HHS Public Access

Author manuscript

ACS Chem Neurosci. Author manuscript; available in PMC 2021 October 07.

Published in final edited form as:

ACS Chem Neurosci. 2020 October 07; 11(19): 2944–2961. doi:10.1021/acschemneuro.0c00460.

Prevalence of Chemosensory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis Reveals Significant Ethnic Differences

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Abstract

A significant proportion of people who test positive for COVID-19 have chemosensory deficits. However, the reported prevalence of these deficits in smell and taste varies widely, and the reason for the differences between studies is unclear. We determined the pooled prevalence of such chemosensory deficits in a systematic review and meta-analysis. We searched the COVID-19 portfolio of the National Institutes of Health for studies that reported the prevalence of smell and/or taste deficits in patients diagnosed with COVID-19. One-hundred-four studies reporting on 38,198 patients qualified and were subjected to a systematic review and meta-analysis. Estimated random prevalence of olfactory dysfunction was 43.0%, of taste dysfunction was 44.6%, and of overall chemosensory dysfunction was 47.4%. We examined the effects of age, gender, disease severity, and ethnicity on chemosensory dysfunction. Prevalence of smell and/or taste dysfunction decreased with older age, male gender, and with disease severity. Ethnicity was highly significant: Caucasians had a three times higher prevalence of chemosensory dysfunctions (54.8%) than Asians (17.7%). The finding of geographic differences points to two, not mutually exclusive causes. A virus mutation (D614G) may cause differing infectivity, while, at the host level, genetic, ethnicity-specific variants of the virus-binding entry proteins may facilitate virus entry in the olfactory epithelium and taste buds. Both explanations have major implications for infectivity, diagnosis and management of the COVID-19 pandemic.

Graphical abstract

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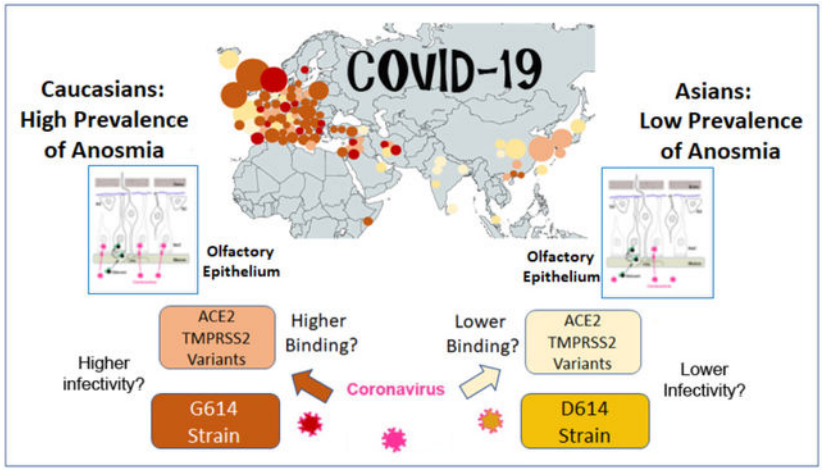
Author Contributions

Christopher von Bartheld and Rafal Butowt designed the study and wrote the manuscript, Molly Hagen prepared the meta-analysis, and all authors edited and approved the final version of the manuscript.

None of the authors have any proprietary interests or conflicts of interest related to this submission.

Conflicts of Interests

The authors have declared no competing interests.



Keywords

Anosmia; Smell; Taste; SARS-CoV-2; Prevalence; Ethnicity

Introduction

The first reports of more frequent disturbances of smell and taste in COVID-19 patients emerged in February and March of 2020. Initially, these reports were anecdotal, but soon articles consistently described an increased prevalence of chemosensory deficits. The findings of many of the earlier studies were compiled in 14 recent reviews.[1–14] Six of these reviews conducted a meta-analysis (of ten studies,[10] 12 studies,[13] 22 studies,[11] 24 studies,[1] 34 studies,[5] and 55 studies,[12]), the other eight are narrative reviews.[2–4, 6–9, 14] Studies reported prevalence of chemosensory dysfunction with wide ranges, between 3% and 98% for anosmia, and between 6% and 93% for taste dysfunctions.[1, 4, 10, 12] The reasons for differences in the prevalence reported in different studies were thought to be due to differences in the age of patients, in assessment methods,[1, 5, 10,] in the severity of the disease,[8, 10] and regional distribution.[4, 12] Patient selection was thought to play a role – since some data were from hospitalized patients, others from clinic visits, and cohorts were from different countries, and data obtained with different study designs. Most studies relied on the patients' subjective impressions about changes in the sensation of smell or taste.[1, 5, 10, 12]

Although several series of studies have been compiled and analyzed in multiple reviews, it has remained unclear to what extent age, gender, disease severity, methods of assessment, and geographic region or ethnicity are relevant factors that affect prevalence of chemosensory dysfunction in COVID-19. Since many additional studies are now available, a larger set of data can be considered to answer these outstanding questions. To gain a more comprehensive and conclusive account of the prevalence of chemosensory deficits in COVID-19, we conducted a systematic review and meta-analysis of 104 studies that reported on the chemosensory status of 38,198 patients diagnosed with COVID-19. We included published studies as well as preprints of not yet peer-reviewed studies, up to the posting or publication on August 15, 2020. Because we considered a larger number of studies and

larger cohort numbers than previous reviews, we provide a clearer picture of the true prevalence, and, importantly, we used subgroup analyses to examine confounding variables such as age, gender, methodology, disease severity, and geographic region/ethnicity. We provide evidence, for the first time, that geography/ethnicity is a significant factor that explains variation in the prevalence of chemosensory deficits. The effect of geography/ethnicity (difference between populations in Asia and in Western countries) was not clear in previous studies, primarily because there were not sufficient numbers of studies from Asia, and especially South Asia, to make this determination. The finding of true population differences, apparently due to virus mutations and/or to genetic variants in host entry proteins, has important implications for the diagnosis and spread of COVID-19, and therefore for the management of the pandemic in countries with different populations.

Results

We adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA), as shown in the flowchart (Fig. 1). Our search strategy retrieved 104 studies that fulfilled the inclusion criteria, with prevalence information on a total of 38,198 patients from 26 different countries. The mean or median age of subjects in the 104 studies ranged from 26 to 77 years. Studies reported on subjects from multiple countries (n=5),[15–19] from Australia (n=1),[20] Belgium (n=1),[21] Brazil (n=1),[22] Canada (n=2),[23, 24] China (n=7),[2, 19, 25–29] France (n=12),[19, 30–39] Germany (n=10),[19, 40–46] Greece (n=1),[49] Iceland (n=1),[50] India (n=2)[51, 52] Iran (n=3),[53–55] Iraq (n=2),[56, 57] Israel (n=4),[58–61] Italy (n=19),[62–80] Japan (n=1),[81] Korea (n=3),[82–84] Netherlands (n=1),[85] Poland (n=1),[86] Qatar (n=1),[87] Singapore (n=2),[88, 89] Spain (n=6),[90–95] Sri Lanka (n=1),[96] Sweden (n=1),[97] Switzerland (n=1),[98] Taiwan (n=1),[99] Turkey (n=4),[100–103] UK (n=3),[104–106] and USA (n=9).[104, 107–114]

The overall estimated random prevalence of smell loss among COVID-19 patients, calculated from a total of 91 studies containing 25,750 patients, was 43.04% [95% confidence interval (CI), 36.39–49.96%]. The meta-analysis indicated that between-study variability in prevalence of smell loss was high (τ^2 = 1.7399; heterogeneity I^2 = 98.5% with Q = 5994.5; according to Higgins and Thompson,[115] and examination of the funnel plots, as expected, showed evidence of some publication bias (Fig. 2a).

The 71 cohorts with information on taste loss contained a total of 21,125 patients. The overall estimated random prevalence of taste loss among COVID-19 patients was 44.62% [95% CI, 38.47–50.94%]; the analysis indicated that between-study variability was high (τ^2 = 1.1213; heterogeneity I^2 = 97.9% with Q = 3378.75; Fig. 2b). When smell and taste loss were combined, the overall estimated random prevalence obtained from 38,198 patients in 104 cohorts was 47.36% [95% CI, 40.93–53.88%]; the analysis showed high heterogeneity with some publication bias (τ^2 = 1.7630; heterogeneity I^2 = 98.8% with Q = 8427.67; Fig. 2c). Because many of our subgroup tests were statistically significant, some of the heterogeneity detected can be explained by differences associated with variation in subgroup parameters between studies.

