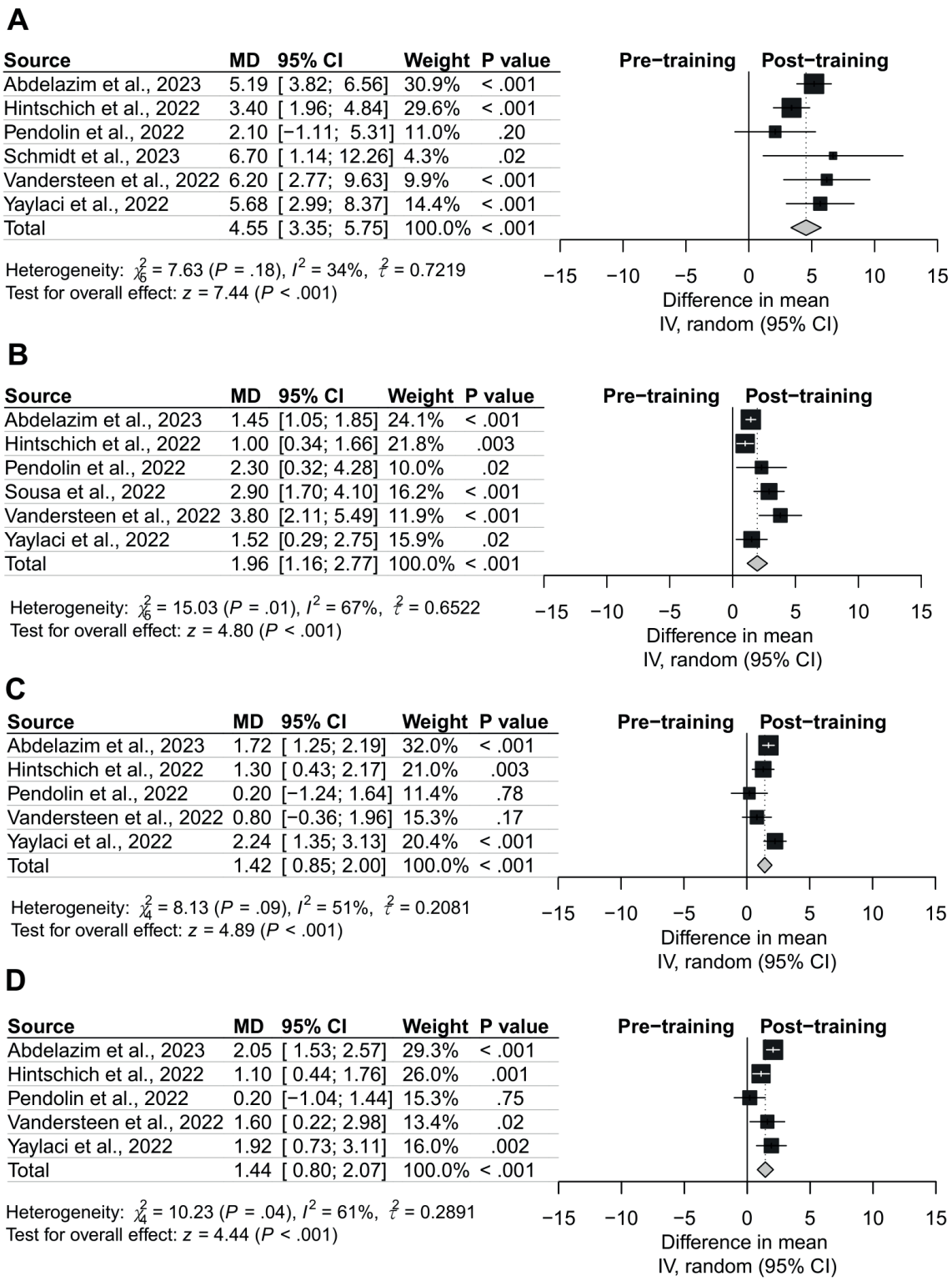

Figure 3. Improvements in (A) SST-TDI, (B) SST-T, (C) SST-D and (D) SST-I scores. MD indicates difference in mean; CI indicates confidence interval; IV indicates inverse variance method. The results are based on threshold (T), discrimination (D) and identification (I) scores in Sniffin' Sticks test (SST).

sing post-viral OD [23] and is particularly effective in dealing with OD in cases of infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19 [28]. Note that some of the assessment tools used to evaluate olfactory outcomes (e.g., self-reporting scores) lack reliability [51]. Combining outcomes from ratings and psychophysical testing involving a diversity of olfactory test results could introduce bias due to heterogeneity. In the current study, we categorized

