

# Coronavirus Disease 2019 (Covid-19) and Prevalence of Olfactory Dysfunction: Systematic Review and Meta-Analysis

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## Abstract

**Background:** In the context of Covid-19 infections, acute Olfactory Dysfunction (OD) is defined as decreased or altered sense of smell of duration of 14 days or less, in the absence of chronic rhinosinusitis, a history of head trauma, or neurotoxic medications. OD can be associated with flavor (smell+taste) dysfunction. However, Covid-19 may also affect real taste (sweet, salty, bitter, acidic, umami). OD is estimated to afflict 3%-20% of the population. Post-viral anosmia accounts for up to 40% of cases of anosmia or coronaviruses are thought to account for 10%-15% of these cases. As such, it is plausible that Covid-19 may cause OD. **Aim:** This work aims to determine the prevalence of olfactory dysfunction in coronavirus disease 2019 (Covid-19) patients. **Materials & Methods:** A systematic search was performed over different medical databases to identify sss studies, which studied the prevalence of olfactory dysfunction in Covid-19 patients. We conducted a meta-analysis process on the pooled prevalence of olfactory dysfunction as a primary main outcome. **Results:** Twelve studies were identified involving 16866 Covid-19 patients. Our meta-analysis process showed a pooled prevalence of olfactory dysfunction in Covid-19 patients=42.7% (95% CI=28.83 to 57.24) (p<0.001). **Conclusion:** To conclude, olfactory dysfunction is common in Covid-19 and maybe the only symptom. Coronavirus disease 2019-related OD can be severe and prolonged. Mucosal infiltration by CD68+ macrophages expressing SARS-CoV-2 viral antigen may contribute to Covid-19-related OD.

**Keywords:** Covid-19; Olfactory dysfunction; Rhinosinusitis; Post-viral anosmia

## Introduction

Human Coronaviruses (HCoV) had been first recognized in the nasal cavities of patients with the common cold in the 1960s, being answerable for 10%-15% of these cases, second simplest to rhinoviruses. Although most cases of HCoV infection show signs compatible with the common cold or moderate flu-like syndromes, the decreased respiration tract may be critically affected, as in outbreaks because of the SARS-CoV, MERS-CoV species, and now with the new coronavirus (SARS-COV-2), which causes the Covid-19 disorder. In China, the evaluation of 72,314 instances up to February 11, 2020, confirmed that 14% of sufferers with Covid-19 had an intense disorder and 5% had been severely unwell, main to a case fatality fee of two. 3%. In Brazil, at the start of can also 2020, there have been already extra than 145,000 showed instances, with a case fatality fee reaching 6.8%. [1] At the same time as early reports of SARS-CoV-2 infections rarely referred to olfactory and taste disorders, several studies, especially in Europe and the USA, have now shown these symptoms as an early key feature of Covid-19. Meanwhile, also the WHO lists olfactory problems as a symptom of Covid-19. In particular, in Europe, about 70% of sufferers appear to experience a reduction in smell and taste over the direction of the disease. [2] In the context of Covid-19 infections, acute Olfactory Dysfunction (OD) is defined as a decreased or altered sense of smell of duration of 14 days or less, in the

absence of chronic rhinosinusitis, a history of head trauma, or neurotoxic medications. OD can be associated with flavor (smell+taste) dysfunction. However, Covid-19 may also affect real taste (sweet, salty, bitter, acidic, umami). OD is estimated to afflict 3%-20% of the population. Post-viral anosmia accounts for up to 40% of cases of anosmia or coronaviruses are thought to account for 10%-15% of these cases. As such, it is plausible that Covid-19 may cause OD. [3] This work aims to determine the prevalence of olfactory dysfunction in Coronavirus Disease 2019 (Covid-19) patients.

## Materials and Methods

Our review came following the (PRISMA) statement guidelines. [4]

### Study eligibility

The included studies should be in English, a journal published article, and a human study describing Covid-19 patients.

