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The Prevalence of Olfactory and Gustatory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis

Jane Y. Tong[1]*, Amanda Wong[2]*, Daniel Zhu[2]*, Judd H. Fastenberg, MD[2,3], and Tristan Tham, MD[2,3]

Abstract

Objective. To determine the pooled global prevalence of olfactory and gustatory dysfunction in patients with the 2019 novel coronavirus (COVID 19).

Data Sources. Literature searches of PubMed, Embase, and Scopus were conducted on April 19, 2020, to include arti cles written in English that reported the prevalence of olfac tory or gustatory dysfunction in COVID 19 patients.

Review Methods. Search strategies developed for each data base contained keywords such as *anosmia, dysgeusia*, and *COVID 19*. Resulting articles were imported into a systema tic review software and underwent screening. Data from articles that met inclusion criteria were extracted and ana lyzed. Meta analysis using pooled prevalence estimates in a random effects model were calculated.

Results. Ten studies were analyzed for olfactory dysfunction (n 1627), demonstrating 52.73% (95% CI, 29.64% 75.23%) prevalence among patients with COVID 19. Nine studies were analyzed for gustatory dysfunction (n 1390), demon strating 43.93% (95% CI, 20.46% 68.95%) prevalence. Subgroup analyses were conducted for studies evaluating olfactory dys function using nonvalidated and validated instruments and demonstrated 36.64% (95% CI, 18.31% 57.24%) and 86.60% (95% CI, 72.95% 95.95%) prevalence, respectively.

Conclusions. Olfactory and gustatory dysfunction are common symptoms in patients with COVID 19 and may represent early symptoms in the clinical course of infection. Increased awareness of this fact may encourage earlier diagnosis and treatment, as well as heighten vigilance for viral transmis sion. To our knowledge, this is the first meta analysis to report on the prevalence of these symptoms in COVID 19 patients.

Keywords

COVID 19, coronavirus, SARS CoV 2, anosmia, olfactory, ageusia, gustatory

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The 2019 novel coronavirus (COVID 19) was first identified in Wuhan, Hubei province, China, on December 31, 2019, in association with a severe human respiratory disease.[1-3] Since then, it has spread rap idly, with 2,626,321 confirmed cases reported by the World Health Organization at the time of the writing of this article.[4] Some have postulated that the sinonasal tract may play a sig nificant role in the pathogenesis of this viral infection.[5] Notably, concurrent with the COVID 19 pandemic, authors have reported a recent increase in patients presenting with anosmia,[6] with Mao et al[7] initially reporting on this finding in February 2020. Since then, many anecdotal reports have described new onset olfactory or gustatory dysfunction in conjunction with other well established symptoms of COVID 19 infection, as well as in patients with known pos itive diagnosis of COVID 19 by laboratory testing.[8-13] Due to increasing awareness of olfactory or gustatory dysfunc tion as potential early symptoms of COVID 19 infection, the Centers for Disease Control and Prevention (CDC) recently added ''new loss of taste or smell'' to its list of symptoms that may appear 2 to 14 days after exposure to COVID 19.[14]

In light of these reports, and in an effort to facilitate con fidential reporting of olfactory dysfunction associated with COVID 19, on March 26, 2020, the American Academy of Otolaryngology Head and Neck Surgery (AAO HNS) released the COVID 19 Anosmia Reporting Tool for Clinicians. A pre liminary review of the first 237 submissions to this platform

[1]Drexel University College of Medicine, Philadelphia, Pennsylvania, USA
[2]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, USA
[3]Department of Otolaryngology Head and Neck Surgery, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health System, Hempstead, New York, USA
*These authors contributed equally to this work.

Corresponding Author:
Tristan Tham, MD, Department of Otolaryngology Head and Neck Surgery, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, 130 East 77th Street, 10th Floor, New York, NY 10075, USA.
Email: ttham@northwell.edu

demonstrated that anosmia was present in 73% of cases prior to laboratory diagnosis of COVID 19 and was the presenting symptom in 26.6%.[15,16] Other studies have similarly reported new onset anosmia in the absence of any other symptoms asso ciated with COVID 19.[10]

Although a recent review examined the upper airway symptoms associated with COVID 19, it was limited by the fact that it considered only hospitalized patients and did not include any studies that addressed olfactory or gustatory dis turbances.[17] Given the scale of the current pandemic and the uncertain pathogenesis of COVID 19, a thorough under standing of the related symptomatology is critical to facili tate early diagnosis, treatment, and appropriate vigilance for viral spread. In this context, we performed a systematic review and meta analysis of the literature to further delineate the global prevalence of olfactory and gustatory dysfunction in COVID 19 patients.

