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Interventions for the treatment of persistent post-COVID-19 olfactory dysfunction (Review)

O'Byrne L, Webster KE, MacKeith S, Philpott C, Hopkins C, Burton MJ

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[Intervention Review]

Interventions for the treatment of persistent post-COVID-19 olfactory dysfunction

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ABSTRACT

Background

Olfactory dysfunction is an early and sensitive marker of COVID-19 infection. Although self-limiting in the majority of cases, when hyposmia or anosmia persists it can have a profound effect on quality of life. Little guidance exists on the treatment of post-COVID-19 olfactory dysfunction, however several strategies have been proposed from the evidence relating to the treatment of post-viral anosmia (such as medication or olfactory training).

Objectives

To assess the effects (benefits and harms) of interventions that have been used, or proposed, to treat persisting olfactory dysfunction due to COVID-19 infection. A secondary objective is to keep the evidence up-to-date, using a living systematic review approach.

Search methods

The Cochrane ENT Information Specialist searched the Cochrane COVID-19 Study Register; Cochrane ENT Register; CENTRAL; Ovid MEDLINE; Ovid Embase; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished studies. The date of the search was 16 December 2020.

Selection criteria

Randomised controlled trials including participants who had symptoms of olfactory disturbance following COVID-19 infection. Only individuals who had symptoms for at least four weeks were included in this review. Studies compared any intervention with no treatment or placebo.

Data collection and analysis

We used standard Cochrane methodological procedures. Primary outcomes were the recovery of sense of smell, disease-related quality of life and serious adverse effects. Secondary outcomes were the change in sense of smell, general quality of life, prevalence of parosmia and other adverse effects (including nosebleeds/bloody discharge). We used GRADE to assess the certainty of the evidence for each outcome.

Main results

We included one study with 18 participants, which compared the use of a 15-day course of oral steroids combined with nasal irrigation (consisting of an intranasal steroid/mucolytic/decongestant solution) with no intervention. Psychophysical testing was used to assess olfactory function at baseline, 20 and 40 days.

Systemic corticosteroids plus intranasal steroid/mucolytic/decongestant compared to no intervention

Recovery of sense of smell was assessed after 40 days (25 days after cessation of treatment) using the Connecticut Chemosensory Clinical Research Center (CCCRC) score. This tool has a range of 0 to 100, and a score of ≥ 90 represents normal olfactory function. The evidence is very uncertain about the effect of this intervention on recovery of the sense of smell at one to three months (5/9 participants in the intervention group scored ≥ 90 compared to 0/9 in the control group; risk ratio (RR) 11.00, 95% confidence interval (CI) 0.70 to 173.66; 1 study; 18 participants; very low-certainty evidence).

Change in sense of smell was assessed using the CCCRC score at 40 days. This study reported an improvement in sense of smell in the intervention group from baseline (median improvement in CCCRC score 60, interquartile range (IQR) 40) compared to the control group (median improvement in CCCRC score 30, IQR 25) (1 study; 18 participants; very low-certainty evidence).

Serious adverse events and**other adverse events** were not identified in any participants of this study; however, it is unclear how these outcomes were assessed and recorded (1 study; 18 participants; very low-certainty evidence).

Authors' conclusions

There is very limited evidence available on the efficacy and harms of treatments for persistent olfactory dysfunction following COVID-19 infection. However, we have identified other ongoing trials in this area. As this is a living systematic review we will update the data regularly, as new results become available.

For this (first) version of the living review we identified only one study with a small sample size, which assessed systemic steroids and nasal irrigation (intranasal steroid/mucolytic/decongestant). However, the evidence regarding the benefits and harms from this intervention to treat persistent post-COVID-19 olfactory dysfunction is very uncertain.

PLAIN LANGUAGE SUMMARY

Interventions for the treatment of persistent smell disorders (olfactory dysfunction) after COVID-19 infection

Why this is important

The sense of smell is critical to one's enjoyment of odours and tastes, and is important for safety. During the COVID-19 pandemic there has been an increasing focus on change in sense of smell as one of the early symptoms associated with infection. This can be a reduction, change or complete loss of the sense of smell. For most people this is temporary, however for some this lasts weeks or even months. If a person has lost their sense of smell for a long time (over four weeks after having COVID-19), we do not know if there are any treatments that might help it to recover.

How we identified and assessed the evidence

We searched the medical literature, identifying relevant studies and summarising the results. We assessed the quality of the studies as well as the certainty of the evidence. Factors influencing this included the size of the studies, the methods used to perform them and how results were reported by researchers. Based on this, we classed the evidence as being of very low, low, moderate or high certainty.

What we found

The only complete study we found included 18 people. All patients had problems with their sense of smell that had lasted for at least four weeks, and started after a COVID-19 infection. Problems with the sense of smell were identified using special smell identification tests carried out by the research team. The patients were randomly divided into two groups: those who would receive treatment and those who would not. The treatment in this case was a course of steroid tablets, given with a nasal spray (consisting of a mix of steroids, decongestant and an agent that breaks down mucus). The researchers followed them for 40 days and the results are presented below:

Systemic corticosteroids and nasal irrigation (intranasal corticosteroids/decongestant/mucolytic) compared to no treatment

We do not know whether steroid tablets with nasal irrigation is better or worse than no treatment at:

- restoring the sense of smell back to normal after 40 days;
- changing the sense of smell after 40 days;
- causing any unwanted side effects.

This is because the evidence that we found was of very low certainty, mainly due to the fact that only study was identified and included a small number of patients.

We did find a number of other studies that are being carried out, but no results from these studies are yet available to be included in this review.

What this means

It is unclear whether using steroids with nasal irrigation treats problems with the sense of smell after COVID-19, or whether it can potentially cause any harm.

Other treatments are under investigation. This review is a 'living systematic review', meaning that we will keep checking for new studies that might be relevant, and the review will be continually updated when any extra results are available.

How up-to-date is this review?

The evidence in this Cochrane Review is current to December 2020.

Summary of findings 1. Systemic corticosteroids plus intranasal steroid/mucolytic/decongestant compared to no intervention for persistent post-COVID-19 olfactory dysfunction

Systemic corticosteroids plus intranasal steroid/mucolytic/decongestant compared to no intervention for persistent post-COVID-19 olfactory dysfunction

Patient or population: adults with olfactory dysfunction for ≥ 4 weeks following COVID-19 infection
Setting: two hospitals in Italy
Intervention: systemic corticosteroids plus intranasal steroid/mucolytic/decongestant
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with systemic corticosteroids plus intranasal steroid/mucolytic/decongestant				
Psychophysical testing for recovery of sense of smell Assessed with: CCCRC test score (range 0 to 100, normal olfactory function classed as a score of 90 or 100) Follow-up: 1 to 3 months	Study event rate^ 0/9	5/9	RR 11.00 (0.70 to 173.66)	18 (1 RCT)	⊕⊖⊖⊖ **very low** [1,2]	—
Disease-related quality of life	No studies reported on this outcome.					
Serious adverse events Follow-up: 1 to 3 months	Study event rate^ No events were reported for either group.		Not estimable	18 (1 RCT)	⊕⊖⊖⊖ **very low** [1,3]	—
Psychophysical testing for change in sense of smell Assessed with: CCCRC psychophysical testing Follow-up: 1 to 3 months	This study reported a median improvement in CCCRC score of +60 (IQR 40) in the group receiving systemic steroids and nasal irrigation compared to a median improvement of +30 (IQR 25) in the control group (P = 0.024).		Not estimable	18 (1 RCT)	⊕⊖⊖⊖ **very low** [1,4]	—

Generic quality of life	No studies reported on this outcome.				
Presence of parosmia	No studies reported on this outcome.				
Other adverse outcomes Follow-up: 1 to 3 months	Study event rate^ No events were reported for either group.	Not estimable	18 (1 RCT)	⊕⊖⊖⊖ **very low** [1,3]	—

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
^We present the study event rate as there were no events in the comparator group for this trial.
CI: confidence interval; **IQR:** interquartile range; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Serious risk of performance bias due to a lack of blinding to treatment allocation.
[2]Very serious imprecision as the sample size does not reach the optimal information size (considered to be 400 participants) and the 95% CI is consistent with the possibility of important benefit or harm.
[3]Very serious imprecision as the sample size does not reach the optimal information size (considered to be 400 participants) and no estimate of effect could be determined, due to the lack of events in either group.
[4]Very serious imprecision as the sample size does not reach the optimal information size (considered to be 400 participants) and no estimate of effect could be determined (data presented as median and IQR).

BACKGROUND

Description of the condition

Loss of olfactory function (the sense of smell) emerged as a marker of COVID-19 infection in March 2020 (Hopkins 2020a). Since that time, it has become established that this is a cardinal symptom of COVID-19 infection (Menni 2020), with a high predictive value (Gerkin 2020). This usually takes the form of complete or partial loss of olfactory function (anosmia and hyposmia respectively) (Lechien 2020).

Olfactory dysfunction, through loss (quantitative changes) or distortion (qualitative changes) of smell, is a debilitating condition with a variety of causes and has a major impact on quality of life (Croy 2014; Erskine 2020; Philpott 2014). It also has safety implications, through the inability to detect odours that may signal danger (such as smoke, gas or spoilt food). Through its intimate relationship with the sense of taste, the disturbance of olfactory function can also hamper the ability to enjoy food.

Post-infectious olfactory dysfunction (PIOD) is one of the most common causes of olfactory dysfunction, representing up to 20% of all cases in specialist olfactory clinics (Cain 1988; Damm 2004; Seiden 2001). Many viruses have been implicated in PIOD, including the coronavirus family. However, the prominence of SARS-CoV-2 (which causes COVID-19) as a causative agent has been notable, and can perhaps be attributed to the spotlight created by it being the cause of a pandemic.

Accurate estimates of the prevalence of olfactory dysfunction resulting from COVID-19 are difficult to obtain, and may vary according to the clinical presentation of the disease (which ranges from mild, or relatively asymptomatic, to serious complications requiring intensive care). A recent systematic review identified an overall prevalence of smell loss of 43%, however the authors noted high variation between the estimates from different studies (von Bartheld 2020). Another systematic review showed a prevalence of 62% across the range of studies included (Rocke 2020). A large European cohort, which included hospitalised individuals with mild-moderate symptoms, as well as individuals who did not require hospital treatment, reported the prevalence of olfactory dysfunction to be 85.6% (Lechien 2020). The majority of individuals included in this study reported anosmia, with a minority reporting hyposmia (20.4%).

The incidence of anosmia or olfactory dysfunction related to COVID-19 appears to vary across the world, with studies from the USA and Europe typically demonstrating much higher incidence than those from Asia (Meng 2020; von Bartheld 2020). A study from Wuhan, China, reported abnormalities of olfactory function in only 5.1% of their cohort (214 patients, with both severe and mild forms of the disease) (Mao 2020). It is not clear why this may be. Gender and age have also been suggested as possible effect modifiers, with some reviews suggesting preponderance in females (Meng 2020), and others suggesting an increased incidence in younger age groups (Fuccillo 2020).

The incidence of olfactory dysfunction may also vary depending on the method used to diagnose it. Studies that used self-reported symptoms of loss of smell identified a lower prevalence than those that utilised some form of objective assessment (von Bartheld 2020). It is well recognised that, for healthy individuals, self-rating of the sense of smell may correlate poorly with scores achieved on psychophysical testing (Landis 2003; Lötsch 2019). Correlation is better for those who report olfactory dysfunction (particularly anosmia), but on an individual level there is still considerable variation between the severity of the reported loss, and that identified with psychophysical tests (Welge-Luessen 2005). With larger numbers reporting COVID-19 symptoms in general, the data collected by the COVID tracker app is more likely to reflect the prevalence of olfactory dysfunction in the non-hospitalised population (Menni 2020).

A further complication in obtaining accurate estimates of prevalence is the variety of data sources that are available. Studies conducted in a hospitalised population may present very different estimates to those where data are gathered from internet-based surveys. This may reflect genuine differences in the presence of olfactory dysfunction in these varied populations, different methods of ascertaining olfactory function, or potentially a different preponderance to report symptoms. Internet-based surveys may have a greater propensity for responder bias than other cross-sectional studies - those who have symptoms may be more likely to participate or complete the required data, resulting in inflated estimates of prevalence. However, some prospective series have also identified a high prevalence of olfactory dysfunction (Spinato 2020).

Other symptoms of olfactory dysfunction include phantosmia (qualitative dysfunction in the absence of an odour, or 'olfactory hallucinations') and parosmia (distorted perception of an odour stimulus) (Hummel 2016). A recent survey of individuals with COVID-19 indicated that these symptoms occurred in fewer than 10% in the short term (Parma 2020). However, longer-term follow-up may demonstrate further problems at a later stage, and reports of persisting parosmia as a consequence of COVID-19 are increasing (Hopkins 2020b).

The exact mechanism by which the SARS-CoV-2 virus triggers olfactory dysfunction remains unclear (reviewed in Butowt 2020). Many viruses cause conductive olfactory impairment, with inflammation, nasal congestion and rhinorrhoea preventing detection of odours during the acute phase of the infection. These symptoms are not as common in COVID-19 and, when present, do not correlate well with the degree of olfactory dysfunction (Parma 2020). Symptoms may also be caused by direct damage to, or death of, olfactory neurons or cells within the olfactory bulb. However, olfactory neurons lack ACE2 receptors (which facilitate viral entry to cells) and the rapid recovery for most individuals with COVID-19 related smell loss makes this less likely. Infection of supporting cells (sustentacular cells) within the olfactory epithelium has been reported (reviewed in Bilinska 2020). These cells play a critical role in supporting the function of olfactory neurons, and their infection may consequently have an adverse effect on olfactory processing.