There was a significant difference in the prevalence of smell, taste and any chemosensory dysfunction between countries with a majority Asian population and Western countries with

a majority Caucasian population. Ethnicity was tested for all three measures (loss of smell, loss of taste, and loss of smell and/or taste) and was highly significant in all three categories with $p \leq 0.0001$ in call cases (Fig. 3a–c). There were 77 studies available on smell loss in Caucasians and 14 studies on Asians. Ethnicity of participants explained a significant amount of heterogeneity in smell loss (Q = 20.21, df = 1, $p < 0.0001$; Fig. 3a).

The estimated random prevalence of smell loss was 49.02% [95% CI, 42.25–55.84%] among Caucasians and 16.70% [95% CI, 9.67–27.27%] among Asians (Fig. 3a). According to 11 studies on Asians and 60 studies on Caucasians, the estimated prevalence of patients with loss of taste was 50.88% [95% CI, 45.11–56.62%] among Caucasians and significantly lower, 17.58% [95% CI, 11.02–26.88%], among Asians (Q = 27.45, df = 1, $p < 0.0001$; Fig. 3b). According to 18 studies on Asians, and 86 studies on Caucasians, the overall estimates of any chemosensory deficits were three times higher among Caucasians (54.82%) than Asians (17.72%), and also showed high heterogeneity and evidence of some publication bias (Figs. 2c and 3c). Differences in chemosensory deficits between Asians and Caucasians are further illustrated in Figure 4a, with the prevalence shown in a world heat map, with the cohort size indicated by the size of the circles. The difference in prevalence between Caucasians and Asians was quantified as shown in the bar graphs in Figure 4b.

Disease severity.

As a measure of disease severity, we used information about hospitalization rates within cohorts. The weighted regression analyses showed a significant negative influence of disease severity on the proportion of patients with loss of smell, loss of taste, and loss of smell and/or taste (Table 1). The beta coefficients for the effect of disease severity on loss of smell (b = −0.019, $p < 0.0001$) and taste (b = −0.013, $p = 0.0032$) showed that deficits were reported less frequently in cohorts as the number of individuals in the cohort who were hospitalized increased. This result was also highly significant when loss of smell and taste were combined (b = −0.020, $p < 0.0001$; Table 1). Accordingly, patients with severe COVID-19 report fewer smell/taste dysfunctions.

Age.

The subgroup tests for the effect of cohort age on smell loss showed a negative association (b = −0.047, $p = 0.0008$), and tests for the effect of cohort age on loss of taste showed the same result (b = −0.005, $p = 0.0032$; Table 1). A highly significant negative association was found when loss of smell and taste were combined (b = −0.043, $p = 0.0016$), suggesting that increasing age results in a lower reporting of loss of chemosensory deficits in general. These results are consistent with the conclusions of a previous meta-analysis.[1]

Gender.

Data on chemosensory dysfunction was reported specifically for males and females in 22 studies on smell loss,[18, 21, 26, 27, 35, 45, 53, 54, 58, 63, 64, 70–75, 86, 87, 93, 98, 102] and in 15 studies on taste loss.[21, 26, 27, 53, 64, 70–74, 86, 87, 93, 102] Results of weighted random effects meta-analyses estimated the prevalence of smell loss among females to be 64.63% (95%CI = 53.48–74.38%) and among males to be 51.78% (95%CI= 41.78–61.65%). Because these confidence intervals overlap, we cannot conclude that females experience higher smell loss

than males ($p \geq 0.05$). Similarly, taste loss was more frequent among females than males (females = 59.91%, 95%CI = 45.42–72.86; males = 49.49%, 95%CI = 37.40–61.84%), but this difference also did not reach statistical significance. There was an insufficient number of studies with such information for "any chemosensory dysfunction" (n=4 studies) to conduct a gender analysis in this category.

Methodology.

The subgroup test to compare studies that used subjective or objective assessments showed a larger prevalence in studies using objective tests than studies that used subjective reporting for "smell" and "smell and/or taste" ($p = 0.0006$, and $p = 0.0009$, respectively), but no significant difference for taste ($p = 0.6693$). For loss of smell, studies that used objective measures had an estimated random prevalence of 65.52% [95% CI, 52.26–76.74%], while those that used subjective measures had a prevalence of 38.84% [95%CI, 31.96–46.20%]. For loss of taste, the prevalence among the studies with subjective measures was higher than among those with objective measures (q = 0.18, $p = 0.6693$), with an estimated random prevalence of 45.12% [95% CI, 38.22–52.20%] and 41.94% [CI 95%, 36.49–53.99%], for subjective vs. objective measures, but the difference was statistically not significant. When the two endpoints were combined (loss of smell and/or taste), the resulting prevalence for objective measures was 68.70% [95%CI, 56.10–79.04%], which was significantly higher than that of subjective measures (43.86% [95%CI, 37.09–50.87%]; q = 11.02, $p = 0.0009$), see also Fig. 5. These data are consistent with the conclusions from previous reviews.[1, 5, 10, 12] Sample sizes were as follows: smell: objective measures n=15, subjective measures n=75; taste: objective measures n=11, subjective measures n=60; smell and/or taste: objective measures n=15, subjective measures n=88.

Nasal congestion/rhinorrhea.

If the anosmia was caused by nasal congestion, as is common in cases of viral infection, then most, if not all, COVID-19 patients with anosmia would be expected to have nasal congestion/rhinorrhea. However, our data shows that a weighted mean of 66.9% of COVID-19 patients with anosmia did not have nasal congestion/ obstruction or rhinorrhea, based on the reports of n=37 studies with a total cohort size of 11,142 patients with olfactory dysfunction, consistent with the conclusion of previous reports.[3, 6, 8–10, 91, 119]

Duration of chemosensory dysfunction.

Based on the studies that provided such information, the average duration of smell dysfunction was 8.90 days ± 0.74 (SEM, n= 20 studies with a total cohort number of 5,357), and 8.29 ± 0.91 days for taste dysfunction (n=13 studies with a total cohort number of 2,970).

Possibility of bias.

The majority of the studies are cross-sectional, retrospective observational studies, and therefore, recollection bias may be present. Most studies are similar to those previously graded as "moderate risk of bias."[3, 5, 10–12, 14] Studies with high risk of bias (e.g., Bagheri et al., 2020[120])[14] were not included in our analysis, based on our inclusion criteria. Potential

weaknesses are that measures mostly were not validated,[7] but it has to be considered that data were collected during an unprecedented pandemic and at a time when using more time-consuming assessment tools often was not possible due to increased risk of virus spreading. The sample size for Asian studies was smaller than for Caucasian studies, but with n = 11–18, it was sufficient for each of the reported comparisons.[121]

Discussion

The literature on the prevalence of chemosensory dysfunctions in COVID-19 has been evolving at a rapid pace. In the first two months of the COVID-19 pandemic, such deficits were considered a rare occurrence,[37, 122–124] as recently reviewed.[4] The first report of smell and taste dysfunction that recognized this condition as a much more prevalent symptom (66.7% of COVID-19 patients) was on March 16th, 2020 by a German virologist.[48] The majority of subsequent studies have confirmed such a high prevalence outside of Asia (Figs. 3, 4, 5b).

