Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

MAYO CLINIC

ORIGINAL ARTICLE

Smell and Taste Dysfunction in Patients With COVID-19: A Systematic Review and Meta-analysis

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Abstract

Objective: To estimate the prevalence of olfactory and gustatory dysfunctions (OGDs) among patients infected with novel coronavirus disease 2019 (COVID-19).

Methods: A systematic review was conducted by searching MEDLINE, EMBASE, and the preprint server MedRxiv from their inception until May 11, 2020, using the terms *anosmia* or *hyposmia* or *dysosmia* or *olfactory dysfunction* or *olfaction disorder* or *smell dysfunction* or *ageusia* or *hypogeusia* or *dysgeusia* or *taste dysfunction* or *gustatory dysfunction* or *neurological* and *COVID-19* or *2019 novel coronavirus* or *2019-nCoV* or *SARS-CoV-2*. The references of included studies were also manually screened. Only studies involving patients with diagnostic-confirmed COVID-19 infection were included. Random-effects meta-analysis was performed.

Results: Twenty-four studies with data from 8438 patients with test-confirmed COVID-19 infection from 13 countries were included. The pooled proportions of patients presenting with olfactory dysfunction and gustatory dysfunction were 41.0% (95% CI, 28.5% to 53.9%) and 38.2% (95% CI, 24.0% to 53.6%), respectively. Increasing mean age correlated with lower prevalence of olfactory (coefficient = −0.076; P=.02) and gustatory (coefficient = −0.073; P=.03) dysfunctions. There was a higher prevalence of olfactory dysfunctions with the use of objective measurements compared with self-reports (coefficient = 2.33; P=.01). No significant moderation of the prevalence of OGDs by sex was observed.

Conclusion: There is a high prevalence of OGDs among patients infected with COVID-19. Routine screening for these conditions could contribute to improved case detection in the ongoing COVID-19 pandemic. However, to better inform population screening measures, further studies are needed to establish causality.

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Novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an outbreak that emerged in China in December 2019, has rapidly evolved into a global pandemic.[1] To contain the outbreak, effective screening, rapid diagnosis, and isolation of infected individuals are essential. These measures require sound understanding of the clinical presentation of the disease. Early observations in China revealed several nonspecific signs and symptoms related to COVID-19 infection, including fever, dry cough, dyspnea, myalgia, and anorexia.[2,3]

Recently, an association between COVID-19 and olfactory and gustatory dysfunctions (OGDs) has been raised.[4] In the United Kingdom, a surge in patients seeking medical advice for recent onset of self-diagnosed loss of sense of smell has been reported.[5] Similarly, an outbreak of olfactory dysfunctions in Iran was observed.[6] Furthermore, Walker et al[7] have noted an increase in Internet searches for smell-related information in several countries and hypothesize

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that smell dysfunction may be an underrecognized symptom of COVID-19 infection. Consequently, the British Association of Otorhinolaryngology[8] and the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS)[9] proposed that symptoms of OGDs be added to the list of screening tools for possible COVID-19 infection. Nevertheless, the proportion and characteristics of patients infected with COVID-19 who experience OGDs are not thoroughly understood.

Thus, we conducted a systematic review and meta-analysis to estimate the prevalence of OGDs among patients infected with COVID-19. We also examined the potential effects of factors such as age, sex, and assessment method on the prevalence of OGDs. At the time of commencing this review (May 3, 2020), no systematic review and meta-analysis on the topic had been published.

METHODS

This systematic review follows the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[10] and the Cochrane collaboration handbook[11] (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). Given the urgent need for information to inform clinical decision making in the context of the COVID-19 pandemic, prior registration of the review protocol was not feasible.

Database Search

To identify appropriate studies for the review, searches were performed in MEDLINE, EMBASE, and the preprint server MedRxiv using the terms *anosmia* or *hyposmia* or *dysosmia* or *olfactory dysfunction* or *olfaction disorder* or *smell dysfunction* or *ageusia* or *hypogeusia* or *dysgeusia* or *taste dysfunction* or *gustatory dysfunction* or *neurological* and *COVID-19* or *2019 novel coronavirus* or *2019-nCoV* or *SARS-CoV-2* (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org). The search was initially performed on May 3, 2020, and last updated on May 11, 2020. No language restrictions were applied. The reference lists of included studies were also hand-searched for additional articles.