For many individuals with COVID-19 related olfactory dysfunction, the condition is temporary, and they recover a normal sense of smell relatively quickly (Chary 2020; Klopfenstein 2020). Complete recovery by two weeks was reported for most people (96.7%) in the study by Lechien 2020. A second case series of individuals with mild coronavirus symptoms found that 89% had complete or partial recovery of olfactory function by four weeks from the onset of the disease (Boscolo-Rizzo 2020). However, for some individuals the problem persists. Some studies report a much higher prevalence of persisting olfactory loss, despite resolution

of other COVID-19 symptoms. Data from the Global Consortium of Chemosensory Research indicates that up to 50.7% of individuals may have persisting olfactory dysfunction at up to 40 days from the onset of COVID-19 (Gerkin 2020). It remains unclear why some individuals experience longer lasting olfactory deficits. This may be due to differing extents of damage (as suggested by Butowt 2020), or different mechanisms for olfactory loss (Hopkins 2020c; Saussez 2020). Differing features of COVID-19 related smell loss may include a potential impact on true gustatory function, as well as a greater severity of olfactory loss itself (Huart 2020); many larger studies are limited by the reliance on self-reporting, so this is more difficult to corroborate.

This review is one of a pair that consider the effects of interventions to prevent or treat persisting olfactory dysfunction following COVID-19. For this review, we considered treatment for individuals who already have persisting olfactory dysfunction at four weeks (or longer) following a diagnosis of COVID-19. For the companion review ('Interventions for the prevention of persisting olfactory dysfunction following COVID-19'; Webster 2021a), we considered interventions that may be used in the acute phase (less than four weeks since diagnosis), aiming to prevent individuals from developing persisting olfactory dysfunction.

Description of the intervention

As COVID-19 related persistent olfactory dysfunction is a relatively new condition, there are no established treatments for it. However, a number of interventions have been used for other, post-viral, causes of anosmia. Steroids are commonly prescribed for olfactory dysfunction - these are typically administered locally as a nasal spray, drops or rinse for conductive causes of olfactory loss - where the nasal cavity is blocked, or partially blocked, by inflammation and oedema. Systemic (oral) steroids may also be used, particularly in cases where no conductive cause is identified.

Olfactory training is also frequently suggested for reduced or absent sense of smell - this involves regular exposure to a number of specific odours. It can be performed in a variety of different ways, using household items or essential oils.

A large number of other interventions have been used for PIOD, and may therefore be of use for post-COVID-19 olfactory dysfunction. A variety of vitamins, minerals and nutritional supplements have been proposed to be of benefit - either taken as an oral supplement or, in some instances, used intranasally (such as intranasal vitamin A drops). Glutamate antagonists and xanthine derivatives are used occasionally in the treatment of post-viral olfactory dysfunction and may therefore be assessed in relation to COVID-19. Trials of acupuncture have also taken place.

Olfactory dysfunction has a considerable impact on quality of life and may be a long lasting or even permanent condition. Psychological therapies, such as counselling or cognitive behavioural therapy, may therefore help to develop coping mechanisms and improve quality of life, even in the absence of objective improvement in the sense of smell.

Clinical trials are ongoing to assess a variety of interventions for the treatment of COVID-19. These include antivirals, such as remdesivir, and monoclonal antibodies. It is possible that these interventions may also benefit individuals with olfactory dysfunction, if these symptoms are assessed.

For many individuals, smell loss is anticipated to improve with time. There is no intervention that could currently be regarded as standard care for individuals with post-COVID-19 related anosmia. Interventions are therefore likely to be compared to no treatment, or to placebo (dummy) treatment. However, olfactory training is often suggested as an intervention with few, if any, adverse effects, and may be used alongside other treatments, therefore we anticipated that this may be advised to be undertaken concurrently in some studies.

How the intervention might work

Steroids are frequently prescribed to ensure that any intranasal inflammatory component that is exacerbating the PIOD is adequately treated. Whether steroids have a persisting effect after discontinuation is unclear. Intranasal steroids are used for a number of other conditions, and serious side effects are rare, but they may cause nasal irritation, nosebleeds or other localised complications. Steroids may also be administered systemically - typically as oral tablets, or sometimes parenterally.

Olfactory training aims to stimulate the olfactory neurons with a variety of odours in order to enhance smell detection. It is unclear whether any changes occur within the olfactory epithelium itself, in the olfactory bulb, or involve reorganisation of neural olfactory pathways. Although olfactory training may not restore olfactory function, it may improve the performance of the olfactory system. Two recent reviews suggest that olfactory training may give some benefit to those with olfactory disorders (Pekala 2016; Sorokowska 2017). However, the majority of included studies were prospective cohorts, with only one RCT included.

A number of vitamins and minerals have been suggested to have a beneficial effect on the olfactory epithelium, including vitamins A, B12 and D, and zinc. It is thought that metabolites of vitamin A may play a role in regeneration of tissue in the olfactory epithelium or olfactory bulb, and this has been used intranasally to treat individuals with post-viral olfactory loss (Hummel 2017). Vitamin B12 is known to be important in the maintenance of central and peripheral nervous function, and deficiency of vitamin B12 has been associated with olfactory impairment (Derin 2016). Vitamin D deficiency has also been linked to olfactory impairment (Bigman 2020), and there is ongoing interest in the potential use of vitamin D to prevent or treat other symptoms of COVID-19 infection (Martineau 2020). Zinc deficiency has also been shown to have an association with olfactory dysfunction and zinc was historically used intranasally as a potential treatment for anosmia, although there are concerns over toxicity (Alexander 2006).

Antioxidants, such as alpha lipoic acid and omega 3 fatty acids, have also been suggested as possible interventions to treat anosmia (Hummel 2002). They are thought to have neuroprotective properties that may help restore function within olfactory neurons or the olfactory bulb. Minocycline has also been trialled in post-viral olfactory loss - due to its neuroprotective properties, rather than its traditional role as an antibiotic (Reden 2011).

The impact of olfactory dysfunction on quality of life is substantial. Adjusting to, and learning to cope with, this life-changing symptom may be helped through psychological therapies, counselling or cognitive behavioural therapy.

It is possible that antiviral agents, some of which have already been shown to impact on the severity of COVID-19, may also affect the olfactory dysfunction. Reducing viral replication (and consequently lowering the viral load in an individual) may result in reduced severity of olfactory loss, or hasten the recovery. Monoclonal antibodies have also been used to treat COVID-19, and could also have an impact on the severity and persistence of olfactory impairment.

There have also been small studies to assess the possible benefit of acupuncture in olfactory loss (Dai 2016; Vent 2010).

Glutamate plays an important role in neurotransmission for olfactory neurons and within the olfactory bulb. Glutamate antagonists, such as caroverine, have been proposed to help protect against neurotoxicity, and consequently improve olfactory function (Quint 2002). Finally, xanthine derivatives such as theophylline and pentoxifylline have been proposed to stimulate olfactory neuron activity, and may therefore have an effect on olfactory function.

It is possible that individuals with a longer duration of anosmia have a different underlying disease process than those with temporary olfactory dysfunction related to COVID-19. Consequently, the efficacy of different interventions may vary between these groups.

Why it is important to do this review

The COVID-19 pandemic has resulted in an enormous number of individuals becoming infected with SARS-CoV-2. Fortunately, many individuals recover completely. However, the long-term consequences of infection are only just becoming apparent. Although the prevalence of persisting olfactory dysfunction may be small, with huge numbers of global infections the actual number of individuals suffering from post-COVID-19 related persistent anosmia is large. We can assume an estimated 60% suffer olfactory dysfunction at the onset of the infection and that at least 10% of these go on to experience PIOD. Given the number of infections (> 125 million infections worldwide, as of March 2021), we estimate that up to 7.5 million people may have been affected to date. The burden of this disorder is also considerable, with significant effects on quality of life, as well as safety implications (due to the inability to detect harmful or dangerous smells). Therefore, identification of potential treatments that may improve the outcome for sufferers is timely and important.

Many interventions carry a risk of adverse effects. If the beneficial effect of treatment is small or negligible, then side effects may be such that individuals do not consider treatments worthwhile. With this review we aimed to comprehensively assess the benefits and harms of interventions to treat post-COVID-19 related olfactory dysfunction, to ensure that patients can make an informed choice regarding the management of their condition.

Given the recent emergence of COVID-19, there is currently a great deal of uncertainty about how best to manage the olfactory dysfunction that occurs as a result of the virus. The sheer number of infected individuals worldwide also means that evidence that supports decision-making for the management of COVID-19 is a priority for decision-makers globally. There is also a strong emphasis on COVID-19 research at present, and we anticipate that there is likely to be new evidence available over the coming months and years. Therefore, this review will be a living systematic review, which will be continually updated to incorporate any important new evidence as it becomes available.

OBJECTIVES

To assess the effects (benefits and harms) of interventions to treat persisting olfactory dysfunction due to COVID-19 infection.

A secondary objective is to keep the evidence up-to-date, using a living systematic review approach.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials and quasi-randomised trials (where trials were designed as RCTs, but the sequence generation for allocation of treatment used methods such as alternative allocation, birth dates, alphabetical order etc.).

We considered that olfactory dysfunction is unlikely to be stable over long periods of time, and individuals may experience considerable fluctuation of symptoms over a given time period. Therefore, cross-over trials are unlikely to be identified in this area. If we do identify any cross-over studies, we will only include data from the first phase of these studies in the review.

We included studies where the main purpose of the trial was to assess the effect of treatment on olfactory function. Many interventions are used in the treatment of COVID-19 (such as steroids, antivirals); these may have beneficial effects on olfactory function, but the primary aim of most trials will be to assess their impact on other features of the disease (such as need for ventilation, mortality etc.). Therefore, we only included studies where olfactory function had been assessed at the trial baseline, and the main aim of the study was to determine the effect of an intervention on olfaction.

We only included studies where patients were followed up for at least one week. The aim of this review is to synthesise evidence for treatments that may have a lasting effect on olfactory function, rather than those that may have a very brief or temporary impact.

We included studies regardless of their publication status or language of publication. We planned to include outcome data reported on a trial registry, even if no published results were available. This was not applicable to any identified study in the current version of this review. If we identify material from a pre-print server then we will initially note this in the 'What's new' section of the review, pending the identification of fully published data. If no published data are identified within four months of the pre-print article being made available then we will incorporate the data in the review.

Types of participants

We included adult participants (aged 18 years or older) with persisting abnormalities of their sense of smell as a consequence of COVID-19. For the purpose of this review, the term 'persisting' refers to olfactory dysfunction being present at four weeks following a diagnosis of COVID-19. We anticipated that some studies will report this as four weeks of olfactory dysfunction, rather than four weeks

since a positive test for COVID-19 - either of these measures will be included in the review.

We included individuals with anosmia (absent sense of smell) or hyposmia (reduced sense of smell). We anticipated that some trials may also include a small number of individuals with symptoms of pure parosmia or phantosmia. We included data from these trials, providing the majority of participants (≥ 80%) report anosmia or hyposmia.

We included studies where olfactory dysfunction was identified with either psychophysical (objective) testing, or through self-report of symptoms. We investigated whether this has any impact on the effect estimates using subgroup analysis (see Subgroup analysis and investigation of heterogeneity).

We included studies where COVID-19 has been diagnosed through either objective testing (e.g. viral polymerase chain reaction (PCR) from nasopharyngeal swabs) or through a clinical diagnosis (for example, sudden onset of olfactory dysfunction with other symptoms of COVID-19, or in the context of contact with an infected individual).

For inclusion in this review, all participants in the trial must have abnormalities of their sense of smell. We did not include studies where only some participants are eligible (i.e. not all participants had olfactory dysfunction at the start of the trial).

Types of interventions

Interventions

We included any intervention proposed specifically to treat olfactory disturbance. We anticipated that this may include the following interventions:

- Intranasal steroid drops/rinses
- Intranasal steroid sprays
- Systemic steroids
- Olfactory training
- Intranasal vitamin A
- Zinc
- Antioxidants (e.g. omega 3 fatty acids, alpha lipoic acid)
- Counselling
- Antiviral agents (e.g. remdesivir)
- Other antimicrobials (e.g. minocycline)
- Other vitamins and nutritional supplements (to be analysed according to the type of vitamin/supplement, rather than as a pooled comparison)
- Acupuncture
- Monoclonal antibodies
- Glutamate antagonists (e.g. caroverine)
- Xanthine derivatives (e.g. theophylline, pentoxifylline)

If we had identified studies of additional interventions then these would also have been included.

All routes of administration, doses and duration of treatment were included.

We excluded studies that consider surgery, as this is not currently an intervention of interest for post-viral olfactory loss.

We considered olfactory training to be a complex intervention, as the method of delivery varies considerably in different studies. We planned to assess this using subgroup analysis, if we identified any trials of this intervention (see below).

Comparator(s)

The main comparison is:

- placebo or no treatment.

Concurrent treatments

We anticipated that some studies may include olfactory training (or other interventions) as concurrent therapy for both arms. We placed no limits on the type of concurrent treatments used. We planned to pool these studies with those where no concurrent treatment was used and use sensitivity analyses to determine whether the effect estimates are changed because of this.

Types of outcome measures

We analysed the following outcomes in the review, but we did not use them as a basis for including or excluding studies. Where possible, all outcomes were reported at three time points:

- 1 to 3 months (this was the main time point of interest);
- > 3 months to 12 months;
- > 12 months to 3 years.

These time points relate to the time when the treatment was started.

We considered outcomes at less than four weeks following COVID-19 too short to comprehensively assess whether individuals have persisting olfactory problems. However, in the absence of other evidence they may provide some indication about the likely efficacy of treatments to prevent later problems.

