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Title:

Sudden onset, acute loss of taste and smell in coronavirus disease 2019 (COVID-19): A systematic review

Running title: Dysgeusia and anosmia in COVID-19 disease

Keywords: loss of taste and smell, dysgeusia, anosmia, chemosensory dysfunction, SARS-CoV-2, COVID-19

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Abstract:

Early detection, isolation, and management of COVID-19 patients are crucial to contain the current pandemic. The CDC in USA recently included "sudden loss of taste (dysgeusia/ageusia) and smell (anosmia/hyposmia)" as symptoms of COVID-19. If these symptoms are reliable forerunner symptoms of COVID-19, then it may facilitate early detection and containment of the disease. Hence, we systematically evaluated the contemporary evidence on dysgeusia and anosmia as trigger symptoms in COVID-19. Ovid MEDLINE, EBSCO host, and Web of Science databases were searched between December 25, 2019-May 30, 2020.Of the 13 identified records, eight (totaling 11,054 COVID-19 patients), were included, as per the selection criteria. The studies emanated mostly from the European community, as well as China, the USA, and Iran. In total, anosmia and dysgeusia symptoms were present in 74.9 % and 81.3% ambulatory as well as hospitalized, mild-to-severe cases of COVID-19 patients, respectively. The European, US, and Iran data indicate that olfactory, and gustatory symptoms appear prior to general COVID-19 symptoms in a majority of the patients. To our knowledge, this is the first systematic review analyzing the prevalence of chemosensory dysfunction in COVID-19. Further, studies are essential to evaluate their utility as harbingers of COVID-19 onset, and to establish clinical practice guidelines.

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Introduction:

The etiopathology and the symptomatology of the coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are reasonably well characterized. It is generally accepted that angiotensin-converting-enzyme 2 (ACE_2) abundantly present in the epithelia including the oral and nasal mucosa, and several human organs are the crucial, functional host cell receptor for SARS-CoV-2 (Hamming et al., 2004; Sungnak et al., 2020; Xu et al., 2020; Zhou et al., 2020), and hence the primary access route of the virus. Furthermore, although labeled as respiratory viruses, in addition to being epitheliotropic, coronaviruses, in general, are also known to be neurotropic and neuro-invasive (Desforges, Le Coupanec, Brison, Meessen-Pinard, & Talbot, 2014).

New information of this pandemic disease is regularly unfolding. Several studies from across the globe have emerged on the loss of smell and taste as notable early symptoms in a majority of COVID-19 patients (Giacomelli et al., 2020; Lechien et al., 2020; Xydakis et al.). Due to the strength of such data on chemosensory dysfunction in SARS-CoV-2 infection (Russell et al., 2020; Xydakis et al.), US Centers for Disease Control and Prevention (CDC) recently included "sudden loss of taste (dysgeusia/ageusia) and smell (anosmia/hyposmia)" as symptoms of COVID-19 (Update, 2020). Sensorineural dysgeusia or anosmia due to neurotropic or neurovirulent SARS-CoV-2 infection targeting the gustatory or the olfactory systems appears to be the pathological basis for these symptoms.

If these easily recognizable symptoms of dysgeusia, and anosmia, are relatively reliable harbingers of COVID-19, then there is the interesting possibility of identifying patients in the prodromal and/or the pre-symptomatic phase of the disease either through self-diagnosis or through tele diagnosis. Despite the recognition of the loss of taste and smell as premonitory symptoms of COVID-19, there are no systematic analyses in the English language literature on this subject. Therefore, we systematically reviewed the contemporary evidence on dysgeusia and anosmia as trigger prodromal symptoms in COVID-19 patients.

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Methods:

Outcome: The primary outcome sought was the systematic evaluation of currently reported prodromal symptoms of loss of taste and smell in patients with COVID-19. In particular, to understand the temporality and the periodicity of the appearance of these clinical manifestations in terms of the progress of SARS-CoV-2 infection.

