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# Evidence of Olfactory Disorder in COVID-19 Patients: A Systematic Review and Meta-Analysis

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**Abstract**

Olfactory disorders (OD) associated with COVID-19 have received a lot of attention during the pandemic. We wanted to look at the overall pooled odds ratio of olfactory impairment and its subcategoriesto trace a more solid evidence, which must announce this symptom as a core indicator of COVID-19. 1,104 databases were searched for studies published between December 1, 2019, and March 22, 2022. After inclusion and excluding criteria, 78 (N = 14105 individuals) studies were included. Heterogeneity analysis, outlier identification, and influential studies diagnosis were used to determine whether any of the studies influenced our findings. The outcomes were presented as odds ratios with 95% confidence intervals (CIs). We performed random-effects model estimation for meta-analysis to assess the overall effects and consistency between patients and control group as substantial heterogeneity was identified ($I^2 = 96\%$). The odds ratio for olfactory impairment was 7.58 [CI: 5.67-10.11]. Objective assessments revealed a higher odd of olfactory impairment than subjective assessments (8.77 vs. 7.37). Anosmia, hyposmia, and parosmia were found to have odds ratios of 5.69, 5.16, and 88.8. Our sensitivity analysis revealed that the findings regarding the frequency with which COVID-19 patients experienced problems with their sense of smell were robust and reasonable. The findings provide support that in cases of olfactory dysfunction, objective assessments were more common than subjective judgments. Anosmia was the most frequent subtype for olfactory dysfunction, followed by hyposmia.

**Keywords:** COVID-19, Olfactory, Smell, Anosmia, Hyposmia, Meta-analysis, Confidence interval (CI).

***PROSPERO Registration number:*** *CRD42022364087.*

## 1.Introduction

Recent outbreaks of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the virus responsible for coronavirus illness in 2019, have been reported around the world (COVID-19). On December 8, 2019, it was reportedly seen for the first time in the province of Wuhan in China. Within a relatively short amount of time, this fatal illness spread to every single part of the earth. On January 30, 2020, the World Health Organization (WHO, 2021) issued a statement

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that a public health emergency of worldwide significance existed. As of December 27, 2021, the World Health Organization (WHO, 2021) reports that the disease has now developed into a pandemic, with over 281,808,270 confirmed cases of COVID-19, including 5,411,759 deaths.At this time, the SARS-Cov-2 infection is most often identified by its most common symptoms, which include fever, cough, breathing problem, muscle pain, joint pain, and diarrhea (Chen et al. 2020 and Pang et al. 2020). Initially, a limited number of studies discovered that persons with the COVID-19 virus had problems with their sense of smell (Makaronidiset al. 2021 and Karni et al.).

The OD caused by COVID-19 is characterized by a fast onset of olfactory impairment, which may take place with or without the manifestation of any additional symptoms. Other basic symptoms on this list include anxieties, and sore throat etc (Giacomelli et al. 2020). In the earliest research studies, it was discovered that patients with the Covid-19 virus had issues relating to their sense of smell. Anosmia and hyposmia were recommended to be added as symptoms during the COVID-19 screening on March 22, 2020, by the American Academy of Otolaryngology. According to data that has not been published and reports made informally, olfactory issues should be resolved in about two weeks. However, due to a lack of patients being followed over a prolonged period of time, it is not known how many patients have persistent post infectious OD after an infection.

Symptoms of olfactory impairment are becoming increasingly prevalent as the number of individuals diagnosed with covid (Kavazet al. 2021, Leeet al. 2020 and Parmaet al. 2020) recently published a meta-analysis based on 60 studies that identified taste abnormalities in 56 percent of COVID-19 patients. The authors issued a disclaimer (Lee, D.et al. 2020), stating that their findings contain a high degree of heterogeneity and may be skewed as a result of the inadequate data that was provided. In addition, the circumstance is always evolving, and fresh pieces of research are increasingly becoming available that will analyze the earlier ones (Adler et al.,2000 and Ahmed et al. ,2012). In order to demonstrate and identify the significance of the link between COVID-19 infection and anomalies in olfactory perception, a more robust design and meta-analysis is necessary (Alharbi et al. ,2022,Amanoet al. ,2021, Arslan et al. ,2021, Beltrán-Corbelliniet al. ,2020 and Carignanet al. ,2020).The purpose of this systematic review and meta-analysis was therefore to evaluate: (i) the overall pooled odds ratio by random effect model of OD on COVID-19 patients, and (ii) examined by geographic location and kind of olfactory dysfunction (anosmia, hyposmia, and parosmia) for subgroup analysis to identify this symptom as a key indicator of COVID-19.

## 2. Methods

To identify reports of olfactory issues in COVID-19 patients worldwide, we conducted this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2009). The study protocol was prepared by two authors and submitted to the International Prospective Register of Systematic Reviews (PROSPERO) website with registration No. CRD42022364087.

### *2.1 Search Strategy and Selection Criteria*

Electronic searches were undertaken in the following database: PubMed, Scopus, Web of Science, Embase, and Google Scholar to find studies that had been published between December 1, 2019, and March 22, 2022, and language constraints were not taken into account. Corona virus, COVID-19, COVID19, nCoV, SARS-CoV-2, SARS-CoV2, olfactory, anosmia, odor, hyposmia, parosmia, smell, and normosmia were some of the important phrases that were searched for in this study. Supplemental Table 1 contains exhaustive information regarding the search methodology. In order to guarantee the accuracy of the search process, the references of the studies that were included were also examined. This systematic review and meta-analysis included the following criteria: (1) are observational studies, clinical trials, and case series that reported the clinical characteristics of COVID-19, particularly olfactory dysfunction symptoms such as anosmia, hyposmia, parosmia, and others as the severity of the condition, with its prevalence and distribution of patients. Excluded studies met the following criteria: (1) duplicate; (2) reviews, case studies, animal studies; (2) reported irrelevant results Two reviewers independently evaluated and chose the studies based on the mentioned criteria.