As most individuals with temporary problems should have complete resolution of their olfactory symptoms by four weeks (Boscolo-Rizzo 2020), we considered this time frame (> 4 weeks) to be of importance to identify those who truly have persisting problems. However, we recognised that some individuals may experience fluctuations in their symptoms, and develop recurrent olfactory problems at a later stage. We therefore included outcomes that were measured at a later point to identify whether treatment provided sustained recovery.

Primary outcomes

- Recovery of sense of smell:
  - as assessed by the participants;
  - as assessed with psychophysical testing, using Sniffin' Sticks, University of Pennsylvania Smell Identification Test (UPSIT) or another validated test.
- Disease-related quality of life, as assessed by the Olfactory Disorders Questionnaire, or another validated questionnaire (which specifically relates to olfactory dysfunction).
- Serious adverse effects (as defined by the trialists).

It is well recognised that self-rated sense of smell correlates poorly with the results of psychophysical testing of olfactory function. Therefore, we have included both types of outcome measurements separately for the outcome domains that relate to sense of smell.

If data had been obtained for both of these measures we would not have combined them, but would have reported them as two separate analyses. However, at present the only included study includes data using psychophysical testing only.

Secondary outcomes

- Change in sense of smell:
  - as assessed by the participants;
  - as assessed by psychophysical testing, using Sniffin' Sticks, UPSIT or another validated test.
- Overall, generic quality of life, as assessed by validated methods (e.g. EQ-5D).
- Presence of parosmia, as reported by the participants.
- Other adverse effects (including nosebleeds/bloody discharge).

We recognise that parosmia is a challenging symptom to define and assess. If we had identified data for this outcome then we would have included any results reported by the study authors, and described the definitions used in the study. However, this outcome was not assessed by the study included in the review.

Where possible, we planned to compare the threshold for appreciable change in these outcomes to published minimally important differences (MID). These have been reported for psychophysical olfactory testing using Sniffin' Sticks (MID 5.5 points, Gudziol 2006) and the Olfactory Disorders Questionnaire (MID 5.2 points, Mattos 2018). However, we did not identify any data for these outcomes in the review.

Search methods for identification of studies

The Cochrane ENT Information Specialist conducted systematic searches for randomised controlled trials and controlled clinical trials. There were no language or publication status restrictions. Some of the search terms were limited by publication year, due to the novel nature of post-COVID-19 olfactory dysfunction. We contacted the original authors for clarification and further data if trial reports were unclear and arranged translations of papers where necessary.

Electronic searches

The Information Specialist searched:

- the Cochrane ENT Trials Register (searched via the Cochrane Register of Studies to 16 December 2020);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (searched via the Cochrane Register of Studies to 16 December 2020);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to 16 December 2020);
- Ovid Embase (1974 to 16 December 2020);
- Web of Knowledge, Web of Science (1945 to 16 December 2020);
- ClinicalTrials.gov, www.clinicaltrials.gov:
  - searched via the Cochrane Register of Studies to 16 December 2020;
  - searched via www.clinicaltrials.gov to 16 December 2020;
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP):
  - searched via the Cochrane Register of Studies to 16 December 2020;
  - searched via https://apps.who.int/trialsearch/ to 16 December 2020;
- Cochrane COVID-19 Study Register, https://covid-19.cochrane.org/ (searched via the Cochrane Register to 16 December 2020);
- World Health Organization (WHO) COVID-19 'Global literature on coronavirus disease', https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov (searched to 16 December 2020).

The Information Specialist modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the Technical Supplement to Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* version 6.1) (Lefebvre 2020). Search strategies for major databases including CENTRAL are provided in Appendix 1.

Clinical trials are ongoing to assess a variety of interventions for the treatment of COVID-19. As few studies have currently been published, the search strategy developed is highly sensitive in order to try to capture all interventions as they are introduced. The Information Specialist will review the search methods (the sources and search frequency) and the search terms (index terms and free text terms) on an annual basis. The search strategy may evolve over time, as a greater body of literature is published and a more focused list of interventions are identified.

Living systematic review considerations

As a living systematic review, the Information Specialist will conduct monthly searches of the sources listed above, except the following, which will be searched less frequently and, as a minimum, on a:

- quarterly basis:
  - World Health Organization (WHO) COVID-19 'Global literature on coronavirus disease' https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov (search to date);
  - COAP COVID-19 Living Evidence, Institute of Social and Preventive Medicine (ISPM), University of Bern https://zika.ispm.unibe.ch/assets/data/pub/search_beta/ (search to date); or
- an annual basis:
  - ClinicalTrials.gov (search via www.clinicaltrials.gov to date);
  - World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (search via https://apps.who.int/trialsearch/ to date).

Clinical trials are ongoing to assess a variety of interventions for the treatment of COVID-19. We plan to conduct surveillance activity and commence monthly searches when we anticipate that the first trials will have data available.

The Information Specialist will apply appropriate date restrictions and auto alerts as available and appropriate, and will provide details in an appendix to the published review.

Searching other resources

We scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. The Information Specialist also ran non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

We did not perform a separate search for adverse effects. We considered adverse effects described in included studies only.

We planned to make efforts to identify full-text papers regardless of language of publication and endeavour to seek help with translation; however, we did not encounter this issue. Any papers that we were unable to source in time for the scheduled living review update, or were unable to get translated, would be listed as awaiting assessment. Fortunately, we were able to identify and locate all papers of relevance for this review, and did not require any translation.

Living systematic review considerations

As a living systematic review, we scanned the reference lists of identified publications for additional trials and contacted trial authors if necessary. In addition, the Information Specialist searched on an **annual** basis Ovid MEDLINE to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. The Information Specialist conducted **annual** searches of the Web Knowledge Science Citation Index for articles referencing the published review and its included studies and carried out non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

Data collection and analysis

Selection of studies

The Cochrane ENT Information Specialist used the first two components of Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components:

1. Known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as 'a RCT' or as 'not a RCT'.
2. The machine learning classifier (RCT model) (Wallace 2017), available in the Cochrane Register of Studies (CRS-Web), which assigns a probability of being a true RCT (from 0 to 100) to each citation. For citations that are assigned a probability score below the cut-point at a recall of 99% we will assume these to be non-RCTs. For those that score on or above the cut-point we will either manually dual screen these results or send them to Cochrane Crowd for screening.
3. Cochrane Crowd is Cochrane's citizen science platform where the Crowd help to identify and describe health evidence. For more information about Screen4Me and the evaluations that have been done, please go to the Screen4Me website on the Cochrane Information Specialist's portal and see Marshall 2018, McDonald 2017, Noel-Storr 2018 and Thomas 2017.

We did not use the third component because of the relatively small number of results retrieved by the search.

Two review authors (LOB, KW) independently screened the remaining titles and abstracts retrieved by the search to identify potentially relevant studies. The same authors independently evaluated the full text of each potentially relevant study to determine whether it met the inclusion/exclusion criteria for this review. We resolved any differences by discussion and consensus. We planned to involve a third author where necessary, but this was not required.

Living systematic review considerations

We immediately screened any new citations retrieved by the monthly searches using the approach outlined above.

Data extraction and management

Two review authors (LOB/KW) independently extracted outcome data from each study using a standardised data collection form. Where a study had more than one publication, we retrieved all publications to ensure complete extraction of data. Any discrepancies in the data extracted by the two authors were checked against the original reports, and differences were resolved through discussion and consensus, with recourse to a third author where necessary. If required, we contacted the study authors for clarification.

We collected information on study design and setting, participant characteristics (including disease severity and age), study eligibility criteria, details of the intervention(s) given, the outcomes assessed, the source of study funding and any conflicts of interest stated by the investigators. We also included details of the baseline characteristics of trial participants, with particular regard to prognostic features such as age, gender, severity of infection and duration of time since COVID-19 infection.

The primary effect of interest for this review was the effect of treatment assignment (which reflects the outcomes of treatment for people who were assigned to the intervention) rather than a per protocol analysis (the outcomes of treatment only for those who completed the full course of treatment as planned). For the outcomes of interest in this review, we extracted the findings from the studies on an available case basis, i.e. all available data from all participants at each time point, based on the treatment to which they were randomised. This was irrespective of compliance, or whether participants had received the intervention as planned.

In addition to extracting prespecified information about study characteristics and aspects of methodology relevant to risk of bias, we extracted the following summary statistics for each trial and outcome:

- For continuous data: the mean values, standard deviation and number of patients for each treatment group at the different time points for outcome measurement. Where endpoint data were not available, we extracted the values for change-from-baseline data instead. If values for the individual treatment groups are not reported, where possible we extracted summary statistics (e.g. mean difference) from the studies.
- For binary data: we extracted information on the number of participants experiencing an event, and the number of participants assessed at that time point. If values for the

individual treatment groups were not reported, where possible we extracted summary statistics (e.g. risk ratio) from the studies.

- For ordinal scale data: if we identified data reported on an ordinal scale and if the data appeared to be normally distributed, or if the analysis performed by the investigators indicated that parametric tests were appropriate, then we treated the outcome measure as continuous data. Alternatively, if data were available, we converted these to binary data.
- For time-to-event data: if we identified data reported as time-to-event then, where possible, we extracted data on hazard ratios from individual studies. If these data were not provided then we extracted alternative measures of treatment effect, such as the observed and expected number of events in each group, a P value and the number of events in each arm, or data in a Kaplan Meier curve.

We pre-specified time points of interest for the outcomes in this review. Where studies reported data at multiple time points, we took the longest available follow-up point within each of the specific time frames. For example, if a study reported an outcome at 4 weeks, 8 weeks and 12 weeks of follow-up then we included the 12-week data for the time point 1 to 3 months

Assessment of risk of bias in included studies

Two authors undertook assessment of the risk of bias of the included trials independently, with the following taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We used the Cochrane risk of bias tool in RevMan 5.4 (RevMan 2020), which involved describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias. Any discrepancies in judgement between the two authors was resolved through discussion, and with recourse to a third author where necessary.

Measures of treatment effect

We summarised the effects of dichotomous outcomes (e.g. recovery of sense of smell) as risk ratios (RR) with 95% confidence intervals (CIs). For the key outcomes that we presented in the summary of findings tables, we also expressed the results as absolute numbers based on the pooled results and compared to the assumed risk. For future iterations of this living review we may also calculate the number needed to treat to benefit (NNTB) using the pooled results. The assumed baseline risk was either (a) the median of the risks of the control groups in the included studies - this being used to represent a 'medium-risk population' or, alternatively, (b) the average risk of the control groups in the included studies - used as the 'study population' (Handbook 2020). As a single study was included, we used the baseline risk from this study for all calculations. If a large number of studies are available in future (and where appropriate) we may also present additional data based on the assumed baseline risk in (c) a low-risk population and (d) a high-risk population.

For continuous outcomes, we planned to express treatment effects as a mean difference (MD) with standard deviation (SD) or as a standardised mean difference (SMD) where different scales had been used to measure the same outcome. We planned to provide a clinical interpretation of the SMD values using either Cohen's d or by conversion to a recognised scale if possible.

For time-to-event outcomes we planned to summarise the effects as a hazard ratio (HR) with 95% CI. If necessary, and where possible (if sufficient alternative data were provided), we planned to estimate the HR from individual studies according to the methods outlined in Tierney 2007. However, no time-to-event data were identified for the review.

Unit of analysis issues

Cross-over trials and cluster-randomised trials were not anticipated for this review topic, and none were identified. Post-COVID-19 related anosmia is unlikely to be a stable condition, and interventions may not have a temporary effect. If cross-over trials were identified then we planned to use only the data from the first phase of the study. If cluster-randomised trials were identified then we would have ensured that analysis methods were used to account for clustering in the data (Handbook 2020).

If we had identified multi-arm trials for inclusion in the review, we would have ensured that multiple intervention groups were analysed in an appropriate way to avoid arbitrary omission of groups or double counting of participants. This may have included combining intervention groups (if appropriate) or splitting the 'shared' group into two or more groups with a smaller sample size. However, no multi-arm trials were identified.

Dealing with missing data

We planned to contact study authors via email whenever an outcome of interest was not reported, if the methods of the study suggested that the outcome had been measured. We planned to do the same if not all data required for meta-analysis had been reported, unless the missing data were standard deviations. If standard deviation data was not available, we would have approximated these using the standard estimation methods from P values, standard errors or 95% CIs if these were reported as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2020). If it was impossible to estimate these, we would have contacted the study authors.

Apart from imputations for missing standard deviations, we planned to conduct no other imputations. We extracted and analysed all data using the available case analysis method.

Assessment of heterogeneity

We planned to assess clinical heterogeneity (which may be present even in the absence of statistical heterogeneity) by examining the included trials for potential differences between studies in the types of participants recruited, interventions or controls used and the outcomes measured. However, this was not possible due to the inclusion of a single study.

We planned to assess statistical heterogeneity by visually inspecting the forest plots and by considering the Chi^2 test (with a

significance level set at P value < 0.10) and the I^2 statistic, which calculates the percentage of variability that is due to heterogeneity rather than chance (Handbook 2020). Again, this was not necessary due to the inclusion of a single study.

Assessment of reporting biases

We assessed reporting bias as within-study outcome reporting bias and between-study publication bias.

Outcome reporting bias (within-study reporting bias)

We assessed within-study reporting bias by comparing the outcomes reported in the published report against the study protocol or trial registry, whenever this could be obtained. If the protocol or trial registry entry was not available, we compared the outcomes reported to those listed in the methods section. If results were mentioned but not reported adequately in a way that allows analysis (e.g. the report only mentions whether the results were statistically significant or not), bias in a meta-analysis is likely to occur. We sought further information from the study authors. If no further information was found, we noted this as being a 'high' risk of bias when the risk of bias tool is used. If there was insufficient information to judge the risk of bias we noted this as an 'unclear' risk of bias (Handbook 2011).