Methods

Design

In this meta analysis, our search was performed in accor dance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA)[18] and the Cochrane Handbook of DTA Chapter on searching[19] statements and guidelines. We followed the Meta analysis Of Observational Studies in Epidemiology (MOOSE) Checklist as well.[20] This study was a meta analysis, so registration with our institu tional review board was not required.

Search strategy

Our search used the PubMed (via the web), Scopus, and Embase databases on April 19, 2020, using variations of the following keywords: *coronavirus, COVID 19, anosmia, smell, dysgeusia*, and *taste*. The full search strategy can be found in Supplemental Table S1 (in the online version of the article). In addition, hand searched articles unavailable at the time of the initial search were identified and also included.

Article selection

Two of the authors (A.W., J.Y.T.) independently selected articles in 2 phases: title and abstract screening and full text screening. In the title and abstract screening phase, articles were included if they reported olfactory or gustatory dys function in patients with COVID 19 either in the title or abstract. If the content of the abstract was unclear, the article was selected for full text review.

Full text articles were screened in the second phase using predetermined inclusion and exclusion criteria with their rea sons for exclusion listed in Supplemental Table S2 (in the online version of the article). Through consensus with a third reviewer (D.Z.), full text disagreements were resolved. The following criteria were applied during the second phase of screening. Inclusion criteria: (1) the article reports on preva lence of olfactory or gustatory dysfunction in COVID 19 patients, (2) English language, (3) full text publication, and (4) article is peer reviewed. Exclusion criteria: (1) case report or reviews/meta analyses, (2) animal or laboratory studies, and (3) duplicate literature and duplicate data. There were no disagreements during the article selection process.

Figure 1 depicts the PRISMA flowchart of this meta anal ysis.[18] Using our search strategy, our initial search yielded 119 results. These results were then imported into a systema tic review manager, Covidence.[21] Covidence merged results pertaining to the same study and removed duplications, further reducing the results to 90. Three additional articles were iden tified via hand searching. These 93 articles then underwent title and abstract screening, yielding 24 articles. These 24 arti cles underwent full text review, resulting in the exclusion of 14 studies and yielding a total of 10 studies included for analysis.

Quality Assessment

The risk of bias of included studies was assessed by 2 authors (A.W., D.Z.) using a quality assessment checklist for prevalence studies adapted from Hoy et al.[22] The tool is based on 9 items: representativeness of the national popula tion, representativeness of the target population, use of random selection, likelihood of nonresponse, data source, acceptable case definition, validity of study instrument, simi larity in mode of data collection, and report of numerators and denominators for the parameter of interest. Each item is scored either as 0 (low risk) or 1 (high risk), and the values were summed to generate a rating of low (0 3), moderate (4 6), or high (7 9) risk of bias for the entire main domain. A third author (J.Y.T.) reconciled any disagreements in scoring of the items. Supplemental Table S3 (in the online version of the article) contains each study's score breakdown on each of the 9 items.

Data Extraction

Two authors (A.W., J.Y.T.) reviewed the 10 studies included in the data extraction process, and a third author (D.Z.) was consulted to resolve disagreements. Data points collected include first author's name, year of publication, country of population studied, study design, sample size, age, method of evaluating for olfactory and/or gustatory dysfunction, and reported prevalence of olfactory and/or gustatory dysfunc tion. For studies that stratified different severities of olfac tory or gustatory dysfunction, results were grouped together as either olfactory or gustatory dysfunction, respectively. Vaira et al[23] reported 62 cases of ''chemosensory dysfunc tion'' without specifying whether they represented olfactory or gustatory dysfunction; as a result, the value of 62 was used in both analyses of olfactory and gustatory dysfunction.

