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Is loss of sense of smell a diagnostic marker in COVID-19: A Systematic Review and Meta-analysis

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Abstract

Aims

1. To systematically review the currently available evidence investigating the association between olfactory dysfunction (OD) and the novel coronavirus (COVID-19).

2. To analyse the prevalence of OD in patients who have tested positive on Polymerase Chain Reaction (PCR) for COVID-19.

2. To perform a meta-analysis of patients presenting with olfactory dysfunction, during the pandemic, and to investigate the Positive Predictive Value for a COOVID-19 positive result in this population.

3. To assess if olfactory dysfunction could be used as a diagnostic marker for COVID-19 positivity and aid public health approaches in tackling the current outbreak.

Methods

We systematically searched MedLine (PubMed), Embase, Health Management Information Consortium (HMIC), Medrxiv, the Cochrane Library, the Cochrane COVID-19 Study Register, NIHR Dissemination centre, Clinical Evidence, National Health Service Evidence and the National Institute of Clinical Excellence to identify the current published evidence which associates coronaviridae or similar RNA viruses with anosmia.

The initial search identified 157 articles. 145 papers were excluded following application of our exclusion criteria. The 12 remaining articles, that presented evidence on the association between COVID-19 and olfactory dysfunction, were critically analysed.

Results

OD has been shown to be the strongest predictor of COVID-19 positivity when compared to other symptoms in logistic regression analysis. In patients who had tested positive for COVID-19 there was a prevalence of 62% of OD. In populations of patients who are currently reporting OD there is a positive predictive value of 61% for a positive COVID-19 result.

Conclusion

Our review has shown that there is already significant evidence which demonstrates an association between OD and the novel coronavirus – COVID-19. It is unclear if this finding is unique to this coronavirus as individual viral phenotypes rarely present in such concentrated large numbers. We have demonstrated that OD is comparatively more predictive for COVID-19 positivity compared to other associated symptoms. We recommend that people who develop OD during the pandemic should be self-isolate and this guidance should be adopted internationally to prevent transmission.

Introduction

There was already a wealth of anecdotal evidence that suggested olfactory dysfunction(OD)was animportant symptom in patients who had contracted the novel SARS-CoV-2 coronavirus (COVID-19) prior to the main outbreak in the United Kingdom. Initial reports made in newspapers from Germany indicated that as many as two thirds of cases of COVID-19 reported loss of smellwhilst in South Korea,15.3% of patients who have tested positive had perceived disturbance of smell or taste(1). Since these initial reports a number of studies have demonstrated a clear association between OD and COVID-19. This is the first worldwide pandemic where reporting of symptoms, aided by social media and telecommunication systems, has been shared so widely. High profile public figures have reported both symptoms which has led to widespread interest in the symptoms across both the press and the public(2).

It has previously been demonstrated that the geneticallysimilar SARS-CoVvirus can spread via a synapse-connected route to the medullary cardiorespiratory centre(3).Coronaviral RNA has been identified post mortem concentrated in the brain-stem of human patients during the previous SARS-CoV pandemic, and studies in mice have shown that previously described corona viruses can invade intracranially when administered intranasally indicating that the virus may travel via the olfactory nerves.Helms et al present a series of patients infected during the current COVID-19 outbreak and demonstrate numerous neurological sequelae and abnormalities on cross-sectional imaging of the brain(4).

Brann et al (in a paper made available prior to peer review) have identified non-neuronal cell types, such as sustentacular and olfactory stem cells as well as horizontal basal cells are the potential target of COVID-19 in the human olfactory epithelium via the ACE2 receptor and the spike protein protease TMPRSS2. This presents three main theories for potential loss of smell in COVID-19. Firstly, a local inflammatory response affecting sensory function, secondly damage to supporting cells and finally

escalating damage to the architectural structure of the entire olfactory epithelium, due to damage to sustentacular cells and Bowman's glands(5) .

Viral upper respiratory tract infection (URTI) is one of the known major identifiable causes of olfactory dysfunction (OD) due to the degeneration of olfactory epithelium(6).Due to the widespread and insidious nature of viral URTI there is no data relating to the incidence of post-viral OD for specific viruses but post-viral cases typically account for 11% of all cases of OD in the community(7) with cases presenting to specialist clinics typically representing 20% of cases (8). This group is often represented as a higher proportion in online surveys and patient fora at around 30%(9)(10). Patients often present to the Otolaryngologist in persistent cases but those that resolve soon after the infective process has subsided are likely rarely reviewed or reported(11).

