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.

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Review

Systematic review and meta-analysis of olfactory and gustatory dysfunction in COVID-19

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ABSTRACT

Background: Chemosensory disorders associated with COVID-19 have been widely discussed during the pandemic. We performed a meta-analysis to assess the risk factors for olfactory and gustatory dysfunction in patients with COVID-19.

Methods: Three databases (PubMed, Embase, and Cochrane Library) were searched for studies published between December 1, 2019, and August 31, 2021. We selected random-effects model or fixed-effects model to pool data based on heterogeneity. The results were reported as odds ratios (ORs) or standardized mean differences (SMDs) and the corresponding 95% confidence intervals (CIs). Heterogeneity was reported as I^2.

Results: Twenty-six studies with a total of 13,813 patients were included. The pooled data indicated that sex (OR 1.47; 95% CI 0.93–2.31), age (SMD −5.80; 95% CI −13.35 to 1.75), smoking (OR 2.04; 95% CI 0.72–5.79), and comorbidity (OR 1.21; 95% CI 0.58–2.53) of patients with COVID-19 had no effect on gustatory dysfunction. Olfactory dysfunction was more likely to occur in older patients with COVID-19 (SMD, −5.22; 95% CI, −8.28 to −2.16). Patients with COVID-19 with nasal congestion (OR 3.41; 95% CI 2.30–5.06) and rhinorrhea (OR 2.35; 95% CI 1.60–3.45) were more prone to olfactory dysfunction.

Conclusion: These findings emphasize that older patients with COVID-19 are more likely to experience olfactory dysfunction. Symptoms of nasal congestion and rhinorrhea may affect the recognition of olfactory dysfunction.

Introduction

COVID-19, which started at the end of 2019 (Chen et al., 2020), is still prevalent worldwide. It has caused more than 200 million infections and 4.3 million deaths, with infection and death numbers continuing to be updated. Individuals infected with the virus usually develop nonspecific symptoms in the prodromal stage of the disease, in which fever, cough, dyspnea, muscle pain, and fatigue are the most common symptoms (Huang et al., 2020 Wang et al., 2020;). In the early stages of the outbreak, the focus was on individuals with the infection and people exposed to them. Owing to the shortage of test kits, asymptomatic carriers were not tested even in high-income countries with good health care systems. With the improvement of global detection capabilities, asymptomatic carriers were finally diagnosed; most of them presented with complaints of chemosensory disorders, such as changes in olfactory and gustatory function (Desiato et al., 2021 Aziz et al., 2021;).

Self-reported chemosensory changes can predict the likelihood of a positive test result for SARS-CoV-2. A recent observational study involving more than 2 million participants reported that the loss of smell and taste was a stronger predictor than all other symptoms, including fatigue, fever, or cough. However, most of these studies lack objective evaluation methods, which increases the possibility that chemical sensory disorders are more common than currently recognized.

Recent meta-analyses and systematic reviews have reported the prevalence of gustatory and olfactory dysfunction in COVID-19. However, the data vary widely: the incidence of olfactory disorders is between 3% and 98%, and that of gustatory disorders is between

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6% and 93% (Tong et al., 2020 Agyeman et al., 2020;). This difference may be related to age, sex, disease severity, and race. The selection of participants may also be responsible for the difference because some data are obtained from outpatient departments and some from inpatient departments. Although multiple reviews have summarized and analyzed numerous original studies, the effects of age, sex, disease severity, geographic region, and race on COVID-19–related gustatory and olfactory dysfunction are still unclear. In addition, confirmed cases are usually accompanied by nasal congestion and rhinorrhea, which may affect olfactory function. Therefore, we conducted a systematic review and meta-analysis based on the existing evidence to comprehensively understand the role of the previously mentioned factors in COVID-19–related gustatory and olfactory dysfunction.

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline (Moher et al., 2009; Stroup et al., 2000). This study was registered on PROSPERO (CRD42021253869), but the protocol was not prepared.

