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ORIGINAL ARTICLE

Self-reported olfactory and gustatory dysfunction and psychophysical testing in screening for COVID-19: A systematic review and meta-analysis

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Additional Supporting Information can be found in the online version of this article.

Conflicts of interest
K.S.: speaker's honoraria from Organon, Mylan, and Menarini; D.D.S.: research support, advisory board fees from GlaxoSmithKline and Sanofi, and speaker's fees from Medtronic; the remaining authors have no conflicts of interest.

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Abstract

Background: A substantial proportion of coronavirus disease-2019 (COVID-19) patients demonstrate olfactory and gustatory dysfunction (OGD). Self-reporting for OGD is widely used as a predictor of COVID-19. Although psychophysical assessment is currently under investigation in this role, the sensitivity of these screening tests for COVID-19 remains unclear. In this systematic review we assess the sensitivity of self-reporting and psychophysical tests for OGD.

Methods: A systematic search was performed on PubMed, EMBASE, and ClinicalTrials.gov from inception until February 16, 2021. Studies of suspected COVID-19 patients with reported smell or taste alterations were included. Data were pooled for meta-analysis. Sensitivity, specificity, and diagnostic odds ratio (DOR) were reported in the outcomes.

Results: In the 50 included studies (42,902 patients), self-reported olfactory dysfunction showed a sensitivity of 43.9% (95% confidence interval [CI], 37.8%-50.2%), a specificity of 91.8% (95% CI, 89.0%-93.9%), and a DOR of 8.74 (95% CI, 6.67-11.46) for predicting COVID-19 infection. Self-reported gustatory dysfunction yielded a sensitivity of 44.9% (95% CI, 36.4%-53.8%), a specificity of 91.5% (95% CI, 87.7%-94.3%), and a DOR of 8.83 (95% CI, 6.48-12.01). Olfactory psychophysical tests analysis revealed a sensitivity of 52.8% (95% CI, 25.5%-78.6%), a specificity of 88.0% (95% CI, 53.7%-97.9%), and a DOR of 8.18 (95% CI, 3.65-18.36). One study used an identification test for gustatory sensations assessment.

Conclusion: Although demonstrating high specificity and DOR values, neither self-reported OGD nor unvalidated and limited psychophysical tests were sufficiently sensitive in screening for COVID-19. They were not suitable adjuncts in ruling out the disease.

KEYWORDS
COVID-19, gustatory, olfactory, sensitivity, smell, specificity, taste

1 | INTRODUCTION

Olfactory and gustatory dysfunctions (OGDs) have been acknowledged worldwide as cardinal features of coronavirus disease-2019 (COVID-19).[1,2] Recently, the prevalence of OGD among the COVID-19 population has been widely investigated and found to affect 50% to 56% of COVID-19 patients.[3–5] However, failure to recognize OGD due to other serious comorbidity, in addition to some patients' lack of awareness of these symptoms, may underestimate the true prevalence of OGD in COVID-19.[6] In addition, there was a surge of reports investigating the use of disposable psychophysical test kits in assisting diagnosis of COVID-19. Both self-reported OGD and psychophysical tests have been employed in screening COVID-19 patients in countries with a high incidence of disease.[7–9]

Such hypotheses are of interest in the investigation of the value of acute loss of smell and taste as a predictor of COVID-19 disease. To date, the sensitivity of these tests for screening severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection remains unclear, although they have been preliminarily utilized as screening tools. We systematically searched the literature and pooled the data of current studies to assess the accuracy of self-reporting and psychophysical tests for OGD as screening tools for COVID-19 diagnosis.

2 | METHODS

The study protocol was registered on PROSPERO under registration number CRD42021235047. This systematic review followed The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[10]

2.1 | Study selection

Systematic searches were performed on electronic databases, including PubMed, EMBASE, and ClinicalTrials.gov, from inception until February 16, 2021. Manual searches for references of included studies and additional sources were conducted. See Table S1 for more details regarding the search strategy. Experimental (randomized controlled trials [RCTs] or quasi-RCTs) and observational (case-control, cohort) studies of participants of all ages that reported the diagnostic accuracy values of OGD and the corresponding 95% confidence interval (CI) for COVID-19 were included. The "gold standard" diagnostic criteria for COVID-19 infection were based on reverse transcriptase–polymerase chain reaction (RT-PCR). Olfactory dysfunction (OD) was defined as loss of pure olfactory function (hyposmia, anosmia).[7] Gustatory dysfunction (GD) was categorized as taste-GD (loss of sweet, sour, bitter, salty, and umami),[2,7] flavor-GD (loss of olfactory patterns of taste),[2,7,11] and unspecified GD with no clear definition. Non-English articles and preprints were excluded. Two reviewers (H.P. and P.S.) independently performed titles and abstracts screening. The full texts of first-round screening were assessed for final eligibility. Any disagreement during the study selection was resolved by the judgment of the corresponding author (K.S.).

2.2 | Data extraction

Two reviewers (M.P.H. and P.S.) extracted data from eligible studies following the predetermined data sheet, which included study design, characteristics of the population, olfactory and gustatory functions tests, features of OGD. The outcomes were sensitivity, specificity, and diagnostic odds ratio (DOR), and positive and negative likelihood ratio (LR) of self-reported and psychophysical screening tests of OGD, OD, and GD.