Publication bias (between-study reporting bias)

We assessed funnel plots if sufficient studies (more than 10) were available for an outcome. If we observed asymmetry of the funnel plot, we conducted more formal investigation using the methods proposed by Egger 1997. We also reported on whether there were any studies identified through trial registries and other sources (Searching other resources) with unpublished reports.

Data synthesis

Where possible and appropriate (if participants, interventions, comparisons and outcomes were sufficiently similar in the trials identified) we planned to conduct a quantitative synthesis of results. We planned to conduct all meta-analyses using a fixed-effect method in RevMan 5.4. However, at present a single study is included in this review, precluding meta-analysis.

We planned to include all studies in the meta-analyses, regardless of their risk of bias. However, we intended to incorporate a summary assessment of risk of bias in the measure of certainty of the evidence for each outcome, using the GRADE system.

For dichotomous data, we analysed treatment differences as a risk ratio (RR) calculated using the fixed-effect Mantel-Haenszel methods.

For continuous outcomes, we planned to use the inverse variance, fixed-effect method of meta-analysis. If all data were from the same scale, we planned to pool mean follow-up values with change-from-baseline data and report this as a mean difference. If there was a need to report standardised mean differences then we would not have pooled endpoint and change-from-baseline data.

For time-to-event data we planned to use a generic inverse variance, fixed-effect method of meta-analysis.

Sense of smell may be tested using a variety of methods, which consider different aspects of the sense of smell. These are:

- identification - the ability to identify and name a specific odour;
- threshold - the concentration of an odour that can be detected;
- discrimination - the ability to discriminate between odours.

We included methods that considered any or all of the above aspects of sense of smell. If meta-analysis is appropriate in future iterations of this review, we will only pool results that look at the same individual aspect (or aspects) of sense of smell.

If meta-analysis was not possible (for example, due to incompletely reported outcomes/effect estimates or different effect measures that cannot be combined) then we considered presenting alternative synthesis methods. This included summarising the effect estimates from individual studies, combining P values or vote counting based on the direction of effect, depending on the data available.

Living systematic review considerations

Whenever new evidence relevant to the review is identified in our monthly searches, we will extract the data, assess risk of bias and incorporate it into the synthesis every four months, as appropriate. Formal sequential meta-analysis approaches will not be used for updated meta-analyses.

Subgroup analysis and investigation of heterogeneity

A number of factors are likely to impact on the outcomes included in this review. Where possible (if appropriate data are reported), we planned to assess these with subgroup analysis, regardless of whether statistical heterogeneity is identified. These are the following:

- Age of participants in the trial (under 60 years versus those aged 60 or over):
  - age is well recognised to impact on olfactory function, with sense of smell worsening with time. The ability to detect smells may therefore differ considerably between younger and older adults.
- Gender of participants in the trial (female versus male):
  - gender has an influence on olfactory function and may also impact recovery rates.
- Method used to determine olfactory dysfunction at trial baseline (self-reported versus psychophysical testing):
  - rates of olfactory dysfunction vary depending on whether self-report or psychophysical testing is used to identify olfactory loss. Effect estimates in these two groups may therefore differ.

If trials did not report data for particular subgroups of participants we planned to synthesise data at the level of the individual trial, where appropriate. We would have identified studies as belonging to a particular subgroup if more than 2/3 participants (66%) belonged to that category.

If trials presented data for subgroups of individuals within the trial we would have used this for subgroup analysis, where applicable, regardless of whether trials had stratified their randomisation according to those subgroups.

We anticipated that the varying methods used for olfactory training may be a source of heterogeneity in effects. If we identified heterogeneity in the comparison of olfactory training then we would have explored this considering the following factors:

- classical versus modified olfactory training (using the same scents throughout compared to changing the scents);
- the duration of the intervention.

Sensitivity analysis

We planned to carry out sensitivity analyses to determine whether the findings were robust to the decisions made in the course of identifying, screening and analysing the trials. We would have conducted sensitivity analysis for the following factors, whenever possible:

- impact of model chosen: to investigate whether the use of a random-effects model impacts on the effect estimates;
- inclusion of studies with concurrent treatments: to exclude these studies from the pooled estimates of effect for any intervention;
- method of COVID-19 diagnosis: to exclude studies where only a clinical method of COVID-19 diagnosis was used (rather than laboratory confirmed).

Summary of findings and assessment of the certainty of the evidence

Two independent authors (LOB/KW) used the GRADE approach to rate the overall certainty of evidence using GRADEpro GDT (https://gradepro.org/). The certainty of evidence reflects the extent to which we are confident that an estimate of effect is correct and we applied this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high certainty of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low certainty implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high certainty. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision; and
- publication bias.

We included a summary of findings table, constructed according to the recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2020), for the following comparison(s):

- intranasal steroid drops/rinses versus no treatment/placebo;
- intranasal steroid sprays versus no treatment/placebo;
- olfactory training versus no treatment/placebo;
- intranasal vitamin A versus no treatment/placebo.

We included the following outcomes in the summary of findings tables:

- recovery of sense of smell (as reported by the participants);
- disease-related quality of life, as assessed by the Olfactory Disorders Questionnaire (or another validated questionnaire);
- serious adverse effects;
- change in sense of smell (as identified by psychophysical testing);
- overall, generic quality of life, as assessed by validated methods (e.g. EQ-5D);
- presence of parosmia;
- other adverse effects (including nosebleeds/bloody discharge).

Methods for future updates

Living systematic review considerations

We will review the scope and methods of this review approximately yearly (or more frequently if appropriate) in the light of potential changes in the topic area, or the evidence being included in the review (for example, additional comparisons, interventions or outcomes, or new review methods available).

Conditions under which the review will no longer be maintained as a living systematic review

The review will no longer be maintained as a living systematic review once there is high-certainty evidence obtained for the primary effectiveness outcomes of the review; once new studies are not expected to be conducted regularly for the interventions included in this review; or once the review topic is no longer a priority for health care decision-making.

RESULTS

Description of studies

Results of the search

The searches (December 2020) retrieved a total of 1034 records. This reduced to 796 after the removal of duplicates. The Cochrane ENT Information Specialist sent all 796 records to the Screen4Me workflow. The Screen4Me workflow identified four records as having previously been assessed: three had been rejected as not RCTs and one had been assessed as a possible RCT. The RCT classifier rejected an additional 382 records as not RCTs (with 99% sensitivity). We did not send any records to the Cochrane Crowd for assessment. Following this process, the Screen4Me workflow had rejected 385 records and identified 411 possible RCTs for title and abstract screening.

	Possible RCTs	Rejected
Known assessments	1	3
RCT classifier	410	382

Total	**411**	**385**

We screened the titles and abstracts of the remaining 411 records. We discarded 372 records and assessed 39 full-text records. We discarded six additional references at the full-text screening stage.

We excluded 22 records (linked to 21 studies) with reasons recorded in the review (see Excluded studies). We identified one additional reference to a published paper linked to an excluded study identified by the search. The paper was published after the search was run.

We included one completed study (one record) where results were available (Vaira 2020).

We identified eight ongoing studies (10 records). See Characteristics of ongoing studies for further details of all eight ongoing studies.

A flow chart of study retrieval and selection is provided in Figure 1.

Figure 1.

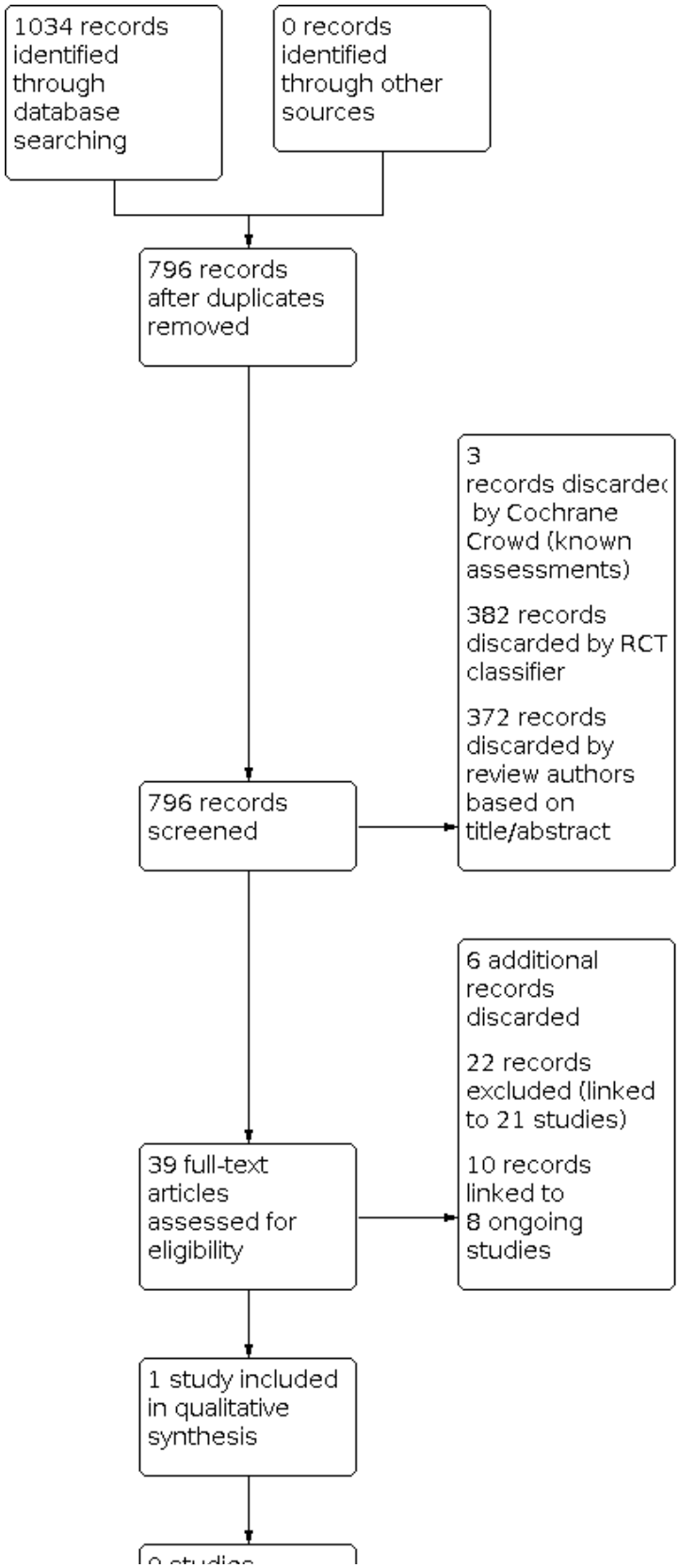
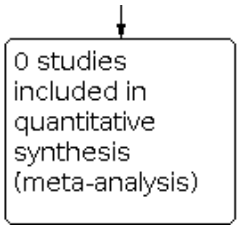


Figure 1. (Continued)



Included studies

One study was included in the review. Vaira 2020 was a randomised controlled trial of systemic corticosteroids (prednisone) plus nasal irrigation with a combination of intranasal corticosteroids (betamethasone), a mucolytic (ambroxol) and a decongestant (rinazine) for 15 days, compared to no treatment. The study included 18 patients, nine in each arm, and was conducted at two sites in Italy.

All patients had olfactory disturbance for at least 30 days post-COVID-19 infection. Anosmia and hyposmia were identified at baseline using psychophysical testing with the Connecticut Chemosensory Clinical Research Center (CCCRC) test score ≤ 40 (e.g. anosmia or severe hyposmia) at 30 days after clinical onset. Sense of smell was assessed using this method at baseline, 20 and 40 days after initiation of treatment. Self-reported olfactory function was not assessed.

Excluded studies

We excluded 21 studies. We present the main reasons for the exclusion of the studies below, although some studies had multiple reasons for exclusion:

Thirteen studies assessed the wrong population:

- Ten studies included all individuals with COVID-19 and not just those with olfactory dysfunction (ACTION (NCT04332107); COPPS (NCT04662060); COVIDAtoZ (NCT04342728); CTRI/2020/08/027477; NCT04414124; NCT04458519; NCT04474483; NCT04513184; NCT04622891; NCT04662086).
- Two studies included those with olfactory dysfunction but for less than four weeks (NCT04484493; NCT04569825).
- One study included any post-viral olfactory dysfunction, not specifically COVID-19 (NCT04406584).

Six studies were incorrectly designed to meet our inclusion criteria:

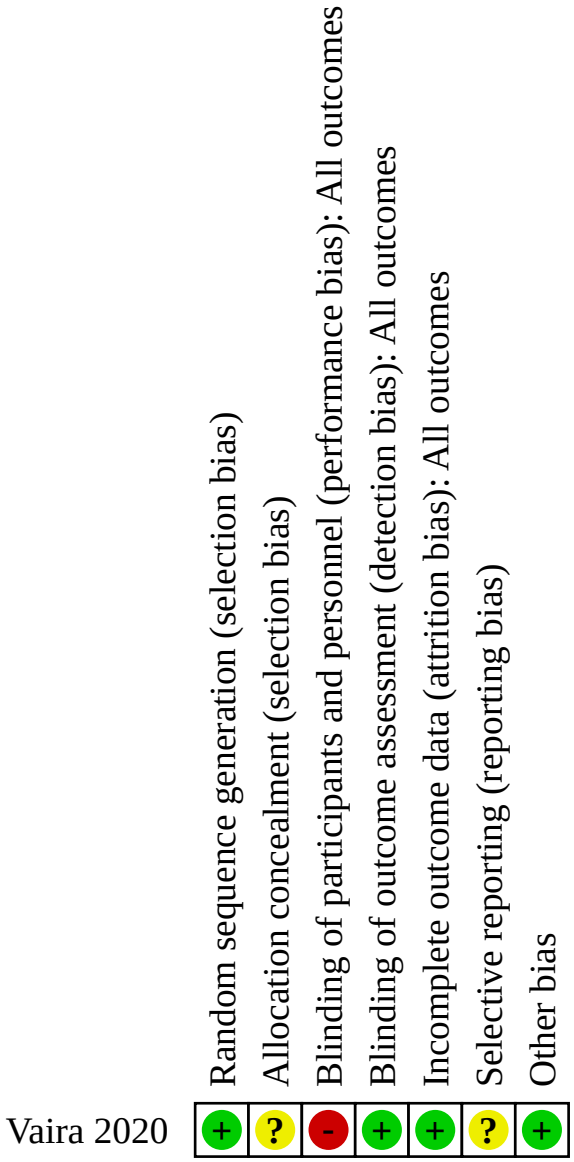
- Two studies were not randomised controlled trials (NCT04382547; NCT04427332).
- Two studies were narrative review articles without any primary data (Begam 2020; Vroegop 2020).
- Two studies were letters to the editor without any primary data (Patel 2021; Pinna 2020).

