Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

COVID-19 Evidence Synthesis.

Interventions to improve Long COVID symptoms: A systematic review

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About the Health Information and Quality Authority (HIQA)

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.

- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.

- **Regulating health services —** Regulating medical exposure to ionising radiation.

- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.

- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.

- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.

- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

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List of abbreviations used in this report

6MWT	six-minute walk test
EAG	expert advisory group
ENO	English National Opera (breathe programme)
HIQA	Health Information and Quality Authority
HRQoL	health related quality of life
HSE	Health Service Executive
ME/CFS	myalgic encephalomyelitis/chronic fatigue syndrome
NICE	National Institute for Health and Care Excellence
PEA-LUT	palmitoylethanolamide and luteolin
QoL	quality of life
RCT	randomised controlled trial
SD	standard deviation
SF-36	36 item short form survey
TDI	Threshold-Discrimination-Identification
TSSP	tetra sodium pyrophosphate spray
VAS	visual analogue scale
WHO	World Health Organisation

Acknowledgments

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Expert Advisory Group and Evaluation Team membership

Membership of the Expert Advisory Group involves review of evidence synthesis documents and contribution to a discussion which informs the advice from HIQA to the HSE. It does not necessarily imply agreement with all aspects of the evidence synthesis or the subsequent advice.

The membership of the EAG was as follows:

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* Ad hoc member for this meeting only.

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Barrie Tyner, Cillian McDowell, Conor Teljeur, Debra Spillane, Fearghal Comaskey, Karen Cardwell, Kieran Walsh, Leah McManus, Louise Larkin, Máirín Ryan, Marie Carrigan, Michelle O'Shea, Michelle O'Neill, Patricia Harrington, Shibu Shrestha, Susan Spillane.

Conflicts of interest

Prof. Susan Smith is a member of the Board of ExWell Medical, a not-for-profit company providing community based medical exercise programmes for people with chronic diseases.

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Advice to the Health Service Executive

The purpose of this evidence synthesis is to provide advice to the Health Service Executive (HSE) on evidence to support interventions that improve Long COVID symptoms to inform updates to the HSE's Long COVID interim model of care. This evidence synthesis is not a clinical guideline. This advice is informed by a systematic review of randomised controlled trials among people with Long COVID and discussion with the HIQA's COVID-19 Expert Advisory Group (EAG). Key points from the review and discussion with the EAG and the ensuing advice to the HSE are reported below.

Key points

- Following an infection with SARS-CoV-2, prolonged and residual symptoms may occur. These symptoms may come and go over time, and novel symptoms and clinical manifestations may appear related to the acute SARS-CoV-2 infection. This condition may be referred to as post-acute COVID-19, post-COVID-19 condition, post-acute sequelae of SARS-CoV-2 infection, long-term effects of COVID, chronic COVID or Long COVID. In this review, the term Long COVID is used.
- Long COVID is associated with a diverse range of symptoms which can have substantial negative physical, mental, social and economic effects. There is substantial variation in the prevalence estimates of Long COVID, ranging from 15.2% to 53.1% in studies based on self-report data, and from 1.8% to 8.3% in studies considering those with a diagnosis of or referral for Long COVID.
- To prevent Long COVID, it is advised to minimise the risk of infection or reinfection with SARS-CoV-2. As those with a severe initial infection are more at risk of developing Long COVID, COVID-19 vaccination, which can reduce the severity of COVID-19 cases, may also reduce the incidence of Long COVID. However, the effectiveness of treatments for Long COVID has remained unclear.
- This systematic review aimed to address the research question "What interventions improve Long COVID symptoms?"
- This systematic review included randomised controlled trials (RCTs) among people with Long COVID. RCTs, studies in which participants are randomly allocated to treatment or comparator groups and outcomes assessed, are considered the gold-standard to address clinical questions relating to the effectiveness and safety of interventions. This is due to randomisation removing many of the biases inherent to other study designs, thereby enabling a better examination of cause and effect between an intervention and outcome.

- In total, 57 RCTs were identified. These studies considered interventions for adults with various Long COVID symptoms (for example, dyspnoea, fatigue, or loss of smell) as opposed to the onset of new conditions such as kidney failure.
- Studies were categorised as pharmaceutical and other medical interventions and non-pharmaceutical interventions:
    - Pharmaceutical and other medical interventions were:
        - those that were being used off-label (that is, products used for an unapproved indication, or in an unapproved age group, dosage, or route of administration and are limited to those that are approved by the Health Product Regulatory Authority or through the central authorisation process by the European Medicines Agency)
        - those that were investigational and or unauthorised (that is, products that are not licensed anywhere or not authorised by the Health Product Regulatory Authority or centrally through the European Medicines Agency).
    - Non-pharmaceutical interventions were supplements and alternative medicine, exercise, physiotherapy and physical rehabilitation, olfactory training, cognitive and neurorehabilitation, and psychological interventions.
    - Twenty-four trials investigated the effectiveness of pharmaceutical and other medical interventions: eight trials investigating off-label interventions and 16 investigating investigational and or unauthorised interventions.
    - Thirty-three trials focused on non-pharmaceutical interventions: eleven investigating supplements and alternative medicine, eight trials on exercise, seven trials on physiotherapy and physical rehabilitation, four on olfactory training, two on cognitive and neurorehabilitation and one trial on psychological interventions.
- Overall, studies were short in duration (pharmaceutical/medical interventions median duration: six weeks; non-pharmaceutical interventions median duration: six weeks) and the longest follow-up period was 20 weeks. Therefore, the long-term effects and safety of interventions could not be assessed. Study sample sizes were also generally small (pharmaceutical/medical interventions median sample size: 71; non-pharmaceutical interventions median sample size: 52). Where reported (n=29 trials), interventions were found to be safe and tolerable, with no studies reporting serious adverse events attributed to the interventions.

- The majority of the studies were deemed to be at a high risk of bias, with 74% of the pharmaceutical and other medical interventions and 71% of the non-pharmaceutical interventions assessed as having a high risk of bias. Additionally, conflicts of interest were present in six (25%) of the pharmaceutical and other medical interventions studies, and in 11 (33%) of non-pharmaceutical intervention studies.
- Overall, there was a diverse range of outcomes considered across the studies. In the pharmaceutical and other medical intervention trials, taste or smell (n=12; 50%) and burden of disease (n=9; 38%) outcomes were most commonly assessed. Whereas, the non-pharmaceutical interventions mostly examined pulmonary/respiratory function (n=19; 58%), physical functioning and sleep (n=17; 52%) and burden of disease (n=16; 49%) outcomes.
- The evidence suggests there are potential short-term improvements from personalised exercise interventions for dyspnoea, fatigue, physical function and the physical domain of quality of life (QoL) among some people with Long COVID. The evidence for physiotherapy and rehabilitation programmes also suggested potential short-term benefits, with breathing-related interventions reporting the potential for improvements in respiratory function, dyspnoea, and QoL. However, long-term changes were not assessed for both interventions and even minimal exertion may worsen symptoms among people with post-exertional malaise (that is, the worsening of symptoms following even minor physical or mental exertion).
- There is currently limited understanding of the pathophysiology of Long COVID. There is also no diagnostic biomarker for Long COVID and different mechanisms or combination of mechanisms may drive different Long COVID phenotypes (or observable characteristics of Long COVID). Improving our understanding of Long COVID may help researchers to design targeted interventions that address the multifaceted nature of Long COVID, potentially leading to more effective interventions and improved patient outcomes.
- The review identified several key limitations in the current evidence base for interventions to improve Long COVID symptoms, for instance, small sample sizes, short study duration and follow-up period, lack of focus on patients with long-standing Long COVID, different Long COVID phenotypes, insufficient examination of intervention safety and subpopulations of interest, use of non-specific interventions, and high risk of bias in most studies. There was also a diverse range of interventions considered within the review, and most interventions were only examined by single studies.
- Overall, effective strategies remain elusive and the proposed interventions for people with Long COVID symptoms included in this review do not yet have sufficient evidence to support them. Future research investigating the

effectiveness and safety of interventions is required, and a large number of trials are currently ongoing. A greater understanding of the pathophysiology of Long COVID would facilitate researchers in designing targeted interventions that address the multifaceted nature of Long COVID. In the absence of strong evidence to support the effectiveness of interventions for Long COVID, a holistic approach should be used to support those living with Long COVID.

COVID-19 Expert Advisory Group

- A meeting of the COVID-19 Expert Advisory Group (EAG) was convened to inform the clinical and technical interpretation of the evidence provided.
- The COVID-19 EAG identified additional factors, which may inform both the current policy question and potential further research and policy questions. These include:
    - Patient representatives agreed that it is important to highlight to the public the potential risks involved in seeking treatments for Long COVID that are not supported by a robust clinical evidence base. However, the patient representatives also highlighted that the level of risk varies between treatments and that the risk associated with exercise in individuals with Long COVID needs to be emphasised given potential safety issues for some patients and a lack of knowledge regarding post-exertional malaise in both the medical and the patient community. Highlighting this issue to the same extent in the report would help ensure that patients are fully informed of the potential for harm.
    - It was mentioned that exercise can be effective for a subset of patients, but not all, and caution should be taken when implementing exercise as an intervention. It was noted that most studies are unclear on how or whether symptom exacerbation was considered in the study outcomes. There is also a need for greater clarity in future studies around defining the Long COVID phenotypes of participants in trials of exercise interventions.
    - Pacing and or energy conservation and other self-management strategies as recommended by NICE were suggested for consideration as an appropriate intervention. In terms of future research, focusing more on physical management rather than exercise specifically may be more useful.
    - It was felt that a multidisciplinary approach is very important and that the approach must be personalised as patients experience a wide range of symptoms and thus may benefit from different interventions and the input

from a variety of specialties. The need for more adequate resources to support this multidisciplinary approach was noted.

- Patient representatives stated that many patients with Long COVID in Ireland have reported a significant worsening of their condition, both in the short-term and the long-term following inappropriate exercise. They also noted that a personalised exercise programme should be developed by someone who understands the nature of post-exertional malaise and the potential effects of over-exertion.
- There may be a gap in our knowledge of the safety of interventions as the included studies may not provide the relevant information. For instance, small sample sizes can limit the ability of studies to detect adverse events. It was also noted that risks with interventions could alter over time, and given that many studies in the review had short follow-up periods this potentially limited the detection of adverse events. It was noted that this should be highlighted, so that patients are well informed of risks. Well-structured interventional trials with appropriate follow-up time are therefore important to fully capture adverse events; also observational studies may provide additional information on adverse events beyond that included in RCTs given their tendency to have larger samples and longer follow-up periods.
- It was noted that that Long COVID is a complex issue requiring a complex approach, and that patients need wider support that is not limited to consideration of their physical recovery alone. Shared decision making with due consideration of patient preferences and available social supports may be particularly important. Some concerns were raised that management may tend to focus solely on medical interventions when a broader approach may be needed. It was suggested that the use of a biopsychosocial model may be beneficial given that this complex condition requires a multifaceted approach. However, the availability of evidence to support the use of the biopsychosocial model in Long COVID was queried. It was highlighted that RCTs including the biopsychosocial model may be helpful to assess the effectiveness of this approach.
- There were concerns raised that given the lack of a biomarker for Long COVID the biological component of biopsychosocial model may be ignored. It was suggested that ideally all aspects of the condition should be fully investigated and implemented under a biopsychosocial model and that biological and psychological aspects of the disease can be linked. It was also noted that most clinical guidelines recommend the biopsychosocial approach for managing chronic conditions due to the

recognised interplay between living with a chronic condition and the individual's capacity to manage it using all intrinsic and extrinsic supports.

- While this review focuses on the symptoms of Long COVID, it was noted that there is a need for the HSE to consider and plan on how to manage existing illnesses and respiratory diseases (for example, asthma) that have been exacerbated and or exposed following a SARS-CoV-2 infection.
- It was noted that there are long processes involving a number of steps between the conduct of an RCT and an intervention becoming authorised and incorporated into clinical practice.
- Many of the included pharmaceutical interventions focus solely on loss of taste or smell which, although present in the Long COVID population, are considerably less debilitating than many other systemic symptoms. As many trials are still ongoing, it was suggested that there may be a need to update the review in order to account for new findings, some of which are targeting symptoms of greater importance and impact to individuals with Long COVID. *(Point added in post EAG discussion with the LCAI.)*
- Patient representatives noted that many previously fit, healthy, young people saw their health disappear overnight due to Long COVID. Many people with Long COVID report that they are not recovering or that they feel they are slowly getting worse. Failure to provide adequate services may result in Long COVID continuing to progress, leading to worse outcomes overall.

Advice

Arising from the findings above, HIQA's advice to the HSE is as follows:

- A systematic review of randomised controlled trials was undertaken, investigating pharmaceutical and non-pharmaceutical interventions to improve Long COVID symptoms. While 57 trials were identified, the evidence was limited and no definitively effective treatments were identified.
    - A wide range of interventions were identified (including pharmaceutical and medical interventions, supplements and alternative medicine, exercise, physiotherapy and physical rehabilitation, olfactory training, cognitive and neurorehabilitation, and psychological interventions), with most only examined in single studies.
    - Studies generally had small sample sizes and short follow-up periods, and did not adequately examine intervention safety.

  - The evidence for personalised exercise interventions suggested potential for short-term improvement in dyspnoea, fatigue, physical function and the physical domain of quality-of-life among some people with Long COVID. However, long-term changes were not assessed and there is also potential for exercise to worsen symptoms among people with post-exertional malaise. The evidence for breathing-related interventions suggested potential for short-term improvements in respiratory function, dyspnoea, and quality-of-life among some people with Long COVID.
- There are hundreds of ongoing trials investigating potential interventions for Long COVID symptoms. Further evidence regarding potentially safe and effective interventions may emerge in due course.
- Considerations for planning clinical guidelines and healthcare delivery for Long COVID should include:
  - a holistic, person-centred approach to the assessment and management of people with Long COVID, given that symptoms are highly diverse, vary in severity, and can fluctuate over time.
  - a multidisciplinary approach to treatment with access to a range of specialities including, but not limited to, neurology, infectious diseases, physiotherapy, clinical psychology, occupational therapy, speech and language therapy, pain management, respiratory, cardiology and rehabilitation.
  - shared decision-making between patients and healthcare providers, with specific support and rehabilitation needs determined in consultation with the patient, considering the best available evidence and patients' phenotypes, preferences, goals, and available social support.
  - continuation of public health advice to minimise risk of infection or reinfection and promotion of the COVID-19 vaccination programme to reduce the severity of COVID-19 cases, and potentially the incidence of Long COVID.

1 Background

As of 14 June 2023 there have been over 767 million laboratory-confirmed COVID-19 cases worldwide.[1] Among people infected with SARS-CoV-2, some will experience Long COVID. Although its definition can vary, Long COVID (also referred to as post-acute COVID-19, post-COVID-19 condition, post-acute sequelae of SARS-CoV-2 infection, long-term effects of COVID, and chronic COVID) typically refers to a range of prolonged and persistent symptoms that occur after the acute SARS-CoV-2 infection period.[2, 3] Long COVID can affect several bodily systems, including, but not limited to, the respiratory, cardiovascular, neurological, gastrointestinal, and musculoskeletal systems.[4] Symptoms of Long COVID can include fatigue and or post-exertional malaise, weakness, breathlessness, impaired usual activity, impaired taste and smell, and depression, among many others,[5-7] and may have substantial negative physical, mental, social, and economic effects.[5, 8, 9]

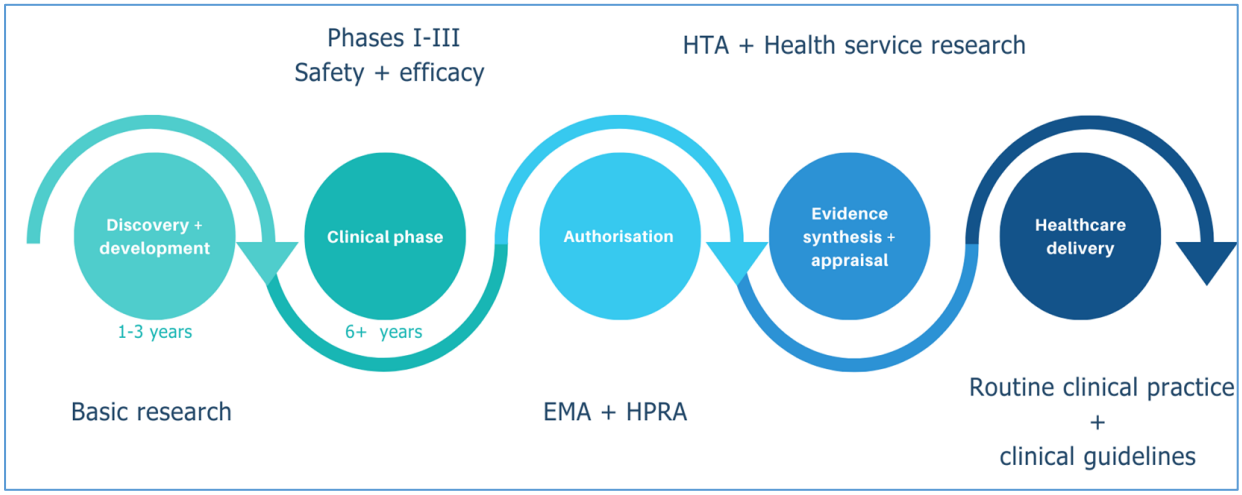
Prevalence estimates of Long COVID vary substantially. For example, a recent HIQA report show a range of prevalence estimates for Long COVID, ranging from 15.2% to 53.1% in studies based on self-report data, and from 1.8% to 8.3% in studies considering those with a diagnosis of or referral for Long COVID.[6] A recent meta-analysis of 194 studies (n=735,006) estimated that at least 45% of people who had COVID-19 were experiencing unresolved symptoms approximately four months after infection. However, pooled estimates from this meta-analysis had very high heterogeneity which was not explained by the study level characteristics of age, sex, follow-up time, or estimated prevalence of 'one or more symptom' in the sample.[5] Long COVID risk factors reported elsewhere include female sex, older age, and pre-existing physical and mental health conditions, although the evidence is uncertain.[6, 10]

The biological mechanisms underpinning Long COVID are still poorly understood. Proposed mechanisms include viral persistence, neuroinflammation, reactivation of latent viruses, excessive blood clotting, autoimmunity triggered by the infection and inflammation-triggered chronic changes leading to tissue dysfunction and damage.[11, 12] Treatments for certain Long COVID components have been effective for some patients, although these are largely informed by evidence for other viral-onset disorders such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a chronic multisymptom illness with symptom overlap with Long COVID.[11]

Evidence-based practice requires decisions about healthcare to be based on the best available, current, valid and relevant evidence.[13] To address clinical questions relating to the effectiveness of therapies and or interventions, randomised controlled trials (RCTs), studies in which participants are randomly allocated to treatment or control groups and outcomes assessed, are considered the gold-standard.[14, 15]

Although often expensive and time consuming, RCTs are considered the best method for studying causal relationships as the randomisation eliminates much of the bias inherent with other study designs.[14] Following RCTs, there are further steps required before therapeutic and medicinal products become authorised and incorporated into guidelines and healthcare delivery, these are illustrated in Figure 1.1.

Figure 1.1 Path to routine clinical practice for therapeutics and medicinal products



Key: EMA – European Medicines Agency; HPRA – Health Products Regulatory Authority; HTA – Health Technology Assessment.

To date, many candidate treatments for Long COVID have been proposed based on treatments used in related illnesses or provisional evidence among people with Long COVID,[11] but reviews have identified few randomised controlled trials investigating the effectiveness of interventions specifically among people with Long COVID.[16-19] However, many clinical trials among people with Long COVID have been registered, results for which are continually being published.[16] Following a request from the Health Service Executive (HSE), HIQA agreed to undertake a review of the effectiveness and safety of interventions among people with Long COVID in order to inform updates to the HSE's interim Long COVID model of care.

2 Methods

This systematic review followed the methods outlined in the protocol. Six distinct steps in the process, listed below and further detailed throughout this section, were completed.

1. Develop a research question and formulate a Population, Intervention, Comparator, Outcomes and Study design (PICOS) framework.
2. Search relevant sources.
3. Screen identified documents.
4. Extract data from included documents
5. Conduct study risk of bias assessments.
6. Summarise findings.

2.1 Research question

The research question was formulated according to the Population, Intervention, Comparator, Outcomes and Study design (PICOS) framework (Table 2.1). The systematic review sought to answer the following question:

- What interventions improve Long COVID symptoms?

2.2 Data sources and searches

Electronic searches were conducted in Medline via EBSCOhost, Embase via OVID, and CENTRAL via The Cochrane Library on 28 February 2023. The search strategy for Medline is presented in Appendix 1. Electronic searches were supplemented by grey literature searches in Clinicaltrials.gov, Cochrane COVID-19 Study Registry, TRIP database, C-19 Living Map - Long COVID 'Segment', and Medrxiv. Recent related reviews and a related HIQA report were screened for relevant studies.[16-20] Forward and backward citation searching of included studies was undertaken. Retrieved studies were de-duplicated in Endnote.

Table 2.1. Population, Intervention, Comparator, Outcomes and Study design (PICOS) criteria for the research question.

Population	Patients with Long COVID, as defined by study investigators. Exclusion criteria: ▪ Signs or symptoms not reasonably attributable to prior SARS-CoV-2 infection. ▪ Insufficient information provided to ascertain inclusion.
Intervention	Any intervention intended to improve Long COVID symptoms. Subgroups: ▪ pharmaceutical and other medical interventions (for example, monoclonal antibodies, co-enzyme drugs, platelet-rich plasma) ▪ non-pharmaceutical interventions (for example, herbal, nutritional, and natural supplements, exercise, physiotherapy and physical rehabilitation, olfactory training). Exclusion criteria: ▪ Intervention is not intended to treat Long COVID (for example, intervention is intended to treat acute COVID-19 or symptoms resulting from severe COVID-19 complications). ▪ Pre- or post-exposure prophylaxis for COVID-19 or the prevention of Long COVID symptoms (for example, administration of the intervention during the acute phase of the disease). ▪ Insufficient information provided to ascertain inclusion.
Comparator	Any comparator (including active and non-active interventions).
Outcomes	Severity or frequency of Long COVID symptoms, including: ▪ pulmonary/respiratory symptoms (for example, breathlessness, dyspnoea and pulmonary function) ▪ energy/fatigue symptoms ▪ mental and cognitive health (for example, anxiety and depressive symptoms and cognitive function) ▪ pain (for example, chest pain and headache) ▪ taste/smell (for example, aguesia and anosmia) ▪ physical functioning and sleep (for example, aerobic capacity, strength and sleep quality) ▪ burden of disease (for example, health-related quality of life, healthcare usage, and recovery). Exclusion criteria: ▪ Qualitative assessment of outcomes.
Study type	Randomised controlled trials.

	Exclusion criteria: ▪ Non-randomised controlled trials. ▪ Single-arm trials ▪ Observational studies. ▪ Case studies. ▪ Retrospective studies. ▪ Studies designed to assess the feasibility or tolerability of an intervention rather than its effects on symptoms. ▪ Animal studies. ▪ Insufficient information provided to ascertain inclusion.

2.3 Study selection

Screening was undertaken using Covidence software. Inclusion and exclusion criteria are detailed in Table 2.1. First, titles and abstracts of identified studies were screened. Subsequently, full texts of potentially eligible studies were screened. When full texts were not available, a copy was requested from the corresponding author. If no response was received, two reminder emails were sent at least one and two weeks after the initial email. In both phases two reviewers screened studies independently. Disagreements were resolved by discussion between both reviewers and a third reviewer, if necessary. Due to the adequate number of randomised controlled trials (RCTs) identified, other interventional study designs (for example, non-RCTs and single-arm trials) were excluded. Alerts for redacted studies were received through Retraction Watch to ensure such studies were not included. No language restrictions were applied although searches were only conducted in English. When studies were not available in English, titles and abstracts, and full texts of potentially eligible studies, were translated using Google Translate.

2.4 Data extraction

Two reviewers extracted data and disagreements were resolved by discussion or a third reviewer, if necessary. A standardised data extraction template was developed and piloted prior to undertaking data extraction. Briefly, data on funding sources, study and participant characteristics, and outcomes were extracted.

2.5 Study risk of bias assessment

Two reviewers assessed study risk of bias independently and disagreements were resolved by discussion or a third reviewer, if necessary. Risk of bias was assessed at the study level using the original Cochrane Risk of Bias tool[21] as opposed to the updated tool (RoB 2)[22] which assesses risk of bias for each outcome at each timepoint reported within studies. Reporting risk of bias at the study level better fits

the primary review focus on interventions as opposed to specific outcomes. Additionally, given the numerous Long COVID outcomes examined across the many included studies, the use of the updated tool would have been particularly challenging and resource intensive. There has been documented evidence of difficulties in the application of ROB 2 due to the assessment of bias at the individual outcome level at each reported timepoint.[23] The Cochrane Risk of bias tool assesses risk of bias in six domains: sequence generation, allocation concealment, blinding of participants and personnel, incomplete data, and selective reporting. Studies were given an overall risk of bias assessment of low (that is, all key domains were low risk), unclear (that is, all key domains were low or unclear risk), or high (that is, at least one key domain was high risk).[21] For the purpose of assessing the overall risk of bias, each of the six domains were considered "key" for consistency of assessment across the diverse intervention types. However, this may result in a conservative overall risk of bias rating.

2.6 GRADE certainty of evidence

The certainty of a body of evidence for specific interventions and outcomes can be evaluated through the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.[24] This framework uses a systematic approach for evaluating the certainty of evidence. However, due to the large variability in interventions and outcomes assessed across studies included in this review, it was not considered feasible nor particularly useful to formally evaluate the certainty of evidence.

2.7 Evidence synthesis

The number of records identified, included and excluded are presented in a PRISMA flow chart.[25] To facilitate comparison of intervention effects across studies and outcomes, Hedges' *d* effect sizes and 95% confidence intervals were calculated when sufficient data were reported.[26] These were calculated by subtracting the mean change in symptom scores in the comparison condition from the mean change in the experimental condition and dividing the difference by the pooled standard deviation of baseline scores and subsequently adjusting for small sample size bias.[26] Effect sizes are reported such that a greater improvement in Long COVID symptoms in the intervention group relative to the control group is represented by a positive effect size. Values of 0.20, 0.50, and 0.80 are often considered to be indicative of small, medium, and large effects, respectively.[27] Due to the heterogeneity of included studies' interventions, comparators and outcomes, meta-analysis was not undertaken and the findings of included studies were narratively synthesised.

Results were reported stratified into Pharmaceutical and other medical interventions and Non-pharmaceutical interventions.

Pharmaceutical and other medical interventions was split into two subcategories:

- Off-label use (that is, products that are being used for an unapproved indication or in an unapproved age group, dosage, or route of administration and are limited to those that are approved by the Health Product Regulatory Authority or through the central authorisation process by the European Medicines Agency)
- Investigational and or unauthorised (that is, products that are not licensed anywhere or not authorised by the Health Product Regulatory Authority or centrally through the European Medicines Agency).

Non-pharmaceutical interventions was split into six subcategories:

- Supplements and alternative medicine
- Exercise
- Physiotherapy and physical rehabilitation
- Olfactory training
- Cognitive and neurorehabilitation
- Psychological.

Additionally, registered randomised controlled trials that met inclusion criteria but had not published results by 28 February 2023 (that is, the date the data search concluded) were listed.

3 Results

3.1 Search results

After removal of duplicates, 4,394 articles remained, of which 3,826 records were excluded based on title and abstract screening. Of the 569 full texts screened for eligibility, 512 were excluded on reading. Two studies that considered interventions for new onset conditions following acute COVID-19 infection (sarcopenia and pulmonary fibrosis),[28, 29] and one study that considered interventions for COVID-19 infection-related exacerbation of a pre-existing condition (prostatitis),[30] were excluded. Forty-two interventional studies that were not RCTs but otherwise met inclusion criteria were excluded. Full texts for three studies could not be accessed and were excluded.[31-33]

Fifty-seven articles were included in the narrative synthesis.[34-90] Agreement between the four reviewers who independently screened titles and abstracts was high (Cronbach's α range: 0.71 to 0.90), as was agreement between the two reviewers who independently screened full texts (Cronbach's α=0.85). Figure 3.1 presents a flow diagram of the article screening process. Studies excluded after full text screening with the rationale for their exclusion are listed in Appendix 2. Included study characteristics are presented in Table 3.1 and Appendix 3 and interventions organised by Long COVID symptoms targeted are presented in Table 3.2.

3.2 Study characteristics

3.2.1 Pharmaceutical and other medical interventions

Study characteristics for the 24 pharmaceutical and medical interventions and 33 non-pharmaceutical interventions are presented in Table 3.1, Table 3.2 and Appendix 3. In summary, eight trials investigating off-label interventions[34, 37, 46, 52, 55, 56, 80, 85] and 16 trials of investigational/unauthorised interventions were included.[35, 36, 39, 41, 48-52, 62, 68, 72, 73, 79, 81, 88] Of these 24 trials, three (13%) were specified as Phase II,[41, 51, 52] and one (4%) as Phase IIa.[49] The phase for remaining trials (n=20; 83%) was not specified.[34-37, 39, 46, 48, 50, 52, 55, 56, 62, 68, 72, 73, 79-81, 85, 88] Conflicts of interest were present in six (25%) studies,[41, 49, 50, 52, 55, 88] with one study not reporting any details to allow assessment of potential conflicts of interest.[37] Of the six studies that declared conflicts of interest, five of these had support or funding from the pharmaceutical industry.[41, 49, 50, 52, 88] Regarding comparators, 14 studies used an active comparator,[34-37, 39, 46, 55, 62, 68, 72, 73, 79-81] nine used a placebo or sham,[41, 48-52, 56, 88, 90] and one used no treatment.[85] The median trial duration was six weeks (range: 10 days to 140 days). The median sample size was 71 (range: 18 to 979). No studies examined paediatric populations.

Studies were conducted in Africa (n=5; 21%),[34-36, 39, 48] Asia (n=3; 13%),[46, 52, 56] Europe (n=12; 50%),[37, 41, 49, 52, 55, 62, 68, 73, 79-81, 85] North America (n=3; 13%)[50, 51, 88] and one study (4%) was conducted in multiple sites across Asia and Europe.[72] European studies included six from Russia (25%),[37, 41, 62, 68, 73, 81] two from Italy (8%),[79, 85] and one each (4%) from Denmark,[52] Germany,[55] the Netherlands[80] and the UK.[49] The most common method of Long COVID assessment was doctor diagnosis (n=8; 33%).[35-37, 39, 52, 56, 81, 88] Seven studies were self-reported (29%),[34, 48, 68, 73, 79, 80, 90] with five being objectively assessed for Long COVID (21%).[41, 46, 49, 55, 85] The remaining four studies being self-reported with validated symptom measures (17%).[50, 51, 62, 72] The two most common outcomes examined were taste and or smell (n=12; 50%)[34-36, 39, 51, 55, 56, 72, 80, 85, 88, 90] and burden of disease (n=9; 38%)[37, 41, 46, 51, 52, 73, 79, 80, 90] Respiratory and or pulmonary (n=7; 29%),[37, 41, 46, 52, 68, 79, 90] mental and or cognitive (n=7; 29%) and physical functioning and or sleep (n=8; 33%)[37, 41, 46, 48, 49, 73, 81, 90] were also frequently examined.

