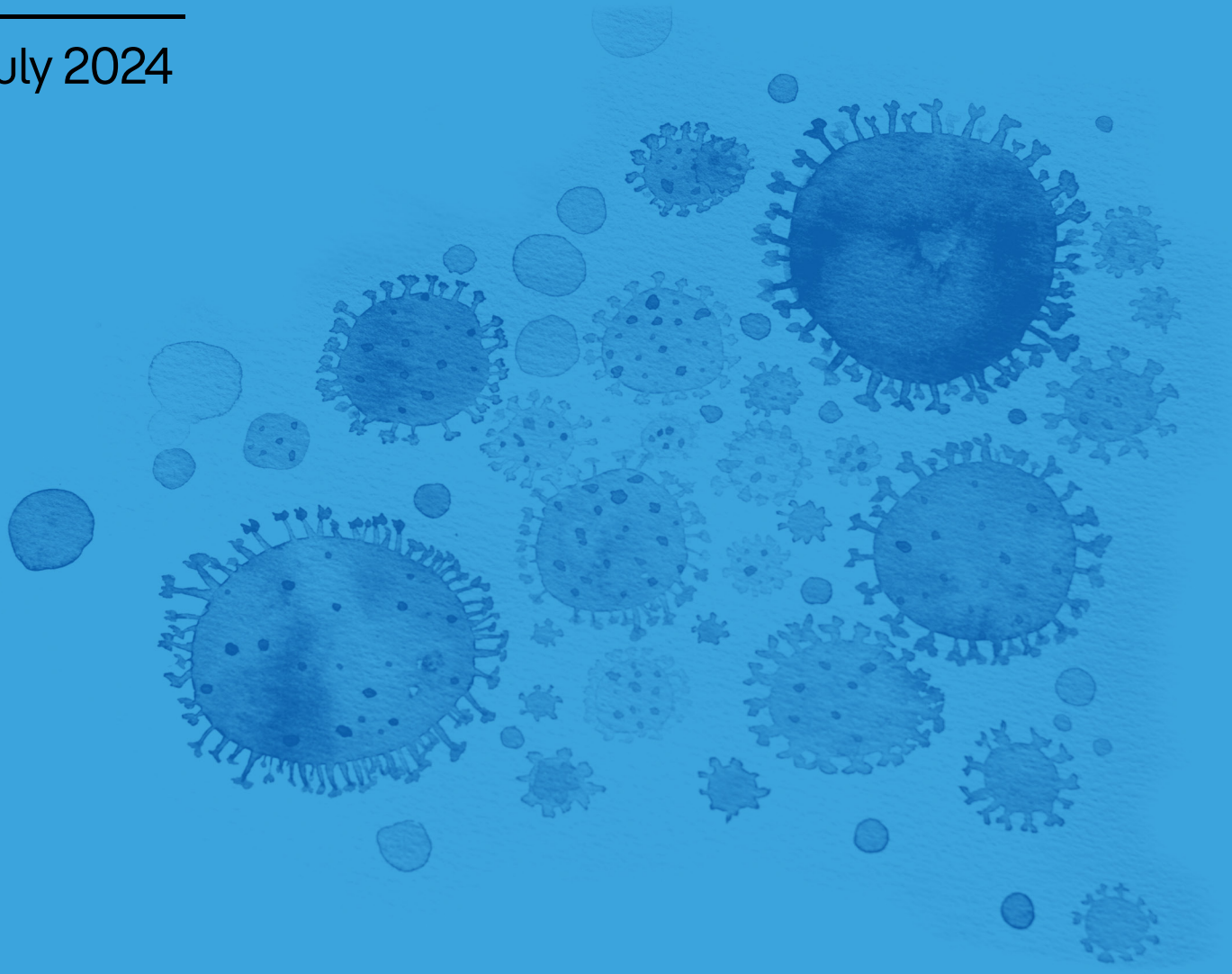
NIHR Policy Research Programme Reviews Facility

Supporting national policy development and implementation

# Treatment and rehabilitation of Long COVID

## A scope of the literature: update

July 2024



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# Treatment and rehabilitation of Long COVID: A scope of the literature. Update July 2024

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Raine G, Khouja C, Fulbright H, Sutcliffe K, Sowden A (2024) Treatment and rehabilitation of Long COVID: A scope of the literature. Update July 2024. London: EPPI Centre, UCL Social Research Institute, UCL Institute of Education, University College London.

**Funding**
This review was commissioned by the National Institute for Health Research (NIHR) Policy Research Programme (PRP) for the Department of Health and Social Care (DHSC). It was funded through the NIHR PRP contract with the EPPI Centre at UCL (Reviews facility to support national policy development and implementation, NIHR200701). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the DHSC.

**Conflicts of interest**
There were no conflicts of interest in the writing of this report.

**Contributions**
The opinions expressed in this publication are not necessarily those of the EPPI Centre or the funders. Responsibility for the views expressed remains solely with the authors.

This report should be cited as:
Raine G, Khouja C, Fulbright H, Sutcliffe K, Sowden A (2024) *Treatment and rehabilitation of Long COVID: A scope of the literature. Update July 2024*. London: EPPI Centre, UCL Social Research Institute, UCL Institute of Education, University College London.

Editorial & design by: Lionel Openshaw

ISBN: 978-1-911605-61-4

## Summary


- We identified 19 randomised controlled trials published between March and June 2024 that were focused on Long COVID treatment or rehabilitation. Across our nine reports produced to date, we have identified and assessed 140 trials published between January 2022 and June 2024.
- Eight of the 19 trials focused on treating generalised or multiple symptoms of Long COVID. Four trials focused specifically on respiratory or cardiovascular function or physical fitness. Four other trials focused solely on treating persistent problems with the sense of smell or taste (olfactory/gustatory dysfunction) and three trials evaluated treatments for fatigue.
- Two trials were rated positively for 10 out of the 13 quality criteria that we assessed. The other 17 trials gained a positive rating for between four and nine criteria.


## Introduction

This is the ninth report in an ongoing series of quarterly evidence scans requested by NHS England and the Department of Health and Social Care. It was conducted to identify and quality assess randomised controlled trials (RCTs) evaluating treatment or rehabilitation for Long COVID published in the three-month period between March and June 2024.

## Method

### Identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) using a range of key terms that have been used in the literature to describe symptoms and effects persisting beyond the acute stage of COVID-19 infection. Searches of MEDLINE, Embase, PsycINFO and CINAHL were also conducted to identify any trials that had not been incorporated into CENTRAL. We translated the CENTRAL search strategy for use in each database and used study design search filters to restrict retrieval to randomised controlled trials.

Searches were limited to studies added to the databases or published between 2022 and 2024, and no language restrictions were applied. Preprints were removed from the searches in MEDLINE and Embase. Due to the rapid nature of the project, the database searches were designed to balance the need to retrieve as many relevant trials as possible against the limited time available for screening. Records were downloaded into EndNote and deduplicated against the search results from previous updates. Full search strategies can be found in Appendix 1 (page 18).