Study Selection and Evaluation

Only studies with data for patients with test-confirmed COVID-19 status were eligible for inclusion. Moreover, because our objective was to estimate the prevalence of smell and taste dysfunctions separately, studies that reported a composite of smell and taste dysfunction without presenting individual data for each outcome were excluded. When studies from the same center recruiting patients during the same period were present, we selected the one with the larger sample size or more detailed information. Furthermore, we excluded case series involving fewer than 10 patients, as well as commentaries, editorials, and reviews.

Quality Assessment

The methodological quality of each study was assessed using a tool developed by Murad et al.[12] This tool involves 8 items under 4 domains: selection, ascertainment, causality, and reporting (Supplemental Table 3, available online at http://www.mayoclinicproceedings.org). Only items applicable to the studies included in the review were evaluated. Numeric scoring was not performed and an overall judgment about methodological quality of the included studies was made as per the questions deemed most critical in the specific clinical scenario.[12]

Data Extraction and Analysis

Data were extracted independently by 2 reviewers (A.A.A. and R.O.-A.), and any disagreements were resolved through consensus. For each study, first author name, country, participant mean age, proportion of females, and percentage with smell or taste disorders were extracted. If a study assessed OGDs based on patients' self-report and objective measurements, we prioritized the data from the objective assessments.

Analyses were conducted using Stata SE software, version 16 (StataCorp). Meta-analysis of prevalence was conducted using

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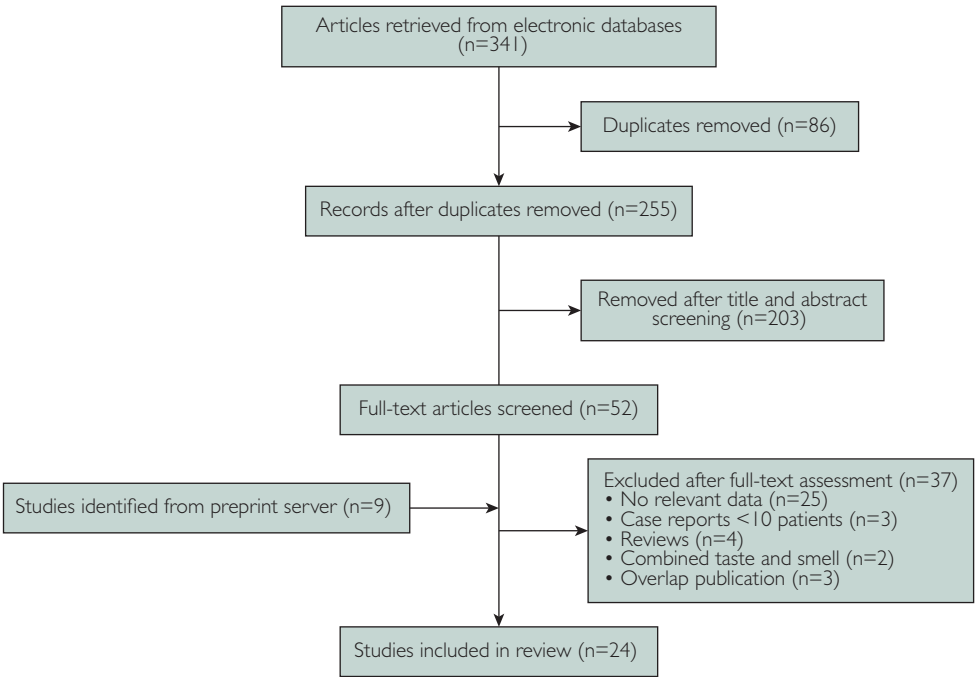

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of study selection process.