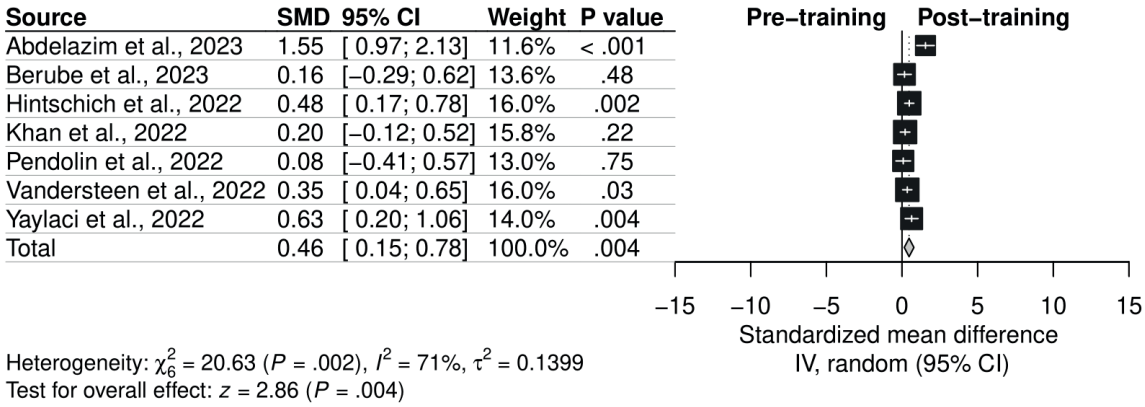

Figure 4. Improvements in pooled identification test results. SMD indicates standardized mean difference; CI indicates confidence interval; IV indicates inverse variance method.

a variety of assessment tools and examined the corresponding outcomes individually. Our results revealed that OT is beneficial in restoring olfactory function, as assessed through subjective ratings and three measurable domains (odor detection threshold, odor discrimination, and odor identification).

Two previous meta-analyses addressing the efficacy of OT (due to various causes) revealed that this method had more pronounced effects on discrimination and identification than on detection threshold levels [24, 25]. This implies a generalized improvement in higher-level cognitive processing of olfactory information. This assertion is supported by neuroimaging evidence that OT induces functional reorganization of the brain network [52, 53], resulting in increases in the volume of olfactory bulbs and brain regions associated with olfactory processing [54, 55]. Unilateral administration of OT has been shown to induce similar changes in both olfactory bulbs, suggesting neuroplasticity from central to more peripheral olfactory pathways [56]. This top-down process may partly explain the observed improvement in detection threshold levels in COVID-19 patients following OT [52, 57, 58].

Nevertheless, since SARS-CoV-2 primarily targets the peripheral neuroepithelium, a bottom-up mechanism is also likely, especially in the context of COVID-19-related OD. OT has been shown to enhance neural activity and electrophysiological responses in olfactory mucosa [59-61]. The observed restoration of neuroepithelial activity may be attributed to an increase in the expression of genes related to neurotrophic factors as well as markers associated with stem cells, glial cells, and receptor cells [61]. This suggests that OT initiates the neural regenerative process via olfactory receptor stimulation, inducing peripheral neuronal plasticity through the activity of neurotrophic factors. The precise effects of OT on the human neuroepithelium after SARS-CoV-2 damage have yet to be directly investigated; however, the results of the current meta-analysis suggest that OT restores both peripheral neuronal activity and central cognitive processing.

Notably, parosmia—the most common qualitative olfactory disorders reported after COVID-19—has been hypothesized to reflect, for example, disordered regeneration or aberrant rewiring of peripheral olfactory neurons. In this regard, several included studies observed dynamic changes in parosmia during the course of olfactory training. For instance, Bérubé et al. reported a significant reduction in parosmia frequency following OT [50], whereas Vandersteen et al. observed a paradoxical increase, possibly indicative of early-stage regeneration [45]. These findings suggest that the emergence or resolution of parosmia may serve as a clinical marker of peripheral neuronal remodeling in response to OT. However, due to the lack of widely accepted, standardized tools for quantifying parosmia other than self-report, we did not predefine it as an outcome of interest and therefore did not include it in our pooled analysis. Future research should aim to incorporate robust and standardized measures of qualitative dysfunction to better capture the full spectrum of COVID-19-related olfactory sequelae.