### *2.2 Data Extraction*

In a present Excel file, the following data was taken: Study design, participant nation, data collecting time, number of COVID-19 patients, age, positive RT-PCR for SARS-CoV-2 RNA, as well as the confirmatory process, and symptom following the beginning of the sickness.

### *2.3 Study Quality and Publication Bias*

We used the critical assessment procedures created by the Joanna Briggs Institute (JBI) to evaluate the quality of the research that was included and to determine whether or not the studies were cross-sectional or case-control designs (Munn et al. 2020). In addition to this, it is essential to determine whether or not the results of the quality evaluation can be trusted. If the studies received an overall score of less than fifty percent, it was determined that they were at high-risk of bias (low quality). In order to investigate publication bias, A funnel plot was

constructed to compare the prevalence estimate to the standard error. The reason behind the asymmetry of the funnel plot was described by applying the contour-enhance method.

### *2.4 Data Analyses*

The epidemiology with 95% CIs for olfactory abnormalities in COVID-19 individuals was calculated using a random effects model. The $I^2$ statistic was applied to quantify study heterogeneity ($I^2$>75 % indicates significant heterogeneity), as well as the Cochran's Q test to determine the significance of heterogeneity. A Galbraith plot, L'abbe plot, Baujat plot (Baujat et al. 2002), Cook;s distance, Hat values were also created to identify the outlier research and the origins of heterogeneity (Viechtbauer,2020). All of the analyses and graphs were created using Metaprop scripts in the meta (version 4.1.0) and metafor (version 3.0-2) packages of R (version 4.1.2).

### *2.5 Subgroup and Sensitivity Analyses*

The incidence of olfactory problems in COVID-19 patients was examined by geographic location and kind of olfactory dysfunction (anosmia, hyposmia, and parosmia) for subgroup analysis. Sensitivity analyses were undertaken using the following methodologies to identify the origin of variability and to test the robustness of the outcome:

i. only cross-sectional studies are taken into account,
ii. omitting minor studies (n < 100),
iii. eliminating outlier studies,
iv. omitting studies that did not provide a COVID-19 confirmation assay,
v. eliminating studies of poor quality (high risk of bias).

## 3. Results

### *3.1 Study Selection*

During the search, a total of 1104 articles were identified. After removing 589 pieces of research because they were duplicates, we were left with 515 papers to evaluate their abstracts. Due to the absence of pertinent and appropriate prevalence data, the authors of 318 of the papers were disqualified from the process of data extraction after the title and abstract were reviewed. After finishing the full article, we discovered that the systematic review and meta-analysis included 78 separate pieces of research (Figure 1).

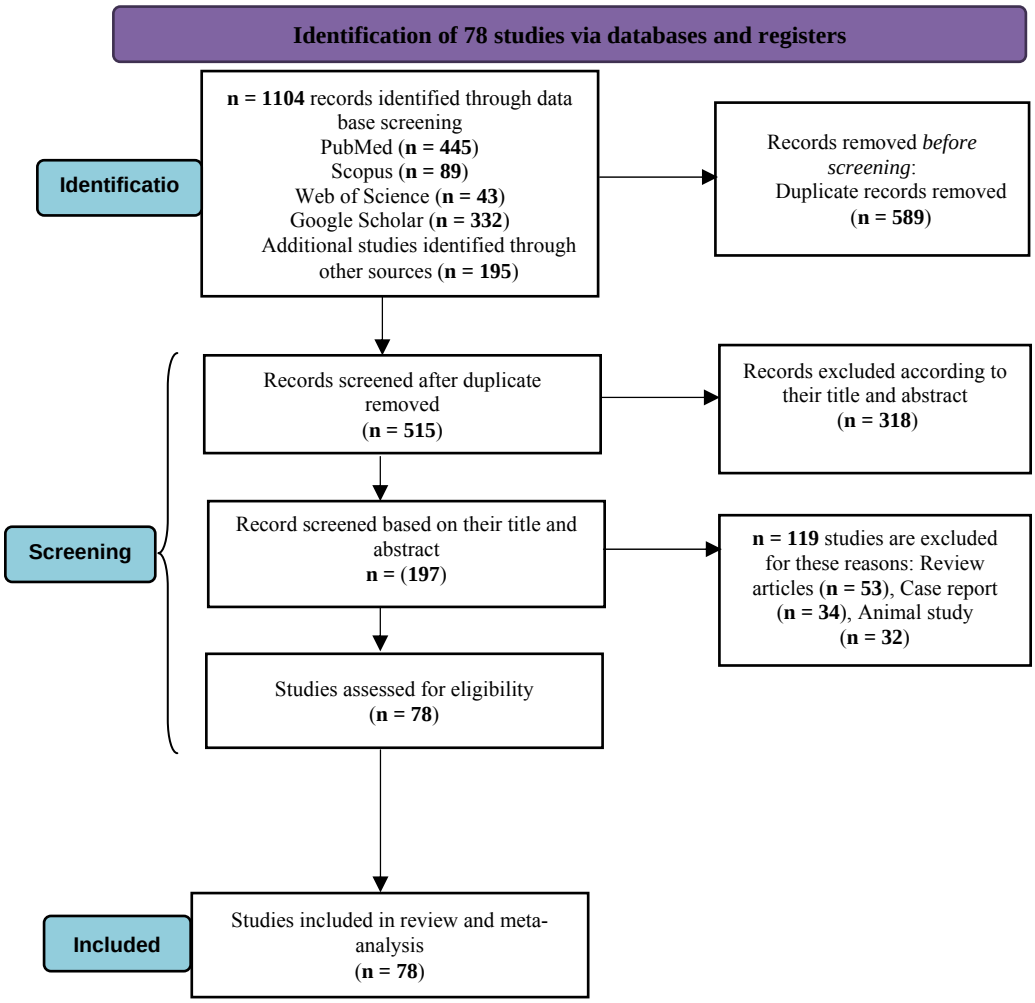


**Figure 1.**Flow Diagram of the Study Selection Process for Systematic Reviews and Meta-Analyses (PRISMA)

### *3.2 Study Characteristics*

The specific characteristics and references of the included studies are provided in Supplemental Table 1. This meta-analysis contains 20539 COVID-19 data points in total. The COVID-19 patients in this ranged in age from 28.0 ± 16.4 to 70.2 ± 13.9 (mean ± SD; range, 18.0-149) years old. There were 27 countries (Japan, India, Hong Kong, Brazil, Hungary, Denmark, Mexico, Thailand, Korea, Spain, Germany, Italy, France, Ireland, Belgium, the UnitedKingdom, the Netherlands, Poland, Israel, China, Saudi Arabia, Turkey, Iran, Singapore, Australia, Canada, and the United States) represented in the studies, which were from five continents: Europe (n = 12667), Asia (n = 2787), North America (n = 4709), South America (n = 348), and

