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

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[Intervention Review]

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

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ABSTRACT

Background

Loss of olfactory function is well recognised as a cardinal symptom of COVID-19 infection, and the ongoing pandemic has resulted in a large number of affected individuals with abnormalities in their sense of smell. For many, the condition is temporary and resolves within two to four weeks. However, in a significant minority the symptoms persist. At present, it is not known whether early intervention with any form of treatment (such as medication or olfactory training) can promote recovery and prevent persisting olfactory disturbance.

Objectives

To assess the effects (benefits and harms) of interventions that have been used, or proposed, to prevent 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CENTRAL; Ovid MEDLINE; Ovid Embase; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished studies.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. Individuals who had symptoms for less than 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. Our primary outcomes were the presence of normal olfactory function, serious adverse effects and change in sense of smell. Secondary outcomes were the prevalence of parosmia, change in sense of taste, disease-related quality of life 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 of 100 participants, which compared an intranasal steroid spray to no intervention. Participants in both groups were also advised to undertake olfactory training for the duration of the trial. Data were identified for only two of the prespecified outcomes for this review, and no data were available for the primary outcome of serious adverse effects.

Intranasal corticosteroids compared to no intervention (all using olfactory training)

Presence of normal olfactory function after three weeks of treatment was self-assessed by the participants, using a visual analogue scale (range 0 to 10, higher scores = better). A score of 10 represented "completely normal smell sensation". The evidence is very uncertain about the effect of intranasal corticosteroids on self-rated recovery of sense of smell (estimated absolute effect 619 per 1000 compared to 520 per 1000, risk ratio (RR) 1.19, 95% confidence interval (CI) 0.85 to 1.68; 1 study; 100 participants; very low-certainty evidence).

Change in sense of smell was not reported, but the self-rated score for sense of smell was reported at the endpoint of the study with the same visual analogue scale (after three weeks of treatment). The median scores at endpoint were 10 (interquartile range (IQR) 9 to 10) for the group receiving intranasal corticosteroids, and 10 (IQR 5 to 10) for the group receiving no intervention (1 study; 100 participants; very low-certainty evidence).

Authors' conclusions

There is very limited evidence regarding the efficacy of different interventions at preventing persistent olfactory dysfunction following COVID-19 infection. However, we have identified a small number of additional ongoing studies in this area. As this is a living systematic review, the evidence will be updated regularly to incorporate new data from these, and other relevant studies, as they become available.

For this (first) version of the living review, we identified a single study of intranasal corticosteroids to include in this review, which provided data for only two of our prespecified outcomes. The evidence was of very low certainty, therefore we were unable to determine whether intranasal corticosteroids may have a beneficial or harmful effect.

P L A I N   L A N G U A G E   S U M M A R Y

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

Why this is important

COVID-19 has been found to cause problems with the sense of smell. Sometimes this is a reduction in the ability to smell things, and sometimes it is a complete loss of the sense of smell. For many people this recovers in a short time, but for others it may last for weeks or months. This review considers whether there are treatments that people might take as soon as they have lost their sense of smell (within four weeks of the symptoms starting), to try and stop this becoming a long-standing problem.

How we identified and assessed the evidence

We searched for all relevant studies in the medical literature to summarise the results. We also looked at how certain the evidence was, considering things like the size of the studies and how they were carried out. Based on this, we classed the evidence as being of very low, low, moderate or high certainty.

What we found

We only found one study that had been completed. This included 100 people, all of whom had problems with their sense of smell for a short time (less than four weeks) at the start of the study. The study compared people who were treated with a steroid spray that goes into the nose, with people who were given no treatment. All of the people in the study were also recommended to carry out 'olfactory training' – to spend a short time each day practising smelling particular scents, to try and stimulate their sense of smell to return. The researchers followed them for three weeks to see what happened. The findings from this one comparison are presented here:

Intranasal corticosteroids compared to no treatment (all using olfactory training)

We do not know whether a nasal steroid spray is better or worse than no treatment at:

- making people feel that their sense of smell is back to normal after three weeks;
- resulting in a change in the sense of smell after three weeks.

This is because the evidence was of very low certainty.

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

What this means

We do not know whether using a nasal steroid spray has any benefit in preventing longer-term loss of the sense of smell that is related to COVID-19, or whether it causes any harm. We do not have any evidence about other treatments. 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

Summary of findings 1.   Intranasal steroids compared to no intervention for the prevention of persistent post-COVID-19 olfactory dysfunction

Intranasal steroids compared to no intervention for the prevention of persistent post-COVID-19 olfactory dysfunction

Patient or population: adults with olfactory dysfunction for < 4 weeks following COVID-19 infection

Setting: one hospital in Egypt

Intervention: intranasal corticosteroid spray

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 treatment	**Risk with intranasal steroids**				
Self-rated presence of normal olfactory function Assessed with: score of 10 on a visual analogue scale (rated 0 to 10, where 10 = "completely normal smell sensation")[1] Follow-up: ≤ 4 weeks	Study population		RR 1.19 (0.85 to 1.68)	100 (1 RCT)	⊕⊖⊖⊖ **very low** [2,3]	—
	520 per 1000	619 per 1000 (442 to 874)				
Serious adverse effects	No studies reported on this outcome.					
Self-rated change in sense of smell Assessed with: numeric rating scale (0 to 10, higher = better) Follow-up: ≤ 4 weeks	Change in sense of smell was not reported, only endpoint data. One study reported a median sense of smell score of 10 (IQR 9 to 10) in those receiving intranasal steroids and a median score of 10 (IQR 5 to 10) in those who did not receive steroids at 3 weeks' follow-up (P = 0.16).		—	100 (1 RCT)	⊕⊖⊖⊖ **very low** [2,4]	—
Prevalence of parosmia	No studies reported on this outcome.					
Change in sense of taste	No studies reported on this outcome.					
Disease-related quality of life	No studies reported on this outcome.					

Other adverse effects	No studies reported on this outcome.

*__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).