the STATA *Metaprop* command,[13] using the Freeman-Tukey double arcsine transformed proportions to account for variance instability.[11] Owing to the anticipated between-study heterogeneity, a random-effects model was used. Between-study heterogeneity was quantified using the I^2 statistic.[11] An I^2>50% was considered to represent substantial heterogeneity. Leave-1-out sensitivity analyses were performed to assess the stability of pooled estimates. Using the STATA *Metareg* command,[14] meta-regression was conducted to determine the influence of study mean age, proportion of females, assessment method (subjective vs objective), and region of study (Europe vs other) on the pooled prevalence. The syntax for the metaregression was "Metareg logitEventRate age [proportion of females] region [assessment method], wsse(logitEventSE)," where logitEventRate=log(p/(1 − p)) and logitEventSE=[sqrt(1/(p×Total) + 1/((1 − p)×Total))], and p indicates proportion and Total indicates sample size. A 2-tailed P<.05 was considered significant. Because our study relied on published literature, institutional ethical review was not required.

RESULTS

Study Characteristics

The searches in MEDLINE and EMBASE retrieved 341 citations. Following removal of duplicates and screening of titles and abstracts, 52 articles were selected for full-text evaluation. Fifteen articles were retained after full-text assessment. Nine additional studies were identified from the preprint server, resulting in 24 studies being included in the review (Figure 1).[15-38] The included studies were from China (n=1),[24] the Netherlands (n=1),[15] United Kingdom (n=1),[19] Iran (n=1),[23] Israel (n=1),[25] South Korea (n=1),[30] United States (n=2),[21,29] France (n=4),[17,18,26,37] Germany (n=4),[20,31,32,36] Italy (n=4),[16,27,35,38] Spain (n=2),[22,34] Belgium (n=1),[33] and 1 multicountry study across Europe (France, Spain, Italy, Belgium, and Switzerland).[28] The studies involved a total of 8438 patients.

TABLE. Characteristics of Included Studies

Reference, year	Countries	OGD Assessment Method	Sample Size	Mean Age (y)	Female (%)	Olfactory Dysfunction, n (%)	Gustatory Dysfunction, n (%)
Tostmann et al,[15] 2020	Netherlands	Self-report (questionnaire)	79	NR	NR	37/79 (46.8)	NR
Giacomelli et al,[16] 2020	Italy (Milan)	Self-report (interview)	59	60.0	32.2	14/59 (23.7)	17/59 (28.8)
Bénézit et al,[17] 2020	France (Western)	Self-report (questionnaire)	68	NR	NR	31/68 (45.6)	42/68 (61.8)
Klopfenstein et al,[18] 2020	France (Eastern)	Self-report (medical files)	114	NR	NR	54/114 (47.4)	NR
Tomlins et al,[19] 2020	UK (Bristol)	Self-report (admission records)	95	75.0	37	3/95 (3.2)	NR
Luers et al,[20] 2020	Germany (Cologne)	Self-report (questionnaire)	72	38.0	43.1	53/72 (73.6)	50/72 (6.4)
Yan et al,[21] 2020	US (California)	Self-report (medical files or telephone interview)	Admitted = 26 Ambulatory = 102	Admitted = 53.5 Ambulatory = 43.0	Admitted = 65.4 Ambulatory = 49.0	Admitted = 7/26 (26.9) Ambulatory = 68/102 (66.7)	Admitted = 6/26 (23.1) Ambulatory = 64/102 (62.7)
Beltrán-Corbellini et al,[22] 2020	Spain (Madrid)	Self-report (questionnaire)	79	61.6	39.2	25/79 (31.6)	28/79 (35.4)
Moein et al,[23] 2020	Iran	Objective measurement (UPSIT microencapsulation test)	60	46.6	33.3	59/60 (98.3)	NR
Mao et al,[24] 2020	China (Wuhan)	Self-report (interview)	214	52.7	59.3	11/214 (5.1)	12/214 (5.6)
Levinson et al,[25] 2020	Israel (Tel Aviv)	Self-report (questionnaire)	42	34.0	45.2	14/42 (33.3)	15/42 (35.7)
Fontanet et al,[26] 2020	France (Northern)	Self-report (questionnaire)	171	NR	67.8	50/171 (29.2)	52/171 (30.4)
Vaira et al,[27] 2020	Italy	Objective measurement (CCCRC test)	33	47.2	66.6	25/33 (75.8)	18/33 (54.5)
Lechien et al,[28] 2020	Europe (France, Spain, Italy, Belgium, Switzerland)	Self-report (questionnaire)	1420	39.2	67.7	997/1420 (70.2)	770/1420 (54.2)
Aggarwal et al,[29] 2020	US (Des Moines, Iowa)	Self-report (electronic medical records or physical notes)	16	65.5	25.0	3/16 (18.8)	3/16 (18.8)
Lee et al,[30] 2020	South Korea (Daegu city)	Self-report (interview)	3191	44.0	63.6	389/3191 (12.2)	353/3191 (11.1)
Hornuss et al,[31] 2020	Germany (Freiburg)	Objective measurement (Sniffin Sticks)	45	56.0	44.4	38/45 (84.4)	NR
Just et al,[32] 2020	Germany (North Rhine-Westphalia, Rhineland-Palatinate, Hesse, Saxony-Anhalt)	Self-report (structured documentation form)	27	NR	NR	7/27 (25.9)	NR
Lechien et al,[33] 2020	Belgium (Mons)	Objective measurement (olfactory dysfunction: Sniffin Sticks tests) Self-report (gustatory dysfunction, validated NHANES questionnaire)	28	44.0	67.9	21/28 (75.0)	17/28 (60.7)

