

Manuscript Title: Sniffing out the evidence for olfactory symptoms as a clinical feature of COVID-19: A Systematic Scoping Review.

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Key Points

Question: What is the existing evidence surrounding olfactory symptoms (anosmia and hyposmia) as a clinical feature of SARS-CoV-2?

Findings: The existing evidence is currently limited to emerging anecdotal clinical observations from clinicians, and one non-peer reviewed study which reported hyposmia in 11 of 214 (5.1%) of patients with confirmed SARS-CoV-2; however significance was not reached in this study ($p=0.338$).

Meaning: More evidence is required to establish whether there is a link between changes in olfaction and SARS-CoV-2; we therefore encourage clinicians to incorporate questions around loss of olfactory sensation into their clinical practice when assessing patients with suspected SARS-CoV-2.

Abstract

Importance: We seek to understand the current evidence behind emerging claims suggesting that olfactory symptoms, such as anosmia (complete loss of smell) and hyposmia (reduced sensation of smell), could be a clinical feature of SARS-CoV-2 infection. This could be a potentially important, but under-recognised symptom of SARS-CoV-2 and could have important clinical implications for testing and self-isolation guidance during the current pandemic.

Objective: To understand the existing evidence surrounding olfactory symptoms (anosmia and hyposmia) as a clinical feature of SARS-CoV-2.

Evidence review: We conducted a rapid systematic scoping review of the literature and searched 5 major databases (Medline; Embase; via Ovid; CINAHL via Ebsco; Web of Science and Scopus; via ProQuest), in addition to combining a search of the grey literature with expert consultation. Studies or evidence published between the 31st of December 2019 and the 23rd of March 2020 was eligible for inclusion. No restrictions were placed on language. Included evidence was graded using the Oxford Centre for Evidence-based Medicine (CEBM) Levels of Evidence guideline.

Findings: We identified four relevant pieces of evidence suggesting that olfactory symptoms could be a potential clinical feature of SARS-CoV-2. These included a non-peer reviewed study from China where 11 of 214 (5.1%) patients with confirmed SARS-CoV-2 complained of hyposmia, and three expert statements from the American, British and French associations of otorhinolaryngology. Overall the evidence was graded as ‘inconclusive’ (Grade D) using the CEBM guideline. Through the systematic-review process we also identified 56 peer-

reviewed studies which described clinical features in confirmed cases of SARS-CoV-2. None of these studies mention olfactory symptoms as a clinical feature of SARS-CoV-2.

Conclusions and Relevance: The preliminary current evidence for olfactory symptoms as a potential feature of SARS-CoV-2 is inconclusive at this time. Given the novel and uncertain nature of this topic, we encourage clinicians to specifically incorporate questions around loss of olfactory sensation into their clinical practice when assessing patients with suspected SARS-CoV-2 to help build the emerging and rapidly evolving evidence-base around symptomatology.

Introduction

On the 11th of March, The World Health Organization (WHO) declared SARS-CoV-2 (*the novel coronavirus that causes coronavirus disease 2019, or COVID-19*) a pandemic.¹ To date (23rd March 2020), there have been 334,981 confirmed cases and 14,652 deaths attributed to SARS-CoV-2, across 190 countries.²

Emerging studies from Wuhan, China, where SARS-CoV-2 was first described, suggest that the clinical features of SARS-CoV-2 are variable, but commonly include a dry cough, fever, dyspnoea and fatigue.³⁻⁵

On the 21st of March 2020, a press release was issued by ENT UK and The British Rhinological Society, suggesting that new-onset olfactory symptoms, such as anosmia (inability to smell) and hyposmia (reduced ability to smell), should be also be considered as a potential marker of SARS-CoV-2 infection.⁶ The press release suggested that anosmia has been a feature in patients with confirmed SARS-CoV-2 across multiple countries including China, Germany, Italy, South Korea and the United Kingdom. It stated that there was “good evidence” that in Germany 66% of confirmed cases have anosmia as a clinical feature and in South Korea “30% of patients testing positive have had anosmia as their major presenting symptom in otherwise mild cases”.⁶ This press release has resulted in major news outlets across the world running news articles, suggesting that loss of olfactory symptoms could be a potential clinical feature of SARS-CoV-2.⁷⁻⁹