Data sources:

Principal investigator (LPS) performed an electronic search of English language manuscripts using PubMed via Ovid, EBSCO host, and Web of Science databases. Published clinical reports were accessed between December 25, 2019, and May 30, 2020. A specific review question was formulated using the **PICO** framework (Schardt, Adams, Owens, Keitz, & Fontelo, 2007) as follows:

Intervention (**I**) **:** SARS-CoV-2 infection leading to COVID-19 impacting gustatory (taste) and olfactory (smell) perception of humans; Comparison (**C**): Other chronic medical/dental conditions that affect chemosensory perception such as certain medications, diabetes, renal ailments, cardiac conditions, nicotine, nutritional deficiency, post-operative ENT surgeries, sinusitis, and other similar sino-nasal diseases; xerostomia and ill-fitting dentures; syndromes such as Sjogren's that may all lead to either dysgeusia and/or anosmia/hyposmia; Outcome (**O):** results in various degrees of affection of gustatory (taste) and olfactory (smell) perception due to SARS-CoV-2 infection: Problem/Patients **(P):** SARS coronavirus-2 (SARS-CoV-2) infected adults (males and females).

Search keywords and combinations of keywords were structured corresponding to the **PICO** model. Heading (MeSH) and text words: (COVID-19 OR SARS-COV-2 OR COVID OR coronavirus infection) AND (taste OR smell) AND (ageusia OR dysgeusia) AND (anosmia OR hyposmia) AND (loss of smell OR loss of taste) AND (chemosensory OR chemosensory dysfunction)

The identified research articles were compiled using bibliographic software, Endnote version 9. (Clarivate Analytics, USA).

The study was registered under Prospero registration number: CRD42020183714.

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Electronic data search and analysis:

To ensure a systematic and comprehensive method, we followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Liberati et al., 2009; Moher, Liberati, Tetzlaff, & Altman, 2009). The search approach used, and results generated, are presented in (Fig. 1).

A three staged electronic data search and analysis were carried out, as follows: Stage one: the titles and abstracts of all pertinent studies meeting set inclusion criteria were screened by two investigators (LPS and KSF). Stage two: a full-text review of all the articles was performed, which gave a full detail of the data. During the full-text review of the retrieved literature, the investigators (LPS, KSF, and CP) used spreadsheets, ensuring that the eligibility criteria were met and the reported outcomes were following the study objectives. References of the included studies were checked as a backward search. Stage three: the reviewer extracted and evaluated the data.

After the full-text review, specific points related to the characteristics of each study were logged using the Cochrane model. This enabled in identifying the study design, the setting, and the country. Moreover, sample size, evaluation time, assessment methods, and study outcomes were comprehensively examined.

Data extraction:

After screening different electronic databases, a total of eight studies, including four cross-sectional studies, three case-control, and a retrospective observational case- series, were identified. Reports from bulletins, webinars, and national reports were removed. A single publication with data only on anosmia/hyposmia was not considered. Summary of the characteristics of included studies and the reported results on the clinical manifestation of gustatory and olfactory symptoms (dysgeusia/ageusia and anosmia/hyposmia) are provided in (Table 1).

Inclusion Criteria:

1. Population: Adolescent -elderly (≥17-≥80), COVID -19 symptoms (dysgeusia and/or anosmia) in ambulatory cases, non-severe to severe COVID-19 hospitalized patients

2. Study design: Cross-sectional studies and retrospective, observational case series

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3. Outcome: evaluation of chemosensory dysfunction (gustatory and olfactory) clinical symptoms in patients with Coronavirus-positive disease (COVID-19)

Exclusion Criteria:

1. Conference proceedings, newspaper articles, news broadcasts, opinion articles

2. Studies only about olfactory (anosmia/hyposmia) clinical symptoms

3. Past studies on COVID-19 related SARS and Middle East Respiratory Syndrome (MERS) coronavirus infection

Quality Assessment and Overall Risk of bias:

The quality assessment of the eligible observational studies (case-control and cross-sectional) were performed according to the nine-item checklist for prevalence study by two investigators (LPS and KSF), independently (Hoy et al., 2012). In case of disagreement, a third reviewer (CP) was consulted. The items in the checklist were scored as low risk (0) or high risk (1). The summated values are rated as low (0-3), moderate (4-6), and high (7-9) for the listed domains (Table 2). Studies falling under high-risk of bias were excluded from the review.