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TABLE. Continued

Reference, year	Countries	OGD Assessment Method	Sample Size	Mean Age (y)	Female (%)	Olfactory Dysfunction, n (%)	Gustatory Dysfunction, n (%)
Borobia et al,[34] 2020	Spain (Madrid)	Self-report (clinical records)	2226	61.0	51.7	284/2226 (12.8)	NR
Cavagna et al,[35] 2020	Italy (Lombardy, Emilia-Romagna, Piedmont, and Veneto)	Self-report (telephone interview)	14	60.5	28.6	5/14 (36)	4/14 (28.6)
Härter et al,[36] 2020	Germany (human immunodeficiency virus centers)	Self-report (clinical notes)	33	48.0	9.1	6/32 (18.8)	NR
Allenbach et al,[37] 2020	France (Paris)	Self-report (standard form)	152	77	40.1	17/150 (11.3)	NR
Vaira et al,[38] 2020	Italy (Sessari)	Objective measurement (Chemosensitive test)	72	49.2	62.5	60/72 (83.3)	35/72 (48.6)

CCCRC = Connecticut Chemosensory Clinical Research Center; NHANES = National Health and Nutrition Examination Survey; NR = not reported; OGD = olfactory and gustatory dysfunction; UPSIT = University of Pennsylvania Smell Identification Test.

The reported mean age ranged from 34.0 to 77.0 years, and 58.7% (4785 of 8150; 20 studies) of the patients were females (Table).

The methodological assessment of the individual studies is presented in Supplemental Table 4 (available online at http://www.mayoclinicproceedings.org). Because our review included only patients with COVID-19 infection with diagnostic confirmation, bias from nonascertainment of exposure was minimized. However, very few studies had reported use of objective assessment of OGDs, with most relying on unvalidated questionnaires. Thus, studies may experience ascertainment bias. Most studies (20/24; 83%) did not explore other potential causes that may explain the outcome, and they could not establish with certainty that OGDs were absent before COVID-19 infection and therefore causality cannot be implied.

Olfactory Dysfunctions

Of the 24 studies that reported the prevalence of olfactory dysfunction, 21% (5/24) used objective assessments, whereas the rest (19/24; 79%) mainly relied on self-reports. The reported prevalence of olfactory dysfunction ranged from 3.2% to 98.3%, and the pooled prevalence was 41.0% (95% CI, 28.5% to 53.9%; I^2=99.1%; Figure 2). A leave-1-out sensitivity analysis did not significantly change the results (point estimate ranged from 38.1% to 42.1%). The pooled prevalence tended to decrease with increasing mean age of study participants (coefficient = −0.076; 95% CI, −0.135 to −0.016; P=.02) and was higher when objective measurements were used compared with self-reports (coefficient = 2.33; 95% CI, 0.57 to 4.09; P=.01) but was not significantly moderated by sex (coefficient = −0.018; 95% CI, −0.062 to 0.026; P=.39) or study region (coefficient = 0.564; 95% CI, −0.818 to 1.946; P=.40). The variables included in the metaregression altogether explained 51.7% of the between-study variance relative to the prevalence of olfactory dysfunctions. There was no strong evidence of publication bias (funnel plot, Supplemental Figure 1, available online at http://www.mayoclinicproceedings.org; Eggers test, P=.306).