Despite this emerging evidence, several major international and national bodies have yet to include anosmia as a potential symptom of COVID-19. For example WHO states that

common symptoms of COVID-19 include “a dry cough, fever and tiredness”, whereas less common symptoms include “shortness of breath; aches and pains; sore throat; diarrhoea, nausea or a runny nose”.¹⁰ Similarly the National Health Service (NHS) England website suggests that individuals with a fever and a new continuous cough should self-isolate for a period of between 7 and 14 days,¹¹ and the United States Centers for Disease Control and Prevention (CDC) does not mention olfactory symptoms as a potential feature of SARS-CoV-2.¹²

As such this study seeks to understand

1. What is the existing evidence surrounding olfactory symptoms (anosmia and hyposmia) as a clinical feature of SARS-CoV-2?

Methods

Nature of review

We chose to conduct a scoping review given the novel and emerging nature of the SARS-CoV-2 virus. A scoping review has been defined as a way to “map rapidly the key concepts underpinning a research area and the main sources and types of evidence available... especially where an area is complex or has not been reviewed comprehensively before”.¹³ Furthermore a scoping review has been highlighted as an important way to explore “key concepts, types of evidence, and gaps in research”.¹⁴ We followed Arksey and O’Malley’s widely used methodological framework for conducting scoping reviews to ensure rigor and potential for replicability.¹⁵

We adhered to the Preferred Reporting Items for Systematic reviews and Meta Analyses (PRISMA) guidelines for conducting a scoping review.¹⁶

Search strategy

Following a manual search of the Cochrane Library, the Campbell Collaboration, the International Prospective Register of Systematic Reviews (PROSPERO) and grey literature, we identified no existing or scheduled reviews on the topic of olfactory changes as a feature of SARS-CoV-2.

We then searched the following five databases for relevant peer-reviewed literature:

- Medline; Embase; via Ovid
- CINAHL via Ebsco;
- Web of Science and Scopus; via ProQuest.

We also searched the following sources for non-peer reviewed, grey-literature:

- <https://www.medrxiv.org/> (a pre-print server for unpublished manuscripts in the field of health-sciences).
- Member websites of The International Federation of Otorhinolaryngology (ORL) Societies (IFOS) (e.g. American Academy of Otolaryngology - Head and Neck Surgery; Canadian Society of Otolaryngology - Head and Neck Surgery; ENT UK (British Association of Otorhinolaryngologists Head and Neck Surgeons) etc.)
- Websites of relevant Professional bodies (e.g. Society of Sensory Professionals, Fifth Sense UK).

Finally, we used consultation techniques with relevant experts (identified through the IFOS websites) to ensure we had not missed any relevant or important studies.

Search Dates

We searched the peer-reviewed and grey literature between 31st December 2019 and March 22nd 2020. The 31st of December 2019 was chosen as the starting date for this rapid review given that this was the first date that COVID-19 was reported to the WHO by the Chinese authorities.¹⁷

Search Terms

The following combination of search terms were used to search the literature:

- “SARS-CoV-2” OR “2019-nCoV” OR “Coronavirus” OR “COVID-19”

AND

- “Anosmia” OR “Hyposmia” OR “loss of smell” OR “symptom*” OR “clinical feature*” OR “Smell” OR “olfact*”

For the non-peer reviewed grey-literature (e.g. <https://www.medrxiv.org/>) the above search terms were adapted and the websites of professional bodies were searched manually.

Inclusion and exclusion criteria

Evidence was eligible for final inclusion if it described:

1. Clinical features of SARS-CoV-2 – specifically those related to olfactory symptomatology.

Evidence was excluded from the final analysis if it:

1. Was not focussed on adult human subjects (*paediatric patients were excluded since it was assumed they would not be able to report loss of smell*).
2. Was not focussed on SARS-CoV-2 e.g. evidence on MERS-CoV was excluded.