Statistical Analysis

All statistical analyses were performed using the MedCalc Statistical Software version 19.2.1 (MedCalc Software Ltd).[24] MedCalc uses a Freeman Tukey transformation[25] to calculate the weighted summary proportion (prevalence) under the fixed or random effects model.[26] Since prevalence would be affected by the spectrum of populations included, as well as

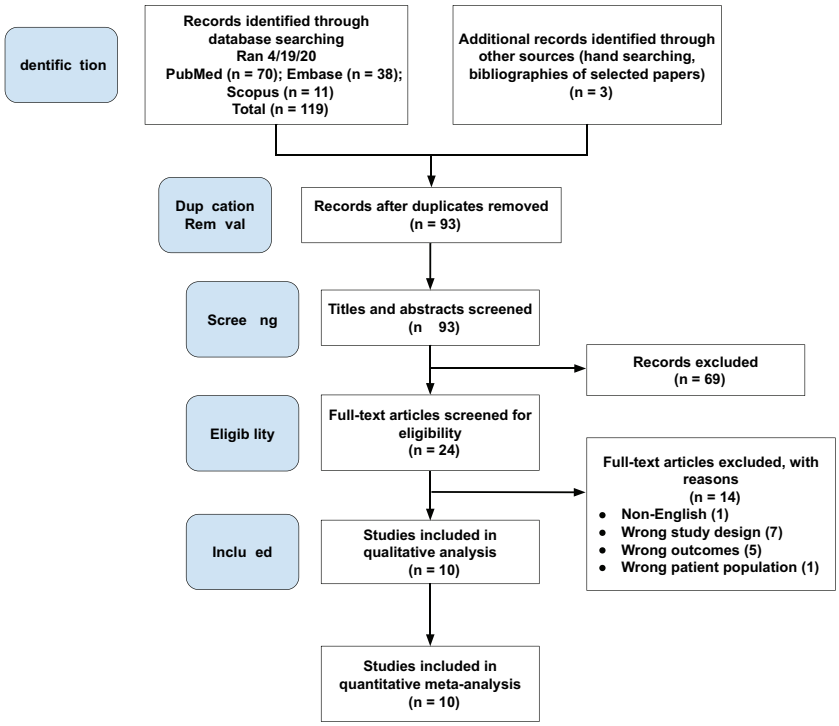

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

the types of instruments used to evaluate for olfactory or gus tatory dysfunction, we expected to find significant heteroge neity across the studies. Thus, an a priori decision was made to select the random effects model because this would give more conservative estimates in scenarios with heterogeneity. Forest plots were created to display the random effects model of the pooled prevalence and 95% confidence interval. The Cochran's Q and Higgins's I^2 statistics were used to assess heterogeneity. A Cochrane's Q P value of $<.1$ and an I^2 $>40\%$ were considered markers of heterogeneity. We planned to perform a subgroup analysis if heterogeneity was detected. Planned subgroup analysis was performed in studies using validated instruments vs studies that did not. Validated instruments included both objective tests and validated subjec tive surveys. Subgroup analysis was not performed for gusta tory dysfunction because there were insufficient studies using validated reporting of gustatory dysfunction.

Results

Study Characteristics

A total of 10 studies, all published in 2020, were included for analysis. **Table 1** summarizes the study characteristics of the included studies. The total sample size of the 10 included studies was 1627 patients, with individual sample sizes rang ing from 59 to 417 patients. The studies were conducted across 9 countries, with 2 studies being multinational.[15,27] Four studies reported data from Italy,[15,23,27,28] 3 from France,[27,29,30] 2 from the United States,[15,31] 2 from Spain,[27,32] and 1 from Iran[33] and China.[7] Other countries that provided data were Belgium, the United Kingdom, and Mexico.[15,27] Three studies assessed olfactory dysfunction via validated instruments[15,27,33] and the other 7 studies via nonvalidated surveys, patient history, and/or physical exami nation findings.[7,23,28-32]