### Study selection

Studies were screened for inclusion against the following criteria:

**Population -** patients with Long COVID, which we conceptualised broadly as experiencing at least one symptom or effect that persists or develops after acute COVID-19 infection. No restrictions were placed on the socio-demographic characteristics of participants or COVID severity. We also did not apply criteria relating to the time period after acute infection owing to variation in how Long COVID has been defined in the literature.

**Interventions** - any intervention aimed at treating or rehabilitating patients with Long COVID. This could include, but was not limited to, medication, supplements, and physical therapy.

Interventions that had a primary focus on general rehabilitation from COVID-19 following hospitalisation or severe infection were excluded.

**Outcomes** - any outcome related to the effectiveness, cost-effectiveness, safety or side effects of interventions. Studies could also report outcomes related to the implementation of interventions.

**Study design** - prospective trials with random allocation of participants to intervention and comparator groups. When designed and conducted to a high standard, a randomised controlled trial is often the most robust type of primary study design for investigating intervention effectiveness.[1]

**Publication type and status -** any publication type, except pre-prints and conference abstracts, which reports findings from a RCT (e.g., full papers, research letters, brief reports etc).

### Quality assessment

Each study was appraised according to the Joanna Briggs Institute (JBI) Checklist for Randomized Controlled Trials.[2] In contrast to the Cochrane Risk of Bias Tool,[3] the JBI checklist does not require an assessment of bias for specific outcomes. It provides instead a general appraisal of each trial as a whole, which was needed in this piece of work as we were not seeking to extract and synthesise outcome data. Assessments were conducted by one reviewer and checked by another. The appraisal identified potential sources of bias and threats to the validity and reliability of study findings. The full checklist is provided in Appendix 2 (page 26).

## Key findings

We screened 345 records and included 19 RCTs that had been published since March 2024.[4-22] We included a similar number of trials in three of our previous eight reports: January 2024 (n=21);[23] July 2023 (n=18);[24] and April 2023 (n=18).[25] The number of trials included in our other five reports was: April 2024 (n=15);[26] October 2023 (n=12);[27] January 2023 (n=12);[28] October 2022 (n=11)[29] and July 2022 (n=14).[30] The flow of studies through the current update is shown in Appendix 3 (page 27). Table 1 (page 6) presents the aim(s) and key characteristics of the 19 trials.

### Interventions

Eight trials focused on individuals experiencing generalised or multiple symptoms of Long COVID.[4, 9, 11-14, 17, 22] Five of the eight trials evaluated physical rehabilitation programmes. Of these, two evaluated multicomponent cardiopulmonary rehabilitation programmes comprising activities such as aerobic exercise, respiratory muscle training, and resistance training.[9, 11] One trial assessed inspiratory muscle training combined with aerobic exercise and neurorehabilitation (olfactory and gustatory training) for individuals experiencing both persistent dyspnoea and loss of their sense of smell or taste.[17] One trial evaluated resistance training for treating older adults (65 years old and over).[13] Another trial compared the effects of virtual reality-simulated treadmill exercise and conventional treadmill exercise.[4]

Of the remaining three trials focused on people with generalised or multiple symptoms of Long COVID, one evaluated a psychological programme (PsiCoRes) based on third-generation therapies (elements of Acceptance and Commitment Therapy and mindfulness).[12] One trial investigated biosound therapy, which comprised biofeedback, vibroacoustic therapy synchronised with binaural beats, and video content.[14] The third trial evaluated the

consumption of hydrogen-rich water on individuals with both persistent fatigue and dyspnoea.[22]

Four trials assessed treatments for individuals who primarily had problems with respiratory or cardiovascular function or physical fitness.[10, 16, 18, 21] Three of the four trials focused on assessing the effectiveness of exercise-based rehabilitation programmes and/or inspiratory muscle training; [10, 16, 21] The fourth trial focused primarily on the feasibility and safety of a virtual pulmonary rehabilitation programme delivered through group or self-directed sessions, and participants' satisfaction with the programme; several effectiveness measures were assessed as secondary outcomes.[18]

Four trials focused solely on persistent problems with the sense of smell or taste and investigated various potential treatments: topical platelet-rich plasma;[8] frequency-controlled ear acupuncture;[15] topical nasal corticosteroid (mometasone furoate monohydrate) and olfactory training (OT);[19] and ultramicronized palmitoylethanolamide and luteolin (umPEALUT) with OT; alpha-lipoic acid with OT; and combined therapy (umPEALUT, alpha-lipoic acid and OT).[6]

Three trials focused on treatments primarily for fatigue. One assessed RSLV-132 (a catalytically active RNase Fc fusion protein)[5] and another evaluated an asynchronous multimodal telerehabilitation programme.[7] The third trial investigated the effects of creatine supplementation with or without glucose and required participants to have fatigue plus one other persistent COVID symptom.[20]

Approximately half of the trials included in both the current update (10 out of 19 RCTs) and our previous report in April 2024 (7 out of 15 RCTs)[26] evaluated interventions incorporating an exercise component and/or breathing training. None of our other seven reports included a larger proportion. As detailed previously, four out of the 19 trials in the current update had a focus on treating olfactory/gustatory dysfunction. This proportion is larger than we included in our April report (two out of 15 RCTs)[26] and is similar to the proportion included in our January 2024 report (4 out of 19 RCTs).[23] Four out of our other six reports all included a larger proportion of trials addressing olfactory/gustatory dysfunction.[24, 25, 27, 29]

### Participants

Eight trials recruited participants who had experienced persistent effects, on average, for at least four weeks after the onset of COVID symptoms or diagnosis.[5, 8, 10, 13-15, 17, 22] In five of the eight trials, participants had persistent effects for at least 12 weeks after symptom onset or diagnosis.[5, 8, 10, 13, 17]

Participants in two trials reported persistent symptoms at least three months after infection[18] or, on average, five months (4–40 weeks) before study recruitment.[19] In another trial, participants reported persistent symptoms after having COVID in the previous three to four months.[4]

Three trials recruited individuals at least four weeks;[9] three to 24 months;[6] and approximately two years (median 31 months) after recovery or hospital discharge.[21] In one trial, recruitment occurred within the first two weeks after discharge.[7] Participants in another trial were recruited whilst in hospital and had an initial assessment two days prior to discharge. On average, these participants had been hospitalised for 80 days.[16] The remaining three trials recruited individuals with persistent symptoms, but no time-related details were reported.[11, 12, 20]

## Countries

Three trials were conducted in Spain[7, 12, 17] and the USA.[5, 8, 14] Two trials were conducted in Canada;[10, 18] Egypt;[4, 9] Germany;[19, 21] and Italy.[6, 16] One trial was conducted in Brazil;[11] China;[22] Iran;[15] Poland;[13] and Serbia.[20]

## Trial quality

Assessments of the trials against the JBI criteria are provided in Table 2 (page 13). None of the trials were assessed as having a low risk of bias for more than ten of the 13 appraisal criteria. Two trials met ten criteria[15, 17] and 17 were rated positively for between four and nine criteria.[4-14, 16, 18-22]

A number of common issues were identified across the 19 trials. For example, in 13 trials, we could not tell if an appropriate procedure had been used to prevent researchers from knowing whether the next patient would be allocated to the treatment or comparator group (allocation concealment) (Q2).[5, 7, 8, 10, 12-16, 18, 20-22] In another trial,[19] participants were assigned to groups on an alternating basis and consequently we could not give this study a positive rating for allocation concealment.

