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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Taste alteration in COVID-19: Significant geographical differences exist in the prevalence of the symptom

Nicola Cirillo

Melbourne Dental School, The University of Melbourne, 720 Swanson Street, 3053 Carlton, Victoria, Australia

ABSTRACT

Early detection of COVID-19 is important for reduction in the spread of the disease and gustatory disturbances (GD) are known to have a strong predictive value. In the present study, we aimed to map the geographical differences in the prevalence of GD in individuals infected with SARS-CoV-2 during the first wave of COVID-19 in order to improve case identification and to facilitate prioritization. We undertook a rapid scoping review of articles published in the repository of the National Library of Medicine (MEDLINE/PubMed) and medRxiv from their inception until 3rd September, 2020. The minimum requirements for completing a restricted systematic review were fulfilled. Of the 431 articles retrieved, 61 studies (28,374 cases confirmed with COVID-19) from 20 countries were included in the analysis. GD were most prevalent in the Americas [66.78%, 95% CI 54.77–78.79%] compared to Europe [57.18%, 95% CI 52.35–62.01%], the Middle East [38.83%, 95% CI 27.47–50.19%] and East Asia [13.1%, 95% CI 0.14–26.06%]. No differences of GD prevalence were evident between February and August 2020. The data demonstrate that there is a marked geographical distribution of GD in COVID-19 patients which, possibly, might be explained by differences in diagnostic criteria for COVID-19 case definition during the early phase of the pandemic.

© 2021 The Author(s). Published by Elsevier Ltd on behalf of King Saud Bin Abdulaziz University for Health Sciences. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Introduction

The early identification and confirmation of suspected cases of Coronavirus Disease 2019 (COVID-19) is fundamental to limiting the spread of the disease but is particularly challenging for asymptomatic or pauci-symptomatic patients. The sudden loss of taste (ageusia), with or without loss of smell (anosmia), have been cited as independent signs of the disease although, more frequently, these symptoms occur in association with the most common manifestations of the disease, namely, fever, cough and fatigue [1]. Unlike early studies [2,3], recent systematic reviews have indicated that gustatory dysfunction (GD), including ageusia, hypogeusia and dysgeusia, is common in COVID-19 patients [4]. Furthermore, loss of taste and smell have been reported to be distinguishing symptoms of COVID-19 which have a high predictive value [5]. The European Centre for Disease Prevention and Control (ECDC) was one of the first public health bodies to include sudden onset anosmia, ageusia or dysgeusia as clinical criteria to identify possible COVID-19 cases [6]. Unfortunately, these symptoms have not been used unanimously for case identification and for testing prioritization. On 5th August 2020, however, the Centers for Disease Control and Prevention in the USA updated their COVID-19 case definition to include GD as an important clinical criterion for diagnosis [7]. Soon afterwards (7th August, 2020), the World Health Organization updated its COVID-19 case definition to include recent onset ageusia, in the absence of any other identifiable cause, as suggestive of COVID-19 infection [8].

In the present study, we hypothesized that differences in the criteria used for COVID-19 identification by national and/or local public health bodies may reflect, at least in part, the changes of known prevalence rates of these symptoms over time and in a geographically specific manner. Specifically, we undertook a rapid systematic review of the prevalence of GD in COVID-19 cases and examined worldwide data from East Asia, the Middle East (including Turkey), Europe (including Britain) and the Americas.

Results

We identified 431 studies; 91 relevant articles met the inclusion criteria. 61 of the 91 studies were included for data analysis (Fig. 1). The studies were from 20 different countries; 5 studies were derived from multi-national collaborations. The majority of cohorts were from Europe (n = 40), followed by the Middle East (n = 8), North and South America (n = 6 and n = 2, respectively), East Asia (n = 6) and Africa (n = 1). Two articles [9,10] pooled multinational data within Europe and 3 studies [11–13] included cases from two main geographical areas. The study populations and prevalence range are depicted graphically in Fig. 2.