Search strategy and selection criteria

We systematically searched the PubMed, Embase, and Cochrane databases from December 1, 2019, to August 31, 2021, to obtain any designed observational studies (cohort, case-control, or cross-sectional) that reported on patients with COVID-19 with olfactory and gustatory dysfunction. Table 1 in the Supplement provides the detailed query strategy. Two researchers independently screened all the titles and abstracts identified from the search and resolved differences through discussion. The references of relevant studies were cross-checked to identify other studies that were not found by the electronic search.

Selection and data extraction

Articles that met the following criteria were included: (1) observational studies recording data on olfactory and gustatory dysfunction in patients with COVID-19 and (2) studies reporting on patients with COVID-19 with and without olfactory and gustatory dysfunction. We excluded (1) animal studies and (2) brief reports, case reports, letter to editor, reviews, abstracts, and studies that were not available in full text.

Two researchers independently extracted data using a predesigned data extraction table and resolved any disagreements through discussion. The extracted information included study characteristics (eg, publication year, country of origin, study period, study design, follow-up time, and funding sources), participant characteristics (eg, sample size, age, and sex), and selection of cases and controls. For each study that reported risk factor data, we obtained the risk ratio or odds ratio (OR) and the corresponding 95% confidence interval (CI) or the number of participants. For cohort and case-control studies, we assessed the risk of bias using the Newcastle-Ottawa Scale and assessed studies with scores greater than 6 to have a lower overall risk of bias (Stang, 2010). Cross-sectional studies were evaluated using the 11-item checklist recommended by the Agency for Healthcare Research and Quality (AHRQ) (Jue et al., 2019).

Statistical analysis

We defined dysgeusia, ageusia, taste disorders, taste loss, hypogeusia, change in taste, taste loss, and taste disorder as gustatory dysfunction; hyposmia, anosmia, smell impairment, loss of smell, and olfactory disorder were defined as olfactory dysfunction. We pooled data using a random- or fixed-effect model based on the degree of heterogeneity and reported results using OR estimates with corresponding 95% CI. Heterogeneity was classified as moderate (I^2 = 25%–50%), substantial (I^2 = 50%–75%), or considerable ($I^2 \geq$ 75%). We also conducted a sensitivity analysis based on the results. We performed a predefined subgroup analysis based on race (Caucasian and Asian) to assess the potential source of heterogeneity. If the number of included studies was sufficient, the possibility of publication bias was assessed. Variables were compared using the χ^2 test. All tests were 2-tailed, and a P value less than .05 was considered statistically significant.

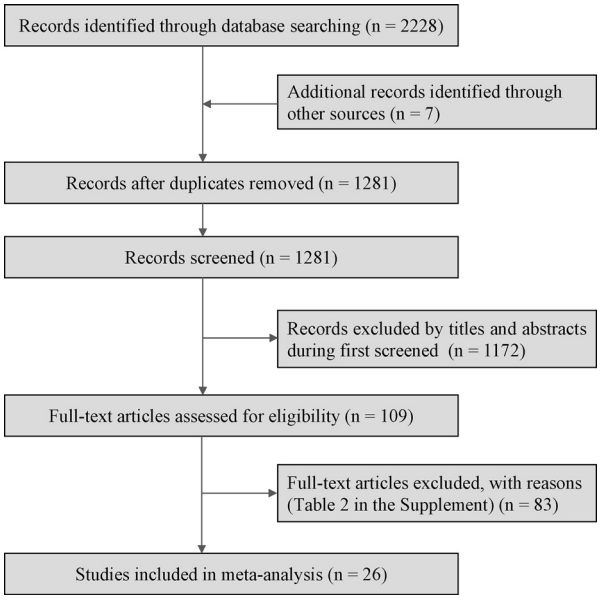


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Results

A total of 2235 articles were screened, 109 full-text articles were scrutinized, and ultimately, 26 studies met the inclusion criteria for meta-analysis (Figure 1). These studies documented patients with and without olfactory and gustatory dysfunction (Le Bon et al., 2021 Sanli et al., 2021; Rojas-Lechuga et al., 2021; Sayın et al., 2021; Dev et al., 2021; Sheng et al., 2021; Elibol and Baran, 2021; Samimi et al., 2021; Sahoo et al., 2021; Singer-Cornelius et al., 2021; Porta-Etessam et al., 2021; Gupta et al., 2021; Soh et al., 2021; Tabari et al., 2021; Jain et al., 2021; Lee et al., 2021; Cheng et al., 2021; Ahn and Min, 2021; Klopfenstein et al., 2020; Lv et al., 2020; Jalessi et al., 2020; Petrocelli et al., 2020; Prajapati et al., 2020; Shah et al., 2020; Altundag et al., 2020; Tham et al., 2020;). The 83 excluded articles and the reasons for exclusion are provided in Table 2 in the Supplement.