An Intention to treat (ITT) analysis was not conducted in 12 trials (Q9)[4-6, 8-11, 13, 14, 16-18] and in another study, we could not tell if it had been used.[12] It was unclear if an appropriate statistical analysis had been conducted in ten trials as no information was provided about the sample size requirements of the study (Q12).[4-7, 10, 14, 18-20, 22]

In four trials that we rated positively for nine[7, 9, 11] or ten[17] of the 13 criteria, there was no blinding of trial participants (Q4) and the personnel who administered the treatment (Q5). However, the nature of the intervention in these trials is likely to have precluded the use of blinding as all four evaluated rehabilitation programmes. In one of the four trials, we were unable to tell if the outcome assessors were blinded.[9]

It was unclear whether trial participants were blinded in two of the remaining 15 trials (Q4).[6, 21] In ten of the 15 trials, we also could not tell if there was blinding of the personnel who administered the treatment (Q5)[6, 20] and/or the outcome assessors (Q6).[5, 12, 13, 15, 16, 18-21] In six of the 15 trials, there was no blinding of participants (Q4) and the personnel who administered the treatment (Q5).[10, 12, 13, 16, 18, 19] In two trials, there was no blinding of the personnel who administered the treatment (Q5).[15, 21] Neither the personnel who administered the treatment nor those who assessed outcomes were blinded in two trials.[8, 22] There was no blinding of trial participants, the personnel who administered the treatment nor outcome assessors in two other trials.[4, 14] The nature of the intervention in some of these 15 trials may have prevented the blinding of participants and/or study personnel.

## Conclusion

To conclude, in this evidence scan, we identified 19 RCTs published between March and June 2024 that examined interventions for the treatment or rehabilitation of people with Long COVID. Across our nine reports produced to date, we have identified and assessed 140 trials published since January 2022. Eight trials in the current update focused on treating generalised or multiple symptoms of Long COVID. Eight other trials focused specifically on cardiovascular function/physical fitness (n=4) or olfactory/gustatory dysfunction (n=4). Three trials evaluated treatments for fatigue (n=3). All trials were rated positively for between four and ten of the 13 quality criteria we assessed.

## Table 1: Study characteristics (n=19)

| First author (year)<br><br>Country | Aim of study | Main symptom or effect experienced | Post COVID time | Participants' gender (n) and % female | Primary outcome(s) of interest | Comparator |
|---|---|---|---|---|---|---|
| Ahmad (2024)[4]<br><br>Egypt | To assess the effects of traditional treadmill exercise compared to virtual reality-simulated treadmill exercise on fatigue, cognitive function, sleep quality, and participant satisfaction with the exercise programme in post-COVID-19 subjects | General/multiple: persistent dyspnoea and fatigue, oxygen saturation ≥94%, and mild cognitive impairment | Unclear/not stated: a history of COVID-19 infection within three to four months | Mixed (20; 16 analysed)<br><br>85% female (17/20) | Fatigue: Chalder Fatigue Scale<br><br>Cognitive: Montreal Cognitive assessment (MoCA)<br><br>Psychological: Pittsburgh Sleep quality index (PSQI) | Traditional treadmill exercise programme, without the virtual reality |
| Andrews (2024)[5]<br><br>USA | To assess whether intravenous doses of RSLV-132 would improve inflammation, neuroinflammation, and fatigue associated with post-acute sequelae of SARS-CoV-2 infection (PASC) | Fatigue/lack of energy | After diagnosis: 24 or more weeks after testing positive or diagnosis | Mixed (108; 95 analysed)<br><br>50% female (53/105) | Fatigue: PROMIS Fatigue SF 7a | Placebo |
| Cantone (2024)[6]<br><br>Italy | To investigate whether treatment regimens involving ultramicronized palmitoylethanolamide and luteolin (umPEALUT), alpha-lipoic acid (ALA), or both, combined with olfactory training could ameliorate parosmia or quantitative | Olfactory and/or gustatory dysfunction | After recovery: 3-24 months from post-COVID negative nasopharyngeal swab to initial olfactory evaluation. Participants had | Mixed (120; 89 analysed)<br><br>57% female (51/89) | Olfactory and/or gustatory function: resolution of parosmia (parosmia questionnaire) | Olfactory training only |

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| | smell dysfunction in patients with chronic olfactory dysfunction after SARS-CoV-2 infection | | tried olfactory training and failed to improve | | | |
| Carpallo-Porcar (2024)[7]<br><br>Spain | To preliminarily analyse whether a multimodal rehabilitation programme using asynchronous telerehabilitation in post-acute COVID-19 is as effective and feasible on fatigue, physical condition, and quality of life as traditional rehabilitation models | Fatigue/lack of energy | After discharge: within two weeks of discharge | Mixed (35; 27 completed)<br><br>57% female (20/35) | Fatigue: Fatigue Severity Scale (FSS) | The same multimodal exercise programme via a booklet only |
| Duffy (2024)[8]<br><br>USA | To investigate the use of topical platelet-rich plasma for the treatment of post-COVID-19 olfactory dysfunction | Olfactory and/or gustatory dysfunction | After diagnosis: positive test and six months or more of symptoms | Mixed (85; 83 analysed)<br><br>71% female (59/83) | Olfactory and/or gustatory function: Brief Smell Identification Test (BSIT) | Placebo: saline impregnated Surgifoam treatment |
| Elyazed (2024)[9]<br><br>Egypt | To investigate the effect of home-based pulmonary rehabilitation on exercise capacity in patients with post COVID-19 syndrome | General/multiple: post-COVID syndrome, and fatigue, dyspnoea, and exercise intolerance | After recovery: at least one month after acute phase recovery | Mixed (68; 60 analysed)<br><br>45% female (27/60) | Pulmonary/respiratory or cardiovascular function: Modified Medical Research Council (mMRC) scale<br><br>Physical fitness: Six-Minute Walk Test (6MWT); Harvard Step Test (Physical Fitness Index, PFI) | Usual medical care |

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| | | | | | Quality of life: Short Form 36 (SF-36)<br>Fatigue: Chalder Fatigue Scale | |
| Gaudreau-Majeau (2024)[10]<br><br>Canada | To assess the effectiveness of an eight-week cardiopulmonary rehabilitation programme on cognition, psychological well-being, and sleep quality in individuals with Long COVID-19 | Respiratory or cardiovascular function or physical fitness: dyspnoea or asthenia (or a one-point increase in dyspnoea on the mMRC dyspnoea scale, compared with pre-COVID) | After diagnosis: three months after initial positive test | Mixed (40; 32 analysed)<br><br>66% female (25/38) | Psychological: Perceived-Stress Scale (PSS); Pittsburgh Sleep-Quality (PSQI); Geriatric Depression Scale (GDS); State-Trait Anxiety Inventory (STAI and TRAI)<br><br>Cognitive: Montreal Cognitive Assessment (MoCA); Hopkins Verbal Learning Test (HVLT); Digit Span, (a subtest of the Weschler Adult Intelligence Scale-IV); Trail Making Test, Mental Alternating Test; Verbal fluency tests | Usual activities (no change to diet or exercise) |
| Gomes dos Santos (2024)[11]<br><br>Brazil | To analyse the effects of cardiopulmonary rehabilitation (respiratory, aerobic, and resistance muscle training) on exercise tolerance, dyspnoea, fatigue, and body composition in individuals with post-COVID-19 syndrome | General/multiple: Post COVID syndrome - respiratory or functional symptoms including dyspnoea, cough and fatigue | Unclear/not stated: after acute infection, confirmed by PCR | Mixed (34; 33 analysed)<br><br>61% female (20/33) | Physical fitness: functional capacity (6MWT) | Biweekly remote health education lectures, delivered by a physical therapist; and maintain daily activities |