Quality Assessment

The quality assessment checklist for prevalence studies adapted from Hoy et al[22] was used to assess all the studies in this meta analysis across 9 different domains. **Table 2** con tains the overall score for each study and its risk of bias. Analysis of the studies demonstrated high risks of selection bias due to nonrandom selection methods and poor response rates of patients. Most of the studies had low risk of proce dure bias since surveys were administered similarly to patients, but there was a high risk of measurement bias across studies due to many surveys being nonvalidated. Overall, the risk of bias of the studies ranged from moderate to high. The mean overall score of 5.1 indicates an overall moderate risk of bias. Supplemental Table S3 (in the online version of the article) contains each study's breakdown across each of the domains. The studies in this article were mainly cross sectional or retrospective observational studies, which contain an inherent risk of bias if they did not accurately report the number of patients excluded or the reasons for doing so. There is also a risk of recall bias for surveys that were dis tributed to patients after discharge from the hospital as patients

Table 1. Summary of Included Studies.

Source	Country	Study design	Age, y	Total No.	COVID-19 testing	Mode of testing anosmia/dysgeusia	Olfactory dysfunction, No. (%)	Gustatory dysfunction, No. (%)
Beltrán-Corbellini et al[32]	Spain	Case control	Mean (61.6)	79	RT-PCR	Self-report survey	25 (31.65)	28 (35.44)
Bénézit et al[30]	France	CS	Not reported	68	RT-PCR	Self-report survey	51 (75.00)	63 (92.65)
Giacomelli et al[28]	Italy	CS	Median (60)	59	Not reported	Self-report survey	14 (23.73)	17 (28.81)
Kaye et al[15]	United States, Italy, United Kingdom, Mexico, other	CS	Mean (39.6)	237	Not reported[a]	Validated survey[b]	172 (72.57)	Not reported
Klopfenstein et al[29]	France	CS	Mean (47)[c]	114	RT-PCR	History, physical exam	54 (47.37)	46 (40.35)
Lechien et al[27]	Belgium, France, Spain, Italy	CS	Mean (36.9)	417	RT-PCR	Validated survey[d]	357 (85.61)	342 (82.01)
Mao et al[7]	China	Retrospective observational case series	Mean (52.7)	214	RT-PCR	History, physical exam	11 (5.14)	12 (5.61)
Moein et al[33]	Iran	CS	Median (46.6)	60	RT-PCR	Validated instrument,[e] self-report	59 (98.33)	14 (23.33)
Vaira et al[23]	Italy	CS	Not reported	320	Not reported	History, physical exam	62 (19.38)	62 (19.38)
Yan et al[31]	United States	CS	Not reported	59	RT-PCR	Self-report survey	40 (67.80)	42 (71.19)

Abbreviations: COVID-19, coronavirus disease 2019; CS, cross-sectional; RT-PCR, reverse transcription polymerase chain reaction.
[a]Due to limitations in testing, study also included patients with presumed COVID-19.
[b]Using American Academy Otolaryngology Head and Neck Surgery's COVID-19 Anosmia Reporting Tool for Clinicians.
[c]Mean age was only reported for anosmic COVID-19 patients.
[d]Using the short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS) and the National Health and Nutrition Examination Survey (NHANES).
[e]Using the University of Pennsylvania Smell Identification Test (UPIST).

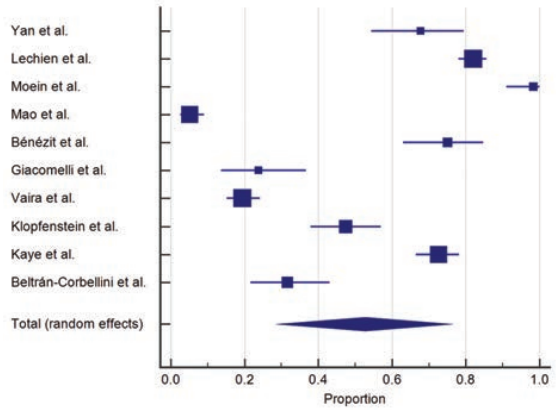

Figure 2. Prevalence of olfactory dysfunction in patients with the 2019 novel coronavirus (COVID-19). Forest plot meta-analysis of the prevalence of olfactory dysfunction in patients with COVID-19 (according to random-effect estimations) demonstrated a 52.73% (95% CI, 29.64%-75.23%) pooled prevalence, as represented by the diamond. Individual study estimates are represented (squares) with 95% confidence intervals (horizontal lines).