Results and Discussion:

The final search outcome was a total of eight studies that fulfilled all our inclusion criteria. Four of the studies were from the European countries, France (x2), Italy, Spain, and Belgium, while the remainder were from the USA, China, and Iran (Table 1). In general, the included studies had many data lapses, particularly on the presentation sequence (i.e. the temporality) of anosmia and dysgeusia. Additionally, the data related to the incidence of both these symptoms in a given patient population were presented mostly as cumulative numbers. Hence it was difficult to decipher whether a specific patient suffered from either anosmia and dysgeusia at different periods or simultaneously, in tandem, at a given time point. Despite these reporting lapses, we were able to garner the following from the review.

The pervasiveness of anosmia and dysgeusia in COVID-19:

The cumulative data from the eight studies were related to a total of 11,054 cases of SARS-CoV-2 infection, with the sample sizes of each study ranging from 59 to10,069 patients. All included

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studies reported COVID-19 presenting with clinical manifestation of either anosmia and dysgeusia at some stage of the disease. Almost three quarters of the total cohort evaluated i.e. 8283 [74.9 %; range 5.1%-85.6%; proportion 48.8%; 95% CI, 22.37-71.12] presented with/developed anosmia/hyposmia whilst four-fifths i.e., 8984 [81.3%; range 5.6%-88.8%; proportion 51.3%; 95% CI, 27.35-72.39] presented with/developed dysgeusia/ageusia during the observation period.

Taken together, available data to-date, indicate the presence of anosmia or dysgeusia or both these symptoms in some three quarters to two-fifth of COVID-19 patients. However, the data are somewhat cloudy as in some studies the patient numbers did not add up, possibly due to mutual exclusivity. The multicenter, European study from France, Belgium, Spain, and Italy, reported over 85% with mild to moderate COVID-19 with chemosensory dysfunction, as well as a significant positive association between olfactory and gustatory dysfunction in COVID-19 confirmed cases (Lechien et al., 2020). Several other studies have also reported of the simultaneous presence of both dysgeusia and anosmia (Beltrán-Corbellini et al., 2020; Giacomelli et al., 2020; Lechien et al., 2020; Moein et al., 2020; Yan, Faraji, Prajapati, Boone, & DeConde, 2020),.

Anosmia and dysgeusia: a prodromal trigger symptom signaling SARS-CoV-2 infection?

The cumulative data from our review indicate that both anosmia and dysgeusia presenting as prodromal sub-clinical/ clinical manifestations in 64.5% and 54.0 % of the ambulatory patients, respectively. One patho-physiological explanation for this finding is the profuse presence of ACE_2 receptors, in the epithelial linings of the nasal mucosa and the tongue (Hamming et al., 2004; Sungnak et al., 2020; Xu et al., 2020). It is now known tharACE_2 , as the primary host-cell receptor for SARS-CoV-2, plays a pivotal role in the viral entry, and subsequent disseminated infection (Ciaglia, Vecchione, & Puca, 2020; Xu et al., 2020). Taken together, this evidence seems to signify why over one-half of the COVID-19 patients presented with loss of smell and taste sensation.

We also addressed the question of how long before the definitive early symptoms such as fever, sore throat, etc., do dysgeusia and anosmia appear, especially in otherwise asymptomatic, ambulatory patients in the community. Of the eligible studies, three of the reports (Lechien et al., 2020; Mao et al., 2020; Yan et al., 2020) noted the temporality of occurrence of either dysgeusia

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or anosmia individually at the prodromal phase, signaling COVID-19 infection. A US study (Yan et al., 2020) reported (71.0%) dysgeusia, and (68%) anosmia as early symptoms in (n=59), laboratory-confirmed, symptomatic ambulatory, COVID-19 cases. Another Italian report by Giacomelli and colleagues also revealed taste alterations (dysgeusia) in about 91% of the patients before hospitalization (Giacomelli et al., 2020). Moein et al., have also confirmed that up to a third (35%) of their patients develop anosmia prior to hospitalization, thus substantiating the preceding reports (Moein et al., 2020).