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| Gonzalez-Moreno (2024)[12]<br><br>Spain | To analyse the effectiveness of a psychological programme (PsiCoRes) based on third-generation therapies (mindfulness, and acceptance and commitment therapy) for improving psychological and emotional needs of patients with Long COVID | General/multiple: persistent COVID-19 | Unclear/not stated: a diagnosis of persistent COVID-19 | Mixed (70)<br><br>93% female (65/70) | Psychological: Subjective Happiness Scale (SHS); Self Compassion Scale (SCS); Perceived Stress Scale; State-Trait Anxiety Questionnaire; Beck Depression Inventory-II (BDI-II) | Waiting list |
| Kaczmarczyk (2024)[13]<br><br>Poland | To develop and implement a specific and well-tolerated resistance exercise programme to reduce muscle weakness in older adults impacted by COVID-19 | General/multiple: one or more post-COVID symptom (e.g., fatigue, muscle weakness, dizziness, headache, memory and concentration disorders, exercise intolerance or depression) | After diagnosis: positive test three to 12 months before the start of the study | Mixed (51; 46 analysed)<br><br>50% female (23/46) | Physical fitness: static and dynamic muscle strength; functional tests (timed up and go test, TUG; chair sit-to-stand tests, CS-30 and 5STS) | Usual activities |
| Korapatti (2024)[14]<br><br>USA | To assess the impact of biosound therapy on Long COVID symptoms | General/multiple: at least three persistent COVID symptoms | After diagnosis: at least 30 days after positive COVID test | Mixed (14; 13 analysed)<br><br>77% female (10/13) | Psychological: Patient Health Questionnaire (PHQ-9); Generalized Anxiety Disorder (GAD-7)<br><br>General or multiple: COVID-19 Persistent Symptom Questionnaire (developed by the study authors)<br><br>Cognitive: Cambridge Brain Science (CBS) tasks; COVID- | Control group not described |

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| | | | | | 19 Persistent Symptom Questionnaire - memory | |
| Mohebbi (2024)[15]<br><br>Iran | To investigate the efficacy of frequency-controlled ear acupuncture in treating COVID-19-related olfactory dysfunction | Olfactory and/or gustatory dysfunction | After diagnosis: 10 to 20 weeks of loss of smell after a positive test or close contact with a confirmed positive case | Mixed (40)<br><br>60% female (24/40) | Olfactory and/or gustatory function: Smell Identification Test | Sham treatment (laser switched off) |
| Paneroni (2024)[16]<br><br>Italy | To evaluate the efficacy of home-based rehabilitation (aerobic reconditioning and muscle strengthening) with teleconsultations with a specialist nurse for patients with persistent effects following hospitalisation for COVID-19 | Respiratory or cardiovascular function or physical fitness: persistent exercise intolerance or hypoxia at rest and/ or during exercise (unable to walk predicted distance 6MWT; or on oxygen all day with a target of 94% or during exertion) | After discharge: first assessment was in the two days before hospital discharge. In-hospital stay averaged about 80 days | Mixed (79; 74 analysed; 55 at two-month follow-up)<br><br>28% female (22/79) | Physical fitness: effort tolerance (6MWT) | Remote teleconsultation with nursing staff |
| Sanchez (2024)[17]<br><br>Spain | To test the efficacy of respiratory physiotherapy based on instrumental breathing training and aerobic exercise combined with olfactory and gustatory training in patients with Long COVID | General/multiple: symptoms of dyspnoea and loss or decrease of sense of smell or taste | After diagnosis: more than five months after symptom onset and diagnosis | Mixed (209; 200 analysed)<br><br>51% female (101/200) | Pulmonary/respiratory or cardiovascular function: spirometry - Forced Vital Capacity (FVC); maximum volume of exhaled air in the first second of the forced vital capacity (FEV1); FEV1/FVC ratio; Modified Borg Scale; mMRC dyspnoea scale | No treatment |

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| | | | | | Olfactory and/or gustatory function: The Singapore Smell and Taste Questionnaire (SSTQ) | |
| Sarmento (2024)[18]<br><br>Canada | To assess the feasibility, safety, and satisfaction associated with an eight-week virtual pulmonary rehabilitation (PR) programme with the exercise component delivered through group or self-directed sessions | Respiratory or cardiovascular function or physical fitness: severe persistent respiratory symptoms | Unclear/not stated: three or more months after confirmed or suspected infection | Mixed (19; 14 analysed)<br><br>86% female (12/14) | Feasibility, tolerability and/or safety: feasibility, recruitment rate, completion rate, drop-out rate, safety, and satisfaction<br><br>(Secondary outcomes: lung function, dyspnoea, fatigue, sit-to-stand capacity, and HRQoL) | Two intervention groups: 1) virtual PR program delivered in groups sessions via video conference by a physiotherapist<br><br>2) Self-directed exercise: the same PR programme performed unsupervised at home by following a pre-recorded video |
| Schmidt (2024)[19]<br><br>Germany | To investigate topical nasal corticosteroid with olfactory training, versus olfactory training alone, for persistent olfactory dysfunction after a proven infection with SARS-CoV-2 | Olfactory and/or gustatory dysfunction: loss of smell | Unclear/not stated: acute infection was on average 5 months (4–40 weeks) before recruitment | Mixed (20; 16 completed)<br><br>70% female (14/20) | Olfactory and/or gustatory function: Sniffin' Sticks; retro-nasal olfactory function test | Olfactory training only |