Our findings indicate that OT is a promising intervention for the management of COVID-19-related OD. The appeal of OT lies in its cost-effectiveness, ease of administration, negligible adverse effect, and compatibility with concurrent medical therapies. Among the included articles, complications related to OT were reported in only one study, with two instances of headaches and one instance of worsening parosmia [49]. In some randomized control studies, OT was incorporated as a positive control. We deliberately selected studies that aimed to evaluate other therapies but only included their control groups receiving "OT only" [44, 46-48]. In contrast, those studies in which the control group was administrated an additional placebo medication were excluded [62-64]. Overall, OT was found to be a promising standalone treatment for COVID-19-related OD.

The current study was subject to several limitations. First, the

pooled result of SST-TDI score did not reach the threshold of minimal clinically important difference (MCID), which requires an improvement of at least 5.5 [65]. This renders the observed improvement suboptimal in clinical practice. Second, we observed some variability in the protocols used for OT, particularly in the selection of training odors and training duration. Most studies utilized the conventional four odors [42-45, 47-49], whereas two studies substituted orange for lemon [46, 50]. Third, the studies selected for inclusion were from different countries with distinct cultural backgrounds, which may have introduced demographic differences contributing to data heterogeneity. Fourth, there is no way to confirm the degree of compliance in OT, thereby precluding a precise determination of the actual training duration for everyone. Fifth, this study did not address the time course of recovery. It is very likely that an investigation of whether the restoration of olfactory function begins with the threshold component or the discrimination/identification components could unveil the mechanism(s) underlying the observed effects (i.e., whether OT exerts a top-down or bottom-up effect). Sixth, despite the high correlation (0.81–0.85) and valid interchangeability between SST-I and UPSIT scores [66, 67], there is potential bias in pooling these two scales due to differences in test format, administration methods, and cultural sensitivity [67]. Finally, most of the studies did not address variables that could have potentially influenced the efficacy of OT, and subsequent post-hoc analysis was not feasible. Due to the potential heterogeneity among studies, such as OT methodology or protocols, this research adopts a random-effects model to more effectively handle the variability in study outcomes.

Although our analysis demonstrates significant olfactory improvement following OT, the single-arm pre-post design limits our ability to determine whether OT is significantly more effective than a control. Among the included studies, three incorporated control groups with no treatment [42, 43, 49] and one featured a placebo training group [50], making them suitable for pairwise meta-analysis; however, the cumulative sample size was insufficient, resulting in low statistical power and a high risk of unreliable conclusions. Therefore, pairwise meta-analysis was not conducted in this study. While OT shows promise in benefiting patients with long-term COVID-19-related OD across multiple dimensions, further studies, particularly those involving pairwise comparisons against a control group, are needed to establish the definitive efficacy of OT.

Conclusion

This meta-analysis highlights the multidimensional benefits of OT in patients with COVID-19-related OD, particularly for those with a disease duration exceeding 16 weeks. Our results demonstrated that OT significantly enhanced olfactory function, based on subjective ratings as well as objective measurements in the domains of odor detection threshold, odor discrimination, and odor identification. Given its cost-effectiveness and ease of administration, OT should be prioritized in clinical settings.

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Authorship contribution

Conceptualization: CHC, CFS, TH, YTC. Data curation: CHC, CFS, YTC. Formal analysis: CHC, CFS. Funding acquisition: YTC. Investigation: CHC, CFS. Methodology: YTC. Project administration: YTC. Resources: YTC. Supervision: TH, YTC. Writing – original draft: CHC, CFS, YTC. Writing – review & editing: TH, YTC.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Yun-Ting Chao, MD, PhD
Division of Rhinology
Department of Otorhinolaryngology
Head and Neck Surgery
Taipei Veterans General Hospital
Taipei
Taiwan
No.201, Sec. 2, Shipai Rd.
Beitou District
Taipei City
Taiwan 11217

Tel: +886 2 2875 7337
Fax: +886 2 2875 7338
E-mail: yunting001@gmail.com

Chih-Hao Chen[1,2,3,4,#], Chiu-Fang Shih[1,#], Thomas Hummel[5], Yun-Ting Chao[1,2]

[1] Department of Otorhinolaryngology-Head and Neck Surgery, Taipei Veterans General Hospital, Taipei, Taiwan
[2] Department of Otolaryngology, National Yang Ming Chiao Tung University, Taipei, Taiwan
[3] Institute of Brain Science, National Yang Ming Chiao Tung University, Taipei, Taiwan
[4] Department of Otorhinolaryngology, Kaohsiung Show Chwan Memorial Hospital, Kaohsiung, Taiwan
[5] Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Dresden, Germany

[#] equal contribution

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SUPPLEMENTARY MATERIAL

Table S1. Detailed search strategy.