Study characteristics

Detailed information on the included studies is provided in Table 1. Most of these studies had a retrospective design and involved single-center cohorts. Among the 26 studies, 14 included patients of Asian descent, whereas the others included patients of European descent. The case group reported olfactory and/or gustatory dysfunction, whereas the control group did not report complaints in this regard. The quality of the study was moderate quality, with an

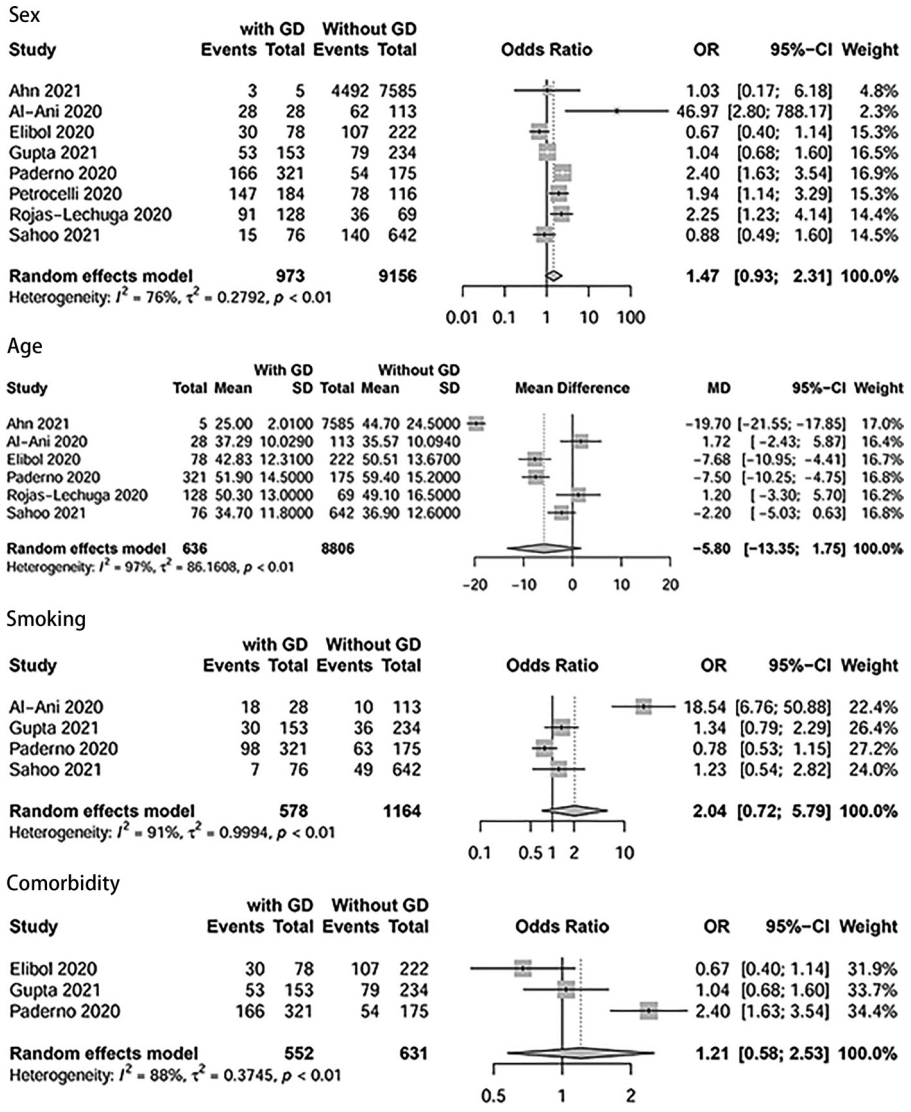


Figure 2. Forest plot of sex, age, smoking, and comorbidity on the risk of gustatory dysfunction in patients with COVID-19. CI, confidence interval; GD, gustatory dysfunction; MD, mean difference; OD, olfactory dysfunction; OR, odds ratio; SD, standard deviation.

average score of 6.2 (1.70). All COVID-19 cases were confirmed by reverse transcription-polymerase chain reaction, and olfactory and gustatory dysfunction were confirmed by self-reporting or testing.