Worldwide, 14,486 of 28,374 confirmed COVID-19 cases (51.05%) reported subjective and/or objective GD (Table 1). Strikingly, there were significant differences of prevalence between subgroups (ANOVA, p = 0.000106; Kruskal–Wallis, p = 0.00071). Further, when each geographical region was compared, there were significant differences between all of the subgroups except Europe vs America (Suppl Table 1). Studies from East Asia reported the lowest prevalence of GD (13.1%, 95% CI 0.14–26.06%), followed by the Middle East (38.83%, 95% CI 27.47–50.19%), Europe (57.18%, 95% CI 52.35–62.01%) and the Americas (66.78%, 95% CI 54.77–78.79). We could not highlight trends of increased GD prevalence in COVID-19 patients over time, except in East Asia (Supplementary Fig. 1).

Discussion

An awareness of the association between taste alterations and COVID-19 infection is important for diagnosing the disease, particularly in dental and oral health settings [14]. In the present study, we followed a streamlined approach to synthesizing evidence (the rapid review) which is typically used for informing emergent decisions faced by decision-makers in health care settings. The results of this rapid systematic review show that there are distinct geographical patterns of GD in patients with established SARS-CoV-2 infection. The first systematic assessments of the evidence available up to March 2020 failed to identify associations between anosmia/ageusia and COVID-19 [2,3]. For example, in an early systematic review involving a total of 1556 patients, olfactory or gustative dysfunctions were not reported [2]. In another early study which examined evidence of anosmia in COVID-19 patients, researchers found the symptom to be of “limited and inconclusive” value [3]. The first study reporting a 5.1 and 5.6% prevalence.
of hyposmia and hypogeusia, respectively, was a pre-print (non-peer-reviewed) case series of a Chinese population [15]. In sharp contrast, the most recent meta-analysis analyzing smell and taste alterations not only reported that almost half of COVID-19 patients had these symptoms but also, that 15% of patients had olfactory and gustatory abnormalities as their initial presenting symptoms [16].

Recent systematic reviews have assessed chemosensory alterations in COVID-19 patients [4,16–30]. Only one review, however, has focused specifically on taste changes [31]. In their pooled analysis, Aziz et al. [31] found that almost half of patients (49.8%) with COVID-19 had altered taste sensation. Similarly, when the data was pooled in the reviews assessing chemosensory alterations, the prevalence of olfactory and gustatory alterations occurred in approximately half of COVID-19 patients but when these symptoms were considered individually, there was a marked range of prevalence (3.2–100% olfactory symptoms; 0–92.6% gustatory disturbances). The results of the present study are in agreement with the existing literature on the worldwide prevalence of GD associated with COVID-19 disease: of 28,374 confirmed COVID-19 cases, 14,486 (51.05%) reported GD. Taken together, and in association with other findings [32], there is strong evidence to suggest that gustatory alterations are cardinal symptoms of COVID-19.

A major limitation of the present study is that it includes research with diverse study designs and patients with different disease severity, e.g. severe, mild, or asymptomatic COVID-19 cases. Further, the majority of the studies that were analysed were cross-sectional, retrospective and observational, hence recollection bias may have been present. Most studies were similar to those previously graded as “moderate risk of bias” [29]. Importantly, the presence of taste alterations may not have been reported in the presence of other more severe symptoms such as dyspnea, fever and productive cough which could explain the lack of association between GD and COVID-19 in the first studies published in February and March 2020. For these reasons, the true prevalence of ageusia, hypogeusia and dysgeusia might be significantly higher than reported [31].