Studies were not excluded based on language, nor were they excluded based on study design, given that we were interested in mapping the existing scope of evidence.

Study selection, data extraction and analysis

All studies identified through the initial search of the databases and grey literature were imported into EndNote referencing software (Version 9). An automated function in EndNote was used to remove duplicate results, and remaining studies were then manually checked by one author (JOD) to ensure all duplicates had been removed. Two authors then screened all remaining studies for potential relevance based on the full title and abstract (JOD, NJ). At this

stage studies were eligible if they indicated they would report clinical features or symptoms of SARS-CoV-2. For any potential disagreements it was agreed that a third reviewer would be consulted to break ties (ST).

At the end of this process the full texts of potentially relevant studies were obtained and independently screened by three of the study authors for final inclusion or exclusion against the pre-defined criteria outlined above. Each reviewer was assigned 20 studies and read the full text of each study (JOD, NJ, ST). They extracted data from each study into a data charting form regarding study title, date, location, design, number of patients involved and whether or not it reported olfactory symptoms associated with SARS-CoV-2. The use of a data charting form has been recommended as a key stage of conducting a scoping review.¹⁴

Quality of evidence assessment

To assess the quality of evidence we used the Oxford Centre for Evidence-based Medicine (CEBM) Levels of Evidence guideline (March 2009).¹⁸ This is a five point ranking scale from 1 to 5. For example, Level 1a evidence is classed as “a Systematic Review (with homogeneity*) of Randomized Controlled Trials”; Level 5 evidence is an “expert opinion without explicit critical appraisal, or based on physiology, bench research or *first principles*”.¹⁸

Ethical approval

Ethical approval was not sought for this study, because this is a review of existing published literature and does not directly involve human subjects.

Results

Search Results

The literature search of five databases yielded 596 results, in addition to a further four identified through a combination of a search of the peer-reviewed grey-literature, snowball sampling and expert consultation.

After duplicates were removed, a total of 321 results were left for title and abstract screening. This process resulted in documents being excluded, leaving 60 documents for a full text review. Following a full text review, 56 documents were excluded, leaving four documents for inclusion in the final analysis.

For further information, including reasons for study exclusion at the full text screening stage, please refer to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Figure 1).