Australia (n = 28). The RT-PCR method was used to confirm COVID-19 patients in 85.89% of the included studies; two studies used IgG/IgM; one article used CovPCR; one study used RNA PCR; and one study used the COVID-19 self-assessment tool to confirm COVID-19 patients; and five studies did not provide the method.

### 3.3 Outcomes

Figure 2, show that olfactory disorder significantly more likely to affected the COVID-19 patients where the pooled estimate is OR: 7.5759 [95%$CIs: 5.68 - 10.12, I^2 = 96\%$), $p < 0.01$].

Table 1 reveals that COVID-19 has an effect on olfactory impairment in distinct subgroups. North America has the highest heterogeneity (96.1%) compared to Asia (95.3%), Europe (84.8%), and South America (50.2%). The heterogeneity test has a p-value of 0.01 in both individual and combined cases. Anosmia, hyposmia, and parosmia odds ratios were found in 5.69, 5.16, and 88.8 percent of COVID-19 patients, respectively. In the events of olfactory impairment, objective assessments are more common than subjective judgments.

**Table 1.**Olfactory Dysfunction in COVID-19 Subgroups

| **COVID-19 Subgroups** | **OlfactoryDisorder Odds Ratio [95% CIs] (%)** | **Analyzed Studies** | **COVID-19 patients** | **Heterogeneity** | | |
|---|---|---|---|---|---|---|
| | | | | $I^2$ | **P Value** | $\widehat{Q}$**(df)** |
| **Olfactory dysfunction in different regions** | | | | | | |
| Asia | 6.68 [3.46; 12.91] | 22 | 2787 | 95.3 | <.0001 | 447.6(21) |
| Europe | 7.18 [5.12; 10.09] | 37 | 12667 | 84.8 | <.0001 | 236.9(36) |
| North America | 11.80 [5.74; 24.25] | 15 | 4709 | 96.1 | <.0001 | 357.8(14) |
| South America | 2.47 [1.16; 5.24] | 3 | 348 | 50.2 | <.0001 | 4.01(2) |
| Oceania | 6.16 [2.52; 15.04] | 1 | 80 | 60.3 | <.0001 | 0.00 |
| **Different types of olfactory dysfunction** | | | | | | |
| Anosmia | 5.69[3.61: 8.99] | 15 | 1738 | 93.0 | 0.0001 | 85.36(14) |
| Hyposmia | 5.16 [ 2.04; 13.01] | 7 | 476 | 70.1 | 0.0001 | 46.83(6) |
| Parosmia | 88.8 [26.29; 300.30] | 1 | 82 | 62.1 | 0.0001 | 0.0 |
| **Evaluation types of olfactory dysfunction** | | | | | | |
| Subjective | 7.37 [6.62; 9.83] | 54 | 8965 | 90.3 | 0.244 | 547.43(53) |
| Objective | 8.77 [4.11; 18.74] | 22 | 4958 | 98.2 | 0.244 | 1188.9(21) |