Meta-analysis of patients with COVID-19 with and without gustatory dysfunction

Previous studies have emphasized the contribution of age, sex, and race to olfactory and gustatory dysfunction, but the results are inconsistent. Here, we investigated the role of these risk factors in 26 studies. The results suggested that sex (OR 1.47; 95% CI 0.93–2.31), age (SMD −5.80; 95% CI −13.35 to 1.75), smoking (OR 2.04; 95% CI 0.72–5.79), and comorbidities (OR 1.21; 95% CI 0.58–2.53) had no effect on the occurrence of gustatory dysfunction (Figure 2).

Meta-analysis of patients with COVID-19 with and without olfactory dysfunction

The pooled results emphasize that sex (OR 0.86; 95% CI 0.62–1.19), smoking (OR 0.99; 95% CI 0.78–1.25), and comorbidities (OR 0.83; 95% CI 0.61–1.11) have no effect on olfactory dysfunction (Figure 3). However, we found that age contributed to olfactory dysfunction (SMD −5.22; 95% CI −8.28 to −2.16) (Figure 4), as older patients with COVID-19 were more likely to develop olfactory dysfunction. Interestingly, nasal congestion (OR 3.41; 95% CI 2.30–5.06; $P < 0.00$) and rhinorrhea (OR 2.35; 95% CI 1.60–3.45; $P < 0.00$) were more common in patients with olfactory dysfunction than in patients with COVID-19 without olfactory dysfunction (Figure 5) and could be possible reasons for olfactory function effects.

Subgroup analysis

Previous studies suggested that COVID-19–related gustatory and olfactory dysfunction may be related to region and race. However, subgroup analysis performed on the basis of race in our research did not indicate any difference between Caucasians and Asians, suggesting that gustatory and olfactory dysfunction in patients with COVID-19 may not be related to race (Figures 1 and 2 in the Supplement).

Sensitivity analysis

A total of 5 (50%) pooled effect estimates were found to be significantly heterogeneous. We performed sensitivity analysis by