Disturbance of taste sensation can occur as a result of local and systemic conditions, including oral, nasal, and sinus disease, metabolic (obesity, diabetes, poor nutrition, hypertension), neurological (epilepsy, Alzheimer’s and Parkinson’s disease, schizophrenia, multiple sclerosis), tumours and radiation associated with cancer treatment, drugs (allopurinol, anti-hypertensives, atarins, lithium), head trauma, and certain habits (smoking, cocaine snorting). Significantly, in the published literature, the measures for assessing GD have not been validated and the definition of dysgeusia has not been unanimously accepted. Further, the more patients and doctors are aware of the possibility of GD with COVID-19, the more cases would have been reported and investigated over time [12] although in the present study, the data failed to show a trend of increased GD prevalence over time except in East Asia. By contrast to other studies [2], our analysis focused on geographical location rather than ethnicity. Whilst this approach may have failed to identify individual genetic/ethnic determinants of infection, we believe that our methodology was better suited to study the clinical manifestations of the disease and to inform the decisions of public health surveillance bodies.

The data that were examined in the present study involved the subjective (self-reported) and objective (testing with the four basic tastes of sweet, sour, salty and bitter modalities sprayed onto the tongue in a supra-threshold doses) interpretation of GD. Previous findings, however, have shown that there are no significant differences between the subjective and objective interpretation of gustatory function [18] and, therefore, we suggest that self-reported taste alterations can be considered a reliable parameter for GD in COVID-19 patients.

In conclusion, we show that GD in COVID-19 exhibits distinct geographical patterns of prevalence. Given the potential usefulness of taste assessment in the diagnosis of mildly and paucisymptomatic patients, we believe that it is imperative to recognize
ageusia/hypogeusia/dysgeusia as a potential clinical manifestation of COVID-19, particularly in Europe and America. Dentists, therefore, may be the first healthcare providers to diagnose taste disturbances and are likely to play an important role in case identification and early diagnosis of COVID-19 cases in the future.

### Methods

#### Study design and literature search

This study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.
(PRISMA) guidelines and used a rapid review approach due to time constraints [89]. The study complied with the minimum requirements for completing a restricted systematic review [90]. Accordingly, the search was performed by one investigator (N.C.) and verification of a random sample of full texts for accuracy of title/abstract screening and data extraction was undertaken by the same reviewer. Key terms used for the search were (SARS-COV-2 or COVID or COVID-19) in association with taste or ageusia or hypogeusia or dysgeusia or gustatory. The search was conducted in PubMed/MEDLINE as well as medRxiv using the advanced search (title and abstract) tool.

Study selection and data extraction

The exclusion criteria were as follows: articles not in English, duplicate publications, irrelevant articles, studies where the infection status was not clearly confirmed, studies that did not evaluate gustatory outcomes individually, simple case reports, and review or systematic review articles. Studies using telephone surveys or Apps were only included where the respondents had a confirmed COVID-19 diagnosis. For studies reporting cases from two or more geographical areas (e.g. East Asia and Europe), the data for subgroup analysis were extracted only when information from individual countries was available. Where the date of patient recruitment was not provided, the date of the article submission was used as a surrogate source of information. The primary outcome was to assess the prevalence of gustatory alterations (ageusia, hypogeusia, dysgeusia) in confirmed COVID-19 cases worldwide and in distinct geographical areas; the secondary outcome was to establish a spatio-temporal pattern of GD in published cases. No constraints were placed on the size of the cohorts to ensure a comprehensive search and to identify the maximum number of potential articles.

Statistical analysis

Subgroup analyses were based on the country of origin of the studies by pooling the actual data reported in each individual study. Differences in prevalence (% and category) among subgroups were assessed with chi-square statistics and one-way ANOVA, as appropriate. Tukey’s post-hoc test or Student’s t tests were used for comparison between group pairs. By making a further assumption that the dependent variable may not be normally distributed, the Kruskal-Wallis test was also used to compare overall differences in prevalence. Where appropriate, Pearson’s coefficient was used to assess the correlation between time and prevalence. A level of p < 0.05 was chosen to determine statistical significance.

Ethics approval and consent to participate

Not applicable.

Consent for publication

N.C. approved the final version of the manuscript.

Availability of data and material

The datasets used and/or analyzed during the current study can be made available by the corresponding author on a reasonable request.

Competing interests

The author declares no conflict of interest.