The excluded studies were either animal or non-English studies.

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**Study identification**

Basic searching was done over the pubmed, cochrane library, and google scholar using the following keywords: Covid-19, olfactory dysfunction.

**Data extraction**

Comparative studies, clinical trials, and Randomized Controlled Trials (RCTs), which studied the outcome of a group versus B group of Covid-19 patients, will be reviewed. Outcome measures included the pooled prevalence of olfactory dysfunction (as a primary main outcome).

**Study selection**

We found 350 records, 290 excluded because of the title; 60 articles are searched for eligibility by full-text review; 21 articles cannot be accessed; 27 studies were reviews and case reports. The studies which met all inclusion criteria were 12 studies.

**Statistical analysis**

Pooled proportions (%), with 95% Confidence Intervals (CI) assessed, using a statistical package (MedCalc, Belgium). The meta-analysis process was established via I<sup>2</sup>-statistics (either the fixed-effects model or the random-effects model), according to the Q test for heterogeneity.

**Results**

The included studies were published between 2019 and 2021.

Regarding patients’ characteristics, the total number of Covid-19 patients in all the included studies was 16866 patients. The mean age of all patients was (47 years) [Table 1]. Our meta-analysis included 12 studies; with a total number of patients (N=16866) [Table 2].<sup>[5-16]</sup>

**Each outcome was measured by**

Pooled Prevalence (%)

- For the pooled prevalence of olfactory dysfunction in Covid-19 patients.

Concerning the primary efficacy outcome measures, we found 12 studies reported a prevalence of olfactory dysfunction in Covid-19 patients. I<sup>2</sup> (inconsistency) was 99.7%, Q test for heterogeneity (p<0.0001), so random-effects model was carried out. Random-effects model of the meta-analysis process revealed a pooled prevalence of olfactory dysfunction in Covid-19 patients=42.7% (95% CI=28.83 to 57.24) (p<0.001) [Figure 1]. The funnel plot showed significant publication bias, Egger’s test (p=0.025) [Figure 2].

**Discussion**

This work aims to determine the prevalence of olfactory dysfunction in Coronavirus Disease 2019 (Covid-19) patients. The included studies were published between 2019 and 2021. Regarding patients’ characteristics, the total number of Covid-19 patients in all the included studies was 16866 patients. The mean

**Table 1: Patients and study characteristics.**

N	Author	Country	Number of patients Total	Age (average years)	COVID-19 confirmation procedure	Type of assessment for olfactory dysfunction
1	Borowczyk et al. [5]	European	1420	39	RT-PCR	Subjective
2	Alshami et al. [6]	Saudi Arabia	128	39.6	RT-PCR	Subjective
3	Karadaş et al. [7]	Turkey	239	46.4	RT-PCR	Subjective
4	Lapostolle et al. [8]	France	1487	44	RT-PCR	Subjective
5	Lechien et al. [9]	European	2581	44.5	RT-PCR	Subjective
6	Menni et al. [10]	UK	6452	41.2	RT-PCR	Subjective
7	Paderno et al. [11]	Italy	508	55	RT-PCR	Subjective
8	Qiu et al. [12]	China	394	---	RT-PCR	Subjective
9	Sierpiński et al. [13]	Poland	1942	50	RT-PCR	Subjective
10	Tudrej et al. [14]	Switzerland	198	---	RT-PCR	Subjective
11	Vaira et al. [15]	Italy	345	48.5	RT-PCR	Objective
12	Song et al. [16]	China	1172	61	RT-PCR	Subjective

**Table 2: Summary of outcome measures in all studies.**

N	Author	Total patients	Primary main outcome	
			Prevalence of olfactory dysfunction	Olfactory dysfunction prevalence
1	Borowczyk et al.	1420		997
2	Alshami et al.	128		28
3	Karadaş et al.	239		18
4	Lapostolle et al.	1487		415
5	Lechien et al.	2581		1916
6	Menni et al.	6452		4668
7	Paderno et al.	508		283
8	Qiu et al.	394		93
9	Sierpiński et al.	1942		956
10	Tudrej et al.	198		82
11	Vaira et al.	345		241
12	Song et al.	1172		134