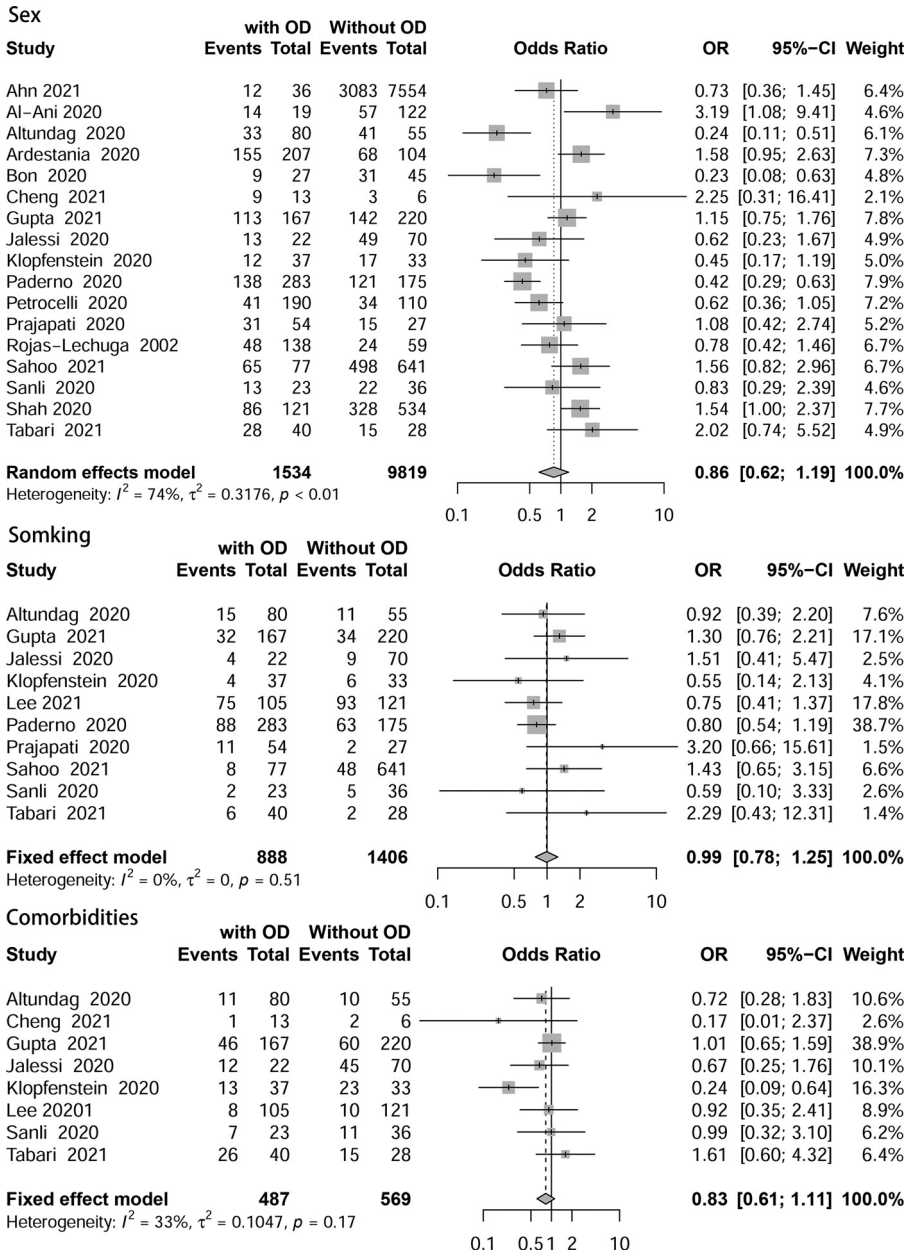


Figure 3. Forest plot of sex, smoking, and comorbidity on the risk of olfactory dysfunction in patients with COVID-19. CI, confidence interval; OD, olfactory dysfunction; OR, odds ratio.

deleting each study and this in turn did not result in a substantial change in the results. However, the recalculation of the data set does not reduce the heterogeneity.

Publication bias

The assessment of publication bias is based on sufficient number of primary studies (>9). Neither the visual funnel plot nor the Egger regression asymmetry test demonstrated statistical publication bias (Figure 3 in the Supplement).

Discussion

This systematic review and meta-analysis assessed several related risk factors for gustatory and olfactory dysfunction in patients with COVID-19. The findings indicated that sex, age, smoking, and comorbidity of patients with COVID-19 had no effect on gustatory dysfunction. Older patients with COVID-19 were more likely to develop olfactory dysfunction. More importantly, olfactory dysfunction may be related to symptoms of rhinorrhea and nasal congestion. No evidence was found for the effect of racial factors on gustatory and olfactory dysfunction.

There have been multiple reviews investigating gustatory and olfactory dysfunction after COVID-19 infection. Our work shows that gustatory and olfactory dysfunction do not seem to be related to race, sex, smoking, or comorbidities, a finding that is inconsistent with a previous meta-analysis (von Bartheld et al., 2020). Interestingly, olfactory dysfunction is more likely to be caused by nasal congestion and rhinorrhea, although some studies have found that SARS-CoV-2 could damage the olfactory nerve.