BMJ best practice have recently published an update on Coronavirus and the range of symptoms that are associated with this. They quote the anecdotal evidence published by ENT UK(1) and the American Academy of Otolaryngology(12)regarding the link between anosmia and coronavirus. Both these international bodies have recommended self-isolation for patients who develop these symptoms(13)Fortunately following lobbying by ENT UK and the British Rhinological Society(BRS)OD has now been incorporated in to national public health policy with Public Health England (PHE) following the WHO in recognising loss of smell and taste as a key symptom of covid-19 infection (2) .

The aim of this systematic review and metanalysis is to identify the currently available evidence for the relationship between COVID-19 and self-reported loss of smell. This will include assessing the potential for OD as a diagnostic marker in COVID-19, outlining the current peer-reviewed evidence relating to this relationship and how it can be utilised going forwards in clinical practice.

We decided to focus on OD and not include loss of taste in this review. OD will lead to reduced retronasal olfaction and subsequently impact the perception of taste in these patients. Flavour perception involves input from ortho and retronasal olfaction and gustation, complemented by trigeminal stimulation through touch and pain fibres. Patients typically find it difficult to isolate true gustatory sensations from retronasal olfaction without objective gustatory testing(14) . Given the difficulties in interpreting this symptom, in the absence of more detailed questions regarding taste perception, we decided to solely review OD.

Methods

We systematically searched MedLine (PubMed), Embase, the Health Management Information Consortium (HMIC),Medrxiv,the Cochrane Library, the Cochrane COVID-19 Study Register, NIHR Dissemination centre, Clinical Evidence, National Health Service Evidence and the National Institute of Clinical Excellence to identify the current published evidence which associates coronaviridae or similar

RNA viruses with anosmia.The search strategy for MedlineandEmbase are demonstrated in Appendix 1. The final search was undertaken in 18th April 2020. We included all years and all languages in the search.

The initial search identified 157 articles. 145 articles were excluded as they did not investigate a link between the current coronavirus outbreak and OD, were conference abstracts, isolated case reports or did not have an English version available. The literature search is presented in the Prisma flow diagram (Figure 1). One case series presented loss of smell and taste in combination, where patients were included if they had experienced either symptom. As such we were unable to isolate olfactory dysfunction in their population. Reporting related but independent symptoms in this way prevents formal analysis of their individual epidemiological factors and impact on patient outcomes.

We used the ROBINS-E (Risk of Bias in Non-randomised Studies – of Exposures) tool to assess the studies for bias. The articles were assessed across 7 parameters; confounding factors, selection of participants, classification of exposures, departures from intended exposures, missing data, measurement of outcomes and the reported result. All the studies were assessed at "serious" risk of bias due these common themes; lack of adjustment for confounding variables, differences in follow up and the start of exposure, variation in reporting, and numerous different subgroups reported.

Results

1. Methodology

There were 12articlesthat have investigated the association between COVID-19 and OD. The studies vary in their methodology and in the patient populations that they target. A summary of the studies evaluated, their study methodology and the quality of the evidence is presented below in Table 1. Several of the studies had not completed the peer review process and this status is also demonstrated in the table.

Table 1

2. Description of studies

2.1 Cross-sectional Questionnaire

The most common methodology for assessment in the articles searched was a cross-sectional questionnaire which were conducted over a variety of mediums i.e. face to face, mobile applicationor web-based forms.The cohort of patients targeted also varied between inpatient and outpatient populations and in their geographical location (Tables 2 and 3). Whilst there are clear limitations to this approach and it is not possible to demonstrate a direct causal relationship between COVID-19 and ODbut they are able to present associations in the symptomatology of this pandemic.

2.2 Case Series

The majority of the remaining studies present case series. They present similar cross-sectional evidence to the questionnaire designed studies with a common aim of investigating the symptomatology of anosmia in the COVID-19 era. This approach should contribute to limiting the level of bias in their results when compared to an outcome-based case series but they are similarly only able to demonstrate association and not causal effect. The complementary data output, between the questionnaire and case-series approaches, allows us to compare the two approaches concurrently in a meta-analysis.