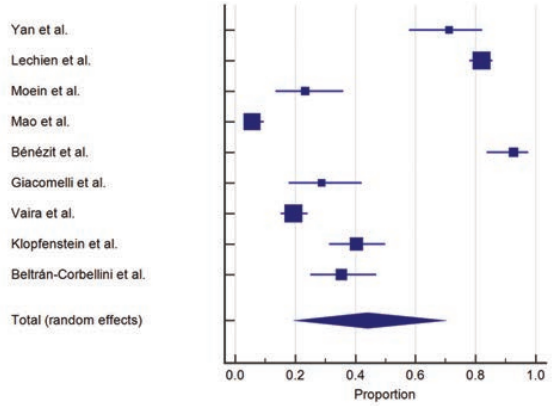

Figure 3. Prevalence of gustatory dysfunction in patients with the 2019 novel coronavirus (COVID-19). Forest plot meta-analysis of the prevalence of gustatory dysfunction in patients with COVID-19 (according to random-effect estimations) demonstrated a 43.93% (95% CI, 20.46%-68.95%) pooled prevalence, as represented by the diamond. Individual study estimates are represented (squares) with 95% confidence intervals (horizontal lines).

Table 2. Summary of Overall Risk of Bias for Included Studies.

Source	Points scored	Overall risk of bias
Beltrán-Corbellini et al[32]	4	Moderate
Bénézit et al[30]	5	Moderate
Giacomelli et al[28]	5	Moderate
Kaye et al[15]	4	Moderate
Klopfenstein et al[29]	5	Moderate
Lechien et al[27]	4	Moderate
Mao et al[7]	6	Moderate
Moein et al[33]	4	Moderate
Vaira et al[23]	9	High
Yan et al[31]	5	Moderate

may not correctly remember if they had olfactory or gustatory dysfunction or the timing of these symptoms.

Prevalence of Olfactory Dysfunction in COVID-19 Patients

A total of 1627 patients were identified for evaluation of olfactory dysfunction. Of these, 845 total patients reported some level of olfactory dysfunction. Reported prevalence of olfactory dysfunction by individual studies ranged from 5.14% to 98.33%. Meta analysis using a random effects model of the 10 studies included in this review demonstrated a 52.73% prevalence of olfactory dysfunction among the 1627 COVID 19 patients (95% CI, 29.64% 75.23%). Heterogeneity was detected with an I^2 of 98.88% ($P <$ .0001), which confirmed the use of the random effects model (**Figure 2**). A detailed table of the statistical analysis results can be found in Supplemental Table S4 (in the online version of the article).

Prevalence of Gustatory Dysfunction in COVID-19 Patients

The study by Kaye et al[15] was excluded from the meta analysis performed to evaluate prevalence of gustatory dysfunction because the COVID 19 Anosmia Reporting Tool used in this study does not distinguish between olfactory and gustatory dys function but rather considers gustatory dysfunction a conse quence of olfactory dysfunction. Of the 1390 COVID 19 patients in the remaining 9 studies, 626 total patients reported some level of gustatory dysfunction. Reported prevalence of gustatory dysfunction by individual studies ranged from 5.61% to 92.65%. Meta analysis using a random effects model demon strated a 43.93% prevalence of gustatory dysfunction (95% CI, 20.46% 68.95%). Heterogeneity was detected with an I^2 of 98.85% ($P <$ .0001), which confirmed use of the random effects model (**Figure 3**). A detailed table of the statistical anal ysis results can be found in Supplemental Table S5 (in the online version of the article).