Compared with previous systematic reviews and meta-analyses,[1–14] our review considers a much larger number of studies (104) and total number of subjects in the cohorts (38,198). Our review on smell, taste and “smell and/or taste” dysfunction differs from Hannum et al.[5] which focused on subjective versus objective assessment exclusively of olfactory dysfunction. Our study differs from some of the earlier reviews (e.g., Agyeman et al; Tong et al; Kim et al.),[1, 10, 12] in that we considered not only studies reporting separately on olfactory dysfunction and taste dysfunction, but also studies that did not distinguish between the two modalities and grouped them as “smell and/or taste dysfunction.” Some reviews did not include multi-center studies,[12] or any editorials (letters to the editor), even when they otherwise included a full description of relevant parameters of the study,[6, 10] or they required peer-review (and therefore excluded preprints),[9, 10] thereby reducing the number of qualifying studies. We did not include the study by Bagheri et al.,[120] because subjects in this cohort did not have COVID-19 confirmed diagnoses and therefore did not meet the inclusion criteria, although many of the cases likely were related to COVID-19.[125]

Geography/Ethnicity/Genetics

Previously, uncertainties remained about the significance and contribution of factors influencing the prevalence of chemosensory dysfunction in COVID-19, including age, gender, severity of disease, methods of assessment, and ethnicity. Our review now clarifies and confirms some of these effects, and, importantly, shows that geography/ethnicity is a major factor. Some researchers had commented on a possible difference in the frequency of chemosensory deficits between East Asians and Caucasians with COVID-19, based on smaller numbers of studies and without considering populations from South Asia.[2, 4, 12, 16, 17, 19, 35, 126, 127] With the much more extensive datasets included in our review (28,878 mostly Caucasians and 9,320 Asians), we now show that there indeed is a significant difference in prevalence between Caucasians and Asians: 3-fold higher for smell, taste, and for “smell and/or taste” impairment in Caucasians (Fig. 4b).

Why are chemosensory deficits much less frequent in Asians with COVID-19 compared to Caucasians? Two potential explanations need to be considered, one at the level of the virus, the other at the level of the host.[4, 12, 17, 19, 35] Could the SARS-CoV-2 virus have mutated to be more infectious and damaging to chemosensory structures in Western populations than in Asian populations? Only one virus mutation, the substitution of D614 to G614, has been identified that increases viral transmission or infectivity with a difference in geography.[128–130] Is it possible that Asians have less chemosensory dysfunction because they were infected mostly by the D614 strain, while Caucasians were mostly infected by the G614 strain? Consistent with this hypothesis, when the pandemic started in Asia, the D614 strain was more dominant, while the G614 strain rapidly became dominant when the pandemic progressed in Western countries.[128] A previous report on the chronology of chemosensory dysfunction prevalence showed that the prevalence initially increased,[12] consistent with a switch from D614 to G614, but then decreased, which is hard to explain. Furthermore, the initial increase could also be due to extensive publicity of chemosensory deficits in the media, and these confounding variables are difficult to discern. There were no associations between the age or sex of subjects and their D614 or G614 status,[128] which differs from our finding of an association between younger age and a strong trend for female sex in subjects with chemosensory dysfunction. Within some populations, chemosensory prevalence increased when the G614 virus strain replaced the initial D614 strain, but the evidence is not yet compelling. Accordingly, it is not known to what extent the virus mutation contributes to the chemosensory phenotype in COVID-19.[12, 128]

A second explanation for the difference in chemosensory prevalence between populations is that the frequency in genetic variants of the entry proteins for the virus differs between populations, as pointed out by multiple investigators[4, 1217, 126, 127] Such ethnic differences have been shown for ACE2[131–135] and TMPRSS2.[131, 136] Some of the variants in ACE2 and TMPRSS2 indeed occur with frequencies that differ significantly between different ethnic populations, especially between East Asians and Caucasians. However, previous work has focused on variants of these proteins in lung tissue and correlations with lung disease severity. It is now known that the functional significance of variants may differ between tissues and cell types, and that non-coding regions of the genes and different combinations of variants need to be considered for functional interpretations, and that post-translational modifications may also play important roles in protein expression.[132] Variations in the ACE2 protein can change human coronavirus binding by up to 20-fold,[137] and glycosylation sites relevant to the virus binding may be tissue-specific.[129, 138] The importance is that ACE2 and TMPRSS2 variants are genetically determined and that some of them are known to differ in frequency between Europeans and Asians.[131–136] If Caucasians have more often ACE2 and/or TMPRSS2 variants expressed in the olfactory epithelium (specifically in the sustentacular cells of the olfactory epithelium),[138–140] then these cells may bind SARS-CoV-2 with higher affinity, resulting in increased numbers of cases of anosmia, whereas Asians may express less of these ACE2 variants, and therefore will less often have anosmia as part of the COVID-19 symptoms. However, frequencies of variants within different ethnicities remain to be shown to be associated with chemosensory dysfunction.

Are there other possible explanations for the ethnic difference in prevalence? An important potential confounding variable in this context is that publicity of the COVID-19 associated

chemosensory dysfunction occurred after the pandemic had mostly run its course in East Asia, and therefore under-reporting in East Asia is difficult to exclude as a contributing factor. However, more recent studies, including those from South Asia, also report a low prevalence of chemosensory dysfunction, and it would be odd if such under-reporting continued over several months solely in Asia, including South Asia. The study by Qiu et al examined a sub-cohort of 90 Chinese COVID-19 patients with objective methods, and found only 11% chemosensory dysfunction,[19] which is much lower than the percentage in studies on Caucasians (Fig. 5b), suggesting that under-reporting alone cannot explain the population difference. Recognizing that smell dysfunctions may be less common in China than in Europe, Chung et al[2] suggested a reason based on differential drug use: interferon-α is widely prescribed in China for COVID-19 infection, and this drug was thought to decrease virus replication in the nasal epithelium, thereby potentially reducing olfactory dysfunction in China. However, other Asian countries such as Korea do not prescribe interferon-α, and studies from Korea, Japan, Singapore and India report similarly low prevalence of olfactory dysfunction as the studies from China (Fig. 4a; Table 2). Furthermore, regulation of ACE2 expression by interferon is now known to be tissue- and cell type-specific and does not reduce ACE2 expression in nasal epithelial cells.[141] Therefore, differential drug treatment is unlikely to account for the now well-established regional difference in the prevalence of chemosensory dysfunction.

Since the nasal epithelium has a higher viral load than the respiratory epithelium[142–146] – and the nasal epithelium has increased expression of entry proteins for the virus[138] – ethnic differences have potentially far-reaching implications for infectivity, spread of the virus (frequency of asymptomatic super-spreaders),[147] and therefore for successful management of the pandemic. The frequency of ACE2 and/or TMPRSS2 variants in the population may make it more difficult in some ethnicities to control the pandemic, and easier in other ethnicities. The presence of those different variants in the olfactory epithelium may, in part, explain the more rapid spread of COVID-19 in Caucasians, including Latinos, as compared to Asians, in addition to the well-known cultural and political differences in approaches of containment, attitudes about social distancing, and the frequency of use of protective equipment such as face masks.

Other Factors that may affect Prevalence

Methodology to assess deficits.

Most studies rely on the subject telling the researcher about their subjective impressions of chemosensory deficits. Reports on how many cases of hyposmia may be missed in studies using self-reporting vs. objective tests varies between 10% and nearly 60%,[1, 5, 10, 12, 148] but self-reporting may often be the only feasible way of data collection during a raging pandemic. A relatively small number of studies (13/104) used objective tests to assess or confirm chemosensory dysfunction in COVID-19 patients.
[2, 19, 36, 44, 45, 49, 54, 55, 74, 78–80, 149, 150] When smell and taste were objectively tested and compared with the patients' reporting of subjective impressions, the percentage of subjects with dysfunction increased in most of those studies,[5, 7, 54] although in two studies, one third of subjective chemosensory loss could not be objectively confirmed.[36, 44] The effect of

methodology was assessed in several recent systematic reviews,[1, 5, 10, 12] and it was found that studies with objective tests report a larger prevalence of chemosensory dysfunction than studies with subjective reporting (Fig. 5a, b). Our own analysis revealed a similar difference (overall 68.7% vs. 43.9%), but curiously, there was no significant difference in prevalence between studies with objective vs subjective measures for taste.

Olfaction vs. taste.

Some of the studies reporting on smell and taste impairment did not examine taste dysfunction separately from smell dysfunction, but rather asked patients about ”smell and/or taste dysfunction” or “recent changes.” The pooled prevalence of chemosensory dysfunction that we report is likely an underestimate, because many studies reported only how many patients had smell deficits and how many had taste deficits, but they did not report on the potential overlap (there were many patients who had both types of chemosensory dysfunction, in at least 31/104 cohorts). Those cases were listed in our review conservatively, meaning that we did not simply add all cases with smell dysfunction to those with taste dysfunction, because we know that there is overlap in a substantial fraction of patients (Tables 2 and 3). Nevertheless, there is no doubt that a large fraction of COVID-19 patients (including otherwise asymptomatic carriers) have chemosensory deficits. Olfaction is used for tasting food (culinary experience) and it can be difficult to subjectively separate the two modalities.[7] Since most studies asked about *changes* to chemosensory perception, subjects with pre-existing loss of smell or taste would generally not have been included and would not have given false positives; some studies actively excluded patients with a history of pre-existing anosmia or ageusia.