Database	Query
PubMed	((((("COVID-19"[Mesh]) OR ("COVID-19/analysis"[Mesh] OR "COVID-19/complications"[Mesh] OR "COVID-19/therapy"[Mesh])) OR "SARS-CoV-2"[Mesh]) OR ("SARS-CoV-2/analysis"[Mesh] OR "SARS-CoV-2/drug effects"[Mesh]) OR "COVID-19"[TIAB] OR " COVID 19"[TIAB] OR "SARS-CoV-2 Infection"[TIAB] OR "SARS CoV 2 Infection"[TIAB] OR "SARS-CoV-2 Infections"[TIAB] OR "2019 Novel Coronavirus Disease"[TIAB] OR "2019 Novel Coronavirus Infection"[TIAB] OR "2019-nCoV Disease"[TIAB] OR "2019 nCoV Disease"[TIAB] OR "2019-nCoV Diseases"[TIAB] OR "COVID-19 Virus Infection"[TIAB] OR "COVID 19 Virus Infection"[TIAB] OR "COVID-19 Virus Infections"[TIAB] OR "Coronavirus Disease 2019"[TIAB] OR "Coronavirus Disease-19"[TIAB] OR "Coronavirus Disease 19"[TIAB] OR "Severe Acute Respiratory Syndrome Coronavirus 2 Infection"[TIAB] OR "SARS Coronavirus 2 Infection"[TIAB] OR "COVID-19 Virus Disease"[TIAB] OR "COVID 19 Virus Disease"[TIAB] OR "2019-nCoV Infection"[TIAB] OR "2019 nCoV Infection"[TIAB] OR "2019-nCoV Infections"[TIAB] OR "COVID-19 Pandemic"[TIAB] OR "COVID 19 Pandemic"[TIAB] OR "COVID-19 Pandemics"[TIAB] OR "SARS Coronavirus 2"[TIAB] OR "Coronavirus Disease 2019 Virus"[TIAB] OR "2019 Novel Coronavirus"[TIAB] OR "2019 Novel Coronaviruses"[TIAB] OR "Wuhan Seafood Market Pneumonia Virus"[TIAB] OR "SARS-CoV-2 Virus"[TIAB] OR "SARS CoV 2 Virus"[TIAB] OR "SARS-CoV-2 Viruses"[TIAB] OR "2019-nCoV"[TIAB] OR "COVID-19 Virus"[TIAB] OR "COVID 19 Virus"[TIAB] OR "COVID-19 Viruses"[TIAB] OR "Wuhan Coronavirus"[TIAB] OR "COVID19 Virus"[TIAB] OR "COVID19 Viruses"[TIAB] OR "Severe Acute Respiratory Syndrome Coronavirus 2" [TIAB] OR "COVID-19" OR "COVID 19" OR "SARS-CoV-2 Infection" OR "SARS CoV 2 Infection" OR "SARS-CoV-2 Infections" OR "2019 Novel Coronavirus Disease" OR "2019 Novel Coronavirus Infection" OR "2019-nCoV Disease" OR "2019 nCoV Disease" OR "2019-nCoV Diseases" OR "COVID-19 Virus Infection" OR "COVID 19 Virus Infection" OR "COVID-19 Virus Infections" OR "Coronavirus Disease 2019" OR "Coronavirus Disease-19" OR "Coronavirus Disease 19" OR "Severe Acute Respiratory Syndrome Coronavirus 2 Infection" OR "SARS Coronavirus 2 Infection" OR "COVID-19 Virus Disease" OR "COVID 19 Virus Disease" OR "2019-nCoV Infection" OR "2019 nCoV Infection" OR "2019-nCoV Infections" OR "COVID-19 Pandemic" OR "COVID 19 Pandemic" OR "COVID-19 Pandemics" OR "SARS Coronavirus 2" OR "Coronavirus Disease 2019 Virus" OR "2019 Novel Coronavirus" OR "2019 Novel Coronaviruses" OR "Wuhan Seafood Market Pneumonia Virus" OR "SARS-CoV-2 Virus" OR "SARS CoV 2 Virus" OR "SARS-CoV-2 Viruses" OR "2019-nCoV" OR "COVID-19 Virus" OR "COVID 19 Virus" OR "COVID-19 Viruses" OR "Wuhan Coronavirus" OR "COVID19 Virus" OR "COVID19 Viruses" OR "Severe Acute Respiratory Syndrome Coronavirus 