Systematic review

Please complete all mandatory fields below (marked with an asterisk *) and as many of the non-mandatory fields as you can then click *Submit* to submit your registration. You don't need to complete everything in one go, this record will appear in your *My PROSPERO* section of the web site and you can continue to edit it until you are ready to submit. Click *Show help* below or click on the icon
to see guidance on completing each section.
This record cannot be edited because it has been rejected

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Clinical characteristics and epidemiological features of olfactory dysfunction in coronavirus disease 2019

(COVID-19): a comprehensive systematic review and meta-analysis

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

12/06/2020

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

03/08/2020

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Dr. Tom Wai-Hin Chung

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Chung

7. * Named contact email.

Give the electronic mail address of the named contact.

tomchungwaihin@gmail.com

8. Named contact address

Give the full postal address for the named contact.

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China.

Organisation web address:

http://www.microbiology.hku.hk/

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country are now mandatory fields for each person.**

Dr Tom Wai-Hin Chung. Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China.
Dr Yat-Fung Shea. Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China.
Rosemond Tan. Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China.
Wai-Tak Victor Li. Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China.
Sheung-Chit Chu. Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China.
Wing-Zi Shum. Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China.
Hang-Long Li. Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China.
Dr Fergus Kai-Chuen Wong. Department of Ear, Nose and Throat Surgery, Pamela Youde Nethersole Eastern Hospital, Hong Kong, China.
Dr Siddharth Sridhar. Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China.
Dr Vincent Chi-Chung Cheng. Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China.
Professor Ivan Fan-Ngai Hung. Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China.
Professor Kwok-Yung Yuen. Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China.

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

Shaw Foundation Hong Kong

Richard Yu and Carol Yu

May Tam Mak Mei Yin

Jessie & George Ho Charitable Foundation

Perfect Shape Medical Limited

Respiratory Viral Research Foundation

Hui Ming, Hui Hoy and Chow Sin Lan Charity Fund Limited

Sanming Project of Medicine in Shenzhen, China (SZSM201911014)

High Level-Hospital Program, Health Commission of Guangdong Province, China

Consultancy Service for Enhancing Laboratory Surveillance of Emerging Infectious Diseases and Research Capability on Antimicrobial Resistance for the Department of Health of the Hong Kong Special Administrative Region Government, Hong Kong, China

Theme-Based Research Scheme of the Research Grants Council of the Hong Kong Special Administrative Region Government, Hong Kong, China

Grant number(s)

Theme-Based Research Scheme (T11/707/15) of the Research Grants Council of the Hong Kong Special Administrative Region Government, Hong Kong, China

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

The authors declare no conflict of interest

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country are now mandatory fields for each person.**

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

[A] What are the clinical characteristics of olfactory dysfunction (OD) in coronavirus disease (COVID-19) patients infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)?

1. What is the prevalence of isolated OD as the only symptom in COVID-19 patients?

2. What is the onset of OD relative to other symptoms of COVID-19 infection (i.e. OD as the first and presenting symptom of COVID-19)?

3. Is there an association between COVID-19-related OD and SARS-CoV-2 viral load?

4. What is the symptom duration of COVID-19-related OD?

5. What are the otolaryngologic symptoms associated with OD in COVID-19 infection, if any?

6. What are the neurologic symptoms associated with OD in COVID-19 infection, if any?

7. What are the health and life-style disturbances (e.g. skipped meals, loss of appetite, weight loss) associated with COVID-19-related OD?

8. Are there any risk factors which may predispose COVID-19 patients to develop OD?

9. What is the prognostic significance of COVID-19-related OD in the overall clinical outcome of SARS-CoV-2 infected patients, if any?

[B] What are the global epidemiological features of olfactory dysfunction (OD) in COVID-19 patients?

1. Are young COVID-19 patients more prone to OD?

2. Is there a gender difference in the prevalence of OD?

3. Is there an ethnic difference in the prevalence of OD?

16. * Searches.

State the sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period). Do NOT enter the full search strategy (it may be provided as a link or attachment.)

PubMed articles from 1st January 2020 to 10th June 2020 will be searched. non-English articles are

excluded.