2.3 | Risk-of-bias assessment

The methodologic quality of included studies was assessed using the updated Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tools with 4 domains: patient selection; index test; reference standard; and flow and timing.[12] This scoring system estimated the quality of each study by giving a score of 1 point for each "low" value, 0 point for each "high" value, and 0.5 point for each "unclear" value. The maximum score was 7. Two reviewers (M.P.H. and P.S.) independently appraised the risk of bias of each item as low, high, or unclear. Any discrepancies were resolved by the corresponding author (K.S.).

2.4 | Data synthesis and statistical analysis

We created 2 × 2 tables for the binary COVID-19 outcome of each study to compute true positives/false positives/true negatives/false negatives of OGD. Data synthesis for any index test reported in at least 4 studies was undertaken using bivariate mixed-effects logistic regression models employing xtmelogit (MIDAS and METANDI packages) from STATA version 16.1 (StataCorp LP, College Station, TX).[13,14] The pooled sensitivity, specificity, LR, and DOR for OGD were presented in a random-effects model. Forest plots for sensitivity and specificity were presented

as summary points and 95% CI with Cochran's Q and I^2 statistic. Hierarchical summary receiver-operating characteristic (HSROC) curves and prediction contours were plotted to illustrate the summary operating point and confidence region, including the calculated area under curve (AUC). Publication bias was investigated by funnel plot and Deek's test. $p < 0.1$ was considered as indicative of plot asymmetry.[15]

2.5 | Subgroup and meta-regression analyses

We conducted subgroup and univariate meta-regression analyses to explore the heterogeneity and potential factors that may influence DTA when having at least 10 studies. The potential covariables were location of study (Europe, North America, South America, Asia, Australia, and Africa), study design (case-control, cohort), onset pattern (clear acute onset, unclear onset), blinding of reference test result (blinded, unblinded), type of OGD (OD, taste-GD, flavor-GD, unspecified GD), study participant (health-care workers, unspecified population), QUADAS-2 score (continuous data), and sample size (continuous data).

3 | RESULTS

3.1 | Study selection

A total of 2113 abstracts were retrieved for screening, 114 full-text articles were assessed for eligibility, and 50 studies[7–9,16–62] meeting inclusion criteria were selected in the qualitative synthesis. Data from 49 studies[7-9,16-43,45-62] were pooled in the meta-analysis. Figure 1 displays the flowchart of study selection adhering to PRISMA criteria.

3.2 | Description of studies

There were 42,902 participants (9059 COVID-19 patients) among 50 studies. Of 36,168 patients with sex reported, 22,068 were women. Mean age ranged from 28 to 67 years. Table 1 presents the characteristics of included studies.[7–9,16–62] There were 16 case-control studies[21–23,26–28,32,33,36,44,45,47,53,55,59,62] and 34 cohort studies.[7–9,16–20,24,25,29–31,34,35,37–43,46,48–52,54,56–58,60,61] Sample size ranged from 83 to 11,483 patients. Studies originated from 6 continents including Europe, North America, South America, Asia, Australia, and Africa. Thirteen studies[18,20,25,34–37,40,43,45,49,56,59] were carried out with clusters of health-care workers. Presence of blinding of RT-PCR test results was adhered to in 22 (44%) of the studies.[7–9,19,20,24,28,29,31,34,35,37,38,40–42,48,49,55,57–59] The definition of acute onset (<14-day duration) of OGD was clearly described in 11 studies.[8,20,24,29,32,33,35,39,40,54,60] Further details of included studies are presented in Table S2.

3.3 | Evaluation of bias

Patient selection, index tests, and flow and timing contributed significant sources of bias (Figs. S1 and S2). The included studies were prone to selection bias. Case-control studies had a bias when they selected specific populations such as health-care workers. In addition, reporting RT-PCR test results before assessment of OGD and a notable difference in time interval between RT-PCR and OGD test led to potential blinding and timing bias. The mean QUADAS-2 score was 4.3 of 7 for studies using self-reported smell and taste loss and 4.8 of 7 for psychophysical chemosensory tests.

3.4 | Diagnostic value of self-reported olfactory dysfunction

The pooled estimate from 37 studies[7,16–24,26,29–36,38,39,43,45,47–59,61,62] yielded an overall sensitivity of 43.9% (95% CI, 37.8%-50.2%) and specificity of 91.8% (95% CI, 89.0%-93.9%) for predicting COVID-19 infection. The pooled positive LR was 5.36 (95% CI, 4.20-6.81) and negative LR was 0.61 (95% CI, 0.55-0.67). The pooled DOR was 8.74 (95% CI, 6.67-11.46) (Table 2 and Fig. S3).

3.5 | Diagnostic value of self-reported gustatory dysfunction

The pooled estimate from 24 studies[7,16,17,21–23,26,28,30,32,34,36,38,39,43,45,47,50,51,55,57,58,61,62] displayed an overall sensitivity of 44.9% (95% CI, 36.4%-53.8%) and specificity of 91.5% (95% CI, 87.7%-94.3%) for predicting COVID-19 infection. The pooled positive LR (95% CI) was 5.31 (95% CI, 3.99-7.07) and negative LR was 0.60 (95% CI, 0.52-0.69). The pooled DOR was 8.83 (95% CI, 6.48-12.01) (Table 2 and Fig. S4). Taste-GD, flavor-GD, and unspecified GD were reported in 5,[7,30,32,39,51] 1,[7] and 19 studies,[16,17,21–23,26,28,34,36,38,43,45,47,50,55,57,58,61,62] respectively.