2") AND (("Olfactory Training"[Mesh]) OR ("Olfactory Training/classification"[Mesh] OR "Olfactory Training/history"[Mesh] OR "Olfactory Training/methods"[Mesh] OR "Olfactory Training/standards"[Mesh]) OR "Olfactory Training"[TIAB] OR "Olfactory Trainings"[TIAB] OR "Training, Olfactory"[TIAB] OR "Smell Training"[TIAB] OR "Smell Trainings"[TIAB] OR "Training, Smell"[TIAB] OR "Smell Rehabilitation"[TIAB] OR "Rehabilitation, Smell"[TIAB] OR "Smell Rehabilitations"[TIAB] OR "Olfactory Rehabilitation"[TIAB] OR "Olfactory Rehabilitations"[TIAB] OR "Rehabilitation, Olfactory"[TIAB] OR "Olfactory Training" OR "Olfactory Trainings" OR "Training, Olfactory" OR "Smell Training" OR "Smell Trainings" OR "Training, Smell" OR "Smell Rehabilitation" OR "Rehabilitation, Smell" OR "Smell Rehabilitations" OR "Olfactory Rehabilitation" OR "Olfactory Rehabilitations" OR "Rehabilitation, Olfactory")
Cochrane Library	ID Search Hits #1 MeSH descriptor: [COVID-19] explode all trees 4374 #2 MeSH descriptor: [COVID-19] explode all trees and with qualifier(s): [complications - CO, therapy - TH] 450 #3 MeSH descriptor: [SARS-CoV-2] explode all trees 2282 #4 MeSH descriptor: [SARS-CoV-2] explode all trees and with qualifier(s): [drug effects - DE] 67 #5 COVID-19 OR COVID 19 OR SARS-CoV-2 Infection OR SARS CoV 2 Infection OR SARS-CoV-2 Infections OR 2019 Novel Coronavirus Disease OR 2019 Novel Coronavirus Infection OR 2019 nCoV Disease OR COVID-19 Virus Infection OR COVID 19 Virus Infection OR COVID-19 Virus Infections OR Coronavirus Disease 2019 OR Coronavirus Disease-19 OR Coronavirus Disease 19 OR Severe Acute Respiratory Syndrome Coronavirus 2 Infection OR SARS Coronavirus 2 Infection OR COVID-19 Virus Disease OR COVID 19 Virus Disease OR 2019 nCoV Infection OR COVID-19 Pandemic OR COVID 19 Pandemic OR COVID-19 Pandemics OR SARS Coronavirus 2 OR Coronavirus Disease 2019 Virus OR 2019 Novel Coronavirus OR 2019 Novel Coronaviruses OR Wuhan Seafood Market Pneumonia Virus OR SARS-CoV-2 Virus OR SARS CoV 2 Virus OR SARS-CoV-2 Viruses OR COVID-19 Virus OR COVID 19 Virus OR COVID-19 Viruses OR Wuhan Coronavirus OR COVID19 Virus OR COVID19 Viruses OR Severe Acute Respiratory Syndrome Coronavirus 2 16894 #6 #1 OR #2 OR #3 OR #4 OR #5 16895 #7 MeSH descriptor: [Olfactory Training] explode all trees 1 #8 MeSH descriptor: [Olfactory Training] explode all trees and with qualifier(s): [classification - CL, history - HI, methods - MT, standards - ST] 0 #9 Olfactory Training OR Olfactory Trainings OR Training, Olfactory OR Smell Training OR Smell Trainings OR Training, Smell OR Smell Rehabilitation OR Rehabilitation, Smell OR Smell Rehabilitations OR Olfactory Rehabilitation OR Olfactory Rehabilitations OR Rehabilitation, Olfactory 399 #10 #7 OR #8 OR #9 399 #11 #5 AND #10 77