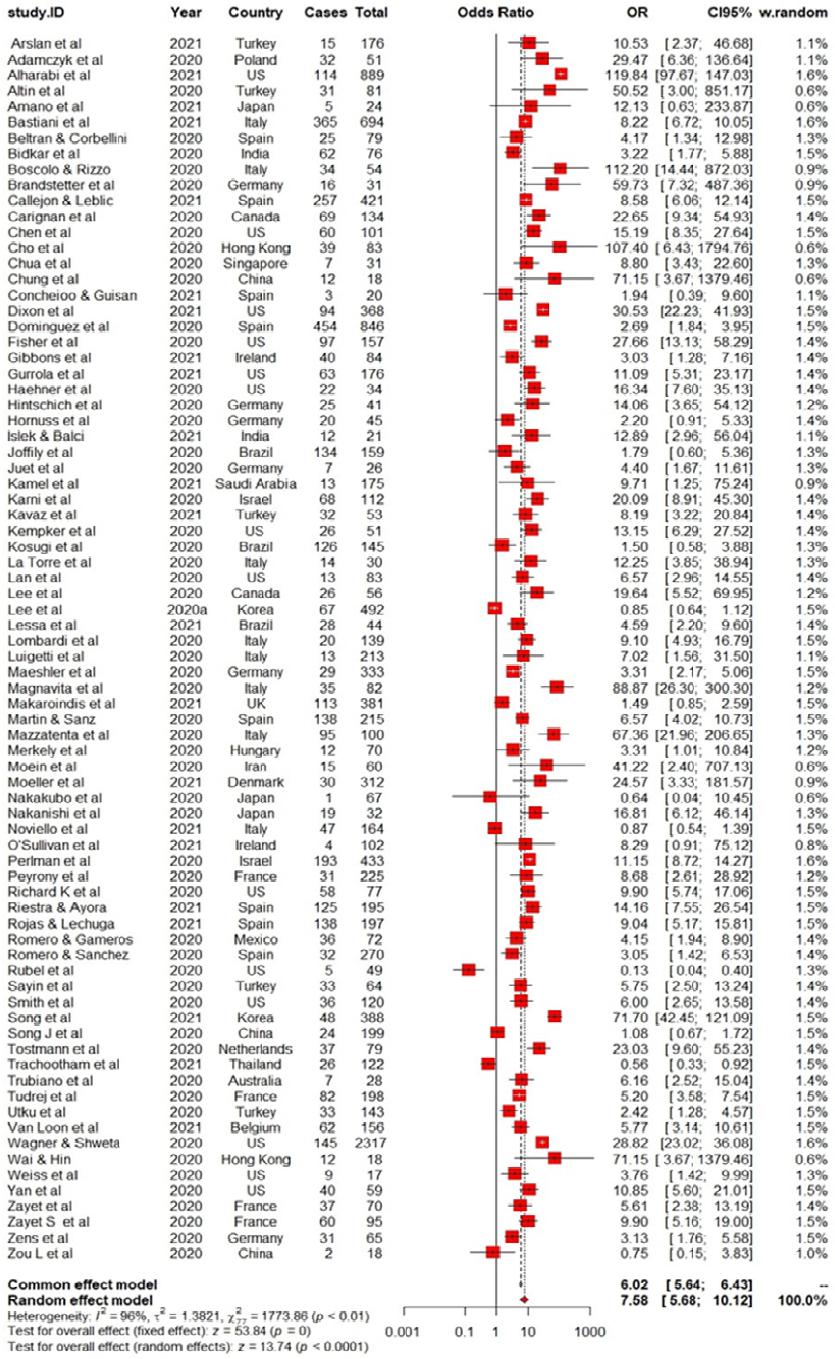


**Figure 2.** The "Forest Plot" of Olfactory Dysfunction in People with COVID-19

A comprehensive analysis of the studies that were used in the analysis can be found in the supporting information (Supplemental Table 2 and Supplemental Table 3).

To summarize, 70.3% of the studies that were evaluated were considered to be of high quality. In general, extremely high levels of heterogeneity (ranging from 85% to 96%) were seen during the estimation of olfactory disorders in both the main analysis and the various subgroup analyses. This was the case regardless of whatever analysis was being performed. A careful examination of the funnel plot and the outcomes of Egger's test revealed that there was no evidence of significant publication bias ($P = 0.1328$) (Figure 3).

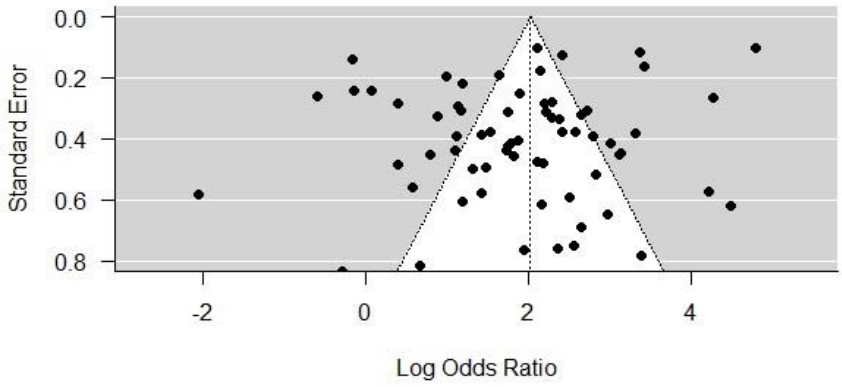


**Figure 3.** Funnel Plot on the Prevalence of Olfactory Disorder in Patients with COVID-19

Assessing olfactory dysfunction in COVID-19 patients using sensitivity analyses that omitted minor studies (n<100), eliminating studies of poor quality (high risk of bias), omitting studies that did not provide a COVID-19 confirmation assay, and only cross-sectional studies were taken into account showed very marginal differences in the overall pooled prevalence (Table 2).

Overall, the results of our sensitivity analyses suggested that the findings on the incidence of olfactory impairment in COVID-19 patients were robust and reasonable. Two further techniques for identifying the factors contributing to heterogeneity are the Bubble plot and the Galbraith plot. It was determined from the Galbraith plot that the outlier studies as potential sources of heterogeneity (on left),and a bivariate scatter plot superimposed with a meta-regression line (on right) explained a significant amount of the heterogeneity in trial effect sizes by the distance from the equatorFigure 4.

**Table 2.** Sensitivity Analysis for Olfactory Disorder

| **Analyses of sensitivity** | **Odds Ratio [95% CIs] %** | **Difference in odds ratio from main result** | **Analyzed studies** | **COVID-19 patients** | **Heterogeneity** | |
|---|---|---|---|---|---|---|
| | | | | | $I^2$ | **P-value** |
| Only cross-sectional studies are taken into account | 8.21 [4.96-13.59] | 0.63% higher | 30 | 5045 | 97 % | <0.01 |
| Omitting minor studies (n<100) | 7.25 [4.65-11.30] | 0.33% lower | 36 | 11546 | 98 % | <0.01 |
| Eliminating outlier studies | 7.23 [5.36-9.74] | 0.35% lower | 72 | 13566 | 95 % | <0.01 |
| Excluding studies without COVID-19 confirmation assay | 8.37 [6.33-11.07] | 0.79% higher | 73 | 13080 | 96 % | <0.01 |
| Eliminating studies of poor quality | 8.58 [5.48-13.45] | 1% higher | 35 | 6036 | 97 % | <0.01 |

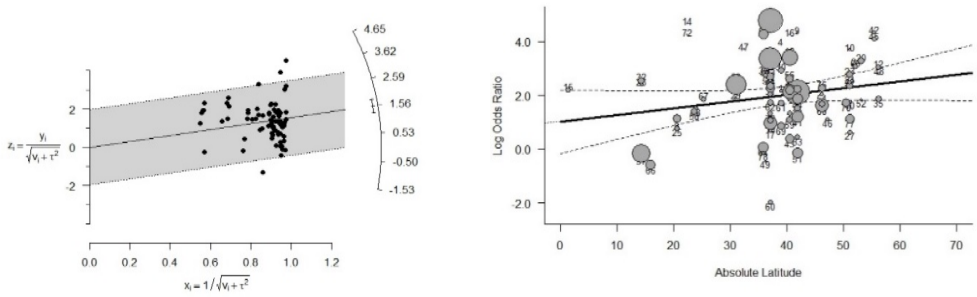


**Figure 4.**The Galbraith Plot, and Bubble Plot.

Outlier diagnostics were shown in Figure 5. The Baujat plot's x-axis displays (on left) each effect size's overall heterogeneity contribution, while the y-axis displays its influence on the combined outcome, and the L'abbe plot (on right) suggests that there is a higher risk in the treatment group.