Age of subjects.

Previous investigators have noted that smell and taste dysfunctions appeared to be more frequent in the younger age groups of COVID-19 patients (e.g., Giacomelli et al),[68] and this was verified by a recent systematic review.[1] Our results are consistent with this conclusion. Reduction of smell with age is a well-known phenomenon,[151] and this may to some extent explain the effect of age, but a sudden loss of function coincident with COVID-19 would still be expected to be noticeable in the older population. However, it is possible that the effect of age on chemosensory deficits is due to confounding and is not a proximate mechanism, because increasing age is also related to increased disease severity. The studies considered here nearly all examined adults; children were not included, with rare exceptions.[19] Two recent studies with focus on children indicate that they have a low prevalence of chemosensory dysfunction, so there may be a bimodal age distribution.[152, 153] The underlying mechanisms of such a bimodal age distribution require further study.

Gender.

Most previous studies concluded that more females with COVID-19 have chemosensory dysfunction than males, e.g.,[26, 27, 86] while a minority of studies reported the opposite,[71, 87] or found no gender difference.[21, 93, 102] Our analysis showed a 13% and 10% higher prevalence of smell and taste dysfunction, respectively, among females than males, but these differences were statistically not significant at the 95% confidence level. Possible reasons for such trends in gender differences include that females are more attentive and sensitive to

olfactory perception,[26] possibly due to hormonal effects, as well as the fact that ACE2 is located on the x chromosome.[26] Additional reasons may be related to variation in age or varying levels of disease severity between cohorts.

Disease severity.

Our study confirms that with increasing disease severity (hospitalization), the prevalence of reported chemosensory dysfunction decreases, as has been previously reported[8, 10, 113] This could have trivial reasons, e.g., it could be due to the fact that with increasing severity of COVID-19, not-life threatening symptoms such as chemosensory deficits become less noticeable and decrease in importance.

Nasal obstruction.

We calculated from 37 studies with such information that 66.9% of COVID-19 patients with anosmia did not have nasal congestion/ obstruction or rhinorrhea. This confirms the conclusions of a number of previous reports[6, 8, 9, 10, 91, 119, 154] which stated that the anosmia in COVID-19 cannot be explained by nasal congestion, although nasal obstruction often is the cause of anosmia in other viral infections.[155]

Duration of chemosensory dysfunction.

Our pooled analysis, based on 20 studies with such information for loss of smell and 13 studies for loss of taste, revealed that the mean duration of the chemosensory dysfunction was 8 to 9 days, with 10 out of 20 studies on olfaction reporting an average duration of 8 days or less. This relatively short time has implications for the pathogenetic mechanism: It seems too short for a functional recovery if such a recovery involved death and regeneration of olfactory neurons, since their replacement by stem cells alone takes 9–10 days.[140, 156, 157] Alternative mechanisms, not requiring olfactory neuron death, that may explain the transient anosmia include a support-cell mediated dysfunction of the olfactory epithelium[138, 140, 158, 159] or a virus-induced short-lasting immune response,[139] although the extent of inflammation in the olfactory epithelium in response to SARS-CoV-2 is still unclear.[160, 161]

Conclusions

The main novel finding of our review is that the prevalence of chemosensory dysfunction in COVID-19 differs significantly between populations, and apparently ethnicities. These population differences may be explained by two different scenarios: at the level of the virus, mutation D614 to G614 may be more infectious and damaging to chemosensory structures, while at the level of the host, different frequencies of genetic variants of the SARS-COV-2 virus entry proteins may be present in the olfactory epithelium and taste buds which may lead to differential susceptibility to chemosensory dysfunctions. It is likely that both, virus and host factors, contribute to the variation in the prevalence of chemosensory dysfunction. Strengths of our study are the larger number of studies and subjects we considered, compared to previous reviews, allowing us to detect geographic/ethnic differences, as well as associations or trends with age, gender, methodology, and new insights regarding the duration of the dysfunction. Limitations are that chemosensory dysfunctions in COVID-19

have not yet been reported (or too rarely) for several populations, such as Africans, Latinos, or Native Americans, as well as for children. Such information will certainly be forthcoming in the near future, allowing to test hypotheses regarding the underlying mechanisms of differential susceptibility to chemosensory dysfunctions in different populations.

Methods

Our study followed the PRISMA guidelines for systematic searches and meta-analyses.[162] We searched the COVID-19 portfolio of the National Institutes of Health (https://icite.od.nih.gov/covid19/search/) with the key words „anosmia," „ageusia," „smell," or „taste" on and before August 15, 2020, resulting in 5,031 records (946 after removal of duplicates), including preprints posted prior to peer review. We also examined and included any relevant references within, and citations of, screened records. Inclusion criteria were that the paper was a novel report of the prevalence of smell and/or taste impairment in patients verified to have COVID-19. We accepted all studies that reported original and quantitative data on prevalence of chemosensory deficits in human subjects diagnosed with COVID-19, either obtained by questioning the subjects, by chart review, or by objective chemosensory testing. When a study reported prevalence based on subjective self-reporting as well as objective testing, as in Moein et al., 2020, Hintschich et al., 2020,[44, 54] we used the prevalence numbers from objective testing for the analysis. We excluded from our quantitative analysis case reports, reports that did not provide quantitative information, reviews only, and reports of cohorts in which a COVID-19 diagnosis was not confirmed clinically or by lab tests. We also excluded studies that targeted *any* patients with chemosensory deficits, regardless of cause, because they would fail to provide a true, unbiased prevalence specifically among COVID-19.[120] We also excluded studies that targeted primarily or exclusively COVID-19 patients *with* chemosensory dysfunction[163, 164] because of inherent population bias in such studies,[5, 14] and we excluded studies when subjects in the cohort apparently were already part of another, larger cohort, e.g.,[21, 165] There were 104 studies that met our inclusion criteria. We kept data on the two senses, olfaction and taste, separate, when the original study reported them separately. The most common way of reporting in studies was „smell deficit," "taste deficit," or „smell and/or taste deficit," and those data were separately compiled and compared. For this reason, the cohort number for olfactory deficits and gustatory deficits differs from that of the combined (smell and/or taste) category. The included studies are listed chronologically and by geographic region: populations from Asia/ Middle East/ Americas/ Australia in Table 2, and from Europe in Table 3. Whether some patients had both, smell and taste dysfunction, was stated explicitly only in a fraction of studies, as is apparent from the numbers given (31/104 cohorts, Tables 2 and 3). A pooled analysis was performed for prevalence, and significance and confidence intervals were calculated in the software R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). To calculate estimates of pooled prevalence and 95% confidence intervals, we used the R-meta package, version 4.9–5, and the metaprop function. We used random effects models with the inverse variance method for pooling and the logit transformation for proportions.[166] For ease of interpretation, we back transformed and rescaled proportions to events per 100 observations. Analysis of the heterogeneity across studies was done using the Maximum-likelihood estimator, Higgins' I^2 and Cochran's Q

method.[115, 166] Publication bias was assessed by visual inspection of funnel plots.[167] In all cases, significance was defined at $\alpha = 0.05$.

Subgroup analysis was conducted by ethnicity, age, hospitalization rate, methodology, and gender. However, sufficient data only existed among Caucasians to examine gender differences in chemosensory deficits. Ethnicity was coded as a categorical variable with two levels: Caucasian and Asian, because of suspected heterogeneity[2, 4, 12, 17, 19, 126] and because these two ethnicities are the only ones for which a sufficient number of studies and a sufficient number of subjects in the cohorts are currently available. We included among the "Caucasians" cohorts from America, Australia, the Middle East and Turkey. Methodology was coded as a binary variable with "objective" or "not objective" as the two levels. All other subgroup tests used continuous variables and the metareg function to adjust the overall meta-analysis for the subgroup. The subgroup age was a created variable that used the center of the sample, either the mean or the median, to mark the center of the age distribution. Hospitalization rate was the percentage of subjects in the sample that were hospitalized for COVID-19 or was the percent of subjects specifically indicated in the study as having a "severe" case of COVID-19. Because sensory deficits were frequently reported separately for males and females, we extracted gender-specific chemosensory loss data from publications and used separate random effects meta-analyses (with the same methods as described above) to obtain weighted overall estimates of chemosensory loss with 95% confidence intervals for males and for females. Stratifying our analyses by gender allowed a precise estimation of the prevalence of chemosensory among males and females because we were able to use outcome data that was specific to each gender.