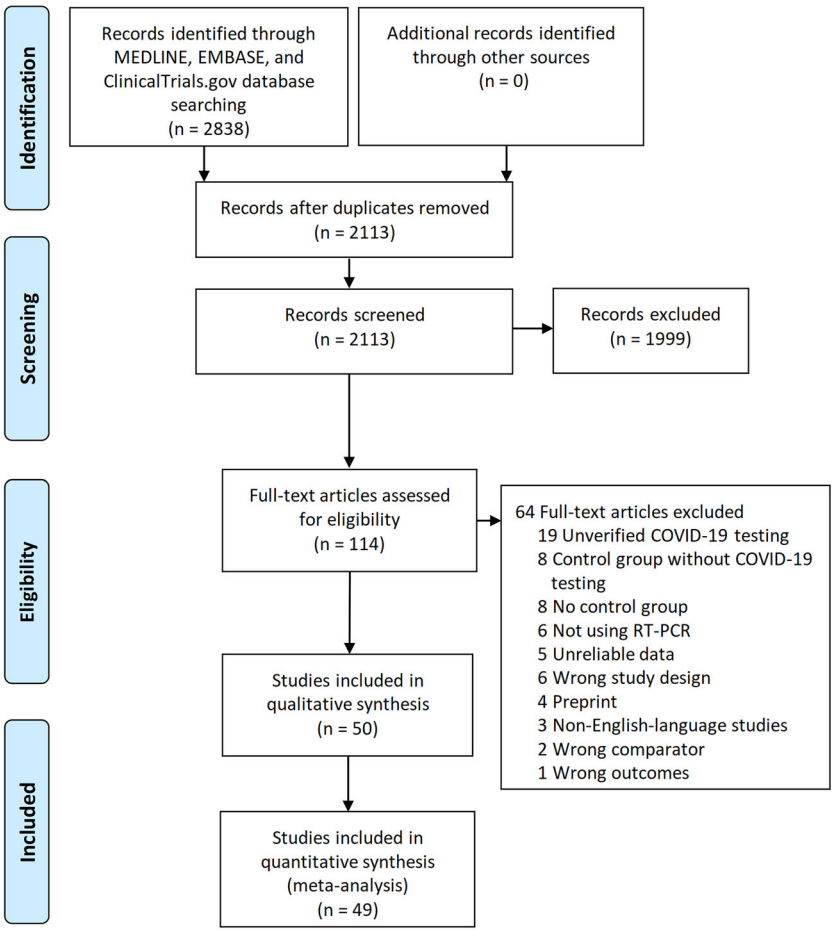

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

3.6 | Diagnostic value of self-reported olfactory or gustatory dysfunction

The pooled estimate from 19 studies[7,16,17,22,25–27,29,33,34,37,40–42,46,54,55,60,62] displayed the overall sensitivity of 45.0% (95% CI, 35.3%- 55.8%) and specificity of 92.7% (95% CI, 88.7%-95.3%). The pooled positive LR was 4.34 (95% CI, 2.99-8.24) and negative LR was 0.61 (95% CI, 0.42-0.90). The pooled DOR was 10.46 (95% CI, 7.85-13.94) (Table 2 and Fig. S5).

3.7 | Subgroup and meta-regression analyses

Statistical heterogeneity and inconsistency were found in most diagnostic values (Figs. 2–4, and Figs. S3–S5 and S7). Subgroup and meta-regression analyses were performed to explore the plausibility of heterogeneity (Tables S3-S6 and Figs. S3-S7).

When subgroup by location was analyzed, there was a significant difference in DOR of OD ($p < 0.01$) and GD ($p < 0.01$), but not OGD ($p = 0.06$). Studies performed in North America yielded the highest DOR, followed by Europe and then South America. There was no difference among regions for sensitivity and specificity. Cohort studies showed significantly lower sensitivity (37.9 [95% CI, 27.6-49.4]) than case-control studies (65.2 [95% CI, 59.8-70.2]) in self-reported OGD ($p = 0.03$). There was no significant difference between subgroups in OD ($p = 0.11$) and GD ($p = 0.54$). The meta-regression showed that a blinded RT-PCR test result ($p < 0.01$) affected the test accuracy. Blinding of RT-PCR test result showed significantly lower sensitivity (34.1 [95% CI, 23.0-47.2]) than unblinded study (53.7 [95% CI, 50.0-65.9]) in self-reported OGD. There was no statistically significant difference between clear acute onset and unclear onset subgroups in accuracy of OD ($p = 0.94$), GD ($p = 0.54$), and OGD ($p = 0.09$). There was no statistically significant difference between healthcare workers and unspecified populations in accuracy of OD ($p = 0.79$), GD ($p = 0.71$), and OGD ($p = 0.31$). Studies with higher QUADAS-2 score tended to have lower sensitivity and higher specificity of OD ($p < 0.01$) and GD ($p < 0.01$), but this was not statistically significant for OGD ($p = 0.09$). Meta-regression showed that sample size may be responsible for heterogeneity in accuracy of OGD ($p = 0.01$), but not in OD ($p = 0.08$) and GD ($p = 0.23$).