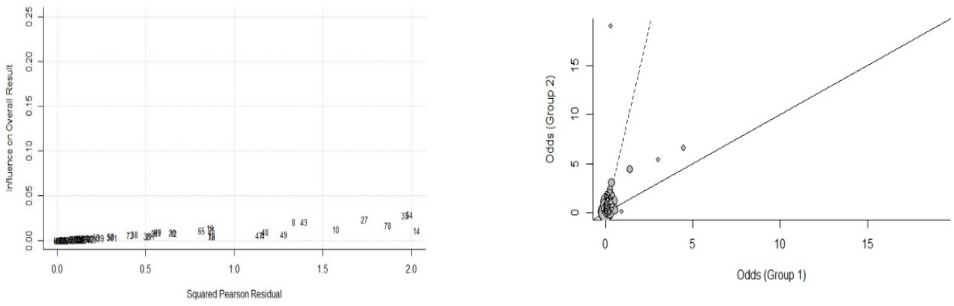


**Figure 5.** The BaujatPlots, and the L'abbe Plot (on right).

Influence diagnostics were shown in Figure 6.Scatter plot of the leverages versus the standardized deleted residuals (top left) and a plot of Cook's distances (top right). Plot of the hat values for the common-and random-effects models (bottom middle). Study 15 has high leverage points that are not outliers and are not significant. Additionally, studies that are outliers but have little leverage likewise have little influence on the results (study 3 and 60).

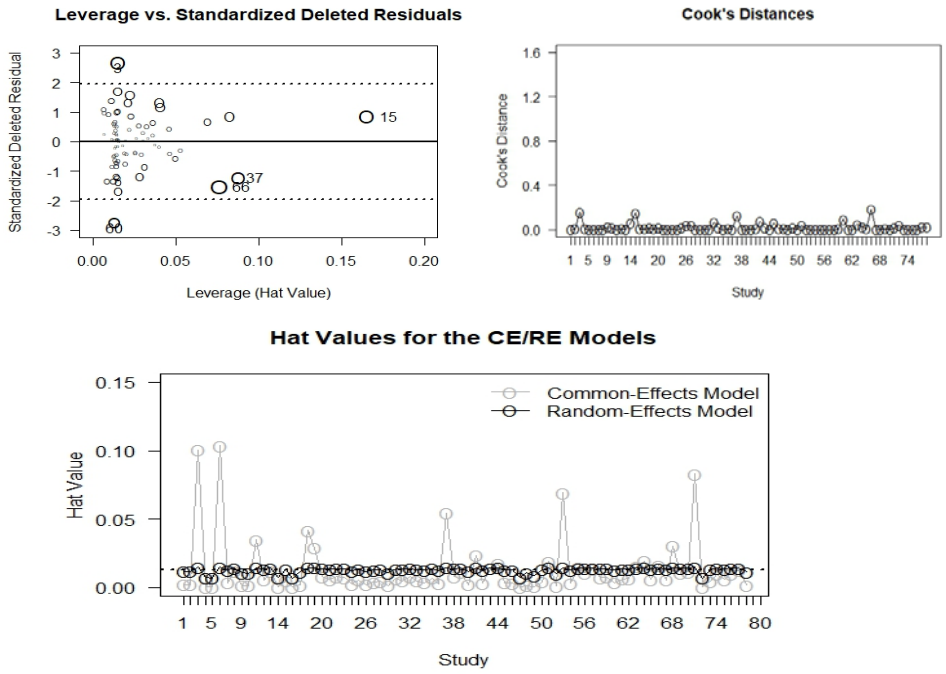


**Figure 6.** Leverages Versus the Standardized Deleted Residuals (top left) and Cook's Distances (top right). Hat Values for the Common-and Random-effects Models (bottommiddle).

## 4. Discussion

The fast spread of SARS-CoV-2 has provided researchers with a huge amount of clinical information on coronavirus infection (Tudrej et al. 2020). Data gathering and analysis are challenging during health emergencies. Clinical disparities between Chinese and European case series are preliminary to arise. According to Chinese experts, olfactory disorders are a side effect of COVID-19 infection. Mao *et al.*(Lorenzetti, & Ghali,2013) found anosmia in 5.1% of the patients who were affected.Based on the first European case collection (Talukderet al. 2021) COVID-19 patients exhibited a high prevalence of allergic conditions, which ranged from 19.4% to 88.4%. Early-stage infection patients who are asymptomatic seem to have higher olfactory changes(Fantozziet al. 2020). These symptoms may indicate SARS-CoV-2 infection (Lessaet al. 2021).Prior research has never included a thorough patient assessment and has only been anamnestic-observational. Determining the degree of dysfunction and tracking treatment both require objective measurement.Olfaction is caused by air molecules. The nose is the pathway via which molecules enter the mouth. They cling to nasal receptor cells. The brain receives information from neurons about whether something smells good or bad (Justet al. 2020).

According to our meta-analysis of 78 publications, olfactory impairment and SARSCOV-2 infection are connected. The majority of research used smart phone apps, online surveys, or surveys to gather subjective data from patients or doctors. Studies that sought to objectively assess olfactory function used the Sniffin test and UPSIT. The odds ratio for investigation that was objective was higher odds (8.77) in our meta-analysis than it was for subjective investigates (7.37). Due to the fact that most COVID-19 patients are not aware of their olfactory impairment, their symptoms may be overstated. The percentage of UPSIT patients (Mohamudet al. 2020) with olfactory impairment who were aware of their symptoms was only 35%.

Consider the fact that the SARS-CoV-2 infection in Europe may have been the catalyst for the huge prevalence of smell problems to become apparent. Olfactory dysfunction is a symptom of the outbreak, which has extended to North America, Western Asia, and Europe and is currently at its peak in those regions (Peyronyet al. 2020 and Riestra-Ayoraet al. 2021). South America is still in the early stages of this outbreak.In our meta-analysis, the odds ratio for North America was larger (11.80) than it was for Asia (6.68). In conclusion, these findings may affect how COVID-19 will be detected and prevented in the future. If isolated olfactory disorders are considered to be sufficient foundation for COVID-19 testing or quarantine to prevent the virus's transmission.