We did not conduct multivariable regression using our five subgroups because ethnicity and methodology were the only subgroups of interest that were consistently reported across studies. Considering all the unreported data among the subgroups of interest, less than 10% of the studies located in this review would have been eligible for the multivariable meta-regression (smell = 9/91 and taste = 7/71). Consequently, in this case the results of multivariable meta-regressions would not be robust or trustworthy.

Acknowledgments

The authors thank Bette Korber (Los Alamos National Laboratory, New Mexico) and two anonymous reviewers for helpful comments.

Funding

Funding was provided by grant GM103554 from the National Institutes of Health and the "Excellence Initiative - Research University" programme at the Nicolaus Copernicus University.

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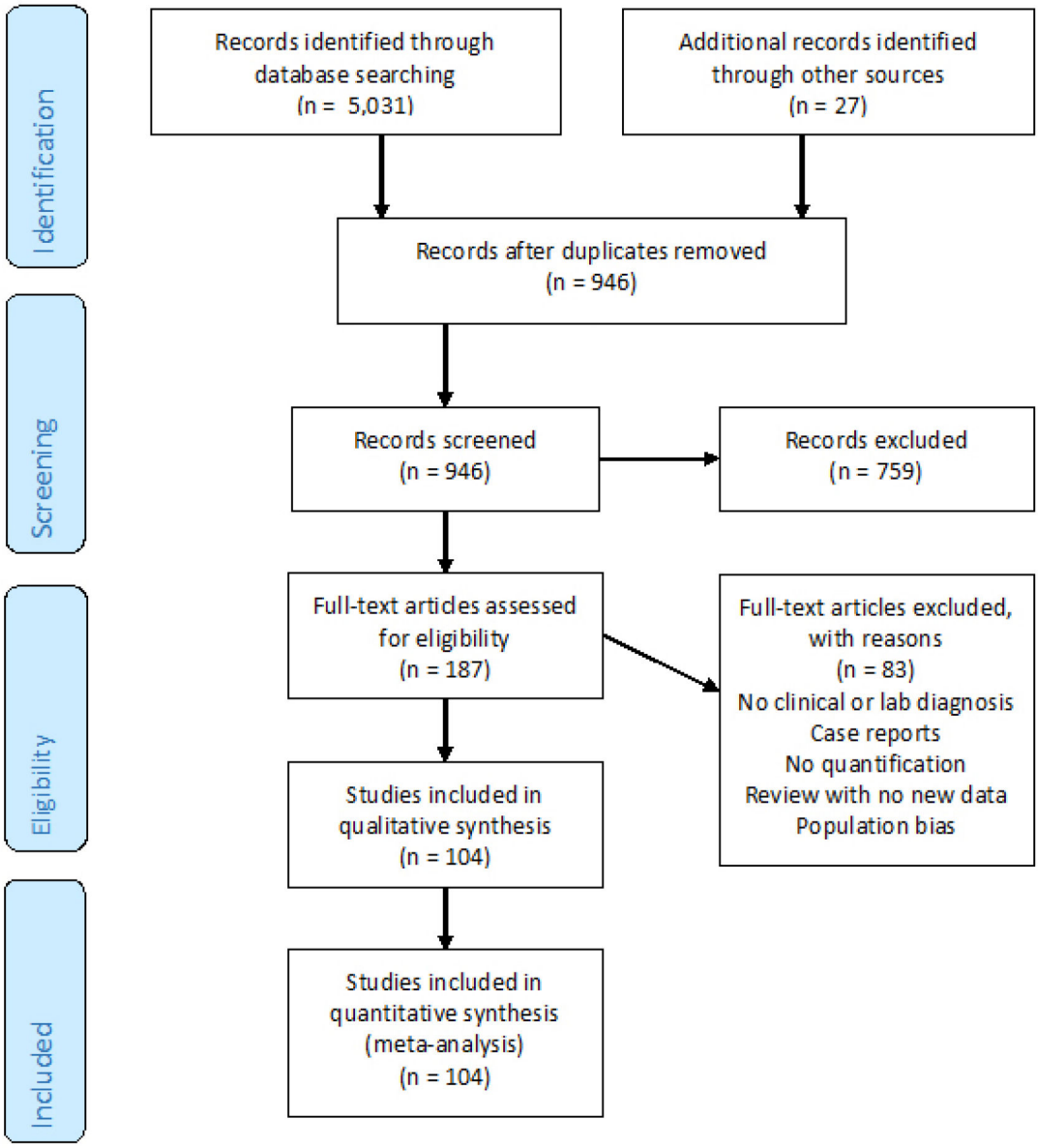

Figure 1.

Flowchart of the search strategy, article selection, application of inclusion and exclusion criteria, and removal of duplicates according to the PRISMA guidelines.

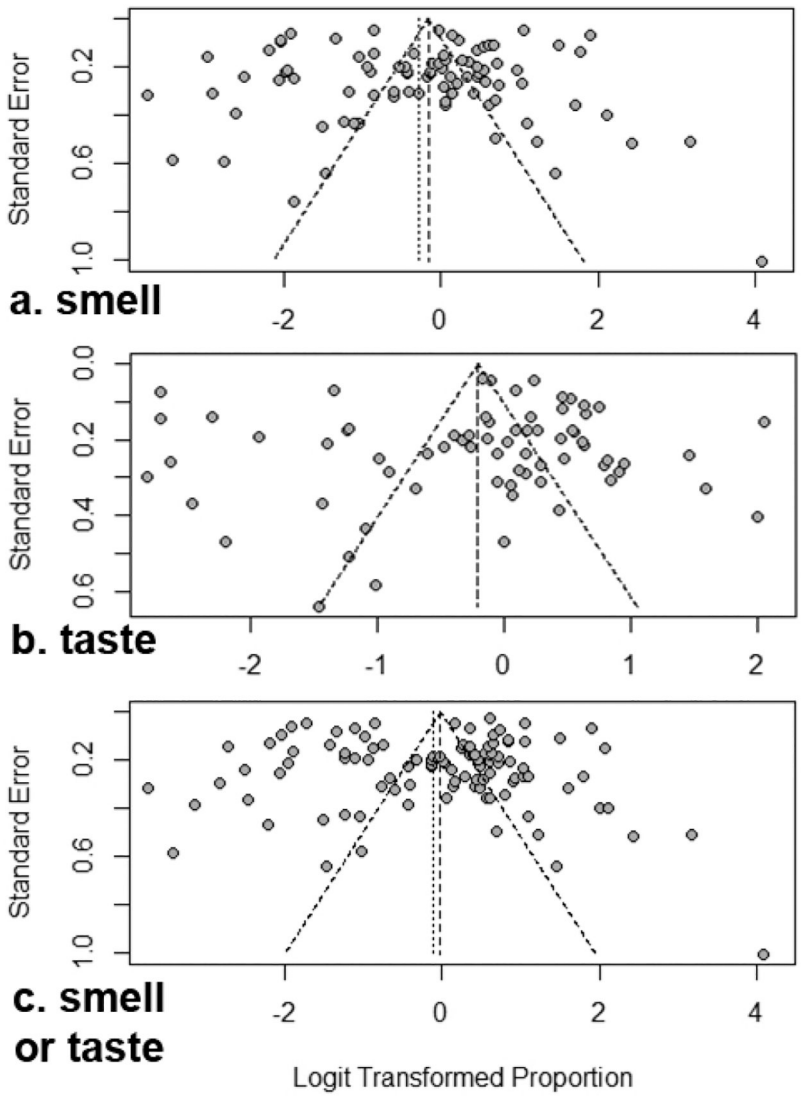

Figure 2a-c.