TABLE 1 Characteristics of the 50 included studies*

Characteristic	Studies (N = 50)	Patients (N = 42,902)
Year of publication		
2020	42 (82.0%)	39,017 (90.9%)
2021	9 (18.0%)	3885 (9.1%)
Study design		
Case-control	16 (32.0%)	3324 (7.7%)
Cohort	34 (68.0%)	39,578 (92.3%)
Region		
Europe	29 (58.0%)	29,059 (67.7%)
North America	9 (18.0%)	2986 (7.0%)
South America	4 (8.0%)	2779 (6.5%)
Asia	6 (12.0%)	2865 (6.7%)
Australia	1 (2.0%)	2935 (6.8%)
Africa	1 (2.0%)	2278 (5.3%)
COVID-19 patients	50 (100.0%)	9059 (21.1%)
Setting of care		
Single hospital/center	30 (60.0%)	15,866 (37.0%)
Multiple hospitals/centers	15 (30.0%)	22,822 (53.2%)
Unclear	5 (10.0%)	4214 (9.8%)
Reference test		
RT-PCR	50 (100.0%)	42,902 (100.0%)
Blinding of RT-PCR test result		
Blinded	28 (56.0%)	27,121 (63.2%)
Unblinded	22 (44.0%)	15,781 (36.8%)
Study participants		
Health-care workers	13 (26.0%)	7213 (16.8%)
Unspecified population	37 (74.0%)	35,689 (83.2%)
Acute onset of OGD (<14 days)		
Clear	11 (22.0%)	6683 (15.6%)
Unclear	39 (78.0%)	36,219 (84.4%)
Focused type of diagnostic testing		
Self-report OGD test	44 (88.0%)	40,733 (94.9%)
OGD Psychophysical test	6 (12.0%)	2169 (5.1%)

*Data expressed as number (%).
COVID-19 = coronavirus disease-2019; OGD = olfactory or gustatory dysfunction; RT-PCR = reverse transcription-polymerase chain reaction.

3.8 | Evaluation of publication bias

Overall, there was an absence of publication bias by evaluation of funnel plot asymmetry regarding OD ($p = 0.10$), GD ($p = 0.10$), and OGD ($p = 0.17$) (Fig. S8).

3.9 | Olfactory and gustatory psychophysical tests

Five studies[7–9,44,52] used 7 chemosensory OGD tests as a screening tool for suspected COVID-19 patients. There were 4 olfactory identification tests with different numbers and types of odors.[7,9,44,52] Two studies reported use of olfactory threshold testing with ethanol[8] and 1-butanol solutions.[44] One study[44] used an identification test to assess gustatory sensations of sweet and salty. Mangal et al reported 2 tests without cutoff and dichotomous data for extracting data.[44] The pooled DTA of olfactory psychophysical tests displayed a sensitivity of 52.8% (95% CI, 25.5%-78.6%) and specificity of 88.0% (95% CI, 53.7%-97.9%). The pooled positive LR was 4.39 (95% CI, 1.46-13.3) and negative LR was 0.54 (95% CI, 0.35-0.82). The pooled DOR was 8.18 (95% CI, 3.65-18.36). Data are shown

TABLE 2 Diagnostic accuracy of olfactory and gustatory tests for diagnosing coronavirus-2019

Test	Patients (studies), n	Sensitivity (95% CI), %	Specificity (95% CI), %	Positive LR (95% CI)	Negative LR (95% CI)	Diagnostic OR (95% CI)
Self-reporting						
OD	23,294 (37)	43.9 (37.8-50.2)	91.8 (89.0-93.9)	5.35 (4.20-6.81)	0.61 (0.55-0.67)	8.74 (6.67-11.46)
GD	14,275 (24)	44.9 (36.4-53.8)	91.5 (87.7-94.3)	5.31 (3.99-7.07)	0.60 (0.52-0.69)	8.83 (6.48-12.01)
Flavor-GD	809 (1)	25.9 (15.3-39.0)	97.7 (96.4-98.7)	11.40 (6.02-21.70)	0.76 (0.65-0.88)	15.10 (7.13-31.90)
Taste-GD	2453 (5)	45.0 (22.1-70.2)	89.6 (73.0-96.5)	4.34 (2.29-8.24)	0.61 (0.42-0.90)	7.07 (3.71-13.49)
Unspecified GD	11,822 (19)	44.7 (36.1-53.7)	91.8 (88.1-94.6)	5.57 (4.07-7.63)	0.61 (0.52-0.69)	9.27 (6.54-13.14)
OGD	26,029 (19)	45.3 (35.3-55.8)	92.7 (88.7-95.3)	6.17 (4.60-8.26)	0.59 (0.50-0.70)	10.46 (7.85-13.94)
Psychophysical assessment						
OD	1915 (4)	52.8 (25.5-78.6)	88.0 (53.7-97.9)	4.39 (1.46-13.3)	0.54 (0.35-0.82)	8.18 (3.65-18.36)
Identification test OD[9]	832 (1)	81.6 (71.0-89.5)	42.1 (38.2-46.1)	1.41 (1.24-1.60)	0.44 (0.27-0.71)	3.22 (1.78-5.83)
Pocket Smell Test[52]	139 (1)	19.4 (11.1-30.5)	95.5 (87.5-99.1)	4.34 (1.31-14.40)	0.84 (0.74-0.96)	5.15 (1.50-17.50)
CODA[7]	809 (1)	34.5 (22.5-48.1)	97.6 (96.2-98.6)	14.40 (8.07-25.6)	0.67 (0.56-0.81)	21.40 (10.6-43.5)
Threshold Test OD[8]	135 (1)	75.9 (56.5-89.7)	67.0 (57.2-75.8)	2.30 (1.64-3.23)	0.36 (0.19-0.70)	6.38 (2.53-16.00)
Identification test GD[9]	832 (1)	84.2 (74.0-91.6)	36.4 (32.9-39.9)	1.32 (1.18-1.48)	0.43 (0.26-0.74)	3.05 (1.63-5.69)