2.3 Search Term Analysis

Walker et al were unique in their approach and used Google Trends to track search terms related to loss of smell. They demonstrate statistically significant association of the Google search terms and theincidence of COVID-19 cases and deaths. The previous figures for the same time period in 2019 and the H1N1 pandemic were used as controls. This correlation was present across numerous countries including Italy, Spain, the United Kingdom (UK), the United States of America (USA), Germany, France, Iran and the Netherlands. They propose that this technique could be used to track disease hot spots internationally where targeted control measures could then be implemented. For this to be effective there needs to be clear data on the positive predictive value of new onset anosmia and COVID-19 positivity(15).

2.4 Case Control Study

In the only study so far to institute validated quantitative olfactory testing Moein et al, in Iran, evaluated 60 patients who had tested positive for COVID-19. Their control group were selected from a group of 141 controls from a previously conducted study. They handpicked age and sex matched individuals from this cohort in an attempt to mirror their COVID-19 positive group. COVID-19 patients completed the Persian version of the 40-odorant University of Pennsylvania Smell Identification Test (UPSIT) assisted by a trained examiner, they do not explain how they administered the test in their previously investigated control group. Ninety-eight percent of their COVID-19 group had some level of OD with 25% of these subjects being completely anosmic. There was a statistically significant reduction in scores, in all 40 stimuli, within the COVID-19 group. There were no differences in demographics between the two groups but the way the control group was matched will have affected this data(16) .

3 Risk of Bias and Limitations

When analysing data related to COVID-19 positivity it is important to recognise the sensitivity of the test is variable. Bronchoalveolar lavage is the most sensitive test (93%) whilst nasal swabs (63%) and pharyngeal swabs (46%) have lower positive rates[14]. Moein et al, who conducted the UPSIT, case control study and Mao et al were the only authors to report the technique and anatomical location of their Polymerase Chain Reaction (PCR) analysis of COVID-19 status. Moien et al used nasal aspirates or washes and Mao et al's group used throat swabs(16,17) . Due to the relatively low sensitivity of the test used

there will be a proportion of false negatives that will falsely lower the incidence of COVID-19 positivity in the OD groups and will therefore also impact on the calculation of sensitivity and specificity.

The majority of the responses to questionnaires were received remotely using electronic response forms of mobile based applications which will cause selection bias. Younger more technologically interactive cohort are more likely to interact and this sub-group seem to be less affected by COVID-19 when compared to older age groups who have a higher morbidity and mortality(18). For example, Menni et al, who used a mobile based application, report an average age of 41.48 (CI = 13.77) for those in their non-PCR-tested group, including over 1.5million people(19). Hospitalised populations are also less likely to interact with these methods due to their disease severity, internet connection or associated interventional treatments.

Cross-sectional questionnaires and case series are prone to bias due to influence of confounding variables, assessment of patients at different time points relative to their exposure and reporting bias. In case series specifically consecutive patients often missed in data collection. In these studies, however the researchers are simply presenting patient factors and associated symptoms rather than treatments or interventions and their subsequent effects or outcomes and this observational nature could help to reduce observer bias. In studies that were conducted requiring historical data from the patients there is a risk of recall bias and under-reporting or inaccuracies of symptoms specifically where onset and duration of symptoms is involved.

4. Comparing COVID positive and Olfactory Dysfunction Populations

Two distinct populations havebeen assessedin the literature. The first groupwere those patients who had received testing and were confirmed positive COVID-19 patients, the prevalence of OD was then analysed. The second were people who had experienced OD and the prevalence of COVID-19 within this cohort. Menni et aland Yan et alreport data from both groups concurrently and presented data for both populations in their results(19,20).

4.1 Prevalence of Olfactory Dysfunction in COVID-19 Positive Patients

Menni et al used the “COVID RADAR” symptom tracker app to extract a cohort of patients who had tested positive for COVID-19and their associated symptomatology. Nearly 2.5million people reported symptoms on this app butonly 15638, were tested and 6452 tested positive. This small proportion of their total population, and limited case definition used for access to testing at the time of the study, and risk of false negatives were the main limitations of this study. They then analysed the COVID-19 positive and negative groups for prevalence of symptoms. In the COVID-19 positive group 64.76% had experienced loss of smell compared to 22.68% in the negative group. For patients reporting loss of smell they report an odds ratio of 6.40 for a positive COVID-19 when compared to a negative result, after adjusting for age,

sex and body mass index. In their model loss of smell and taste was the strongest predictor of a COVID-19 positive result(19).