Database	Query
Embase	('coronavirus disease 2019'/exp OR 'covid 19' OR 'sars-cov-2 infection' OR 'sars cov 2 infection' OR 'sars-cov-2 infections' OR '2019 novel coronavirus disease' OR '2019 novel coronavirus infection' OR '2019-ncov disease' OR '2019 ncov disease' OR '2019-ncov diseases' OR 'covid-19 virus infection' OR 'covid 19 virus infection' OR 'covid-19 virus infections' OR 'coronavirus disease 2019' OR 'coronavirus disease-19' OR 'coronavirus disease 19' OR 'severe acute respiratory syndrome coronavirus 2 infection' OR 'sars coronavirus 2 infection' OR 'covid-19 virus disease' OR 'covid 19 virus disease' OR '2019-ncov infection' OR '2019 ncov infection' OR '2019-ncov infections' OR 'covid-19 pandemic' OR 'covid 19 pandemic' OR 'covid-19 pandemics' OR 'sars coronavirus 2' OR 'coronavirus disease 2019 virus' OR '2019 novel coronavirus' OR '2019 novel coronaviruses' OR 'wuhan seafood market pneumonia virus' OR 'sars-cov-2 virus' OR 'sars cov 2 virus' OR 'sars-cov-2 viruses' OR '2019 ncov' OR 'covid-19 virus' OR 'covid 19 virus' OR 'covid-19 viruses' OR 'wuhan coronavirus' OR 'covid19 virus' OR 'covid19 viruses' OR 'severe acute respiratory syndrome coronavirus 2') AND ('olfactory training'/exp OR 'olfactory training' OR 'olfactory trainings' OR 'training, olfactory' OR 'smell training' OR 'smell trainings' OR 'training, smell' OR 'smell rehabilitation' OR 'rehabilitation, smell' OR 'smell rehabilitations' OR 'olfactory rehabilitation' OR 'olfactory rehabilitations' OR 'rehabilitation, olfactory')
Scopus	TITLE-ABS-KEY ("COVID-19" OR "COVID 19" OR "SARS-CoV-2 Infection" OR "SARS CoV 2 Infection" OR "SARS-CoV-2 Infections" OR "2019 Novel Coronavirus Disease" OR "2019 Novel Coronavirus Infection" OR "2019 nCoV Disease" OR "COVID-19 Virus Infection" OR "COVID 19 Virus Infection" OR "COVID-19 Virus Infections" OR "Coronavirus Disease 2019" OR "Coronavirus Disease-19" OR "Coronavirus Disease 19" OR "Severe Acute Respiratory Syndrome Coronavirus 2 Infection" OR "SARS Coronavirus 2 Infection" OR "COVID-19 Virus Disease" OR "COVID 19 Virus Disease" OR "2019 nCoV Infection" OR "COVID-19 Pandemic" OR "COVID 19 Pandemic" OR "COVID-19 Pandemics" OR "SARS Coronavirus 2" OR "Coronavirus Disease 2019 Virus" OR "2019 Novel Coronavirus" OR "2019 Novel Coronaviruses" OR "Wuhan Seafood Market Pneumonia Virus" OR "SARS-CoV-2 Virus" OR "SARS CoV 2 Virus" OR "SARS-CoV-2 Viruses" OR "COVID-19 Virus" OR "COVID 19 Virus" OR "COVID-19 Viruses" OR "Wuhan Coronavirus" OR "COVID19 Virus" OR "COVID19 Viruses" OR "Severe Acute Respiratory Syndrome Coronavirus 2") AND TITLE-ABS-KEY ("Olfactory Training" OR "Olfactory Trainings" OR "Training, Olfactory" OR "Smell Training" OR "Smell Trainings" OR "Training, Smell" OR "Smell Rehabilitation" OR "Rehabilitation, Smell" OR "Smell Rehabilitations" OR "Olfactory Rehabilitation" OR "Olfactory Rehabilitations" OR "Rehabilitation, Olfactory")
Web of Science	TS=((COVID-19 OR COVID 19 OR SARS-CoV-2 Infection OR SARS CoV 2 Infection OR SARS-CoV-2 Infections OR 2019 Novel Coronavirus Disease OR 2019 Novel Coronavirus Infection OR 2019 nCoV Disease OR COVID-19 Virus Infection OR COVID 19 Virus Infection OR COVID-19 Virus Infections OR Coronavirus Disease 2019 OR Coronavirus Disease-19 OR Coronavirus Disease 19 OR Severe Acute Respiratory Syndrome Coronavirus 2 Infection OR SARS Coronavirus 2 Infection OR COVID-19 Virus Disease OR COVID 19 Virus Disease OR 2019 nCoV Infection OR COVID-19 Pandemic OR COVID 19 Pandemic OR COVID-19 Pandemics OR SARS Coronavirus 2 OR Coronavirus Disease 2019 Virus OR 2019 Novel Coronavirus OR 2019 Novel Coronaviruses OR Wuhan Seafood Market Pneumonia Virus OR SARS-CoV-2 Virus OR SARS CoV 2 Virus OR SARS-CoV-2 Viruses OR COVID-19 Virus OR COVID 19 Virus OR COVID-19 Viruses OR Wuhan Coronavirus OR COVID19 Virus OR COVID19 Viruses OR Severe Acute Respiratory Syndrome Coronavirus 2) AND (Olfactory Training OR Olfactory Trainings OR Training, Olfactory OR Smell Training OR Smell Trainings OR Training, Smell OR Smell Rehabilitation OR Rehabilitation, Smell OR Smell Rehabilitations OR Olfactory Rehabilitation OR Olfactory Rehabilitations OR Rehabilitation, Olfactory))