Gustatory Dysfunctions

Fifteen studies involving 5649 patients reported the prevalence of gustatory dysfunctions. Among these, 13% (2/15) used objective assessments, whereas the rest (13/15; 87%) relied mainly on self-reports. The reported prevalence of gustatory dysfunctions ranged from 5.6% to 62.7%, and the pooled prevalence was 38.2% (95% CI, 24.0% to 53.6%; I^2=98.8; Figure 3). A leave-1-out sensitivity analysis did not significantly change the results (point estimate ranged from 36.1% to 41.2%). The pooled prevalence tended to decrease with increasing mean age (coefficient = −0.073; 95% CI, −0.136 to −0.009; P=.03) and was slightly higher across European studies than studies from elsewhere (coefficient = 1.195; 95% CI, 0.118 to 2.272; P=.03). There was no significant moderation by sex (coefficient = −0.022; 95% CI, −0.066 to 0.022; P=.29) or assessment methods (coefficient = 0.439; 95% CI, −1.192 to 2.071; P=.56). The variables included in the metaregression altogether explained 47.9% of the between-study variance relative to the prevalence of gustatory dysfunctions. There was no strong evidence of publication bias (funnel plot, Supplemental Figure 2, available online at http://www.mayoclinicproceedings.org; Eggers test, P=.604).

DISCUSSION

In this systematic review and meta-analysis, we found that about 41% and 38% of diagnostic-confirmed patients with COVID-19 infection presented with olfactory or gustatory dysfunctions, respectively. Increasing age correlated with lower prevalence of OGDs, whereas the use of objective assessment methods correlated with higher prevalence of olfactory dysfunction. No significant moderation of the prevalence of OGDs by sex was noted.

The exact mechanisms underlying OGDs among patients with COVID-19 infection remain unclear. However, olfactory

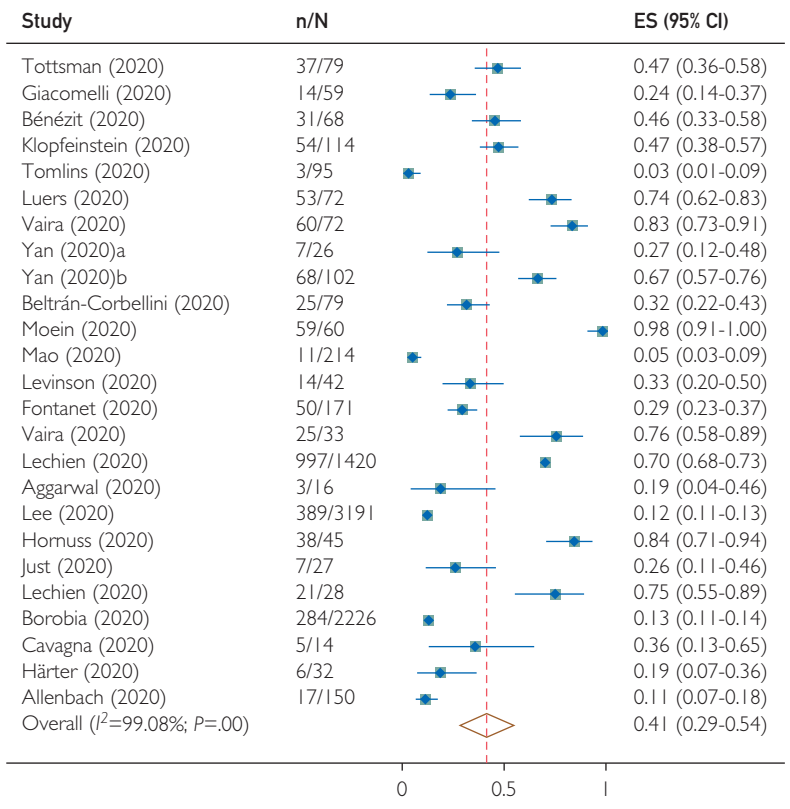

FIGURE 2. Forest plot of proportion of patients with novel coronavirus disease 2019 infection presenting with olfactory dysfunction. ES = proportion; n = number of patients with olfactory dysfunction; N = sample size.