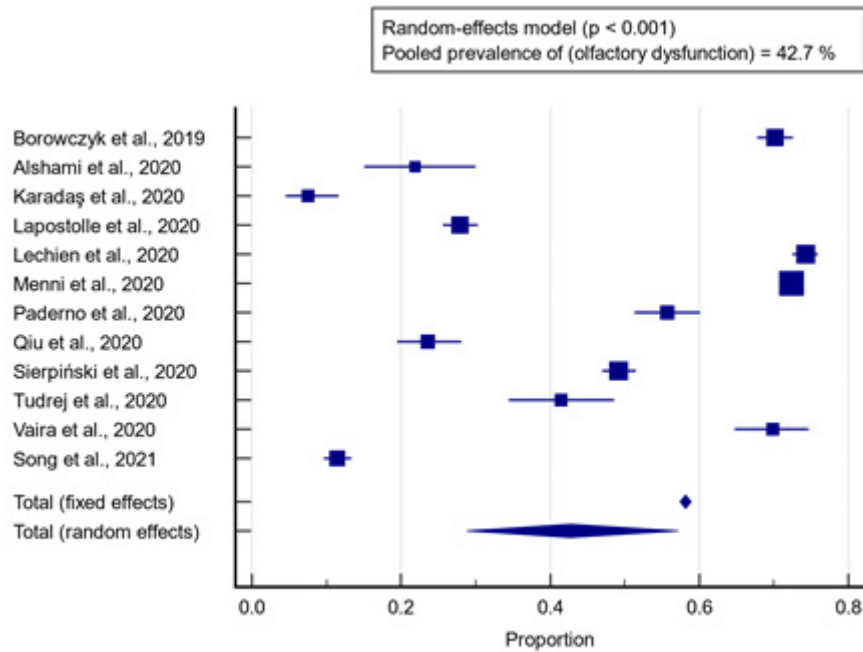


Figure 1: Forest plot (pooled prevalence of olfactory dysfunction).

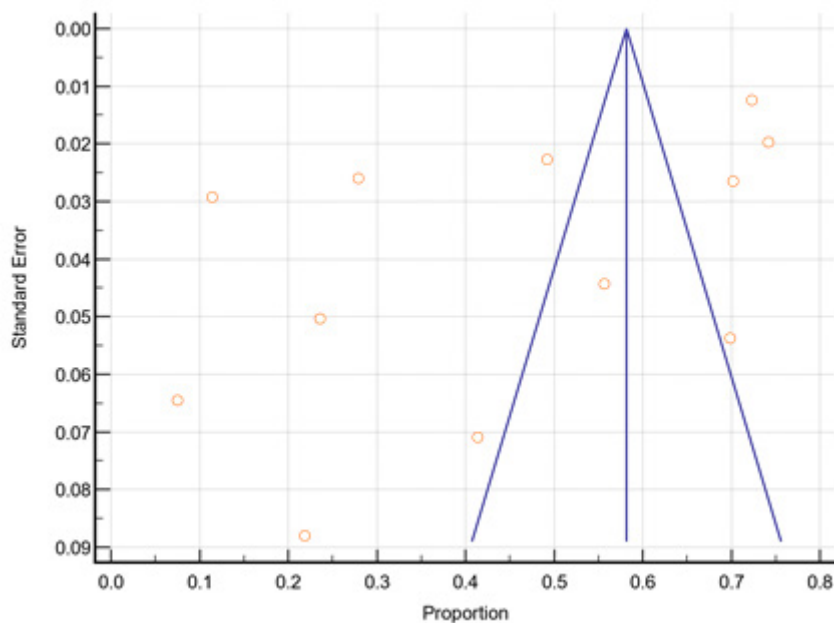


Figure 2: Funnel plot (publication bias was non-significant).