Funnel plots of the prevalence of dysfunction of smell (**a**), taste (**b**), and smell and/or taste (**c**) in COVID-19 patients.

Each dot represents a single study with the x-axis showing the logit transformed proportion of people in each study that lost their sense of (a) smell, (b) taste, and (c) smell and/or taste; the y-axis shows the standard error (SE) as a measure of precision. Most studies are large/precise (higher on y-axis), but medium- and small-size studies are also present (gaps in the y-axis are minor). Many studies fall outside of the 95% CI limit (dotted triangle), suggesting that study heterogeneity is high. There is some evidence that small-study effects are contributing to heterogeneity, as studies with larger SE show slightly smaller logit transformed proportions.

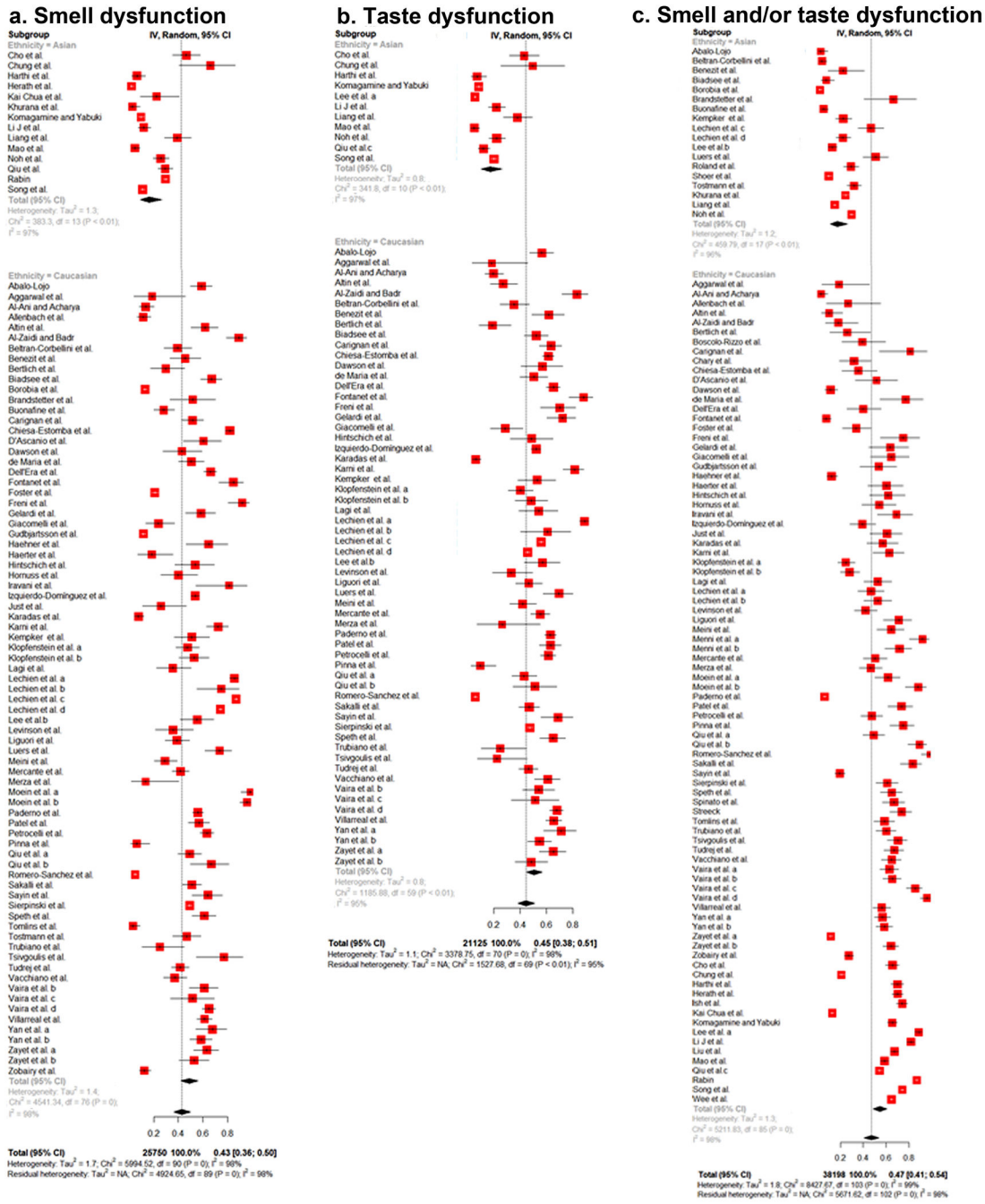

Figure 3a-c.

Forest plots of the prevalence of smell dysfunction (**a**), taste dysfunction (**b**), and smell and/or taste dysfunction (**c**) in COVID-19 patients.

Estimated random proportions are shown by red boxes with 95% confidence intervals (95% CI) extending as whiskers, the overall estimated random proportion of subgroups is shown in gray, and the results for all studies combined are shown in black. Note the difference between Asians and Caucasians.

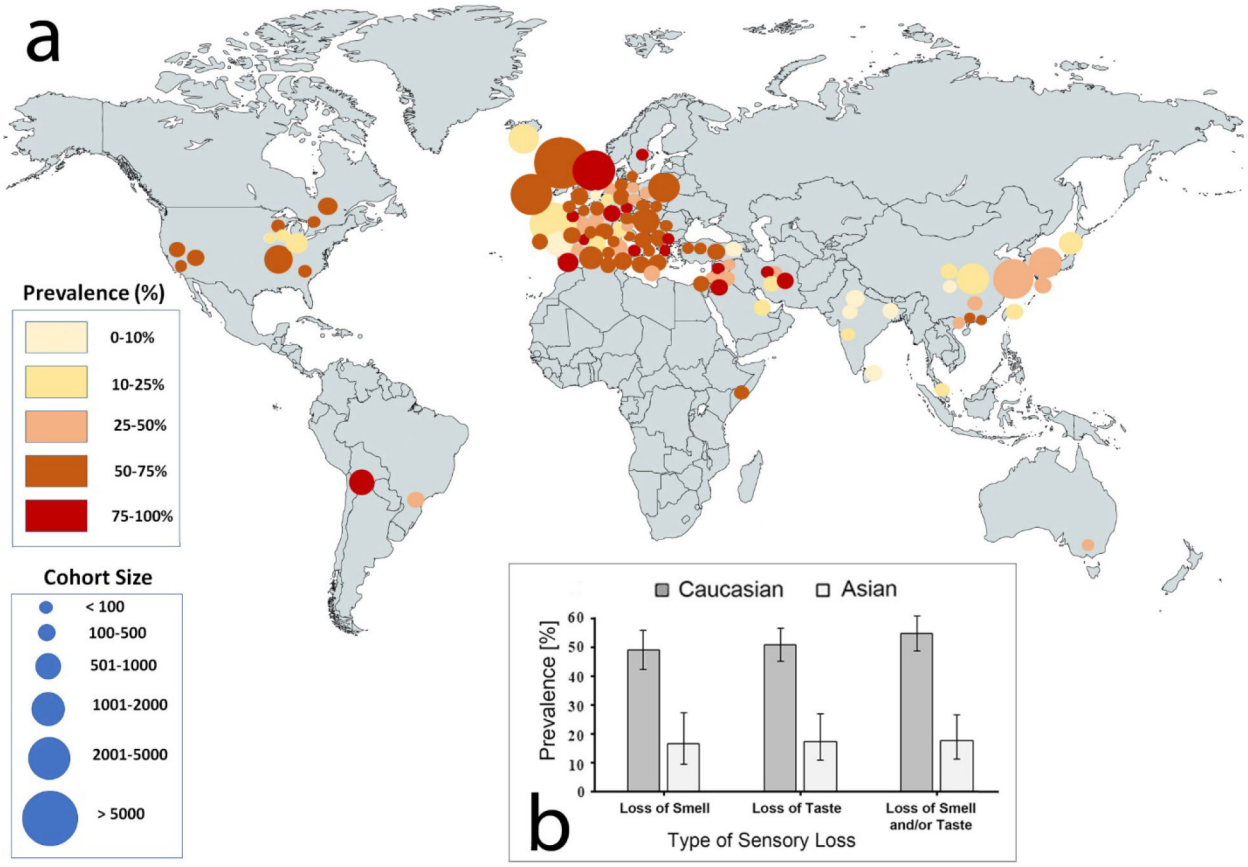

Figure 4a, b.