3.2.2 Non-pharmaceutical interventions

Study characteristics for the 24 pharmaceutical and medical interventions and the 33 non-pharmaceutical interventions are presented in Table 3.1, Table 3.2 and Appendix 3. The 33 non-pharmaceutical interventions were categorised as: Supplements and alternative medicine (n=11; 33%),[43, 44, 47, 54, 59, 61, 74, 83, 84, 87, 89] exercise (n=8; 24%),[57, 58, 64, 67, 75-77, 86] physiotherapy and physical rehabilitation (n=7; 24%),[38, 45, 65, 66, 69, 70, 82] olfactory training (n=4; 12%),[42, 60, 63, 71] cognitive and neurorehabilitation (n=2; 6%),[40, 78] and psychological (n=1; 3%).[53] Conflicts of interest were present in 11 (33%) studies.[54, 59-61, 70, 71, 74, 78, 83, 87, 89] Of these studies, eight had funding or donations from industry.[54, 61, 70, 71, 74, 83, 87, 89] Regarding comparators, 17 studies used an active comparator,[38, 44, 47, 57, 58, 63-67, 70, 71, 76, 77, 82, 83, 86] 11 used placebo or sham,[40, 42, 45, 54, 59, 61, 74, 78, 84, 87, 89] and six used no treatment (note, one study had two comparator groups thus numbers do not add to 33).[43, 53, 60, 69, 75, 83] The median trial duration was six weeks (range: two weeks to three months). The median sample size was 52 (range: 12 to 281). No studies examined paediatric populations. Studies were conducted in Africa (n=3; 9%),[38, 40, 66] Asia (n=5; 15%),[59, 64, 67, 74, 82] Europe (n=19; 58%), North America (n=4; 12%)[42, 54, 60, 89] and South America (n=2; 6%).[71, 78] European studies included five from Spain,[45, 57, 58, 69, 75] four from Italy,[44, 47, 84, 87] three from the UK[63, 65, 70] and France,[53, 76, 86] two from Poland[43, 77] and one each from Slovakia[83] and Russia.[61] The method of Long COVID assessment was mostly conducted using doctor diagnosis (n=14; 42%)[40, 53, 59, 61, 66, 67, 69-71, 75, 77, 78, 82, 84] and self-report (n=11; 33%).[38, 43-45, 54, 57, 58, 65, 74, 83, 89] The other methods of assessment were self-reported with validated symptom measures (n=4; 12%)[64, 76, 86, 87] and objectively assessed (n=4; 12%).[42, 47, 60, 63]

The three most common outcomes examined were pulmonary and or respiratory (n=19; 58%),[38, 45, 53, 57-59, 61, 65-67, 69, 70, 75-77, 82, 83, 85, 89] physical functioning and or sleep (n=17; 52%)[38, 43, 45, 53, 57-59, 64-67, 75, 77, 83, 84, 86, 89] and burden of disease (n=16; 49%).[42, 45, 53, 54, 57-59, 64-67, 71, 76, 78, 86, 89]

Figure 3.1 PRISMA flow diagram of the article screening process

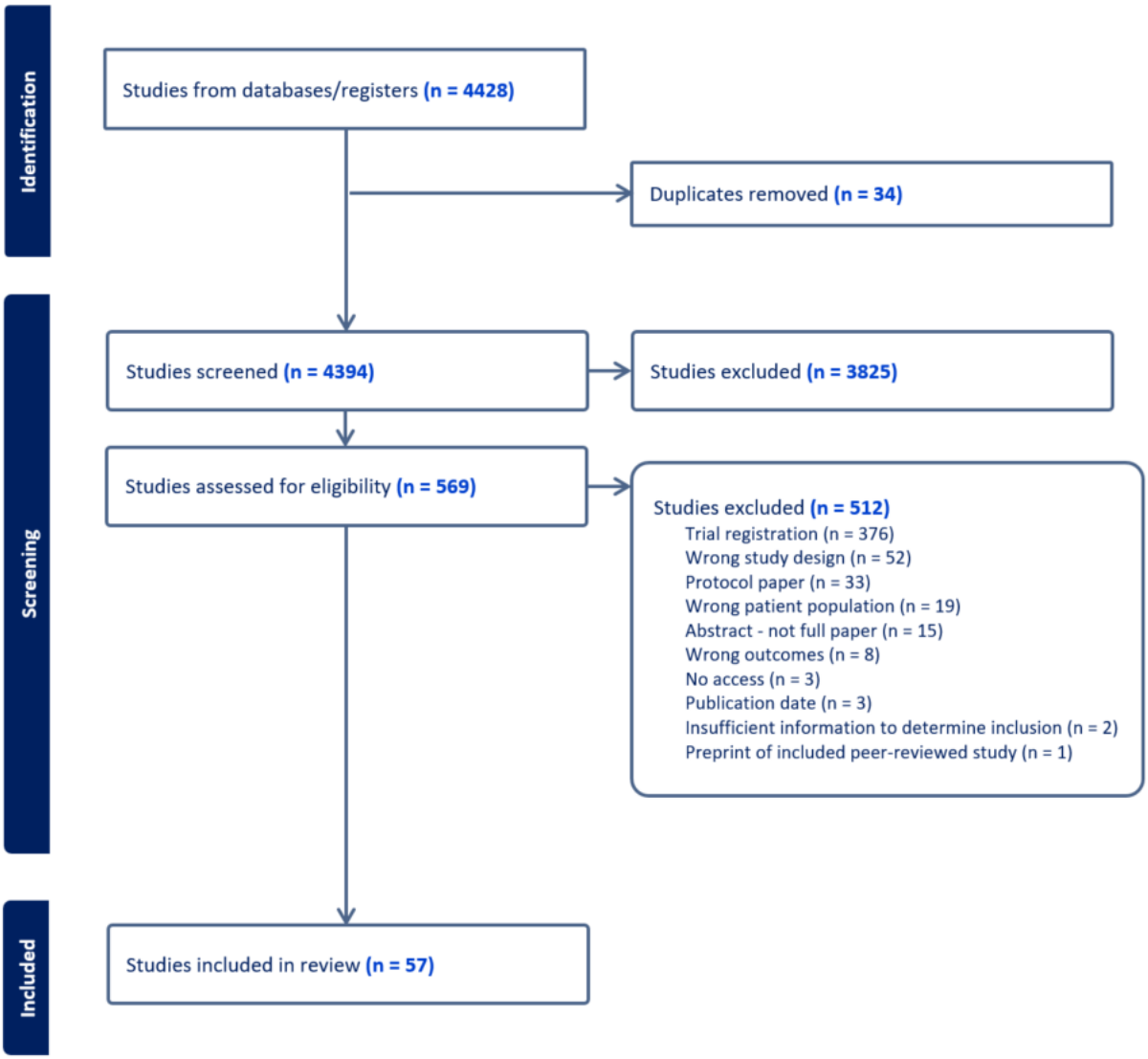


Table 3.1. Characteristics of included studies

Study (country)	Long COVID assessment	Sample size, n	Age, years (mean±SD or range)	Female, n (%)	Intervention (phase of trial were appropriate)	Comparator	Follow-up	Outcomes	CoI
Pharmaceutical and other medical interventions									
Off-label use									
Abdelalim (2021)[34] (Egypt)	Self-report Symptoms: anosmia/ hyposmia Duration: NR	100	29	54 (54)	Mometasone furoate intranasally, 100 µg each side (2 puffs)/day + olfactory training for 3 weeks (NR)	Olfactory training twice a day for 3 weeks	3 weeks	Olfactory function	No
Achabaeva (2022)[37] (Russia)	Doctor diagnosis Symptoms: NS Duration: >4 weeks	168	45 to 65	NR	2 separate MCIs containing direct-acting anticoagulant apixaban, 2.5mg tablet twice daily and levocarnitine 300mg twice daily (NR)	MCI containing direct-acting anticoagulant apixaban	Unclear	Pulmonary function, dyspnoea, exercise tolerance, physical activity, physical recovery, QoL	No
Dhooria (2022)[46] (India)	Objectively assessed Symptoms: dyspnoea/ hypoxaemia Duration: 3-8 weeks	130	57	NR (32)	High-dose prednisolone, 40mg/day down-titrating to 10mg/day over 6 weeks (NR)	Low-dose prednisolone, 10mg/day for 6 weeks	6 weeks	Pulmonary function, exercise capacity, dyspnoea, HRQoL	No
Hansen (2022)[52] (Denmark)	Doctor diagnosis Symptoms: NS Duration: ≥12 weeks	119	49 (22-70)	89 (74.8)	CoQ10 500mg/day for 6 weeks (Phase II)	Placebo	20 weeks	Symptom severity, HRQoL, adverse events	Yes
Hintschich (2022)[55] (Germany)	Objectively assessed Symptoms: olfactory dysfunction	86	47	54 (62.8)	Mometasone furoate intranasally, 100 µg each side twice daily and olfactory training, for 3 months (NR)	Olfactory Training	3 months	Olfactory function	Yes

Study (country)	Long COVID assessment	Sample size, n	Age, years (mean±SD or range)	Female, n (%)	Intervention (phase of trial were appropriate)	Comparator	Follow-up	Outcomes	CoI
	Duration: mean=8.3 months								
Hosseinpoor (2022)[56] (Iran)	Doctor diagnosis Symptoms: olfactory loss Duration: 30-90 days	70	34	45 (64.3)	Mometasone furoate intranasally 0.05% each side twice daily for 4 weeks (NR)	Placebo	4 weeks	Olfactory function	No
Schepens (2022)[80] (The Netherlands)	Self-report Symptoms: smell, taste disorders Duration: >4 weeks	115	49	73 (63.5)	Prednisolone 40mg orally once daily for 10 days and olfactory training twice daily for 12 weeks (NR)	Placebo and olfactory training for 12 weeks	12 weeks	Olfactory function, taste function, QoL, adverse events	No
Vaira (2021)[85] (Italy)	Objectively assessed Symptoms: anosmia/ severe hyposmia Duration: >30 days	18	42	11 (61.1)	Prednisone, 1mg/kg/day tapering the dose, and nasal irrigation with betamethasone, ambroxol and naphazoline, for 15 days (NR)	No treatment	30 days	Olfactory function, adverse events	No
Investigational/unauthorised									
Abdelazim (2022a)[35] (Egypt)	Doctor diagnosis Symptoms: olfactory dysfunction Duration: >90 days	50	39	31 (62)	Sodium gluconate, 1% intranasal 3 sprays each side thrice daily for 1 month (NR)	Intranasal spray of 0.9% sodium chloride	1 month	Olfactory function, adverse events	No
Abdelazim (2022b)[36] (Egypt)	Doctor diagnosis Symptoms: olfactory dysfunction	64	37	38 (59.4)	Tetra sodium pyrophosphate intranasal, 2 sprays each side thrice daily for 1 month (NR)	Intranasal spray of 0.9% sodium chloride	2 months	Olfactory function, adverse events	No

Study (country)	Long COVID assessment	Sample size, n	Age, years (mean±SD or range)	Female, n (%)	Intervention (phase of trial were appropriate)	Comparator	Follow-up	Outcomes	CoI
	Duration: >90 days								
Aref (2022)[39] (Egypt)	Doctor diagnosis Symptoms: anosmia Duration: NR	96	30	24 (25)	Ivermectin intranasal 120mg/L, 2 puffs/day for up to 3 months (NR)	Intranasal spray of 0.9% sodium chloride	3 months	Olfactory function, adverse events	No
Bazdyrev (2022)[41] (Russia)	Objectively assessed Symptoms: dyspnoea, fibrotic changes, decreased lung function Duration: ≥2 months	60	55	33 (55)	Treamid (bisamide derivative of dicarboxylic acid), 50mg/day once daily for 28 days (NR)	Placebo	4 weeks	Pulmonary function, dyspnoea, HRQoL, adverse events	Yes
Elbanna (2022)[48] (Egypt)	Self-report Symptoms: fatigability, decreased functional capacity Duration: NR	100	64 (60-70)	NR	Light therapy/ photobiomodulation laser 3 times/week for 4 weeks (NR)	Placebo	4 weeks	Fatigue, functional status	No
Finnigan (2023)[49] (UK)	Objectively assessed Symptoms: fatigue Duration: ≥12 weeks	41	44 (range: 24-56)	28 (68.3)	AXA1125 (endogenous metabolic modulator comprised of 5 amino acids and N-acetylcysteine) orally 33.9g twice daily for 4 weeks (Phase IIa)	Placebo	4 weeks	Fatigue, exercise capacity, adverse events	Yes
Gaylis (2022)[50] (US)	Self-report (validated) Symptoms: NS	55	49	NR	Leronlimab 700mg subcutaneous weekly doses for 8 weeks (NR)	Placebo	8 weeks	Symptom severity	Yes

Study (country)	Long COVID assessment	Sample size, n	Age, years (mean±SD or range)	Female, n (%)	Intervention (phase of trial were appropriate)	Comparator	Follow-up	Outcomes	CoI
	Duration: NR								
Gupta (2022)[51] (US)	Self-report (validated) Symptoms: NS Duration: 3-12 months	51	45	36 (70.6)	Theophylline intranasally, 400mg twice daily for 6 weeks (Phase II)	Placebo	6 weeks	Olfactory function, HRQoL, adverse events	No
Kutashov (2021)[62] (Russia)	Self-report (validated) Symptoms: fatigue, cognitive impairment Duration: NR	444	68±1.1	302 (68)	Actovegin® (deproteinised hemodialysate of calf's blood) 800mg orally 3 times daily for 60 days (NR)	Basic therapy	60 days	Cognitive function, fatigue, emotional disturbances	No
Orlova (2022)[68] (Russia)	Self-report Symptoms: NS Duration: 12-26 weeks	50	43 to 68 years	42 (84)	Intermittent hypoxia-hyperoxia treatments X 10 and standard rehabilitation for 2 weeks (NR)	Group 1: Matching placebo and standard rehabilitation (2 weeks) Group 2: Standard rehabilitation only (2 weeks)	2 weeks	General health, anxiety, depression, dyspnoea, adverse events	No
Putilina (2021)[73] (Russia)	Self-report Symptoms: >3 ground-glass opacities (<3cm) Duration: 30-90 days	100	40±11.7	43 (43)	Cytoflavin® (Inosine + Nicotinamide + Riboflavin + Succinic Acid) orally (dose NR) twice daily for 25 days (NR)	Other therapy (vitamins, nootropics)	25 days	Fatigue, cognitive function, sleep quality, HRQoL, General health, adverse events	No
Putilina (2022)[72] (Russia)	Self-report (validated) Symptoms: fatigue/	979	55±4.5	651 (66.5)	Cortexin® (a lyophilised extraction of animal cortex) 20mg for 10 days (NR)	Lower dose of Cortexin® (10mg) for 10 days	30 days	Fatigue, olfactory function, adverse events	No

Study (country)	Long COVID assessment	Sample size, n	Age, years (mean±SD or range)	Female, n (%)	Intervention (phase of trial were appropriate)	Comparator	Follow-up	Outcomes	CoI
	cognitive impairment Duration: 1-12 months								
Scaturro (2022)[79] (Italy)	Self-report Symptoms: NS Duration: ≥60 days	60	59±5.4	34 (56.7)	L-acetyl-carnitine 500mg twice daily, intramuscular for 10 days and orally for 40 days and rehabilitation (NR)	Rehabilitation (aerobic and postural exercises, respiratory re-education)	Approx. 11-12 weeks	Dyspnoea, musculoskeletal pain, depression, HRQoL	No
Shogenova (2021)[81] (Russia)	Doctor diagnosis Symptoms: ground-glass opacities Duration: NR	60	52	51 (85)	Hydrogen inhalation X 10 procedures and standard therapy for 10 days (NR)	Standard therapy (physiotherapy and magnesium, B vitamins and L-carnitine) for 10 days	10 days	Exercise capacity, adverse events	No
Yan (2022)[88] (US)	Doctor diagnosis Symptoms: olfactory dysfunction Duration: 6-12 months	30	44	15 (50)	Platelet-rich plasma injections, 1mL submucosally at weeks 0, 2 and 4	Placebo	3 months	Olfactory function, adverse events	Yes
Zilberman-Itskovich (2022)[90] (Israel)	Self-report Symptoms: NS Duration: ≥3 months	73	48	44 (60.3)	Hyperbaric oxygen therapy (40 sessions) over a 2-month period (phase II)	Sham intervention	2 months	Pulmonary function, psychological distress, pain severity, smell and taste function, sleep function, QoL	No
Non-pharmaceutical interventions									
Supplements and alternative medicine									

Study (country)	Long COVID assessment	Sample size, n	Age, years (mean±SD or range)	Female, n (%)	Intervention (phase of trial were appropriate)	Comparator	Follow-up	Outcomes	CoI
Chudzik (2022)[43] (Poland)	Self-report Symptoms: fatigue, exercise intolerance Duration: 1-3 months	50	49	34 (68)	1-MNA, 58mg/day (duration not reported) (NA)	No treatment	1 Month	Fatigue, exercise capacity	No
D'Ascanio (2021)[44] (Italy)	Self-report Symptoms: anosmia/ hyposmia Duration: ≥90 days	12	42±14.1	8 (66.7)	PEA-LUT (Glialia®, 700mg + 70mg) daily and olfactory training twice daily, for 30 days (NA)	Placebo and olfactory training twice daily for 30 days	30 days	Olfactory function	No
Di Stadio (2022)[47] (Italy)	Self-report (validated) Symptoms: anosmia/ hyposmia Duration: >6 months	185	44±14.6	121 (65.4)	PEA-LUT (Glialia®, 700mg + 70mg)/day and olfactory training thrice daily, for 90 days (NA)	Placebo + olfactory training thrice daily for 90 days	90 days	Olfactory function	No
Hawkins (2022)[54] (US)	Self-report Symptoms: fatigue Duration: 6-9 months	44	19-49	44 (100)	Aromatherapy for 15 min twice daily at home for 2 weeks (NA)	Placebo for 2 weeks	2 weeks	Fatigue, QoL, adverse events	Yes
Karosanidze (2022)[59] (Sweden)	Doctor diagnosis Symptoms: NS Duration: 1-3 months	100	49±13.9	85 (85)	ADAPT-232/Chisan®, 30mL orally twice daily for 2 weeks (NA)	Placebo	3 weeks	Duration and severity of symptoms, anxiety and depression, physical activity, length of homestay/ sick-listed time, cognitive performance	Yes
Kharaeva (2022)[61] (Russia)	NR Symptoms: NS Duration: NR	213	35 to 69	107 (50.2)	Fermented fruit (papaya and noni syrups) 14g twice daily for 3 weeks (NA)	Matching placebo	3 weeks	Dyspnoea, self-assessed clinical symptoms	Yes

Study (country)	Long COVID assessment	Sample size, n	Age, years (mean±SD or range)	Female, n (%)	Intervention (phase of trial were appropriate)	Comparator	Follow-up	Outcomes	CoI
Rathi (2021)[74] (India)	Self-report Symptoms: fatigue/ muscle weakness Duration: 2-87 days	200	41	73 (36.5)	Systemic enzymes 1000mg twice daily and probiotics, for 14 days (NA)	Placebo	14 days	Fatigue, adverse events	Yes
Sumbalová (2022)[83] (Slovakia)	Self-report Symptoms: NS Duration: 3-7 months	51	54	23 (45.1)	Rehabilitation programme for 16-18 days and CoQ10 100mg twice a day for approx. 32 days (NA)	1: Matched rehabilitation programme 2: No intervention	32 days	Dyspnoea, pulmonary function, overall symptoms change	Yes
Tosato (2022)[84] (Italy)	Doctor diagnosis Symptoms: fatigue Duration: ≥4 weeks	46	51 (14.0)	30 (65.2)	L-arginine 1.66g + 500mg liposomal vitamin C, orally twice a day for 28 days (NA)	Matching placebo	28 days	Fatigue, exercise capacity, muscular strength	No
Versace (2023)[87] (Italy)	Self-report (validated) Symptoms: fatigue/ cognitive difficulties Duration: mean=297 days	39	50±11.4	26 (66.7)	PEA-LUT (Glialia®, 700mg + 70mg) orally twice daily for 8 weeks (NA)	Placebo	8 weeks	Cognitive function, adverse events	Yes
Young (2022)[89] (US)	Self-report (validated) Symptoms: NS Duration: NR	23	45	13 (56.5)	CBD (Formula C™) 0.25mL and titrated to effect orally for 28 days (NA)	Placebo	56 days (2 x 28 treatment periods) and a safety assessment 2 weeks later on day 70	Anxiety, cognitive function, depression, dyspnoea, fatigue, pain, sleep disturbance, social role participation, change in clinical status, adverse events	Yes
Exercise									

Study (country)	Long COVID assessment	Sample size, n	Age, years (mean±SD or range)	Female, n (%)	Intervention (phase of trial were appropriate)	Comparator	Follow-up	Outcomes	CoI
Jimeno-Almazan (2022)[58] (Spain)	NR Symptoms: NS Duration: >12 weeks	39	45±9.5	29 (74.4)	Supervised strength and aerobic exercise for 8 weeks (NA)	Provided leaflet on self-management (WHO)[91]	8 weeks	Dyspnoea, cardiopulmonary function, fatigue, anxiety, functional status, muscular strength, depression, HRQoL, symptom severity	No
Jimeno-Almazan (2023)[57] (Spain)	Self-report Symptoms: NS Duration: >12 weeks	80	45±8.0	55 (68.8)	1) Strength and aerobic exercise vs 2) inspiratory muscle training vs 3) exercise and inspiratory muscle training, for 8 weeks (NA)	Provided leaflet on self-management (WHO)[91]	8 weeks	Dyspnoea, fatigue, anxiety, depression symptoms, cardiorespiratory fitness, muscle strength, functional status, HRQoL, total number of symptoms	No
Li (2021)[64] (China)	Self-report (validated) Symptoms: dyspnoea Duration: NR	119	51±11.0	66 (55.5)	Telerehabilitation programme containing aerobic exercise via app with weekly teleconsultations for 6 weeks (NA)	Short educational instructions at baseline	6 weeks	Dyspnoea, pulmonary function, functional exercise capacity, strength, HRQoL, adverse events	No
Okan (2022)[67] (Turkey)	Self-report Symptoms: dyspnoea Duration: ≥2 months	52	51	25 (48.1)	Breathing exercises and walking programme for 5 weeks (NA)	Brochure explaining the same programme	5 weeks	Pulmonary function, dyspnoea, exercise capacity, HRQoL, adverse events	No
Rodriguez-Blanco (2023)[75] (Spain)	Doctor diagnosis Symptoms: NS Duration: ≥40 days	48	41	26 (54.2)	Telerehabilitation containing breathing and strength training for 14 days (NA)	No treatment	2 weeks	Dyspnoea, fatigue, exercise capacity, adverse events	No
Romanet (2022)[76] (France)	Self-report (validated) Symptoms: dyspnoea	60	58	23 (38.3)	Supervised strength and aerobic exercise for 10 weeks (NA)	Standard physiotherapy for 10 weeks	10 weeks	Dyspnoea, HRQoL	No

Study (country)	Long COVID assessment	Sample size, n	Age, years (mean±SD or range)	Female, n (%)	Intervention (phase of trial were appropriate)	Comparator	Follow-up	Outcomes	CoI
	Duration: ≥3 months								
Rutkowski (2023)[77] (Poland)	Doctor diagnosis Symptoms: NS Duration: 3-6 months	32	58±4.9	20 (62.5)	Virtual reality aerobic exercise for 3 weeks (NA)	Same as intervention but in-person (no virtual reality) for 3 weeks	3 weeks	Pulmonary function, dyspnoea, fatigue, stress, exercise capacity	No
Vallier (2023)[86] (France)	Self-report (validated) Symptoms: NS Duration: NR	17	55±16.0	5 (29.4)	Hospital-based pulmonary rehabilitation containing aerobic exercise for 4 weeks (NA)	Home-based pulmonary rehabilitation containing aerobic exercise for 4 weeks	4 weeks	Pulmonary function, dyspnoea, fatigue, exercise capacity, HRQoL	No
Physiotherapy and physical rehabilitation									
Ali (2023)[38] (Egypt)	Self-report Symptoms: respiratory issues Duration: NR	60	46	35 (58.3)	Traditional physiotherapy programme with breathing exercises for 12 weeks (NA)	Traditional physiotherapy programme for 12 weeks	12 weeks	Fatigue, exercise capacity	NR
del Corral (2023)[45] (Spain)	Self-report Symptoms: NS Duration: ≥3 months	88	46	63 (71.6)	Inspiratory and respiratory muscle training for 8 weeks (NA)	Sham inspiratory muscle training for 8 weeks	8 weeks	Pulmonary, respiratory muscle function, cognitive function, anxiety and depression, post-traumatic stress, exercise tolerance, physical function, HRQoL	No
McNarry (2022)[65] (UK)	Self-report Symptoms: dyspnoea Duration: NR	281	47±12.2	NR (88)	Inspiratory muscle training for 8 weeks (NA)	Usual care and wait list	8 weeks	Dyspnoea, inspiratory muscle strength, mental health and wellbeing, fitness, sleep, physical fitness, HRQoL	No

Study (country)	Long COVID assessment	Sample size, n	Age, years (mean±SD or range)	Female, n (%)	Intervention (phase of trial were appropriate)	Comparator	Follow-up	Outcomes	CoI
Nagy (2022)[66] (Egypt)	Self-report (validated) Symptoms: mild/ moderate lung fibrosis Duration: ≥4 weeks	52	40	0 (0)	Diaphragm release and inspiratory muscle training for 6 weeks (NA)	Inspiratory muscle training for 6 weeks	6 weeks	Dyspnoea, fatigue, exercise capacity	No
Palau (2022)[69] (Spain)	NR Symptoms: NS Duration: ≥3 months	26	50±12.2	11 (42)	Home-based inspiratory training for 12 weeks (NA)	No treatment	12 weeks	HRQoL, pulmonary function, adverse events	NR
Philip (2022)[70] (UK)	Doctor diagnosis Symptoms: NS Duration: ≥4 weeks	150	50	121 (80.7)	Online breathing and wellbeing programme (English National Opera Breathe) for 6 weeks (NA)	Usual care and wait list	6 weeks	COPD symptoms, Breathlessness, dyspnoea, anxiety, HRQoL, adverse events	Yes
Srinivasan V (2021)[82] (India)	NR Symptoms: NS Duration: NR	56	18-60	NR	Breathing exercises with Bhastrika Pranayama at home for 6 weeks (NA)	Breathing exercise with incentive spirometry at home for 6 weeks	6 weeks	Pulmonary function	No
Olfactory training									
Bérubé (2022)[42] (Canada)	Objectively assessed Symptoms: olfactory dysfunction Duration: ≥2 months	50	45	33 (66.0)	Olfactory training for 12 weeks (NA)	Placebo	12 weeks	Olfactory function, subjective chemosensory function, prevalence of parosmia, QoL	No
Khan (2023)[60] (US)	Self-report (validated)	170	41±12	146 (86)	Olfactory training for 3 months (NA)	No treatment.	3 months	Olfactory function	Yes

Study (country)	Long COVID assessment	Sample size, n	Age, years (mean±SD or range)	Female, n (%)	Intervention (phase of trial were appropriate)	Comparator	Follow-up	Outcomes	CoI
	Symptoms: olfactory dysfunction Duration: ≥3 months								
Lechner (2022)[63] (UK)	Self-report (validated) Symptoms: olfactory dysfunction Duration: ≥4 weeks	63	42 (23 to 78)	NR (NR)	Olfactory training for 12 weeks (NA)	Safety information only	12 weeks	Olfactory function, quality of life in relation to anosmia, change in symptoms, adverse events	No
Pires (2022)[71] (Brazil)	Doctor diagnosis Symptoms: olfactory dysfunction Duration: ≥4 weeks	80	37±10.3	52 (65)	Advance olfactory training for 4 weeks (NA)	Classical olfactory training for 4 weeks	4 weeks	Olfactory function, taste function, QoL	Yes
Cognitive and neurorehabilitation									
Awaad (2022)[40] (Egypt)	Doctor diagnosis Symptoms: headache Duration: >6 months	30	32	17 (56.7)	Transcutaneous vagus nerve stimulation and physiotherapy programme for 4 weeks (NR)	Sham intervention and physiotherapy programme for 4 weeks	4 weeks	Intensity of headaches, disability resulting from headaches	No
Santana (2023)[78] (Brazil)	Doctor diagnosis Symptoms: fatigue Duration: 3-12 months	70	50	45 (64.3)	High-definition transcranial direct current stimulation and individually tailored rehabilitation programme for 5 weeks (NR)	Sham intervention and individually tailored rehabilitation programme for 5 weeks	5 weeks	Fatigue, anxiety, pain, QoL, adverse events	Yes
Psychological interventions									
Hausswirth (2023)[53]	Doctor diagnosis	49	47	35 (71.4)	Mindfulness based intervention using neuro-	No treatment	4 weeks	Dyspnoea, fatigue, cognitive function,	No

Study (country)	Long COVID assessment	Sample size, n	Age, years (mean±SD or range)	Female, n (%)	Intervention (phase of trial were appropriate)	Comparator	Follow-up	Outcomes	CoI
(France)	Symptoms: anxiety/ depression, fatigue, poor sleep Duration: NR				meditation for 4 weeks (NA)			stress, mood, anxiety and depression, muscular and joint pain, headaches, sleep quality	

Key: 1-MNA - 1 - methylnicotinamide chloride; ADAPT-232 - herbal adaptogen formula; CBD – Cannabidiol; COI – conflicts of interest; CoQ10 - Coenzyme Q10; HRQoL -health-related quality of life; COPD - chronic obstructive pulmonary disease; MCI – multicomponent intervention; NA – not applicable; NR – not reported; PEA-LUT - palmitoylethanolamide co-ultramicronised with antioxidant flavonoid luteolin; SD – standard deviation; QoL -quality of life; WHO – World Health Organisation.