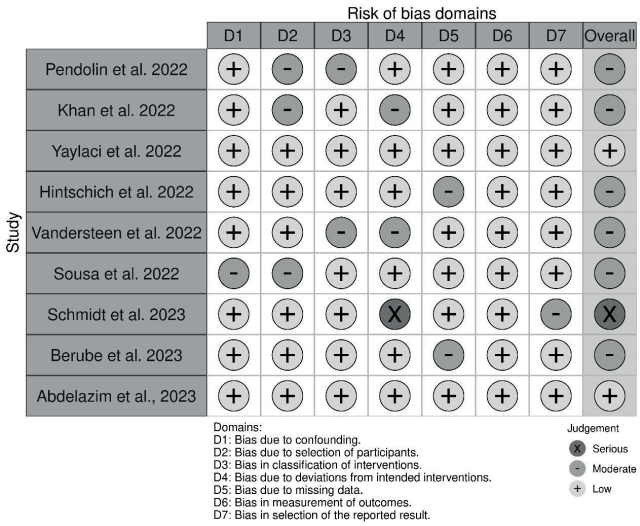

Figure S1. Risk of bias of each included study. The Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was used to evaluate quality of included studies.

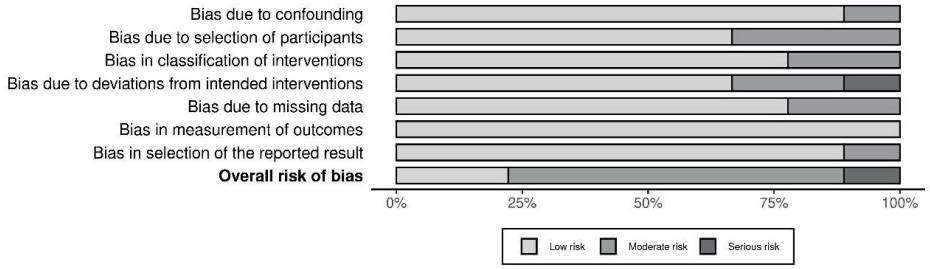

Figure S2. Summary of risk of bias. Overall, 67% of the studies are subject to moderate risk of bias while another 11% are subject to serious risk of bias.

Source	P–value	Tau2	Tau	I2	MD (95% CI)
Omitting Pendolin et al., 2022	< .001	0	0	0%	2.17 [1.71; 2.62]
Omitting Berube et al., 2023	< .001	0	0	0%	2.26 [1.77; 2.76]
Omitting Hintschich et al., 2022	< .001	0	0	0%	1.90 [1.21; 2.59]
Omitting Vandersteen et al., 2022	< .001	0.0492	0.2219	0%	2.05 [1.46; 2.63]
Total	< .001	0	0	0%	2.14 [1.69; 2.58]

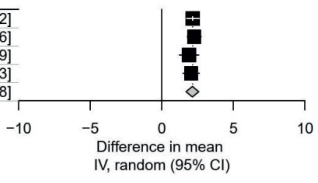

Figure S3. Influence analysis of visual analog scale (VAS). After removing the studies one by one, results of VAS score remain within the confidence interval.