CI = confidence interval; CODA = Clinical Olfactory Dysfunction Assessment; GD = gustatory dysfunction; LR = likelihood ratio; OD = olfactory dysfunction; OGD = olfactory or gustatory dysfunction; OR = odds ratio.

in Table 2 and Table S7. Among the studies noted, Villerabel et al described their Clinical Olfactory Dysfunction Assessment, which yielded the highest DOR of 21.40 (95% CI, 10.60-43.50).[7]

4 | DISCUSSION

In this systematic review and meta-analysis we have provided precise estimates of diagnostic accuracy parameters associated with OGD in predicting COVID-19 infection. The overall DTA of OGD was found to be moderate with an area under the SROC of 0.82. The presence of smell and taste alterations had high specificity (92%) and DOR values (10.5). The false positive rate was low. Based on the likelihood ratio assessed by this study, a positive OGD in a suspected COVID-19 patient with a 20% pretest probability of smell and taste alterations increased the posttest probability of COVID-19 to 61%, and negative OGD reduced the posttest probability to 13%. Several psychophysical tests of OGD have been developed and validated to use as COVID-19 screening tools. However, these tests, and self-reported OGD exhibited poor sensitivity (45%) as revealed by our study and reported in previous studies.[5,63] Given the importance of a screening tool with high sensitivity, OGD should be interpreted carefully before developing a prediction model for COVID-19.[64] When combining symptoms were used for a prediction model and applied to the data from smartphone-based application users, only 17.42% of participants were likely to have COVID-19.[65] A systematic review identified 7 models for identifying people at risk in the general population. Almost all prediction models were poorly reported, and at high risk of bias.[66] Although psychophysical tests had high specificity and DOR values, they were not suitable to rule out disease. Screening with these tests with high risk of false negative may result in undiagnosed COVID-19 patients who have normal smell and taste. Suspected COVID-19 patients with impaired olfactory and gustatory function still require a confirmatory nasopharyngeal and throat swab for RT-PCR.

In general, self-reported OGD results in a sensitivity of <50%. When subgroup analyses were performed, cohort studies showed significantly decreased sensitivity (38%). Blinding of the RT-PCR test result showed significantly decreased sensitivity (34%). Studies with higher QUADAS-2 scores had lower sensitivity. Large sample size was associated with accuracy of OGD. The quality of the included studies impacted the sensitivity of self-reported OGD. In general, higher quality studies reported lower sensitivity. Subgroup analysis by regions showed that studies performed in North America yielded the highest DOR, followed by Europe and then South America. Distinct viral strains in various locations may also lead to discrepancies in olfactory and gustatory alteration based on geography. According to the ZOE COVID Symptom Study app, the Delta variant is currently dominant and responsible for 95% of consecutive cases in the UK in July 2021.[67] COVID-19–infected patients with this variant tend to have symptoms resembling "something like a bad cold," including headache and rhinorrhea rather than shortness of breath