On the other hand, the simultaneous manifestation of olfactory and gustatory dysfunction in the acute SARS-CoV-2 infection has been reported only by Beltrán-Corbellini et al. with 70.9% of their cohort (Beltrán-Corbellini et al., 2020). Finally, the single multicenter, European, cross-sectional study of 417 cases, noted the olfactory dysfunction symptoms in only a relatively small proportion of their patients (11.8%) before the appearance of the general COVID-19 symptoms (Lechien et al., 2020).

These reports indicate dysgeusia and anosmia are either sub-clinical or clinical markers of COVID-19 disease. It is, however, noteworthy that anosmia and dysgeusia may be a result of many medical conditions, nutritional deficiencies, and medications, etc. (Boesveldt et al., 2017; Syed, Hendler, & Koncilja, 2016; van Riel, Verdijk, & Kuiken, 2015). Though, the olfactory impairment linked to SARS-CoV-2 infection seems distinct as it is not accompanied by usual rhinorrhea (Lechien et al., 2020). Hence, patients presenting with acute-onset loss of smell or taste, particularly in the context of a patent nasal airway (i.e., non-conductive injury), should be viewed with a high index of suspicion for concomitant SARS-CoV-2 infection. This would help the early detection of patients and containment that could help save many lives. Other questions that primarily be addressed in this context are i) whether anosmia and/or dysgeusia is/are present in asymptomatic carrier state of SARS-CoV-2 infection, and ii) and, if so, to what extent.

Quality evaluation and risk assessment of the included studies

The reviewed studies included currently available (as of May 30, 2020) mostly cross-sectional (Bagheri et al., 2020; Giacomelli et al., 2020; Lechien et al., 2020; Yan et al., 2020), case-control studies (Beltrán-Corbellini et al., 2020; Benezit et al., 2020; Moein et al., 2020), and a single observational case-series (Mao et al., 2020). Individual scores and the summary of the risk of bias for each study are in Table 21. In essence, their risk of bias ranged from moderate to high.

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As all eligible studies included a select, representative population of laboratory-confirmed COVID-19 patients, the findings could be construed as unbiased estimates of the outcomes sought in the target populations.

There are other deficiencies, too, in some studies. For instance, it is known that the design of research must account for intrinsic selection bias due to investigator-directed case selection, case-matching, and control for confounding factors (Mann, 2003; Skelly, Dettori, & Brodt, 2012). All eight of our select studies except that of Bénézit et al. (Benezit et al., 2020), mentioned adjusting for confounding effects (patient comorbidities such as asthma, diabetes, smoking, etc.). Still, none elaborated if these factors influenced their results. Additionally, only the multicenter European report indicated an association, though not significant, between smell and taste dysfunction, and the patients' underlying medical conditions(Lechien et al., 2020).

A majority of the studies in our review included retrospective surveys that collected data through online questionnaires (Bagheri et al., 2020; Beltrán-Corbellini et al., 2020; Benezit et al., 2020; Giacomelli et al., 2020; Lechien et al., 2020; Yan et al., 2020). The possibility that self-assessment of subjectively perceived chemosensory symptoms, as well as the recall memory, may have corrupted the reported responses. The accuracy of such self-diagnosed symptomatology reported through questionnaires (Bagheri et al., 2020; Beltrán-Corbellini et al., 2020; Benezit et al., 2020; Giacomelli et al., 2020; Lechien et al., 2020; Yan et al., 2020) or telephone surveys (Benezit et al., 2020) may have introduced intrinsic response biases. Additionally, some studies noted the suboptimal response rate in their surveys (Benezit et al., 2020; Yan et al., 2020). This might also have influenced the outcomes by introducing the likelihood of systematic differences between responders and non-responders.