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| Slankamenac (2024)[20]<br><br>Serbia | To investigate the effects of the administration of creatine for eight weeks, with or without glucose, on patient-reported outcomes, exercise tolerance, and tissue creatine levels in patients with Long COVID | Fatigue/lack of energy: moderate fatigue plus one other Long COVID symptom (ageusia, anosmia, body aches, breathing difficulties, difficulties concentrating, headache, lung pain, or general malaise) | Unclear/not stated: individuals with Long COVID symptoms | Mixed (15)<br><br>60% female (9/15) | Physical fitness: walking time to exhaustion<br><br>Fatigue: Multidimensional Fatigue Inventory (MFI-20) test<br><br>General or multiple: severity of Long COVID symptoms (visual analogue scale, VAS)<br><br>Neurophysiological/brain imaging: concentrations of creatine assessed by magnetic resonance spectroscopy (MRS) in the vastus medialis muscle and thalamus, frontal, precentral, paracentral, and parietal white and grey matter of the brain | Glucose alone |
| Spiesshoefer (2024)[21]<br><br>Germany | To investigate the impact of inspiratory muscle training on diaphragm and inspiratory muscle weakness and exertional dyspnoea in individuals with Long COVID | Respiratory or cardiovascular function or physical fitness: persistent diaphragm muscle weakness and associated dyspnoea | After discharge: approximately two years after discharge - median 31 months | Mixed (18; 18 analysed; 14 at six-week follow-up)<br><br>39% female (7/18) | Pulmonary/respiratory or cardiovascular function: change in inspiratory muscle fatiguability (time to task failure in seconds) | Sham inspiratory muscle training |
| Tan (2024)[22]<br><br>China | To investigate the impact of hydrogen-rich water (HRW) on the fatigue and dyspnoea of Long-COVID patients | General/multiple fatigue and dyspnoea | After diagnosis: Reported symptoms for more than four | Mixed (32)<br><br>69% female (22/32) | Pulmonary/respiratory or cardiovascular function: mMRC Dyspnoea Scale<br><br>Physical fitness: 6MWT; 30- | Placebo water |

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| | | | weeks after diagnosis | | second Chair Stand Test (30s-CST)<br><br>Fatigue: FSS | |

Table 2: JBI risk of bias assessment

| First author (year) | Q1. True randomisation? | Q2. Concealed allocation? | Q3. Similar at baseline? | Q4. Participants blind? | Q5. Treatment delivery blind? | Q6. Outcomes assessors blind? | Q7. Identical treatment? | Q8. Follow up complete? | Q9. ITT analysis? | Q10. Same outcome measurement? | Q11. Reliable measurement? | Q12. Appropriate statistical analysis? | Q13. Appropriate trial design? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ahmad (2024) | + | + | + | - | - | - | + | - | - | + | + | ? | + |
| Andrews (2024) | + | ? | ? | + | + | ? | + | + | - | + | + | ? | + |
| Cantone (2024) | + | + | ? | ? | ? | + | + | - | - | + | + | ? | + |
| Carpallo-Porcar (2024) | + | ? | + | - | - | + | + | + | + | + | + | ? | + |
| Duffy (2024) | ? | ? | + | + | - | - | + | + | - | + | + | + | + |
| Elyazed (2024) | + | + | + | - | - | ? | + | + | - | + | + | + | + |
| Gaudreau-Majeau (2024) | + | ? | - | - | - | + | + | + | - | + | + | ? | + |
| Gomes dos Santos (2024) | + | + | ? | - | - | + | + | + | - | + | + | + | + |
| Gonzalez-Moreno (2024) | + | ? | ? | - | - | ? | + | ? | ? | + | + | + | + |
| Kaczmarczyk (2024) | + | ? | - | - | - | ? | + | + | - | + | + | + | + |
| Korapatti (2024) | ? | ? | ? | - | - | - | + | + | - | + | + | ? | ? |
| Mohebbi (2024) | + | ? | + | + | - | ? | + | + | + | + | + | + | + |
| Paneroni (2024) | + | ? | + | - | - | ? | + | + | - | + | + | + | + |
| Sanchez (2024) | + | + | + | - | - | + | + | + | - | + | + | + | + |
| Sarmento (2024) | + | ? | ? | - | - | ? | + | + | - | + | + | ? | + |

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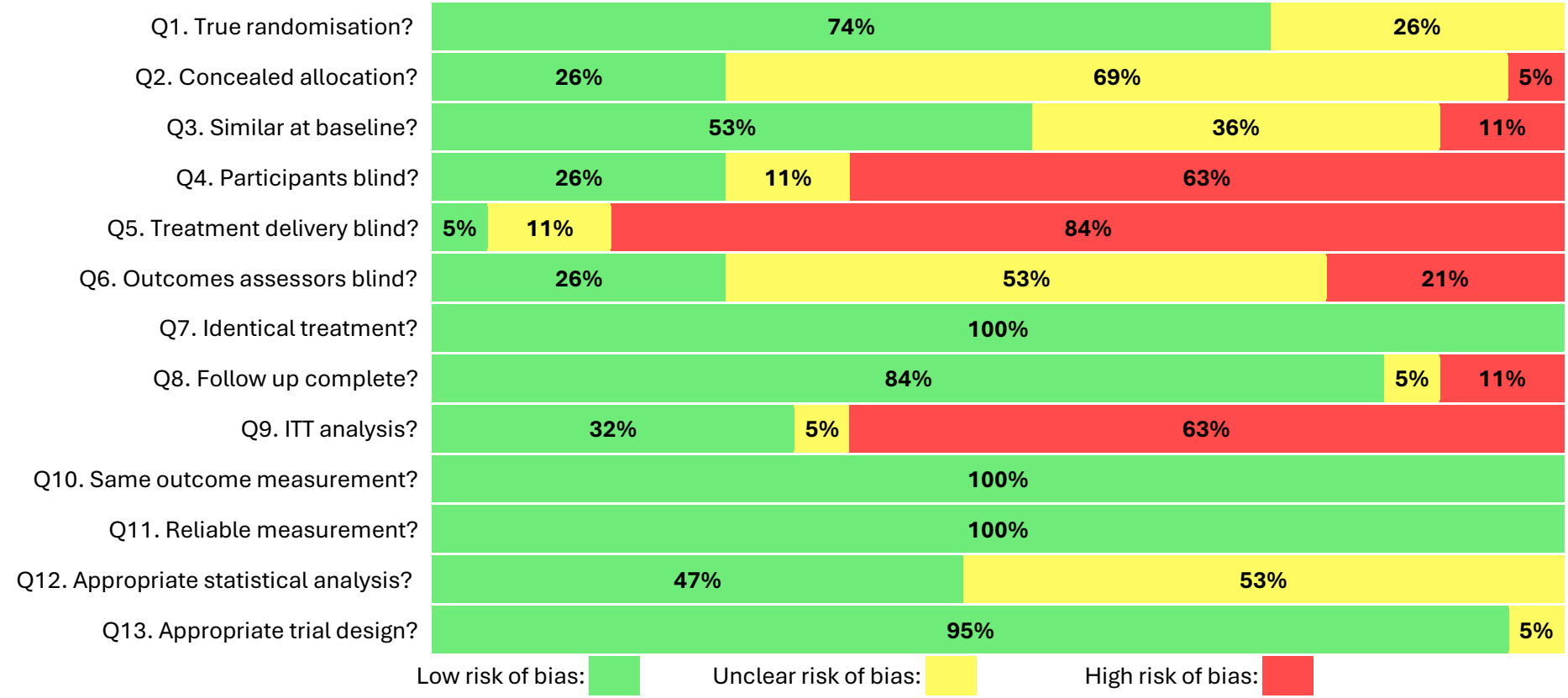
| Schmidt (2024) | ? | - | + | - | - | ? | + | + | + | + | + | ? | + |
| Slankamenac (2024) | ? | ? | ? | + | ? | ? | + | + | + | + | + | ? | + |
| Spiesshoefer (2024) | ? | ? | + | ? | - | ? | + | + | + | + | + | + | + |
| Tan (2024) | + | ? | + | + | - | - | + | + | + | + | + | ? | + |

+ = low risk of bias; ? = unclear risk of bias; - = high risk of bias




NB: figures may not add up to 100% due to rounding. In our reports, we adopt a 'once randomised, always analysed' approach to assessing the use of an ITT analysis (Q9), which is consistent with previous research and guidance.[31-33]

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27. Raine G, Khouja C, Khatwa M, Harden M, Sutcliffe K, Sowden A. Treatment and rehabilitation of Long COVID: A scope of the literature. Update October 2023. London: EPPI Centre, UCL Social Research Institute, UCL Institute of Education, University College London 2023. Available from: https://eppi.ioe.ac.uk/cms/Default.aspx?tabid=3860.