Table 3.2. Interventions of included studies organised by Long COVID symptoms targeted

Pulmonary/respiratory	Energy/fatigue	Mental and cognitive	Taste/smell	Physical functioning and sleep	Burden of disease	Other*
Pharmaceutical and other medical interventions						
Off-label use						
Prednisolone/prednisone[46]	High-dose CoQ10[52]	High-dose CoQ10[52]	Mometasone furoate nasal spray[34, 55, 56]	Prednisolone/ prednisone[46]	Prednisolone/ prednisone[46, 80]	High-dose CoQ10[52]
High-dose CoQ10[52]		MCIs containing direct-acting anticoagulant apixaban and levocarnitine[37]	Prednisolone/ prednisone[80, 85]	MCIs containing direct-acting anticoagulant apixaban and levocarnitine[37]	High-dose CoQ10[52]	L-acetyl-carnitine[79]
MCIs containing direct-acting anticoagulant apixaban and levocarnitine[37]					MCIs containing direct-acting anticoagulant apixaban and levocarnitine[37]	
Investigational/unauthorised						
Intermittent hypoxia-hyperoxia[68]	Light therapy/ photobiomodulation laser[48]	Intermittent hypoxia-hyperoxia[68]	Platelet-rich plasma injections[88]	Light therapy/ photobiomodulation laser[48]	Theophylline intranasally[51]	Intermittent hypoxia-hyperoxia[68]
Treamid (bisamide derivative of dicarboxylic acid)[41]	AXA1125 (endogenous metabolic modulator comprised of 6 amino acids)[49]	L-acetyl-carnitine[79]	Sodium gluconate nasal spray[35]	Hydrogen inhalation[81]	Cytoflavin® (Inosine + Nicotinamide + Riboflavin + Succinic Acid)[73]	Leronlimab[50]
L-acetyl-carnitine[79]	Cytoflavin® (Inosine + Nicotinamide +	Cytoflavin® (Inosine + Nicotinamide +	Tetra sodium pyrophosphate nasal spray[36]	Treamid (bisamide derivative of dicarboxylic acid)[41]	L-acetyl-carnitine[79]	L-acetyl-carnitine[79]

Pulmonary/respiratory	Energy/fatigue	Mental and cognitive	Taste/smell	Physical functioning and sleep	Burden of disease	Other*
	Riboflavin + Succinic Acid)[73]	Riboflavin + Succinic Acid)[73]				
Hyperbaric oxygen therapy**[90]**	Cortexin®[72]	Actovegin®[62]	Theophylline nasal spray[51]	AXA1125 (endogenous metabolic modulator comprised of 6 amino acids)[49]	Treamid (bisamide derivative of dicarboxylic acid)[41]	Hyperbaric oxygen therapy[90]
	Actovegin®[62]	Hyperbaric oxygen therapy[90]	Cortexin®[72]	Cytoflavin® (Inosine + Nicotinamide + Riboflavin + Succinic Acid)[73]	Hyperbaric oxygen therapy[90]	
			Ivermectin intranasal spray[39]	Hyperbaric oxygen therapy[90]		
			Hyperbaric oxygen therapy[90]			
Non-pharmaceutical interventions						
Supplements and alternative medicine						
ADAPT-232/Chisan® oral suspension**[59]**	1-MNA[43]	Glialia® (supplement containing PEA and Luteolin) [87]	Glialia® (supplement containing PEA and Luteolin)[44, 47]	1-MNA[43]	Aromatherapy[54]	Fermented fruit supplement (papaya and noni syrups)[61]
Fermented fruit supplement (papaya and noni syrups)**[61]**	Systemic enzymes and probiotics[74]	ADAPT-232/Chisan® oral suspension[59]	ADAPT-232/Chisan® oral suspension[59]	Rehabilitation programme and CoQ10[83]	ADAPT-232/Chisan® oral suspension[59]	Rehabilitation programme and CoQ10[83]
Rehabilitation programme and CoQ10**[83]**	Aromatherapy[54]	CBD supplement[89]		L-Arginine + Vitamin C[84]	CBD supplement[89]	ADAPT-232/Chisan® oral suspension[59]

Pulmonary/respiratory	Energy/fatigue	Mental and cognitive	Taste/smell	Physical functioning and sleep	Burden of disease	Other*
CBD supplement[89]	ADAPT-232/Chisan® oral suspension[59]			ADAPT-232/Chisan® oral suspension[59]		CBD supplement[89]
	L-Arginine + Vitamin C[84]			CBD supplement[89]		
	CBD supplement[89]					
Exercise						
Supervised strength and aerobic exercise[58, 76]	Supervised strength and aerobic exercise[58]	Supervised strength and aerobic exercise[58]		Supervised strength and aerobic exercise[58]	Supervised strength and aerobic exercise[58, 76]	Supervised strength and aerobic exercise[58]
1) Strength and aerobic exercise vs 2) inspiratory muscle training vs 3) exercise and inspiratory muscle training[57]	1) Strength and aerobic exercise vs 2) inspiratory muscle training vs 3) exercise and inspiratory muscle training[57]	1) Strength and aerobic exercise vs 2) inspiratory muscle training vs 3) exercise and inspiratory muscle training[57]		1) Strength and aerobic exercise vs 2) inspiratory muscle training vs 3) exercise and inspiratory muscle training[57]	1) Strength and aerobic exercise vs 2) inspiratory muscle training vs 3) exercise and inspiratory muscle training[57]	1) Strength and aerobic exercise vs 2) inspiratory muscle training vs 3) exercise and inspiratory muscle training[57]
Telerehabilitation programme containing aerobic exercise[64]	Therapeutic exercise telerehabilitation containing aerobic exercise[75]	Virtual reality aerobic exercise[77]		Telerehabilitation programme containing aerobic exercise[64]	Telerehabilitation programme containing aerobic exercise[64]	
Breathing exercises and walking programme[67]	Virtual reality aerobic exercise[77]			Breathing exercises and walking programme[67]	Breathing exercises and walking programme[67]	
Therapeutic exercise telerehabilitation containing strength training[75]	Hospital-based pulmonary rehabilitation containing aerobic exercise[86]			Therapeutic exercise telerehabilitation containing strength training[75]	Hospital-based pulmonary rehabilitation containing aerobic exercise[86]	
Virtual reality aerobic exercise[77]				Virtual reality aerobic exercise[77]		

Pulmonary/respiratory	Energy/fatigue	Mental and cognitive	Taste/smell	Physical functioning and sleep	Burden of disease	Other*
Hospital-based pulmonary rehabilitation containing aerobic exercise[86]				Hospital-based pulmonary rehabilitation containing aerobic exercise[86]		
Physiotherapy and physical rehabilitation						
Inspiratory/respiratory muscle training[45, 65, 69]	Traditional physiotherapy programme with breathing [38]	Inspiratory/respiratory muscle training[45, 65]		Traditional physiotherapy programme with breathing [38] exercises	Inspiratory/respiratory muscle training[45, 65, 69]	
Breathing exercise with Bhastrika Pranayama[82]	Diaphragm release and inspiratory muscle training[66]	Online breathing and wellbeing programme (ENO Breathe)[70]		Inspiratory/respiratory muscle training[45, 65]	Online breathing and wellbeing programme (ENO Breathe)[70]	
Diaphragm release and inspiratory muscle training[66]				Diaphragm release and inspiratory muscle training[66]		
Online breathing and wellbeing programme (ENO Breathe)[70]						
Olfactory training						
			Olfactory training[42, 60, 63, 71]		Olfactory training[42, 71]	
Cognitive and neurorehabilitation						
	High-definition transcranial direct current stimulation and tailored	High-definition transcranial direct current stimulation and tailored			High-definition transcranial direct current stimulation and tailored	High-definition transcranial direct current stimulation and tailored rehabilitation programme [78]

Pulmonary/respiratory	Energy/fatigue	Mental and cognitive	Taste/smell	Physical functioning and sleep	Burden of disease	Other*
	rehabilitation programme [78]	rehabilitation programme [78]			rehabilitation programme [78]	
		Transcutaneous vagus nerve stimulation and physiotherapy programme[40]				Transcutaneous vagus nerve stimulation and physiotherapy programme[40]
Psychological						
Mindfulness based intervention using neuro-meditation**[53]**	Mindfulness based intervention using neuro-meditation[53]	Mindfulness based intervention using neuro-meditation[53]		Mindfulness based intervention using neuro-meditation[53]		Mindfulness based intervention using neuro-meditation[53]

*Other: includes the following outcomes: disability degree; encephalomyelitis/chronic fatigue syndrome symptoms; general health; global impression of change; Long COVID symptoms (general); musculoskeletal, skin, and gastrointestinal symptoms; organoleptic dysfunction, and hair loss; pain; sweatiness.
Note: adverse events **not** included within 'Other' outcome. Adverse events reported within studies can be found in the results tables in appendices.

Key: CBD – cannabidiol; CoQ10 - Coenzyme Q10; ENO – English National Opera; MCIs – multicomponent interventions; MNA – Methylnicotinamide; PEA - Palmitoylethanolamide

3.3 Pharmaceutical and other medical interventions

3.3.1 Off-label use

Study characteristics for the eight trials investigating off-label use of pharmaceutical interventions are presented in Table 3.1 and results are summarised here and presented in Appendix 4.[34, 37, 46, 52, 55, 56, 80, 85] Studies included in this section investigate products that are being used for an unapproved indication or in an unapproved age group, dosage, or route of administration and are limited to those that are approved by the Health Product Regulatory Authority or through the central authorisation process by the European Medicines Agency. One study had an unclear risk of bias[80] and the remain seven studies were at a high risk of bias (Table 3.3).[34, 37, 46, 52, 55, 56, 85] Two studies reported relevant conflicts of interest.[52, 55] Of the four studies that reported on safety outcomes,[46, 52, 80, 85] none reported serious adverse events attributed to the interventions.

Three studies investigated the use of mometasone furoate intranasal sprays to improve olfactory function. Hosseinpoor et al. compared three weeks of the mometasone furoate nasal spray (0.05% each side twice daily) to a placebo in 70 participants.[56] Both mean smell scores (assessed by the Iran-SIT and visual analogue scale (VAS)) significantly improved more in the mometasone furoate nasal spray group from baseline to week 4 and from week 2 to week 4 (all $p \leq 0.001$) compared to the placebo group. However, there were no significant between group differences in median smell at week 2 or week 4. Hintschich et al. compared three months of the mometasone furoate nasal spray (100 µg each side twice daily) plus olfactory training to the olfactory training alone in 86 participants.[55] Changes in smell (assessed by Sniffin' Sticks and VAS) did not significantly differ between groups. Abdelalim et al. also compared three weeks of a mometasone furoate spray plus olfactory training to olfactory training in 100 participants.[34] There were no significant between group differences for the median smell score (assessed by VAS) at baseline, week 1, week 2, or week 3 (all $p>0.05$), the time from onset of anosmia/hyposmia to full recovery (if achieved within the three-week study period), or the number of patients who completely recovered their smell after three weeks.

Two other studies in this category examined interventions that were intended to improve olfactory function. Vaira et al. compared one month of oral prednisone (1 mg/kg/day, tapered for 15 days) and nasal irrigation with betamethasone (a steroid), ambroxol (a mucolytic), and naphazoline (a decongestant), for 15 days to no treatment in 18 participants.[85] Median olfactory function scores (assessed by the Connecticut Chemosensory Research Centre orthonasal olfaction test) at baseline did not significantly differ between the oral prednisone and nasal irrigation group and the no treatment control group. However, olfactory function was significantly higher in the prednisone and nasal irrigation group compared to the control group at day

20 (40 vs 10; p=0.011) and at day 40 (60 vs 30; p=0.024). Both groups had significantly improved olfactory function from baseline to day 40 (both p<0.05). Schepens et al. compared 12 weeks of prednisolone (40mg orally once daily for 10 days) plus olfactory training to a placebo plus olfactory training in 115 participants.[80] After 12 weeks, there were no significant between group differences in smell (assessed by the Sniffin' Sticks Threshold-Discrimination-Identification (TDI score)), taste (assessed by the Taste Strip Test), and Quality of Life (QoL; assessed by the Sino-nasal Outcome Test and Olfactory Disorders Questionnaire); all p>0.05).

One other study also investigated oral prednisolone but not in the context of olfactory function. Dhooria et al. compared six weeks of high-dose prednisolone (that is, 40 mg/day, titrated down to 10 mg/day over six weeks) to low-dose prednisolone (that is, 10 mg/day for six weeks) in 130 participants.[46] At the end of the intervention, there were no significant between group differences in predicted forced vital capacity, shortness of breath severity (assessed by the Functional Assessment of Chronic Illness Therapy-dyspnoea scale), improvement in shortness of breath (assessed by the modified medical research council dyspnoea scale), improvement in exercise capacity (assessed by the six-minute walk test (6MWT)), or QoL (assessed by the eight component scores of the 36 item short form survey (SF-36); all p>0.05). However, whether high-dose prednisolone performed better than no treatment or placebo was not assessed.

In a cross-over trial, Hansen et al. compared six weeks of high dose coenzyme Q10 supplementation to a placebo (with a four-week washout period) in 119 participants.[52] There was no significant difference between the coenzyme Q10 and placebo groups in pre- to post-intervention change in cardiopulmonary symptoms, fatigue, neurological symptoms, and cognitive symptoms (all assessed by the Post-Covid Condition (PCC)-specific questionnaire). Additionally, QoL (assessed by the EuroQol, Five Dimensions, quality of life index (EQ-5D)) did not significantly improve as a result of the intervention (p=0.40).

One study, investigating a multicomponent intervention containing direct-acting anticoagulant apixaban, reported the intervention in insufficient detail to replicate.[37] Additionally, the paper was not written in English and between group differences in outcomes were unclear in the translation.

3.3.2 Investigational/Unauthorised

Study characteristics for the 16 trials of pharmaceutical and medical interventions that were investigational and or unauthorised are presented in Table 3.1 and results for these studies are summarised here and presented in Appendix 5.[35, 36, 39, 41, 48-51, 62, 68, 72, 73, 79, 81, 88, 90] Studies included in this section include products that are not currently licensed anywhere or are not authorised by the Health Product Regulatory Authority or centrally through the European Medicines Agency. Two studies had a

low risk of bias,[41, 49] in four studies the risk of bias was unclear,[35, 36, 48, 90] and ten studies were deemed to be at a high risk of bias (Table 3.3).[39, 50, 51, 62, 68, 72, 73, 79, 81, 88] Four studies reported relevant conflicts of interest.[41, 49, 50, 88] Of the 12 studies that reported on safety outcomes,[35, 36, 39, 41, 49, 51, 68, 72, 73, 81, 88, 90] none reported serious adverse events attributed to the interventions.

Four studies investigated four different intranasal sprays to improve olfactory function. Abdelazim et al. compared one month of a sodium gluconate nasal spray to a saline nasal spray in 50 participants who had anosmia for 90 days or more.[35] Large improvements in smell (assessed by the Sniffin' Sticks TDI score) were seen in the sodium gluconate spray group relative to the control (*d*=4.22, 3.22 to 5.22), by the end of the intervention. Average absolute TDI score improvement in the intervention group was 5.24 (SD 2.35). Nasal discharge was the commonly reported side effect, in addition to mild burning sensations in the nose or throat. The same author group also compared two months of a tetra sodium pyrophosphate nasal spray (TSSP) to a saline nasal spray in 64 participants.[36] Similar to their previous study, large improvements in smell (assessed by the Sniffin' Sticks TDI score) were seen in the TSSP spray group relative to the saline spray group (*d*=5.95, 4.80 to 7.09). Average absolute TDI score improvement in the intervention group was 5.41 (SD 2.52). Similar to the sodium gluconate nasal spray, nasal discharge was the commonly reported side effect, in addition to mild burning sensations in the nose or throat. Aref et al. compared two months of an ivermectin spray to a saline spray in 96 participants.[39] Cumulative recovery rates for smell (assessed on a VAS) over the two months did not significantly differ between groups (95.9% versus 89.4%; p=0.2), although participants who received the ivermectin nasal spray had a significantly lower median (range) days until recovery (13 (3 to 105) versus 50 (6 to 115); *p*<0.001). The study reported that there were no side effects. Gupta et al. compared two months of a theophylline spray to a placebo in 51 participants, finding no within-or between group improvements for smell or QoL.[51] Two participants who received theophylline reported experiencing considerable parosmia (that is, a distorted sense of smell) and foul taste, resulting in one withdrawal and one with poor compliance.

One other intervention in this category was intended to improve olfactory function. In a sample of 30 participants, Yan et al. compared three platelet-rich plasma injections (at weeks 0, 2, and 4) to a saline placebo injection.[88] Smell was assessed by the Sniffin' Sticks TDI score and a VAS. Between baseline and one month follow-up there were no significant differences in between group changes in the total TDI, Threshold, Discrimination and Identification subscale, or VAS (all p>0.05) scores. By three months follow-up, total TDI (p=0.047; *d*=0.63, -0.12-1.37)) and D (p=0.004; *d*=1.02, 0.25-1.79) scores significantly improved in the platelet-rich plasma group compared to the placebo group, although there remained no significant differences

in between group changes in T, I, or VAS (all p>0.05) scores. Only short-term side effects were reported, mostly related to the injection itself and consisting of nasal congestion and pressure that lasted up to 24 hours.

In a Phase II clinical trial, Finnigan et al. compared the effects of one month of AXA1125 to a placebo in 41 participants with fatigue-predominant Long COVID and impaired mitochondrial oxidative capacity.[49] AXA1125, developed by Axcella Therapeutics, is an endogenous metabolic modulator intended to improve mitochondrial function. Participants who received AXA1125 reported significant and large reductions in fatigue (assessed by the Chalder fatigue scale) relative to those in the placebo group (total fatigue: d=1.07, 0.42 to 1.73; physical fatigue: d=1.08, 0.43 to 1.74; mental fatigue: d=0.70, 0.07 to 1.33). There were no between group differences in changes in exercise capacity (assessed by the 6MWT distance; d=0.00, -0.61 to 0.62). In terms of safety and tolerability, no serious adverse events were attributed to the intervention, although one serious adverse event (syncope, attributed to an imaging procedure) occurred in the AXA1125 group, and 14% of participants who received AXA1125 reported diarrhea and 10% reported nausea.

Scaturro et al. compared L-acetyl-carnitine (administered intramuscularly for ten days and orally for a further 40 days) to a standard rehabilitation programme in 60 participants. Participants who received L-acetyl-carnitine reported larger improvements in musculoskeletal pain (d=2.07, 1.44 to 2.70), depressive symptoms (d=0.53, 0.01 to 1.05), and QoL (d=0.67, 0.15 to 1.19) relative to the control group. There were no between group differences in change in dyspnea or degree of disability. The study did not report on safety outcomes.

Bazdyrev et al. compared four weeks of a Treamid (a bisamide derivative of dicarboxylic acid) intervention to a placebo in 60 participants.[41] There were no significant between group differences in changes in pulmonary function, shortness of breath, 6MWT distance, or QoL (all p>0.05). At week four, participants who received Treamid reported significantly greater improvements in shortness of breath during exercise relative to the placebo group (mean change=-0.9 (SD 0.7) versus -0.4 (SD 0.8); p=0.018). There were no between group differences in rates of adverse events (34.5% versus 29.0%; p=0.65). One (3.4%) participant in the Treamid group reported a treatment-related adverse event compared to none in the placebo group (p=0.48).

Kutashov et al. compared two months of Actovegin® to basic therapy in 444 participants.[62] Actovegin® is a deproteinised hemodialysate of calf's blood proposed to improve cellular uptake and utilisation of glucose and oxygen. Participants who received Actovegin® reported significantly greater improvements from baseline to post-intervention in fatigue (d=1.31, 1.10 to 1.51) and cognitive function (d=0.53,

0.34 to 0.71) relative to the basic therapy control group. The study did not report on safety outcomes.

Orlova et al. compared two weeks of intermittent hypoxia-hyperoxia treatments (ten sessions) plus standard rehabilitation to a placebo plus the same rehabilitation program alone and the same rehabilitation program alone in 50 participants.[68] The hypoxia-hyperoxia intervention involved breathing through a mask for 30 to 40 minutes, while the amount of oxygen participants breathed was increased and decreased at regular intervals. Participants who received intermittent hypoxia-hyperoxia therapy significantly improved breathlessness relative to the rehabilitation only (*d*=0.70, 0.02 to 1.38) and placebo plus rehabilitation (*d*=0.87, 0.15 to 1.59) groups. Anxiety also significantly improved in participants who received intermittent hypoxia-hyperoxia therapy relative to the rehabilitation group (*d*=0.73, 0.05 to 1.42) but not the placebo group. There were no between group differences in changes in depressive symptoms or general health (all p>0.05). The study reported no complications or significant adverse events.

Hyperbaric oxygen therapy was compared to a sham control in a study with 73 participants.[90] Hyperbaric oxygen therapy involves breathing 100% oxygen in a pressurised environment. After adjusting for multiple comparisons, participants who received hyperbaric oxygen therapy reported significantly larger improvements for psychological distress (*d*=0.54, 0.07 to 1.01) and pain interference (*d*=0.61, 0.14 to 1.08) relative to those in the sham control group. However, there were no between group differences for 17 pulmonary function outcomes, six neurocognitive outcomes, three mental health outcomes, pain severity, smell, five taste outcomes, eight sleep outcomes, or eight QoL outcomes. There were no between group differences in rates of adverse events (35.1% versus 38.9%; *p*=0.74).

Elbanna et al. compared four weeks of photobiomodulation therapy (a form of light therapy that uses non-ionising forms of light sources placed near or in contact with the skin for the purpose of making alterations at the molecular, cellular and tissue levels of the body) to a placebo in 100 participants.[48] Participants who received photobiomodulation therapy had significantly improved fatigue (assessed by the Fatigue Severity Scale; *d*=0.89, 0.48 to 1.31) and functional status (assessed by Katz Index of Independence in Tasks of Everyday Living; *d*=0.46, 0.06 to 0.85) relative to the placebo group. The study did not report on safety outcomes.

One study investigated Cytoflavin® (Inosine, Nicotinamide, Riboflavin and Succinic Acid, orally twice daily for 25 days) relative to "other therapy" (vitamins, nootropics) among 100 participants.[73] Participants who received Cytoflavin® reported improvements in fatigue (assessed by the multidimensional fatigue inventory; total score *d*=1.15, 0.72 to 1.57; subscales *d* range=0.58 to 1.49), sleep quality (assessed by the Pittsburgh sleep quality index; *d*=1.25, 0.82 to 1.68), QoL

(assessed by the EQ-5D; *d*=0.83, 0.42 to 1.42), and general health (*d*=1.00, 0.58 to 1.41) relative to those to control group receiving other therapy. No difference in changes in cognition (assessed by the Mini Mental State Examination) were observed. No serious adverse events or side effects associated with treatment were reported.

Three studies reported limited relevant results. Gaylis et al. found no improvements in mean Long COVID symptom scores among participants who received leronmilab (a humanised monoclonal antibody) for eight weeks relative to those who received a placebo.[50] The study did not report on safety outcomes. Shogenova et al. found significant improvements in 6MWT distance among participants who received ten hydrogen inhalation procedures (each session involved 90-minutes of hydrogen inhalation through a nasal cannula) over ten days and no improvements among those who received a placebo. However, between group differences in change were not assessed.[81] The study reported that there were no adverse events. Putilina et al. reported that participants who received either a 10mg or 20mg dose of Cortexin® (a lyophilised extraction of animal cortex) improved:

- fatigue
- general weakness
- olfactory complaints.

However between group differences in change were not assessed and there was no non-Cortexin® comparator.[72] The study reported that there were no adverse events.

3.4 Non-pharmaceutical interventions

3.4.1 Supplements and alternative medicine

Study characteristics for the 11 trials investigating supplements and alternative medicine interventions are presented in Table 3.1 and results are summarised here and presented in Appendix 6.[43, 44, 47, 54, 59, 61, 74, 83, 84, 87, 89] Two studies were at a low risk of bias,[59, 74] four studies had an unclear risk of bias,[54, 61, 84, 87] and five studies were deemed to be at a high risk of bias (Table 3.3).[43, 44, 47, 83, 89] Seven studies reported relevant conflicts of interest.[54, 59, 61, 74, 83, 87, 89] Of the four studies that reported on safety outcomes, none reported serious adverse events attributed to the interventions.[54, 74, 87, 89]

Only one intervention (that is, palmitoylethanolamide and luteolin; PEA-LUT) was assessed in more than one study.[44, 47, 87] Two of the three studies in which it was assessed compared PEA-LUT and olfactory training to a placebo and olfactory training.[44, 47] One of these two studies was a preliminary study with 12 participants

and groups significantly differed at baseline based on smell scores (assessed by Sniffin Sticks TDI score) and smell disorder duration.[44] Change in smell did not significantly differ between groups following 30 days of treatment (*d*=0.38, -0.77 to 1.54). A larger trial with 185 participants from the same author group found that, after 90 days of treatment, participants in the PEA-LUT group had significantly larger improvements in smell (*d*=1.00, 0.66 to 1.33) and were more likely to recover to a normal TDI score (56% versus 10%, *p*<0.00001) compared to the placebo group.[47] The third study investigated the effect of PEA-LUT compared to a placebo on cognition in 39 participants, changes in global cognition (assessed by the Montreal Cognitive Assessment) and executive function (assessed by the frontal assessment battery) did not significantly differ between groups (both *p*>0.05).[87]

Chudzik et al. compared one month of 1-methylnicotinamide chloride (1-MNA) supplementation to no treatment in 50 participants.[43] Although both groups had significant improvements in fatigue (assessed by the Fatigue Severity Score) and exercise capacity (assessed by the 6MWT), changes in these outcomes did not significantly differ between groups (fatigue: *d*=0.21, -0.35 to 0.76; 6MWT: *d*=0.44, -0.12 to 1.00).

Hawkins et al. compared two weeks of aromatherapy to placebo in 44 female participants.[54] After adjusting for several covariates including baseline scores, participants who received aromatherapy had significantly lower fatigue (assessed by the Short Form Multidimensional Fatigue Symptom Inventory; eta squared=0.198; *p*=0.020) and higher QoL (assessed by the Patient Health Questionnaire-9; partial eta squared=0.336; *p*<=0.002) at follow-up.

Karosanidze et al. compared three weeks of ADAPT-232/Chisan® supplementation (a supplement containing the adaptogens Rhodiola Rosea, Elutherococcus Senticosus and Schisandra Chinensis) to placebo in 100 participants.[59] Although both groups significantly improved respiratory symptoms, cough symptoms, fatigue, pain, depressive symptoms, anxiety, cognitive performance, taste and smell, sweatiness, organoleptic dysfunction, and hair loss (all *p*<0.001), changes in these outcomes did not significantly differ between groups (all *p*>0.05). There was also no significant difference between groups in the number of stay at home/sick-listed days or average duration of all symptoms (both *p*>0.05). Participants who received supplements increased their time spent walking (*p*<0.0001) but not their overall physical activity levels (assessed by the Habitual Physical Activity Questionnaire) (*p*>0.05) relative to those who received the placebo.

Kharaeva et al. compared three weeks of fermented fruit supplementation to placebo in 213 participants among people who had a severe or moderate COVID-19 infection.[61] Greater improvements were seen in participants who received the supplement for shortness of breath (severe COVID-19: *d*=0.49, 0.03 to 0.94;

moderate COVID-19: *d*=0.57, 0.13 to 1.01), and average Long COVID symptom score (severe COVID-19: *d*=1.98, 1.45 to 2.52; moderate COVID-19: *d*=1.45, 0.97 to 1.93).

Rathi et al. compared two weeks of systemic enzyme supplementation and probiotics to placebo in 200 participants.[74] After two weeks, fatigue (assessed by the Chalder fatigue scale) had significantly decreased more in the supplement group (25.78 to 8.54) than the placebo group (25.69 to 19.91, $p<0.001$). A greater proportion of participants who received systemic enzymes and probiotics reported being fatigue-free at all time-points (that is, days 4, 8, 11, and 14).

Sumbalová et al. compared one month of a rehabilitation and a coenzyme Q10 supplement intervention to a rehabilitation only intervention in 51 participants.[83] The rehabilitation and supplement group significantly improved their exercise capacity from baseline (assessed by the 6MWT: mean change=61.4m±18.1; p=0.003) but not shortness of breath following exercise (mean change=1.0±0.48, *p*=0.08). The rehabilitation only group significantly improved both exercise capacity (mean change=87.2m±30.1; *p*=0.004) and shortness of breath (mean change=2.1±0.55, *p*=0.004). Participants in the rehabilitation and supplement group reported 62.8% fewer symptoms following the intervention and participants in the rehabilitation only group reported 51.8% fewer symptoms. Whether changes differed between groups were not assessed for any of the outcomes.

Tosato et al. compared one month of L-arginine and vitamin C supplementation to placebo in 46 participants.[84] All participants reported fatigue (assessed by a single question from the Centre for Epidemiological Studies Depression questionnaire) at baseline. At the end of the intervention, fewer participants in the supplement group reported fatigue than in the placebo group ($p<0.0001$). Participants in the supplement group also significantly increased 6MWT distance (mean difference, 95%CI=50m, 20.0 to 80.0m; effect size=0.56) and handgrip strength (mean difference, 95%CI=3.4kg, 0.5 to 9.5kg; effect size=0.37) relative to those in the placebo group.

Young et al. compared cannabidiol supplementation to placebo in 23 participants. However, the placebo unexpectedly contained medical concentration of terpenes (that is, the fragrant components of the cannabis plant) which have shown therapeutic benefits.[89] This trial had a cross-over design whereby Group 1 received the cannabidiol intervention and Group 2 received the placebo (both blinded) for the first four weeks before an open-label cross-over for a further four weeks. In the first intervention period, changes in shortness of breath, fatigue, anxiety, depressive symptoms, cognitive function, pain, sleep, ability to participate in social roles, and satisfaction with social roles did not significantly differ between groups (*d* range=-0.41 to 0.14). Of these outcomes, only anxiety (mean difference=-4.9±6.14,

p=0.009) and sleep (mean difference=-3.1±4.71, p=0.021; both assessed by the Patient-Reported Outcomes Measurement Information System) had significantly improved in Group 1 from baseline. Global impression of change significantly improved in Group 1 from baseline to the end of the first (median scores: 1.0 to 2.0, *p*<0.05) and second (median scores: 1.0 to 3.0, *p*<0.05) intervention periods. Improvements were also seen in Group 2 from the start of the second intervention period to the end (median scores: 2.3 to 4.5, *p*<0.05).

3.4.2 Exercise

Study characteristics for the eight trials investigating exercise interventions are presented in Table 3.1 and results for these studies are summarised here and presented in Appendix 7.[57, 58, 64, 67, 75-77, 86] Of these, two studies examined only whether the effectiveness of exercise differed by setting or method of delivery.[77, 86] Overall, risk of bias was high for all studies (Table 3.3), driven almost entirely by the lack of participant blinding. The high risk of bias in this particular domain is to be expected as designing studies that blind participants to an exercise intervention is unlikely to be possible. However, most (42; 88%) other domains were at low risk of bias across these studies, four (8%) were at unclear risk of bias, and 2 (4%) were at high risk of bias. No studies reported relevant conflicts of interest. Of the five studies that reported on safety outcomes, none reported serious adverse events attributed to the intervention.[57, 58, 64, 67, 75] However, one study did report more mild adverse events in the intervention group.[64] These mostly comprised uncomfortable symptoms including chest tightness, feelings of weakness or reduced physical strength, and cough.

Two studies by the same author group examined the effect of eight weeks of supervised, moderate intensity aerobic and strength training exercise programs (with and without respiratory muscle training) relative to self-management (n=39 and n=80).[57, 58] Across both studies, participants in the exercise training interventions reported significant improvements in fatigue (effect sizes≥0.39), functional limitations (effect sizes ≥ 0.50), and the physical activity domain of QoL (effect sizes≥0.60), although the effect of the interventions on pulmonary or respiratory and mental health outcomes were unclear.

Three studies examined telemedicine interventions.[64, 67, 75] Okan et al. compared a five-week breathing exercises and an unsupervised moderate intensity walking program to short educational instructions in 52 participants.[67] Three of four spirometry measures improved significantly more in the intervention group (forced vital capacity, forced expiratory volume in the first second, and maximum voluntary ventilation), as did shortness of breath, 6MWT distance, and QoL. Rodriguez-Blanco et al. compared a two-week supervised breathing and strength training (intensity not specified) telerehabilitation program to no treatment in 48 participants. Significantly

greater improvements were found in the exercise group for shortness of breath (*d*=1.35, 0.72 to 1.97), fatigue (*d*=0.74, 0.16 to 1.33), 6MWT distance (*d*=0.89, 0.29 to 1.48), and 30 sit-to-stand test (*d*=1.16, 0.55 to 1.77).[75] Li et al. compared a six-week unsupervised exercise programme comprising aerobic and strength training at a personalised intensity, breathing control and thoracic expansion with short educational instructions in 119 participants.[64] At the end of the intervention, participants in the intervention group had a higher risk of improving shortness of breath (risk ratio=1.46, 1.17 to 1.82), although this was not observed at 28-week follow-up (risk ratio=1.22, 0.92 to 1.61). Relative to the control group, physical functioning, assessed by the 6MWT and static squat time, significantly improved in the intervention group at week six (6MWT estimated treatment effect=65.45m, 95% CI=43.80 to 87.10; squat estimated treatment effect=20.12s, 95% CI=12.34 to 27.90) and at 28-week follow-up (6MWT estimated treatment effect=68.62m, 95% CI=46.39 to 90.85; squat estimated treatment effect=22.23s, 95% CI=14.24 to 30.21). Relative to the control group, the physical components of Health Related Quality of Life (HRQoL) significantly improved in the intervention group at week six (estimated treatment effect=3.79, 95% CI=1.24 to 6.35) and at week 28 follow-up (estimated treatment effect=2.69, 95% CI=0.06 to 5.32). However, the mental components of HRQoL did not (week six estimated treatment effect=2.18, 95% CI=-0.54 to 4.90; week 28 estimated treatment effect=1.99, 95% CI=-0.81 to 4.79).