## 5. Conclusion

The main objectives of this study are to evaluate the epidemiology of olfactory disorder and its subcategories, as well as the summary effect size between COVID-19 infection and olfactory abnormalities. This analysis found the odds ratio for olfactory abnormalities was 7.58 [5.67 - 10.11]. Compared to research using subjective assessments, those using objective assessments showed a higher odd of olfactory impairment (8.77 vs 7.37). 7.18 times patients from Europe, 11.80 times from North America, 6.68 from Asia, 2.47 from South America, and 6.16 from Oceania all had the conditions. The odds ratios of anosmia, hyposmia, and parosmia were found in 5.69, 5.16, and 88.8 of COVID-19 patients, respectively. The odds ratios for olfactory abnormalities in COVID-19 patients were 7.58, suggesting that this symptom is a meaningful early sign of SARS-CoV-2 infection. Further investigations with objective assessments are advised to confirm the finding because the majority of the papers pooled in the analysis used subjective criteria. Olfactory impairment therefore appears to be a component of significant symptoms and alert for the COVID-19 diagnosis, particularly in the early stages of the infection. It is advised that while screening suspect people who have been sent to medical facilities, assessments of smell should be taken into account.

**Conflict of Interest**
There were no potential conflicts of interest disclosed by the authors in relation 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 previously published research and the original data was completely anonymous.