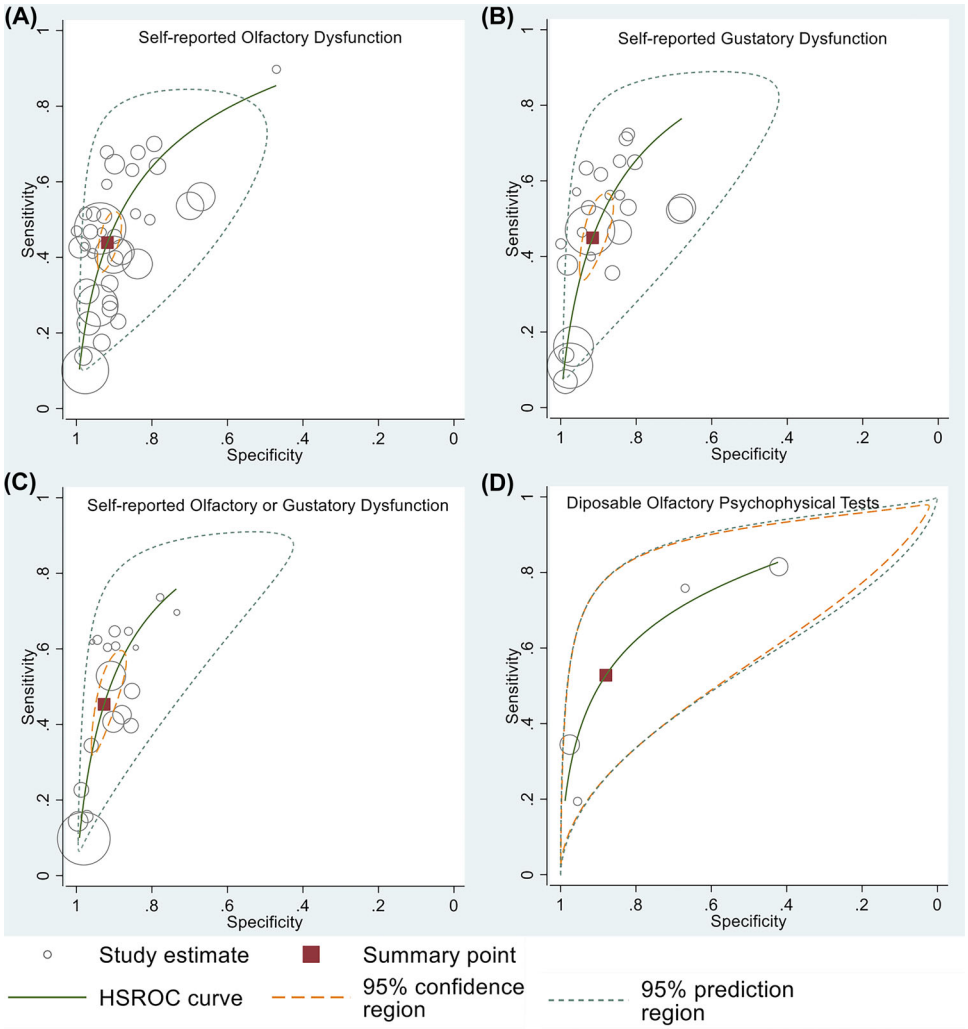

FIGURE 2 Hierarchical summary receiver-operating characteristic curves: **(A)** self-reported olfactory dysfunction; **(B)** self-reported gustatory dysfunction; **(C)** self-reported olfactory or gustatory dysfunction; and **(D)** disposable olfactory psychophysical tests.

and loss of taste and smell.[67] The vaccination status (fully vaccinated, partially vaccinated, and unvaccinated) may also affect olfactory outcomes.[67] Unfortunately, the vaccination rates continue to vary among countries, providing further challenges for interpretation. Moreover, sensory impairments caused by SARS-CoV-2 continue to serve as popular discussion topics and often covered in the lay press.[68] Further meta-analyses should compare the prevalence DTA of OGD in different years that reflect the existence of common virus strains.

Previous studies and meta-analyses pooled unverified, self-reported, and mixed data for OGD, which may overestimate the actual accuracy of screening for OGD.[5,65,69,70] Our study confirms and extends the limited evidence of earlier meta-analyses.[5,69,70] Liou et al pooled data from 6 studies (27,749 participants), 2 of which used data from patients without a verified COVID-19 status and 2 others using a control group without RT-PCR testing.[69] Pang et al pooled data from 19 studies (17,417 participants) to evaluate the diagnostic accuracy of self-reported OD.[5] However, the included studies had discrepancies regarding the definition of self-reported OD, selected controls without proportional representation of the target population (patients with influenza), and type of reference test. Struyf et al conducted a comprehensive systematic review covering all potential symptoms to predict COVID-19 without the evaluation of psychophysical tests.[70] Our findings demonstrate the improvement in precision and clinical utility of diagnostic parameters. For instance, previous meta-analysis[69] reported the specificity for OGD as 81.7% (95% CI, 76.5%-85.9%); with more rigorous study selection criteria, and access to more evidence, we estimated a higher specificity of 92.7% (95% CI, 88.7%-95.3%). We also performed subgroup analysis and meta-regression to investigate interactions of potential confounding factors that may affect screening accuracy. This may have uncovered a missing piece required to address this issue. The results of meta-regression shed light on limited evidence that potential