impairment after upper respiratory tract infection is a common occurrence in clinical settings. In particular, postviral olfactory dysfunction has been implicated in 40% of cases of anosmia in adults,[39] with coronaviruses accounting for 10% to 15% of cases.[5] Olfactory dysfunction in COVID-19 infection could be related to the involvement of the olfactory bulb or to peripheral damage of the olfactory receptor cells in the nasal neuroepithelium.[40] This assertion is based on the potential neurotrophic features of SARS-CoV-2. In particular, it has been demonstrated in transgenic mice that after intranasal administration of SARS-CoV (which shares similarities with SARS-CoV-2), the virus could penetrate into the brain through the olfactory bulb, leading to rapid transneuronal spread.[41] It is also well recognized that alterations in the volume and composition of saliva can disturb taste sensation.[42] Previously, epithelial cells lining salivary gland ducts were found to be early target cells of SARS coronavirus infection in the upper respiratory tracts of rhesus macaques.[43] Phylogenetic similarities between SARS-CoV and SARS-CoV-2 mean that the latter could also alter gustatory sensation in affected patients.

The few studies that have evaluated the clinical utility of OGDs in COVID-19 diagnosis have suggested their low sensitivity (23%-43%) and high specificity (93%-99%).[17,44] Regardless, in one study, the sensitivity and specificity of OGDs were reported to be comparable to the sensitivity and specificity of a history of close contact with a confirmed COVID-19 case.[44] An analysis of 237 entries from the AAO-HNS COVID-19 Anosmia Reporting Tool

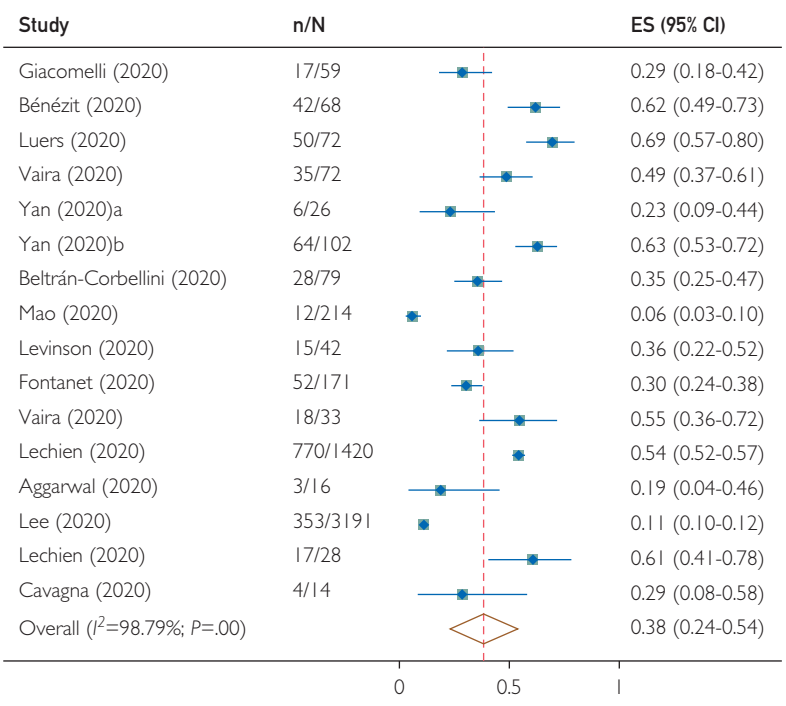

FIGURE 3. Forest plot of proportion of patients with novel coronavirus disease 2019 infection presenting with gustatory dysfunction. ES = proportion; n = number of patients with gustatory dysfunction; N = sample size.