Funding

The author received no specific funding for this study.

Authors’ contributions

N.C. conceived the study, undertook the search and wrote the manuscript.

Acknowledgements

The first version of this article was published in medRxiv on 13 September 2020. N.C. is grateful to Professor Stephen Prime, who kindly reviewed the manuscript and provided critical comments. N.C. would like to acknowledge the support of the Division of Basic and Clinical Oral Sciences, Melbourne Dental School, The University of Melbourne, particularly with reference to Article Processing Charges.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.jiph.2021.07.002.

References

[1] Gaan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.
[2] Lovato A, de Filippis C. Clinical presentation of COVID-19: a systematic review focusing on upper airway symptoms. Ear Nose Throat J 2020;99(9):569–76.
[3] O’ Donovan J, Tanveer S, Jones N, et al. Sniffing out the evidence for olfactory symptoms as a clinical feature of COVID-19: a systematic scoping review. Cen tre for Evidence-Based Medicine; 2020. https://www.cebm.net/wp-content/uploads/2020/03/Rapid-Review-Anosmia-COVID-19.pdf.
[4] Passarelli PC, Lopez MA, Mastandrea Bonaviri GN, Garcia-Godoy F, D’Addonna A. Taste and smell as chemosensory dysfunctions in COVID-19 infection. Am J Dent 2020;33(3):135–7.
[5] Dawson P, Rabold EM, Laws RL, et al. Loss of taste and smell as distinguishing symptoms of COVID-19. Clin Infect Dis 2021;72(4):682–5.
[6] European Centre for Disease Prevention and Control (ECDC). Case definition for coronavirus disease 2019 (COVID-19), as of 29 May 2020. https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition [Accessed 19 August 2020].
[7] Candidates for Disease Prevention and Control (CDC). Coronavirus Disease. (COVID-19) 2020 Interim Case Definition, Approved August 5, 2020; 2019 [Accessed 19 August 2020]. https://www.cdc.gov/mmwr/condi tions/coronavirus-disease-2019-covid-19/case-definition-2020/08/51.pdf.
[8] World Health Organization. WHO COVID-19 Case definition, published 7 August 2020. https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance-Case-Definition-2020 [Accessed 19 August 2020].
[9] Lechien JR, Chiesa-Estomba CM, De Sati DR, et al. Olfactory and gustatory dysfunctions: a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020;277(8):2251–61.
[10] Lechien JR, Chiesa-Estomba CM, Hans S, et al. Loss of smell and taste in 2013 European patients with mild to moderate COVID-19. Ann Intern Med 2020;173(8):672–5.
[11] Chiesa-Estomba CM, Lechien JR, Barillari MR, et al. Patterns of gustatory recovery in patients affected by the COVID-19 outbreak. Virol Sin 2020;35(6):831–7.
[12] Menni C, Valdes AM, Freidin MB, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. Nat Med 2020;26(7):1037–40.
[13] Cui C, Hautefort C, et al. Olfactory and gustatory dysfunction as an early identifier of COVID-19 in adults and children: an international multicenter study. Otolaryngol Head Neck Surg 2020;163(4):714–21.
[14] Cirillo N. COVID-19 outbreak: succinct advice for dentists and oral healthcare professionals. Clin Oral Investig 2020;24:2529–35.
[15] Mao L, Wang M, Chen S, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. medRxiv 2020, http://dx.doi.org/10.1101/2020.02.22.20026500.
[16] Chi H, Chiu MC, Peng CC, et al. One-seventh of patients with COVID-19 had olfactory and gustatory abnormalities as their initial symptoms: a systematic review and meta-analysis. Life (Basel) 2020;10:E158, http://dx.doi.org/10.3390/life10090158.
[17] Abdullahi A, Candan SA, Abba MA, et al. Neurological and musculoskeletal features of COVID-19: a systematic review and meta-analysis. Front Neurol 2020;11:687, http://dx.doi.org/10.3389/fneur.2020.00687.
N. Cirillo  
Journal of Infection and Public Health 14 (2021) 1099–1105
[74] Brandao Neto D, Fornazeri MA, Dib C, et al. Chemosensory dysfunction in COVID-19: prevalences, recovery rates, and clinical associations on a large Brazilian sample. Otolaryngol Head Neck Surg 2020; http://dx.doi.org/10.1177/019459820954825.