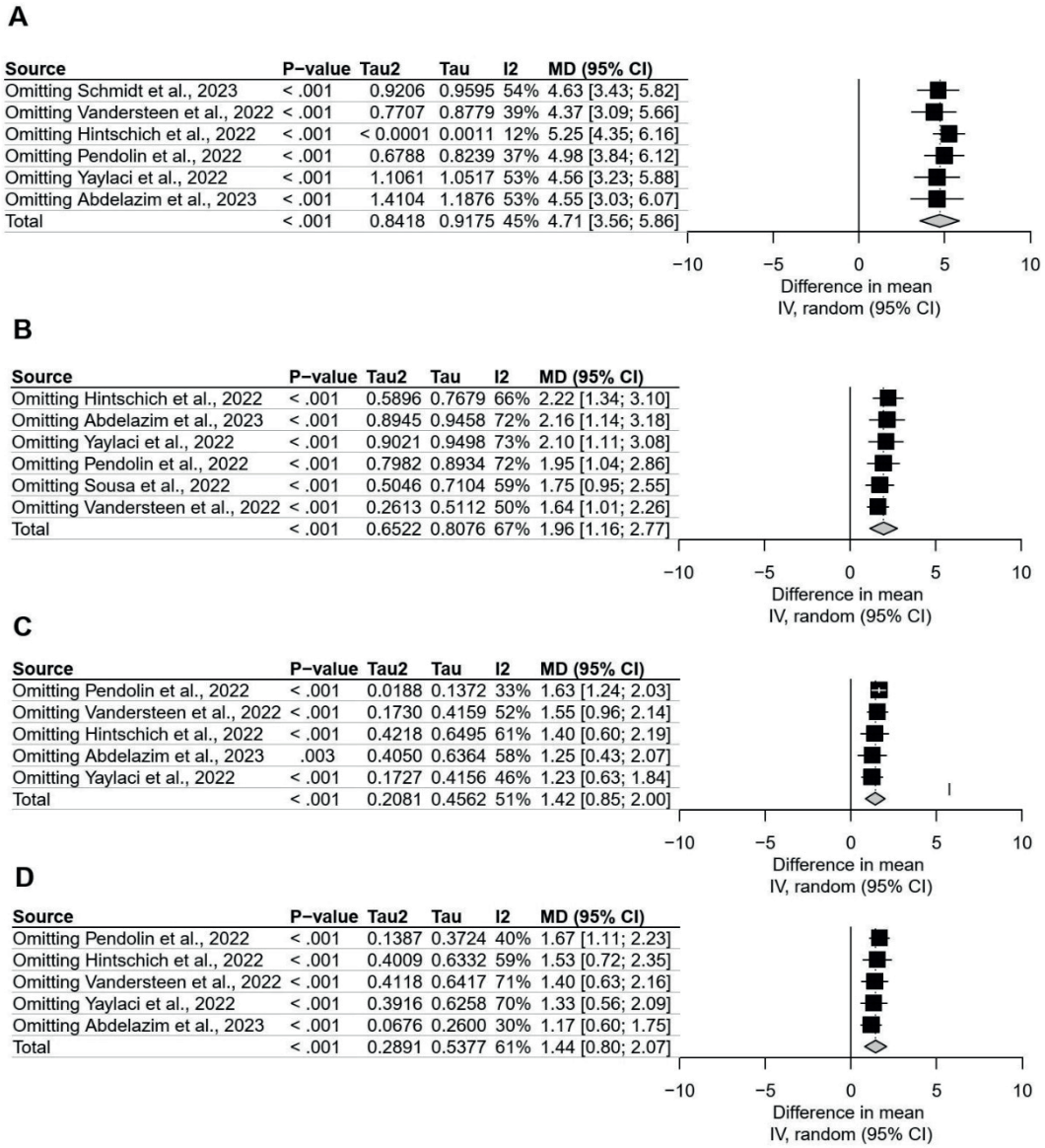

Figure S4. Influence analysis of Sniffin' Sticks test. After study removed one by one, results of (A)TDI, (B) threshold, (C) discrimination, and (D) identification scores remain within the confidence interval of the primary result.

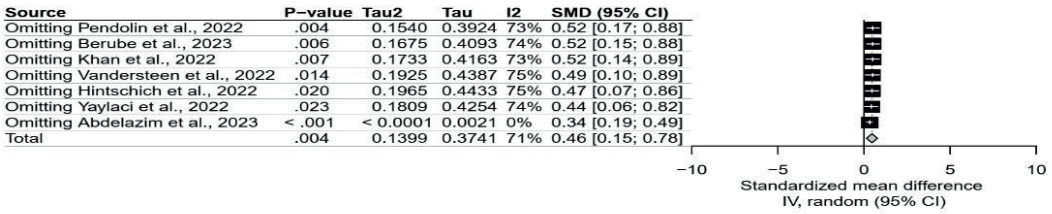

Figure S5. Influence analysis of identification tests. In influence analysis, results remain within the confidence interval of the primary result after removing studied one by one.

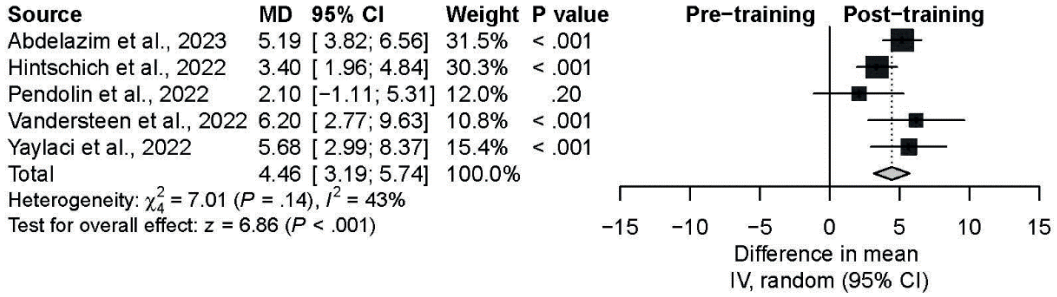

Figure S6. Sensitivity analysis by removing Schimidt et al., 2023 in SST-TDI. After removing Schmidt et al., 2023, the pooled effect size remains statistically significant, indicating that the removal of this study did not alter the overall significance of the findings.