One study compared two one-hour sessions per week of strength and aerobic exercise training for 10 weeks, delivered according to American Thoracic Society/European Respiratory Society guidelines,[92] to two 30-minute sessions of standard physiotherapy per week.[76] Participants who received the strength and aerobic training intervention reported greater improvements in dyspnoea (Multidimensional Dyspnoea Profile total score: *d*=0.82, 0.29 to 1.35; Multidimensional Dyspnoea Profile subscales: *d* range=0.54 to 1.35; modified Medical Research Council dyspnoea scale *d*=1.35, 0.78 to 1.91) and the physical dimension subscale of QoL (*d*=0.52, 0.01 to 1.04) compared to those who received standard physiotherapy. There were no significant between group differences in the change of the total and mental dimension subscale of QoL.

Two small studies examined how the setting and mode of delivery may impact outcomes. Vallier et al. compared a four week, supervised, moderate-intensity, inpatient pulmonary rehabilitation program with the same program delivered in a home setting in 17 participants.[86] This program consisted of a combination of walking, endurance and strength training. Total and general fatigue improved significantly more in the inpatient group compared to the home-based group (total fatigue mean change: -18 versus -5.3, p=0.016; general fatigue mean change: -6 versus -2.4, p=0.028). However, there were no between group differences for a range of other outcomes including shortness of breath, exercise capacity, and QoL.

These findings suggest that the pulmonary rehabilitation program can be performed equally well at home as in a hospital setting, although whether the program performed better than no treatment or any other treatment was not assessed. Similarly, Rutkowski et al. compared a three-week high-intensity aerobic exercise training program administered by virtual reality to the same program administered in-person in 32 participants.[77] Changes in lung function, shortness of breath following exercise, fatigue, stress, and 6MWT distance did not significantly differ between groups (all $p>0.05$), suggesting that the program can be performed equally well via virtual reality as in-person, although whether the program performed better than no treatment or any other treatment was not assessed.

3.4.3 Physiotherapy and physical rehabilitation

Study characteristics for the seven trials investigating physiotherapy and physical rehabilitation interventions are presented in Table 3.1 and results are summarised here and presented in Appendix 8.[38, 45, 65, 66, 69, 70, 82] Overall, the risk of bias was assessed as low for one study[45] and high for the other six studies (Table 3.3). One study reported a relevant conflict of interest.[70] Of the three studies that reported on safety outcomes, none reported serious adverse events attributed to the interventions.[45, 69, 70]

Three studies compared inspiratory and or respiratory muscle training to no treatment (n=26),[69] usual care (n=281),[65] or placebo (n=88).[45] Each study examined respiratory outcomes, finding that the training groups generally improved more than control groups for respiratory muscle function[45, 65] and shortness of breath.[65] Although findings regarding cardiorespiratory fitness were mixed,[45, 65, 69] with the largest study finding no significant difference in estimated VO_2 max (d=0.33, -0.04 to 0.70).[65] QoL and HRQoL generally improved in the intervention groups, although there was some variation across specific domains.[45, 65, 69] Two of the studies examined mental and cognitive outcomes, finding no differences between the intervention and control groups.[45, 65] Inspiratory and or respiratory muscle training also improved sit-to stand score,[45] but not handgrip strength[45] or sleep.[65]

Among a sample of 52 men with moderate Long COVID-19, Nagy et al. found that adding diaphragm release training to inspiratory muscle training for six weeks resulted in greater improvements in shortness of breath (d=1.69, 1.06 to 2.32), fatigue (d=2.26, 1.57 to 2.96), and exercise capacity (d=2.08, 1.40 to 2.75) compared to inspiratory muscle training alone.[66] Ali et al. found that adding an active cycle of breathing technique to a traditional physiotherapy program for a period of 12 weeks resulted in larger improvements in fatigue (d=3.37, 2.58 to 4.16) and 6MWT distance (d=2.35, 1.70 to 3.01).[38]

One study compared an online breathing and wellbeing program (that is, the English National Opera (ENO) Breathe program) to usual care in a sample of 150 participants.[70] ENO Breathe is an ongoing online breathing retraining and wellbeing program created by the ENO in collaboration with healthcare professionals aiming to support people recovering from COVID-19 with persistent breathlessness. Results in the intention to treat population showed that, relative to participants in the usual care group and controlling for the baseline vaules, those in the ENO Breathe group had a larger improvement in breathlessness while running (unstandardised regression coefficient=-10.48, -17.23 to -3.73; p=0.0026; *d*=0.49, 0.17 to 0.82) and the mental health component of the SF-36 QoL questionnaire (unstandardised regression coefficient=2.42, 0.03 to 4.80; p=0.047; *d*=0.25, -0.07 to 0.57). There were no significant between group differences in other pulmonary/respiratory, anxiety, or QoL outcomes.

One study compared breathing exercises to a placebo in 56 participants, finding a relative improvement for the breathing exercises group in one of two pulmonary/respiratory outcomes (forced expiratory volume in the first second: *d*=1.86. 1.18 to 2.54).[82]

3.4.4 Olfactory training

Study characteristics for the four trials investigating olfactory training interventions are presented in Table 3.1 and results for these studies are summarised here and presented in Appendix 9.[42, 60, 63, 71] Overall, the risk of bias was high for all of the studies (Table 3.3). Two studies reported relevant conflicts of interest.[60, 71] No studies reported on adverse events.

Studies compared 12 weeks of olfactory training to a placebo (n=50),[42] three months of olfactory training to a no treatment control (n=298 began but only 170 completed all assessments),[60] and four weeks of advanced olfactory training to standard olfactory training (n=80).[71] Across each study, there were no significant differences between intervention and control groups in change in taste and smell outcomes (assessed by the University of Pennsylvania Smell Identification Test or VAS)[42, 60, 71] or QoL outcomes (assessed by Questionnaire of Olfactory Disorders or VAS).[42, 71] One study compared 12 weeks of olfactory training to safety information only among 63 participants, although the intervention was not reported in sufficient detail to replicate.[63] There were no between group differences in change in smell (assessed by the Brief smell indication test) or return to normal smell at post-intervention.

3.4.5 Cognitive and neurorehabilitation

Study characteristics for the two trials investigating cognitive and neurorehabilitation interventions are presented in Table 3.1 and results summarised here and presented

in Appendix 10.[40, 78] Overall, risk of bias for these studies was low[78] and unclear (Table 3.3).[40] One study reported on safety outcomes, reporting no serious adverse events attributed to the intervention.[78] One study reported a relevant conflict of interest.[78]

In one study (n=30), relative to participants who received a sham, those who received four weeks of transcutaneous vagus nerve stimulation (n=30; *d*=1.09, 0.33 to 1.86) reported significant improvements in pain and Headache Disability Index scores (*d*=1.09, 0.33 to 1.86).[40]

In one study (n=70), relative to participants who received a sham, those who received five weeks of high-definition transcranial direct current stimulation had significant improvements in fatigue (*d*=0.97, 0.48 to 1.47), anxiety (*d*=0.90, 0.40 to 1.39), and QoL (*d*=1.30, 0.78 to 1.81), but not pain (*d*=0.18, -0.29 to 0.65).[78]

3.4.6 Psychological

Study characteristics for the one trial investigating psychological interventions are presented in Table 3.1 and results are summarised here and presented in Appendix 11.[53] Overall, risk of bias for this study was high (Table 3.3).[53] No relevant conflicts of interest were reported. Intervention safety was not reported.

At the end of the intervention (n=49), participants who received four weeks of neuro-meditation reported significantly larger improvements than those in the no treatment control group for fatigue (physical fatigue *d*=5.26, 3.84 to 6.68; mental fatigue *d*=4.66, 3.36 to 5.95), mental health (depressive symptoms *d*=1.25, 0.52 to 1.99; total mood disturbance *d*=1.22, 0.49 to 1.95), and pain outcomes (muscular and joint pain *d*=0.97, 0.26 to 1.69; headaches *d*=0.80, 0.10 to 1.50). There were no significant between group differences in changes in shortness of breath (*d*=0.24, -0.43 to 0.92), anxiety (*d*=0.61, -0.08 to 1.30), cognitive performance (14 outcomes from five computerised cognitive tasks (*d* range=-0.35 to 0.65)) or sleep quality (*d*=0.36, -0.32 to 1.04).

3.5 Study risk of bias assessments

Table 3.3 presents the risk of bias for each included study by the five RoB domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result.[22] In summary, among pharmaceutical and other medical interventions, two (9%) studies had an overall low risk of bias[34, 39, 46, 50-52, 55, 56] while 17 (74%) of the studies had a high risk of bias[34, 39, 46, 50-52, 55, 56] [37, 62, 68, 72, 73, 79, 81, 85, 88] and four (17%) were considered to have unclear risk of bias.[35, 36, 48, 80] Among non-pharmaceutical interventions, four (12%) studies had an overall low risk of bias[45, 59, 74, 78], 24 (71%) had an overall high risk

of bias[38, 42-44, 47, 53, 57, 58, 60, 63-67, 69-71, 75-77, 82, 83, 86, 89] and six (18%) studies had unclear risk of bias.[40, 54, 61, 84, 87, 90] The most common domain for high risk of bias was blinding of participants (pharmaceutical and other medical: n=11, 48%;[34, 37, 46, 50, 55, 62, 72, 73, 79, 81, 85] non-pharmaceutical: n=18, 53%).[38, 43, 53, 57, 58, 63-65, 67, 69-71, 75-77, 82, 83, 86] Across both groups of studies, randomisation sequence generation (pharmaceutical and other medical: n=9, 39%;[34, 37, 50, 55, 62, 68, 72, 73, 80] non-pharmaceutical: n=10, 29%)[38, 42, 43, 53, 54, 61, 63, 71, 83, 87] and allocation concealment were considered to be unclear (pharmaceutical and other medical: n=11, 48%;[34, 37, 50, 55, 62, 68, 72, 73, 81, 85, 88] non-pharmaceutical: n=17, 50%)[38, 40, 42-44, 53, 54, 57, 58, 61, 63, 65, 69, 71, 82-84] as randomisation and allocation methods were generally not well described.

Table 3.3. Risk of bias, assessed using the Cochrane risk of bias for randomised controlled trials

	Randomisation sequence generation	Allocation concealment	Selective reporting	Other	Blinding of participants	Blinding of assessor	Incomplete outcome data	Overall
Pharmaceutical and other medical interventions								
Off-label use								
Abdelalim (2021)[34]	?	?	+	+	-	+	+	High
Achabaeva (2022)[37]	?	?	?	-	-	+	+	High
Dhooria (2022)[46]	+	+	+	+	-	+	+	High
Hansen (2022)[52]	+	+	+	-	+	+	+	High
Hintschich (2022)[55]	?	?	?	+	-	+	-	High
Hosseinpoor (2022)[56]	+	+	+	+	+	+	-	High
Schepens (2022)[80]	?	+	+	+	+	+	+	Unclear
Vaira (2021)[85]	+	?	?	+	-	+	+	High
Investigational/unauthorised								
Abdelazim (2022a)[35]	+	+	?	+	+	+	+	Unclear
Abdelazim (2022b)[36]	+	+	?	+	+	+	+	Unclear
Aref (2022)[39]	+	+	-	+	+	+	+	High
Bazdyrev (2022)[41]	+	+	+	+	+	+	+	Low
Elbanna (2022)[48]	+	+	?	+	+	+	+	Unclear
Finnigan (2023)[49]	+	+	+	+	+	+	+	Low
Gaylis (2022)[50]	?	?	+	-	-	+	+	High
Gupta (2022)[51]	+	+	+	-	+	+	+	High
Kutashov (2021)[62]	?	?	?	-	-	+	+	High
Orlova (2022)[68]	?	?	?	-	+	+	+	High
Putilina (2021)[73]	?	?	?	-	-	+	+	High
Putilina (2022)[72]	?	?	?	?	-	+	+	High
Scaturro (2022)[79]	+	+	?	+	-	+	+	High
Shogenova (2021)[81]	+	?	?	-	-	+	-	High
Yan (2022)[88]	+	?	?	+	+	+	-	High

	Randomisation sequence generation	Allocation concealment	Selective reporting	Other	Blinding of participants	Blinding of assessor	Incomplete outcome data	Overall
Zilberman-Itskovich (2022)[90]	+	+	?	+	+	+	+	Unclear
Non-pharmaceutical interventions								
Supplements and alternative medicine								
Chudzik (2022)[43]	?	?	-	+	-	+	+	High
D'Ascanio (2021)[44]	+	?	+	-	?	+	+	High
Di Stadio (2022)[47]	+	+	+	-	+	+	+	High
Hawkins (2022)[54]	?	?	?	+	+	+	+	Unclear
Karosanidze (2022)[59]	+	+	+	+	+	+	+	Low
Kharaeva (2022)[61]	?	?	?	+	+	+	+	Unclear
Rathi (2021)[74]	+	+	+	+	+	+	+	Low
Sumbalová (2022)[83]	?	?	+	-	-	+	+	High
Tosato (2022)[84]	+	?	?	+	+	+	+	Unclear
Versace (2023)[87]	?	+	+	+	+	+	+	Unclear
Young (2022)[89]	+	+	+	+	+	+	-	High
Exercise								
Jimeno-Almazan (2022)[58]	+	?	?	+	-	+	+	High
Jimeno-Almazan (2023)[57]	+	?	-	+	-	+	+	High
Li (2021)[64]	+	+	+	+	-	+	+	High
Okan (2022)[67]	+	+	?	+	-	+	+	High
Rodriguez-Blanco (2023)[75]	+	+	+	+	-	+	+	High
Romanet (2022)[76]	+	+	+	+	-	+	+	High
Rutkowski (2023)[77]	+	+	-	+	-	+	+	High
Vallier (2023)[86]	+	+	+	+	-	+	+	High
Physiotherapy and physical rehabilitation								
Ali (2023)[38]	?	?	?	+	-	+	+	High
del Corral (2023)[45]	+	+	+	+	+	+	+	Low
McNarry (2022)[65]	+	?	?	+	-	+	-	High

	Randomisation sequence generation	Allocation concealment	Selective reporting	Other	Blinding of participants	Blinding of assessor	Incomplete outcome data	Overall
Nagy (2022)[66]	+	+	+	+	+	+	-	High
Palau (2022)[69]	+	?	+	+	-	+	+	High
Philip (2022)[70]	+	+	+	+	-	+	+	High
Srinivasan V (2021)[82]	+	?	?	?	-	+	+	High
Olfactory training								
Bérubé 2022)[42]	?	?	?	+	+	+	-	High
Khan (2023)[60]	+	+	+	+	+	+	-	High
Lechner (2022)[63]	?	?	+	+	-	+	-	High
Pires (2022)[71]	?	?	?	+	-	+	+	High
Cognitive and neurorehabilitation								
Awaad (2022)[40]	+	?	?	+	+	+	+	Unclear
Santana (2023)[78]	+	+	+	+	+	+	+	Low
Psychological								
Hausswirth (2023)[53]	?	?	?	+	-	+	+	High

Key: + = Low risk of bias; ? = Unclear risk of bias; - = High risk of bias

4 Discussion

4.1 Overview of results

Studies included in this review considered interventions for adults with Long COVID symptoms (for example, dyspnoea, fatigue, or loss of smell as opposed to onset of new conditions such as kidney failure) generally among people with short-term Long COVID (that is, less than one year) without pre-existing chronic illnesses.

There was substantial variation in the interventions and outcomes assessed within and across the intervention categories. Studies were generally short in duration (pharmaceutical/medical interventions median duration: five weeks; non-pharmaceutical interventions median duration: six weeks) and the longest follow-up period was 20 weeks, followed by three months. Therefore, the long-term effects of interventions were not assessed. Study sample sizes were generally small (pharmaceutical/medical interventions median sample size: 70; non-pharmaceutical interventions median sample size: 54).

Three studies examined specific subpopulations, such as older adults or people with pre-existing chronic conditions. People with COVID-19-related exacerbation of pre-existing chronic illnesses or new-onset of a chronic illness likely have different treatment needs to the populations considered in this review. Additionally, people with different phenotypes (or observable characteristics) of Long COVID will likely benefit from different treatments.[93, 94] However, few studies considered the specific Long COVID symptoms that participants presented with at baseline. Interventions that reported safety outcomes (n=29 trials) were observed to be safe and tolerable, with no studies reporting serious adverse events attributed to the interventions. Overall, there was a diverse range of interventions and outcomes, and most interventions were only examined by single studies. As a result of this, the short follow-up periods and the small study sample sizes, there is a limited evidence base to support the effectiveness of these interventions.

Evidence for the effectiveness of the identified pharmaceutical or medical interventions was limited. In the off-label use subcategory, findings indicated no treatment benefit from mometasone furoate nasal spray, prednisone/prednisolone, or high-dose coenzyme Q10 supplementation on olfactory function, QoL or other outcomes. Some investigational and unauthorised interventions showed some potential. However, further research is required as the evidence base for these interventions are small, provisional and limited. For example, a phase II clinical trial showed that AXA1125 may improve fatigue in people with Long COVID and impaired mitochondrial oxidative capacity. However, the sample size was small (n=41) and the proportion of people with Long COVID who have mitochondrial dysfunction is unknown.[49] Therefore, whether these findings are generalisable to the broader

population is yet to be determined. Single studies investigating sodium gluconate and tetra sodium pyrophosphate nasal sprays reported improvements in smell, and single studies investigating L-acetyl-carnitine, actovegin®, photobiomodulation therapy, and intermittent hypoxia-hyperoxia reported short-term improvements in several symptoms. However, further research is required to confirm these findings.

For the non-pharmaceutical interventions, three studies showed symptom improvement following palmitoylethanolamide and luteolin supplements (olfactory function) (n=213),[61] a fermented fruit supplement (dyspnoea and Long COVID symptom score) (n=185)[47] and systemic enzymes and probiotics (fatigue) (n=200),[74] respectively. The evidence for personalised exercise interventions suggested some potential short-term improvements in dyspnoea, fatigue, physical function, and the physical domain of QoL reported. However, long-term effects were not assessed and concerns have been raised around the potential for exercise to exacerbate symptoms in some patients (discussed further in Section 4.8).[95, 96] Physiotherapy and rehabilitation programmes also suggested some potential short-term benefits, with breathing-related interventions reporting the potential for improvements in respiratory function, dyspnoea, and QoL. Findings suggested no treatment benefit from olfactory training. Three small cognitive and neurorehabilitation and psychological interventions showed improvements in a range of symptoms.

4.2 Pharmaceutical and other medical interventions

Eight trials investigated off-label interventions and 16 trials investigated investigational/unauthorised interventions. The evidence did not support the effectiveness of the off-label use pharmaceutical interventions. Four studies investigating off-label products reported adverse events. In one study[85] there were no adverse events among people who received prednisolone, in another study 16% of people who received prednisolone reported mild side effects such as nervousness/restlessness and stomach irritation,[80] and in another study[46] there were no differences in adverse events between people who received high- and low-dose prednisolone. In relation to CoQ10, four grade two (that is, mild) and 15 grade one (that is, moderate) adverse events attributed to the intervention were reported among 13 (11%) participants.[52]

Some investigational interventions had positive findings that merit further research. However, these do not yet have sufficient scientific support for their effectiveness. Particular caution is warranted with regards to interpreting evidence relating to investigational/unauthorised interventions. While off-label interventions are not licensed for Long COVID symptoms specifically, these are licensed for other indications and so there may be longer term safety data associated with their use. Conversely, the use of investigational/unauthorised interventions outside of clinical

trials may be limited and so data pertaining to their use in larger populations, particularly safety outcomes, may not be available.

There are also regulatory issues associated with the use of unauthorised medicinal products, outside of a clinical trial setting. Irish legislation does recognise the possibility for registered doctors and other prescribers to access unauthorised medicines for patients under their care (addressed in the Medicinal Products (Control of Placing on the Market) Regulations, 2007, (SI No 540 of 2007) as amended). The Health Products Regulatory Authority (considers an unauthorised medicine 'exempt' from authorisation when it is supplied to the order/prescription of a registered prescriber for use by their individual patients on the prescriber's direct responsibility in order to fulfil the special needs of those patients. However, the HPRA does not issue approvals for use of exempt medicines as they have not been assessed against the criteria of safety, quality and efficacy.[97, 98] Therefore, it is important to note that off-label prescribing or the use of unauthorised medicines more generally can result in legal and ethical dilemmas for prescribers as legally they are responsible for any harm caused, subject to the common law rules of negligence, and ethically they are met with a poor evidence base for this medicine, but often have no suitable alternatives.[99]

One investigational study, a phase II clinical trial by Finnigan et al., investigated the therapeutic benefits of AXA1125 over four weeks among people with fatigue-predominant Long COVID (n=41).[49] Participants were selected if they had impaired mitochondrial oxidative capacity as mitochondrial dysfunction has been identified as a potential mechanism underpinning fatigue in Long COVID.[11] AXA1125 is an endogenous metabolic modulator comprised of five amino acids and N-acetylcysteine reported to reverse mitochondrial dysfunction. However, there was no pre- to post-intervention change in post-exercise phosphocreatine recovery rate, a marker for potential changes in mitochondrial oxidative metabolism. Nonetheless, participants who received the drug reported large improvements in fatigue relative to those who received a placebo, although the mechanism underpinning this improvement remains unclear. In terms of safety and tolerability, no serious adverse events were attributed to the intervention, although one serious adverse event (syncope, attributed to an imaging procedure) occurred in the AXA1125 group, and 14% of participants who received AXA1125 reported diarrhea and 10% reported nausea. Risk of bias in the study was low, although the study was conceptualised, designed and funded, and data analysed, by the drug manufacturer (Axcella Therapeutics), and four authors reported links (employment, consultancy fees and or stock and or options in the company) to the company. Future research in larger more representative samples of the broader population with fatigue-predominant Long COVID is warranted.

Two investigational studies examined nasal sprays, a sodium gluconate spray and a tetra sodium pyrophosphate spray, among small samples of participants who had clinically confirmed signs of olfactory dysfunction persisting for more than 90 days after SARS-CoV-2 negative testing.[35, 36] The effect of these sprays on smell (assessed by the Sniffin' Sticks TDI score) were large, due to low variability in TDI scores among participants at baseline and a lack of improvement over time in the control groups as opposed to very large improvements in the intervention groups. Average absolute TDI score improvements in both intervention groups were just under 5.5, which has been suggested as a cut-off above which more than 60% of patients recognise improvement of their sense of smell.[100] Future research in larger samples more representative of the broader population with Long COVID olfactory dysfunction is warranted.

Other investigational interventions such as platelet-rich plasma injections, L-acetyl-carnitine, intermittent hypoxia-hyperoxia and photobiomodulation therapy improved symptoms across a number of small studies. In a large trial (n=444), Actovegin® had a large effect on fatigue and a moderate effect on cognitive function. However, safety outcomes were not reported.[62] Actovegin® is a deproteinised hemodialysate of calf's blood proposed to improve cellular uptake and utilisation of glucose and oxygen that is currently authorised for clinical use in some European countries (that is, Austria, Latvia, Romania, and Russia) but not Ireland.

In the study that investigated hyperbaric oxygen therapy, hyperbaric oxygen therapy significantly improved in two of 51 outcomes relative to a sham control after adjustment for multiple comparisons.[90] High rates of mild and moderate adverse events, including barotrauma, cough, and palpitation, have been reported among people with Long COVID who receive hyperbaric oxygen therapy.[90, 101]

Future research on these pharmaceutical and medical interventions may be warranted, but there is not yet sufficient evidence to support their effectiveness. None of the pharmaceutical or medical interventions included in this review were developed for the purpose of treating Long COVID, potentially due to the current limited understanding of the pathophysiology of the illness. Improving the understanding of the pathophysiology of Long COVID this may facilitate researchers in designing targeted interventions that address the multifaceted nature of Long COVID, potentially leading to more effective interventions and improved patient outcomes.

4.3 Supplements and alternative medicine

Eleven trials investigated supplement and alternative medicine interventions. Most supplements were only investigated by single studies and had small sample sizes, limiting their generalisability. As with all studies, follow-up periods were short,

meaning that the long-term effectiveness of supplements was not investigated. Of the four studies that reported on safety outcomes, just one was reported, with one participant who received aromatherapy withdrawing due to headaches, although the study noted that the participant also reported experiencing recurring headaches prior to the start of the study.[54, 74, 87, 89]

Three studies showed symptom improvement following supplementation of palmitoylethanolamide and luteolin (olfactory function),[44] a fermented fruit supplement (dyspnoea and Long COVID symptom score)[61] and systemic enzymes and probiotics (fatigue),[74] respectively. Two of these studies reported conflicts of interest as the study was linked through funding or author affiliation to manufacturers of the products being investigated[61, 74] and the other study was at high risk of bias.[47] Further research on these supplements is required to determine their effectiveness.

One smaller study (n=46) reported large improvements in fatigue in particular following L-arginine and vitamin C supplementation. However, fatigue was assessed using a single question. This finding should be verified in larger samples with a more robust assessment of fatigue. Another study reported improvements in fatigue and QoL following aromatherapy. However, this was also in a small sample (n=44) of females only.[54] Other studies of cannabidiol, a coenzyme Q10 supplement, ADAPT-232/Chisan®, and 1-MNA did not support their effectiveness.[43, 59, 83]

Similar to related conditions such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS),[102] no definitively effective supplements were identified in the current review, although future research for some supplements may be warranted.

4.4 Exercise

In the current review, short-term (up to 10 weeks) improvements in dyspnoea, fatigue, physical function, and the physical domain of QoL following exercise interventions were reported. Long-term effects were not assessed in any of the included studies. Studies examined both strength and aerobic exercise training programs, although six interventions used a personalised approach to exercise prescription in which exercise intensity, volume and progression varied between individuals depending on their specific needs.[57, 58, 64, 75, 77, 86]

Regarding comparator groups, four studies provided participants in the control arms with brief instructions on self-management or exercise at baseline.[57, 58, 64, 67] Typically, such information is not sufficient to alter physical activity levels, often due to low compliance levels without personalised prescription or supervision.[103, 104] Although physical activity levels were not assessed in these included studies, markers of physical fitness did not improve in the control groups, indicating that participants did not increase their levels of activity. One study compared an aerobic

exercise intervention to an active comparator (standard physiotherapy, which contained exercise components) which may diminish the magnitude of the observed effect of the intervention.[76] Two of the eight included studies compared whether the effects of the intervention differed by mode (virtual reality versus in-person) or setting (home-based versus hospital based) of delivery, finding no differences.[77, 86] These findings do not inform whether the interventions were more effective than no treatment or any other treatment, although they can provide relevant information on safety and inform implementation strategies.

Of the five studies that reported on adverse events, four did not record any.[57, 58, 67, 75] One reported that no serious adverse events occurred during the study period, although more mild adverse events occurred in the intervention group in the first six weeks.[64] These mostly comprised uncomfortable symptoms including chest tightness, feelings of weakness or reduced physical strength, and cough. Post-exertional malaise or symptom exacerbation was explicitly considered in two studies, although neither study measured it as an outcome.[58, 64] Of the seven studies that reported relevant information in sufficient detail,[57, 58, 64, 67, 76, 77, 86] one of 252 participants discontinued the exercise intervention due to tolerance-related issues (chest pain).[64] In the eighth study, one person of 26 discontinued the intervention but the reason was not provided.[75] The potential for exercise to exacerbate symptoms in people with Long COVID is discussed in greater detail in Section 4.8.

Baseline information on participants that may inform implementation of exercise interventions was lacking. For example, no studies reported participant fitness or physical function prior to COVID-19 infection which may influence response to the interventions. Additionally, just three studies included participants presenting with specific Long COVID symptoms (dyspnoea),[64, 67, 76] while the others included people presenting with any Long COVID symptom. Regarding hospitalisation status, three studies included only people who had not been hospitalised due to COVID-19,[57, 58, 75] two studies included only people who had been hospitalised,[64, 76] two studies included both,[77, 86] and one study included only people who had received treatment for COVID-19 (hospitalisation status was unspecified).[67] There were not enough studies to assess whether findings may differ according to participant characteristics.

One limitation inherent to exercise interventions is the inability to blind participants to the intervention, and so observed effects may be in part or entirely attributable to placebo. Beyond this, risk of bias was generally low across studies. However, studies were limited in their short follow-up and small sample sizes.

The current evidence suggests the potential effectiveness of personalised exercise to improve symptoms in the short-term in some people with Long COVID. However, exercise may also exacerbate symptoms in others and so a person-specific approach to prescribing exercise, considering each person's individual needs, should be taken.

4.5 Physiotherapy and rehabilitation

The seven studies included in this category investigated physiotherapy and rehabilitation interventions that were lower intensity than those included in the exercise category. Studies generally investigated breathing exercises or inspiratory and or respiratory training (such as breathing retraining, diaphragm release training, or use of an inspiratory muscle trainer). Most studies had small sample sizes, although two were larger, with samples of 281[65] and 150.[70] Six of the seven studies limited participation to people presenting with pulmonary issues or shortness of breath. Four studies had active comparators (usual care, inspiratory muscle training, and standard breathing exercises) which may reduce the magnitude of the relative effect of the intervention. Across these studies, potential short-term, improvements in respiratory function, dyspnoea, and QoL were reported, highlighting the potential for this form of rehabilitation to be effective among people with Long COVID and shortness of breath. Three studies included participants specifically with respiratory issues,[38, 65, 66] and the others did not restrict participant inclusion by their symptoms. Potential causes of these respiratory issues, such as breathing pattern disorder which can be potentially triggered by a SARS-CoV-2 infection,[105, 106] were not considered in the studies. Regarding hospitalisation status, one study included only people who had not been hospitalised due to COVID-19,[66] one study included only people who had been hospitalised,[69] one study included both,[70] and it was not reported in four studies.[38, 45, 65, 82]

Three studies reported on safety outcomes. Of these, none reported serious adverse events attributed to the interventions.[45, 69, 70] In one study, one participant reported symptom exacerbation, although they participated in a sham inspiratory muscle training intervention.[45] One participant withdrew from a breathing exercise group due to dizziness that they attributed to looking at the computer screen for too long during the sessions.[70]

The evidence suggested physiotherapy and rehabilitation focusing on breathing exercises or inspiratory and or respiratory training may be effective in the short-term among people presenting with pulmonary issues or shortness of breath. Therefore, these forms of interventions may potentially form part of an effective rehabilitation strategy.