__CI:__ confidence interval; __IQR:__ interquartile range; __RCT:__ randomised controlled trial; __RR:__ risk ratio; __VAS:__ visual analogue scale

__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]We have assumed that individuals who reported a score of 10 on the VAS were included as those who reported "completely normal smell sensation".
[2]Serious risk of bias as this was an unblinded study, and the outcome was self-assessed by the participants.
[3]Very serious imprecision due to the very small sample size, which does not reach the optimal information size (< 400 participants), and the wide confidence intervals, which range from potential harm to potential benefit.
[4]Very serious imprecision due to the very small sample size, which does not reach the optimal information size (< 400 participants), and because no effect size or confidence interval could be calculated.

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 (Gerkin 2020), 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 effect of interventions to prevent or treat persisting olfactory dysfunction following COVID-19. For this review, 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. For the companion review ('Interventions for the treatment of persisting olfactory dysfunction following COVID-19'; Webster 2021a), we considered treatment for individuals who already have persisting olfactory dysfunction at four weeks (or longer) following a diagnosis of COVID-19.

Description of the intervention

As COVID-19 related persisting olfactory dysfunction is a relatively new condition, there are no established interventions that are known to prevent it. However, a number of interventions have been used for other post-viral causes of anosmia. It is possible that early intervention for those with short-lived symptoms could help to prevent the development of persisting, long-term olfactory dysfunction.

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.

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 anticipate 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 systematic 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).

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 (sometimes given intranasally) 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 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 an intervention is small or negligible, then side effects may be such that individuals do not consider it worthwhile. With this review we aimed to comprehensively assess the benefits and harms of interventions to prevent persisting olfactory dysfunction related to COVID-19, 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 numbers of infected individuals worldwide also means that evidence that supports decision-making for 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 is 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 that have been used, or proposed, to prevent 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 were unlikely to be identified. If we identified any cross-over studies, we planned to 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 was 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 in any language. We planned to include outcome data reported on a trial registry, even if no published results were available. However, we did not identify any studies where this was applicable. If we identified material from a pre-print server then we planned to note this in the 'What's New' section of the review, pending identification of fully published data. If no published data were identified within four months of the pre-print article being made available then we planned to incorporate the data in the review. However, we did not identify any pre-print articles during the searches.

Types of participants

We included studies of adult participants (aged 18 years or older) with a diagnosis of COVID-19 and olfactory dysfunction that had lasted less than four weeks. We anticipated that some studies would report this as less than four weeks of olfactory dysfunction, rather than less than four weeks since a positive test for COVID-19 - either of these measures were 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 planned to include data from these trials, providing the majority (≥ 80% of participants) report anosmia or hyposmia.

We included studies where olfactory dysfunction was identified with either psychophysical (objective) testing, or through self-report of symptoms. We planned to investigate whether this had 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 had 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 to specifically prevent persisting olfactory dysfunction. We anticipated that this may include the following interventions:

- Intranasal steroid drops/rinses
- Intranasal steroid sprays
- Systemic steroids
- Olfactory training
- Vitamin A
- Zinc
- Antioxidants (e.g. omega 3 fatty acids, alpha lipoic acid, minocycline)
- Antiviral agents (e.g. remdesivir)
- 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)
- Saline irrigation

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.

Olfactory training was considered to be a complex intervention, as the method of delivery varies considerably in different studies. We planned to assess this using subgroup analyses, 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 trials 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 trials 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. All outcomes were assessed at three possible time points:

- ≤ 4 weeks;
- > 4 weeks to 3 months (this was the main time frame of interest);
- > 3 months to 6 months.

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

Outcomes at less than four weeks following COVID-19 were considered 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 early intervention could help to prevent these problems from developing.

Primary outcomes

- Presence of normal olfactory function:
  * as assessed by the participants (e.g. self-rated complete recovery);
  * as assessed using psychophysical testing, using Sniffin' Sticks, University of Pennsylvania Smell Identification Test (UPSIT) or another validated test.
- Serious adverse effects (as defined by the trialists).
- Change in sense of smell:
  * as assessed by the participants (e.g. using a visual analogue score);
  * as assessed using psychophysical testing, using Sniffin' Sticks, UPSIT or another validated test.

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 self-reported olfactory function only.

Secondary outcomes

- Prevalence of parosmia, as assessed by the participants.
- Change in sense of taste, as assessed by psychophysical gustatory tests, such as the sip and spit method or other validated tests.
- Disease-related quality of life, as assessed by the Olfactory Disorders Questionnaire, or another validated questionnaire (which specifically relates to olfactory dysfunction).
- 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. 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 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 of Studies 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 conducts monthly searches of the sources listed above, except the following which are 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 will 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 if 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 to endeavour to seek help with translation; however, we intended that this should not hold up the rapid review process. 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 we 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 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 will immediately screen 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 (for example, published articles and details from trial registries). Any discrepancies in the data extracted by the two authors were checked against the original reports, and differences were resolved through discussion and consensus. We planned to consult a third author where necessary, but this was not required. 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 were not reported, we planned to extract 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, we planned to extract 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 planned to treat the outcome measure as continuous data. Alternatively, if data were available, we planned to convert these

to binary data. However, we were not able to confirm that the ordinal data we obtained (from a visual analogue scale of sense of smell) was normally distributed, therefore this was not possible.

- For time-to-event data: if we identified data reported as time-to-event, we planned to extract data on hazard ratios from individual studies. If these data were not reported then we planned to extract 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. However, we did not identify any time-to-event data.

We prespecified time points of interest for the outcomes in this review. Where studies reported data at multiple time points, we planned to take the longest available follow-up point within each of the specific time frames. For example, if a study reported an outcome at 6 weeks, 8 weeks and 12 weeks of follow-up then the 12-week data would have been included for the time point > 4 weeks 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 involves 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.

Measures of treatment effect

We summarised the effects of dichotomous outcomes (e.g. prevalence of olfactory dysfunction) 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 to aid understanding. The assumed baseline risk is typically 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 is 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) if different scales have 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).