Lechian et al's multi-centre study analysedpatient and volunteer health care professionals'who had a PCR positive result for COVID-19 with a questionnaire. Patients in the intensive care unit, patients with previous OD and those without a COVID-19 PCR result were excluded from analysis. The impact of ODwas evaluated using a quality of life tool (sQOD-NS). 85.6% of their cohort of 417 patients reported OD. The majority self-rated as anosmic (79.6%) but others experienced hyposmia, phantosmia and parosmia. Anosmic patients were found to have a significantly lower sQOD-NS score compared with the hyposmic and normosmic individuals. This OD was not significantly associated with rhinorrhoea or nasal obstruction but a significant association was found with females being proportionally more affected than males. In the subgroup of patients who had clinically resolved infection the OD persisted in 63% of cases(21).

Yan et al sent an email invitation to complete a survey to 1480 patients who had undergone COVID-19 testing. They had a 58% response from COVID-19 positive patients and a 15% response from the negative group. Their survey evaluated patient reported symptoms with a focus on smell and taste. Sixty-eight percent of the COVIVD-19 positive group reported OD and similarly to Menni et al they found that loss of sense of smell (and taste) showed the largest magnitudes of association to COVID-19 positivity when compared with other symptoms. Seventy-two percent of the COVID-19 positive patients with OD reported improvement at the time of the survey(20) .

Mao et al were one of the first groups to present the symptomatology of patients presenting with a positive COVID-19 swab result. 5.1% of this group of 214 patients had experienced hyposmia. This was a retrospective analysis of electronic patient data and as such there is a risk that OD was not a symptom explored or documented in individual consultations within this cohort of patients. According to a "diagnostic criteria" that is not described they divided their patients in to severe and non-severe groups. Of the 11 patients who had reported hyposmia 3 were non-severe and 8 were severe(17).

Giacomelli et al interviewed 59 of 88 inpatients with COVID-19 demonstrated on PCR, there were 29 non-respondents due to receiving ventilation, dementia and linguistic barriers. They report combined rates of smell or taste disturbance and as such comparative incidence rates solely for OD was not possible to produce from the data presented. In their cohort the olfactory and gustatory disorders occurred in proportionally younger and more commonly female subjects and no patients had recovered at the time of interview. No data relating to time of interview following onset of symptoms is reported(22) .

In the studies that investigated olfactory symptoms independently we present the prevalence rates in Table 2 to form a meta-analysis for the prevalence of OD in the population of patients that have tested positive.

Table 2

4.2 Prevalence of COVID-19 in New Onset Olfactory Dysfunction Cohorts

Due to the differences in public health approaches and the availability of testing it is difficult to demonstrate clear associations between new onset OD and COVID-19 positivity. There were however three studies that did have PCR results for patients presenting with ODsince the start of the COVID-19 pandemic. In table 2 we demonstrate that there is a high prevalence of COVID-19 positivity in patients currently presenting with OD.

The American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) developed a COVID-19 Anosmia reporting tool for clinicians. Responses were collected from clinicians around the world relating to the association of COVID-19 and anosmia. They do not clearly state if all submitted patients had PCR testing performed. 237 entries were analysed; anosmia was the initial symptom in more than 25% of cases, 27% had noticed some improvement and in 40% was the symptom that led to a test being performed(23).

Bagheri et al conducted a widely completed online survey, of the general population in Iran, to identify patients with OD since the inception of the outbreak in their country. They demonstrated high numbers of people who had experienced OD in their cohort. Their respondents were commonly female (71%) and experienced sudden onset in their OD (76%). Only 1.1% were admitted to hospital for treatment indicating a largely mild disease when OD was experienced(24). In a similar online questionnaire study, conducted in the UK, by Hopkins et al the demographic features were replicated. The majority of this British population with ODreported complete loss of smell (74.4%) and in 16% of cases it was their only symptom. A proportion of these patients did report receiving a PCR test with a 74% positive rate in this sub-group(25).

Gane et al present a case series of 11 patients presenting with sudden onset anosmia during the epidemic in the United Kingdom. In 5 of these patients it was an isolated symptom and just one of these patients were self-isolating(26). Gengler et al present findings(in an unpublished paper made available before peer review) from a French case series, not currently published, which demonstrated a positive COVID-19 nasal PCR swab in 94% of their 55-patient series(27).

Table 3 demonstrates the average ages and gender proportions of the six studies with ODcohorts.