Subgroup Analysis

Analysis of only those studies that used nonvalidated survey measures or questioning to assess olfactory dysfunction showed a 36.64% prevalence of olfactory dysfunction among 913 patients (95% CI, 18.31% 57.24%; $I^2 = 97.35\%$; $P <$ .0001). Analysis of only those studies that used vali dated instruments to assess olfactory dysfunction showed an 86.60% prevalence of olfactory dysfunction among 714 patients (95% CI, 72.95% 95.95%; $I^2 = 94.32\%$; $P <$ .0001). No subgroup analyses were performed with respect to gusta tory dysfunction as only 1 study included in this review used

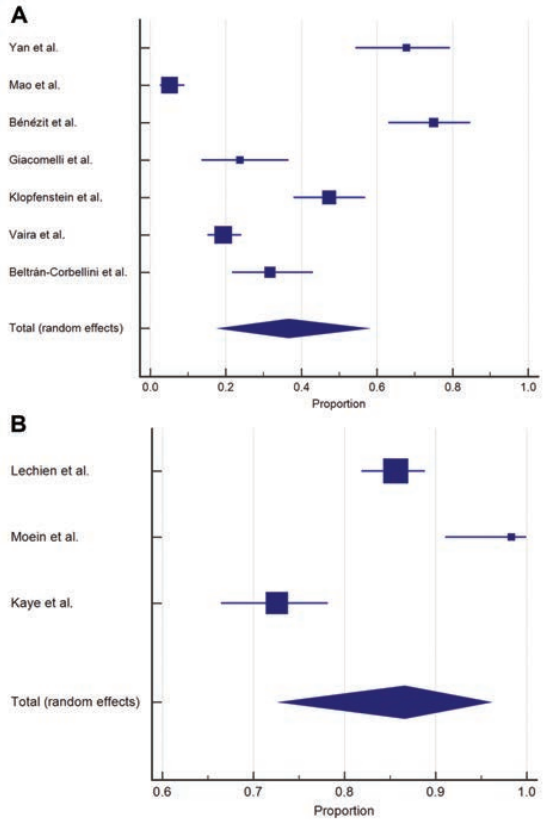

Figure 4. Subgroup analysis for prevalence of olfactory dysfunction. (A) Assessed via nonvalidated instruments in patients with the 2019 novel coronavirus (COVID-19). Forest plot meta-analysis of these studies demonstrated 36.64% (95% CI, 18.31%-57.24%) pooled prevalence, as represented by the diamond. (B) Assessed via validated instruments in COVID-19 patients. Forest plot meta-analysis of these studies demonstrated 86.60% (95% CI, 72.95%-95.95%) pooled prevalence, as represented by the diamond. Individual study estimates are represented (squares) with 95% confidence intervals (horizontal lines).

a validated instrument to assess this symptom. The respective forest plots are depicted in **Figure 4**. A detailed table of the statistical analysis results for nonvalidated and validated studies can be found in Supplemental Table S6 and Supplemental Table S7, respectively (in the online version of the article).

Discussion

In this study, meta analysis using a random effects model demonstrated a significant prevalence of olfactory dysfunction among 1627 patients with COVID 19, both overall and within subgroup analyses. Patients from North America, Europe, and Asia were represented, reflecting the global nature of the current pandemic. Overall cohort analyses showed a 52.73% (95% CI, 29.64% 75.23%) pooled prevalence of olfactory dysfunction. Subgroup analyses were performed based on the method by which olfactory dysfunction was assessed, including validated vs nonvalidated instruments. Studies using nonvalidated instruments showed a 36.64% (95% CI, 18.31% 57.24%) prevalence, while those using validated instruments showed an 86.60% (95% CI, 72.95% 95.95%) prevalence. The higher prevalence demonstrated by validated instruments, including the University of Pennsylvania Smell Identification Test (UPSIT),[33] smell component of the National Health and Nutrition Examination Survey (NHANES) and short version of the Questionnaire of Olfactory Disorders Negative Statements,[27,34,35] and the COVID 19 Anosmia Reporting Tool recently developed by the AAO HNS (face validity only),[15,16] is particularly interesting and may suggest that the overall prevalence determined by this meta analysis is, in fact, an underestimation. This discordance also appears consistent with prior evidence demonstrating that the correlation of self reported olfactory function and objective measures is generally poor,[36] as well as the fact that self report generally underestimates the prevalence of olfactory impairment.[37]