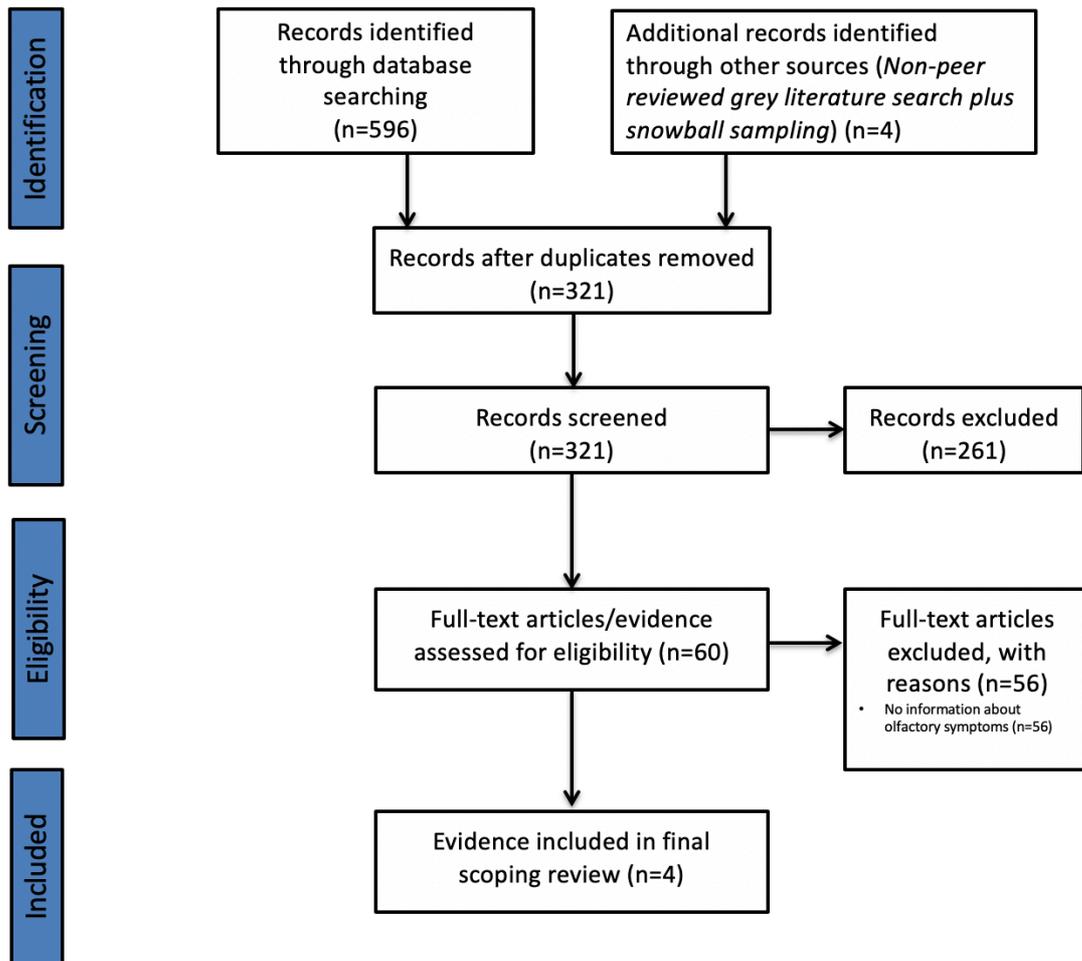


Figure 1. PRISMA diagram detailing the systematic scoping review search process.

Findings

Four pieces of evidence described olfactory symptoms as potentially being associated with SARS-CoV-2.

The retrospective case-series published by Mao et al. (2020),¹⁹ from Wuhan, China, described hyposmia as a clinical feature in 11 of 214 (5.1%) patients with confirmed SARS-CoV-2; however found that this was not significant ($p=0.338$). This evidence ranks as a ‘Grade 4’ using the CEBM Levels of Evidence Guideline.

Three expert bodies from the America,²⁰ France,²¹ and the UK,⁶ have also described anosmia as a potential symptom of SARS-CoV-2 through press release statements. This evidence ranks as a ‘Grade 5’ using the CEBM Levels of Evidence Guideline.

The American Academy of Otolaryngology — Head and Neck Surgery made a statement on the 23rd of March stating that anecdotal evidence suggests anosmia has been seen in patients ultimately testing positive for the SARS-CoV-2 with no other symptoms and suggests that olfactory symptoms should be added to screening tools. They go on to state that changes in olfaction should “*warrant serious consideration for self-isolation and testing of these individuals*”.²⁰

The French expert body (Le Syndicat National des Médecins Spécialisés en ORL et Chirurgie Cervico-Faciale (SNORL)) noted that anosmia without nasal obstruction was diagnosed in young patients who tested positive for SARS-CoV-2.²¹ It suggests that the clinical implications of this are that oral and nasal corticosteroids are not recommended for

management of sudden on-set olfactory symptoms at this present time, given that this may exacerbate symptoms of SARS-CoV-2.

The ENT UK statement (*which has so far received the most traction in the popular media*) stated that they had “good evidence” from multiple countries that patients with confirmed SARS-CoV-2 had also developed olfactory symptoms. After clarifying this information with an ENT UK representative we now know that this was largely based on anecdotal messages shared amongst clinicians on a private online forum for otolaryngologists. Due to privacy regulations we were unable to gain access to the group to analyse the message exchanges.