[75] Sayin I, Yaşar KK, Yazıcı ZM. Taste and smell impairment in COVID-19: an AAO-HNS anosmia reporting tool-based comparative study. Otolaryngol Head Neck Surg 2020;163(3):473–9.

[76] Biadsee A, Biadsee A, Kassem F, Dagan O, Masarwa S, Ormanier Z. Olfactory and oral manifestations of COVID-19: sex-related symptoms—a potential pathway to early diagnosis. Otolaryngol Head Neck Surg 2020;163(4):722–8.

[77] Altim F, Cingi C, Uzun T, Bal C. Olfactory and gustatory abnormalities in COVID-19 cases. Eur Arch Otorhinolaryngol 2020; http://dx.doi.org/10.1007/s00405-020-06284-1 (in press).

[78] Al-Ami RM, Acharya D. Prevalence of anosmia and ageusia in patients with COVID-19 at a Primary Health Center, Doha, Qatar. Indian J Otolaryngol Head Neck Surg 2020, http://dx.doi.org/10.1007/s12070-020-02614-9 (in press).

[80] Sakalli E, Temirbekov D, Bayri E, Alis EE, Enderak SC, Bayraktaroglu M. Ear nose throat-related symptoms with a focus on loss of smell and/or taste in COVID-19 patients. Am J Otolaryngol 2020;41(6):102622, http://dx.doi.org/10.1016/j.amjoto.2020.102622.

[81] Levinson R, Elbaz M, Ben-Ami R, et al. Time course of anosmia and dysgeusia in patients with mild SARS-CoV-2 infection. Infect Dis (Lond) 2020;52(8):600–2.

[82] Çalışa Utku A, Budak G, Karabay O, Güçlü E, Okan HD, Vatan A. Main symptoms in patients presenting in the COVID-19 period. Scott Med J 2020;65(4):127–32.

[83] Lee Y, Min P, Lee S, Kim SW. Prevalence and duration of acute loss of smell or taste in COVID-19 patients. J Korean Med Sci 2020;35.e174, http://dx.doi.org/10.3346/jkms.2020.35.e174.

[84] Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77(6):1–9, http://dx.doi.org/10.1001/jamaneurol.2020.1127.

[85] Kim GU, Kim MJ, Ra SH, et al. Clinical characteristics of asymptomatic and symptomatic patients with mild COVID-19. Clin Microbiol Infect 2020;26(7):848, http://dx.doi.org/10.1016/j.cmi.2020.04.040.

[86] Cho RH, To ZW, Yeung ZW, et al. COVID-19 viral load in the severity of and recovery from olfactory and gustatory dysfunction. Laryngoscope 2020;130(11):2680–5.

[87] Liang Y, Xu J, Chu M, et al. Neurosensory dysfunction: a diagnostic marker of early COVID-19. Int J Infect Dis 2020;98:347–52.

[88] Farah Yusuf Mansud M, Garad Mohamed Y, Mohamed Ali A, Ali Adam B. Loss of taste and smell are common clinical characteristics of patients with COVID-19 in Somalia: a retrospective double centre study. Infect Drug Resist 2020;13:2631–5.

[89] Khangura S, Konnyu K, Cushman R, Grimshaw J, Moher D. Evidence summaries: the evolution of a rapid review approach. Syst Rev 2020;1:10, http://dx.doi.org/10.1186/s40647-020-00531-7.

[90] Plüddemann A, Aronson JK, Onakpoya I, Heneghan C, Mahtani KR. Redefining rapid reviews: a flexible framework for restricted systematic reviews. BMJ Evid Based Med 2018;23(5):201–3.