Meta analysis using a random effects model also demonstrated a significant prevalence of gustatory dysfunction among patients with COVID 19. Analyses of 9 studies showed a 43.93% (95% CI, 20.46% 68.95%) prevalence of gustatory dysfunction among 1390 COVID 19 patients. Kaye et al[15] did not differentiate between olfactory and gustatory dysfunction in the COVID 19 Anosmia Reporting Tool, instead considering gustatory dysfunction a sequela of olfactory dysfunction. Vaira et al[23] attempted to capture gustatory dysfunction in a reported measure of combined ''chemosensory dysfunction.'' All other studies included in this review did attempt to differentiate gustatory dysfunction, and all 8 of these studies reported COVID 19 patients experiencing gustatory disturbances. Only Lechien et al[27] used a validated measure to assess for gustatory dysfunction with the taste component of the NHANES.[34] Given the well established influence of olfactory stimuli on the sensory perception of taste,[38] gustatory dysfunction may also represent an early symptom suggestive of COVID 19 infection, but this symptom appears to have been less robustly studied. As a result, it remains unclear as to whether gustatory dysfunction represents a distinct clinical manifestation of the virus or if this occurs secondary to olfactory dysfunction. Future studies, particularly those that document the temporal relationship in onset of these 2 symptoms, are needed.

The fact that pooled data in this study demonstrated significant heterogeneity confirmed the use of the random effects model in this analysis. The source of this heterogeneity is likely the wide range of reported prevalences of olfactory dysfunction, which fluctuated from 5.14% to 98.33%. Similarly, the reported prevalences of gustatory dysfunction ranged from 5.61% to 92.65%. Potential explanations for this include inherent differences in the studied patient populations, both in regard to disease severity and setting. For example, while 4 studies included in this review involved only patients whose presentation was severe enough to

warrant hospitalization,[7,28,32,33] another 3 involved a mix of both inpatient and outpatient populations,[27,29,31] and a final 3 did not address hospitalization status at all.[15,23,30] Furthermore, studies relied on a wide array of instruments to detect olfactory dysfunction, including verbal interview, nonvalidated questionnaires, validated surveys, and validated objective testing such as the UPSIT. In regard to gustatory dysfunction, specifically, while Lechien et al[27] assessed for the symptom using the taste component of the NHANES,[34] no other studies included in this review used a validated measure.

Although olfactory loss commonly presents in the setting of upper respiratory infections, the pathogenesis responsible for COVID 19 mediated olfactory or gustatory disturbances has not yet been definitively identified.[39] One potential mechanism is that COVID 19 may specifically target cells in the sinonasal tract, including the olfactory epithelium.[33,40] The virus appears to target the angiotensin converting enzyme 2 (ACE2) receptor,[41] perhaps the highest levels of which are expressed in goblet and ciliated cells in the nasal epithelium,[42] as well as in the lung and by respiratory tract epithelial cells.[41,43] Dedicated study of olfactory epithelium cell types has demonstrated that while ACE2 is not expressed directly by olfactory sensory or olfactory bulb neurons, ACE2 can be found on sustentacular and basal cells.[40] This is consistent with a previous study that also identified ACE2 expression in the basal layer of the nasal epithelium.[43]

Furthermore, while frequently recognized as respiratory pathogens, coronaviruses are known to be potentially neuroinvasive in humans. Studies have demonstrated that these viruses can invade the central nervous system through the olfactory bulb following intranasal infection.[44-46] This fact may explain why a relatively high proportion of COVID 19 patients appear to have neurological manifestations.[46] In a cohort of patients with COVID 19 from 3 large hospitals in China, for example, Mao et al[7] recently demonstrated that 36.4% had neurological symptoms, including ''peripheral nervous system complications'' such as taste and smell impairment. Alternative hypotheses to explain olfactory and gustatory impairment in COVID 19, including the role of increased exposure to chemicals and disinfectants, have also been proposed.[47]

There has also been increased focus on the temporal relationship between COVID 19 mediated olfactory dysfunction and other sinonasal symptoms, including rhinorrhea and nasal congestion. Xydakis et al,[48] as well as other anecdotal reports, suggest that these other symptoms may be relatively less common overall.[8] Other studies suggest that olfactory dysfunction may precede other sinonasal symptoms. In a preliminary review of the data obtained through the COVID 19 Anosmia Reporting Tool for Clinicians from the AAO HNS, Kaye et al[15] demonstrated that only 25% of patients reported nasal congestion prior to experiencing anosmia, while only 18% reported rhinorrhea prior to anosmia. Beltrán Corbellini et al[32] demonstrated that only 12.9% of COVID 19 patients experiencing olfactory or gustatory dysfunction in their study also reported nasal obstruction. Similarly, Leichien et al[27] found that in COVID 19 patients without nasal obstruction or rhinorrhea, 79.7% still reported anosmia.