The evidence included in this press release stated that “in Germany it is reported that more than 2 in 3 confirmed cases have anosmia”.⁶ This evidence is from a German virologist who went house-to-house in one district to interview approximately 100 individuals. He reported that two thirds of individuals experienced changes in sensation of smell and that severity of disease was usually mild.

The press release also stated that “in South Korea, where testing has been more widespread, 30% of patients testing positive have had anosmia as their major presenting symptom in otherwise mild cases”.⁶ This evidence refers to a media report by a Korean news outlet. A journalist interviewed doctors at hospitals in Daegu. One doctor was quoted as saying: “If you put together the doctors who conducted ward rounds or spoke to patients on the phone, approximately 30% of the confirmed (COVID-19 positive) patients reported a loss of smell as a symptom”.²²

The press release by ENT UK does caveat that “while there is a chance the apparent increase in incidence could merely reflect the attention COVID-19 has attracted in the media, and that such cases may be caused by typical rhinovirus and coronavirus strains, it could potentially be used as a screening tool to help identify otherwise asymptomatic patients, who could then be better instructed on self-isolation”.⁶

The summary of the above evidence can be found in Table 1. Overall, using the CEBM Evidence Grading tool we rank the current evidence as “Grade D” meaning that the current evidence is inconclusive.

To date none of the 56 peer-reviewed studies describing patient symptomatology in confirmed cases of SARS-CoV-2 have reported olfactory symptoms as a feature, although some do report more general nasal symptoms – such as congestion (see eTable1 in the Supplement).

Discussion

Three expert societies have suggested that, based on emerging clinical observations, changes in olfaction could be a clinical feature of SARS-CoV-2, especially in milder or early cases of the disease.^{6,20,21} In addition, one non-peer reviewed study by Mao et al., from China found that 11 of 214 (5.1%) patients with confirmed SARS-CoV-2 reported hyposmia; however significance was not achieved.¹⁹ Given the high viral load of SARS-CoV-2 in the nasal cavity, it is plausible that olfaction may potentially be affected as part of this disease process; however as of yet this has not been proven.²³

Interestingly, changes in olfaction secondary to SARS-CoV-2 have not been mentioned as a symptom in any of the existing 56 peer-reviewed studies where symptoms of patients with confirmed cases of disease have been reported. This could be for several reasons. First, symptoms around olfaction may not have been elicited and recorded. Where patients have been admitted to hospital with life threatening symptoms, such as shortness of breath and fever, a more niche symptom (such as change in olfaction) may not have been assessed. Additionally, unless patients are consciously monitoring for olfactory loss, many of them may not become aware of this manifestation or seek medical attention for days to weeks.

Secondly, many of the existing peer-reviewed studies report clinical features for hospitalised patients (i.e. critically ill patients and *not* those with milder, self-limiting symptoms); however current best estimates suggest that up to 81% of individuals have a self-limiting form of SARS-CoV-2 and therefore do not present to hospital.²⁴ It could be possible that olfactory symptoms are present in SARS-CoV-2, but in patients with milder cases of the disease.

At this relatively early stage and whilst we are still learning about the virus, we would recommend that clinicians consider integrating questions regarding olfactory changes into their clinical history. This could help us to better understand whether olfactory changes are indeed a clinical feature of SARS-CoV-2. Currently there is no evidence as to whether olfactory symptoms, if indeed linked with SARS-CoV-2, are an early presenting feature or if they occur at later stages of the disease. There is also no evidence to suggest what the presence of olfactory symptoms means for prognosis. Finally, the potential public health impact of recognizing olfactory deficits and strictly self-isolating with presumed SARS-CoV-2 infection is currently unknown.