The exact pathogenesis of the loss of olfaction and taste caused by COVID-19 is still unclear, but a possible explanation is that the virus can affect the central nervous system and damage the nasal epithelium (Butowt and von Bartheld, 2020). Studies have shown

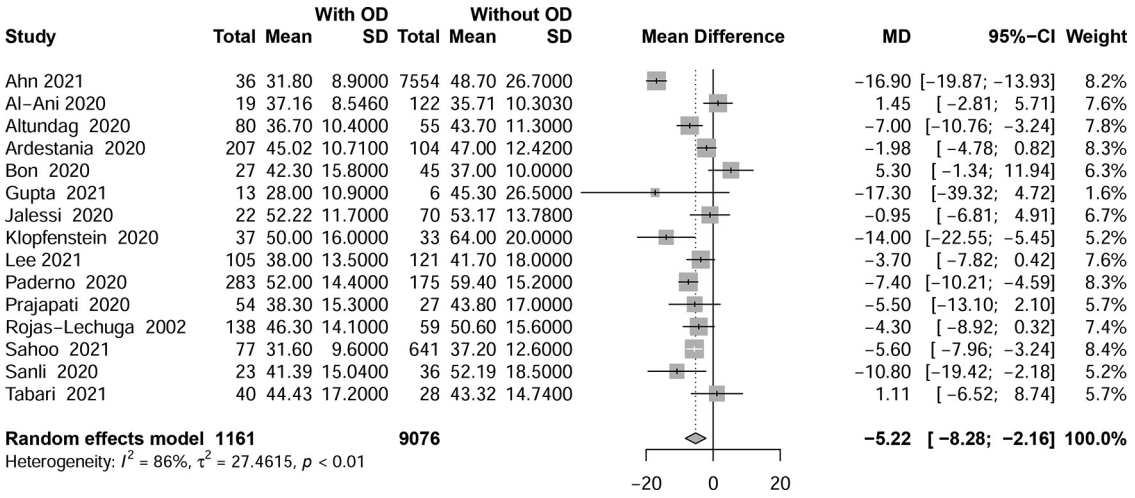
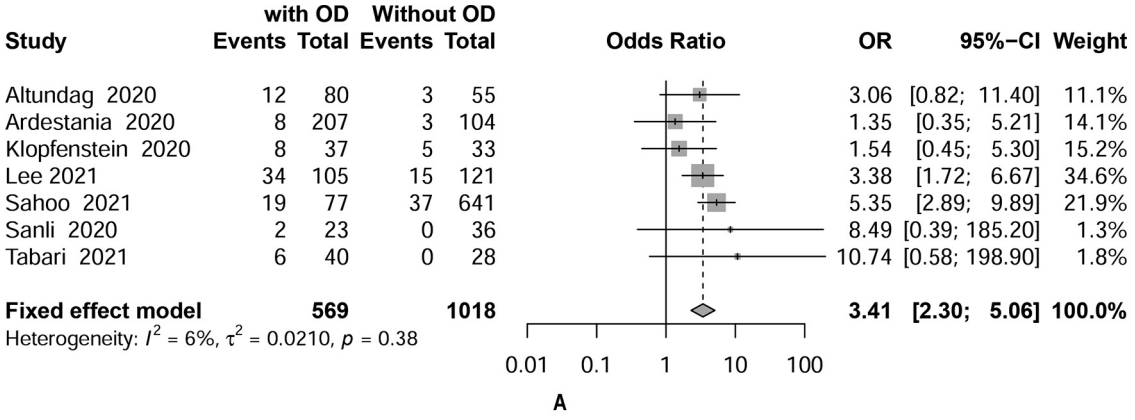


Figure 4. Forest plot of age on the risk of olfactory dysfunction in patients with COVID-19. CI, confidence interval; MD, mean difference; OD, olfactory dysfunction; SD, standard deviation.