4.6 Other interventions

Other studies investigated olfactory training and cognitive and neurorehabilitation, and psychological interventions. Olfactory training has previously been shown to be beneficial for olfactory abilities, with larger effects seen among people with post-infectious olfactory loss.[107] However, the current review did not identify any evidence that olfactory training improves olfactory function in people with Long

COVID. The cognitive and neurorehabilitation and psychological interventions investigated transcutaneous vagus nerve stimulation, high-definition transcranial direct current stimulation, and neuro-meditation, finding large effects on fatigue, mental health, and pain. However, these studies are small, and their generalisability to the broader Long COVID population is limited, further studies are required to assess their effectiveness. Of these interventions, only one, the study on transcranial direct current stimulation, reported on adverse events, that skin redness was the only adverse event that differed between the intervention and sham control group.[78]

4.7 Limitations of the current evidence

The current evidence base for interventions of Long COVID has several key limitations. In this section, eight main limitations identified in the systematic review are discussed:

- inability to perform GRADE
- small sample sizes
- short study duration and follow-up period
- inappropriate comparators
- lack of focus on patients with specific Long COVID phenotypes
- insufficient examination of subpopulations of interest
- use of non-specific interventions, and high risk of bias.

Performing a GRADE assessment of the certainty of evidence was impractical for this review due to the large variability in the types of interventions and outcomes included. Although not formally assessed using GRADE, the certainty of evidence would most likely be considered low to very low given that most interventions included in the current review were examined by single studies and due to the limitations detailed further in this section.

Many of the studies included in our review had small sample sizes (pharmaceutical/medical interventions median sample size: 70; non-pharmaceutical interventions median sample size: 54), which can limit the statistical power and the generalisability of the findings. Small sample sizes increase the risk of a potentially effective intervention mistakenly concluded to be ineffective. Additionally, studies with small sample sizes may not be representative of the broader population of individuals with Long COVID, thus reducing the generalisability of the findings.

All studies had short durations and follow-up periods, the longest follow-up period was 20 weeks. This restricts the understanding of the long-term effectiveness and safety of the investigated interventions. Long COVID can be a persisting condition, and short-term evaluations may not capture the full benefits or potential harms of potential interventions. Longer study durations and follow-up periods would provide a more comprehensive assessment of the interventions' impact on patient outcomes and quality of life.

Many included randomised controlled trials used active comparator groups which may diminish the relative effect of the intervention being examined. Ideally, placebo or sham control groups would be used, where possible.

None of the studies specifically examined patients who had Long COVID for an extended period (greater than one year) or those with severe long COVID and few examined people with specific Long COVID phenotypes (that is, few considered the specific Long COVID symptoms that participants presented with at baseline). This is a crucial limitation, as the treatment needs and responses may differ based on the duration of Long COVID and Long COVID phenotypes. This leaves a significant knowledge gap in the understanding of effective treatment strategies that are more person-specific. Further, there is some evidence that the risk of Long COVID may vary across COVID-19 variants.[108] Larger and longer term studies would facilitate better understanding on whether treatment effects may differ by the initial COVID variant.

Only three studies considered interventions in specific subpopulations (people with hypertension, obesity, osteoarthritis, and older adults).[48, 66, 68] Populations such as pediatric populations, older adults, or people with pre-existing chronic conditions may have unique treatment needs and respond differently to interventions compared with the general Long COVID population. A lack of targeted research on these subgroups may result in suboptimal treatment approaches and lead to greater health disparities among these vulnerable populations.

Most studies considered interventions that were not specifically targeted towards Long COVID, often investigating interventions typically used for other illnesses. This lack of specificity may limit the effectiveness of the interventions to address the unique pathophysiology and symptomatology of Long COVID. This underpins the need to improve the understanding of the pathophysiology of Long COVID so as to facilitate researchers in designing targeted interventions that address the multifaceted nature of Long COVID, potentially leading to more effective interventions and improved patient outcomes.

Most studies included in the review were assessed as having a high risk of bias. The most common reasons for this were a lack of participant blinding, problems with allocation concealment, and issues with random sequence generation. Studies with a

high risk of bias may produce unreliable results, limiting the overall quality and reliability of the evidence base for Long COVID interventions.

Finally, it is not necessarily practical or feasible for every potential intervention to be examined in RCTs among people with Long COVID. For example, there may not be sufficient financial incentive for pharmaceutical and medical device companies to examine treatments that are already being used in practice for Long COVID. Therefore, there may be a reliance on academic and other institutions to fund and run these trials. Additionally, it can be difficult to design and implement RCTs that examine multi-disciplinary, multi-component interventions. Furthermore, RCTs can be time consuming and costly. As a result, it is likely that some potentially effective treatments for Long COVID have not yet been and may not be studied in RCTs among people with Long COVID which may limit their integration into healthcare delivery.

4.8 Treatment considerations

There is an acknowledgement among clinicians treating patients with Long COVID in Ireland that, given the complexity of Long COVID, diversity of symptoms experienced and lack of understanding of the underlying pathogenesis, there may never be a single effective treatment. Current practice in Ireland focuses on providing a holistic, multidisciplinary approach as outlined in the interim model of care.[109] This model of care is broadly consistent with international guidelines.[20] Additionally, public health advice is to minimise the risk of infection or reinfection and promote the COVID-19 vaccination programme to reduce the severity of COVID-19 cases, and thereby potentially the incidence of Long COVID.[110-112]

Regarding exercise, there is ongoing debate over its use as a treatment for Long COVID, primarily due to the potential for exercise to exacerbate symptoms, a phenomenon known as post-exertional malaise or post-exertional symptom exacerbation.[95, 96] Post-exertional malaise is characterised by an increase in pain, fatigue, cognitive problems, and other associated symptoms that persist for an unusually long period of time following mental and/or physical exertion.[113, 114] It is a hallmark feature of ME/CFS – another chronic multisymptom illness with substantial symptom overlap with Long COVID.[115] Even minimal exertion can significantly worsen the entire symptom complex of ME/CFS[114] and exercise challenges, frequently used in ME/CFS research, often lead to increases in symptoms such as fatigue, sore throat, headaches, muscle pain, joint pain, confusion and decreases in energy.[116-120] This typically lasts for days, but patients have reported that it can last for years or that it has never resolved.[121, 122] Post-exertional malaise is a common symptom of Long COVID and many people with Long COVID may meet criteria for ME/CFS.[4, 7, 123, 124]

Early in the pandemic, the National Institute for Health and Care Excellence (NICE) cautioned against using graded exercise therapy for patients recovering from COVID-19.[125] However, in November 2022, they published a rapid guideline on managing the long-term effects of COVID-19, recommending that healthcare providers should collaborate with patients (and their family or carers, if appropriate) to develop a personalised rehabilitation and management plan.[126] This plan should include areas of rehabilitation and interventions based on their assessment, helping the person to decide and work towards goals, manage and monitor their symptoms (taking into account fluctuations), and know what to do if symptoms return or change. In the evidence underpinning this recommendation, the expert panel considered that careful self-pacing of exercise is an important element of self-management, although they could not make specific recommendations in the absence of evidence specifically relating to people with Long COVID.

The evidence on the effects of exercise in people with Long COVID specifically remains limited, and post-exertional malaise or symptom exacerbation was only specifically considered in two exercise studies included in this review.[58, 64] However, given the prevalence of post-exertional malaise and ME/CFS-like symptoms among people with Long COVID, it is likely that exercise could exacerbate symptoms among some patients. Therefore, caution should be used if prescribing exercise and a personalised approach, considering each person's individual needs, should be taken. Additionally, although not a physical activity or exercise programme itself, activity and energy management, which can include pacing strategies,[127] is a tool recommended by NICE for the management of ME/CFS that can apply to these programmes.[128] Pacing strategies are currently recommended by World Physiotherapy to assist Long Covid symptom stabilisation.[129] The key component of energy management is understanding the principle of using energy, considering current activity and evaluation of rest and sleep, in a way to minimise post-exertional malaise.

Finally, caution should be exercised in the use of treatments that are not supported by robust evidence. In some cases, treatments simply may not be effective, but others may be expensive or even actively harmful. Some observational studies or single arm studies (that is, studies with an intervention but no comparator group) may report benefits for some treatments. However, it is likely that symptoms naturally improve over time in some Long COVID patients, as evidenced by improvements seen in participants in the control groups of many studies included in the current review. As a result, single-arm studies cannot discern whether improvements are due to the intervention or other factors, such as placebo or natural improvement over time, and RCTs that eliminate much of the bias inherent with other study designs are required.[14] Caution is required until more robust evidence emerges from the many ongoing RCTs. The development of Long COVID

clinical guidelines would be useful to guide practitioner and patient decisions about appropriate healthcare.

4.9 Ongoing research

The current review includes RCTs published as of 28 February 2023. However, a large number of trials were ongoing at that date. For example, 283 potentially relevant ongoing trials (not limited to RCTs) were identified in the current review. Further, a systematic review by Fawzy et al. identified 388 trials investigating therapeutic modalities for Long COVID that were registered on the WHO International Clinical Trials Platform as of 16 September 2022.[130] This section summarises findings from this systematic review.

Of the 388 reviewed trials, 310 are RCTs. The 388 trials are investigating 406 interventions, of which 368 are mono-therapeutic strategies and 38 are multicomponent interventions. The most common interventions being investigated are rehabilitation (n=169), pharmacological agents (n=76; the most common agent being colchicine), and complementary and alternative medicine (n=64). Fatigue is the most common primary outcome (n=108) and the pulmonary system is the most commonly targeted organ system (n=133). Few trials are studying new interventional agents developed specifically for Long COVID, most repurposed therapies that are being used for similar conditions, such as cancer-associated fatigue syndrome.

Finally, many national and international institutions and organisations are conducting ongoing horizon scanning for evidence of emerging COVID-19 health technologies, practices and interventions. A list of these are presented in a previous HIQA report.

4.10 Future research

To improve our understanding of Long COVID and enhance treatment options, several key areas for future research need to be addressed. These include further data on the safety of interventions, standardising Long COVID definitions, understanding the pathophysiology of Long COVID, examining multicomponent interventions, improved study outcome specificity in relation to the interventions being assessed and study participant Long COVID phenotypes, examining subpopulations of interest, and focusing on patients with long-lasting Long COVID. Additionally, it is essential that researchers consider patient perspectives on interventions to ensure that they are safe, effective and acceptable.

Most (63%) studies included in the current review did not report data on safety outcomes. In addition to assessing the effectiveness of interventions, it is essential that future research assesses their safety and tolerability among participants.

Future studies should adopt standardised definitions of Long COVID, such as those used by the World Health Organisation or NICE.[2, 3] Using consistent definitions will allow for better comparability across studies, enabling a more accurate synthesis of the evidence and the development of evidence-based clinical guidelines. This will support an improvement to the quality of care provided to individuals with Long COVID.

A deeper understanding of the pathophysiology of Long COVID is crucial to develop more targeted interventions. The biopsychosocial model, which considers biological, psychological, and social factors, can provide a comprehensive framework for studying Long COVID.[131-133] This model recognises that Long COVID may result from a complex interplay of factors, including the immune response, mental health, and social determinants of health. This model can allow researchers to design targeted interventions that address the multifaceted nature of Long COVID, leading to more effective treatments and improved patient outcomes.

Few studies included in the current review assessed multicomponent interventions. Multicomponent interventions that address multiple mechanisms underlying Long COVID may be beneficial in addressing the variety of symptoms experienced by people with Long COVID and warrants further research.

Future studies should assess outcomes specific to interventions. For example, post-exertional malaise was not assessed as an outcome in any of the exercise interventions included in this review. Additionally, outcomes should align to the specific Long COVID symptoms that participants presented with at baseline.

Future research should prioritise interventions for specific subpopulations, such as paediatric populations, older adults, and adults with pre-existing chronic conditions. These subpopulations may have unique treatment needs and respond differently to interventions compared with the general Long COVID population. Focusing on these subgroups will help develop tailored treatment approaches and address health disparities among vulnerable populations.

Future research should specifically examine patients who have had Long COVID for an extended period (for example, greater than one year). The treatment needs and responses of this population may differ from those with a shorter duration of Long COVID. Understanding the unique challenges faced by patients with long-lasting Long COVID and developing targeted interventions may help bridge the current knowledge gap and potentially improve treatment options for this patient group. These suggestions are in addition to those made by a previous review,[130] that the duration of Long COVID symptoms required for participants in the trial should be clear, that objective measures of symptom severity and duration be used, and that trials should target the 12 core outcomes identified by an international Delphi consensus study for Long COVID.[134]

5 Conclusions

This review included 57 randomised controlled trials that considered interventions for adults with Long COVID symptoms (for example, shortness of breath, fatigue, or loss of smell, as opposed to onset of new conditions such as kidney failure) generally among people with shorter-term long-COVID (that is, less than one year) without pre-existing chronic illnesses.

There was considerable variability in the types of interventions examined. Studies were generally short in duration with short follow-up periods; therefore, the long-term effectiveness of the included interventions is unclear. Study sample sizes were generally small and few studies examined specific subpopulations, such as older adults or people with pre-existing chronic conditions, potentially limiting the generalisability of study findings. There was also insufficient examination of intervention safety.

Overall, effective strategies remain elusive and the proposed interventions included in this review for people with Long COVID symptoms do not yet have sufficient evidence to support them. The evidence suggests personalised exercise and physiotherapy involving breathing exercise may have short-term benefits for some patients. However, their long-term effects were not assessed and there is potential to worsen symptoms among people with post-exertional malaise. Future research investigating the effectiveness and safety of other treatments is required, and a large number of trials are currently ongoing. A greater understanding of the pathophysiology of Long COVID may facilitate researchers in designing targeted interventions that address the multifaceted nature of Long COVID. In the absence of strong evidence to support the effectiveness of interventions for Long COVID, a holistic approach should be used to support those living with Long COVID.

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Appendices

Appendix 1. Search strategy

Database: Medline Complete via Ebscohost

Search date: 28/02/2023

#	Query	Limiters/Expanders	Results
S17	S10 AND S15	Limiters - Date of Publication: 20201201- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,807
S16	S10 AND S15	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,940
S15	S14 NOT S13	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2,809,692
S14	S11 OR S12	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2,909,253
S13	(MH "Animals") NOT (MH "Humans")	Expanders - Apply equivalent subjects	5,061,258

		Search modes - Boolean/Phrase	
S12	MH "Cohort Studies" OR MH "Longitudinal Studies" OR MH "Prospective Studies" OR MH "Follow Up Studies" OR TI (cohort OR longitudinal OR prospective OR "follow up") N1 (study OR analys* OR design OR method*) OR AB (cohort OR longitudinal OR prospective OR "follow up") N1 (study OR analys* OR design OR method*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,439,536
S11	PT controlled clinical trial OR PT "Randomized Controlled Trial" OR TI trial OR AB trial OR TI placebo* OR TI "single blind*" OR TI "double blind*" OR TI "triple blind*" OR AB placebo* OR AB "single blind*" OR AB "double blind*" OR AB "triple blind*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,692,659
S10	S3 OR S4 OR S5 OR S6 OR S9	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	9,448
S9	S7 AND S8	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	5,670
S8	S1 OR S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	214,849
S7	AB ((Ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or "non recover*" or lasting or continuous* or continual* or continuing* or postacute* or "post acute*" or "long* term*" or "long-term" or "long duration*" or "long last*" or "long standing*" or postinfect* or "post infect*" or postviral* or "post viral*" or postvirus* or "post virus*") N2 (sequela* or illness or symptom* or sign* or indicat* or syndrom* or	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	452,620

	infection*)) OR TI ((Ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or "non recover*" or lasting or continuous* or continual* or continuing* or postacute* or "post acute*" or "long* term*" or "long-term" or "long duration*" or "long last*" or "long standing*" or postinfect* or "post infect*" or postviral* or "post viral*" or postvirus* or "post virus*") N2 (sequela* or illness or symptom* or sign* or indicat* or syndrom* or infection*))		
S6	AB ((Ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or "non recover*" or lasting or continuous* or continual* or continuing* or postacute* or "post acute*" or "long* term*" or "long duration*" or "long last*" or "long standing*" or postinfect* or "post infect*" or postviral* or "post viral*" or postvirus* or "post virus*") N2 (sequela* or illness or symptom* or sign* or indicat* or syndrom* or infection*)) N10 (covid* or coronavirus* or corona* virus* or Cov or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or "severe acute respiratory syndrome*" or Ncov* or "n-cov")) OR TI ((Ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or "non recover*" or lasting or continuous* or continual* or continuing* or postacute* or "post acute*" or "long* term*" or "long duration*" or "long last*" or "long standing*" or postinfect* or "post infect*" or postviral* or "post viral*" or postvirus* or "post virus*") N2 (sequela* or illness or symptom* or sign* or indicat* or syndrom* or infection*)) N10 (covid* or coronavirus* or corona* virus* or Cov or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or "severe acute respiratory syndrome*" or Ncov* or "n-cov"))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	5,327
S5	AB (("long haul*" OR longhaul* OR postacute OR "post acute" OR post-acute) N2 (covid19 OR covid-19 OR "sars-cov-2*" OR "sarscov-2*" OR "sarscov2*" OR "sars-cov2*" OR "severe acute respiratory syndrome*" OR ncov* OR "n-cov")) OR TI (("long haul*" OR longhaul* OR postacute OR "post acute" OR post-acute) N2 (covid19 OR covid-19 OR "sars-cov-2*" OR "sarscov-2*" OR "sarscov2*" OR "sars-cov2*" OR "severe acute respiratory syndrome*" OR ncov* OR "n-cov"))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	976

S4	AB (("post covid" or "post-covid-19" or postcovid or "post coronavirus" or postcoronavirus or "post coronovirus" or postcoronovirus or "post sars cov 2" or "post-sars-CoV-2") N2 (syndrome* OR disorder* OR illness* OR sickness* OR disease* OR condition* OR symptom* OR sign* OR feature* OR manifestation*)) OR TI (("post covid" or "post-covid-19" or postcovid or "post coronavirus" or postcoronavirus or "post coronovirus" or postcoronovirus or "post sars cov 2" or "post-sars-CoV-2") N2 (syndrome* OR disorder* OR illness* OR sickness* OR disease* OR condition* OR symptom* OR sign* OR feature* OR manifestation*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,564
S3	(MH "Post-Acute COVID-19 Syndrome")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,665
S2	(MH "SARS-CoV-2")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	148,015
S1	(MH "COVID-19")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	209,405

Appendix 2. Excluded studies at full text

Exclusion reason
Abstract - not full paper[135-149]
Preprint of included peer-reviewed study[150]
Insufficient information to determine inclusion[151, 152]
No access[31-33]
Protocol paper[153-187]
Publication date[186-188]
Trial registration[189-427][428-564]
Irrelevant outcomes[101, 565-571]
Irrelevant patient population[28-30, 572-588]
Irrelevant study design[589-640]

Appendix 3. Description of included studies' interventions, comparators and outcomes

Study (country)	Intervention	Comparator	Outcomes
Pharmaceutical and other medical interventions			
Off-label use			
Abdelalim (2021)[34] (Egypt)	Two puffs (100 µg) in each nostril once daily of mometasone furoate nasal spray for 3 weeks with olfactory training in the form of sniffing rose, lemon, and clove for 20 seconds each, twice daily.	Olfactory training as per intervention group	Olfactory function (VAS)
Achabaeva (2022)[37] (Russia)	Multicomponent Group 1 was prescribed the same intervention as the control group in addition to drinking mineral water (warm, low-mineralized (1.43 g/l) carbonic sodium bicarbonate-chloride drink, 40 minutes before meals (3-3.5 ml/kg of body weight) 3 times a day for 21 days). Group 2 also received group physical exercises in the mid-mountain natural park of the resort of Nalchik. Group 3 also received small group psychotherapy lasting 1.5 hours were performed 3 times a week.	Multicomponent The control group was prescribed pharmacotherapy (direct-acting anticoagulant apixaban 2.5 mg orally, 1 tablet twice a day; metabolic drug Elcar 300 mg orally 1.5 g twice a day) and physical therapy in accordance with federal clinical recommendations (breathing and physical exercises for 20 minutes every 2 days).	Pulmonary function (FEV1) Dyspnoea (mMRC) Exercise tolerance (6MWT) Physical activity (modified Borg scale) Quality of life (EQ-5D) Physical recovery (unclear)
Dhooria (2022)[46] (India)	High-dose prednisolone (40mg per day for 1 week, followed by 30mg per day for 1 week, 20mg per day for 2 weeks and 10mg per day for 2 weeks).	Low-dose prednisolone (10 mg per day for 6 weeks)	Exercise capacity (6MWT) Pulmonary function (FVC) Dyspnoea (mMRC and FACIT) Health-related quality of life (KBILD and EQ-5D)
Hansen (2022)[52] (Denmark)	CoQ10 capsules for 6 weeks (5 100mg doses per day) After a 4-week washout period, the participants were allocated to the opposite treatment regimen for a second 6-week dosing period.	Placebo	Symptom severity (composite of 32 symptoms scored as 0-4) Health-related quality of life (EQ-5D) Adverse events (CTCAE, v5.0)

Study (country)	Intervention	Comparator	Outcomes
Hintschich (2022)[55] (Germany)	Mometasone furoate (100 µg of nasal spray in each nostril twice daily) and olfactory training (sniff each odorant for 30s in the morning and the evening: phenyl ethyl alcohol, eucalyptol, citronellal, and eugenol).	Olfactory Training (as per intervention)	Olfactory function (Sniffin' Sticks and VAS)
Hosseinpoor (2022)[56] (Iran)	One puff of 0.05% wt/vol mometasone furoate (corticosteroid) intranasal spray on each side twice per day for 4 weeks.	Placebo	Olfactory function (VAS and modified UPSIT) Anosmia frequency
Schepens (2022)[80] (The Netherlands)	Prednisolone 40mg once daily for 10 days and olfactory training (same as control group). 40mg prednisolone once daily for 10 days	Placebo and 12 weeks olfactory training twice a day, coming to a total of 168 sessions	Olfactory function (Sniffin' Sticks) Taste function (Taste Strip Test and patient questionnaire) Impact of smell/taste changes on quality of life (SNOT-22 and ODQ) Adverse events
Vaira (2021)[85] (Italy)	Systemic cortisone therapy with prednisone (starting with 1 mg/kg/day and tapering the dose) and nasal irrigation with betamethasone (a steroid), ambroxol (a mucolytic), and naphazoline (a decongestant) for 15 days.	No intervention	Olfactory function (CCCRC) Adverse events
Investigational/unauthorised			
Abdelazim (2022a)[35] (Egypt)	Intranasal spray of 1% sodium gluconate administered as 3 sprays for every nostril 3 times daily for 1 month.	Intranasal spray of 0.9% sodium chloride	Olfactory function (Sniffin' Sticks) Adverse events
Abdelazim (2022b)[36] (Egypt)	Intranasal spray of 1% TSSP (tetra sodium pyrophosphate) in borate buffer solution with a pH of 8, administered as 2 sprays into each nostril 3 times daily for 1 month.	Intranasal spray of 0.9% sodium chloride	Olfactory function (Sniffin' Sticks) Adverse events
Aref (2022)[39] (Egypt)	Participants were treated by Ivermectin in the form of nanosuspension mucoadhesive nasal spray (2 puffs per day) for up to 3 months.	Placebo	Olfactory function (VAS) Adverse events

Study (country)	Intervention	Comparator	Outcomes
Bazdyrev (2022)[41] (Russia)	50mg Treamid once a day for 28 days.	Placebo	Pulmonary function (FEV1, FVC, FEV1/ FVC ratio, DLCO, TLC, FRC and body plethysmography) Dyspnoea (Modified Borg and mMRC) 6MWT Health-related quality of life (KBILD) Adverse events
Elbanna (2022)[48] (Egypt)	A photobiomodulation laser was used on both of the calf muscles (diode laser, continuous output, stationary in skin contact mode, 100mW, 808nm, beam spot area of 0.0314cm2, 127.39J/cm2/point, 40s) 3 times per week for 4 weeks.	Placebo	Fatigue (FSS) Functional status (Katz ADL)
Finnigan (2023)[49] (UK)	Oral AXA1125 (endogenous metabolic modulator comprised of 6 amino acids) 33.9g reconstituted as a suspension in approximately 180 mL of water and administered twice daily for 4 weeks, with a minimal interval of 4 hours between consecutive doses.	Placebo	Fatigue (CFQ-11) Exercise capacity (6MWT) Adverse events
Gaylis (2022)[50] (US)	Weekly subcutaneous doses of leronlimab (700 mg).	Placebo	Symptom severity (composite of 24 symptoms scored as 0-4 or 0-3)
Gupta (2022)[51] (US)	Saline nasal irrigation with theophylline (400 mg/capsule) dissolved in water twice daily for 6 weeks.	Placebo	Olfactory function (CGI and UPSIT) Health-related quality of life (QOD) Adverse events
Kutashov (2021)[62] (Russsia)	2 Actovegin® tablets (400 mg) orally, 3 times a day.	Basic therapy	Cognitive function (MoCA) Fatigue (MFI-20) Anxiety (Spielberger-Hanin test)

Study (country)	Intervention	Comparator	Outcomes
Orlova (2022)[68] (Russia)	18 participants received 10 hypoxia-hyperoxic therapy procedures and standard rehabilitation (same as control group). These participants breathed hypoxic (FiO2 13–15%) and hyperoxic (FiO2 up to 40%) gas mixture through a mask in the interval mode using a ReOxy device. The duration of 1–4 procedures was 30 min, 5–10 procedures – 40 min.	Group 1: 15 participants received 10 matching placebo procedures and standard rehabilitation which consisted of 10 group sessions of physical exercises with elements of breathing exercises, 10 procedures of magnetic therapy for joints, and 10 sodium chloride baths. Group 2: 14 participants received standard rehabilitation only.	General health (VAS) Anxiety (Spielberger-Hanin) Depression (Beck Depression Inventory) Dyspnoea (Modified Borg) Adverse events
Putilina (2021)[73] (Russia)	2 Cytoflavin® tablets (dose not reported) twice a day for 25 days.	Other therapy (vitamins, nootropics)	Fatigue (MFI-20) Cognitive impairment (MMSE) Sleep quality (PSQI) Health-related quality of life (EQ-5D) General Health Assessment Scale Adverse events
Putilina (2022)[72] (Russia)	20 mg of Cortexin® for 10 days	10 mg of Cortexin® for 10 days	Fatigue (MFI-20) Olfactory function (unclear) Adverse events
Scaturro (2022)[79] (Italy)	L-acetyl-carnitine therapy and rehabilitation (same as control group) L-acetyl-carnitine 500 mg/4 mL intramuscular vials twice a day for 10 days followed by taking L-acetyl-carnitine 500 mg tablet orally twice a day for 40 days.	Rehabilitation only: 60 min supervised rehabilitation sessions were held three times a week (20 min of aerobic exercises, 20 min of postural gymnastics and 20 min of respiratory re-education)	Dyspnoea (NPI) Musculoskeletal pain (Numeric Rating Scale) Depression (PHQ-9) Health-related quality of life (SF-12)
Shogenova (2021)[81]	Adaptive support ventilation and standard therapy (same as control group). Adaptive support ventilation inhalations (H(H2O)m) via Suisonia apparatus connected to nasal cannula, for 10 days.	Standard therapy which was physiotherapy and drug therapy with drugs containing magnesium, B vitamins and L-carnitine	Exercise capacity (6MWT) Adverse events

Study (country)	Intervention	Comparator	Outcomes
Yan (2022)[88] (US)	1 mL of platelet-rich plasma injected submucosally into bilateral olfactory clefts under endoscopic visualisation, at week 0, week 2, and week 4.	Placebo	function (Sniffin' Sticks and VAS) Adverse events
Zilberman-Itskovich (2022)[90] (Israel)	Hyperbaric oxygen therapy: 40 daily sessions in total (5 per week within a 2-month period): breathing 100% oxygen by mask at 2ATA for 90 min with 5-minute air breaks every 20 min. Compression/decompression rates were 1.0 m/min.	The sham protocol included breathing 21% oxygen by mask at 1.03 ATA for 90 min	Pulmonary function (spirometer) Psychological distress (BSI-18) Pain severity (BPI) Smell and taste (Sniffn' Sticks) Sleep function (PSQI) Quality of life (SF-36)
Non-pharmaceutical interventions			
Herbal, nutritional, and natural supplement			
Chudzik (2022)[43] (Poland)	58 mg of 1-MNA in the morning after a meal	No treatment	Fatigue (FSA) Exercise capacity (6MWT)
D'Ascanio (2021)[44] (Italy)	Oral supplement and olfactory training (same as control group) Single dose of PEA-LUT (Glialia®, 700 mg + 70 mg)	Olfactory training through Sniffin' Sticks twice every day (10-minute session) for 30 days	Olfactory function (Sniffin' Sticks)
Di Stadio (2022)[47] (Italy)	Oral supplement and olfactory training (same as control group) Single dose of PEA-LUT (Glialia®, 700 mg + 70 mg), 5-10 minutes before breakfast	Olfactory training for 90 days through Sniffin' Sticks administered 3 times every day for 6 minutes each session	Olfactory function (Sniffin' Sticks)
Hawkins (2022)[54] (US)	Participants sniffed a blend of essential oils from a 15ml bottle (Longevity™) containing thymus vulgaris, citrus sinensis, eugenia caryophyllus and boswellia carterii for 15 min twice a day, for 2 weeks, at home.	The placebo product contained an inert, odourless fractionated coconut oil with the same protocol as the intervention group.	Fatigue (MFSI) Quality of life (PSQ-9) Adverse events
Karosanidze (2022)[59] (Sweden)	30 mL oral solution of ADAPT-232/Chisan®, twice a day, for 2 weeks: contained 180 mg of Rhodiola rosea L., radix et rhizome, 600 mg of Schisandra chinensis Baill., fructus, 156 mg of Eleutherococcus senticosus, and inactive ingredients.	Matching placebo	Duration and severity of symptoms (unclear) Anxiety and depression (HADS) Physical activity (HAQ)

Study (country)	Intervention	Comparator	Outcomes
			Cognitive function (d2 Test of Attention) Length of homestay/sick-listed time (days),
Kharaeva (2022)[61] (Russia)	14g of BioRex Noni (fermented papaya and noni syrups), twice a day, after breakfast and after supper for 3 weeks.	Matching placebo following the same protocol	Dyspnoea (6MWT) Self-assessed clinical symptoms (unclear)
Rathi (2021)[74] (India)	Participants received 2 ImmunoSEB (500 mg/capsule) in the morning and 2 in the evening as well as 2 capsules of ProbioSEB CSC3 (5 billion CFUs /capsule) at lunchtime, for 14 days.	Participants in control group received a placebo supplement (maltodextrin) with matching protocol.	Fatigue (CFQ-11) Adverse events
Sumbalová (2022)[83] (Slovakia)	Group 1: Spa rehabilitation program for 16-18 days: 30 min each of individual respiratory physiotherapy (weekly), group respiratory physiotherapy (3-4 times a week), strength exercises (1 -2 times a week), and other procedures (inhalation, electrotherapy, thermotherapy, mechanotherapy and hydrotherapy). Group 2: Spa rehabilitation program with the addition of 100 mg of CoQ10 twice a day during the program and for 12–14 days at home.	No intervention	Dyspnoea (Borg scale) Pulmonary function (6MWT) Overall symptoms change (unclear)
Tosato (2022)[84] (Italy)	Oral supplement of 1.66g L-arginine plus 500mg liposomal vitamin C twice a day for 28 days.	Matching placebo	Fatigue (item seven from CES-D) Exercise capacity (6MWT) Muscular strength (handgrip strength)
Versace (2023)[87] (Italy)	PEA-LUT (Glialia®, 700mg + 70mg, sublingual microgranule formulation) administered orally twice daily for 8 weeks.	Placebo (sublingual inert microgranules) orally for 8 weeks.	Cognitive function (MoCA and FAB) Adverse events
Young (2022)[89] (US)	CBD drops (Formula C) for 28 days. Each participant was started on 0.25mL per day and titrated up to effect. The PGIC score was used to manage dose titrations up and down.	The placebo was organic hempseed oil.	Anxiety, cognitive function, depression, dyspnoea, fatigue, pain, sleep, sleep, and social role participation (PROMIS)