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy.Do NOT provide links to your search results.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Olfactory dysfunction (OD) has been shown to be an important and common symptom in coronavirus disease 2019 (COVID-19). This systematic review and meta-analysis aims to collate and synthesise all clinical studies that meet prespecified eligibility criteria, in order to provide an in-depth description of the clinical characteristics of COVID-19-related OD, and elucidate the true global prevalence and epidemiological features of COVID-19-related OD.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion criteria: Adult patients (18 years or older), SARS-CoV-2 infection confirmed by reverse transcription polymerase chain reaction (RT-PCR)

Exclusion criteria: Pregnant, Pediatric populations

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Qualitative or quantitative documentation of smell impairment in laboratory confirmed COVID-19 patients

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Comparator: RT-PCR positive COVID-19 patients with olfactory dysfunction

Control: RT-PCR negative COVID-19 patients

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should

be stated. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion criteria: all studies that report clinical data on olfactory dysfunctions in patients will be included, regardless of study type

Exclusion criteria: Literature reviews, comments, correspondences and letters to the editor which do not contain new clinical data will be excluded

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

2. To investigate the global prevalence of olfactory dysfunction (OD) in COVID-19.

This is achieved by only including articles that report clinical data on OD qualitatively or quantitatively.

* Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Odds ratio (OR)

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

To investigate if there is an age, sex, or ethnic predisposition to COVID-19-related OD, the potential association between olfactory neurosensory impairments and other otolaryngologic or neurologic disorders in COVID-19 infection, the prevalence of COVID-19-related OD as an isolated symptom, the onset and duration of COVID-19-related OD, and whether OD is a prognostic indicator for COVID-19 disease severity.

* Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Odds ratio (OR)

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Data will be extracted independently by four authors. Disagreements will be resolved by mutual consensus.

For included articles, the following information will be extracted from the full texts: basic information (first

authors, country, and sample size); patient demographics (age, sex, and ethnicity); disease characteristics [prevalence of abnormal olfaction, presence of associated otolaryngologic symptoms, associated neurologic deficits, potential negative health outcomes (e.g. anorexia, skipped meals, or weight loss), onset of OD relative to other symptoms of COVID-19, duration of COVID-19-related OD, overall clinical outcome]; relevant investigation outcomes (e.g. viral load within the nasal or oropharyngeal cavity, relevant biopsy results); the method(s) used to assess olfaction (qualitative or quantitative assessments, or both); and relevant imaging and endoscopic findings.

27. * Risk of bias (quality) assessment.

Describe the method of assessing risk of bias or quality assessment. State which characteristics of the studies will be assessed and any formal risk of bias tools that will be used.

The methodological quality of studies will be determined using the Newcastle–Ottawa Scale (NOS) with a maximum of nine points (stars) for observational studies. ‘Selection’, ‘Comparability’ and ‘Outcome’ will be the three categories included in the NOS for cohort studies.

28. * Strategy for data synthesis.

Provide details of the planned synthesis including a rationale for the methods selected. This **must not be generic text** but should be **specific to your review** and describe how the proposed analysis will be applied to your data.

The prevalence of OD in COVID-19 patients will be computed for each of the studies. Pooled estimate of the prevalence of COVID-19-related OD will be calculated using the random effects meta-analysis, as the included studies involved different centres, different populations and different tools for olfactory assessment. Analysis of heterogeneity will be performed using the I^2 statistics. Publication bias will be evaluated by inspection of the funnel plot which will relate the standard errors of studies to their event rates. If inspection of the funnel plot suggested possibility of publication bias, the pooled prevalence of COVID-19-related OD will be corrected for publication bias by calculation using the trim-and-fill method. Egger’s test will also be performed. Meta-regression will be used to estimate the extent to which measured covariates (sex ratio, subject ethnicity, mean age of the patients, proportion of subjects with COVID-19-related OD as the first symptom, and the mean SARS-CoV-2 viral load of relevant clinical specimens) could explain the variance between the studies. For all tests, pValue 0.05 will be deemed significant. All analyses will be performed using the comprehensive Meta-Analysis version 3 (https://www.meta-analysis.com/index.php) (Biostat; Englewood, NJ, USA). Descriptive statistics will be used for outcomes which are not suitable for meta-analyses.

29. * Analysis of subgroups or subsets.

State any planned investigation of ‘subgroups’. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

[A] Olfactory analysis and assessments will be conducted by qualitative assessments (e.g. self-reporting,

surveys, questionnaires) only

[B] Olfactory dysfunction in COVID-19 patients, documented by quantitative measurements (e.g. butantol threshold test, smell identification test...)

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
Yes

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
Yes

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
Yes

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care

No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
Yes

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Hong Kong

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

SARS-CoV-2

Olfactory dysfunction

Anosmia

Smell disturbancesSmell loss

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s) or preprints if available.

This field should be left empty until details of the completed review are available OR you have a link to a preprint.

Give the link to the published review.