Perhaps more significantly, it appears that for many patients with COVID 19, olfactory dysfunction may be the initial presenting symptom. In the AAO HNS analysis, this was the case in 26.6% of patients; in 40%, the presence of olfactory dysfunction contributed to the recommendation for laboratory COVID 19 testing.[15] Similarly, Beltrán Corbellini et al[32] reported that olfactory or gustatory dysfunction was the initial symptom in 35.5% of COVID 19 patients, with acute onset in 70.9% of COVID 19 patients experiencing olfactory or gustatory dysfunction included in their study. This phenomenon is supported by other reports describing onset of anosmia in the absence of other symptoms[9,10,23] or early in the clinical course, typically within days of illness onset.[11,13,23]

Taken together, this evidence has significant implications. First, it lends credence to the growing belief that olfactory dysfunction in the absence of other sinonasal symptoms may be indicative of COVID 19 infection.[5] It also highlights the potential utility of screening patients based on the presence of olfactory dysfunction, as inferred by several authors.[13,48] Several national academies have released position statements suggesting that olfactory dysfunction should prompt a high level of clinical suspicion for COVID 19, along with recommendations for self isolation, confirmatory testing, or other COVID 19 related public health measures.[49,50] Last, the fact that other sinonasal symptoms appear to be less common argues against the possibility that COVID 19 mediated olfactory loss is related to nasal inflammation, mucosal edema, and airflow limitation, as is the case with other upper respiratory infections.[39]

There are several important limitations to this review. First, given the controversial relationship between olfactory and gustatory dysfunction and COVID 19, these symptoms may be underreported in many of the studies included. This may have contributed to an underestimation of overall prevalence. As awareness of the prevalence of olfactory and gustatory dysfunction in COVID 19 patients grows, clinicians may more routinely inquire about these symptoms, thereby improving our understanding of the true prevalence. The fact that many of the included studies only focused on specific patient subpopulations, such as those with presentations severe enough to warrant hospitalization, also suggests that this review did not encompass the whole clinical spectrum associated with COVID 19. Studies that were cross sectional or retrospective in nature also were inherently limited. Both factors may have contributed to under or overestimation of true prevalence. Although the inclusion of more prospective studies would have strengthened the data, this was likely not feasible given the rapid development of the current pandemic. Last, the strength of this review is also limited by the variability of instruments used to evaluate for olfactory and gustatory dysfunction. The shortcomings of self reported olfactory and gustatory dysfunction, as used in several of the included

studies, are well known. Furthermore, several of the studies involved patients with a history of olfactory and gustatory dysfunction preceding the COVID 19 outbreak.[30,31] A future prospective study with larger numbers of patients and that uses validated measurement tools is needed to better under stand the nature of this relationship.

Conclusions

Olfactory and gustatory dysfunction are common in patients with COVID 19 and may represent early symptoms in the clinical course of infection. Increased awareness of this fact may encourage earlier diagnosis and treatment of COVID 19, as well as heighten vigilance for viral spread. The significantly higher prevalence detected by validated instruments suggests that the true prevalence of olfactory and gustatory dysfunction in COVID 19 patients may remain underestimated.

Author Contributions

Jane Y. Tong, concept and design; acquisition, analysis, and interpretation of data, drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; **Amanda Wong**, concept and design; acquisition, analysis, and interpretation of data, drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; **Daniel Zhu**, concept and design; acquisition, analysis, and interpretation of data, drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; **Judd H. Fastenberg**, drafting of the manuscript; critical revision of the manuscript for important intellectual content; **Tristan Tham**, concept and design; acquisition, analysis, and interpretation of data, drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis, study supervision.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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