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 were 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 Chi² test (with a significance level set at P value < 0.10) and the I² 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

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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 are 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 planned to seek 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 planned to assess funnel plots if sufficient studies (more than 10) were available for an outcome. If we observed asymmetry of the funnel plot, we planned to conduct more formal investigation using the methods proposed by Egger 1997. We planned to also report 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 model 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 pool 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 consider 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 would have 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.
- Time elapsed between diagnosis and treatment (< 2 weeks compared to 2 to 4 weeks before commencing treatment):
  * currently, patients are likely to be required to self-isolate for two weeks once diagnosed with COVID-19. Therefore, it would be informative to know whether a delay of two weeks in initiating treatment has an impact on outcomes.

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%) belong to that category.

If trials had 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 anticipate that the varying methods used for olfactory training may be a source of heterogeneity in effects. If we had 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 are 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: fixed-effect versus random-effects model;
- inclusion of studies with concurrent treatments: including and excluding 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 will apply 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:

- presence of normal olfactory function (as reported by the participants);
- serious adverse effects;
- change in sense of smell (as reported by the participants);
- prevalence of parosmia;
- change in sense of taste;
- disease-related quality of life;
- 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

R E S U L T S

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 records at the full-text screening stage.

We excluded 25 records (linked to 23 studies) with reasons recorded in the review (see Excluded studies).

We included one completed study (one record) where results were available (Abdelalim 2021). We identified one additional reference to a published paper linked to the study identified by the search. The paper was published after the search was run.

We identified six ongoing studies (seven records). We identified one additional reference to a published paper linked to an ongoing study identified by the search. The paper was published after the search was run. See Characteristics of ongoing studies for further details of all six ongoing studies.

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

Figure 1.

```
┌─────────────┐   ┌─────────────┐
│1034 records │   │0 records    │
│identified   │   │identified   │
│through      │   │through other│
│database     │   │sources      │
│searching    │   │             │
└──────┬──────┘   └──────┬──────┘
       └─────────┬───────┘
                 ▼
         ┌─────────────┐
         │796 records  │
         │after        │
         │duplicates   │
         │removed      │
         └──────┬──────┘
                │
                │            ┌──────────────────┐
                │            │3                 │
                │            │record discarded  │
                │            │by Cochrane       │
                │            │Crowd (known      │
                │            │assessments)      │
                │            │                  │
                │            │382 records       │
                │            │discarded by RCT  │
                │            │Classifier        │
                │            │                  │
                ▼            │372               │
         ┌─────────────┐     │records discarded │
         │796 records  │────▶│by review         │
         │screened     │     │authors on        │
         └──────┬──────┘     │title/abstract    │
                │            └──────────────────┘
                │
                │            ┌──────────────────┐
                │            │6 additional      │
                │            │records discarded │
                │            │                  │
                │            │25 records        │
                │            │excluded (linked  │
                │            │to 23 studies),   │
                ▼            │with reasons      │
         ┌─────────────┐     │                  │
         │39 full-text │     │7 records linked  │
         │articles     │────▶│to                │
         │assessed for │     │6 ongoing studies │
         │eligibility  │     └──────────────────┘
         └──────┬──────┘
                │
                ▼
         ┌─────────────┐
         │1 study      │
         │included in  │
         │qualitative  │
         │synthesis    │
         └──────┬──────┘
                │
                ▼
         ┌─────────────┐
         │0 studies    │
         │included in  │
         └─────────────┘
```
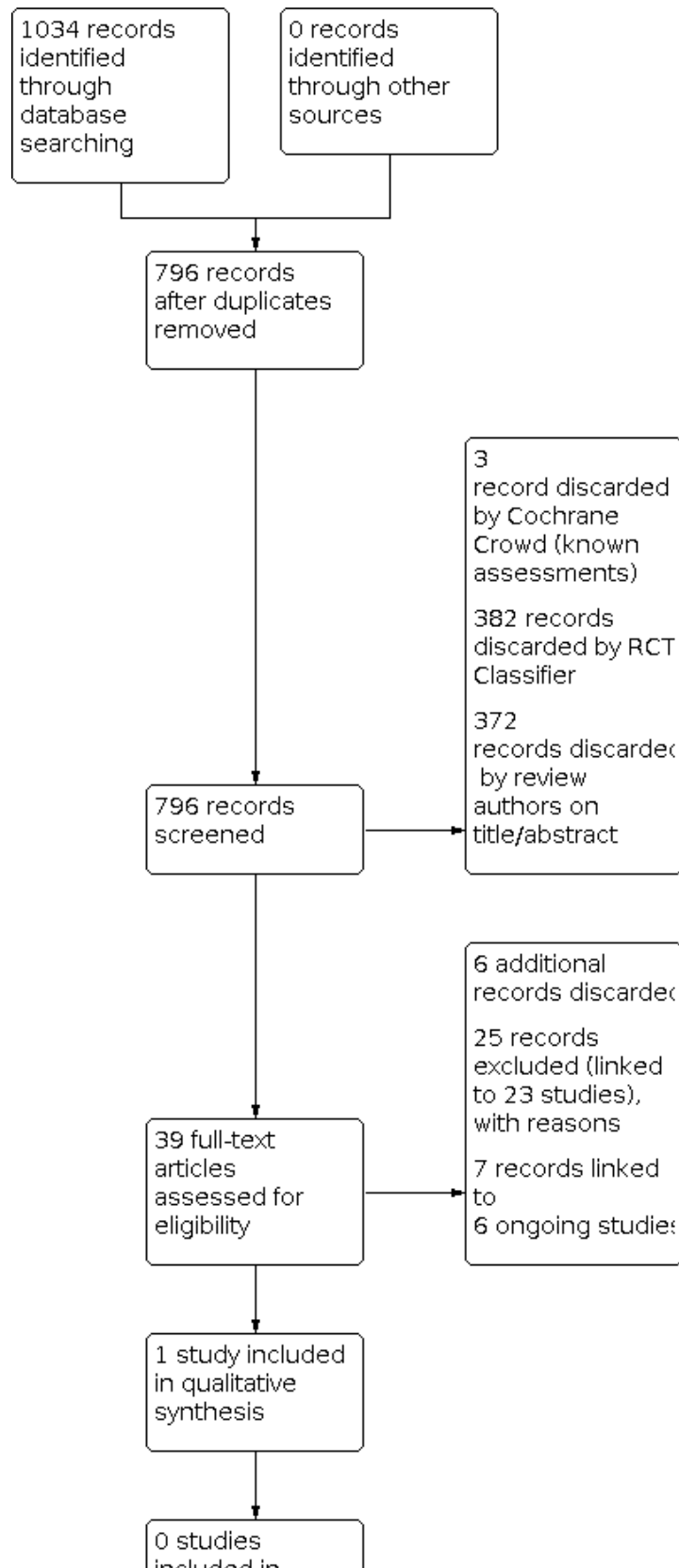
Figure 1. (Continued)