Table 3

Discussion

Our review has shown that there is already significant evidence which demonstrates an association between OD and the novel coronavirus – COVID-19. It is unclear if this finding is unique to this coronavirus as individual viral phenotypes rarely present in such concentrated large numbers. Classically patients present with persistent symptoms following a viral illness many weeks or months after. The

symptomatology during the infective phase of the virus has not previously been studied and therefore it is not possible to draw direct comparison between other similar viruses. Walker et al have however demonstrated trends between increasing cases of COVID-19 and the increase in positive novel coronavirus cases that was not mirrored during the previous H1N1 pandemic in 2009(15).

Due to the rapid spread of COVID-19 in this pandemic it is understandable that there is a lack of studies using objective measures and rigorous controls. The most common methodologies used were cross-sectional questionnaires and case series. These approaches are at risk of bias and we can only discuss associations as a result. Further research will be required to demonstrate clearer links between OD and COVID-19 going forwards.

When we assessedpatients who had experienced OD during the outbreak there were several studies that demonstrated an increase in the prevalence of loss of smell in their populations when compared to previous estimates(19,24,25). The largest data sets, conducted predominantly in the outpatient setting, by Hopkins and Bagheri et al indicated a female preponderance in their cohorts (73% and 71% respectively). These two studies also demonstrated an average affected age between 30-40. It has been demonstrated that both advanced age and the male sex are risk factors for the severe form of the disease and an increased rate of mortality(18). It could be that this cohort of patients were not targeted by this study due to the more elderly populations not interacting with web-based surveys or being within the inpatient population due to their disease severity. Moein et al demonstrated in their study of inpatients that OD was a common finding in this population too when they applied objective UPSIT testing to confirmed cases(16). Further research is needed to identify if the incidence of ODvaries between different ages and genders and as such if particular disease phenotypes for COVID-19 can give clinicians prognostic information.

In areas where testing has not been adopted widely tracking of this ODcould be vital in identifying hot-spots where population-based management strategies can then be targeted. Tracking OD using mobile-based applications, such as the one developed by Menni et al, will allow real time data tracking for aid models in the prediction of national or regional COVID-19 cases(19). This approach could lead to specific social distancing measures being implemented in areas where OD is wide-spread and will also help in modelling when these measures could be relaxed as most patients seem to recover their sense of smell following the illness.

Conclusion

Our meta-analysis has demonstrated that the prevalence of OD in patients who have a positive PCR test for COVID-19 is 62%. OD was demonstrated to be the most strongly associated symptom, for a positive test, when compared to fever, cough, fatigue, dyspnoea and diarrhoea (19,20). In people who reported

OD and had received PCR swab there was a positive predictive value of 61% for a positive result. The evidence to support an association between OD and COVID-19 continues to grow. The symptom has now been recognised by the World Health Organisation and Public Health England (29) . This change in approach should mean an increase in the number of positive COVID-19 cases self-isolating and a subsequent reduction in the chance of spread with benefits for public health and containment of the pandemic.

Disclosure Statement

The authors declare that they have no relevant or material financial interests that relate to the research described in this paper.

Data Sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Appendix 1: Search Strategy, Olfactory Dysfunction in COVID-19

EMBASE	exp ADULT/	View Results (8,180,639)	
2	EMBASE	exp CHILD/	View Results (2,571,562)
3	EMBASE	*(1 OR 2)*	View Results (10,062,017)
4	EMBASE	exp CORONAVIRIDAE/ OR CORONAVIRUS/ OR "CORONAVIRUS INFECTION"/ OR "CORONAVIRUS INFECTIONS"/ OR VIRUS/ OR "(COVID-19).ti,ab" OR "(COVID19).ti,ab"	View Results (61,685)
5	EMBASE	"SARS-RELATED CORONAVIRUS"/ OR "RNA VIRUS"/	View Results (9,106)
6	EMBASE	*(4 OR 5)*	View Results (69,724)
7	EMBASE	"SMELLING DISORDER"/ OR exp ANOSMIA/ OR exp HYPOSMIA/	View Results (9,313)
8	EMBASE	exp "SMELLING DISORDER"/ OR "NEUROLOGIC DISEASE"/	View Results (136,148)
9	EMBASE	ANOSMIA/ OR DYSOSMIA/ OR HYPOSMIA/ OR "OLFACTORY HALLUCINATION"/ OR PAROSMIA/ OR "TASTE ABNORMALITY"/ OR "TASTE ANOMALY"/ OR "TASTE ABSENCE"/	View Results (14,313)
10	EMBASE	*(7 OR 8 OR 9)*	View Results (143,896)
11	EMBASE	*(3 AND 6 AND 10)*	View Results (141)
12	Medline	exp ADULT/	View Results (7,081,727)
13	Medline	exp CHILD/	View Results (1,882,783)
14	Medline	*(12 OR 13)*	View Results (8,276,487)
15	Medline	CORONAVIRUS/ OR exp CORONAVIRIDAE/ OR "RNA VIRUSES"/ OR "(COVID19).ti,ab" OR "(COVID-19).ti,ab"	View Results (20,713)
16	Medline	ALPHACORONAVIRUS/ OR BETACORONAVIRUS/ OR GAMMACORONAVIRUS/	View Results (555)
17	Medline	*(15 OR 16)*	View Results (20,713)
18	Medline	exp "OLFACTION DISORDERS"/ OR "OLFACTORY NERVE DISEASES"/ OR SMELL/ OR "TASTE DISORDERS"/ OR "AGEUSIA"/ OR "DYSGEUSIA"/ OR (hyposmia).ti,ab OR "NEUROLOGIC MANIFESTATIONS"/ OR (anosmia).ti,ab	View Results (28,404)
19	Medline	*(14 AND 17 AND 18)*	View Results (1)