Study (country)	Intervention	Comparator	Outcomes
			Change in clinical status (PGIC) Adverse events
Exercise			
Jimeno-Almazan (2022)[58] (Spain)	A tailored and supervised multicomponent exercise program adapted from the ACSM guidelines for COPD and CVD for 8 weeks consisting each week of 2 days of resistance training aerobic training (moderate intensity and variable training), plus a third day of monitored light intensity continuous training.	Self-management following the WHO guidelines for rehabilitation after COVID-19 related Illness.	Dyspnoea (mMRC) Cardiopulmonary function (ECG, FVC , FEV1, FVC, FEV 25– 75%, MMV and VO_2max) Fatigue (CFQ-11 and FSS) Anxiety (GAD-7) Functional status (PCFS) Muscular strength (standard tests) Depression (PHQ-9) Health-related quality of life (SF-12) Symptom severity (DSQ-14 SF)
Jimeno-Almazan (2023)[57] (Spain)	Group 1: Concurrent training program (adapted from the ACSM guidelines for COPD and cardiovascular disease): 3 days of resistance and endurance supervised sessions per week at low-moderate intensity. Group 2: Inspiratory muscle training with mechanic threshold devices (PowerBreath): 1 set of 30 repetitions (62.5 ± 4.6% of the maximum inspiratory pressure), preceded by a warm-up set, twice a day, every day of the week. Concurrent training program and inspiratory muscle training (as above).	Participants from the control group were advised to follow the WHO guidelines as a home-based program (WHO - Support for Rehabilitation: Self Management after COVID-19-Related Illness)	Dyspnoea (mMRC) Fatigue (FSS and CFS) Anxiety (GAD-7) Depression symptoms (PHQ-9) Cardiorespiratory fitness (Ekblom-Bak protocol) Muscle strength (maximal and submaximal) Functional status (PCFS) Health-related quality of life (SF-12 MH and PA components) Total number of symptoms

Study (country)	Intervention	Comparator	Outcomes
Li (2021)[64] (China)	6-week unsupervised home exercise programme involving 3-4 sessions per week (breathing control and thoracic expansion, aerobic exercise and LMS exercise), via smartphone app called RehabApp and monitored with a chest-worn heart rate telemetry, with weekly teleconsultations with therapists.	Short educational instructions at baseline.	Dyspnoea (mMRC) Pulmonary function (spirometry) Functional exercise capacity (6MWT) Strength (static squat test) Health-related quality of life (SF-12) Adverse events
Okan (2022)[67] (Turkey)	Breathing exercises (respiratory control, pursed lip breathing, and diaphragmatic breathing): 3 sessions a day, 10 exercises each day of the week, 2 hours after meals, for 5 weeks, of which one of the weekly exercises was implemented via telemedicine. The first session was held in the hospital under supervision of the researchers. Also, a mild-intensity walking program of 20 to 30 mins 5 times a week was recommended to the participants.	Brochure explaining on breathing exercises (same as protocol as intervention group) and recommendation of mild-intensity exercise (same as intervention group).	Pulmonary function (FVC, FEV1, FEV1/FVC Ratio, and MVV) Dyspnoea (mMRC) Exercise capacity (6MWT) Health-related quality of life (St George's Respiratory Questionnaire) Adverse events
Rodriguez-Blanco (2023)[75] (Spain)	Physical therapy via 14-day therapeutic exercise telerehabilitation by a physical therapist which consisted of 10 breathing and strength-based exercises performed at home daily, for 14 days, with 12 repetitions (modified according to Borg Scale of perceived effort) per exercise each day for 30 min.	No intervention. Controls were advised home rest, consisting of their daily activities of daily living, without associated physical efforts.	Dyspnoea (D-12) Fatigue (VAS) Exercise capacity (6MWT; Thirty-Second Sit-to-Stand Test) Adverse events
Romanet (2022)[76] (France)	Strength and aerobic training rehabilitation, at the rate of 2 one-hour sessions per week for 10 weeks, according to ATS/ERS guidelines (2013).[92]	Standard physiotherapy.	Dyspnoea (mMRC) Health-related quality of life (SF-12)
Rutkowski (2023)[77] (Poland)	Virtual reality-led high-intensity pulmonary rehabilitation program as well as guided relaxation in a virtual setting, 5 times a week, for 3 weeks. The time components were the same in both groups.	Same high-intensity rehabilitation program as the intervention group but without the use of virtual reality.	Pulmonary function (FEV1, FVC and TLC) Dyspnoea (modified Borg) Fatigue (modified Borg)

Study (country)	Intervention	Comparator	Outcomes
			Stress (PSS-10) Exercise capacity (6MWT)
Vallier (2023)[86] (France)	Hospital-based pulmonary rehabilitation for 4 weeks, consisting of 1) four 60-min walks, 2) four 40-min endurance sessions on ergocycle, 20 min at 90-100% of the HR achieved at the end of the 6MWT, 10 min warm-up and 10 min cool-down, 3) three group gymnastics/muscular strength sessions with and without equipment, 4) one sophrology session, and 5) one medical consultation.	Home-based pulmonary rehabilitation for 4 weeks, consisting of same interventions as intervention group (numbers 1, 2, 4 and 5) with the addition of three individual gymnastics/muscular strength sessions with and without equipment via videoconference instead of in-person.	Pulmonary function (FEV1, TLC, FVC and FEV1/FVC ratio) Dyspnoea (mMRC) Fatigue (MFI) Exercise capacity (6MWT, one-minute sit to stand, and squat jump) Health-related quality of life (VQ11)
Physiotherapy and physical rehabilitation			
Ali (2023)[38]	Traditional physical therapy program (same as control group) combined with an active cycle of breathing technique consisting of thoracic expansion exercises and one forced expiration.	Traditional physiotherapy program consisting of aerobic exercise, strengthening exercises, and diaphragmatic breathing exercise.	Fatigue (FAS) 6MWT
del Corral (2023)[45] (Spain)	Group 1: Inspiratory muscle training using a threshold pressure device for 40 min/day, split into 2 20-min sessions (morning and afternoon), 6 times per week, over 8 weeks. All evening weekly sessions were supervised by a physiotherapist through a virtual platform. Group 2: Respiratory muscle training using a threshold pressure device following the same protocol and supervision as Group 1.	Group 1: Sham inspiratory muscle training. Group 2: Sham respiratory muscle training.	Pulmonary function (FVC, FEV1, FEV1/FVC ratio, FEV) Respiratory muscle function (inspiratory/expiratory muscle strength; inspiratory muscle endurance) Cognitive function (MoCA) Anxiety and depression (HADS) Post-traumatic stress (PCL-C) Exercise tolerance (Ruffier test) Physical function (1-min Sit-to-Stand and handgrip force) Health-related quality of life (EQ-5D)

Study (country)	Intervention	Comparator	Outcomes
McNarry (2022)[65] (UK)	Three sessions (6 blocks of 6 inspirations) of unsupervised inspiratory muscle training per week, on non-consecutive days, for 8 weeks, using a handheld inspiratory flow resistive device (PrO2TM) while maintaining >80% SMIP.	"Usual care" wait list control	Dyspnoea (BDI and TDI) Inspiratory muscle strength (PrO2™ device) Mental health and wellbeing (BPNSS) Fitness (Chester Step Test) Sleep (GT9X accelerometer) Physical fitness (GT9X accelerometer) Health-related quality of Life (K-BILD)
Nagy (2022)[66] (Egypt)	Diaphragm release plus inspiratory muscle training: 18 supervised sessions with a physiotherapist of manual diaphragm release, (3 sessions/week) for 6 weeks. Inspiratory muscle training was the same as the control group.	Inspiratory muscle training: 2 sets of 30 dynamic inspiratory efforts (2-min interval between sets) from an upright sitting position for 4-mins per session, twice daily with a PImax workload of 60%, (3 sessions/week) for 6 weeks.	Dyspnoea (mMRC) Fatigue (FSS) Exercise capacity (6MWT)
Palau (2022)[69] (Spain)	Home-based inspiratory training at a resistance of 25%–30% of their maximal inspiratory pressure (measured weekly), twice daily, for 20-min each session, for 12 weeks, using a threshold inspiratory muscle trainer.	No treatment	Health-related quality of life (EQ-5D-3L tool) Pulmonary function (peakVO2) Adverse events
Philip (2022)[70] (UK)	Online breathing and wellbeing programme (English National Opera Breathe) consisting of one 20-min one-to-one video assessment and overview, then six weekly, 1 h online group workshop sessions led by an English National Opera vocal specialist.	Usual care.	Chronic obstructive pulmonary disease assessment test score (CAT) Breathlessness (VAS) Dyspnoea (D-12) Anxiety (GAD-7) Health-related quality of life (RAND SF-36, SF-6D and SF-36) Adverse events

Study (country)	Intervention	Comparator	Outcomes
Srinivasan V (2021)[82] (India)	Pursed lip breathing exercise with Bhastrika Pranayama, daily for 5 min, 3 times a day, over 6 weeks as a home exercise.	Breathing exercise with incentive spirometry, 5-10 times per cycle, 3 times a day, over 6 weeks as a home exercise.	Pulmonary function (FVC and FEV1)
Olfactory training			
Bérubé (2022)[42] (Canada)	Participants exposed themselves to 4 odours (rose, orange, clove, and eucalyptus) for 10 s, with 10 s rest intervals between each scent, for a total of 5 min, twice daily, for 12 weeks.	Placebo.	Olfactory function (UPSIT) Subjective chemosensory function (0-10 scale) Prevalence of parosmia (self-reported yes/no) Quality of life (Questionnaire of Olfactory Disorders)
Khan (2023)[60] (US)	Group 1: bimodal training with participant-preferred scents. Group 2: bimodal training with physician-assigned scents. Group 3: unimodal training with participant-preferred scents. Group 4: unimodal training with physician assigned scents. Participants sniffed for 15 seconds, with a 30-second rest in between odours, twice a day, for 3 months. Bimodal visual-olfactory training - participants were shown digital images of the essential oil they were smelling.	No treatment.	Olfactory function (UPSIT, CGI and ODOR)
Lechner (2022)[63] (UK)	Olfactory training using Sniffin' Sticks for 12 weeks.	Safety information only.	Olfactory function (BSIT) Quality of life in relation to anosmia (unvalidated) Adverse events
Pires (2022)[71] (Brazil)	Advance olfactory training with 8 essential oils: rose, eucalyptus, clove, lemon, citronella, mint, vanilla, and cedar wood. During training, the participants were exposed to each odour for 15 s twice daily, with a 30 s interval between odours. Video instruction same as control group.	Classical olfactory training set with 4 essential oils: rose, eucalyptus, clove, and lemon. Protocol same as intervention group. Participants also received video instructions a day after initiation and were contacted by telephone after 1 and 3 weeks to ensure adherence.	Olfactory function (VAS and UPSIT) Taste (VAS) Quality of life (referred to as olfactory-annoyance using VAS)

Study (country)	Intervention	Comparator	Outcomes
Cognitive and neurorehabilitation			
Awaad (2022)[40]	Transcutaneous vagus nerve stimulation plus physiotherapy program for 4 weeks.	Placebo transcutaneous vagus nerve stimulation plus physiotherapy program for 4 weeks.	Intensity of headaches (VAS) Disability resulting from headaches (Headache Disability Index)
Santana (2023)[78] (Brazil)	Non-invasive brain stimulation and individually tailored rehabilitation (same as control group) - 3 mA High-Definition transcranial Direct Current Stimulation (HD-tDCS) targeting the left primary motor cortex (M1) for 30 min, for 10 sessions (2 sessions/week) over 5 weeks.	Sham HD-tDCS and individually tailored rehabilitation program based on the consensus guidance statement for treatment of PASC-related fatigue.	Fatigue (MFIS) Anxiety (HAM-A) Pain (McGill questionnaire) Quality of life (WHOQOL-brief) Adverse events
Psychological interventions			
Hausswirth (2023)[53] (France)	Mindfulness based intervention using a non-invasive cognitive stimulation device (Rebalance®), consisting of ten 30 min sessions spread over 4 weeks. Participants lay down in a "zero gravity" position. The 30 min mindfulness training included sound therapy and coach-guided meditation associated with light stimulations (synchromotherapy®).	Two groups (one with Long COVID and one healthy) who each received no treatment.	Dyspnoea (mMRC) Fatigue (Chalder fatigue scale) Cognitive function (choice response time, pattern comparison task , Simon task, pursuit rotor task, and Corsi block-tapping task) Stress (perceived stress scale) Mood (profiles of mood states) Anxiety and depression (HADS) Muscular and joint pain (VAS) Headaches (VAS) Sleep quality (SSQ)

Key: 1-MNA - 1-Methylnicotinamide; 6MWT - 6-Minute walk test; ACSM - the American College of Sports Medicine; ADL - Activities of Daily Living; ATS/ERS - American Thoracic Society and European Respiratory Society; BDI - Baseline Dyspnea Index; BSI-18 - the Brief Symptom Inventory-18; BSIT - Brief Smell

Indication Test; CBD - Cannabidiol; CCCRC - the Connecticut Chemosensory Clinical Research Center test; CES-D - Center for Epidemiological Studies-Depression; CFQ-11 - Chalder Fatigue Scale; CGI - Clinical Global Impressions; COPD - Chronic Obstructive Pulmonary Disease; CTCAE - Common Terminology Criteria for Adverse Events; CT - Computed Tomography; CVD – Cardiovascular Disease; D-12 - Dyspnea-12; DLCO - Diffusing Capacity of the lungs for Carbon monoxide; DSQ-14 SF - The DePaul Symptom short form Questionnaire; ECG – Electrocardiogram; EQ5D - EuroQol, Five Dimensions, quality of life index; FAB - Frontal Assessment Battery; FACIT - Functional Assessment of Chronic Illness Therapy; FEV1 - Forced Expiratory Volume in 1 second; FEV1/FVC ratio - the ratio of the Forced Expiratory Volume in the first one second to the Forced Vital Capacity of the lungs; FRC - Functional Residual Capacity; FSS - Fatigue Severity Scale; FVC - Forced Vital Capacity; GAD-7 - Generalised Anxiety Disorder; HAQ - Health Assessment Questionnaire; HAM-A - Hamilton Anxiety Rating Scale; HD-tDCS - High-Definition transcranial Direct Current Stimulation; HR - Heart Rate; HADS - Hospital Anxiety and Depression Scale; K-BILD - The King's Brief Interstitial Lung Disease; MFI-20 - Multidimensional Fatigue Inventory; MFIS - Modified Fatigue Impact Scale; MMSE - Mini-Mental Status Exam; MMV - Maximum Minute Ventilation; MoCA - Montreal Cognitive Assessment; NPI - Barthel Dyspnea Index; ODOR - Olfactory Dysfunction Outcomes Rating; ODQ - Olfactory Disorders Questionnaire; PCFS - Post-COVID-19 Functional Status; PCL-C - 17-item self-report checklist of PTSD symptoms; PROMIS - Patient-Reported Outcomes Measurement Information System; PSS-10 - Perceived Stress Scale; PSQI - Pittsburgh Sleep Quality Index; PSQ-9 - Patient Health Questionnaire-9; PGIC - Patient Global Impression of Change; PEA-LUT - Palmitoylethanolamide and Luteolin; PHQ-9 - Patient Health Questionnaire-9; PASC - Post-Acute Sequelae SARS-CoV-2 infection; PSS-10 - Perceived Stress Scale; SF-12 - 12-Item Short Form Survey; SMIP - Sustained Maximal Inspiratory Pressure; SNOT-22 - Sino-Nasal Outcome Test; SSQ - Spiegel Sleep Questionnaire; TLC - Total Lung Capacity; TDI - Transition Dyspnea Index; UPSIT - University of Pennsylvania Smell Identification Test; VAS – Visual Analog Scale; VQ-11 - Quality of life questionnaire; WHOQOL-brief - The World Health Organization Quality of Life Brief Version

Appendix 4. Results from studies of off-label use of pharmaceutical interventions

Study	Results
Abdelalim (2021)[34]	**Taste/smell** In all participants, median (interquartile range) smell score improved from 2.0 (0.75-5.0) at baseline to 3.5 (1.0-5.0) at Week 1 (p<0.0001), 5.0 (2.75-9.0) at Week 2 (p<0.0001), and 10 (8.0-10.0) at Week 3 (p<0.0001). Changes from Week 1 to Week 2 and Week 2 to Week 3 were also statistically significant (both p<0.0001). In all participants, the mean duration of anosmia/hyposmia until complete recovery was 26.28 days, and 57% of participants completely recovered their smell by Week 3. There were no differences between the intervention (mometasone furoate, 100µg)and control groups (olfactory training group)for median smell score at baseline, Week 2, Week 2, or Week 3, duration of anosmia/hyposmia, or number of patients who completely recovered their smell after three weeks (all p≥0.08). In exploratory analyses, there were no sex-related differences in outcomes (all p≥0.09). Outcomes did not differ depending on whether participants received systemic steroids throughout the trial (all p≥0.09). Smell scores did not differ by diabetes status of the participants (p≥0.10), but patients with diabetes had a significantly longer duration of anosmia/hyposmia until recovery (35.0±2.31 vs 25.64±6.53; p=0.006) and fewer had fully recovered their smell by week 3 (25% vs 63.1%; p=0.004).
Achabaeva (2021)[37]	**Pulmonary/respiratory** Participants who received a multicomponent intervention containing pharmacotherapy (specifically, direct-acting anticoagulant apixaban, 2.5mg tablets) significantly improved external breathing function (p<0.01). **Mental and cognitive** Participants who received a multicomponent intervention containing pharmacotherapy (specifically, direct-acting anticoagulant apixaban) significantly improved cognitive status (p<0.01) and mental health (p<0.01). **Physical functioning and sleep** Participants who received a multicomponent intervention containing pharmacotherapy (specifically, direct-acting anticoagulant apixaban) significantly improved exercise tolerance (p<0.01) and physical recovery (p<0.01).
Dhooria (2022)[46]	**Pulmonary/respiratory**

Study	Results
	After six weeks, the high- and low-prednisolone (40mg/day which was titrated down to 10 mg/day and 10mg/day for 6 weeks, respectively) groups did not significantly differ based on the percentage of predicted forced vital capacity (FVC) (mean difference: −3.7, −9.4 to 2.0; *p*=0.21) or dyspnoea severity (assessed by the Functional Assessment of Chronic Illness Therapy (FACIT)-dyspnoea scale; mean difference: -2.2, -6.0 to 1.6; *p*=0.25) or improvement in the modified medical research council (mMRC) score (median: 1 vs 2, *p*=0.52). After six weeks there were no significant differences in respiratory health status (assessed by the King's Brief Interstitial Lung Disease (K-BILD); mean difference: -0.7, -5.9 to 4.6, *p*=0.79) **Physical functioning and sleep** After six weeks, the high- and low-prednisolone groups did not significantly differ based on six-minute walk test (6MWT) distance (mean difference: -31.0 to -71.4 to 9.4, *p*=0.15) or improvement in 6MWT distance (median: 86 vs 70, *p*=0.55). **Burden of disease** After six weeks, the high- and low-prednisolone groups did not significantly differ based on the eight component scores of the 36 item short form survey (SF-36) (all *p*≥0.15). **Other** After six weeks, the high- and low-prednisolone groups did not significantly differ based on adverse events (assessed as any, hyperglycaemia, hypertension, cushingold habitus, fatigue, weight gain, dysepsia, and others; all *p*≥0.19).
Hansen (2022)[52]	**Pulmonary/respiratory** There was no significant difference between the effects of Coenzyme Q10 (CoQ10, 500mg/day) and placebo on cardiopulmonary symptoms, as assessed by the Post Covid Condition (PCC)-specific questionnaire (indicated by the 95% confidence interval of the mean regression coefficient containing the null effect). **Energy/fatigue** There was no significant difference between the effects of CoQ10 and placebo on fatigue symptoms, as assessed by the PCC-specific questionnaire (indicated by the 95% confidence interval of the mean regression coefficient containing the null effect). **Mental and cognitive**

Study	Results
	There was no significant difference between the effects of CoQ10 and placebo on neurological symptoms, as assessed by the PCC-specific questionnaire (indicated by the 95% confidence interval of the mean regression coefficient containing the null effect). There was no significant difference between the effects of CoQ10 and placebo on cognition symptoms, as assessed by the PCC-specific questionnaire (indicated by the 95% confidence interval of the mean regression coefficient containing the null effect). **Burden of disease** After adjusting for period and sequence effect, EQ-5D score did not significantly improve as a result of the intervention (beta=0.01, -0.02 to 0.04; *p*=0.40). There were no significant between group differences in change in health index scores in the first treatment period (beta=0.02, -0.01 to 0.05; *p*=0.12) or in the group who received CoQ10 first (beta=0.005, -0.02 to 0.03; *p*=0.80). **Other** After adjusting for sequence and period, the mean difference in the change in overall PCC-specific questionnaire assessed symptom scores between CoQ10 and placebo was −1.18 (95% CI: −3.54; 1.17), indicating no significant between group difference in change in symptom score (p=0.32). There was no significant difference between the effects of CoQ10 and placebo on musculoskeletal symptoms, as assessed by the PCC-specific questionnaire (beta=-0.5 (-1.2 to 0.2)). There was no significant difference between the effects of CoQ10 and placebo on skin symptoms, as assessed by the PCC-specific questionnaire (beta=-0.1 (-0.4 to 0.2)). There was no significant difference between the effects of CoQ10 and placebo on gastrointestinal symptoms, as assessed by the PCC-specific questionnaire (beta=-0.3 (-0.8 to 0.1)). A total of 295 adverse events were registered throughout the study period; 148 of these adverse events were either new or exacerbated symptoms. Overall, 19 adverse events were considered to be related to CoQ10; four of these events were grade 2, and 15 were grade 1. These 19 treatment-related adverse events were registered in 13 participants; thus, 11% of the 119 participants who had study medicine intake experienced an adverse event that was related to CoQ10.
Hintschich (2022)[55]	**Taste/smell**

Study	Results
	Pre- to post-intervention change in Sniffin' Sticks (mometasone furoate intranasal spray (100µg) + olfactory training group mean change=3.0±4.8; olfactory only group mean change=3.4±5.0) and VAS (mometasone furoate intranasal spray+ olfactory training group mean change=2.6±2.2; olfactory only group mean change=2.3±2.0) assessed smell did not significantly differ between groups.
Hosseinpoor (2022)[56]	**Taste/smell** Median and interquartile range smell (assessed by the Iran smell identification test (Iran-SIT) and Visual Analog Scale (VAS)) significantly improved from baseline to week 2 and week 4 within both the mometasone furoate intranasal spray and placebo control groups (all $p \leq 0.001$). However, there were no significant differences between groups at any time point (all $p \geq 0.076$). Mean smell improved significantly more in the mometasone furoate intranasal spray group compared to the placebo group from baseline to Week 4 and Week 2 to Week 4 (all $p \leq 0.001$). There were no between group differences in the proportion of participants who reported anosmia at any time point (all $p \geq 0.172$).
Schepens (2022)[80]	**Taste/smell** Smell, assessed by the Sniffin' Sticks Threshold-Discrimination-Identification (TDI) total score and the Threshold, Discrimination, and Identification subscale scores, the Olfactory Disorders Questionnaire total score, and by Visual Analog Scale (VAS), did not significantly differ between the prednisolone (40mg) group and the placebo group at follow-up (all $p \geq 0.10$). Taste, assessed by the Taste Strip Test and its sweet, sour, salty, and bitter subscales and by VAS did not significantly differ between groups at follow-up (all $p \geq 0.31$). **Burden of disease** Quality of life (QoL), assessed by the Sino-nasal Outcome Test and Olfactory Disorders Questionnaire, did not significantly differ between groups at follow-up (both $p \geq 0.69$). **Other** 14 patients with mild side-effects, of which 9 (15.5%) in the prednisolone group (n=58) and five (8.8%) in the placebo group (n=57). The most reported side-effects were nervousness/restlessness and stomach irritation. All side-effects were mild, common, and lasted a short time or stopped immediately after finishing the ten days of treatment.

Study	Results
Vaira (2021)[85]	**Taste/smell** Median interquartile range (IQR) olfactory function scores (assessed by the Clinical Research Center orthonasal olfaction test (CCRC)) at baseline did not significantly differ between the prednisone (1mg/kg/day) (10 (15)) and no treatment control (20 (30); p=0.586) groups. However, olfactory function was significantly higher in the prednisone group compared to the no treatment group at Day 20 (40 (45) vs 10 (15); p=0.011) and at Day 40 (60 (40) vs 30 (25); p=0.024). Both groups significantly improved olfactory function from baseline to Day 40 (both $p \leq 0.024$). **Other** No patient developed any side effects related to the therapy.

Appendix 5. Results from studies of investigational/unauthorised pharmaceutical and medical interventions

Study	Results
Abdelazim (2022a)[35]	**Taste/smell** The mean±standard deviation (SD) change in Threshold, Discrimination, Identification (TDI) score was 5.24±2.35 among participants who received the sodium gluconate intranasal spray (1%) and 0.192±0.326 among participants who received the sodium chloride control (0.9% intranasal spray). This equates to a very large effect size (*d*=4.22, 3.22 to 5.22) in favour of sodium gluconate. Similarly, larger improvements were seen in the sodium gluconate group compared to the sodium chloride group for T-score (*d*=2.43, 1.70 to 3.16), D-score (*d*=1.49, 0.87 to 2.12), and I-score (*d*=2.11, 1.42 to 2.80). 80% of the sodium gluconate improved olfactory function compared to 0% of the sodium chloride group. 87% of females in the sodium gluconate group improved olfactory function compared to 70% of men. All participants aged 20-50 years in the sodium gluconate improved olfactory function compared to 25% of those aged 50-60 years and 0% of those aged over 60 years. **Other** Sodium gluconate was generally well tolerated. Nasal discharge was the commonest side effect seen. However, mild burning sensations in either the nose or throat were also reported.
Abdelazim (2022b)[36]	**Taste/smell** The mean± standard deviation (SD) change in Threshold, Discrimination, Identification (TDI) score was 0.23±0.36 for the sodium chloride group (0.9% intranasal spray) and 5.41±2.52 for the tetra sodium pyrophosphate spray (TSSP) group. This equates to a very large effect size (*d*=5.95, 4.80 TO 7.09) in favour of TSSP. Similarly, larger improvements were seen in the TSSP group compared to the sodium chloride group for T-score (*d*=2.14, 1.52 to 2.75), D-score (*d*=4.74, 3.78 to 5.70), and I-score (*d*=5.16, 4.14 to 6.18). 81% of the TSSP improved olfactory function compared to 0% of the sodium chloride group. 90% of females in the TSSP group improved olfactory function compared to 67% of men. **Other** TSSP was generally well tolerated. Nasal discharge was the commonest side effect seen. However, mild burning sensations in either the nose or throat were also reported.
Aref (2022)[39]	**Taste/smell**

Study	Results
	A significantly greater proportion of participants who received the ivermectin nasal spray (120mg/L) had recovered their smell (assessed on a visual analogue scale) at Week 1 compared to the placebo control group (59.2% vs 27.7%; $p<0.01$). However, there were no between group differences in recovery rates at Month 1 (55% vs 47.1%; $p=0.60$), Month 2 (44.4% vs 44.4%; $p=0.99$), Month 3 (60% vs 50%; $p=0.7$), or total cumulative recovery (95.9% vs 89.4%; $p=0.2$). The primary outcome stated in the trial registration, recovery rates at Week 2, was not reported. Participants who received the Ivermectin nasal spray had a significantly lower median (range) days until recovery (13 (3 to 105) vs 50 (6 to 115); $p<0.001$). **Other** No side effects were reported.
Bazdyrev (2022)[41]	**Pulmonary/respiratory** In the modified Intention-to-treat (ITT) population, there were small changes in pulmonary function (assessed by spirometry; forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, total lung capacity (TLC), functional residual capacity (FRC), and diffusing capacity of the lungs for carbon monoxide (DLCO)) in both the Treamid (50mg/day)and placebo control groups from baseline to Week 2 and Week 4. However, these changes did not significantly differ between the groups (all $p\geq0.149$). A greater proportion of participants who received Treamid reported clinically significant improvements in FVC and or DLCO compared to the placebo group (41% vs 17%, $p=0.036$). In the modified ITT population, there were moderate improvements in dyspnoea in both the Treamid and placebo groups from baseline to Week 2 and Week 4. However, these changes did not significantly differ between the groups (both $p=0.962$). In the modified ITT population, there were moderate improvements in dyspnoea during exercise (assessed by the modified Borg scale) in both the Treamid and placebo groups from baseline to Week 2 and Week 4. Changes from baseline to Week 2 did not significantly differ between the groups ($p=0.411$) but the Treamid group reported significantly greater improvements than the placebo group from baseline to Week 4 (-0.9±0.7 vs -0.4±0.8; $p=0.018$). Exploratory analysis showed than Treamid may lead to a 0.6 greater reduction in dyspnoea during exercise (assessed by the Dyspnoea Borg Scale) among females compared to males ($p<0.001$). **Physical functioning and sleep** In the modified ITT population, there were small improvements in six minute walk test (6MWT) distance in both the Treamid and placebo groups from baseline to Week 2 and Week 4. However, these changes did not significantly differ between the groups (both $p\geq0.960$). **Burden of disease**

Study	Results
	In the modified ITT population, there were moderate improvements in the King's Brief Interstitial Lung Disease (KBILD) questionnaire total score and its three domains (breathlessness and activities, chest symptoms, and psychological symptoms) in both the Treamid and placebo groups from baseline to Week 2 and Week 4. However, these changes did not significantly differ between the groups (both $p \geq 0.134$). **Other** 34.5% of participants in the Treamid group reported adverse events compared to 29.0% of the placebo group ($p=0.650$). Just one (3.4%) participant in the Treamid group reported a treatment-related adverse event compared to no one in the placebo group ($p=0.483$).
Elbanna (2022)[48]	**Energy/fatigue** Fatigue significantly improved from pre- to post-treatment among participants in both the photobiomodulation and placebo control groups (photobiomodulation group % change: 13.13%, $p<0.05$; placebo group % change: 8.1%, $p<0.05$). The photobiomodulation group improved significantly more than the placebo group ($d=0.89$, 0.48 to 1.31). **Physical functioning and sleep** Both the photobiomodulation and placebo groups reported significantly improved functional status from pre- to post-treatment (photobiomodulation group % change: 32.2%, $p<0.05$; placebo group % change: 19.1%, $p<0.05$). The photobiomodulation group improved significantly more than the placebo group ($d=0.46$, 0.06 to 0.85).
Finnigan (2023)[49]	**Energy/fatigue** Participants who received AXA1125 (33.9 g) and placebo reported reductions from baseline to Day 28 in pre-exercise Chalder Fatigue scale (CFQ-11) total (AXA1125: -5.25±5.49; Placebo: -2.25±2.92), physical (AXA1125: -3.67±0.75; Placebo: -1.30±3.05), and mental (AXA1125: -1.57±1.99; Placebo: -0.30±1.19) fatigue scores compared to those who received the placebo. Reductions were greater in the AXA1125 group for each outcome (Total: $d=1.07$, 0.42 to 1.73; Physical: $d=1.08$, 0.43 to 1.74; Mental: $d=0.70$, 0.07 to 1.33). **Physical functioning and sleep** Participants who received AXA1125 and placebo reported improvements from baseline to Day 28 in six-minute walk test (6MWT) distance (AXA1125: 25.57±54.0; Placebo: 25.3±12.1). Improvements did not differ between the groups ($d=0.00$, -0.61 to 0.62). **Other** Eleven (52.4%, AXA1125) and 4 (20.0%, placebo) participants reported treatment-emergent adverse events (TEAEs) during the study. None were serious or led to death or treatment discontinuation. In the AXA1125 group, 10 of 11 TEAEs (91%) were mild and 1 (9%) was severe (syncope, considered treatment-unrelated). In the placebo group, TEAEs were either mild or moderate (50% each). The most common TEAEs were diarrhoea

Study	Results
	(14.3%, AXA1125 group), abdominal distension (10.0%, placebo group), and nausea (9.5%, AXA1125 group). Among these, 2 cases were deemed to be treatment-related. One grade 3 TEAE (syncope associated with the imaging procedure) was reported in the AXA1125 group.
Gaylis (2022)[50]	**Other** The adjusted mean symptom score change from baseline to the latest available time point from day 30–56 for leronlimab (700 mg) vs placebo was –1.0 (not statistically significant).
Gupta (2022)[51]	**Taste/smell** There was no significant difference in the number of responders (that is, the number of participants who self-reported at least a "slightly better" improvement in their sense of smell in the Clinical Global impression-Improvement (CGI-I scale) in the theophylline (400 mg) (n=13; 59%) and placebo (n=10; 43%) groups (difference=15.6%, −13.2% to 44.5%). University of Pennsylvania Smell Identification test (UPSIT) score did not significantly improve from baseline to week 6 in either the theophylline or placebo groups (as indicated by median change scores' 95% CI crossing the null effect). Additionally, the change in score on each of the 4 metrics through study visits was not significantly different between the study arms (p-value not reported). There was no significant difference in the number of responders (that is, the number of participants who self-reported at least a "slightly better" improvement in their sense of smell in the UPSIT scale) in the theophylline (n=11; 50%) and placebo (n=6; 26%) groups (difference=24%, −4% to 52%). **Burden of disease** None of the quality of life metrics (quality of life; quality of life-negative statements; parosmia; sincerity) significantly improved from baseline to week 6 in either the theophylline or placebo groups (as indicated by median change scores' 95%CI crossing the null effect). Additionally, the change in score on each of the 4 metrics through study visits was not significantly different between the study arms (p-values not reported). **Other** There were no severe adverse effects. Two participants assigned to the theophylline arm reported experiencing considerable parosmia and foul taste with the intervention, resulting in one withdrawal and one with poor compliance (>30% of pills remaining at 6 weeks).
Kutashov (2021)[62]	**Energy/fatigue** At baseline, the Actovegin® group (800 mg) reported significantly higher fatigue (assessed by the Multidimensional Fatigue Inventory) than the basic therapy control group (mean±SE: 70.50±1.12 vs 64.64±0.76; $p<0.05$). Improvements from baseline to day 15 ($d=0.87$, 0.68 to 1.07) and posttreatment day 60 ($d=1.31$, 1.10 to 1.51) were significantly greater in the Actovegin® group compared to the basic therapy group.