Only three studies, which include a multi-center European survey (Lechien et al., 2020), the retrospective case-series from China (Mao et al., 2020), and the case-control Iranian study (Moein et al., 2020) reported using validated instruments. Thus, the use of a non-validated questionnaire by others might have introduced the risk of measurement-bias in their reports.

Moreover, in the eight studies we reviewed, the prevalence of dysgeusia and anosmia in the participants vary considerably. The result of studies with a larger sample size (Bagheri et al., 2020) may have confounded the results of other studies with a smaller sample size (Beltrán-Corbellini et al., 2020; Bénézit et al.; Giacomelli et al., 2020; Lechien et al., 2020; Mao et al.,

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2020; Moein et al., 2020; Yan et al., 2020). Given the lethality of the current pandemic, more quality controlled studies are urgently required to ascertain the precise clinical value of dysgeusia and anosmia as symptoms heralding the full-blown COVID-19.

Conclusions:

The current review is the first to summarize the contemporary evidence from eight different studies from various regions of the world, on the COVID-19 associated symptomatic manifestations of anosmia and dysgeusia. We also describe the potential clinical implications of these symptoms in terms of the early diagnosis, management, and mitigating the spread of COVID-19.

Our review indicates a fair prevalence of acute onset impaired olfactory and gustatory symptoms in patients with COVID-19. Summarized evidence from Europe, China, Iran, and the USA strongly supports the view that sudden, acute onset of anosmia or dysgeusia could possibly be identified and recognized as harbingers of SARS-CoV-2 infection. However, the quality of several studies evaluated was uncertain due to the inherent study biases discussed above (Table 4).

Hence, further, rigorously controlled, multi-center studies are urgently needed. These should include ambulatory patients, as well as otherwise asymptomatic carriers, to validate the current relatively meager database on the symptomatology of dysgeusia and anosmia in COVID-19. If indeed, these early symptoms of COVID-19 are confirmed as highly prevalent, as it seems to be, then it could save many a life in the future. This may also indirectly impact the economies of many societies by mitigating the effect of the current pandemic and forestalling the predicted next wave of the disease