Table 1: Summary of Papers in Review

Article Title	Primary Author	Methodology	Peer review completed
Real-time tracking of self-reported symptoms to predict potential COVID-19	C Menni	Cross sectional questionnaire (via symptom reporting app)	Yes
Olfactory and gustatory dysfunction as a clinical presentation of mild-to-moderate forms of the coronavirus disease: a multicentre European Study	J Lechian	Cross sectional questionnaire	Yes
Self reported olfactory and taste disorder sin SARS-CoV-2 patients: a cross-sectional study	A Giacomeli	Cross sectional questionnaire	Yes
Coincidence of COVID-19 Epidemic and olfactory dysfunction outbreak	S Bagheri	Cross sectional questionnaire	Yes
Presentation of new onset anosmia during the COVID-19 pandemic	C Hopkins	Cross sectional questionnaire	Yes
Association of Chemosensory Dysfunction in COIVD-19 Patients Presenting with Influenza- like Symptoms	C Yan	Cross sectional questionnaire	Yes
COVID-19 Anosmia Reporting Tool: Initial Findings	R Kaye	Clinician Reporting Tool / Cross sectional questionnaire	Yes
Isolated sudden onset anosmia in COVID19 infection. A novel syndrome	S Gane	Case Series	Yes
Neurological Manifestations of Hospitalised Patients with COVID-19 in Wuhan , China: a retrospective case series study	L Mao	Case Series	Yes
Sinonasal pathophysiology of SARS CoV 2 and COVID19: a systematic review of the current evidence	I Gengler	Case series reported within SR	Systematic Review published but Case series not peer-reviewed

The Use of Google Trends to Investigate the loss of smell related searches during the COVID-19 outbreak	A Walker	Search Term Analysis	Yes
Smell dysfunction: A Biomarker for COVID-19	ST Moein	Case control study	Yes

Table 2: Meta-analysis of patients with COVID-19 positive PCR result and prevalence of Olfactory Dysfunction

Lead Author	n COVID-19 positive	N with OD	Percentage with OD	Average age with OD	Proportion Female	Setting	Location
C Menni	579	344	59%	41	69%	Outpatient based	UK based
J Lechian	417	357	86%	No data	No data	Inpatient and Outpatient	Belgium, Spain, France, Italy
C Yan	59	40	68%	No data	No data	Outpatient based	USA
ST Moein	60	58	97%	47	33%	Inpatient	Iran
L Mao	214	11	5%	No data	No data	Inpatient	China
Totals	**1329**	**819**	**62% prevalence of OD in COVID+ve population**				