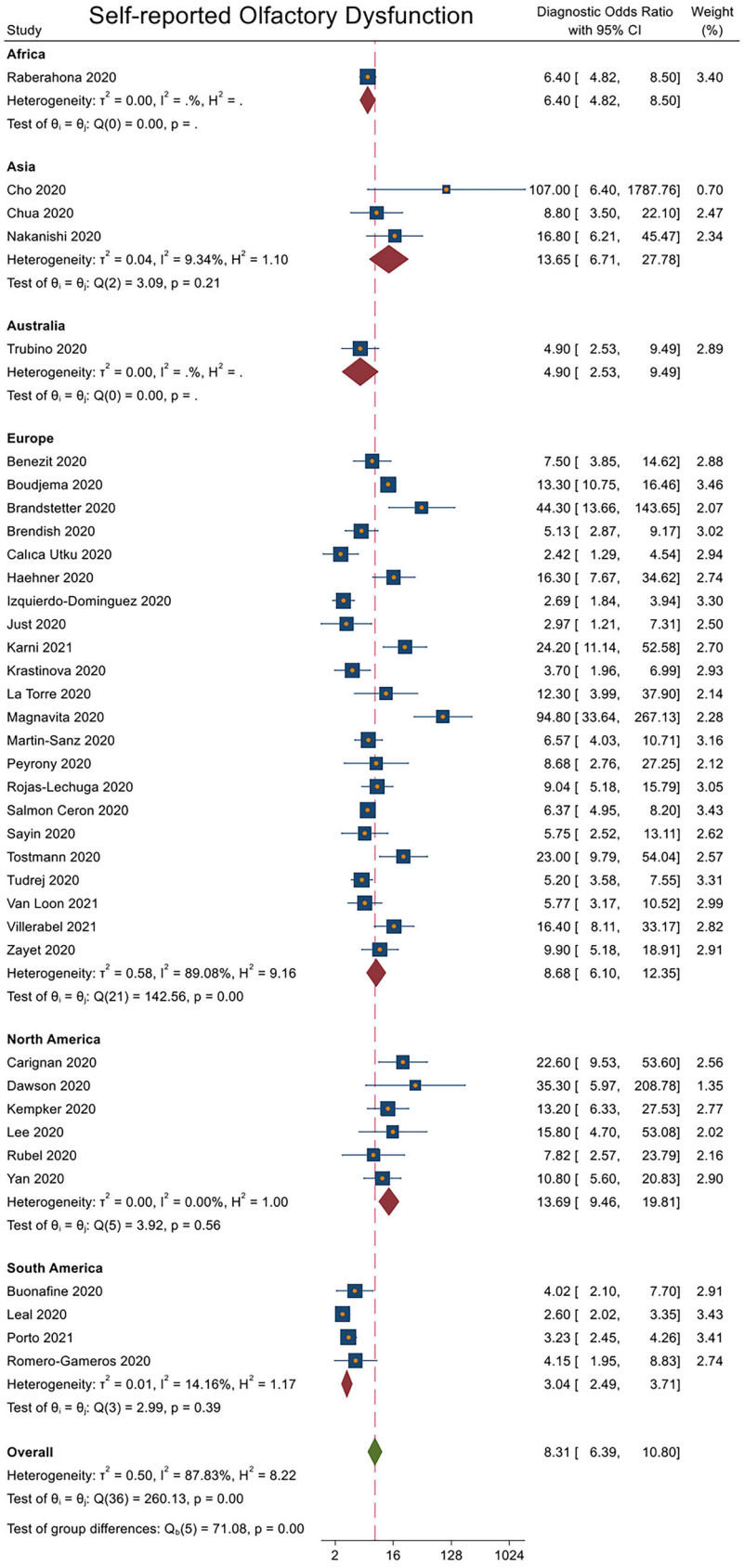

FIGURE 3 Summary diagnostic odds ratios of self-reported olfactory and subgroup analyses by region.