suggested that anosmia was noted in 73% of patients before the COVID-19 diagnosis and was the initial symptom in 26.6%.[45] Yan et al[21] have also suggested that OGDs may be associated with a milder course of COVID-19 infection. This may also potentially explain the lower prevalence of OGDs with increasing mean age because older people are more likely to experience severe COVID-19 infection compared with younger individuals.[46] Consequently, the potential higher burden of OGDs in patients with milder COVID-19 disease is concerning because such patients may be less likely to be tested but could continue to spread the virus. Thus, public education about symptoms of OGDs may be necessary, and patients experiencing such symptoms should be advised to self-isolate pending confirmatory testing.[9]

It is not yet clear whether the COVID-19–related OGDs are transient or permanent. However, among 23 patients with COVID-19 infection with anosmia in Iran, 75% reported significant improvement over 2 weeks.[32] Moreover, among 237 patients with anosmia on the AAO-HNS COVID-19 Anosmia Reporting platform, 27% reported improvement in symptoms, with the mean time to improvement being 7.2 days.[45] Owing to the high occurrence of anosmia in COVID-19–positive individuals, the indiscriminate use of corticosteroids, particularly in the absence of known head trauma or allergic symptoms, should be discouraged because corticosteroids may escalate COVID-19 infection.[47] Moreover, as more evidence evolves around COVID-19, further studies addressing therapeutic approaches to OGDs among infected patients will be needed.

Our study has some key strengths. Although a recent meta-analysis by Tong et al[48] reported the pooled prevalence of olfactory and gustatory dysfunction among patients with COVID-19 infection as

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52.73% (95% CI, 29.64% to 75.23%) and 43.93% (95% CI, 20.46% to 68.95%), respectively, their analysis was based on 10 studies and involved fewer than 1700 patients. Our study has provided pooled prevalence estimates of OGDs based on data from 24 studies involving more than 8400 patients with diagnostic-confirmed COVID-19 infection from 13 countries. Furthermore, our analysis provides new insights into the potential role of individual-level characteristics such as age and sex in the presentation of OGDs among patients with COVID-19 infection that were not explored in the study by Tong et al.[48]

Despite the strengths of our study, the findings should be interpreted in light of some limitations. There was high statistical heterogeneity, which is largely attributable to the observational nature of the studies. Further investigations revealed that the heterogeneity was not entirely explained by differences in patients' age, proportion of females, region, or OGD assessment methods.

From a methodological perspective, the design of most of the included studies preclude the confirmation of causality between COVID-19 and OGDs. Thus, to better inform population screening measures, further well-designed prospective studies using validated or objective measurement techniques are needed to establish causality. Most studies also recruited patients in European settings, which may affect the generalizability of our findings.

Moreover, few studies used objective assessment methods for establishing the presence of OGDs, whereas most relied on self-reports. These may lead to bias in the ascertainment of OGDs. For example, it is possible for patients to confuse taste function and aroma sense perception,[49] but it was not clear from most studies whether this distinction had been made. In one study by Lechien et al[33] that made this distinction, among 28 patients with COVID-19 infection, 86% experienced aroma disorders, whereas 60.7% experienced taste disorders. However, it was unclear what proportion of patients experienced both symptoms.[33]

Last, because the metaregression relied on study-level characteristics such as mean age and proportion of females, ecological fallacy cannot be entirely ruled out.[11,50] Thus, future studies adopting methods such as the use of individual participant data meta-analysis[11,50] may be essential toward confirming our findings.

CONCLUSION

This study found a high prevalence of OGDs among patients infected with COVID-19. Hence, the consideration of OGDs as part of the screening and diagnostic approaches for COVID-19 could help improve case detection and further curtail the spread of the virus. However, to better inform population screening measures, further well-designed studies are needed to establish causality between COVID-19 and the occurrence of OGDs.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AAO-HNS** = American Academy of Otolaryngology—Head and Neck Surgery; **CCCRC** = Connecticut Chemosensory Clinical Research Center; **COVID-19** = novel coronavirus disease 2019; **NHANES** = National Health and Nutrition Examination Survey; **NR** = not reported; **OGD** = olfactory and gustatory dysfunction; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **UPSIT** = University of Pennsylvania Smell Identification Test

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