> 0 studies
> included in
> quantitative
> synthesis
> (meta-analysis)

Included studies

One study was included in the review. Abdelalim 2021 was an open-label randomised controlled trial of intranasal corticosteroids (100 μg mometasone furoate in each nostril, once daily) compared to no treatment. The study was conducted in Egypt. Participants in both arms of the study were also recommended to use olfactory training with rose, lemon and cloves for 20 seconds each, twice per day. The authors of the study confirmed that all participants had symptoms of olfactory disturbance, which had lasted between 10 and 28 days at baseline. The study included 100 participants, all of whom self-reported olfactory disturbance at the start of the study (no psychophysical testing was used). Treatment was given for three weeks, and outcomes were assessed at the end of the treatment period.

Excluded studies

We excluded 23 studies from the review. We present the main reasons for the exclusion of the studies below, although some studies had multiple reasons for exclusion:

Fifteen studies assessed the wrong population:

- 10 of these studies included all individuals with a diagnosis of COVID-19, not just those with olfactory dysfunction (ACTION (NCT04332107); COPPS (NCT04662060); COVIDAtoZ (NCT04342728);

CTRI/2020/08/027477; NCT04414124; NCT04458519; NCT04474483; NCT04513184; NCT04622891; NCT04662086);
- a further four studies included participants with more than four weeks of olfactory dysfunction prior to enrolment (COVIDORL (NCT04361474)); IRCT20200522047542N1; Odorat-Covid (NCT04598763); Vaira 2020); and
- one further study included participants with any post-viral olfactory disturbance, not specifically COVID-19 (NCT04406584).

Two studies were not randomised controlled trials (NCT04382547; NCT04427332).

Two articles were narrative reviews, without any primary data (Begam 2020; Vroegop 2020).

Two articles were letters to a journal editor, without any primary data (Patel 2021; Pinna 2020).

Finally, two studies would have been relevant for this review, but the studies were withdrawn prior to any participant enrolment (Co-STAR (NCT04422275); NCT04374474).

Risk of bias in included studies

A single study was included in this review (Abdelalim 2021). Overall, we considered there to be a high risk of performance and detection bias due to the lack of blinding in the study. We considered other domains to be at low or unclear risk of bias. See Figure 2.

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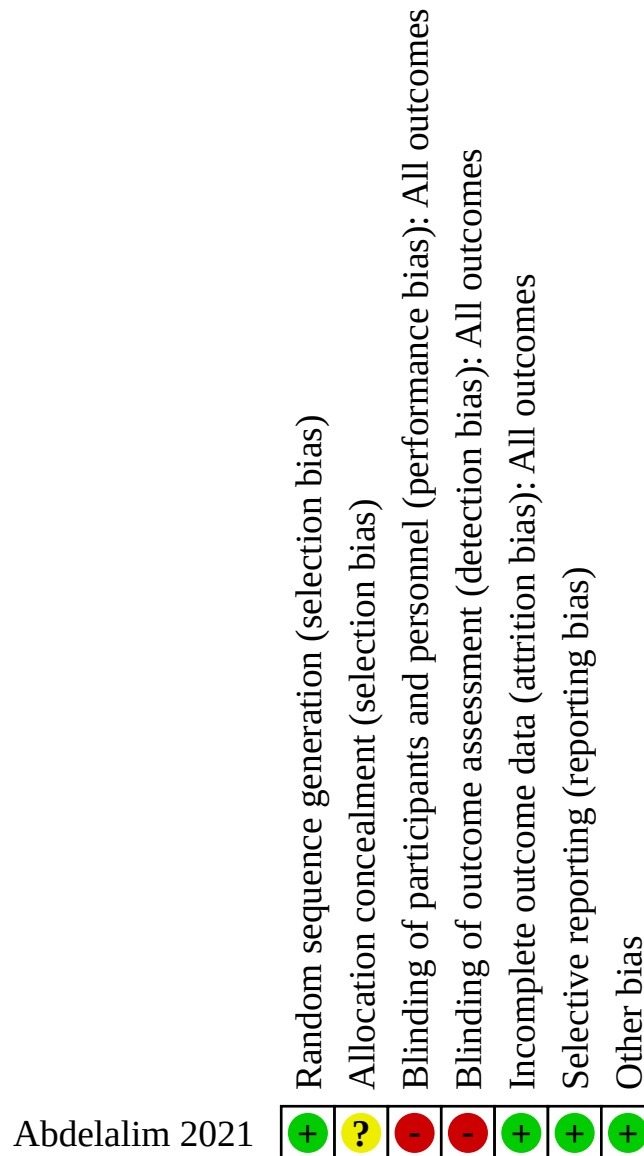
Allocation

Abdelalim 2021 described using random allocation, but did not provide further details of the method used, or details regarding concealment of the allocation sequence. Correspondence with the study authors confirmed that an adequate method was used for randomisation (simple randomisation, using drawing of lots).

Blinding

Abdelalim 2021 was an open-label study with no placebo group. The only included outcome was self-reported olfactory function (as

rated by the participants themselves) therefore we judged this to be at high risk of performance and detection bias.