Prevalence of any chemosensory deficit (smell and/or taste) in COVID-19 patients.

a. World map as a heat map showing the size and approximate location of cohorts. Three studies (from Germany, India, and Somalia) were inadvertently missed and not included in the meta-analysis, but their cohorts were added to the world map.[116–118]

b. Estimated random prevalence of chemosensory dysfunction - comparison of Caucasians and Asians. Error bars indicate 95% confidence intervals. Note the significant 3-fold difference in prevalence between Caucasian and Asian populations.

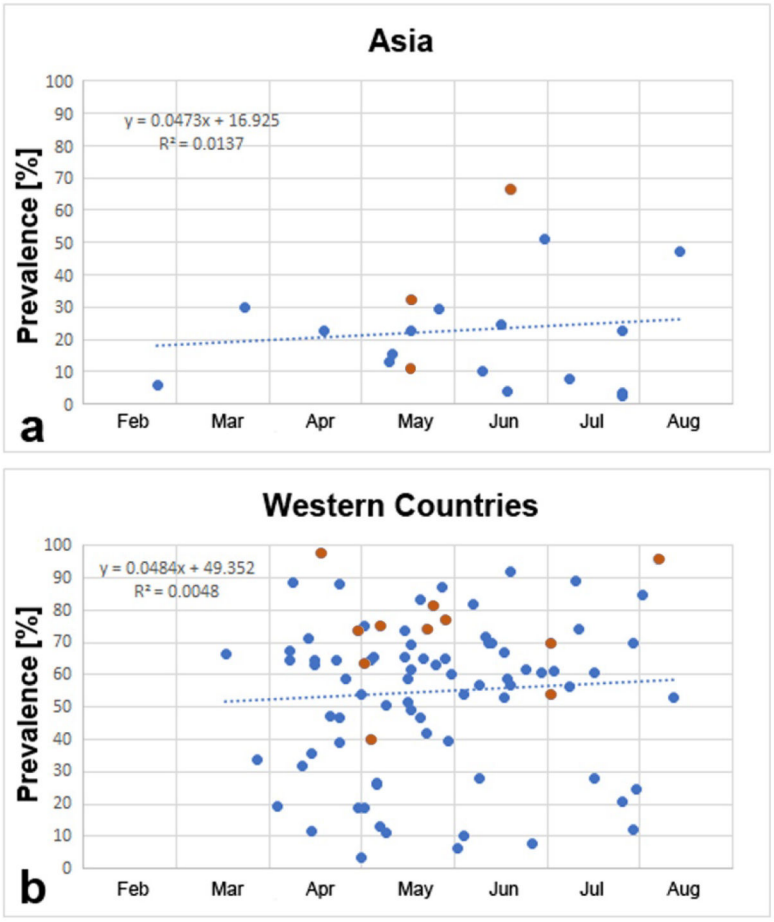

Figure 5a-b.

Comparison of the prevalence of chemosensory dysfunction between cohorts from Asia (**a**), and from Western countries (**b**). The trendline for studies from February through August 2020 is very slightly increasing, with a similar slope in Asia as in Western countries. The prevalence data based on subjective self-reporting is shown with blue dots, the data based on objective tests is shown with orange dots.

TABLE 1.

Subgroup test results for continuous variables: age and disease severity (percent of patients hospitalized).

	Smell Loss			Taste Loss			Smell and/or Taste Loss		
Subgroup	**b**	**se**	***p*-value**	**b**	**se**	***p*-value**	**b**	**se**	***p*-value**
Age	−0.047	0.014	**0.0008**	−0.033	0.013	**0.0083**	−0.043	0.014	**0.0016**
Hospitalizations	−0.019	0.004	< **0.0001**	−0.013	0.005	**0.0032**	−0.020	0.004	< **0.0001**

The beta coefficients “b” show the degree of change in each outcome variable for every 1-unit of change in the predictor variable; the standard error of the beta coefficient is shown as “se”; and the *p*-value shows the likelihood that the beta coefficient is significantly different from zero. P-values below 0.05 indicating significance are shown in bold font.

TABLE 2.

Smell and Taste Dysfunction in COVID-19: Chronology of Studies in Asia, Middle East, America and Australia

Author and Reference #	First Post	Publication Date	Country or Region	Cohort #	Age mean, m median, M	Smell disorder %	Taste disorder %	Any Chemo-Sensory disorder %	Journal or Preprint Archive
EAST ASIA									
Mao 28	2 24 20	4 10 20	China	214	m 53	5.1	5.6	5.6	JAMA Neurol
Rabin 84		3 22 20	Korea	2,000		30		30	New York Times
Wee 89		4 18 20	Singapore	154				22.7	Eur Arch Otorhinolaryngol
Liu 99		5 9 20	Taiwan	321	most 20–39			13.1	Int J Environ Res Publ Health
Lee 82		5 10 20	Korea	3,191	24–59			15.3	J Korean Med Sci
Kai Chua 88		5 16 20	Singapore	31		22.6		22.6	Ann Emerg Med
Qiu 19	5 16 20	6 16 20	China	239	**M** 31	29.7	12.6	32.2	MedRxiv, Otolaryngol Head Neck Surg
Noh 83		5 25 20	Korea	199	m 38	26.1	22.6	29.6	J Infect
Komagamine 81	6 09 20		Japan	628		10	9.1	10	Reseach Square
Song 29	6 15 20		China	1,172	**M** 61	11.4	20.6	24.8	medRxiv
Chung 2		6 18 20	China	18	**M** 28	66.7	50.0	66.7	Int Forum Infect Dis
Liang 27		6 29 20	China	86	**M** 26	39.5	38.4	51.2	J Infect Dis
Li 26	7 24 20		China	187	m 54	12.3	22.5	22.5	Research Square
Cho 25		8 13 20	China	83	m 36	47	43.4	47	Laryngoscope
SOUTH ASIA									
Ish 52		6 17 20	India	170				4.1	Laryngoscope
Harthi 16	7 07 20		South Asia	102	m 26	6.9	7.8	7.8	Research Square
Herath 96	7 24 20		Sri Lanka	431	m 37	2.3		2.3	Research Square
Khurana 51	7 24 20		India	94	m 36	3.2		3.2	medRxiv
MIDDLE EAST AND TURKEY									
Levinson 60	4 14 20	6 18 20	Israel	42	**M** 34	35.7	33.3	35.7	medRxiv, Infect Dis
Moein 54		4 17 20	Iran	60	m 47	98		98	Int Forum Allergy Rhinol
Merza 56		5 05 20	Iraq	15	m 28	13.3	26.7	26.7	Diabetes Metab Syndr
Shoer 61		6 08 20	Israel	498	m 49			27.8	medRxiv