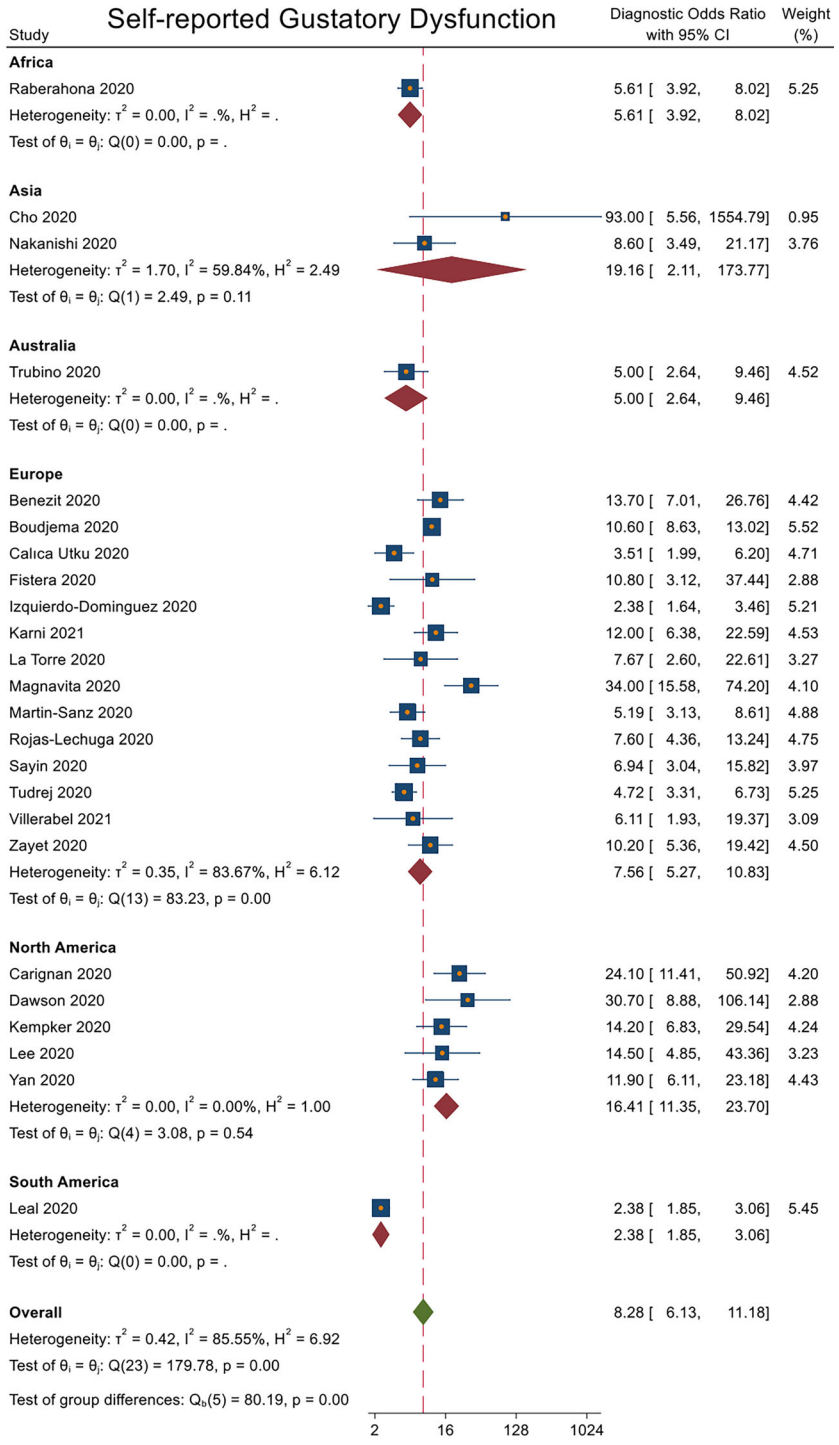

FIGURE 4 Summary diagnostic odds ratios of self-reported gustatory and subgroup analyses by region.

confounders should be recognized when conducting a diagnostic study of OGD.

This is the first systematic review and meta-analysis that has focused on both self-reporting and psychophysical OGD tests for COVID-19 and there appears to be no correlation between them. Bordin et al found the lack of correlation when observing the olfactory recovering in patients with COVID-19.[71] Le Bon et al showed inconsistency between self-reporting gustatory dysfunction and "Taste Strips" test score.[72] However, these studies alone cannot lead to a firm conclusion due to limitations of time-frame between onset of symptoms and performance of psychophysical tests.[71,72] A visual analog scale has been used for the quantitative evaluation of OGD in the included studies and demonstrated a significant difference in self-rated olfactory and gustatory function between positive and negative COVID-19 groups.[8,23,29,30,32,51–53,55] Psychophysical tests have been modified from previously

validated tests[8] or developed as rapid assessment tools[7,9] to assess OGD in patients with suspected COVID-19. A general lack of validation in terms of odors and poorly designed methodology resulted in unreliable diagnostic accuracy.[44] The discrepancy of the time-frame between the onset and the assessment of sensory impairments[72] and the lack of measuring the most affected domain "threshold" of OD[71,73] may cause heterogeneous sensitivity. Despite the enthusiasm for developing quick COVID-19 screening tools, the current disposable tests for OGD cannot replace RT-PCR or serology tests. However, formal validated psychophysical tests are recommended to assess olfactory and gustatory recovery.[1,72]

Our systematic review has several limitations. Self-reported OGD was the predominant assessment tool, subject to the heterogeneity of self-report questionnaires and symptom-onset time-points. The meta-regression showed no statistically significant difference in diagnostic accuracy between patients with and without acute onset of OGD. However, additional studies with well-designed questionnaires are needed to confirm these summary estimates. Furthermore, our study also included case-control studies, which often influence diagnostic accuracy.[66] Although sensitivity and specificity of a test are not affected by the prevalence and characteristics of the disease, the lack of data from specific regions led to inconclusive summary estimates. When interpreting the DOR of OGD, a high value was observed in every meta-analysis, indicating that smell and taste alteration is helpful for predicting potential COVID-19. However, if false positives and negatives are weighted differently, DOR is less valuable and inadequate as a differentiator of disease.[74] Influenza patients also have smell alteration and may produce false positives, especially during flu season.

Significant heterogeneity was found in many subjective assessments and subgroup analyses. Additional studies with a nested case-control or cohort design are needed to limit selection bias and confirm the summary estimates of OGD. Future studies in different geographic regions, phases of disease, strains of SARS-CoV-2, and seasons are warranted to explore plausible confounders that may affect the accuracy of screening for COVID-19.

5 | CONCLUSION

This study highlights the roles of self-reporting olfactory and gustatory dysfunction and psychophysical tests in screening for COVID-19. With reported DOR and specificity, the presence of new-onset smell and taste alterations may suggest a high probability of positive COVID-19 PCR testing, especially with well-documented history or confirmed psychophysical assessment. Nevertheless, neither self-reporting nor unvalidated psychophysical tests were sufficiently sensitive in screening for COVID-19 and their potential correlation should thus be interpreted with caution. This systematic review and meta-analysis has provided critical findings that could aid in developing future studies and diagnostic advancements to aid in the utility of OGD for predicting COVID-19. When subgroup by location was analyzed, studies performed in North America yielded the highest DOR, followed by Europe and then South America.

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AUTHOR CONTRIBUTIONS

M.P.H.: conception, study design, search, study selection, data collection, data analysis, drafting the article, and final approval; P.S: search, study selection, data collection, drafting the article, and final approval; T.M.: drafting the article, and final approval; D.D.S.: drafting the article, and final approval; K.S.: conception, study design, data analysis, drafting the article, and final approval.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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