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**Supplemental Material**

**Supplemental Table 1.** Study characteristics

| Study Name | Study Design | Country | Data Collection Period | Covid-19 patients | Age (years) (Mean±SD/Median (IQR))/Range | COVID-19 Confirmation Procedure | Subjective/objective olfactory assessment | Method of Assessing Olfactory Dysfunction |
|---|---|---|---|---|---|---|---|---|
| Arslan 2021 | Cross-sectional | Turkey | 20 March - 31 May, 2020 | 176 | 79 (34–149) | RT-PCR | Subjective | Medical record review |
| Adamczyk 2020 | Case–control | Poland | April - May 2020 | 51 | 21.7 (19; 26) | RT-PCR | Objective | Flavour concentrations |
| Alharbi 2021 | Cross-sectional | US | June 2015-April 2020 | 889 | NR | RT-PCR | Objective | ICD-10 |
| Altin 2020 | Case–control | Turkey | 25 March–20 April 2020 | 81 | 54.1 ± 16.9 | RT-PCR | Objective | Sniffin' Sticks test |
| Amano 2021 | Case–control | Japan | 20 February - 21 May, 2020 | 24 | 63.5 (57.5±69.5) | RT-PCR | Subjective | Medical record review |
| Bastiani 2021 | Case–control | Italy | Apr-20 | 694 | 55.5 (18.06) | IgG/IgM | Objective | NPS |
| Beltran-Corbellini 2020 | Case–control | Spain | 23–25 March 2020 | 79 | 61.6 ± 17.4 | RT-PCR | Subjective | Self-reported questionnaire survey |
| Bidkar 2020 | Case–control | India | NR | 76 | NR | RT-PCR | Subjective | By asking the patient |
| Boscolo-Rizzo 2020 | Cross-sectional | Italy | March - April 2020 | 54 | NR | RT-PCR | Subjective | Telephone interview |
| Brandstetter 2020 | Cross-sectional | Germany | NR | 31 | 18.0 – 65.0 | RT-PCR | Subjective | Self-reported |
| Callejon-Leblic 2021 | Case–control | Spain | March - April 2020 | 421 | NR | RT-PCR | Objective | VAS |
| Carignan 2020 | Case–control | Canada | 10–23 March 2020 | 134 | 57.2 (42.6–64.4) | RT-PCR | Subjective | Telephone interview |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Chen 2020 | Case–control | US | 9 March - 15 April 2020 | 101 | 46.89 ± 15.34 | GI symptoms | Subjective | Predesigned questionnaire |
| Cho 2020 | Cross-sectional | Hong Kong | 8 February - 15 April 2020 | 83 | 36.4 ± 16.3 | PCR | Subjective | Phone contact or Online questionnaire |
| Chua 2020 | Cross-sectional | Singapore | 23 March–4 April 2020 | 31 | NR | RT-PCR | Subjective | Self-reported |
| Concheioo-Guisan 2021 | Case–control | Spain | March–May 2020 | 20 | NR | RT-PCR | Objective | 7-odorant identification test (Kradeo®) |
| Dixon 2021 | Cohort-study | US | Apr-20 | 368 | NR | RT-PCR | Subjective | In person interview |
| Dominguez 2020 | Cross-sectional | Spain | 21 March - 18 April 2020 | 846 | 56.8 (15.7) | RT-PCR | Objective | VAS |
| Fisher 2020 | Case–control | US | 1 July - 29 July 2020 | 157 | NR | RT-PCR | Subjective | Self-reported |
| Gibbons 2021 | NR | Ireland | Apr-20 | 84 | NR | RT-PCR | Subjective | Self-reported |
| Gurrola 2021 | Cross-sectional | US | 31 March - 24 April 2020 | 176 | NR | NR | Subjective | By asking the patient |
| Haehner 2020 | Cross-sectional | Germany | NR | 34 | 43.2 ± 11.6 | RT-PCR | Subjective | Self-reported questionnaire survey |
| Hintschich 2020 | Cross-sectional | Germany | NR | 41 | 37 (NR) | RT-PCR | Subjective | Online questionnaire survey |
| Hornuss 2020 | Cross-sectional | Germany | Apr-20 | 45 | 56.0 ± 16.9 | RT-PCR | Objective | Sniffin' Sticks test |
| Islek-Balci 2021 | Cross-sectional | India | March 2020 - April 2020 | 21 | 49.2 ± 13.5 | RT-PCR | Objective | CCCRC |
| Joffily 2020 | Cross-sectional | Brazil | 26 March - 11 April 2020 | 159 | NR | RT-PCR | Subjective | Data survey produced in Google Forms |
| Just 2020 | Cross-sectional | Germany | NR | 26 | 44.0 (31.0–59.0) | CovPCR | Objective | RKI testing |
| Kamel 2021 | Case–control | Saudi Arabia | 18 March - 18 May 2020 | 175 | NR | RT-PCR | NR | NR |
| Karni 2020 | Case–control | Israel | March 2020–May 2020 | 112 | NR | RT-PCR | Subjective | Telephone interview |
| Kavaz 2021 | NR | Turkey | 10 March - 5 June | 53 | 42.75 ± 14.12 | RT-PCR | Objective | AAO-HNS |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 2020 | | | | | |
| Kempker 2020 | Case–control | US | NR | 51 | NR | RT-PCR | Subjective | Electronic health record |
| Kosugi 2020 | Cross-sectional | Brazil | 25 March - 30 April 2020 | 145 | NR | NR | Subjective | Online survey |
| La Torre 2020 | Case–control | Italy | 11 March - 28 March | 30 | 43.6 (12.9) | RT-PCR | Subjective | Structured interview |
| Lan 2020 | Cross-sectional | US | 9 March – 15 April 2020 | 83 | 43.6 (12.9) | HCWs and RT-PCR | Subjective | telephonic visit. |
| Lee 2020 | Cross-sectional | Canada | 16 March–15 April 2020 | 56 | 38.0 (31.8–47.2) | RT-PCR | Subjective | Telephone questionnaire survey |
| Lee 2020a | Cross-sectional | Korea | 8 March - 31 March 2020 | 492 | 44.0 (25.0–58.0) | NR | Subjective | By asking the patient |
| Lessa 2021 | Case–control | Brazil | June 2020-August 2020 | 44 | 38.3±13 | RT-PCR | Objective | U-smell-it™ |
| Lombardi 2020 | Cross-sectional | Italy | 24 February–31 March 2020 | 139 | NR | RT-PCR | Subjective | Self-reported |
| Luigetti 2020 | Case–control | Italy | 14 March–20 April 2020 | 213 | 70.2 ± 13.9 | RT-PCR | Subjective | Self-reported |
| Maeshler 2020 | Cross-sectional | Germany | Mar-20 | 333 | 34 (26 - 47) | RT-PCR | Subjective | Online questionnaire survey |
| Magnavita 2020 | Cross-sectional | Italy | 27 March–30 April 2020 | 82 | NR | RT-PCR | Subjective | Self-reported questionnaire |
| Makaroindis 2021 | Case–control | UK | 23 April - 14 May 2020 | 381 | 39.67 ± 12.12 | IgG/IgM | Objective | UPSIT |
| Martin-Sanz 2020 | Case–control | Spain | 15 March–7 April 2020 | 215 | 42.9 ± 0.6 | RT-PCR | Objective | VAS |
| Mazzatenta 2020 | Cross-sectional | Italy | NR | 100 | 63 ± 15 | RT-PCR | Objective | CCCRC |
| Menni 2020 | Cross-sectional | UK | Apr-20 | 6452 | 40.79 ± 11.84 | RT-PCR | Subjective | Smartphone-based App survey |
| Merkely 2020 | NR | Hungary | NR | 70 | 48.7 (18.0) | PCR | Subjective | Telephone questionnaire survey |
| Moein 2020 | Case–control | Iran | 21–23 March 2020 | 60 | 28.0 ± 16.4 | RT-PCR | Objective | UPSIT |
| Moeller 2021 | Case– | Denmark | 1 April - 20 April | 312 | 51 (22.42) | PCR | Subjective | Medical record |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | control | | 2020 | | | | | review |
| Nakakubo 2020 | Case–control | Japan | 13 March - 31 May | 67 | 68 (50–78) | RNA PCR | Subjective | Medical record review |
| Nakanishi 2020 | NR | Japan | 14 February - 15 May 2020 | 32 | NR | PCR | Objective | First medical examination |
| Noviello 2021 | Cohort-study | Italy | February and April 2020 | 164 | 44.1 (23–60) | PCR | Subjective | Structured questionnaire |
| O'Sullivan 2021 | Case–control | Ireland | March - May 2020 | 102 | 44.1 ± 11.2 | PCR | Subjective | Structured questionnaire |
| Perlman 2020 | Cohort-study | Israel | 8 April - 20 June 2020 | 433 | 34.5 (13.9) | COVID-19 self-assessment tool | Objective | AI-driven symptom checker |
| Peyrony 2020 | Cross-sectional | France | 9 March–4 April 2020 | 225 | 43.6 ± 12.2 | RT-PCR | Subjective | Self-reported |
| Richard K 2020 | NR | US | 29 March - 8 June 2020 | 77 | 43.3 (14.1) | RT-PCR | Subjective | online or by phone |
| Riestra-Ayora 2021 | Case–control | Spain | 15 March - 15 October 2020 | 195 | 46.5 (20–64) | RT-PCR | Objective | VAS |
| Rojas-Lechuga 2021 | Cross-sectional | Spain | 21 March - 18 April 2020 | 197 | 46.5 (14.5) | RT-PCR | Subjective | Self-reported questionnaire survey |
| Romero-Gameros 2020 | Cross-sectional | Mexico | 25 May - 30 June 2020 | 72 | 39.02 ± 10.45 | RT-PCR | Subjective | Self-reported questionnaire survey |
| Romero-Sanchez 2020 | Cross-sectional | Spain | 1 March–1 April 2020 | 270 | NR | RT-PCR | Subjective | Medical record review |
| Rubel 2020 | Case–control | US | NR | 49 | 43.1 ± 15.3 | NR | Objective | UPSIT |
| Sayin 2020 | Case–control | Turkey | NR | 64 | 37.8 ± 12.5 | RT-PCR | Subjective | Self-reported questionnaire survey |
| Smith 2020 | NR | US | 10 March - 23 September 2020 | 120 | NR | PCR | Subjective | Electronic medical record |
| Song 2021 | NR | Korea | 11 March - 30 April | 388 | 30.3 ± 12.2 | PCR | Subjective | Health questionnaire survey |
| Song J 2020 | Cross-sectional | China | 27 January–10 March 2020 | 199 | 61.0 (48.0–68.0) | RT-PCR | Subjective | Telephone interview |
| Tostmann 2020 | Cross- | Netherlan | 10–30 March | 79 | NR | NR | Subjective | Self-reported |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | sectional | ds | 2020 | | | | | questionnaire survey |
| Trachootham 2021 | Case–control | Thailand | April - June 2020 | 122 | 39.3 ± 15.12 | RT-PCR | Objective | VAS |
| Trubiano 2020 | Cross-sectional | Australia | 1–22 April 2020 | 28 | 55.0 (46.0–63.5) | RT-PCR | Subjective | Medical record review |
| Tudrej 2020 | Cross-sectional | France | 24 March–14 April 2020 | 198 | NR | RT-PCR | Subjective | Self-reported questionnaire survey |
| Utku 2020 | Cross-sectional | Turkey | NR | 143 | NR | RT-PCR | Subjective | Self-reported questionnaire survey |
| Van Loon 2021 | Case–control | Belgium | 9 March - 17 April 2020 | 156 | NR | RT-PCR | NR | NR |
| Wagner & Shweta 2020 | NR | US | NR | 2317 | NR | PCR | Subjective | Electronic Health Records |
| Wai-Chung 2020 | Cohort-study | Hong Kong | 6 April - 9 April 2020 | 18 | 28 ± 19 (18–59) | RT-PCR | Objective | BTT |
| Weiss 2020 | Cohort-study | US | NR | 17 | 30.0 (26.0, 48.0) | RT-PCR | Subjective | Parosmia screening questionnaire |
| Yan 2020 | Case–control | US | 3 March–8 April 2020 | 59 | 53.5 (40.0–65.0) | RT-PCR | Subjective | Self-reported |
| Zayet 2020 | Cross-sectional | France | 26 February–14 March 2020 | 70 | 56.7 ± 19.3 | RT-PCR | Subjective | Self-reported questionnaire |
| Zayet S 2020 | Case–control | France | 30 March–3 April 2020 | 95 | 39.8 ± 12.2 | RT-PCR | Subjective | Medical record review |
| Zens 2020 | NR | Germany | 8 April - 15 May 2020 | 65 | 42.65 (13.33) | RT-PCR | Subjective | App-based daily self-reporting tool |
| Zou L 2020 | Cross-sectional | China | 1 February–3 March 2020 | 18 | 58.0 (50.0–68.5) | RT-PCR | Subjective | Medical record review |