Incomplete outcome data

Few dropouts were reported for the study (7.4% in total) and these were balanced across the two groups, therefore we judged Abdelalim 2021 to be at low risk of attrition bias. We noted that a per protocol analysis appeared to have been conducted, with the exclusion of two participants from each group due to non-compliance (use of additional medication, or no use/irregular

use of the study medication). However, due to the low numbers involved, we considered that this was unlikely to introduce a high risk of bias in the reported results.

Selective reporting

We were able to identify a registered protocol for Abdelalim 2021, and the outcomes were reported according to the trial registration, therefore we judged this at low risk of reporting bias.

Other potential sources of bias

We did not detect any additional potential sources of bias for Abdelalim 2021.

Effects of interventions

See: **Summary of findings 1** Intranasal steroids compared to no intervention for the prevention of persistent post-COVID-19 olfactory dysfunction

Comparison 1: Intranasal steroids compared to no intervention

One study (100 participants) investigated intranasal steroids compared to no intervention. See Summary of findings 1.

Presence of normal olfactory function

At ≤ 4 weeks

Recovery of sense of smell was assessed using a visual analogue scale (VAS) of 0 to 10, where 0 represented total loss of smell and 10 represented completely normal smell sensation. At three weeks follow-up, 31 out of 50 participants in the intranasal steroid group reported completely normal smell sensation, compared to 26 out of 50 in the control group (we assume that this equates to a score of 10 on the VAS). The evidence is very uncertain as to whether intranasal steroids affect the number of people who report completely normal smell sensation at up to four weeks, given the small number of participants included and the wide confidence intervals around the effect (risk ratio (RR) 1.19, 95% confidence interval (CI) 0.85 to 1.68; 1 study; 100 participants; very low-certainty evidence; Analysis 1.1).

No data were reported for later time points of interest in this review, and no data were reported using psychophysical tests of olfactory function.

Serious adverse effects

These were not assessed or reported.

Change in sense of smell

At ≤ 4 weeks

Change in sense of smell was also reported according to the VAS of 0 to 10, with higher scores representing better olfactory function. An estimate of the change in sense of smell was not available - the only data reported were endpoint data, comparing the median sense of smell in the two groups after the treatment period (three weeks). As the data were reported as median values no effect estimate could be calculated. The evidence is very uncertain about the effect of intranasal steroids on change in sense of smell at up to four weeks. Those receiving steroids had a median sense of smell score of 10 (interquartile range (IQR) 9 to 10) and those not receiving steroids

had a median score of 10 (IQR 5 to 10) (P = 0.16; 1 study; 100 participants; very low-certainty evidence).

No data were reported for later time points of interest in this review, and no data were reported using psychophysical tests of olfactory function.

Prevalence of parosmia

This was not assessed or reported.

Change in sense of taste

This was not assessed or reported.

Disease-related quality of life

This was not assessed or reported.

Other adverse effects

These were not assessed or reported.

D I S C U S S I O N

Summary of main results

This review includes a single study that assessed the effect of intranasal steroids compared to no intervention for the prevention of persisting olfactory dysfunction related to COVID-19. All participants were encouraged to use olfactory training methods whilst participating in the study, and all had symptoms of olfactory dysfunction, which had lasted less than four weeks. At three weeks follow-up, the effect of intranasal steroids on the number of participants with self-reported recovery of their sense of smell, or change in their sense of smell, is very uncertain.

Overall completeness and applicability of evidence

A major limitation to the findings of this review is the identification of a single study, with a very small sample size, which addressed the efficacy of just one intervention. This study provides a very small amount of evidence regarding the effect of intranasal steroids on self-rated recovery of normal olfactory function and change of sense of smell. However, we did not identify any evidence for other outcomes, including serious adverse effects, presence of parosmia, change in sense of taste, disease-related quality of life and other (non-serious) adverse effects. The duration of follow-up for this study was also limited, with outcomes being reported at three weeks (immediately after treatment was stopped). Therefore, we are unable to assess whether the intervention may have persisting effects beyond this time, or whether the discontinuation of treatment may affect the outcomes.

Adverse effects were not reported by the single study included in this review. However, if the adverse effect profile is similar to that seen when intranasal steroids are used for other sinonasal disease, then the adverse events are likely to be modest. They may include epistaxis, gastrointestinal disturbance and headache (Demoly 2008). Systemic effects are thought to be rare (Allen 2000).

The sense of smell is also important to 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 both outcomes assessed. This was predominantly due to the small sample size, leading to a lack of precision in the effect estimates. The study design was also a factor, as the unblinded nature of the study may have led to bias in the effect estimates.

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. Therefore, we excluded studies from this review if participants had more than four weeks of olfactory disturbance at baseline - these studies are included in the companion review on treatment of olfactory dysfunction (Webster 2021a). We considered that this was an appropriate distinction, due to the high rate of resolution of olfactory dysfunction in the first four weeks after COVID-19 infection.

A limitation of this review is the focus on studies where all participants had olfactory dysfunction at baseline. Whilst these are the population of interest, additional evidence for the prevention of persisting olfactory dysfunction may be available from studies of other interventions for COVID-19. We are aware that many studies will have enrolled participants with COVID-19 (regardless of the presence of olfactory dysfunction at baseline) and may have reported on olfactory outcomes. These studies are excluded from this review, as the overall population do not adhere to the inclusion criteria. However, they may provide additional evidence of the benefits and harms of interventions for preventing persisting olfactory dysfunction.

Agreements and disagreements with other studies or reviews

We are not aware of any other systematic reviews that consider the prevention of persisting olfactory dysfunction related to COVID-19, therefore there are no relevant reviews to compare our findings to.

AUTHORS' CONCLUSIONS

Implications for practice

At present there are very few data to assess the effects of interventions on preventing persistent olfactory dysfunction following COVID-19. The only evidence available is for intranasal steroids, and this is of very low certainty, based on one study. Therefore, we are unable to draw any conclusions regarding the efficacy - or potential adverse effects - of intranasal steroids at preventing persistent olfactory dysfunction following COVID-19 infection. As this is a living systematic review, the data will be updated regularly as new evidence becomes available.

Implications for research

We are aware of a number of ongoing studies that may be relevant for this review on publication. As a living systematic review, we will update this review as new data become available.