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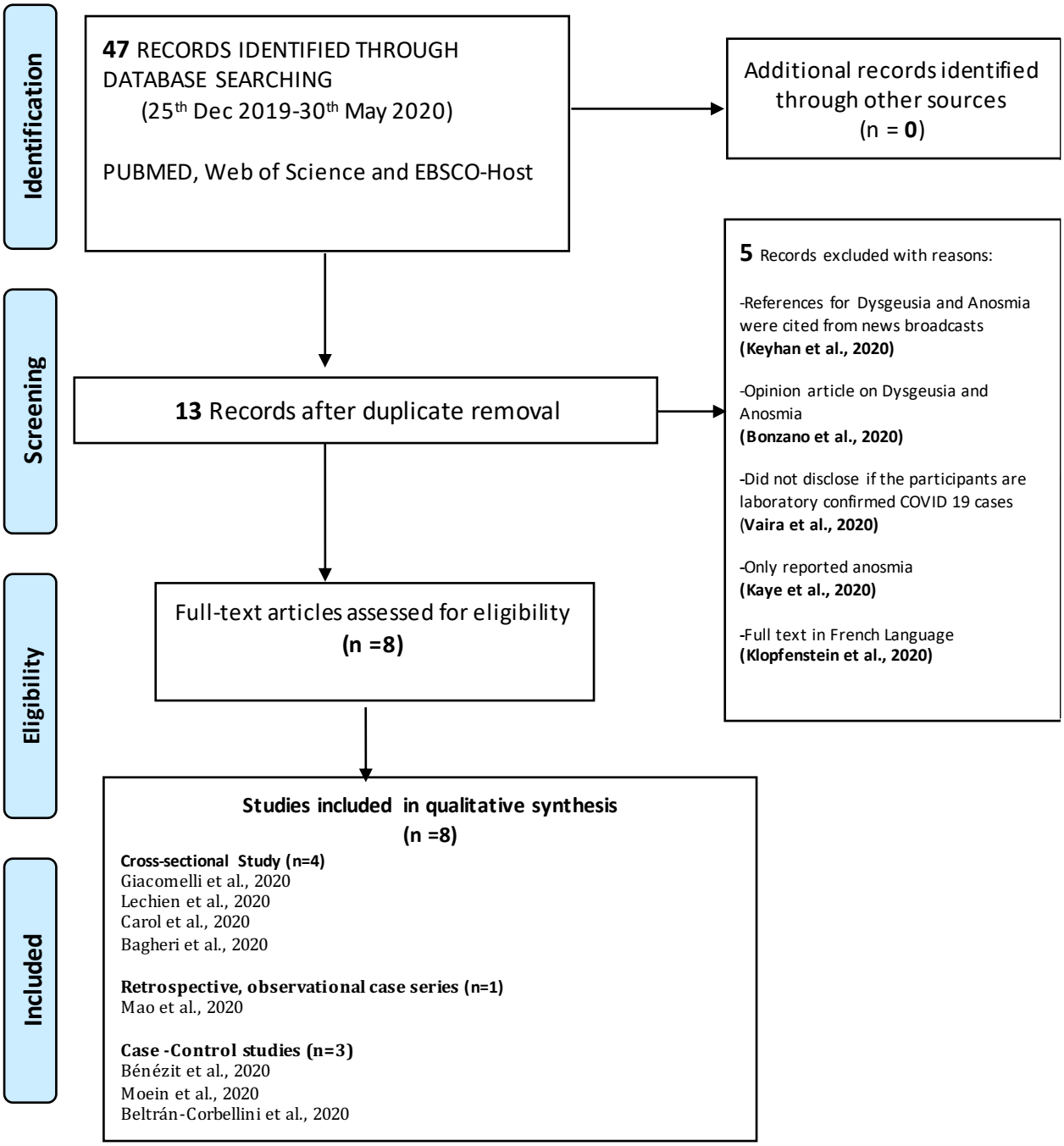

Figure 1 PRISMA flow-chart of the literature search and study selection

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Table 1. Summary of the Included studies

Study	Population	Study type	No. of patients	Country	Onset of Symptom	Severity of cases	Co-morbidities (%)	Instrument/s Used	No. of patients with dysgeusia (gustatory dysfunction) N (%)	No. of patients with anosmia (olfactory dysfunction) N (%)
Bénézit et al., 2020 (Published article)	Male: NA Female: NA Age (NA)	Case Control	68	**France**	NA	NA	NA	Self-report via telephone survey and questionnaire	42 (62%) 29 (43%) patients had both dysgeusia and hyposmia	31 (45%) 29 (43%) patients had both dysgeusia and hyposmia
Lechien et al., 2020 (Published article)	Male:154 Female: 263 >18 years (19-77)-years-old	Cross sectional	417	Multicenter **European** Study (**12 - Centers**) **5 Belgium** **2 France** **2 Spain** **3 Italy**	In 11.8% olfactory dysfunction appeared prior to the appearance of general COVID-19 symptoms. In (65.4%) the olfactory and gustatory dysfunctions appeared at the same time as the general COVID-19 symptom	Mild to moderate	Allergic patients (15) Asthma (7) Hypertension (7) Diabetes (2) Cardiac ailment (3) Hypothyroidism (6) Cancer (2) Neurological disorder /Depression (3) GERD (3)	Questionnaire survey	342 (82.0%)	357 (85.6%) *[284 (79.6%) with anosmia, and 73 (20.4%) with hyposmia]*
Giacomelli et al., 2020 (Published article)	Male:40 Female: 19 50-74 years	Cross sectional	59	**Italy**	91% reported taste alteration (dysgeusia) before hospitalization	Mild to moderate	Dementia (n=14)	Interview and questionnaire survey	6 (10.2%) 11 (18.6%) patients had both dysgeusia and hyposmia	3 (5.1%) 11 (18.6%) patients with dysgeusia and anosmia/ hyposmia
Moein et al., 2020 (Accepted article)	Male:40 Female: 20 -Mean age 46.5 (±12.2) years	Case Control	60	**Iran**	35% reported anosmia before hospitalization	Severe - hospitalized patients	NA	Clinical examination - UPSIT* instrument	14 (23.3%) 10 (17%) patients had both dysgeusia and hyposmia	35 (58%) 10 (17%) patients had both dysgeusia and hyposmia
Mao et al. 2020	Male: 87 Female: 127	Retrospe ctiveobse	214	**China**	Patients develop taste and olfactory	Non-severe to severe	Hypertension (51)	Clinical records	12 (5.6%)	11 (5.1%)