Author and Reference #	First Post	Publica-tion Date	Country or Region	Cohort #	Age mean, m median, M	Smell disorder %	Taste disorder %	Any Chemo-Sensory disorder %	Journal or Preprint Archive
Sayin 103		6 10 20	Turkey	64	m 38	64.1	68.8	71.9	Otolaryngol Head Neck Surg
Biadsee 58		6 16 20	Israel	128	m 36	67	52	67	Otolaryngol Head Neck Surg
Altin 100		6 23 20	Turkey	81	m 54	61.7	27.2	61.7	Eur Arch Otorhinolaryngol
Karadas 101		6 25 20	Turkey	239	m 46	7.5	6.7	7.5	Neurol Sci
Sakalli 102		7 07 20	Turkey	172	m 38	51.2	47.1	56.4	Am J Otolaryngol
Al-Zaidi 53		7 09 20	Iraq	65	m 41	89.2	83.1	89.1	Research Square
Zobairy 57	7 28 20		Iran	203	m 49	12.3		12.3	medRxiv
Al-Ani 87	7 29 20		Qatar	141	m 36	13.5	19.9	24.8	Research Square
Karni 59		8 01 20	Israel	112	**M** 35	72	81	85	medRxiv
Moein 55		8 06 20	Iran	100	m 57	53	42.8	53	Int Forum Allergy Rhinol
AMERICA									
Menni 104	4 07 20	5 11 20	USA	726	m 45			67.5	Nature Med
Yan 113		4 13 20	USA	59	M 46	67.8	71.2	71.2	Int Forum Allergy Rhinol
Yan 114		4 25 20	USA	128	**M** 46	58.6	54.7	58.6	Int Forum Allergy Rhinol
Aggarwal 107		4 29 20	USA	16	**M 67**	19	19	19	Diagnosis
Roland 112		5 04 20	USA	145	m 40			65.5	Int Forum Allergy Rhinol
Dawson 108	5 16 20	6 21 20	USA	42		42.9	57.1	61.9	medRxiv, Clin Infect Dis
Carignan 23		5 29 20	Canada	134	m 57	51.5	63.4	64.9	Can Med Assoc J
Pinna 111		6 03 20	USA	50	m 60	6	10	10	J Neurol Sci
Chiesa-Estomba 15		6 06 20	South America	542	m 34	81.9	61.4	81.9	Am J Otolaryngol
Lee 24		6 08 20	Canada	56	m 38	55.4	57.1	57.1	Can J Emerg Med
Kempker 110		6 28 20	USA	51		51	52.9	60.7	Clin Infect Dis
Buonafine 22	7 15 20		Brazil	125	**M** 34	28		28	Research Square
Foster 109		7 24 20	USA	949	m 48	20.9		20.9	Annal Allergy Asthma Immunol
AUSTRALIA									
Trubiano 20		5 28 20	Australia	28	**M** 55	25	25	39.3	Clin Infect Dis

TABLE 3.

Smell and Taste Dysfunction in COVID-19: Chronology of Studies in Europe.

Author and Reference #	First Post	Publication Date	Country or Region	Cohort #	Age mean, m median, M	Smell defect %	Taste defect %	Smell and /or Taste defect %	Journal or Preprint Archive
Streeck 48		3 16 20	Germany	100				66.7	Frankf Allg Zeitung
Giacomelli 68		3 26 20	Italy	59	**M** 60	23.8	28.9	33.9	Clin Infect Dis
Vaira 77		4 03 20	Italy	320				19.4	Laryngoscope
Menni 104	4 07 20		UK	6,452	m 41			64.7	Nature Med
Lechien 17		4 08 20	Europe	417	m 37	85.6	88.8	88.8	Eur Arch Otorhinolaryngol
Bertlich 40	4 11 20		Germany	47	m 64	29.8	19.1	31.9	SSRN
Gudbjartsson 50		4 14 20	Iceland	1,044	m 44	11.5		11.5	NEJM
Benezit 31		4 15 20	France	68		45.6	61.8	64.7	Lancet
Patel 105	4 15 20	6 02 20	UK	141	m 46	56.7	63	63	Clin Microbiol Infect
Klopfenstein 34		4 20 20	France	114	m 47	47	40.5	47	Med Mal Infect
Spinato 75		4 22 20	Italy	202	**M** 56			64.4	JAMA
Beltran-Corbellini 91		4 23 20	Spain	79	m 62	31.7	35.4	39.2	Eur J Neurol
Fontanet 33		4 23 20	France	59	m 37	84.7	88.1	88.1	medRxiv
Tostmann 85		4 23 20	Holland	79	m 38	46.8		46.8	Euro Surveill
Vaira 78		4 29 20	Italy	72	m 49	46.1	44.2	73.6	Head Neck
Lagi 69		4 30 20	Italy	48	**M** 62	35.4	54.1	54.1	Euro Surveill
Tomlins 106		4 30 20	UK	95	**M** 75	3.2		3.2	J Infect
Härter 43	5 01 20	5 11 20	Germany	32	m 48	19		19	MedRxiv, Infection
Luers 47		5 01 20	Germany	72	m 38	74	69	75	Clin Infect Dis
Vaira 79		5 01 20	Italy	33	m 52	51.5	51.5	63.6	Head Neck
De Maria 65		5 08 20	Italy	95		50.5	50.5	50.5	J Med Virol
Brandstetter 41		5 15 20	Germany	31		51.6		51.6	Pediatr Allergy Immunol
Hornuss 45	5 03 20	5 22 20	Germany	45	**M** 56	40		40	Clin Microbiol Infect
Haehner 42	5 03 20	6 11 20	Germany	34	m 39	64.7		64.7	medRxiv, ORL
Just 46	5 05 20		Germany	27	M 52	25.9		25.9	medRxiv
Lechien 36	5 06 20		France	28	m 44	75	60.1	75	medRxiv
Borobia 92	5 06 20	6 04 20	Spain	2,226	**M** 61	12.8		12.8	medRxiv, J Clin Med

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Zayet 38		5 14 20	France	95	m 40	63.2	65.3	73.7	Infection
Paderno 73		5 14 20	Italy	508	m 55	56	63	65.6	Int Forum Allergy Rhinol
Tudrej 37	5 15 20	6 09 20	France	198	**M** 45	41.4	46.5	58.6	Research Square, J Gen Int Med
Qiu 19	5 16 20	6 16 20	France	116	**M** 48	49.1	43.1	49.1	medRxiv, Otolaryngol Head Neck Surg
Qiu 19	5 16 20	6 16 20	Germany	39	**M** 43	66.7	51.3	69.2	medRxiv, Otolaryngol Head Neck Surg
Gelardi 67		5 19 20	Italy	72	m 50	58.3	72.2	83.3	Acta Biomed
Liguori 70		5 19 20	Italy	103	m **55**	38.8	46.6	46.6	Brain Behav Immun
Speth 98		5 20 20	Switzerland	103	m 47	61.2	65	65	Otolaryngol Head Neck
Meini 71	5 21 20	6 04 20	Italy	100	m 63	29	42	42	Eur Arch Otorhinolaryngol
Vaira 80		5 21 20	Italy	345	m **49**	65	67.8	74.2	Head Neck
Iravani 97	5 23 20	7 06 20	Sweden	16	m 47	81.3		81.3	medRxiv, Chem Senses
Boscolo-Rizzo 62		5 26 20	Italy	54				63	Eur Arch Otorhinolaryngol
Lechien 21		5 26 20	Belgium	2,013	m 40	87	56	87	Ann Int Med
Tsivgoulis 49		5 27 20	Greece	22	m 55	77.3	23	77.3	J Neurol
Abalo-Lojo 90		5 29 20	Spain	131	m 50	58.8	56.5	60.3	Ann Otol Rhinol Laryngol
Romero-Sanchez 94		6 01 20	Spain	841	m 66	4.9	6.2	6.2	Neurology
Sierpinski 86		6 03 20	Poland	1,942	**M** 50	49.2	47.5	54.2	Pol Arch Int Med
Allenbach 30	6 08 20		France	150	**M** 77	11.3		11.3	medRxiv
Dell'Era 64		6 11 20	Italy	355	**M** 50	66.1	65.4	70	Head Neck
Chary 32		6 12 20	France	115	m 47			70	Am J Rhinol Allergy
Zayet 39		6 16 20	France	70	m 57	52.9	48.6	52.9	Microbes Infect
Izquierdo-Domínguez 93		6 17 20	Spain	846	m 57	53.7	52.2	58.7	J Investig Allergol Clin Immunol
Freni 66		6 18 20	Italy	50	m 38	92	70	92	Am J Otolaryngol
Mercante 72		6 18 20	Italy	204	m 53	41.7	55.4	56.9	JAMA Otolaryngol Head Neck Surg
Hintschich 44		7 01 20	Germany	41	**M** 37	54	8	54	Int Forum Allergy Rhinol
Petrocelli 74		7 01 20	Italy	300	m 43	63.3	61.3	70	J Laryngol Otol
Vacchiano 76		7 02 20	Italy	108	**M** 59	37	61	61	Neurol Sci

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Lechien 18	7 10 20		Europe	2,581	m 45	74.2	45.8	74.2	Research Square
D'Ascanio 63		7 15 20	Italy	43		60.5		60.5	Otolaryngol Head Neck Surg
Villarreal 95		7 28 20	Spain	256	**M** 43	68	70	70	Eur Arch Otorhinolaryngol
Klopfenstein 35		8 11 20	France	70	m 57	53	42.8	53	J Infect Dis