Study	Results
	Mental and cognitive At baseline, there were no significant differences in cognitive function (assessed by the Montreal Cognitive Assessment test) between the Actovegin® and basic therapy control groups (mean±SE: 21±0.2 vs 20±0.3; p>0.05). Improvements from baseline to day 15 (d=0.53, 0.34 to 0.71) and post treatment day 60 (d=0.53, 0.34 to 0.71) were significantly greater in the Actovegin® group compared to the basic therapy group. After 60 days follow-up, participants who received Actovegin® had lower emotional disturbances (assessed by the Spielberger-Hanin test) scores than the basic therapy group (p<0.05; scores unclear from translated text).
Orlova (2022)[68]	**Pulmonary/respiratory** There were no significant between group differences in breathlessness at baseline (all p>0.05). Only the hypoxia-hyperoxic therapy group significantly improved from baseline to post-intervention (week 2; 2.64±2.02 to 0.76±0.64; p<0.05). From baseline to post-intervention, improvements in breathlessness in the hypoxia-hyperoxic therapy group were significantly greater than those in the placebo group (d=0.87, 0.15 to 1.59) and the standard rehabilitation group (d=0.70, 0.02 to 1.38). **Mental and cognitive** There were no significant between group differences in reactive anxiety at baseline (all p>0.05). Only the hypoxia-hyperoxic therapy group significantly improved from baseline to post-intervention (week 2; 38.8±14.2 to 29.6±17.5; p<0.05). From baseline to post-intervention (week 2), improvements in reactive anxiety in the hypoxia-hyperoxic therapy group were significantly greater than those in the standard rehabilitation group (d=0.73, 0.05 to 1.42) but not the placebo group (d=0.43, -0.27 to 1.12). There were no significant between group differences in depressive symptoms at baseline (all p>0.05). All groups significantly improved from baseline to post-intervention (all p<0.05). From baseline to post-intervention (week 2), changes in depressive symptoms in the hypoxia-hyperoxic therapy group did not significantly differ from those in the placebo group (d=0.35, -0.34 to 1.04) or the standard rehabilitation group (d=0.47, -0.20 to 1.14). **Other** There were no significant between group differences in general health at baseline (all p>0.05). The hypoxia-hyperoxic therapy and standard rehabilitation only groups significantly improved from baseline to post-intervention (week 2; both p<0.05), but not the placebo group (p>0.05). From baseline to post-intervention (week 2), changes in general health in the intervention group did not significantly differ from those in the placebo group (d=0.70, 0.00 to 1.41) or the standard rehabilitation group (d=0.46, -0.21 to 1.13). There were no complications or significant adverse events of interval hypoxic-hyperoxytherapy and other rehabilitation methods used in the study.

Study	Results
Putilina (2021)[73]	**Energy/fatigue** Participants who received Cytoflavin® significantly improved fatigue (assessed by the multidimensional fatigue inventory (MFI-20)) from pre- to post-intervention relative those in the other therapy control group (*d*=1.15, 0.72 to 1.57). This was true for each of the five MFI-20 subscales (*d* range=0.58 to 1.49). **Mental and cognitive** There was no significant between group difference in change in cognition (assessed by the mini mental state examination) from pre- to post-intervention (*d*=0.31, -0.09 to 0.70). **Physical functioning and sleep** Participants who received Cytoflavin® significantly improved sleep (assessed by the Pittsburgh sleep quality index (PSQ1)) from pre- to post-intervention relative those in the other therapy control group (*d*=1.25, 0.82 to 1.68). **Burden of disease** Participants who received Cytoflavin® significantly improved Quality of life (QoL) (assessed by the EQ-5D) from pre- to post-intervention relative those in the other therapy control group (*d*=0.83, 0.42 to 1.42). This was true for three of the five EQ-5D subscales (usual activities, pain/discomfort, and anxiety/depression; *d* range=0.4 to 0.81). Participants who received Cytoflavin® significantly improved general health relative those in the other therapy group (*d*=1.00, 0.58 to 1.41). **Other** During the observation period, no serious adverse events and side effects associated with treatment were noted in any participants.
Putilina (2022)[72]	**Energy/fatigue** The proportion of participants who received Cortexin® 20mg reporting fatigue and general weakness decreased from 92% to 25% ($p<0.001$) and 87% to 17% (both $p<0.001$), respectively. The proportion of participants who received Cortexin® 10mg reporting fatigue and general weakness decreased from 96% to 31% ($p<0.001$) and 92% to 20% ($p=0.004$), respectively. Between group differences in change were not assessed. **Mental and cognitive**

Study	Results
	Results on cognitive function (as assessed by the Mental State Assessment Scale (MMSE) were not clearly reported. **Taste/smell** The proportion of participants who received Cortexin® 20mg reporting olfactory complaints decreased from 39% to 20% (p<0.001). The proportion of participants who received Cortexin® 10mg reporting olfactory complaints decreased from 39% to 19% (p<0.001). Between group differences in change were not assessed. **Other** No cases of therapeutic interactions between Cortex and other drugs used by study participants were seen, nor any adverse events.
Scaturro (2022)[79]	**Pulmonary/respiratory** Dyspnoea (assessed by the Barthel Dyspnoea Index) did not significantly change from pre- to post-intervention in either of the L-acetyl-carnitine 500mg plus rehabilitation or rehabilitation only groups (both p≥0.10). Dyspnoea change did not significantly differ between the intervention and control groups (d=0.04, -0.47 to 0.55). **Mental and cognitive** Depressive symptoms (assessed using the Patient Health Questionnaire (PHQ-9)) significantly improved from pre- to post-intervention in the L-acetyl-carnitine plus rehabilitation group (13.03±3.51 to 9.84±3.02; p<0.05) but not the rehabilitation only group (13.74±3.08 to 12.34±2.89; p=0.09). The intervention group had a moderate improvement in depressive symptoms relative to the control group (d=0.53, 0.01 to 1.05). **Burden of disease** Quality of Life (assessed using the 12-Item Short Form Survey (SF-12) significantly improved from pre- to post-intervention in both the L-acetyl-carnitine plus rehabilitation (26.18±2.88 to 30.45±2.49; p<0.05) and rehabilitation only (25.07±3.19 to 27.29±3.16; p<0.05) groups. However, the intervention group had a moderate improvement in quality of life relative to the control group (d=0.67, 0.15 to 1.19). **Other** Musculoskeletal pain (assessed on the Numeric pain rating (NRS) scale) significantly improved from pre- to post-intervention in the L-acetyl-carnitine plus rehabilitation group (7.18±0.9 to 4.9±0.75; p<0.05) but not the rehabilitation only group (7.22±0.87 to 6.8±0.92; p=0.08). The intervention group had a large improvement in musculoskeletal pain relative to the control group (d=2.07, 1.44 to 2.70).

Study	Results
	Disability degree (assessed using the Fibromyalgia Impact Questionnaire (FIQ)) significantly improved from pre- to post-intervention in both the L-acetyl-carnitine plus rehabilitation (50.66±10.63 to 41.96±8.68; p<0.05) and rehabilitation only (49.55±6.44 to 43.03±5.86; p<0.05) groups. The change did not significantly differ between groups (d=0.24, -0.27 to 0.75).
Shogenova (2021)[81]	**Physical functioning and sleep** Six-minute walk test (6MWT) significantly increased in the group that received hydrogen inhalation in addition to standard procedures and standard therapy (430m±45 to 397m±30; p<0.0001) but not the control group who only received standard therapy (data not reported). **Other** No complications were reported by participants who received the intervention.
Yan (2022)[88]	**Taste/smell** Between baseline and one month follow-up, there was no significant difference between changes in the platelet-rich plasma and placebo control group Threshold (T) (p=0.100), Discrimination (D) (p=0.793), Identification (I) (p=0.098), Total TDI (p=0.131), or Visual analogue scale (VAS) (p=0.694) scores. Between baseline and three month follow-up, Total TDI (p=0.047; d=0.63, -0.12-1.37)) and D (p=0.004; d=1.02, 0.25-1.79) scores significantly improved more in the platelet-rich plasma group compared to the placebo group. There was no significant difference between platelet-rich plasma and placebo group T (p=0.935), I (p=0.239), or VAS (p=0.167) score changes. At 1-month post-intervention, 7/17 (41.2%) participants in the platelet-rich plasma group had clinically significant improvement in olfactory function compared to 3/12 (25.0%) subjects in the placebo arm (OR=2.0, 0.4 to 17.0). At 3-month post-intervention, it was 8/14 (57.1%) vs 1/12 (8.3%) (OR=12.5, 2.2–116.7). **Other** No participants reported long-standing adverse effects related to the injections. Short-term side effects were related to the injection itself and consisted of nasal congestion and pressure that lasted up to 24 hours, experienced by both trial arms.
Zilberman-Itskovich (2022)[90]	**Pulmonary/respiratory**

Study	Results
	The effects of Hyperbaric oxygen therapy (HBOT) on the 17 pulmonary function outcomes (assessed by spirometer) did not significantly differ from that of the sham (all $p \geq 0.230$; Cohen's d range: -0.287 to 0.155). **Mental and cognitive** The effects of HBOT on the 6 neurocognitive performance outcomes (assessed by the Mindstreams computerized cognitive testing battery including an overall score and individual scores for the domains of memory, executive function, attention, information processing speed, and motor skills) did not significantly differ from that of the sham (all $p \geq 0.038$; Cohen's d range: 0.111 to 0.495). Participants who received HBOT had significant greater improvements in their psychological distress (assessed by the Brief Symptom Inventory 18 (BSI-18)) than those who received the sham ($p=0.008$; Cohen's $d=-0.636$; Hedges' $d=0.54$, 0.07 to 1.01). However, no differences were seen between groups in the individual domains of somatization, depression, and anxiety (all $p \geq 0.014$; Cohen's d range: -0.636 to -0.417). **Taste/smell** The effects of HBOT on the one smell (assessed by the Sniffin' Sticks Test) and 5 taste (assessed by the Taste Strip Test) outcomes did not significantly differ from that of the sham in the total population or in the subpopulation with abnormal taste or smell at baseline (all $p \geq 0.102$; Cohen's d range: 0.046 to 0.626). **Physical functioning and sleep** The effects of HBOT on the sleep outcomes (assessed by the PSQI including an overall score and individual scores for the domains of sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep medication, and daytime dysfunction) did not significantly differ from that of the sham (all $p \geq 0.042$; Cohen's d range: -0.486 to 0.047). **Burden of disease** The effects of HBOT on quality of life (assessed by the 36 item short form survey (SF-36) including individual scores for the domains of physical functioning, physical limitations, emotional limitations, energy, emotional wellbeing, social function, pain, and general health) did not significantly differ from that of the sham (all $p \geq 0.023$; Cohen's d range: -0.269 to 0.546). **Other**

Study	Results
	The effects of HBOT on pain severity (assessed by the Brief Pain Inventory (BPI)) did not significantly differ from that of the sham (p=0.917; Cohen's d=0.011). However, participants who received HBOT had significant greater improvements in their pain interference (evaluated by the BPI) more than those who received the sham (p=0.001; Cohen's d=-0.784; Hedges' d=0.61, 0.14 to 1.08). No adverse effects reported showed any significance (p=0.739).

Appendix 6. Results from studies of supplements and alternative medicine

Study	Results
Chudzik (2022)[43]	**Energy/fatigue** Both the 1-MNA supplement group (58 mg/day) and the no treatment control group reported an increase in fatigue (assessed by the Fatigue Severity Score (FSS); Intervention: 4.53 to 4.94; Control: 4.28 to 4.42). There was no significant between group difference in pre- to post-intervention change in fatigue (*d*=0.21, -0.35 to 0.76). **Physical functioning and sleep** Both groups reported an increase in six-minute walk test (6MWT) distance (Intervention: 515.8 to 557.8, *p*<0.001; Control: 519.24 to 532.52, *p*=0.068). There was no significant between group difference in pre- to post-intervention change in 6MWT distance (*d*=0.44, -0.12 to 1.00).
D'Ascanio (2021)[44]	**Taste/smell** There were significant baseline between group differences: compared to the olfactory training only group, the Palmitoylethanolamide and Luteolin (PEA-LUT, 700mg+70mg) + olfactory training group had worse smell scores (assessed by Sniffin Sticks Threshold Discrimination and Identification (TDI) score; 28.8±1.2 vs 21.1±5.5, *p*=0.01) and had smell disorders for longer (9.7±2.5 vs 4.6±3.6 months). Change in smell did not significantly differ between groups (*d*=0.38, -0.77 to 1.54).
Di Stadio (2022)[47]	**Taste/smell** Smell (assessed by Sniffin Sticks Threshold Discrimination and Identification (TDI) score) significantly improved in the Palmitoylethanolamide and Luteolin (PEA-LUT, 700mg+70mg) + olfactory training group (20.6±7.9 to 29.8±7.5, *p*<0.001) but not the placebo plus olfactory training group (18.2±7.9 to 19.5±7.3, *p*=0.4). Participants in the PEA-LUT group had significantly larger improvements (*d*=1.00, 0.66 to 1.33) and were more likely to recover to a normal TDI score (56% vs 10%, *p*<0.00001).
Hawkins (2022)[54]	**Energy/fatigue** Controlling for baseline scores, employment status, Body mass index (BMI), olfactory function, and time since diagnosis, participants in the aromatherapy group had significantly better fatigue (assessed by the Multidimensional Fatigue Symptom Inventory, Short Form) at the end of the intervention than those in the placebo group (partial η^2=0.198; *p*=0.020). After adjusting for various covariates, the aromatherapy group also significantly improved relative to the placebo group in five of the ten Multidimensional Fatigue Symptom Inventory subscales (global, behavioural, general, mental fatigue, and vigour; partial η^2 range=0.146 to 0.240, all *p*≤0.044).

Study	Results
	Burden of disease Controlling for baseline scores, employment status, BMI, olfactory function, and time since diagnosis participants in the aromatherapy group had significantly better Quality of Life (assessed by the Patient Health Questionnaire (PHQ-9)) at the end of the intervention than those in the placebo group (partial η^2=0.336; p=0.002; adjusted for baseline scores, employment status, BMI, olfactory function, and time since diagnosis) **Other** One participant in the intervention group reported experiencing headaches and withdrew on day 13. This participant also reported experiencing recurring headaches prior to the start of the study, which is common among individuals with post-COVID-19 symptoms. No other adverse effects were identified.
Karosanidze (2022)[59]	**Pulmonary/respiratory** Severity of respiration problems and cough symptoms significantly improved from baseline in both the ADAPT-232 (30ml) and placebo control groups (both p<0.0001) but changes did not significantly differ between groups (respiration problems: p=0.7679; cough symptoms: p=0. 1466). There was no significant between group difference in the time from randomisation to when respiration problems disappeared (6.6 days vs 6.9 days; p=0.7619). Cough symptoms disappeared significantly more quickly among participants in the placebo group (6.3 days vs 8.1 days; p=0.0219). **Energy/fatigue** Severity of fatigue significantly improved from baseline in both the ADAPT-232 and placebo groups (p<0.0001) but changes did not significantly differ between groups (p=0.9823). There was no significant between group difference in the time from randomisation to when respiration problems disappeared (12.0 days vs 13.0 days; p=0.2662). **Mental and cognitive** Depression and anxiety (assessed by the Hospital Anxiety and Depression Scale) and cognitive performance (assessed by the d2 test of attention and memory) significantly improved from baseline in both the ADAPT-232 and placebo groups (all p<0.0001) but changes did not significantly differ between groups (depression: p=0.6839; anxiety: p=0.8735; cognitive performance: p=0.9946). **Taste/smell** Taste and smell significantly improved from baseline in both the ADAPT-232 and placebo groups (p<0.0001) but changes did not significantly differ between groups (p=0.9180). **Physical functioning and sleep**

Study	Results
	Time spent walking (assessed by the Habitual Physical Activity Questionnaire) significantly improved from baseline in both the ADAPT-232 and placebo groups (p<0.0001). Participants who received the ADAPT-232 treatment significantly increased their time spent walking relative to those who received the placebo (p<0.0001). Physical activity level (assessed by the Habitual Physical Activity Questionnaire) significantly improved from baseline in both the ADAPT-232 and placebo groups (p<0.0001) but changes did not significantly differ between groups (p=0.9802). **Burden of disease** There was no significant difference in the number of stay at home/sick-listed days between the ADAPT-232 and the placebo groups (5.9 days vs 5.9 days; p=0.9839). **Other** Severity of pain in muscles, chest and joints and headache significantly improved from baseline in both the ADAPT-232 and placebo groups (both p<0.0001) but changes did not significantly differ between groups (pain: p-value not reported; headache: p=0.983). There was no significant between group difference in the time from randomisation to when pain (10.7 days vs 11.8 days, p=0.3668) or headache (10.4 days vs 9.2 days, p=0.3582) disappeared. Sweatiness, organoleptic dysfunction, and hair loss significantly improved from baseline in both the ADAPT-232 and placebo groups (all p<0.0001) but changes did not significantly differ between groups (sweatiness: p=0.9964; organoleptic dysfunction: p=0.9180; hair loss: p=0.9441). There was no significant between group difference in the time from randomisation to when sweatiness (12.1 days vs 12.2 days, p=0.7605), organoleptic dysfunction (11.6 days vs 10.6 days, p=0.8383), or hair loss (16.7 days vs 15.4 days, p=0.3317) disappeared. There was no significant difference in the average duration of all symptoms between the ADAPT-232 and the placebo groups (7.6 days vs 7.5 days; p=0.5375).
Kharaeva (2022)[61]	**Pulmonary/respiratory** In participants who had severe COVID-19, dyspnoea significantly improved in both the supplement (that is, fermented papaya and noni syrups, 14g) and placebo control groups (both p<0.05), although greater improvements were seen in the supplement group compared to the placebo (d=0.49, 0.03 to 0.94). In participants who had moderate COVID-19, dyspnoea significantly improved in the supplement (p<0.05), but not the placebo, group. Greater improvements were seen in the supplement group compared to the placebo (d=0.57, 0.13 to 1.01). **Other**

Study	Results
	In participants who had severe COVID-19, 13/21 assessed clinical symptoms had significantly greater improvements in the supplement group compared to the control (all $p<0.05$). The total average symptom score improved in both the supplement and control groups (both $p<0.05$), although greater improvements were seen in the supplement group ($d=1.98$, 1.45 to 2.52). In participants who had moderate COVID-19, 8/22 assessed clinical symptoms had significantly greater improvements in the supplement group compared to the control (all $p<0.05$). The total average symptom score improved in both the supplement and control groups (both $p<0.05$), although greater improvements were seen in the supplement group ($d=1.45$, 0.97 to 1.93).
Rathi (2021)[74]	**Energy/fatigue** A greater proportion of participants who received systemic enzymes and probiotics (1000mg) reported being fatigue-free (that is, a Chalder Fatigue Scale (CFQ-11) score of 0) at all time-points (Day 4: 10% vs 0%; Day 8: 44% vs 2%; Day 11: 87% vs 7%; Day 14: 91% vs 15%). This was also reflected in mean fatigue scores, which decreased more in the intervention group (25.78 at baseline to 8.54 at Day 14) than the placebo group (25.69 at baseline to 19.91 at Day 14, $p<0.001$). Findings were the same for both the physical and mental fatigue subscales. **Other** No subject in either group reported any adverse events. Compliance with product intake was 100% and no subject reported having to skip any dose or stop supplement intake due to an adverse reaction.
Sumbalová (2022)[83]	**Pulmonary/respiratory** Exercise dyspnoea (measured by the Borg Scale) significantly decreased in the mountain spa rehabilitation group (2.1±0.55, $p=0.004$) but not the mountain spa rehabilitation + CoQ10 group (1.0±0.48, $p=0.08$). Between group differences in change were not assessed. **Physical functioning and sleep** Distance walked in six-minute walk test (6MWT) significantly increased from pre- to post-intervention in both the mountain spa rehabilitation group (87.2m±30.1; $p=0.004$) and the mountain spa rehabilitation + CoQ10 group groups (61.4m±18.1; $p=0.003$). Between group differences in change were not assessed. **Other** Compared to baseline, participants in the mountain spa rehabilitation group reported 51.8% fewer symptoms and participants in the mountain spa rehabilitation + CoQ10 group reported 62.8% fewer symptoms following the interventions. Between group differences in change were not assessed.
Tosato (2022)[84]	**Energy/fatigue**

Study	Results
	All participants reported fatigue (assessed by the question "I felt that everything I did was an effort") at baseline. On Day 28 post-intervention, fewer participants in the L-arginine (1.66g) plus Vitamin C (500mg) supplementation group reported fatigue than in the placebo group (8.7% vs 80.1%; $p<0.0001$). **Physical functioning and sleep** Participants who received L-arginine plus vitamin C significantly increased six minute walk test (6MWT) distance from baseline to day 28 (median (IQR) change=30.0m (40.5)) compared with those who received the placebo (0.0m (75.0), $p=0.001$; mean difference=50m, 20.0 to 80.0m; effect size=0.56). Participants who received L-arginine plus vitamin C significantly increased handgrip strength from baseline to day 28 (median (IQR) change=3.4kg (7.5)) compared with those who received the placebo (1.0kg (6.6), $p=0.03$; mean difference=3.4kg, 0.5 to 9.5kg; effect size=0.37).
Versace (2023)[87]	**Mental and cognitive** Both the Palmitoylethanolamide and Luteolin (PEA-LUT, 700 mg+70 mg) and placebo groups reported minor improvements in global cognition (assessed by the Montreal Cognitive Assessment (MoCA)) and executive function (assessed by the Frontal Assessment Battery (FAB)) from pre- to post-intervention. However, these changes did not significantly differ between groups (both $p\geq0.33$). **Other** No side effects were reported
Young (2022)[89]	**Pulmonary/respiratory** Over the first four week treatment period, Group 1 received the Cannabidiol (CBD) intervention and Group 2 received placebo. Changes in dyspnoea scores did not significantly differ between groups over this period ($d=0.08$, -0.73 to 0.90). After eight weeks (that is, by the end of the cross-over period), dyspnoea had not significantly changed from baseline in Group 1 (-0.9±5.48, $p=0.291$). **Energy/fatigue** Changes in fatigue scores did not significantly differ between groups over the first intervention period ($d=-0.30$, -1.12 to 0.52). After eight weeks, there had been no significant change in fatigue from baseline in Group 1 (-2.9±9.25, $p=0.154$). **Mental and cognitive**

Study	Results
	Over the first four week treatment period, Group 1 received the intervention and Group 2 received placebo. Changes in anxiety scores did not significantly differ between groups over this period (*d*=0.14, -0.68 to 0.96). After eight weeks (that is, by the end of the cross-over period), anxiety had significantly improved from baseline in Group 1 (-4.9±6.14, *p*=0.009). Changes in depression scores did not significantly differ between groups over the first intervention period (*d*=-0.27, -1.10 to 0.55). After eight weeks, anxiety had not significantly changed from baseline in Group 1 (-1.8±5.5, *p*=0.137). Changes in cognitive function did not significantly differ between groups over the first intervention period (*d*=-0.40, -1.22 to 0.43). After eight weeks, cognitive function had not significantly changed from baseline in Group 1 (1.4±7.37, *p*=0.261). **Physical functioning and sleep** Over the first four week treatment period, Group 1 received the intervention and Group 2 received placebo. Changes in sleep scores did not significantly differ between groups over this period (*d*=0.12, -0.70 to -0.93). After eight weeks (that is, by the end of the cross-over period), sleep had significantly improved from baseline in Group 1 (-3.1±4.71, *p*=0.021). **Burden of disease** Over the first four week treatment period, Group 1 received the intervention and Group 2 received placebo. Changes in ability to participate in social roles did not significantly differ between groups over this period (*d*=-0.31, -1.14 to 0.51). After eight weeks (that is, by the end of the cross-over period), ability to participate in social roles had not significantly changed from baseline in Group 1 (3.8±7.63, *p*=0.056). Changes in satisfaction with social roles did not significantly differ between groups over the first intervention period (*d*=-0.08, -0.90 to 0.74). After eight weeks (that is, by the end of the cross-over period), satisfaction with social roles had not significantly changed from baseline in Group 1 (2.3±7.69, *p*=0.158). **Other** Changes in pain did not significantly differ between groups over the first intervention period (*d*=-0.41, -1.24 to 0.41). After eight weeks, pain had not significantly changed from baseline in Group 1 (1.1±6.72, *p*>0.05). Over the first four week treatment period, Group 1 received the intervention and Group 2 received placebo. Global impression of change significantly improved in Group 1 over this period (median scores: 1.0 to 2.0, *p*<0.005) and to Day 56 (median scores: 1.0 to 3.0, *p*<0.05). In Group 2, global impression of change significantly improved from Day 28 to Day 56 (median scores: 2.3 to 4.5, *p*<0.05) No adverse events were reported.