Although olfactory disturbance is a common symptom of COVID-19, the natural course of the disease does have a relatively high spontaneous resolution rate. Therefore, we believe that it is essential for researchers to clearly define the affected population included in their trial, according to the duration of their symptoms. The risks and benefits of treatment in the early stages of olfactory disturbance may be very different to those for individuals with a longer duration of symptoms.

We recognise that there may be poor agreement between self-rated olfactory function and that assessed using psychophysical testing. A recent study demonstrated that only 18% of patients with COVID-19 self-reported ongoing olfactory dysfunction at six months' follow-up (Boscolo-Rizzo 2021). However, 60% of participants were shown to have some olfactory impairment on psychophysical testing. Given this discrepancy, we consider it important to assess recovery of the sense of smell using both patient-reported and psychophysical testing, to better understand the impact of any interventions.

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References to other published versions of this review

Webster 2021b

Webster KE, MacKeith S, Philpott C, Hopkins C, Burton MJ. Interventions for the prevention of persistent post-COVID-19 olfactory dysfunction. *Cochrane Database of Systematic Reviews* 2021, Issue 3. Art. No: CD013877. [DOI: 10.1002/14651858.CD013877]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abdelalim 2021

Study characteristics	
Methods	Two-arm, non-blinded, parallel-group randomised controlled trial with 3 weeks' duration of treatment and follow-up
Participants	**Location:** Egypt, single-centre study
	Setting of recruitment and treatment: recruited at Benha University Hospital
	Sample size: 108
	• **Number randomised:** 54 to intervention, 54 to comparison
	• **Number completed:** 50 in intervention, 50 in comparison
	Participants:
	• Patients who have recently recovered from proven COVID-19 infection, suffering from anosmia or hyposmia
	Baseline characteristics:
	• **Age:** intervention group: median 28.0 years (IQR 20.5 to 38.0); control group: median 30.0 years (IQR 22.5 to 39.0)
	• **Gender:** intervention group: 24 (48%) male, 26 (52%) female; control group: 22 (44%) male, 28 (56%) female
	• **Olfactory function at baseline:** baseline smell score reported with VAS (0 to 10); intervention group: median 2.0 (IQR 0.5 to 5.0); control group: median 2.0 (IQR 1.0 to 5.0)
	• **Diagnosis of olfactory dysfunction at baseline:** self-reported, no psychophysical testing
	• **Duration of symptoms:** all participants had between 10 and 28 days of olfactory disturbance at baseline (confirmed with study authors)
	Inclusion criteria for the study:
	• Aged 18 years or older
	• Confirmed case of COVID-19 (positive PCR)
	• Subsequent recovery (2 negative PCR)
	• Acute onset of anosmia/hyposmia, with or without loss of taste
	• Hospitalised or home isolated
	Exclusion criteria for the study:
	• Use of nasal steroids for other co-morbidities
	• Previous chronic rhinological pathology
	• Use of systemic steroids for other systemic disease
	• Anosmia that improved before recovery from COVID-19
	• Pregnancy
	• Loss to follow-up
Interventions	**Intervention group:**
	Topical corticosteroid spray (mometasone furoate nasal spray), 2 puffs (100 μg) once daily in each nostril for 3 weeks
	Comparator group: no intervention

Abdelalim 2021 *(Continued)*

	Use of additional interventions in both groups: none reported
Outcomes	<u>**Outcomes of interest in the review:**</u> **Primary outcomes:** Presence of normal olfactory function • Patient reported "complete normal smell sensation", using a VAS score of 0 to 10, where score 10 = completely normal smell sensation. Participants were recommended some substances to use when self-assessing their olfactory function, such as mint, coffee and garlic. Assessed at baseline, 1 week, 2 weeks and 3 weeks. • Psychophysical testing not assessed Serious adverse effects • Not assessed Change in sense of smell • Patient reported sense of smell, using a VAS score of 0 to 10, where 0 = total loss of smell and 10 = completely normal smell sensation. Participants were recommended some substances to use when self-assessing their olfactory function, such as mint, coffee and garlic. Assessed at baseline, 1 week, 2 weeks and 3 weeks. • Psychophysical testing not assessed **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) • Not assessed <u>**Other outcomes reported by the study:**</u> None reported
Funding sources	No financial support was reported for the study
Declarations of interest	No conflict of interest was declared
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Low risk	Quote: "The participants in this study were randomly assigned to two groups (simple 1:1 randomisation)". Comment: correspondence from the author confirmed that adequate methods were used (random selection of groups from an envelope).

Abdelalim 2021 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: no information was provided regarding concealment of allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: open-label study, with no placebo group. Participants were aware of their allocation.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: open-label study, with no placebo group. The only outcome assessed was self-reported by the (unblinded) participants.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: few dropouts (7.4%) and balanced across the groups. Two participants in each group may have been excluded due to non-adherence to the trial protocol (intervention group: 1 discontinued treatment, 1 used treatment inconsistently, control group: 2 received other medications). However, the impact of this on the results was not felt to be sufficient to result in high risk of bias.
Selective reporting (reporting bias)	Low risk	Comment: trial protocol accessed on clinical trial registry, and no further outcomes were planned.
Other bias	Low risk	Comment: no other source of bias detected.