28. Raine G, Khouja C, Khatwa M, Sutcliffe K, Sowden A. Treatment and rehabilitation of Long COVID: A scope of the literature. Update January 2023. London: EPPI Centre, UCL Social Research Institute, UCL Institute of Education, University College London; 2023. Available from: https://eppi.ioe.ac.uk/cms/Default.aspx?tabid=3860.

29. Raine G, Khouja C, Harden M, Sutcliffe K, Sowden A. Treatment and rehabilitation of Long COVID: A scope of the literature. Update October 2022. London: EPPI Centre, UCL Social Research Institute, UCL Institute of Education, University College London; 2022. Available from: https://eppi.ioe.ac.uk/cms/Default.aspx?tabid=3860.

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## Appendix 1 – search strategies

**Cochrane Controlled Register of Trials (CENTRAL)**
via Wiley http://onlinelibrary.wiley.com/
Issue: Issue 5 of 12, May 2024
Date searched: 3rd June 2024
Records retrieved: 1624

Although 1624 records were identified overall in CENTRAL, trial register records were removed from this set, leaving a total of 1323 records downloaded for this update.

#1 [mh ^"Post-Acute COVID-19 Syndrome"] 234
#2 [mh ^COVID-19/co] 320
#3 [mh ^COVID-19] 7751
#4 [mh ^SARS-CoV-2] 3228
#5 [mh ^Syndrome] 6616
#6 [mh ^Survivors] 1805
#7 #3 or #4 8009
#8 #5 or #6 8415
#9 #7 and #8 104
#10 #1 or #2 or #9 605
#11 (long next (covid* or "covid-19" or covid19 or coronavirus) or longcovid*):ti,ab,kw 472
#12 (post next (covid* or "covid-19" or covid19 or coronavirus or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2") or postcovid*):ti,ab,kw 806
#13 ((post next acute or postacute) near/2 (covid* or "covid-19" or covid19 or coronavirus or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2")):ti,ab,kw 293
#14 PASC:ti,ab,kw 69
#15 (sequela* near/6 (covid* or "covid-19" or covid19 or coronavirus or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2")):ti,ab,kw 177
#16 (chronic near/2 (covid* or "covid-19" or covid19 or coronavirus or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2")):ti,ab,kw 43
#17 (ongoing next (covid* or "covid-19" or covid19 or coronavirus or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2")):ti,ab,kw 113
#18 ((long* term or longterm) near/3 (covid* or "covid-19" or covid19 or coronavirus or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2")):ti,ab,kw 862
#19 (persist* near/6 (covid* or "covid-19" or covid19 or coronavirus or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2")):ti,ab,kw 291
#20 ((post next discharg* or postdischarg*) near/4 (covid* or "covid-19" or covid19 or coronavirus or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2")):ti,ab,kw 17
#21 ((long next haul* or longhaul*) near/6 (covid* or "covid-19" or covid19 or coronavirus or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2")):ti,ab,kw 16
#22 (surviv* near/3 (covid* or "covid-19" or covid19 or coronavirus or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2")):ti,ab,kw 207
#23 (after next (covid* or "covid-19" or covid19 or coronavirus or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2")):ti,ab,kw 340
#24 ((ongoing or lasting or prolonged or fluctuat* or residual* or continu* or linger*) near/6 (symptom* or effect* or complication* or sequela* or syndrome or illness* or disorder* or dysfunction* or impair* or impact* or consequence*) near/6 (covid* or "covid-19" or covid19 or coronavirus or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2")):ti,ab,kw 193
#25 {OR #11-#24} 2215
#26 #10 or #25 with Publication Year from 2022 to 2024, in Trials 1517

#27 #10 or #25 with Cochrane Library publication date Between Jan 2022 and Mar 2024, in Trials 1498
#28 #26 or #27 1624

**MEDLINE ALL**
(includes: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE)
via Ovid http://ovidsp.ovid.com/
Date range: 1946 to May 30, 2024
Date searched: 3rd June 2024
Records retrieved: 1098

The MEDLINE strategy below includes a search filter to limit retrieval to RCTs using the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity and precision-maximizing version (2023 revision); Ovid format.

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from: www.training.cochrane.org/handbook.

1 Post-Acute COVID-19 Syndrome/ (3413)
2 COVID-19 post-intensive care syndrome.mp. (6)
3 COVID-19/co (17814)
4 COVID-19/ or SARS-CoV-2/ (270941)
5 Syndrome/ (124047)
6 Survivors/ (31587)
7 5 or 6 (155510)
8 4 and 7 (1143)
9 1 or 2 or 3 or 8 (20394)
10 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,kf,ot,bt. (5451)
11 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,kf,ot,bt. (11091)
12 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (1103)
13 PASC.ti,ab,kf,ot,bt. (982)
14 (sequela$ adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (3037)
15 (chronic adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (361)
16 (ongoing adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (3492)
17 ((long$ term or longterm) adj3 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (2556)
18 (persist$ adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (4663)
19 ((post discharg$ or postdischarg$) adj4 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (97)

20 ((long haul$ or longhaul$) adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (281)
21 (surviv$ adj3 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (3349)
22 (after adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (10404)
23 ((ongoing or lasting or prolonged or fluctuat$ or residual$ or continu$ or linger$) adj6 (symptom$ or effect$ or complication$ or sequela$ or syndrome or illness$ or disorder$ or dysfunction$ or impair$ or impact$ or consequence$) adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (3225)
24 or/10-23 (36728)
25 9 or 24 (50460)
26 exp randomized controlled trial/ (615611)
27 randomized controlled trial.pt. (614044)
28 controlled clinical trial.pt. (95541)
29 randomi?ed.ab. (772640)
30 placebo.ab. (248731)
31 clinical trials as topic.sh. (202499)
32 randomly.ab. (434508)
33 trial.ti. (310251)
34 or/26-33 (1652190)
35 exp animals/ not humans.sh. (5226717)
36 34 not 35 (1524360)
37 25 and 36 (1639)
38 limit 37 to yr="2022-Current" (1118)
39 (2022* or 2023* or 2024*).dt. (3836722)
40 37 and 39 (1079)
41 38 or 40 (1126)
42 preprint.pt. (24563)
43 41 not 42 (1112)
44 remove duplicates from 43 (1098)