Finally, two studies were withdrawn prior to participant enrolment and therefore may have been relevant but could not be included in this review (Co-STAR (NCT04422275); NCT04374474).

Risk of bias in included studies

We considered the only study included, Vaira 2020, to carry a high risk of performance bias due to a lack of blinding of participants. Other risks of bias were either low or unclear (see Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Vaira 2020 ensured adequate randomisation using computer-generated random sequences. Concealment of allocation sequence was not discussed in the text. Correspondence with the author revealed that a list was compiled but it remains unclear how this was concealed.

Blinding

In this study there was no blinding of participants and the control group did not receive any treatment; we felt this represented a high risk of performance bias. However, both the researcher who performed the pre- and post-treatment psychophysical assessment of smell and the statistician who analysed the data were blinded to the patient allocation group, therefore we judged this to be at low risk of detection bias.

Incomplete outcome data

As all 18 participants in the Vaira 2020 study completed follow-up with no incomplete data reported, we concluded that there was a low risk of attrition bias.

Selective reporting

A published trial protocol could not be located for Vaira 2020 and the author confirmed no such protocol was published, therefore we believe there is an unclear risk of reporting bias.

Other potential sources of bias

We did not detect any additional potential sources of bias for Vaira 2020.

Effects of interventions

See: **Summary of findings 1** Systemic corticosteroids plus intranasal steroid/mucolytic/decongestant compared to no intervention for persistent post-COVID-19 olfactory dysfunction

Comparison 1: Systemic corticosteroids plus intranasal steroid/mucolytic/decongestant versus no intervention

One study (18 participants) investigated systemic corticosteroids with intranasal steroid/mucolytic/decongestant therapy in comparison to no treatment (see Summary of findings 1).

Recovery of sense of smell

At one to three months

Vaira 2020 used psychophysical testing with the CCCRC score (0 to 100) to measure olfactory function at baseline, 20 and 40 days. Normosmia was defined as a CCCRC score of ≥ 90. At 40 days, five participants had normal olfactory function in the intervention group (5 out of 9) compared to no participants with normal olfactory function in the control group (0 out of 9). However, the evidence is very uncertain for the effect of the intervention on the presence of normal olfactory function at one to three months given the small sample size and the very wide confidence intervals around the effect (risk ratio (RR) 11, 95% confidence interval (CI) 0.70 to 173.66; 1 study; 18 participants; very low-certainty evidence; Analysis 1.1).

No data were reported for later time points of interest in this review, and no data on self-rated olfactory function were reported.

Disease-related quality of life

This was not assessed or reported.

Serious adverse effects

At one to three months

Vaira 2020 reported that no patient had an adverse event, however it is unclear how this outcome was assessed (1 study; 18 participants; very low-certainty evidence).

No data were reported for later time points of interest in this review.

Change in sense of smell

At one to three months

Vaira 2020 reported a median change in smell using the CCCRC score at 40 days. As the data were reported using medians no effect estimate could be calculated. This study reported an improvement in sense of smell in the intervention group from baseline (median improvement in CCCRC score 60, interquartile range (IQR) 40) compared to the control group (median improvement in CCCRC score 30, IQR 25) (P = 0.024; 1 study; 18 participants; very low-certainty evidence). The evidence is very uncertain regarding the efficacy of systemic corticosteroids and nasal spray and change in olfactory function at one to three months.

No data were reported for later time points of interest in this review, and no data on self-rated olfactory function were reported.

Generic quality of life

This was not assessed or reported.

Prevalence of parosmia

This was not assessed or reported.

Other adverse effects

At one to three months

Vaira 2020 reported that no patient had an adverse event, however it is unclear how this outcome was assessed (1 study; 18 participants; very low-certainty evidence).

No data were reported for later time points of interest in this review.

DISCUSSION

Summary of main results

This review includes a single randomised controlled trial evaluating the effect of systemic corticosteroids and nasal irrigation (intranasal corticosteroid/mucolytic/decongestant) used for 15 days compared to no treatment. All patients had persistent hyposmia or anosmia symptoms for 30 days following COVID-19 infection, defined as a score of ≤ 40 using the Connecticut Chemosensory Clinical Research Center (CCCRC) score. Olfactory function was assessed at 40 days using psychophysical testing with the CCCRC. At 40 days follow-up the effect of systemic corticosteroids and nasal irrigation with intranasal corticosteroids, a mucolytic and a decongestant on recovery and change of sense of smell and adverse events remains very uncertain.

Overall completeness and applicability of evidence

This review is inherently limited by only having one complete study included. Furthermore, this study only included 18 patients (nine randomised to treatment and nine to no treatment). This study provided only a small amount of evidence regarding the use of intranasal corticosteroids in the recovery of, or change in, olfactory function post-COVID-19 infection. No adverse events were noted in the study, however the methods for systematic collection of data for this outcome were unclear. We did not identify any evidence for other outcomes, including presence of parosmia, change in sense of taste and disease-related quality of life. This review could only assess the utility of one intervention in the treatment of olfactory dysfunction following COVID-19 infection at a short interval (40 days) after initiation. Therefore, the long-term effects of this intervention remain unknown.

The sense of smell is also important to help distinguish flavour – whilst the true tastes of sweet, sour, salty, bitter and umami can be sensed with the tongue, awareness of different flavours requires a functioning olfactory system. Consequently, changes in olfactory function are typically accompanied by altered flavour perception. Assessment of taste using self-reporting is challenging (due to the need to distinguish between true taste and retronasal

olfaction) and there is a lack of widespread use of psychophysical testing methods, which are needed to determine the accurate picture of olfactory and gustatory performance. Therefore we have focused predominantly on the sense of smell for this review, but we acknowledge that an impaired sense of taste may be a real or perceived issue for many individuals who are recovering from COVID-19.

Quality of the evidence

We judged the certainty of the evidence to be very low for all outcomes assessed. This was largely a consequence of the fact that we only identified one study with a small sample size leading to a lack of precision in the effect estimates. In addition, concerns around high risk of performance bias existed in relation to the lack of blinding of participants.

Potential biases in the review process

This review is one of a pair that address the prevention and treatment of olfactory dysfunction related to COVID-19. As olfactory dysfunction has been found to carry a high rate of resolution within the first month after COVID-19 infection we felt this was a clinically important distinction to make in evaluating prospective interventions for prevention and treatment. Therefore, we excluded studies from this review if participants had less than four weeks of olfactory disturbance at baseline - these studies are included in the companion review on the prevention of olfactory dysfunction.

Agreements and disagreements with other studies or reviews

To the best of our knowledge this is the first and only review of its kind evaluating the treatment of persistent anosmia post-COVID-19 infection therefore it is impossible to draw any comparisons to other studies or reviews.

AUTHORS' CONCLUSIONS

Implications for practice

Currently there are only data available from one study. This review could only find very low-certainty evidence of the effects of systemic steroids coupled with intranasal corticosteroids, a mucolytic and a decongestant on the treatment of persisting olfactory dysfunction following COVID-19. Therefore, we are unable to draw any definite conclusions on the efficacy and risks of treatments involved in treating anosmia in this setting. As this is a living systematic review the data will be updated regularly, as new evidence becomes available.

Implications for research

The treatment of persistent anosmia as a sequela of COVID-19 infection is a rapidly evolving field therefore this review will be maintained as a living systematic review. We are aware of several ongoing trials in the area and will incorporate emerging evidence into this review as data become available.

The natural history of COVID-19 infection as well as the associated olfactory dysfunction remains to be seen. High rates of spontaneous resolution have been reported but further research is required into the area to specifically determine which groups will benefit from therapy and what the associated risks may be. The distinction between prevention and treatment is an important one to make when designing clinical trials to investigate this complex group of patients.

As with the treatment of post-viral olfactory dysfunction the method of evaluation of olfactory dysfunction is of particular importance with a combination of psychophysical testing and self-rated evaluation giving greater opportunities to assess the meaningful impact of treatment interventions.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Vaira 2020

Study characteristics	
Methods	Multicentre randomised controlled trial with 40 days of follow-up
Participants	**Location:** multicentre, Italy, Belgium, UK **Setting of recruitment and treatment:** University Hospital of Sassari and the Bellaria-Maggiore Hospital in Bologna (Italy) **Sample size:** 18 • **Number randomised:** 9 to intervention, 9 to comparison • **Number completed:** 9 to intervention, 9 to comparison

Vaira 2020 *(Continued)*

Participants:

Participants with COVID-19 related anosmia for more than 30 days defined as a Connecticut Chemosensory Clinical Research Center (CCCRC) test score ≤ 40

Baseline characteristics:

- **Age:** intervention group: median 44.5 years (IQR: 36 to 50.5); control group: median 42 years (IQR: 34 to 48)
- **Gender:** intervention group: 4 (44.44%) male and 5 (55.56%) female; control group: 3 (33.33%) male and 6 (66.67%) female
- **Olfactory function at baseline**
  - Measured using CCCRC scores
    - Normal (score 90 to 100)
    - Mild hyposmia (70 to 80)
    - Moderate (50 to 60)
    - Severe (20 to 40)
    - Anosmia (0 to 10)
- Intervention group: median 10 (IQR 15); control group: median 20 (IQR 30)

Inclusion criteria for the study:

- > 18 years of age
- SARS-CoV-2 infection confirmed
- Recovery from SARS-CoV-2 infection confirmed by at least 2 negative swabs
- CCCRC test score ≤ 40 (i.e. anosmia or severe hyposmia) at 30 days after clinical onset

Exclusion criteria for the study:

- Previous olfactory dysfunction
- Trauma
- Nasal surgery
- Radiation therapy in the oral or nasal cavities
- Self-reported allergic rhinitis or rhinosinusitis
- Psychiatric or neurological disease
- Contraindication to corticosteroid

Interventions	**Intervention group:** systemic cortisone therapy with prednisone starting with 1 mg/kg and tapering the dose for 15 days accompanied by nasal irrigation with betamethasone, ambroxol and rinazine for 15 days **Comparator group:** the control group did not receive any therapy **Use of additional interventions:** none noted
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** Presence of normal olfactory function • Using psychophysical testing (CCCRC) • The CCCRC includes a butanol threshold assessment and odour identification test. These scores are converted into CCCRC composite scores, which allows classification of patients • Normosmia (recovery) defined as a CCCRC score of 90 to 100 • Assessed at baseline, 20 and 40 days Serious adverse effects • None noted

Vaira 2020 *(Continued)*

Change in sense of smell

- Using psychophysical testing (CCCRC)
- The CCCRC includes a butanol threshold assessment and odour identification test. These scores are converted into CCCRC composite scores, which allows classification of patients
- Assessed at baseline, 20 and 40 days

Secondary outcomes:

Prevalence of parosmia

- Not assessed

Change in sense of taste

- Not assessed

Disease-related quality of life

- Not assessed

Other adverse effects (including nosebleeds/bloody discharge)

- None noted

Other outcomes reported by the study:

- None reported

Funding sources	None reported
Declarations of interest	No conflicts of interest declared
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients included in the study were randomly divided into two groups using a computer generated random number table" Comment: author contacted and confirmed randomisation
Allocation concealment (selection bias)	Unclear risk	No information provided Comment: author contacted; remains unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Study was not blinded to participants. No placebo was used for the comparator group." Comment: the control group did not undergo any placebo treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both the researcher who performed the pre- and post-treatment psychophysical assessment of smell and the statistician who analyzed the data were blinded to the patient allocation group" Comment: appropriate blinding performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all 18 patients enrolled were followed up and outcomes reported

Vaira 2020 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol or registration could be identified to assess this
Other bias	Low risk	Comment: no additional sources of bias detected

CCCRC: Connecticut Chemosensory Clinical Research Center
IQR: interquartile range