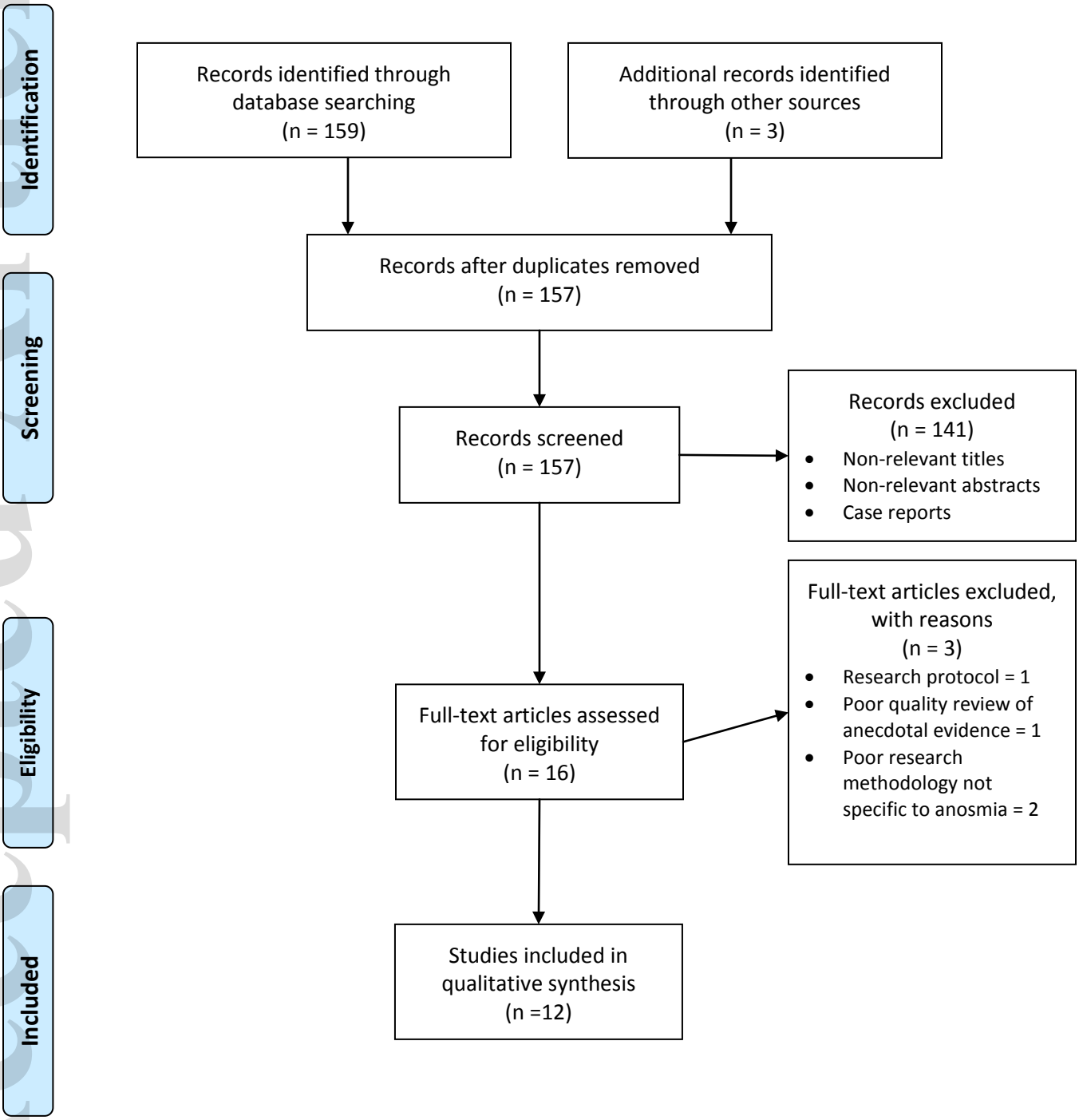
Key: OD = Olfactory dysfunction

Table 3: Meta-analysis of patients with new onset olfactory dysfunction and prevalence of COVID-19 positivity

Lead Author	N with OD	N COVID +ve test	Percentage COVID +ve	Average Age	Female	Setting	Location
S Bagheri	10069	No data	No data	32.5	71%	Outpatient based	Iran
S Gane	11	No data	No data	37.6	27%	Outpatient	UK
C Hopkins	2428	No data	No data	30-39	73%	Outpatient based	UK
I Gengler*	55	52	94%	No data	No data	No data	France
C Yan	73	40	55%	No data	No data	Outpatient based	USA
C Menni	557	345	62%	No data	No data	Outpatient based	UK
Underlined values where patients with olfactory dysfunction were PCR tested for COVID-19 and included in meta-analysis below (Yan et al, Menni et al):							
Total	**630**	**385**	**61% PPV for COVID+ve test in OD**				

OD = Olfactory dysfunction, * = awaiting peer-review

Prisma 2009 Flow Diagram: Olfactory Dysfunction in COVID-19



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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