(Pre-print)	37-68-years-old	rvational case series			symptoms after 2-days of hospitalization		Diabetes (30) Cardiac or Cerebrovascular disease (15) Malignancy (13) Chronic kidney disease (6)			
Beltrán-Corbellini et al., 2020 (Published article)	Male: 48 Female: 31 >18 years - over 60-years-old	Case Control	79	**Spain**	Among patients with dysgeusia and anosmia presentation: 22 (70.9%) recalled an acute onset In 11 (35%) an initial manifestation	Non-severe to severe	NA	Questionnaire survey	28 (35.4%) *Ageusia 14 (45.2%)* *Hypogeusia 7 (22.6%)* *Dysgeusia 8 (25.8%)* 31 (39.2%) patients had both dysgeusia and anosmia	25 (31.7%) 31 (39.2%) patients had both dysgeusia and anosmia
Yan et al., 2020 (Published article)	Male: 29 Female: 29 Diverse gender: 1 18-≥80-years-old	Cross sectional	59	**USA**	NA	Symptomatic -ambulatory COVID-19 patients	Allergic rhinitis (20) Hypertension (8) Diabetes (5) Cardiac ailment (3) COPD (3) -Cancer (2) -Sinusitis (2)	Questionnaire survey	42 (71%)	40 (68%)
Bagheri et al., 2020 (Pre- print)	Male: 2970 Female: 7099 (7-78)-years-old	Cross sectional	10069	**Iran**	NA	NA	NA	Questionnaire survey	8400 (83.4%) patients have dysgeusia with anosmia	7680 (76.2%)

*UPSIT= University of Pennsylvania Smell Identification Test

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Table 2: Quality Assessment of Included studies (Risk of bias)

Risk of bias items	Bénézit et al., 2020	Lechien et al., 2020	Giacomelli et al., 2020	Moein et al., 2020	Mao et al. 2020	Beltrán-Corbellini et al., 2020	Yan et al., 2020	Bagheri et al., 2020
Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	1	1	1	1	1	1	1	1
Was the sampling frame a true or close representation of the target population?	1	1	1	1	1	1	1	1
Was some form of random selection used to select the sample?	1	1	1	1	1	1	1	1
Was the likelihood of non-response bias minimal?	1	1	1	0	1	1	1	1
Were data collected directly from the subjects (as opposed to a proxy)?	0	0	0	0	1	0	0	0
Was an acceptable case definition used in the study?	0	0	0	0	0	0	1	1
Was the study instrument that measured the parameter of interest shown to have reliability and validity	1	0	1	0	0	1	1	1
Were the numerator(s) and denominator(s) for the parameter of interest appropriate	0	0	1	1	0	0	0	1
Was the same mode of data collection used for all subjects?	0	0	0	0	0	0	0	0
Total Points	**5**	**4**	**6**	**4**	**5**	**5**	**6**	**7**
Summary on the overall risk of study bias (Low risk=0-3) (Medium risk=4-6) (High risk=7-9)	**Medium**	**Medium**	**Medium**	**Medium**	**Medium**	**Medium**	**Medium**	**High**

0= Yes, Low Risk; 1= No, High Risk

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8-10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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