IQR interquartile range; PCR polymerase chain reaction; VAS visual analogue scale

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)	Although this study fits the inclusion criteria for the review, it was withdrawn prior to any participant enrolment
COVIDAtoZ (NCT04342728)	Wrong population: study does not specifically include participants with olfactory dysfunction
COVIDORL (NCT04361474)	Wrong population: all participants in the study have had symptoms of olfactory disturbance for at least 4 weeks. This study is relevant for the companion review "Interventions for the treatment of persistent post-COVID-19 olfactory dysfunction" (Webster 2021a).
CTRI/2020/08/027477	Wrong population: study does not specifically include participants with olfactory dysfunction
IRCT20200522047542N1	Wrong population: all participants in the study have had symptoms of olfactory disturbance for at least 4 weeks. This study is relevant for the companion review "Interventions for the treatment of persistent post-COVID-19 olfactory dysfunction" (Webster 2021a).
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

Study	Reason for exclusion
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
NCT04513184	Wrong population and wrong comparator: study does not specifically include participants with olfactory dysfunction; intervention is compared to intravenous dexamethasone
NCT04622891	Wrong population: study does not specifically include participants with olfactory dysfunction
NCT04662086	Wrong population: study does not specifically include participants with olfactory dysfunction
Odorat-Covid (NCT04598763)	Wrong population: all participants in the study have had symptoms of olfactory disturbance for at least 4 weeks. This study is relevant for the companion review "Interventions for the treatment of persistent post-COVID-19 olfactory dysfunction" (Webster 2021a).
Patel 2021	Letter to the editor: no primary data included
Pinna 2020	Letter to the editor: no primary data included
Vaira 2020	Wrong population: all participants in the study have had symptoms of olfactory disturbance for at least 4 weeks. This study is relevant for the companion review "Interventions for the treatment of persistent post-COVID-19 olfactory dysfunction" (Webster 2021a).
Vroegop 2020	Narrative review article: no primary data

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

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 results, obtained through nasopharyngeal swab
	• Patients with COVID-19 diagnosis, but without self-reported anosmia

NCT04495816 *(Continued)*

- 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
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** Presence of normal olfactory function • Not reported Serious adverse effects • Not reported 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. **Secondary outcomes:** Prevalence of parosmia • Not reported Change in sense of taste • 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 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 rhi-

NCT04495816 *(Continued)*

nosinusitis, 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 fewer 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
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	<u>**Outcomes of interest in the review:**</u>
	Primary outcomes:
	Presence of normal olfactory function
	• Time to recovery from anosmia (no further details provided)
	Serious adverse effects
	• Not reported
	Change in sense of smell
	• Not reported
	Secondary outcomes:

NCT04528329 *(Continued)*

Prevalence of parosmia

- Not reported

Change in sense of taste

- Time to recovery from ageusia (no further details provided)

Disease-related quality of life

- Not reported

Other adverse effects (including nosebleeds/bloody discharge)

- Not reported

Other outcomes reported by the study:

- Time to recovery (1 to 6 weeks), no further details provided

Starting date	30 August 2020
Contact information	Emad R Issak 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:**

NCT04530409 *(Continued)*

Primary outcomes:

Presence of normal olfactory function

- Time to recovery from anosmia (no further details provided)

Serious adverse effects

- Not reported

Change in sense of smell

- Not reported

Secondary outcomes:

Prevalence of parosmia

- Not reported

Change in sense of taste

- Not reported

Disease-related quality of life

- Not reported

Other adverse effects (including nosebleeds/bloody discharge)

- Not reported

Other outcomes reported by the study:

Primary:

- Percentage of cases that will need hospitalisation
- Percentage of cases that deteriorate to acute respiratory distress syndrome

Secondary:

- 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:**

NCT04530409 *(Continued)*

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.

NCT04569825

Study name	Effect of nasal steroid in the treatment of anosmia due to COVID-19 disease
Methods	Parallel-group randomised controlled trial
Participants	Individuals with a confirmed diagnosis of COVID-19 (real-time PCR) with recent onset of anosmia and or ageusia
	Inclusion criteria:
	• Adults, aged 18 years or over
	• Proven case of COVID-19 by real-time PCR of nasopharyngeal/oropharyngeal swabs
	• Recent onset of anosmia, with or without ageusia and other symptoms of COVID-19
	Exclusion criteria:
	• Pregnant women
	• Psychological disturbances
	• Previous history of anosmia
	• Severe sinonasal disease
	• Previous sinonasal surgery
	• Refusal to participate
	• Lost to follow-up
	Planned sample size: estimated enrolment 250 participants
Interventions	**Intervention:** intranasal opthamesone (steroid) drops (frequency and duration not stated)
	Comparator: intranasal normal saline drops (frequency and duration not stated)
Outcomes	<u>**Outcomes of interest in the review:**</u>
	Primary outcomes:
	Presence of normal olfactory function
	• Recovery rate of anosmia, and time to recovery of anosmia (no further details provided)
	Serious adverse effects
	• Not reported
	Change in sense of smell
	• Not reported
	Secondary outcomes:
	Prevalence of parosmia
	• Not reported
	Change in sense of taste
	• Not reported

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NCT04569825 *(Continued)*

Disease-related quality of life

- Not reported

Other adverse effects (including nosebleeds/bloody discharge)

- Not reported

Other outcomes reported by the study:

- No other outcomes are reported

Starting date	1 August 2020
Contact information	Raid M Al-Ani
	Email: med.raed.alani2003@uoanbar.edu.iq
Notes	Estimated study completion date: 15 October 2020
	Trial registered in Iraq
	Correspondence from the trial investigator confirms that all participants in this trial will have had recently diagnosed COVID-19, and that symptoms of anosmia will have lasted for less than 2 weeks at the start of the trial.

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
- 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:
	
	 Presence of normal olfactory function
	
	 • Not reported
	
	 Serious adverse effects
	
	 • Not reported
	
	 Change in sense of smell
	
	 • Not reported
	
	 Secondary outcomes:
	
	 Prevalence of parosmia
	
	 • Not reported
	
	 Change in sense of taste
	
	 • 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 PHQ-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.
	