*** AAO-HNS = American academy of otolaryngology–head and neck surgery; CCCRC = Connecticut chemosensory clinical research center orthonasal olfaction test; IQR = interquartile range; NR = not reported; RT-PCR = Reverse transcription polymerase chain reaction; SD = standard deviation; UPSIT = University of Pennsylvania smell identification test; VAS = visual analog scale; RKI testing=Robert-Koch Institute; ICD 10 = Tenth edition of the International Classification of Diseases.

**SupplementalTable2.**Cross-sectional quality assessment

| No. | Study ID | Cross-sectional quality assessment | | | | | Yes (%) |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | |
| 1 | Brandstetter 2020 | Y | Y | Y | Y | N | 80 |
| 2 | Chua 2020 | N | Y | Y | N | N | 40 |
| 3 | Haehner 2020 | Y | Y | N | Y | N | 40 |
| 4 | Hintschich 2020 | N | Y | Y | N | N | 40 |
| 5 | Hornuss 2020 | N | Y | Y | U | N | 40 |
| 6 | Kosugi 2020 | Y | Y | Y | Y | Y | 100 |
| 7 | Lee 2020 | Y | Y | Y | Y | N | 80 |
| 8 | Lee 2020a | Y | Y | Y | Y | Y | 100 |
| 9 | Lombardi 2020 | Y | Y | Y | N | Y | 80 |
| 10 | Magnavita 2020 | Y | Y | Y | Y | Y | 100 |
| 12 | Peyrony 2020 | Y | Y | Y | Y | N | 80 |
| 13 | Romero-Sánchez 2020 | Y | Y | Y | Y | N | 80 |
| 14 | Song J 2020 | Y | Y | Y | Y | N | 80 |
| 15 | Tostmann 2020 | Y | Y | Y | Y | N | 80 |
| 16 | Trubiano 2020 | Y | Y | N | N | Y | 60 |
| 17 | Tudrej 2020 | Y | Y | Y | Y | Y | 100 |
| 18 | Zayet 2020 | Y | Y | N | Y | Y | 80 |
| 19 | Zou L 2020 | Y | Y | Y | Y | Y | 100 |
| 20 | Alharbi 2021 | Y | Y | N | N | Y | 60 |
| 21 | Arslan 2021 | Y | Y | N | N | Y | 60 |
| 22 | Boscolo-Rizzo 2020 | N | Y | N | Y | N | 40 |
| 23 | Cho 2020 | Y | Y | Y | Y | N | 80 |
| 24 | Dominguez 2020 | Y | Y | N | Y | Y | 80 |
| 25 | Gurrola 2021 | Y | Y | N | U | N | 40 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 26 | İşlek-Balcı 2021 | N | Y | N | U | N | 20 |
| 27 | Joffily 2020 | Y | Y | N | N | Y | 60 |
| 28 | Just 2020 | N | Y | Y | U | N | 40 |
| 29 | Maeshler 2020 | N | Y | N | Y | Y | 60 |
| 30 | Mazzatenta 2020 | Y | Y | Y | Y | Y | 100 |
| 31 | Rojas-Lechuga 2021 | N | Y | N | Y | N | 40 |
| 32 | Romero-Gameros 2020 | Y | Y | Y | Y | Y | 100 |

Were the inclusion criteria for the sample well defined? 2.Were the study participants and environment described in detail? 3. Was the measurement of exposure valid and reliable? 4. Were objective, standardized criteria utilized to assess the condition? 5. Have confounding variables been identified? Y=Yes, N=No, and U=Unclear.