It is also interesting to note how this evidence has been communicated by the media to the general public. In a New York Times article from the 23rd of March 2020, it was stated that “a study from South Korea, where widespread testing has been done, found that 30 percent of some 2,000 patients who tested positive for the coronavirus reported experiencing anosmia”.⁸ We now know that this data actually came from anecdotal observations published in a national newspaper, rather than in a formal study as the article claims. The figure of 2000 patients has also been used out of context, since it appeared much earlier in the original news report and referred to an estimate of the total number of patients who have been screened in Daegu more generally.²² Reporting on topics such as this by the general media should therefore be done cautiously and prudently, so as not to unnerve the general public. It is important that primary sources are researched diligently before such statements are made, especially at this time of heightened anxiety and when the existing evidence base is emerging and inconclusive. As Ioannidis notes, “it is important to differentiate promptly the true epidemic from an epidemic of false claims and potentially harmful actions”.²⁵

Study Limitations

Given the speed at which this review was conducted, we may have inadvertently missed some relevant literature. The reason for conducting this review so quickly was that we hope to inform emerging clinical practice and policy decisions during the current SARS-CoV-2 pandemic.

Conclusion

These highly preliminary findings suggest that link between olfactory symptoms and SARS-CoV-2 is largely based around emerging anecdotal clinical observations from otolaryngologists. To date there have been no documented cases of olfactory disturbance in the peer-reviewed literature from over 56 studies.

Given this uncertainty and the novelty of the virus, we encourage clinicians to explicitly ask about olfactory symptoms during clinical history taking from patients with suspected SARS-CoV-2. This will help us to help build the emerging and rapidly evolving evidence-base around SARS-CoV-2 symptomatology to improve accuracy of public health messages.

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Data sharing: All data are contained within the main body of the text and in the on-line supplementary material.

Figure Legend.

The PRISMA diagram outlines each stage of the scoping review.

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Authors and Title	Date	Location	Type of evidence	Number of patients in study	Summary Details	CEBM Level of Evidence
Mao L, et al. Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study.	2020	China	Non-peer reviewed retrospective case series	214	11/214 (5.1%) of patients in this study experienced hyposmia as a symptom.	4
American Academy of Otolaryngology — Head and Neck Surgery. Anosmia, Hyposmia, and Dysgeusia Symptoms of Coronavirus Disease.	2020	U.S.A.	Non-peer reviewed expert body press release	Not Applicable (N/A)	Statement: “Anecdotal evidence is rapidly accumulating from sites around the world that anosmia and dysgeusia are significant symptoms associated with the COVID-19 pandemic. Anosmia, in particular, has been seen in patients ultimately testing positive for the coronavirus with no other symptoms. We propose that these symptoms be added to the list of screening tools for possible COVID-19 infection. Anosmia, hyposmia, and dysgeusia in the absence of other respiratory disease such as allergic rhinitis, acute rhinosinusitis, or chronic rhinosinusitis should alert	5

					physicians to the possibility of COVID-19 infection and warrant serious consideration for self-isolation and testing of these individuals.”	
Le Syndicat National des Médecins Spécialisés en ORL et Chirurgie Cervico-Faciale Alerte Anosmie COVID-19	2020	France	Non-peer reviewed expert body press release	N/A	Anosmia without nasal obstruction was diagnosed in young patients who tested positive for SARS-CoV-2. The clinical implications of this were that corticosteroids are not recommended given that this may exacerbate symptoms of SARS-CoV-2.	5
ENT UK Loss of sense of smell as marker of COVID-19 infection.	2020	UK	Non-peer reviewed expert body press release	N/A	This press release refers to anecdotal evidence from Germany, South Korea, China and the UK regarding emerging clinical observations of anosmia in otherwise mild cases of SARS-CoV-2. The majority of evidence was from anecdotal emerging clinical observations shared between otolaryngologists on a private online chat forum.	5

Table 1. A summary of existing evidence on anosmia as a clinical feature of SARS-CoV-2.

Supplementary Material

Table 1. Results from individual database searches.

Database	Number of Hits
Medline and Embase via Ovid	432
CINAHL via Ebsco	51
Web of Science via ProQuest	30
Scopus vis ProQuest	83
Grey literature, snowball sampling, expert consultation	3