	 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

NCT04638673 *(Continued)*

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
Outcomes	**Outcomes of interest in the review:**
	Primary outcomes:
	Presence of normal olfactory function
	• Not reported
	Serious adverse effects
	• Not reported
	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
	Secondary outcomes:
	Prevalence of parosmia

NCT04657809 *(Continued)*

- Not reported

Change in sense of taste

- Not reported

Disease-related quality of life

- 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 fewer than 4 weeks from the onset of COVID-19

ALT: alanine aminotransferase; BiPAP bilevel positive airway pressure; BSIT Brief Smell Identification Test; CPAP continuous positive airway pressure; CRP: c-reactive protein; LDH: lactate dehydrogenase; mQOD-NS Modified Brief Questionnaire of Olfactory Dysfunction; SNOT-22 Sinonasal Outcomes Test

DATA AND ANALYSES

Comparison 1. Intranasal steroids compared to no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Presence of normal olfactory function at ≤ 4 weeks (as assessed by participants)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.85, 1.68]

Analysis 1.1. Comparison 1: Intranasal steroids compared to no intervention, Outcome 1: Presence of normal olfactory function at ≤ 4 weeks (as assessed by participants)

Study or Subgroup	Intranasal steroids		No intervention		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Abdelalim 2021	31	50	26	50	100.0%	1.19 [0.85 , 1.68]	
Total (95% CI)		**50**		**50**	**100.0%**	**1.19 [0.85 , 1.68]**	
Total events:	31		26				

Heterogeneity: Not applicable

Test for overall effect: Z = 1.00 (P = 0.32)

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Favours no intervention   Favours intranasal steroids
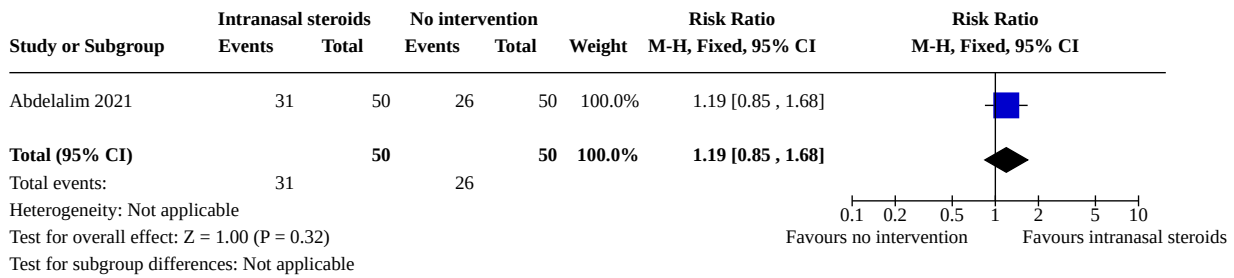
APPENDICES

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 2844

2 ((Wuhan and (coronavirus or "corona virus"))):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 124

3 (((coronavirus or "corona virus" or COVID) adj3 "2019")):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 582

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

5 ((coronavirus or "corona virus" or COVID)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 2919

6 (2020 or 2021):YR AND CENTRAL:TARGET 63399

7 #5 AND #6 AND CENTRAL:TARGET 2801

8 #1 OR #2 OR #3 OR #4 OR #7 AND CENTRAL:TARGET 2877

9 MESH DESCRIPTOR Olfaction Disorders EXPLODE ALL AND CENTRAL:TARGET 118

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 1201

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 424

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 151

13 #9 OR #10 OR #11 OR #12 AND CENTRAL:TARGET 1474

14 #13 AND #8 AND CENTRAL:TARGET 34

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. 64357

2 (Wuhan and (coronavirus or "corona virus")).ab,ti. 2686

3 (coronavirus or "corona virus" or COVID) adj3 "2019").ab,ti. 14622

4 (wuhan adj2 (disease or virus)).ab,ti. 69

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. 27706

6 (coronavirus or "corona virus" or COVID).ab,ti. 73711

7 limit 6 to yr="2020 -Current" 64172

8 1 or 2 or 3 or 4 or 5 or 7 68776

9 exp olfaction disorders/ 4393

10 (Olfaction or olfactory or Dysosmia* or Paraosmia* or Anosmia* or hyposmia* or phantosmia* or Cacosmia* or microsmia*).ab,ti. 49706

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. 2401

12 (smell* adj6 (prevent* or rehab* or recover* or therap* or train* or retrain*)).ab,ti. 180

13 9 or 10 or 11 or 12 51681

14 8 and 13 768

15 randomized controlled trial.pt. 516072

16 controlled clinical trial.pt. 93905

17 randomized.ab. 496684

18 placebo.ab. 212020

19 drug therapy.fs. 2246822

20 randomly.ab. 343595

21 trial.ab. 525027

22 groups.ab. 2108399

23 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 4824610

24 exp animals/ not humans.sh. 4750713

25 23 not 24 4189853

26 14 and 25 72

Cochrane COVID-19 Study Register (CRS)

1 MESH DESCRIPTOR Olfaction Disorders EXPLODE ALL AND COVID19:INREGISTER 5

2 (Olfaction or olfactory or Dysosmia* or Paraosmia* or Anosmia* or hyposmia* or phantosmia* or Cacosmia* or microsmia*) AND COVID19:INREGISTER 392

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 180

4 (smell* adj6 (prevent* or rehab* or recover* or therap* or train* or retrain*)) AND COVID19:INREGISTER 17

5 #1 OR #2 OR #3 OR #4 483

6 (interventional):SY AND COVID19:INREGISTER 3460

7 #6 AND #5 37

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 Interventiona

H I S T O R Y

Protocol first published: Issue 3, 2021

C O N T R I B U T I O N S   O F   A U T H O R S

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

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

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.

D E C L A R A T I O N S   O F   I N T E R E S T

Katie Webster: none known.

Lisa O' Byrne: 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.

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Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK

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- NIHR COVID-19 Recovery and Learning programme, UK

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:

- presence of normal olfactory function (as reported by the participants);
- serious adverse effects;
- change in sense of smell (as identified by psychophysical testing);
- prevalence of parosmia;
- change in sense of taste;
- disease-related quality of life;
- other adverse effects (including nosebleeds/bloody discharge).

No data were available from psychophysical testing for the outcome "Change in sense of smell". However, we did identify data for this outcome that had been self-reported by the participants, therefore these data were included in the summary of findings table.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Intranasal; Adrenal Cortex Hormones [*administration & dosage]; Bias; Citrus; Confidence Intervals; COVID-19 [*complications]; Mometasone Furoate [*administration & dosage]; Olfaction Disorders [*drug therapy] [etiology] [prevention & control]; Phytotherapy [*methods]; Recovery of Function; Syzygium; Visual Analog Scale

MeSH check words

Humans