age of all patients was (47 years). Our meta-analysis included 12 studies; with a total number of patients (N=16866). We found 12 studies reported prevalence of olfactory dysfunction in Covid-19 patients. Random-effects model of the meta-analysis process revealed a pooled prevalence of olfactory dysfunction in Covid-19 patients=42.7% (95% CI=28.83 to 57.24) ( $p < 0.001$ ). Which came in agreement with Otte et al.; Sedaghat et al.; Li et al.; Chung et al.; Speth et al.; Kosugi et al.; Pang et al. [1-3,17-20] Otte et al. reported that 80 sufferers had experienced unexpected olfactory loss in the course of the direction of the disorder, and at the time of testing, 33 patients subjectively still had an impaired olfactory experience. Around eight weeks had exceeded since the onset of signs. 45.1% of the tested people had been nonetheless hyposmic consistent with the olfactory test while 53.8% showed an olfactory performance in the

regular range. Sufferers' self-assessment correlated poorly with the measured olfactory performance. [2] Sedaghat et al. reported that current evidence indicates that OD is extraordinarily established in Covid-19, with as much as 80% of sufferers reporting subjective OD and objective olfactory checking out probably showing even higher prevalence. OD is often followed through taste disorder. Up to 25% of Covid-19 sufferers may revel in unexpected-onset OD because of the first symptom. A huge proportion of Covid-19 OD cases may clear up over a few weeks. [17] Li et al. reported that it's been stated that loss of smell may be an early Sign of extreme Acute Respiratory Syndrome Coronavirus 2 (SARSCoV- 2) contamination, even earlier than other standard signs which include cough, fever, and shortness of breath for sufferers with coronavirus disorder 2019 (Covid-19). Dysosmia was identified in 5.1% of the patients

with Covid-19 in Wuhan, China. Previous studies have shown that the olfactory dysfunction will be resolved within 2 to four weeks in most of the people of sufferers with Covid-19. [18]

Chung et al. reported that we included 18 Covid-19 patients and 18 controls. Among Covid-19 patients, 12 of 18 (67%) reported olfactory symptoms, and OD was confirmed in 6 patients by BTT and SIT. Olfactory dysfunction was the only symptom in 2 patients. Mean BTT score of patients was worse than controls ( $P=0.004$ , difference in means=1.8; 95% confidence interval, 0.6-2.9). [19] Speth et al. reported that occurrence of OD turned into 61.2%, and severity of OD changed into strongly correlated with the severity of lack of taste experienced ( $r=0.87$ ,  $P<.001$ ). OD turned into skilled on the first day of Covid-19 by 8.7% and the general took place at median infection day three (suggest, 3.4; variety, 0-12). [20]

Kosugi et al. reported that 253 sudden olfactory dysfunction patients were included, of which 59.1% were ladies with a median age of 36 years, with a mean observe-up length of 31 days. 183 sufferers (72.3%) have been examined for Covid-19, and of these 145 (79.2%) tested positive. patients that tested nice for Covid-19 greater often showed non-unique inflammatory symptoms (89.7% vs. 73.7%;  $p=0.02$ ), a decrease fee of overall healing of surprising olfactory disorder (52.6% vs. 70.3%;  $p=0.05$ ). [1] Pang et al. reported that, the pooled frequency of OD in Covid-19 positive patients (17,401 patients, 60 studies) was 0.56 (0.47-0.64) but differs between detection *via* smell testing (0.76 (0.51-0.91)) and survey/questionnaire report (0.53 (0.45-0.62)), although not reaching statistical significance ( $p=0.089$ ). [3]

## Conclusion

To conclude, olfactory dysfunction is common in Covid-19 and maybe the only symptom. Coronavirus disease 2019-related OD can be severe and prolonged. Mucosal infiltration by CD68+ macrophages expressing SARS-CoV-2 viral antigen may contribute to Covid-19-related OD.

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