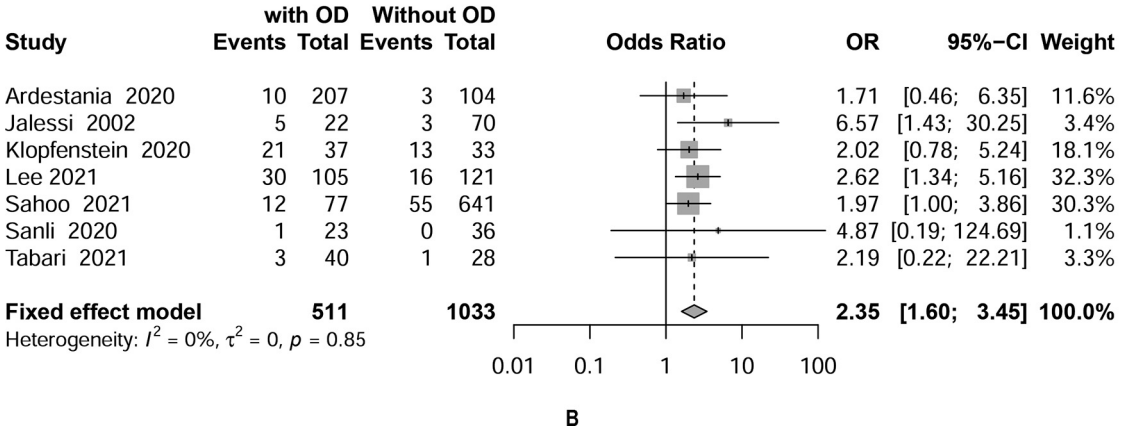


Figure 5. Forest plot of nasal congestion and rhinorrhea on the risk of olfactory dysfunction in patients with COVID-19. CI, confidence interval; OD, olfactory dysfunction; OR, odds ratio.

that SARS-CoV-2 may infect the human central nervous system through the nose near the olfactory epithelium and may be neuroinvasive to humans (Chen and Zheng, 2020). SARS-CoV-2 enters the central nervous system through the olfactory nerve or the peripheral trigeminal nerve. The resulting damage to the trigeminal nerve and olfactory nerve in turn could lead to olfactory and taste disorders in patients with COVID-19. Another explanation could be that SARS-CoV-2 infection reduces the reflex sensitivity of sensory neurons. Furthermore, the wide use of chemicals and disinfectants during the ongoing pandemic may have caused olfactory and taste disorders (Keyhan et al., 2020). However, despite the previously mentioned evidence, whether SARS-CoV-2 enters the brain through the olfactory nerve and affects brain function is still inconclusive. According to our data, COVID-19–related olfactory dysfunction may be related to nasal symptoms such as nasal congestion and rhinorrhea.

Nevertheless, COVID-19–related gustatory and olfactory dysfunction may not cause permanent damage because gustatory and olfactory function can spontaneously return to normal in a few weeks after recovery. However, to avoid the long-term existence

of gustatory and olfactory dysfunction, timely remedial strategies are necessary. A study found that a combination of short-term oral corticosteroids and olfactory training may help patients with COVID-19 with persistent olfactory disorders (Le Bon et al., 2021). Another study used nasal steroids to reduce the severity and duration of olfactory disorders (Singh et al., 2021). Similarly, Varia et al. (Vaira et al., 2021) found that drug management, including steroids, maybe a potential strategy for alleviating COVID-19–related gustatory and olfactory dysfunction.

Limitations and strengths

This study has some limitations that need to be addressed. First of all, different biases should be considered in observational studies. We combined the results of different types of studies, potentially leading to considerable heterogeneity. Most studies are retrospective, and recall bias may affect the results. Second, because most studies have inconsistent descriptions of olfactory and gustatory dysfunction, we have redefined the data set, which may lead to biased results. Third, some of the included studies reported very limited case data, thus limiting our analysis. Fourth, of the 58 studies included, 28 reported gustatory and olfactory dysfunction based on patients' subjective reports. Owing to data limitations, we did not conduct an independent analysis of subjective complaints and objective tests.

Our systematic review and meta-analysis have several advantages. To date, this is the largest review of gustatory and olfactory dysfunction in patients with COVID-19. These data allowed us to study risk differences based on study design and regions. In particular, for patients with different severity of the disease, we further explored their gustatory and olfactory dysfunction. The second advantage is that we have also studied the risk factor data in detail. This allowed us to add several new risk factors for gustatory and olfactory dysfunction that have not been reported in the literature. In addition, our systematic review and meta-analysis included an extensive and comprehensive literature search and an overview of all data, making our results more reliable.

Conclusion

This meta-analysis emphasizes that older patients with COVID-19 are more likely to experience olfactory dysfunction; however, they may recover quickly once the symptoms of nasal congestion and rhinorrhea resolve.

Declaration of Competing Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics approval statement

This study did not require ethical approval because the meta-analysis was based on published research, and the original data are anonymous.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.02.004.

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