**Embase**
via Ovid http://ovidsp.ovid.com/
Date range: 1974 to 2024 May 31
Date searched: 3rd June 2024
Records retrieved: 1719

The Embase strategy below includes a search filter to limit retrieval to RCTs:

Lefebvre C, Eisinga A, McDonald S, Paul N. Enhancing access to reports of clinical trials published world-wide - the contribution of EMBASE records to the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library. *Emerg Themes Epidemiol* 2008;5:13

1 long COVID/ (7741)
2 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,kw,ot. (5674)
3 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,kw,ot. (14271)
4 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (1006)
5 PASC.ti,ab,kw,ot. (1238)

6 (sequela$ adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (3797)
7 (chronic adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (470)
8 (ongoing adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (3622)
9 ((long$ term or longterm) adj3 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (3197)
10 (persist$ adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (5952)
11 ((post discharg$ or postdischarg$) adj4 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (188)
12 ((long haul$ or longhaul$) adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (303)
13 (surviv$ adj3 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (4915)
14 (after adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (14164)
15 ((ongoing or lasting or prolonged or fluctuat$ or residual$ or continu$ or linger$) adj6 (symptom$ or effect$ or complication$ or sequela$ or syndrome or illness$ or disorder$ or dysfunction$ or impair$ or impact$ or consequence$) adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (3975)
16 or/2-15 (46619)
17 1 or 16 (47363)
18 random$.ti,ab. (2074920)
19 factorial$.ti,ab. (49513)
20 crossover$.ti,ab. (93967)
21 cross-over$.ti,ab. (38838)
22 placebo$.ti,ab. (380097)
23 (doubl$ adj blind$).ti,ab. (252616)
24 (singl$ adj blind$).ti,ab. (33235)
25 assign$.ti,ab. (513836)
26 allocat$.ti,ab. (214324)
27 volunteer$.ti,ab. (303164)
28 Crossover Procedure/ (78221)
29 double blind procedure/ (219652)
30 Randomized Controlled Trial/ (824645)
31 single blind procedure/ (54978)
32 controlled clinical trial/ (473278)
33 or/18-32 (3201959)
34 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (6999489)
35 33 not 34 (2859089)
36 17 and 35 (3145)
37 limit 36 to yr="2022 -Current" (2326)
38 (2022$ or 2023$ or 2024$).dd. (1503749)
39 36 and 38 (842)
40 37 or 39 (2447)
41 (conference abstract or "conference review").pt. (5186136)
42 40 not 41 (1844)
43 limit 42 to "remove preprint records" (1719)

**PsycINFO**
via Ovid http://ovidsp.ovid.com/
Date range: 1806 to May Week 5 2024
Date searched: 5th June 2024
Records retrieved: 465

The PsycINFO strategy below includes a search filter to limit retrieval to RCTs developed by the information specialist at the Cochrane Common Mental Disorders Group.

1 post-covid-19 conditions/ (226)
2 covid-19/ (36179)
3 coronavirus/ (6086)
4 syndromes/ (18215)
5 sequelae/ (4049)
6 2 or 3 (38639)
7 4 or 5 (22195)
8 6 and 7 (364)
9 1 or 8 (557)
10 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,id,ot. (347)
11 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,id,ot. (1174)
12 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (59)
13 PASC.ti,ab,id,ot. (61)
14 (sequela$ adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (237)
15 (chronic adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (26)
16 (ongoing adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (399)
17 ((long$ term or longterm) adj3 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (221)
18 (persist$ adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (325)
19 ((post discharg$ or postdischarg$) adj4 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (7)
20 ((long haul$ or longhaul$) adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (24)
21 (surviv$ adj3 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (343)
22 (after adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (644)
23 ((ongoing or lasting or prolonged or fluctuat$ or residual$ or continu$ or linger$) adj6 (symptom$ or effect$ or complication$ or sequela$ or syndrome or illness$ or disorder$ or dysfunction$ or impair$ or impact$ or consequence$) adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (385)
24 or/10-23 (3235)
25 Randomized Clinical Trials/ (556)
26 randomized controlled trials/ (1075)

27 clinical trials/ (12359)
28 clinical trial.md. (42470)
29 (randomi#ed or randomi#ation or randomi#ing).ti,ab,id. (115884)
30 randomly.ti,ab,id. (87054)
31 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster* or control* or crossover or cross over or pragmatic or quasi or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or recruit* or split or substitut* or treat*))).ti,ab,id. (135661)
32 (groups or (control* adj3 group*)).ab. (634113)
33 ((control* or trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,hw. (20154)
34 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,id. (30039)
35 trial.ti. (40687)
36 (placebo or sham).ti,ab,id,hw. (59936)
37 treatment outcome.md. (24978)
38 treatment effectiveness evaluation/ (29762)
39 mental health program evaluation/ (2495)
40 or/25-39 (842343)
41 9 or 24 (3411)
42 40 and 41 (538)
43 limit 42 to yr="2022 -Current" (398)
44 (2022$ or 2023$ or 2024$).up. (464765)
45 42 and 44 (454)
46 43 or 45 (466)
47 remove duplicates from 46 (465)

**CINAHL Ultimate**
via Ebsco https://www.ebsco.com/
Date range: Inception to 20241231
Date searched: 3rd June 2024
Records retrieved: 898

The CINAHL strategy below includes a search filter to limit retrieval to RCTs developed by Glanville et al.:
Glanville J, Dooley G, Wisniewski S, Foxlee R, Noel-Storr A. Development of a search filter to identify reports of controlled clinical trials within CINAHL Plus. *Health Info Libr J* 2019;36:73-90.

S1 (MH "Post-Acute COVID-19 Syndrome") (1,375)
S2 TI ( long N1 (covid* or covid-19 or covid19 or coronavirus) or longcovid* ) OR AB ( long N1 (covid* or covid-19 or covid19 or coronavirus) or longcovid* ) (1,654)
S3 TI ( post N1 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) or postcovid* ) OR AB ( post N1 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) or postcovid* ) (1,844)
S4 TI ( ("post acute" or post-acute or postacute) N3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) OR AB ( ("post acute" or post-acute or postacute) N3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) (394)
S5 TI PASC OR AB PASC (119)

S6 TI ( sequela* N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) OR AB ( sequela* N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) (646)

S7 TI ( chronic N2 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) OR AB ( chronic N2 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) (291)

S8 TI ( ongoing N1 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) OR AB ( ongoing N1 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) (742)

S9 TI ( (long* N1 term or long-term or longterm) N3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) OR AB ( (long* N1 term or long-term or longterm) N3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) (1,146)

S10 TI ( persist* N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) OR AB ( persist* N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) (1,036)

S11 TI ( (post N1 discharg* or post-discharg* or postdischarg*) N4 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) OR AB ( (post N1 discharg* or post-discharg* or postdischarg*) N4 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) (51)

S12 TI ( (long N1 haul* or long-haul* or longhaul*) N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) OR AB ( (long N1 haul* or long-haul* or longhaul*) N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) (90)

S13 TI ( surviv* N3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) OR AB ( surviv* N3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) (1,127)

S14 TI ( after N1 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) OR AB ( after N1 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) (4,606)