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTION (NCT04332107)	Wrong population: study does not specifically include participants with olfactory dysfunction
Begam 2020	Narrative review article, no primary data
COPPS (NCT04662060)	Wrong population: study does not specifically include participants with olfactory dysfunction
Co-STAR (NCT04422275)	Study withdrawn
COVIDAtoZ (NCT04342728)	Wrong population: study does not specifically include participants with olfactory dysfunction
CTRI/2020/08/027477	Wrong population: study does not specifically include participants with olfactory dysfunction
NCT04374474	Although this study fits the inclusion criteria for the review, it was withdrawn prior to any participant enrolment
NCT04382547	Wrong study design: not a randomised controlled trial
NCT04406584	Wrong population: includes participants with any post-viral olfactory disturbance (not specifically COVID-19)
NCT04414124	Wrong population: study does not specifically include participants with olfactory dysfunction
NCT04427332	Wrong study design: observational study, not a randomised controlled trial
NCT04458519	Wrong population: study does not specifically include participants with olfactory dysfunction
NCT04474483	Wrong population: study does not specifically include participants with olfactory dysfunction
NCT04484493	Wrong population: all participants in the study have had symptoms of olfactory disturbance for less than 4 weeks. This study is relevant for the companion review 'Interventions for the prevention of persistent post-COVID-19 olfactory dysfunction'.
NCT04513184	Wrong population and wrong comparator: study does not specifically include participants with olfactory dysfunction, intervention is compared to intravenous dexamethasone
NCT04569825	Wrong population: all participants in the study have had symptoms of olfactory disturbance for less than 4 weeks. This study is relevant for the companion review 'Interventions for the prevention of persistent post-COVID-19 olfactory dysfunction'.
NCT04622891	Wrong population: study does not specifically include participants with olfactory dysfunction
NCT04662086	Wrong population: study does not specifically include participants with olfactory dysfunction

Study	Reason for exclusion
Patel 2021	Letter to the editor: no primary data
Pinna 2020	Letter to the editor: no primary data
Vroegop 2020	Narrative review article: no primary data

Characteristics of ongoing studies *[ordered by study ID]*

COVIDORL (NCT04361474)

Study name	Trial evaluating the efficacy of local budesonide therapy in the management of hyposmia in COV-ID-19 patients without signs of severity (COVIDORL)
Methods	Parallel-group randomised controlled trial
Participants	Individuals with persistent hyposmia at 30 days following the onset of SARS-CoV-2 infection **Inclusion criteria for the study:** • Patients over 18 years of age • Patient with a suspected SARS-CoV-2 infection (whether or not confirmed by PCR), or contact close to a PCR-confirmed case, typical chest CT scan (unsystematised frosted glass areas predominantly sub-pleural, and at a later stage of alveolar condensation with no excavations neither nodules nor masses) or positive serology • Isolated acute hyposmia persisting at 30 days after SARS-CoV-2 symptom onset • Absence of PCR-confirmed SARS-CoV-2 carriage at the time of inclusion **Exclusion criteria for the study:** • Hypersensitivity to budesonide or any excipients of the medicine • Haemostasis disorder, or epistaxis • Oral/nasal/ophthalmic herpes virus infection • Long-term corticosteroid infection • Treatment with CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone or HIV proteases) • Respiratory signs or other symptoms of SARS-CoV-2 persisting at day 30 from the onset of infection • Hyposmia persisting for more than 90 days after onset of symptoms • Other causes of hyposmia revealed on interrogation or MRI **Planned sample size:** estimated enrolment 120 participants
Interventions	**Intervention:** nasal irrigation with budesonide and physiological saline (budesonide 1 mg/2 mL diluted in 250 mL of physiological saline: 3 syringes of 20 mL in each nasal cavity, morning and evening, for 30 days **Comparator:** nasal irrigation with physiological saline only: 3 syringes of 20 mL in each nasal cavity, morning and evening, for 30 days **Additional intervention to be used in both groups:** olfactory training twice a day
Outcomes	**Outcomes of interest in the review** **Primary outcomes:** Recovery of sense of smell

COVIDORL (NCT04361474) *(Continued)*

- Self-reported by the participants, as a response to the question "Have you fully recovered the olfactory capacities that you had before the onset of the symptoms of COVID-19?"

Disease-related quality of life

- Not reported

Serious adverse effects

- Protocol states "evaluate the tolerance of budesonide" with a description of serious adverse events

Secondary outcomes:

Change in sense of smell

- Percentage of patients who show an improvement in sense of smell of more than 2 points on the ODORATEST score. From the protocol: ODORATEST overall score, and detection and identification subscores at 30 days.
- Measured after 30 days of treatment

Overall, generic quality of life

- Not reported

Prevalence of parosmia

- Not reported

Other adverse effects (including nosebleeds/bloody discharge)

- Protocol states "evaluate the tolerance of budesonide" with a description of serious adverse events

Other outcomes reported by the study:

- Olfactory and gustatory capacities of the patients using a self-assessment questionnaire
- Presence of inflammatory filling of the olfactory cleft on MRI or the presence of neurological damage to the olfactory bulb

Starting date	18 May 2020
Contact information	Mary Daval Email: mdaval@for.paris
Notes	Estimated study completion date: 25 May 2021 Trial registered in France. A further extension study is planned for those who have not fully recovered by day 30, including additional budesonide for 30 days for those in the intervention arm, and starting budesonide for those in the placebo arm.

IRCT20200522047542N1

Study name	Effect of inhaled corticosteroids in the treatment of anosmia in patients with COVID-19
Methods	Parallel-group randomised controlled trial

IRCT20200522047542N1 *(Continued)*

Participants	Individuals with COVID-19, confirmed by RT-PCR testing or COVID-19 IgG/IgM Rapid Test Cassette who had persistent (more than 30 days) olfactory dysfunction **Inclusion criteria:** • Aged 18 to 65 years • Patients with COVID-19 who have been referred or admitted to Qaem, Imam Reza or Shariati Hospital diagnosed with a protocol defined by the World Health Organization • Confirmed COVID-19 cases by positive RT-PCR or the COVID-19 IgG/IgM Rapid Test Cassette • Have not experienced any signs of reduced sense of smell and taste for at least 2 weeks before the onset of the first manifestation of COVID-19 • Diagnosed with hyposmia or anosmia (persisting for more than 30 days) **Exclusion criteria:** • People with certain underlying conditions, such as: Parkinson's, Alzheimer's, severe nutritional disorders, acute rhinitis, acute catarrhal sinusitis, SICA syndrome (especially after radiation), nasal mucosal congestion, for example after rhinoplasty, olfactory nerve damage in trauma, etc. • People who experienced other viral and bacterial infections simultaneously with COVID-19 • History of asthma and allergies • Refusal to participate in follow-up, provide data or withdrew consent **Planned sample size:** estimated enrolment 70 participants
Interventions	**Intervention:** • Intranasal corticosteroid spray (0.05% mometasone), one puff twice daily in each nostril for 4 weeks **Comparator:** • Intranasal sodium chloride spray (0.65%, Decosalin), one puff twice daily in each nostril for 4 weeks
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** Recovery of sense of smell • Not reported Disease-related quality of life • Not reported Serious adverse effects • Not reported **Secondary outcomes:** Change in sense of smell • Assessed with a 10-point VAS (0 = worst, 10 = best) • Measured at day 7, 14 and 30 after treatment Overall, generic quality of life • Not reported Prevalence of parosmia

IRCT20200522047542N1 *(Continued)*

	• Not reported Other adverse effects (including nosebleeds/bloody discharge) • Not reported **Other outcomes reported by the study:** • None reported
Starting date	18 July 2020
Contact information	Dr Masoomeh Hosseinpoor Email: drmh2018@gmail.com
Notes	Trial registered in Iran Estimated recruitment end date: 18 September 2020

NCT04495816

Study name	Randomised control trial of omega-3 fatty acid supplementation for the treatment of COVID-19 related olfactory dysfunction
Methods	Parallel-group randomised controlled trial
Participants	Adults with self-reported new onset olfactory dysfunction and COVID-19 infection **Inclusion criteria:** • Adults (18 years of age or older) with self-reported new onset olfactory dysfunction • Positive COVID-19 diagnosis **Exclusion criteria:** • Patients who are less than 18 years of age • Patients without a positive COVID-19 PCR result, obtained through nasopharyngeal swab • Patients with COVID-19 diagnosis, but without self-reported anosmia • Patients with severe COVID-19 disease, as defined by the Mount Sinai Health System (requiring high flow nasal cannula, nonrebreather, CPAP/BiPAP, mechanical ventilation, pressor medication or evidence of end-organ damage) • Pre-existing self-reported olfactory dysfunction • History of chronic nasal/sinus infections (rhinosinusitis) or history of endoscopic sinus surgery • Use of nasal steroid sprays or irrigations for any reason • Prisoners of the state • Presence of psychiatric or developmental conditions that may impair the ability to provide informed consent • Allergy to fish or omega-3 supplements, or do not eat fish/fish-containing substances for any reason **Planned sample size:** estimated enrolment 126 participants (from clinical trial register). Additional publication states estimated sample size of 176 (88 per group)
Interventions	**Intervention:** omega-3 fatty acid, 1000 mg (administered as 2 soft gels, containing 683 mg eicosapentaenoic acid and 252 mg docosahexaenoic acid) twice daily for 6 weeks **Comparator:** placebo (administered as 2 placebo soft gels) twice daily for 6 weeks

NCT04495816 *(Continued)*

Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** Recovery of sense of smell • Not reported Disease-related quality of life • Assessed with the mQOD-NS. This is a 17-item instrument: each item is graded 0 to 3, with a total score range of 0 to 51. Higher scores indicate better olfactory-specific quality of life. • Measured at 1 week, 2 weeks, 4 weeks and 6 weeks after initiation of treatment. Serious adverse effects • Not reported **Secondary outcomes:** Change in sense of smell • Assessed with the BSIT (psychophysical testing). This is a 12-item instrument, with a total score range of 0 to 12. Higher scores indicate better olfactory performance. • Measured at 6 weeks after initiation of treatment Overall, generic quality of life • Not reported Prevalence of parosmia • Not reported Other adverse effects (including nosebleeds/bloody discharge) • Not reported **Other outcomes reported by the study:** • SNOT-22. This is a 22-item instrument, with a total range of 0 to 110. Higher scores indicate more severe quality of life impact. It was designed to address the burden of symptoms of chronic rhinosinusitis, rather than anosmia or hyposmia. It will be measured at 1, 2, 4 and 6 weeks after initiation of treatment.
Starting date	15 July 2020
Contact information	Alfred-Marc Iloreta Email: alfred-marc.iloreta@mountsinai.org
Notes	Estimated study completion date: June 2021 It is unclear from the description of this trial whether participants will have symptoms of olfactory disturbance for longer than 4 weeks from the onset of COVID-19. Correspondence with the study team has confirmed that they will recruit a mixed population, comprising individuals with fewer than and longer than 4 weeks of symptoms.

NCT04528329

Study name	Anosmia and/or ageusia and early corticosteroid use

NCT04528329 *(Continued)*

Methods	Randomised controlled trial
Participants	Adult participants with mild to moderate severity COVID-19 **Inclusion** • Diagnosis of COVID-19 • ≥ 18 years of age • Mild to moderate severity **Exclusion** • Diabetes • Contraindication to dexamethasone • Mental disability **Planned sample size:** 300 participants
Interventions	**Intervention:** "Early dexamethasone use as early as confirmation of inflammation" **Comparator:** "Late dexamethasone use as soon as deterioration"
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** Recovery of sense of smell • Time to recovery from anosmia (no further details provided) Disease-related quality of life • Not reported Serious adverse effects • Not reported **Secondary outcomes:** Change in sense of smell • Not reported Overall, generic quality of life • Not reported Prevalence of parosmia • Not reported Other adverse effects (including nosebleeds/bloody discharge) • Not reported **Other outcomes reported by the study:** • None reported
Starting date	30 August 2020
Contact information	Emad R Issak

NCT04528329 *(Continued)*

	Email: dr.emad.r.h.issak@gmail.com
Notes	Estimated study completion date: 15 December 2020 Trial registered in Egypt **Uncertainty over future inclusion in the review:** It is not clear from the description provided whether participants will all have olfactory dysfunction at baseline and, if so, whether they will have ≥ 4 weeks of olfactory dysfunction. We are awaiting confirmation from the study authors.

NCT04530409

Study name	Timing of corticosteroids in COVID-19
Methods	Randomised controlled trial
Participants	Adult participants with mild or moderate COVID-19 **Included** • Any case with COVID-19 more than or equal to 18 years • Mild and moderate severity **Excluded** • Any contraindication to steroids • Mental disability **Planned sample size:** 450 patients
Interventions	**Intervention:** "Early dexamethasone use as early as confirmation of inflammation" **Comparator:** "Late dexamethasone use as soon as deterioration"
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** Recovery of sense of smell • Time to recovery from anosmia (no further details provided) Disease-related quality of life • Not reported Serious adverse effects • Not reported **Secondary outcomes:** Change in sense of smell • Not reported Overall, generic quality of life • Not reported

NCT04530409 *(Continued)*

	Prevalence of parosmia • Not reported Other adverse effects (including nosebleeds/bloody discharge) • Not reported **Other outcomes reported by the study:** **Primary outcomes:** • Percentage of cases that will need hospitalisation • Percentage of cases that deteriorate to acute respiratory distress syndrome **Secondary outcomes:** • Percentage of cases with increased d-dimer • Time to recovery of diarrhoea • Percentage reduction in CRP • Percentage reduction in LDH • Percentage reduction in ALT • Percentage reduction in ferritin • Time to recovery of lymphopenia • Time to recovery of cough • Time to recovery of fever • Time to recovery of myalgia • Time to recovery of dyspnoea
Starting date	26 August 2020
Contact information	Emad R Issak Email: dr.emad.r.h.issak@gmail.com
Notes	Estimated study completion date: 1 December 2020 Trial registered in Egypt **Uncertainty over future inclusion in the review:** It is not clear from the description provided whether participants will all have olfactory dysfunction at baseline and, if so, whether they will have ≥ 4 weeks of olfactory dysfunction.