Appendix 7. Results from studies of exercise interventions

Study	Results
Jimeno-Almazan (2022)[58]	**Pulmonary/respiratory** Change in dyspnoea scores from pre- to post-intervention did not significantly differ between the exercise intervention and no treatment control groups (*d*=0.30, -0.33 to 0.93). Changes in seven pulmonary function measures (Forced vital capacity (FVC), %FVC, Forced expiratory volume in the first second (FEV-1), %FEV-1, FEV-1/FVC, FEV25-75%, maximum voluntary ventilation (MVV), and %MVV) did not significantly differ between the intervention and control groups (*d* range=-0.20 to 0.50), although improvements in FEV-1/FVC were significantly greater in the control group compared to the exercise group (*d*=-0.65, -0.01 to -1.29). **Energy/fatigue** Improvements in the three fatigue scores from pre- to post-intervention were significantly greater for the exercise group compared to the control group (Chalder fatigue scale (CFQ-11) (bimodal): *d*=1.17, 0.49 to 1.85; CFQ-11 (Likert): *d*=1.24, 0.55 to 1.92; FSS: *d*=0.77, 0.12 to 1.42). **Mental and cognitive** Changes in anxiety and depression scores from pre- to post-intervention did not differ between the exercise and control groups (anxiety: *d*=-0.06, -0.69 to 0.57; depression: *d*=0.24, -0.39 to 0.87). **Physical functioning and sleep** Improvements in functional limitations from pre- to post-intervention were significantly greater in the exercise group compared to the control group (*d*=0.75, 0.10 to 1.40). Changes in VO2max from pre- to post-intervention did not differ between the exercise and control groups (*d*=0.23, -0.40 to 0.86). Improvements in 2 of 5 muscular strength measures from pre- to post-intervention were significantly greater in the exercise group compared to the control group (bench press propulsive velocity: *d*=1.02, 0.35 to 1.69; half-squat propulsive velocity: *d*=1.42, 0.71 to 2.12); there were no significant between group differences in the sit-to-stand test, handgrip strength, or leg extension force (*d* range=-0.04 to 0.06). **Burden of disease**

Study	Results
	The physical activity component, but not the mental health component, of quality of life significantly improved from pre- to post-intervention in the exercise group compared to the control group (physical activity: *d*=0.70, 0.06 to 1.35; mental health: *d*=-0.06, -0.69 to 0.57). **Other** Changes in myalgic encephalomyelitis/chronic fatigue syndrome symptoms from pre- to post-intervention did not differ between the exercise and control groups (*d*=0.49, -0.14 to 1.13). There were no adverse events during the training sessions. One participant in the intervention group abandoned the training program because of commitment problems.
Jimeno-Almazan (2023)[57]	**Pulmonary/respiratory** In the entire cohort (that is, the concurrent training, respiratory muscle training, concurrent training program with respiratory muscle training, and no treatment control groups) the number of participants without dyspnoea (that is, modified Medical Research Council (mMRC) <2) increased from 55% to 79% ($p<0.001$). However, there were no significant differences between groups (all $p\geq0.063$). At 8wk follow-up, no significant differences between groups were detected in the estimated VO2max ($p>0.05$), although significant individual improvements were identified in the concurrent training (Δ7.5%; $p<0.05$) and concurrent training program with respiratory muscle training (Δ7.8%; $p<0.05$) groups. **Energy/fatigue** Fatigue significantly improved in the concurrent training only group (Fatigue Severity Scale (FFS): effect size=0.50, $p<0.001$; Chronic Fatigue Syndrome (CFS): effect size=0.50, $p<0.001$) and in the concurrent plus respiratory muscle training group (FFS: effect size=0.50, $p<0.05$; CFS: effect size=0.39, $p<0.05$), but not the respiratory muscle training only or control groups (effect sizes and p-values not reported). **Mental and cognitive** There were no significant differences between groups for anxiety (assessed by the Generalised Anxiety Disorder (GAD-7); all $p\geq0.063$). Distress (assessed by the Patient health questionnaire (PHQ-9)) significantly improved in the concurrent training only group (effect size=0.50, $p<0.001$) and in the concurrent plus respiratory muscle training group (effect size=0.50, $p<0.05$), but not the respiratory muscle training only or control groups (effect size and p-value not reported). **Physical functioning and sleep**

Study	Results
	Significant pre-post improvements were detected in maximal and submaximal upper body strength following concurrent training only and concurrent training program with respiratory muscle training (7.8 to 39.5%; $p<0.05$), without relevant changes in the respiratory muscle training only and control groups (-1.4 to 3.8%; $p>0.05$). No inter- or intragroup interactions were found for the dominant hand grip strength ($p>0.05$). Functional limitations (assessed on the Post-COVID-19 functional status (PCFS) scale) significantly improved in the concurrent training only group (effect size=0.50, $p<0.001$), but not the concurrent training program with respiratory muscle training ($p=0.102$), respiratory muscle training only, or control groups (effect sizes and p-values not reported). **Burden of disease** The physical activity domain of the 12 item Short Form Survey (SF-12) QoL questionnaire significantly improved in the three intervention groups (concurrent training: effect size=1.18, $p<0.001$; concurrent training with respiratory muscle training: effect size=0.60, $p<0.001$; respiratory muscle training: effect size=0.64, $p<0.05$) but not the control group. The mental health domain of the SF-12 QoL questionnaire significantly improved in the CTRM intervention group (effect size=0.51, $p<0.05$) but not the CT ($p=0.09$), RM, or control groups (effect sizes and p-values not reported). **Other** Both of the groups that did concurrent training had a significantly greater reduction in total number of Long COVID symptoms compared to the respiratory muscle training only and control groups ($p<0.05$). No adverse events occurred during the training sessions.
Li (2021)[64]	**Pulmonary/respiratory** In the intention to treat (ITT) population, significantly greater improvements in dyspnoea were seen in the pulmonary rehabilitation group compared to the no treatment control group at week 6 post-intervention (RR=1.46, 1.17 to 1.82) but not Interim weeks 2 (RR=1.27, 0.88 to 1.82) or 4 (RR=1.08, 0.82 to 1.42) or week 28 follow-up (RR=1.22, 0.92 to 1.61). In the ITT population, changes in pulmonary function (Forced Expiratory Volume in the first second (FEV1), forced vital capacity (FVC), FEV1/FVC, Maximum Voluntary Ventilation (MVV), or Peak expiratory flow (PEF) at week 6 or week 28 follow-up did not significantly differ (as indicated by the estimated treatment effect 95% confidence intervals containing the null effect), except for MVV at week 6 (estimated treatment effect=10.57L/min, 3.26 to 17.88). **Physical functioning and sleep**

Study	Results
	In the ITT population, significantly greater improvements in functional exercise capacity (assessed by the 6 minute walk test) were seen in the intervention group compared to the control group at the 2 time points it was assessed: week 6 post-intervention estimated treatment effect=65.45m, 43.80 to 87.10); week 28 follow-up estimated treatment effect=68.62m, 46.39 to 90.85). In the ITT population, significantly greater improvements in functional exercise capacity (assessed by static squat time) were seen in the intervention group compared to the control group at week 6 post-intervention (estimated treatment effect=20.12s, 12.34 to 27.90) and week 28 follow-up (estimated treatment effect=22.23s, 14.24 to 30.21). **Burden of disease** In the ITT population, significantly greater improvements in the physical, but not mental, components of Health-related quality of life (HRQoL) were seen in the intervention group compared to the control group at week 6 post-intervention (physical: estimated treatment effect=3.79, 1.24 to 6.35; mental: estimated treatment effect=2.18, -0.54 to 4.90) and week 28 follow-up (physical: estimated treatment effect=2.69, 0.06 to 5.32; mental: estimated treatment effect=1.99, -0.81 to 4.79). **Other** In the ITT population, no serious adverse events occurred during the study period. Eight participants (five in the intervention group and three in the control group) were hospitalised, all for non-life-threatening reasons unrelated to COVID-19 or the intervention and all in the follow-up period. More mild adverse events occurred in the intervention group in the first 6 weeks.
Okan (2022)[67]	**Pulmonary/respiratory** There were no significant baseline differences between the breathing exercises and walking (via telemedicine) group and the no treatment control group for any of the spirometry measures (all $p \geq 0.480$). Two-way repeated measures-ANOVAs revealed significant group-by-time interactions for forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and Maximum voluntary ventilation (MVV) (all $p=0.001$), but not the FEV1/FVC ratio ($p=0.349$). Pre- to post-test improvements in the intervention group were significantly larger than in the control group for FVC (partial eta squared=0.216), FEV1 (partial eta squared=0.193), and MVV (partial eta squared=0.537). There was no significant between group differences at baseline for dyspnoea (assessed by the mMRC; $p=0.787$). Two-way RM-ANOVAs revealed a significant group-by-time interaction ($p=0.001$). Pre- to post-test improvements in the intervention group were significantly larger than in the control group (partial eta squared=0.721). **Physical functioning and sleep**

Study	Results
	There were no significant between group differences at baseline for the six minute walk test (6MWT) (p=0.523). Two-way RM-ANOVAs revealed a significant group-by-time interaction for the 6MWT (p<0.001). Pre- to post-test improvements in the intervention group were significantly larger than in the control group (partial eta squared=0.646). **Burden of disease** There was no significant between group differences at baseline for Quality of Life (assessed by the St George's Respiratory Questionnaire; p=0.125). Two-way RM-ANOVAs revealed a significant group-by-time interaction (p<0.001). Pre- to post-test improvements in the intervention group were significantly larger than in the control group (partial eta squared=0.721). **Other** No adverse events occurred during the study.
Rodriguez-Blanco (2023)[75]	**Pulmonary/respiratory** Dyspnoea significantly improved in both the exercise (mean change=-10.21, -13.01 to -7.40) and no treatment control (mean change=-0.37, -0.64 to -0.10) groups. Significantly greater improvements were seen in the exercise group (d=1.35, 0.72 to 1.97). **Energy/fatigue** Fatigue significantly improved in the exercise group (mean change=-2.00, -2.96 to -1.03) and not the control group (mean change=-0.17, -0.46 to 0.12). A significantly greater improvement was seen in the exercise group (d=0.74, 0.16 to 1.33). **Physical functioning and sleep** Both exercise capacity variables significantly improved in the exercise group (Six Minute Walk Test (6MWT) mean change=147.92, 78.00 to 217.83; 30 seconds sit to stand test (30STST) mean change=3.08, 1.90 to 4.26) and not the control group (6MWT mean change=-0.37, -4.88 to 4.13); 30STST mean change=0.21, -0.30 to 0.72). A significantly greater improvement was seen in the exercise group (6MWT: d=0.89, 0.29 to 1.48; 30STST: d=1.16, 0.55 to 1.77). **Other** No side effects were recorded during the implementation of the intervention.
Romanet (2022)[76]	**Pulmonary/respiratory**

Study	Results
	The strength and aerobic training group significantly improved in all measures of dyspnoea relative to the standard physiotherapy group: Multidimensional dyspnoea profile (MDP) total score (*d*=0.82, 0.29 to 1.35), MDP breathing discomfort subscale (*d*=0.97, 0.43 to 1.51), MDP sensory dimensions subscale (*d*=0.78, 0.25 to 1.31), MDP emotional response (*d*=0.54, 0.02 to 1.06), and mMRC (*d*=1.35, 0.78 to 1.91). **Burden of disease** The strength and aerobic training group significantly improved in the short form survey (SF-12) physical dimension subscale Quality of Life relative to the standard physiotherapy group (*d*=0.52, 0.01 to 1.04), but not the total SF-12 score (*d*=0.34, -0.17 to 0.85) or the mental dimension subscale (*d*=0.05, -0.46 to 0.56). **Other** Adverse events not reported.
Rutkowski (2023)[77]	**Pulmonary/respiratory** Lung function (assessed as forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), and total lung capacity (TLC)) did not significantly improve from pre- to post-intervention in either the virtual reality high-intensity pulmonary rehabilitation group or the traditional pulmonary rehabilitation group (all *p*≥0.087), although the FEV1/FVC measure significantly worsened in the virtual reality group (84.3±6.89 to 81.4±7.77; *p*=0.028). Changes in lung function did not significantly differ between groups (all *p*≥0.100). Dyspnoea following the six minute walk test (6MWT) improved from pre- to post-intervention in both the virtual reality (median (Interquartile range (IQR))= 2.0 (3.0) to 0.0 (2.0); *p*=0.033) and traditional pulmonary rehabilitation (median (IQR)= 2.0 (2.75) to 0.5 (2.0), *p*=0.004) groups. However, these changes did not differ between groups (*p*=0.621). **Energy/fatigue** Fatigue following the 6MWT improved from pre- to post-intervention in the traditional pulmonary rehabilitation group (median (IQR)=3.0 (1.0) to 2.0 (1.0), *p*=0.010) but not the virtual reality group (median (IQR)=3.0 (1.0) to 2.0 (1.0), *p*=0.055). However, these changes did not differ between groups (*p*=0.523). **Mental and cognitive** Both the virtual reality (23.1±4.2 to 20.7±3.5, *p*=0.015) and traditional (23.8±3.1 to 22.2±3.8, *p*=0.004) pulmonary rehabilitation groups reported significantly improved stress from pre- to post-test. Stress score changes did not significantly differ between groups (*p*=0.719; *d*=0.21, -0.49 to 0.91).

Study	Results
	Physical functioning and sleep Both the virtual reality (502±48.4 to 558±76) and traditional (512±54.3 to 552±49.1) pulmonary rehabilitation groups significantly improved their 6MWT distance from pre- to post-test (both (p<0.001). Test score change did not significantly differ between groups (p=0.264; d=0.31, -0.40 to 1.01). **Other** Adverse events not reported.
Vallier (2023)[86]	**Pulmonary/respiratory** There was no statistically significant effect of time (that is, pre vs post-effect) on the pulmonary function test or dyspnoea scores (all p≥0.009). There was also no statistically significant interaction between time and group (that is, inpatient pulmonary rehabilitation and home pulmonary rehabilitation groups; all p≥0.215). **Energy/fatigue** Only inpatient pulmonary rehabilitation significantly reduced general fatigue. There was a statistically significant effect of time (that is, pre vs post-effect) on the Multidimensional Fatigue Inventory (MFI) total score, MFI general fatigue, and MFI physical fatigue (all p<0.001), but not on MFI mental fatigue, MFI decrease physical activity, or MFI decrease motivation (all p≥0.138). There was a statistically significant interaction between time and group (that is, inpatient pulmonary rehabilitation and home pulmonary rehabilitation groups) for MFI total score (p=0.016) and MFI general fatigue (p=0.028) such that only inpatient pulmonary rehabilitation reduced fatigue (p<0.05). In the inpatient pulmonary rehabilitation group, mean MFI total score improved by 18 points and mean MFI general fatigue score improved by 6 points, compared to 5.3 and 2.4 point improvements in the home pulmonary rehabilitation group. There was no statistically significant interaction between time and group for MFI physical fatigue, MFI decrease physical activity, or MFI decrease motivation (all p≥0.051). **Physical functioning and sleep** Exercise capacity significantly improved as a result of the interventions. There was a statistically significant effect of time (that is, pre vs post-effect) on all of the exercise capacity variables (six-minute walk test (6MWT), one-minute sit to stand, squat jump max force, and squat jump max power; all p<0.001). However, there were no statistically significant interactions between time and group (all p≥0.295). In the inpatient pulmonary rehabilitation group, mean 6MWT score improved by 95m, mean 1min-STS improved by 9.5reps, mean squat jump max force improved by 159N, and mean squat jump max power improved by 286W, compared to 62m, 7.5 reps, 101N, and 195W in the home pulmonary rehabilitation group. **Burden of disease**

Study	Results
	Quality of life (QoL; assessed by the VQ11) significantly improved as a result of the interventions. There was a statistically significant effect of time (that is, pre vs post-effect) on all of the QoL variables (VQ11 total score, $p<0.001$; VQ11 functional component, $p<0.001$; VQ11 psychological component, $p=0.004$; VQ11 social component, $p=0.002$). However, there were no statistically significant interactions between time and group (all $p\geq0.750$).In the inpatient pulmonary rehabilitation group, mean VQ11 total score improved by 8.1, mean VQ11 functional component score improved by 3.5, mean VQ11 psychological component score improved by 2.8, and mean VQ11 social component score improved by 1.8, compared to 8.6, 4.0, 2.5, and 2.2 in the home pulmonary rehabilitation group. **Other** Adverse events not reported.

Appendix 8. Results from studies of physiotherapy and physical rehabilitation interventions

Study	Results
Ali (2023)[38]	**Energy/fatigue** Participants in both the active cycle of breathing technique (ACBT) and traditional physiotherapy and traditional physiotherapy only groups reported significant improvements in fatigue (ACBT + physio mean change: -23.6; physio mean change: -14.03; both $p<0.001$). However, a larger improvement was seen in the ACBT group (d=-3.37, -4.16 to -2.58). **Physical functioning and sleep** Participants in both the ACBT and traditional physiotherapy and traditional physiotherapy only groups reported significant improvements in the 6-minute-walk-test (6MWT) (ACBT + physio mean change: 105.27m; physio mean change: 21.61m; both p=0.001). However a larger improvement was seen in the ACBT group (d=2.35, 1.70 to 3.01).
del Corral (2023)[45]	**Pulmonary/respiratory** The inspiratory training (IMT), respiratory training (RMT), sham inspiratory training (IMTsham), and sham respiratory training (RMTsham) groups reported significant improvements from baseline to post-intervention (week 8) in all respiratory muscle function outcomes (maximum static inspiratory and expiratory pressures (MIP and MEP) and inspiratory muscle endurance (IME); all $p\leq0.032$). There were statistically significant interactions between the time and group factors for all respiratory muscle function outcomes (all $p<0.001$). At week 8, both real training groups showed a statistically significant and large (all d≥0.8, $p<0.05$) increase in MIP and IME compared with the sham groups. At weeks 4 and 8, expiratory muscle strength significantly improved in the RMT group compared with the other three groups (all d≥0.9, $p<0.05$), both at 4-week follow-up and at the post intervention. The IMT and RMT groups, but not the IMTsham or RMTsham groups, reported significant improvements ($p<0.05$) in cardiorespiratory fitness (CRF) assessed by both Ruffer index. There were no statistically significant interactions between the time and group factors, indicating that there were no significant difference between groups at week 4 or 8. **Mental and cognitive** Cognitive and psychological status outcomes (cognitive function, anxiety, depression, distress, and post-traumatic stress) significantly improved for all groups from baseline to week 8 (all $p\leq0.022$), except for distress in the RMTsham group (p=0.083). For all of the outcomes there were no statistically significant interactions between the time and group factors, indicating that there were no significant difference between groups differences at week 4 or 8 (all $p>0.05$).

Study	Results
	Physical functioning and sleep The IMT and RMT groups, but not the IMTsham or RMTsham groups, reported significant improvements (p<0.05) from baseline to post-intervention (week 8) in sit-to-stand score. There was a statistically significant interactions between the time and group factors (p=0.001), such that there were no statistically significant differences in sit-to-stand scores between groups at week 4, but at week 8 there were significantly larger improvements in the real training groups compared to the sham groups (all d≥0.8, p<0.05). All four groups reported significant improvements (p<0.05) from baseline to post-intervention (week 8) in handgrip strength. There were no statistically significant interactions between the time and group factors, indicating that there were no significant differences between groups at week 4 or 8. **Burden of disease** The IMT and RMT groups, but not the IMTsham or RMTsham groups, reported significant improvements (p<0.05) in Health-related Quality of Life assessed by both the EQ-5D-5L (index) and EQ-5D-5L (VAS). There were statistically significant interactions between the time and group factors (EQ-5D-5L index: p=0.031; 5D-5L VAS: p=0.004), such that there were no statistically significant between group differences week 4, but at week 8 there was a significantly larger improvement in HRQoL in the RMT group compared to the RMTsham group (EQ-5D-5L index: d=1.0, p<0.01; 5D-5L VAS: d=1.0, p<0.01). **Other** Only one person presented adverse effects during the study (symptom exacerbation). However, this person belonged to the IMTsham group, so the worsening was not considered due to the intervention.
McNarry (2022)[65]	**Pulmonary/respiratory** In the intention to treat (ITT) population, respiratory muscle strength (assessed as maximal inspiratory pressure (cmH2O), maximal inspiratory pressure (% predicted), Fatigue Index Test, and sustained maximal inspiratory pressure) significantly improved from pre- to post-intervention in the inspiratory muscle training (IMT) group (all p<0.05), but not in the control group. There were significantly larger improvements in the IMT group than the control group for maximal inspiratory pressure (cmH2O; d=0.56, 0.18 to 0.94), maximal inspiratory pressure (% predicted; d=0.46, 0.08 to 0.84), and sustained maximal inspiratory pressure (d=0.43, 0.06 to 0.81), but not the Fatigue Index Test (d=0.09, -0.28 to 0.46). In the ITT population, physical fitness (estimated V02max) significantly improved from pre- to post-intervention in the inspiratory muscle training (IMT) group (38.3±15.to 42.0±16.4; p<0.05), but not in the control group. There was no significant difference between groups in change in estimated V02max (d=0.33, -0.04 to 0.70).

Study	Results
	There were no baseline between group differences in dyspnoea (assessed by the Baseline Dyspnoea Index; $p>0.05$). In the ITT group, participants who received IMT reported lower dyspnoea scores (assessed by the Transition Dyspnoea Index) than the control group at post-intervention (2.0±2.0 versus 0.9±1.7; $p=0.005$). **Mental and cognitive** In the ITT population, perceived competence (assessed on the Perceived Competence Scale) significantly improved from pre- to post-intervention in both the inspiratory muscle training (IMT) group (14.3±8.0 to 15.4±8.2, $p<0.05$) and the control group (14.1±9.3 to 16.7±8.9, $p<0.05$). There was no significant difference between groups in change in perceived competence scores (d=-0.18, -0.55 to 0.19). In the ITT population, neither group reported significant changes from pre- to post-intervention in the three subscales of the Basic Needs Satisfaction Scale (autonomy, competence, and relatedness; all $p>0.05$). There were no significant differences between groups in change in scores on these three subscales (d range=-0.24 to 0.00). **Physical functioning and sleep** In the ITT population, neither sleep duration nor sleep efficiency significantly improved from pre- to post-intervention in either the inspiratory muscle training or control groups (both $p>0.05$). There was no significant difference between groups in change in estimated sleep duration (d=0.15, -0.22 to 0.52) or sleep efficiency (d=-0.10, -0.48 to 0.27). **Burden of disease** In the per-protocol population (as it was not reported for the ITT population), Health Related Quality of Life (HRQoL) significantly improved from pre- to post-intervention in the inspiratory muscle training (IMT) group (56.8±12.4 to 67.8±14.4; $p<0.05$), but not in the control group. There was a larger improvement in the IMT group than the control group (d=0.80, 0.41 to 1.20). These findings were broadly comparable in the breathlessness and activities, psychological, and chest symptoms subscales. However, the control group also significantly improved from pre- to post-intervention in the psychological subscale ($p<0.05$) and there was no significant difference in the change in chest symptoms between groups (d=0.38, 0.00 to 0.77).
Nagy (2022)[66]	**Pulmonary/respiratory** The diaphragm release and inspiratory muscle training group had significantly greater reductions in dyspnoea than the control group who only received inspiratory muscle training (48.9% vs 12.8%; d=1.69, 1.06 to 2.32). **Energy/fatigue**

Study	Results
	The intervention group had significantly greater reductions in fatigue than the control group (33.9% vs 6.4%; *d*=2.26, 1.57 to 2.96). **Physical functioning and sleep** The intervention group had significantly greater improvements in exercise capacity than the control group (13.5% vs 3.9%; *d*=2.08, 1.40 to 2.75).
Palau (2022)[69]	**Pulmonary/respiratory** The inspiratory muscle training (IMT) group significantly improve peak V02 from baseline to post-intervention (week 12; mean change=3.4mL/kg/min, 2.1 to 4.6, *p*<0.001) and the no treatment control group significantly worsened (mean change=-1.09mL/kg/min, -1.8 to -0.38, *p*=0.006). Improvements in the IMT group were significantly greater than the control group (*d*=0.85, 0.04 to 1.65). **Burden of disease** Quality of Life (QoL) was assessed as the mobility, self-care, usual activities, pain/discomfort, and anxiety/depression dimensions of the EQ-5D-3L questionnaire and by visual analogue scale. Participants in the intervention group reported significant improvement in usual activities (mean change=-0.31, -0.54 to -0.07, *p*=0.013) and anxiety/depression (mean change=-0.53, -0.67 to -0.40, *p*<0.001), with no significant changes in the control group. IMT also resulted in a non-significant improvement in both groups' mobility, self-care and pain/discomfort dimensions. Participants in the intervention group also reported significant improvement self-rated health on a vertical visual analogue scale dimension (mean change=21.1, 12.9 to 29.4, *p*<0.001). **Other** There were no reports of adverse effects following or during exposure to IMT.
Philip (2022)[70]	**Pulmonary/respiratory** In the intention to treat (ITT) population, change in chronic obstructive pulmonary disease assessment, dyspnoea, and breathlessness while at rest, walking or on the stairs test scores did not statistically significantly differ between groups (all *p*≥0.12). Participants in the English National Opera (ENO) Breathe group had a larger improvement in breathlessness while running compared with the usual care group (unstandardised regression coefficient -10.48 [95% CI -17.23 to -3.73]; *p*=0.0026; *d*=0.49, 0.17 to 0.82). **Mental and cognitive** In the ITT population, change in anxiety did not statistically significantly differ between groups (*p*=0.085; *d*=0.22, -0.10 to 0.54). **Burden of disease**

Study	Results
	Participants in the ENO Breathe group had an improvement in the 36 item short form survey (SF-36) mental health composite (MHC) compared with the usual care group (unstandardised regression coefficient 2.42 [95% CI 0.03 to 4.80]; *p*=0.047), SF-36 and physical health composite (PHC) did not differ significantly between the groups (0.60 [–1.33 to 2.52]; *p*=0.54). Hedges' *d* effect sizes showed small, non-significant effects in favour of the intervention: MHC *d*=0.25, -0.07 to 0.57; PHC *d*=0.15, -0.17 to 0.47. Change in the individual SF-36 subscales or the SF-6D did not statistically significantly differ between groups (all *p*≥0.12). A greater proportion of participants in the ENO Breathe group improved their SF-36 MHC baseline score by 10% (45% vs 30%, *p*=0.073) and 5% (40% vs 17%, *p*=0.038) than the usual care group. Proportions were similar across groups for the SF-36 PHC (10%: 35% vs 27%, *p*=0.34; 5%: 22% vs 17%, *p*=0.43). **Other** No serious adverse events were reported. One participant withdrew from the ENO Breathe group due to dizziness that they attributed to looking at the computer screen for too long during the sessions.
Srinivasan V (2021)[82]	**Pulmonary/respiratory** Improvements in forced expiratory volume in one second (FEV1) (*d*=1.86. 1.18 to 2.54), but not FVC (*d*=0.43, -0.15 to 1.00), were significantly larger in the breathing exercises group than the placebo control group.

Appendix 9. Results from studies of olfactory training interventions

Study	Results
Bérubé (2022)[42]	**Taste/smell** There was no significant difference in change in The University of Pennsylvania Smell Identification Test (UPSIT) score between the olfactory training and placebo control groups (*d*=0.08, -0.54 to 0.70). Pre- to post-intervention changes in self-reported smell and taste function (assessed on a 0-10 scale) did not significantly differ between the olfactory training and placebo control groups (*p*=0.091). Pre-intervention, the proportion of participants who reported having parosmia did not significantly differ between the olfactory training (16/20, 80%) and placebo control groups (19/22, 86%; *p*=0.58). After training, there was a significant difference between groups (14/19, 74% in the training group vs 21/22, 95% in the placebo group; *p*=0.049). **Burden of disease** Pre- to post-intervention changes in Quality of Life (assessed by the Questionnaire of Olfactory Disorders) did not significantly differ between the olfactory training and placebo control groups (*p*>0.05).
Khan (2023)[60]	**Taste/smell** Olfactory function (assessed by the University of Pennsylvania Smell Identification test (UPSIT)) improved over time in the control and four intervention trial arms (Group 1: bimodal training with participant-preferred scents, Group 2: bimodal training with physician-assigned scents, Group 3: unimodal training with participant-preferred scents, Group 4: unimodal training with physician assigned scents). No clinically meaningful difference was observed in the mean change in the UPSIT score between and within the four intervention arms and control group. Moreover, no meaningful difference was observed between 1) participants randomized to bimodal and unimodal olfactory training (marginal mean difference=1.10, -2.92 to 0.74) or 2) between participants randomised to participant-preferred and physician-assigned olfactory training (marginal mean difference=0.73, -1.10 to 2.56). However, the proportion of participants who experienced a clinically meaningful improvement in UPSIT score was highest in the bimodal arms (participant-preferred: 53%; physician-assigned: 41%) and smallest in the unimodal training with physician-assigned Olfactory training (29%) and control (24%) arms. The greatest proportion of participants self-reporting improvement (Clinical Global Impression – Improvement scale (CGI)) were in the bimodal training with physician-assigned scents arm (46%), followed by unimodal training with physician-assigned scents (37%), bimodal with participant-preferred scents (35%), unimodal with participant-preferred scents (32%), and control groups (19%). The change in Olfactory Dysfunction Outcomes Rating (ODOR) score was not clinically important nor different between intervention arms.

Study	Results
Lechner (2022)[63]	**Taste/smell** Change in Brief smell indication test (BSIT) score from baseline to week 12 and 1-year follow-up did not significantly differ between the olfactory training and no treatment control groups (week 12 effect size=0.22, -0.34 to 0.77; 1-year effect size=0.31, -0.38-1.01). Participants in the olfactory training group had non-significantly higher odds of having normal smell at Week 12 than those in the no treatment control group (week 12 OR=2.38, 0.73 to 7.76, *p*=0.15; 1-year OR=2.33, 0.37-14.61, *p*=0.37). **Burden of disease** Unclear.
Pires (2022)[71]	**Taste/smell** The advanced olfactory training group did not significantly improve relative to the classical olfactory training group for any taste or smell outcomes: the University of Pennsylvania Smell Identification test (UPSIT) (*d*=0.10, -0.37 to 0.57); olfaction (assessed by VAS; *d*=-0.22, -0.69 to 0.25); nasal symptoms (assessed by VAS; *d*=-0.20, -0.67 to 0.27); gustation (assessed by VAS; *d*=0.22, -0.25 to 0.69). **Burden of disease** The advanced olfactory training group did not significantly improve relative to the classical olfactory training group for QoL (assessed by visual analogue scale; *d*=0.22, -0.25 to 0.69).

Appendix 10. Results from studies of cognitive and neurorehabilitation interventions

Study	Results
Awaad (2022)[40]	**Mental and cognitive** A larger improvement in Headache Disability Index scores was seen in the tVNS group than the placebo control group (*d*=1.09, 0.33 to 1.86). **Other** A larger improvement in pain (assessed by visual analogue scale) was seen in the Transcutaneous vagus nerve stimulation (tVNS) group compared to the placebo control group (*d*=1.09, 0.33 to 1.86).
Santana (2023)[78]	**Energy/fatigue** Relative to the sham group, the High-definition transcranial direct current stimulation (HD-tDCS) group reported significantly larger pre- to post-intervention improvements in the total fatigue (*d*=0.97, 0.48 to 1.47) and cognitive (*d*=0.99, 0.49 to 1.48) and psychosocial (*d*=1.59, 1.05 to 2.12) fatigue subscale scores, but not physical (*d*=0.14, -0.32 to 0.61) subscale scores. **Mental and cognitive** A larger improvement from pre- to post-intervention in anxiety (assessed by the Hamilton rating scale for anxiety HAM-A) was seen in the HD-tDCS group compared to the sham group (*d*=0.90, 0.40 to 1.39). **Burden of disease** A larger improvement from pre- to post-intervention in Quality of Life (assessed by the World Health Organisation Quality of Life Brief Version (WHOQoL brief)) was seen in the HD-tDCS group compared to the sham group (*d*=1.30, 0.78 to 1.81). **Other** There was no significant difference in change from pre- to post-intervention in pain (assessed by the McGill questionnaire) between the HD-tDCS and sham groups (*d*=0.18, -0.29 to 0.65). No serious adverse events were reported. Skin redness was the only adverse event that differed significantly between groups: there were 37 occurrences in the active group compared to 13 in the sham group (*p*<0.001).

Appendix 11. Results from studies of psychological interventions

Study	Results
Hausswirth (2023)[53]	**Pulmonary/respiratory** At baseline, both of the Long COVID groups had significantly higher dyspnoea compared to the healthy controls (all $p<0.001$). The neuro-meditation group significantly improved dyspnoea (1.5±0.9 to 1.1±0.7) from baseline to post-intervention ($p<0.05$) but the Long COVID control and healthy control groups did not. Changes in dyspnoea (assessed by the modified medical research council dyspnoea scale (mMRC)) in the neuro-meditation group did not significantly differ compared to the Long COVID no treatment control group (d=0.24, -0.43 to 0.92). **Energy/fatigue** At baseline, both of the Long COVID groups had significantly higher physical and mental fatigue compared to the healthy controls (all $p<0.001$). The neuro-meditation group significantly improved both physical (17.8±2.2 to 4.8±4.1) and mental (10.4±1.6 to 2.7±3.1) fatigue from baseline to post-intervention (both $p<0.001$). Significantly larger improvements in physical and mental fatigue (assessed by the Chalder fatigue scale (CFQ11)) were seen in the neuro-meditation group compared to the Long COVID no treatment control group (physical: d=5.26, 3.84 to 6.68; mental: d=4.66, 3.36 to 5.95). **Mental and cognitive** Larger improvements in anxiety (statistically non-significant) and depressive (statistically significant) symptoms (both assessed by the Hospital Anxiety and Depression Scale and total mood disturbance (assessed by the Profiles of Mood States; statistically significant) were seen in the neuro-meditation group compared to the Long COVID no treatment control group (anxiety: d=0.61, -0.08 to 1.30; depression: d=1.25, 0.52 to 1.99; mood: d=1.22, 0.49 to 1.95). Changes from baseline to post-intervention the 14 outcomes from five computerized cognitive tasks (choice response time, pattern comparison, Simon, pursuit rotor task, and Corsi block-tapping task) did not significantly differ between the neuro-meditation and no treatment control group (d range=-0.35 to 0.65). **Physical functioning and sleep** Changes from baseline to post-intervention in sleep quality (assessed by the Spiegel sleep questionnaire (SSQ)) did not significantly differ between the neuro-meditation and no treatment control group (d=0.36, -0.32 to 1.04). **Other** Larger improvements in muscular and joint pain and headaches (all assessed using visual analogue scales) were seen in the neuro-meditation group compared to the Long COVID no treatment control group (muscular and joint pain: d=0.97, 0.26 to 1.69; headaches: d=0.80, 0.10 to 1.50).

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