S15 TI ( (ongoing or lasting or prolonged or fluctuat* or residual* or continu* or linger*) N6 (symptom* or effect* or complication* or sequela* or syndrome or illness* or disorder$ or dysfunction* or impair* or impact* or consequence*) N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) OR AB ( (ongoing or lasting or prolonged or fluctuat* or residual* or continu* or linger*) N6 (symptom* or effect* or complication* or sequela* or syndrome or illness* or disorder$ or dysfunction* or impair* or impact* or consequence*) N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) ) (960)

S16 (MH "Randomized Controlled Trials+") (145,077)

S17 (MH "Double-Blind Studies") (54,356)

S18 (MH "Single-Blind Studies") (16,110)

S19 (MH "Random Assignment") (85,617)

S20 (MH "Pretest-Posttest Design") (56,469)

S21 (MH "Cluster Sample") (5,604)

S22 TI randomised OR randomized (336,176)

S23 AB random* (404,285)

S24 TI trial (194,929)

S25 MH (sample size) AND AB (assigned OR allocated OR control) (4,499)

S26 MH (placebos) (14,455)

S27 PT (randomized controlled trial) (157,346)

S28 AB (control W5 group) (149,479)
S29 MH (crossover design) OR MH (comparative studies) (503,294)
S30 AB (cluster W3 RCT) (509)
S31 MH animals+ (102,413)
S32 MH (animal studies) (156,706)
S33 TI (animal model*) (3,957)
S34 S31 OR S32 OR S33 (250,134)
S35 MH (human) (2,807,550)
S36 S34 NOT S35 (215,464)
S37 S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 (1,059,698)
S38 S37 NOT S36 (1,010,880)
S39 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 (12,104)
S40 S38 AND S39 (1,222)
S41 S38 AND S39 Limiters - Publication Date: 20220101-20241231 (881)
S42 (ZD 2022* or 2023* or 2024*) (362,127)
S43 S40 AND S42 (268)
S44 S41 OR S43 (898)

## Appendix 2

### The Joanna Briggs Institute Critical Appraisal Checklist for Randomized Controlled Trials

Q1 Was true randomization used for assignment of participants to treatment groups? Yes, No, Unclear, NA

Q2 Was allocation to treatment groups concealed? Yes, No, Unclear, NA

Q3 Were treatment groups similar at the baseline? Yes, No, Unclear, NA

Q4 Were participants blind to treatment assignment? Yes, No, Unclear, NA

Q5 Were those delivering treatment blind to treatment assignment? Yes, No, Unclear, NA

Q6 Were outcomes assessors blind to treatment assignment? Yes, No, Unclear, NA

Q7 Were treatment groups treated identically other than the intervention of interest? Yes, No, Unclear, NA

Q8 Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? Yes, No, Unclear, NA

Q9 Were participants analyzed in the groups to which they were randomized? Yes, No, Unclear, NA

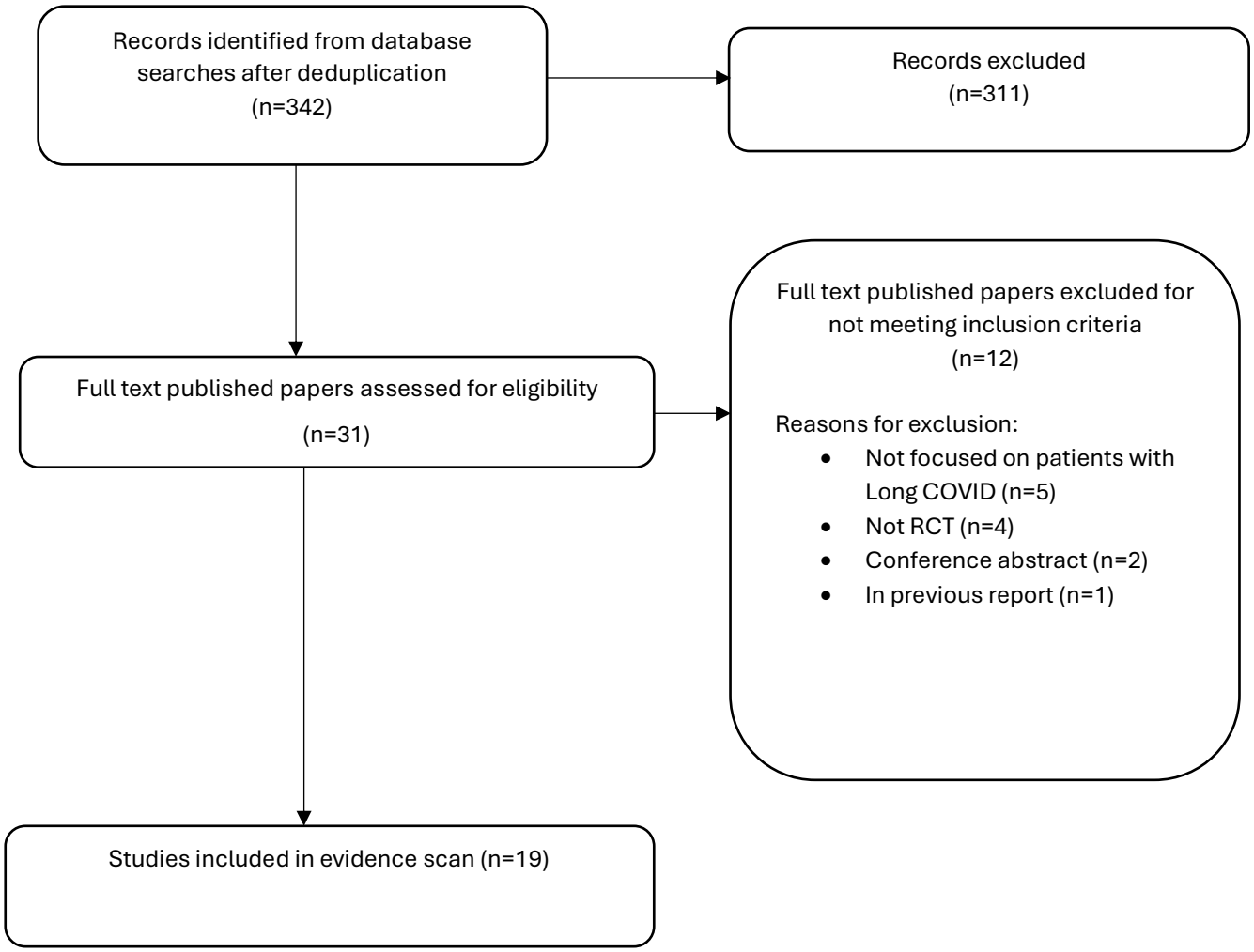
Q10 Were outcomes measured in the same way for treatment groups? Yes, No, Unclear, NA

Q11 Were outcomes measured in a reliable way? Yes, No, Unclear, NA

Q12 Was appropriate statistical analysis used? Yes, No, Unclear, NA

Q13 Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial? Yes, No, Unclear, NA

## Appendix 3: Flow of studies through the review



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- Producing new and improved methods for undertaking reviews
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and the London School of Hygiene and Tropical Medicine.

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First produced in 2024 by:

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