NCT04638673

Study name	NeuroCovid rehab and recovery related to COVID-19 diagnosis
Methods	To evaluate a transcutaneous auricular vagus nerve stimulation (taVNS) in the treatment of the neurological symptoms of COVID-19 termed NEUROCOVID
Participants	Patients with COVID-19 suffering from the neurological symptoms associated with infection **Inclusion criteria:** • COVID-positive • At home • Afebrile • Anxiety

NCT04638673 *(Continued)*

- Depression
- Vertigo
- Anosmia
- Headaches
- Irritability
- Cognitive processing

Exclusion criteria:

- Damage to left ear anatomy
- Unstable haemodynamic effects
- Ischaemic or haemorrhagic stroke after developing COVID
- Unable to give consent, follow instructions
- Unable to read or write or speak English
- No access to home WiFi

Planned sample size: estimated enrolment 30 participants

Interventions

Intervention group

Active-Active Stimulation Group

- Participants will receive active taVNS stimulation for weeks 1 to 4 of the stimulation portion of this study using Soterix taVNS model 0125-LTE

Comparator Group

Sham-Active Stimulation Group

- Participants will receive sham taVNS stimulation for weeks 1 and 2 and active stimulation for weeks 3 and 4 of the stimulation portion of this study

Outcomes

Outcomes of interest in the review:

Primary outcomes:

Recovery of sense of smell

- Not reported

Disease-related quality of life

- The primary outcome was change in score of Patient Health Questionnaire-9 from baseline to week 4 (end of treatment)
- The PPHQ-9 is a 9-question instrument given to patients in a primary care setting to screen for the presence and severity of depression. Scores range from 0 to 27. Higher scores mean worse symptoms. For the purpose of this study:
  - remission: minimal to absence of symptoms; PHQ-9 score < 5;
  - response: 50% or greater decrease in PHQ-9 baseline severity; residual symptoms remain;
  - partial response: 26% to 49% decrease in PHQ-9 baseline severity;
  - non-response: less than 25% decrease in PHQ-9 baseline severity.

Serious adverse effects

- Not reported

Secondary outcomes:

Change in sense of smell

- Not reported

NCT04638673 *(Continued)*

	Overall, generic quality of life • Not reported Prevalence of parosmia • Not reported Other adverse effects (including nosebleeds/bloody discharge) • Not reported **Other outcomes reported by the study:** • None reported
Starting date	19 November 2020
Contact information	Sarah Huffman Email: huffmans@musc.edu Morgan Dancy Email: maddoxm@musc.edu
Notes	Estimated study completion date: June 2021 Trial registered in USA **Uncertainty over future inclusion in the review:** It is not clear from the description provided whether participants will all have olfactory dysfunction at baseline and, if so, whether they will have had ≥ 4 weeks of olfactory dysfunction. We are awaiting confirmation from the study authors.

NCT04657809

Study name	Clinical assessment of insulin fast dissolving film in treatment of post infection anosmia
Methods	Parallel-group randomised controlled trial
Participants	Adult participants with loss of sense of smell after COVID-19 infection **Inclusion criteria** • Aged 18 to 70 years • Anosmia after COVID-19 infection (no further details provided) **Exclusion criteria** • Nasal polyps • Fracture of the nose < 6 months before enrolment to the trial • Nasal surgery < 6 months before enrolment to the trial **Planned sample size:** estimated enrolment 40 participants
Interventions	**Intervention:** insulin fast-dissolving film containing 100 IU of insulin applied intranasally 3 times a week for 4 weeks **Comparator:** formulated bio-adhesive fast-dissolving film containing no drugs applied intranasally 3 times a week for 4 weeks

NCT04657809 *(Continued)*

Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** Recovery of sense of smell • Not reported Disease-related quality of life • Not reported Serious adverse effects • Not reported **Secondary outcomes:** Change in sense of smell • Improvement in sense of smell as measured with the butanol threshold test. This test establishes smell threshold through identification of an odour (butyl alcohol) versus water. The detection threshold is recorded as the concentration at which the patient correctly identifies the butanol on 5 consecutive trials. The scoring relates the patient's threshold to a normal subject population. • Measured at 4 weeks Overall, generic quality of life • Not reported Prevalence of parosmia • Not reported Other adverse effects (including nosebleeds/bloody discharge) • Not reported **Other outcomes reported by the study:** • No additional outcomes are reported
Starting date	1 December 2020
Contact information	Soad Ali; no contact details provided
Notes	Estimated study completion date: 15 January 2021 Trial registered in Egypt It is unclear from the description of this trial whether participants will have symptoms of olfactory disturbance for longer than 4 weeks from the onset of COVID-19.

Odorat-Covid (NCT04598763)

Study name	Evaluation of two methods of olfactory rehabilitation in post-viral loss of smell: classic and intensive (Odorat-Covid)
Methods	Parallel-group randomised controlled trial

Odorat-Covid (NCT04598763) *(Continued)*

Participants	Individuals presenting to the otolaryngology clinic with > 5 weeks (and less than 12 months) of acute olfactory dysfunction linked to a viral infection (including SARS-CoV-2) **Inclusion criteria:** • 18 years and older • Sudden loss of smell for > 5 weeks, linked to a viral infection (including SARS-CoV-2) of the upper respiratory tract • Willing to undertake olfactory rehabilitation • Confirmed hyposmia/anosmia, as assessed by the Sniffin' Sticks kit • Affiliated to/beneficiary of a social security scheme • Informed consent **Exclusion criteria:** • Persons referred to in Articles L. 1121-5 to L. 1121-8 and L1122-2 of the Public Health Code: pregnant woman, parturient or nursing mother, persons deprived of liberty by a judicial or administrative decision, persons undergoing psychiatric treatment under Articles L.3212-1 and L.3213-1 of the Public Health Code Minor (non-emancipated), adult person subject to a legal protection measure (guardianship, curatorship, safeguard of justice), adult person unable to express consent and who is not the subject of a legal protection measure. • Qualitative smell disorder (cacosmia, hyperosmia, phantosmia, parosmia) • Neurological, post-traumatic, neurodegenerative, congenital odour disorders • Post-infectious loss of smell > 12 months **Planned sample size:** 80 participants
Interventions	**Intervention:** The "intensive" group receiving olfactory rehabilitation using 8 scents (rose, eucalyptus, lemon, cloves, strawberries, cut grass, lavender, spruce). Regardless of the randomisation group, the patient will smell each odour for 10 seconds with a 10-second interval between odours. The patient will carry out olfactory rehabilitation at home twice a day (morning and evening) for 32 weeks (i.e. 448 sessions). Each training will be recorded by the patient in their olfactory rehabilitation agenda. **Comparator:** The "classic" group receives classic olfactory rehabilitation using 4 scents most used in the literature (rose, eucalyptus, lemon, clove) Regardless of the randomisation group, the patient will smell each odour for 10 seconds with a 10-second interval between odours. The patient will carry out olfactory rehabilitation at home twice a day (morning and evening) for 32 weeks (i.e. 448 sessions). Each training will be recorded by the patient in their olfactory rehabilitation agenda.
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** Recovery of sense of smell • Self-assessment by participants using a VAS of smell with score 0 (no smell) to 10 (normal smell) • Psychophysical testing using Sniffin Sticks score to classify patients with normosmia, hyposmia and functional anosmia • Both assessed at 8 months Disease-related quality of life

Odorat-Covid (NCT04598763) *(Continued)*	• Self-assessment using the Dynachron-olfaction questionnaire (assesses 6 domains related to chronic nasal dysfunction, including quality of life aspects) Serious adverse effects • Not reported **Secondary outcomes:** Change in sense of smell • Improvement in smell based on the comparison of the results of the olfactory assessment before/after rehabilitation assessed with: Psychophysical testing (Sniffin' Sticks) Threshold Test Score and Actual Identification Test Score. TI score: sum of the individual scores of the threshold and identification measures (TI score varying from 0 to 32). It is used to classify patients in terms of normosmia, hyposmia and functional anosmia based on normative values of "Sniffin' Sticks" (according to the age and sex of each subject) with the threshold at the tenth percentile. Self-assessment by patients using a digital scale of smell, from 0 (no smell) to 10 (normal smell). Overall, generic quality of life • Not reported Prevalence of parosmia • Not reported Other adverse effects (including nosebleeds/bloody discharge) • Not reported **Other outcomes reported by the study:** • No additional outcomes reported
Starting date	1 July 2020
Contact information	Julie Lecomte Email: ju.lecomte@chru-nancy.fr Duc Trung Nguyen Email: dt.nguyen@chru-nancy.fr
Notes	Trial registered in France Estimated study completion: 1 January 2021

ALT: alanine transaminase; BiPAP: bilevel positive airway pressure; BSIT: Brief Smell Identification Test; CPAP: continuous positive airway pressure; CRP: c-reactive protein; LDH: lactate dehydrogenase; MRI: magnetic resonance imaging; mQOD-NS: Modified Brief Questionnaire of Olfactory Dysfunction; RT-PCR: real time polymerase chain reaction; SNOT-22: Sinonasal Outcomes Test; VAS: visual analogue scale

DATA AND ANALYSES

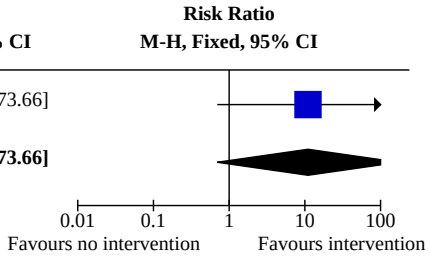
Comparison 1. Systemic corticosteroids plus intranasal steroid/mucolytic/decongestant versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Recovery of sense of smell at 1 to 3 months, as assessed by psychophysical testing	1	18	Risk Ratio (M-H, Fixed, 95% CI)	11.00 [0.70, 173.66]

Analysis 1.1. Comparison 1: Systemic corticosteroids plus intranasal steroid/mucolytic/decongestant versus no intervention, Outcome 1: Recovery of sense of smell at 1 to 3 months, as assessed by psychophysical testing

Study or Subgroup	Intervention Events	Intervention Total	No intervention Events	No intervention Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vaira 2020	5	9	0	9	100.0%	11.00 [0.70 , 173.66]
Total (95% CI)		**9**		**9**	**100.0%**	**11.00 [0.70 , 173.66]**
Total events:	5		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.70 (P = 0.09)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategies

CENTRAL (CRS)

1 (("2019 nCoV" or 2019nCoV or "COVID 19" or COVID19 or "new coronavirus" or "novel coronavirus" or "novel corona virus" or "SARS CoV-2" or SARS-CoV2 or SARSCoV2 or "2019-novel CoV" or ncov19 or ncov-19 or nCov 2019 or COVID-19 or SARSCoV-2 or SARS-CoV-2)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET

2 ((Wuhan and (coronavirus or "corona virus"))):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET

3 (((coronavirus or "corona virus" or COVID) adj3 "2019")):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET

4 ((wuhan adj2 (disease or virus))):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET

5 ((coronavirus or "corona virus" or COVID)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET

6 (2020 or 2021):YR AND CENTRAL:TARGET

7 #5 AND #6 AND CENTRAL:TARGET

8 #1 OR #2 OR #3 OR #4 OR #7 AND CENTRAL:TARGET

9 MESH DESCRIPTOR Olfaction Disorders EXPLODE ALL AND CENTRAL:TARGET

10 (Olfaction or olfactory or Dysosmia* or Paraosmia* or Anosmia* or hyposmia* or phantosmia* or Cacosmia* or microsmia*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET

11 (smell* adj6 (disorder* or loss or distort* or alter* or dsyfunction or impair* or abscen* or reduce* or different* or sensation* or abnormal* or perception* or change* or expected or decreas* or deficit*)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET

12 (smell* adj6 (prevent* or rehab* or recover* or therap* or train* or retrain*)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET

13 #9 OR #10 OR #11 OR #12 AND CENTRAL:TARGET

14 #13 AND #8 AND CENTRAL:TARGET

MEDLINE (Ovid)

1 ("2019 nCoV" or 2019nCoV or "COVID 19" or COVID19 or "new coronavirus" or "novel coronavirus" or "novel corona virus" or "SARS CoV-2" or SARS-CoV2 or SARSCoV2 or "2019-novel CoV" or ncov19 or ncov-19 or nCov 2019 or COVID-19 or SARSCoV-2 or SARS-CoV-2).ab,ti.

2 (Wuhan and (coronavirus or "corona virus")).ab,ti.

3 (coronavirus or "corona virus" or COVID) adj3 "2019").ab,ti.

4 (wuhan adj2 (disease or virus)).ab,ti.

5 ("LAMP assay" or "COVID-19" or "COVID-19 drug treatment" or "COVID-19 diagnostic testing" or "COVID-19 serotherapy" or "COVID-19 vaccine" or "severe acute respiratory syndrome coronavirus 2" or "spike protein, SARS-CoV-2").os.

6 (coronavirus or "corona virus" or COVID).ab,ti.

7 limit 6 to yr="2020 -Current"

8 1 or 2 or 3 or 4 or 5 or 7

9 exp olfaction disorders/

10 (Olfaction or olfactory or Dysosmia* or Paraosmia* or Anosmia* or hyposmia* or phantosmia* or Cacosmia* or microsmia*).ab,ti.

11 (smell* adj6 (disorder* or loss or distort* or alter* or dsyfunction or impair* or abscen* or reduce* or different* or sensation* or abnormal* or perception* or change* or expected or decreas* or deficit*)).ab,ti.

12 (smell* adj6 (prevent* or rehab* or recover* or therap* or train* or retrain*)).ab,ti.

13 9 or 10 or 11 or 12

14 8 and 13

15 randomized controlled trial.pt.

16 controlled clinical trial.pt.

17 randomized.ab.

18 placebo.ab.

19 drug therapy.fs.

20 randomly.ab.

21 trial.ab.

22 groups.ab.

23 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

24 exp animals/ not humans.sh.

25 23 not 24

26 14 and 25

Cochrane COVID-19 Study Register (CRS)

1 MESH DESCRIPTOR Olfaction Disorders EXPLODE ALL AND COVID19:INREGISTER

2 (Olfaction or olfactory or Dysosmia* or Paraosmia* or Anosmia* or hyposmia* or phantosmia* or Cacosmia* or microsmia*) AND COVID19:INREGISTER

3 (smell* adj6 (disorder* or loss or distort* or alter* or dsyfunction or impair* or abscen* or reduce* or different* or sensation* or abnormal* or perception* or change* or expected or decreas* or deficit*)) AND COVID19:INREGISTER

4 (smell* adj6 (prevent* or rehab* or recover* or therap* or train* or retrain*)) AND COVID19:INREGISTER

5 #1 OR #2 OR #3 OR #4

6 (interventional):SY AND COVID19:INREGISTER

7 #6 AND #5

Cochrane ENT Register (CRS)

1 (("2019 nCoV" or 2019nCoV or "COVID 19" or COVID19 or "new coronavirus" or "novel coronavirus" or "novel corona virus" or "SARS CoV-2" or SARS-CoV2 or SARSCoV2 or "2019-novel CoV" or ncov19 or ncov-19 or nCov 2019 or COVID-19 or SARSCoV-2 or SARS-CoV-2)):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER

2 ((Wuhan and (coronavirus or "corona virus"))):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER

3 (((coronavirus or "corona virus" or COVID) adj3 "2019")):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER

4 ((wuhan adj2 (disease or virus))):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER

5 ((coronavirus or "corona virus" or COVID)):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER

6 (2020 or 2021):YR AND INREGISTER

7 #5 AND #6 AND INREGISTER

8 #1 OR #2 OR #3 OR #4 OR #7 AND INREGISTER

9 MESH DESCRIPTOR Olfaction Disorders EXPLODE ALL AND INREGISTER

10 (Olfaction or olfactory or Dysosmia* or Paraosmia* or Anosmia* or hyposmia* or phantosmia* or Cacosmia* or microsmia*):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER

11 (smell* adj6 (disorder* or loss or distort* or alter* or dsyfunction or impair* or abscen* or reduce* or different* or sensation* or abnormal* or perception* or change* or expected or decreas* or deficit*)):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER

12 (smell* adj6 (prevent* or rehab* or recover* or therap* or train* or retrain*)):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER

13 #9 OR #10 OR #11 OR #12 AND INREGISTER

14 #13 AND #8 AND INREGISTER

Embase (Ovid)

1 ("2019 nCoV" or 2019nCoV or "COVID 19" or COVID19 or "new coronavirus" or "novel coronavirus" or "novel corona virus" or "SARS CoV-2" or SARS-CoV2 or SARSCoV2 or "2019-novel CoV" or ncov19 or ncov-19 or nCov 2019 or COVID-19 or SARSCoV-2 or SARS-CoV-2).ab,ti.

2 (Wuhan and (coronavirus or "corona virus")).ab,ti.

3 ((coronavirus or "corona virus" or COVID) adj3 "2019").ab,ti.

4 (wuhan adj2 (disease or virus)).ab,ti.

5 (coronavirus or "corona virus" or COVID).ab,ti.

6 limit 5 to yr="2020 -Current"

7 1 or 2 or 3 or 4 or 6

8 exp smelling disorder/

9 (Olfaction or olfactory or Dysosmia* or Paraosmia* or Anosmia* or hyposmia* or phantosmia* or Cacosmia* or microsmia*).ab,ti.

10 (smell* adj6 (disorder* or loss or distort* or alter* or dsyfunction or impair* or abscen* or reduce* or different* or sensation* or abnormal* or perception* or change* or expected or decreas* or deficit*)).ab,ti.

11 (smell* adj6 (prevent* or rehab* or recover* or therap* or train* or retrain*)).ab,ti.

12 8 or 9 or 10 or 11

13 7 and 12

14 Randomized controlled trial/

15 Controlled clinical study/

16 Random$.ti,ab.

17 randomization/

18 intermethod comparison/

19 placebo.ti,ab.

20 (compare or compared or comparison).ti.

21 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.

22 (open adj label).ti,ab.

23 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

24 double blind procedure/

25 parallel group$1.ti,ab.

26 (crossover or cross over).ti,ab.

27 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant $1)).ti,ab.

28 (assigned or allocated).ti,ab.

29 (controlled adj7 (study or design or trial)).ti,ab.

30 (volunteer or volunteers).ti,ab.

31 human experiment/

32 trial.ti.

33 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32

34 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab.

35 comparative study/ or controlled study/

36 randomi?ed controlled.ti,ab.

37 randomly assigned.ti,ab.

38 35 or 36 or 37

39 34 not 38

40 Cross-sectional study/

41 randomized controlled trial/ or controlled clinical study/ or controlled study/

42 (randomi?ed controlled or control group$1).ti,ab.

43 41 or 42

44 40 not 43

45 (((case adj control$) and random$) not randomi?ed controlled).ti,ab.

46 (Systematic review not (trial or study)).ti.

47 (nonrandom$ not random$).ti,ab.

48 "Random field$".ti,ab.

49 (random cluster adj3 sampl$).ti,ab.

50 (review.ab. and review.pt.) not trial.ti.

51 "we searched".ab.

52 review.ti. or review.pt.

53 51 and 52

54 "update review".ab.

55 (databases adj4 searched).ab.

56 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

57 39 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 53 or 54 or 55

58 33 not 57

59 13 and 58

Web of Science (Web of Knowledge)

#1 TS=("2019 nCoV" or 2019nCoV or "COVID 19" or COVID19 or "new coronavirus" or "novel coronavirus" or "novel corona virus" or "SARS CoV-2" or SARS-CoV2 or SARSCoV2 or "2019-novel CoV" or ncov19 or ncov-19 or nCov 2019 or COVID-19 or SARSCoV-2 or SARS-CoV-2)

#2 TS=(Wuhan and (coronavirus or "corona virus"))

#3 TS=(((coronavirus or "corona virus" or COVID) NEAR/3 "2019"))

#4 TOPIC: (wuhan NEAR/2 (disease or virus))

#5 TS=(coronavirus or "corona virus" or COVID)

#6 #5 OR #4 OR #3 OR #2 OR #1

#7 TS=(Olfaction or olfactory or Dysosmia* or Paraosmia* or Anosmia* or hyposmia* or phantosmia* or Cacosmia* or microsmia*)

#8 TS=(smell* NEAR/6 (disorder* or loss or distort* or alter* or dsyfunction or impair* or abscen* or reduce* or different* or sensation* or abnormal* or perception* or change* or expected or decreas* or deficit*))

#9 TS=(smell* NEAR/6 (prevent* or rehab* or recover* or therap* or train* or retrain*))

#10 #9 OR #8 OR #7

#11 #10 AND #6

#12 TS=((randomised OR randomized OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)) OR (blind* AND (single OR double OR treble OR triple))))

#13 #12 AND #11

World Health Organization (WHO) COVID-19 'Global literature on coronavirus disease'

(ti:(olfaction OR olfactory OR dysosmia* OR paraosmia* OR anosmia* OR hyposmia* OR phantosmia* OR cacosmia* OR microsmia* OR smell*)) OR (mh:(olfato OR l'olfaction OR cacosmia OR paraosmia OR anosmia))

Trial Registry Records (CENTRAL via CRS)

1 (("2019 nCoV" or 2019nCoV or "COVID 19" or COVID19 or "new coronavirus" or "novel coronavirus" or "novel corona virus" or "SARS CoV-2" or SARS-CoV2 or SARSCoV2 or "2019-novel CoV" or ncov19 or ncov-19 or nCov 2019 or COVID-19 or SARSCoV-2 or SARS-CoV-2)) AND CENTRAL:TARGET

2 ((Wuhan and (coronavirus or "corona virus"))) AND CENTRAL:TARGET

3 (((coronavirus or "corona virus" or COVID) adj3 "2019")) AND CENTRAL:TARGET

4 ((wuhan adj2 (disease or virus))) AND CENTRAL:TARGET

5 (coronavirus or "corona virus" or COVID) AND CENTRAL:TARGET

6 (2020 or 2021):YR AND CENTRAL:TARGET

7 #5 AND #6

8 #1 OR #2 OR #3 OR #4 OR #7

9 (Olfaction or olfactory or Dysosmia* or Paraosmia* or Anosmia* or hyposmia* or phantosmia* or Cacosmia* or microsmia* or smell*) AND CENTRAL:TARGET

10 #8 AND #9

11 http*:SO AND CENTRAL:TARGET

12 (NCT0* or ACTRN* or ChiCTR* or DRKS* or EUCTR* or eudract* or IRCT* or ISRCTN* or JapicCTI* or JPRN* or NTR0* or NTR1* or NTR2* or NTR3* or NTR4* or NTR5* or NTR6* or NTR7* or NTR8* or NTR9* or SRCTN* or UMIN0*):AU AND CENTRAL:TARGET

13 #11 OR #12

14 #10 AND #13

ICTRP (WHO Portal)

covid* AND anomsia OR covid* AND smell OR covid* AND olfact* OR coronavirus AND anomsia OR coronavirus AND smell OR coronavirus AND olfact* OR SARS-CoV* AND anomsia OR SARS-CoV* AND smell OR SARS-CoV* AND olfact*

ClinicalTrials.gov

(COVID-19 OR 2019-nCoV OR SARS-CoV-2 OR 2019 novel coronavirus OR severe acute respiratory syndrome coronavirus 2 OR Wuhan coronavirus OR coronavirus) AND (anosmia OR smell OR Olfaction or olfactory)

AND Interventional

WHAT'S NEW

Date	Event	Description
27 August 2021	Amended	This is a living systematic review: searches are run and screened monthly. The last search date was 17 August 2021. We are in the process of incorporating data from the following newly published study: D'Ascanio 2021. We have also identified 12 new ongoing studies: IRCT20210205050247N; IRCT20210311050671N1; NCT04764981; NCT04797936; NCT04900415; NCT04951362; NCT04952389; NCT04959747; NCT04964414; SCENT2 (NCT04789499); UMIN000043537; VOLT (NCT04710394).

HISTORY

Protocol first published: Issue 2, 2021
Review first published: Issue 7, 2021

Date	Event	Description
16 August 2021	Amended	This is a living systematic review: searches are run and screened monthly. The last search date was 22 July 2021. We are in the process of incorporating data from the following newly published study: D'Ascanio 2021. We also identified 12 new ongoing studies: IRCT20210205050247N; IRCT20210311050671N1; NCT04764981; NCT04797936; NCT04900415; NCT04951362; NCT04952389; NCT04959747; NCT04964414; SCENT2 (NCT04789499); UMIN000043537; VOLT (NCT04710394).

CONTRIBUTIONS OF AUTHORS

Lisa O'Byrne: sifted studies, carried out data extraction and risk of bias assessment, performed analyses and GRADE assessment for included studies, drafted and revised the review.

Katie Webster: scoped, designed and drafted the protocol with the help of the other authors. Sifted studies, carried out data extraction, risk of bias and GRADE assessment.

Samuel MacKeith: clinical guidance at all stages of project scoping and protocol development; commented on and edited the draft review, and agreed the final version.

Carl Philpott: clinical guidance at all stages of project scoping and protocol development; commented on and edited the draft review, and agreed the final version.

Claire Hopkins: clinical guidance at all stages of project scoping and protocol development; commented on and edited the draft review, and agreed the final version.

Martin Burton: clinical guidance at all stages of project scoping and protocol development; commented on and edited the draft review, and agreed the final version.

DECLARATIONS OF INTEREST

Lisa O' Byrne: none known.

Katie Webster: none known.

Samuel MacKeith: Sam MacKeith is Assistant Co-ordinating Editor of Cochrane ENT, but had no role in the editorial process for this review.

Carl Philpott: Professor Carl Philpott sees and treats patients with COVID-19 related smell loss. He has written various online publications on the topic and conducted interviews and webinars internationally. He is a Trustee for the charity Fifth Sense. He is the senior author on the Clinical Olfactory Working Group consensus document on the management of post-infectious olfactory dysfunction and the consensus document on the use of systemic corticosteroids in COVID-19 related olfactory dysfunction.

Claire Hopkins: Professor Claire Hopkins sees and treats patients with COVID-19 related smell loss. She has spoken on the association between COVID and smell loss in multiple media outlets. She is senior author of the British Rhinological Society position paper on management of COVID-19 related smell loss.

Martin Burton: Professor Martin Burton is Co-ordinating Editor of Cochrane ENT, but had no role in the editorial process for this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK

  Infrastructure funding for Cochrane ENT

- National Institute for Health Research (NIHR) COVID-19: Recovery and Learning programme, UK

  Award NIHR132103

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

When preparing the protocol for this review we intended to present the following outcomes in the summary of findings table:

- recovery of sense of smell (as reported by the participants);
- disease-related quality of life, as assessed by the Olfactory Disorders Questionnaire (or another validated questionnaire);
- serious adverse effects;
- change in sense of smell (as identified by psychophysical testing);
- overall, generic quality of life, as assessed by validated methods (e.g. EQ-5D);
- presence of parosmia;
- other adverse effects (including nosebleeds/bloody discharge).

No participant-reported data were available for the outcome "Recovery of sense of smell". However, we did find data for this outcome that had been identified by psychophysical testing, therefore these data were included in the summary of findings table.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Ambroxol [administration & dosage]; Betamethasone [administration & dosage]; Bias; COVID-19 [*complications]; Expectorants [*administration & dosage]; Glucocorticoids [*administration & dosage]; Nasal Decongestants [*administration & dosage]; Nasal Lavage [methods]; Olfaction Disorders [*drug therapy] [etiology]; Prednisone [administration & dosage]; Prevalence; Quality of Life; Recovery of Function; Smell [drug effects]; Time Factors

MeSH check words

Humans