STATENS BEREDNING FÖR MEDICINSK OCH SOCIAL UTVÄRDERING

Bilaga till rapport

Postcovid - En kartläggning av behandlings- och rehabiliteringsstudier/Post covid condition - an evidence map of treatment and rehabilitation studies, rapport 413 (2026)

Bilaga 3 Inkluderade randomiserade, kontrollerade studier/Appendix 3 Included randomised controlled trials

I avsnittet nedan redovisas de 103 RCT-studier, rapporterade i 105 artiklar, som ingår i denna kartläggning om behandlingsinsatser för personer med postcovid/Listed below is the 103 randomized controlled trials (RCTs), reported in 105 articles, that are included in this mapping of treatment interventions for individuals with postcovid.

Al-Jabr et al. 2025

Author	Al-Jabr et al. [1]
Year	2025
Country	United Kingdom
Study design	Feasibility randomised controlled trial
Setting	Conducted across the UK; sessions delivered by university-based research team; recruitment via LC clinics, social media, and word of mouth
Population	Adults ≥18 diagnosed with long covid; n=60; mean age 44 years; majority female (82%); predominantly White British
Inclusion criteria	Age ≥18; confirmed covid-19 and long covid diagnosis; able to communicate in English; able to provide consent
Exclusion criteria	Not reported
Intervention Participants (n) Dropouts (n)	Usual care plus LC-Optimal Health Programme (minimum 5 weekly 1-hour sessions plus 3-month booster), a psychoeducational self-efficacy programme on mental and physical dimensions of health and wellbeing 28 5
Control Participants (n) Dropouts (n)	Usual care 32 5
Follow up time points	Baseline, 3 months, 6 months
Outcomes Measured	PHQ-9 (depression), GAD-7 (anxiety), GSE (self-efficacy), EQ-5D-5L (quality of life, VAS), FAS (fatigue)
Results	**Mean change from baseline at 6 months (SD)** <u>PHQ-9:</u> I: -2.69 (4.18) C: -4.48 (6.22) <u>GAD-7:</u> I: -1.43 (3.69) C: -3.96 (5.84) <u>GSE:</u> I: 1.04 (4.69) C: -0.56 (8.34) <u>FAS:</u> I: -3.22 (6.97) C: -5.07 (8.34)

	EQ-5D-5L (QoL): I: 0.08 (0.22) C: 0.12 (0.22) EQ-5D-5L (VAS): I: 6.09 (17.50) C: 10.29 (17.11) (Results at 3 months are also reported in study)
Limitations Noted	Limited demographic diversity; predominantly white and female sample; social-media heavy recruitment; variability in usual care; lead researcher delivered intervention; small sample size typical for feasibility trials
Risk of bias	Moderate

Bai et al. 2024

Author	Bai et al. [2]
Year	2024
Country	China
Study design	Randomised controlled trial (single-center, parallel-group, open-label)
Setting	Cardiac rehabilitation clinic at Guangdong Provincial People's Hospital, Southern Medical University, Guangzhou, China
Population	24 patients aged 18–75 years (mean age 46.5 years) with long covid symptom such as fatigue, cognitive impairment, chest discomfort, etc., persisting ≥2 months post-infection; 58.3% female; median time from covid-19 diagnosis to enrollment was 14 weeks.
Inclusion criteria	History of SARS-CoV-2 infection; symptoms persisting ≥2 months post-infection; positive RT-PCR or antigen test with negative result ≥4 weeks before inclusion; symptoms include at least one of such as cough, fatigue, cognitive impairment, chest tightness, palpitations, etc.
Exclusion criteria	Conditions worsened by exercise (acute cardiac insufficiency, exercise-induced asthma, epilepsy); serious comorbidities (unstable angina, oxygen saturation <93%, uncontrolled arrhythmia, uncontrolled hypertension or type 2 diabetes); physical disabilities due to bone/joint or neuromuscular diseases; pregnancy or lactation
Intervention Participants (n) Drop-outs (n)	Training group 4-week supervised aerobic training on cycling ergometer, 3 sessions/week (12 sessions total), using moderate- or high-intensity interval training based on peak VO2 and work rate 12 0
Control Participants (n) Drop-outs (n)	Control group: standard healthy lifestyle guidance and WHO self-management recommendations 12 0
Follow up time points	Baseline and 4 weeks (post-intervention) assessments using CPET and questionnaires (SF-12, PHQ-9, GAD-7, ISI, Perceived Stress Scale)
Outcomes Measured	Primary: Changes in persistent symptoms (total number, specific symptoms) Secondary: Cardiopulmonary fitness (peak VO2, AT VO2, exercise time, maximum load, O2 pulse, HRmax) and mental health (PHQ-9, GAD-7, stress, insomnia, SF-12 scores)
Results	**Results reported for between-group differences** Reduced number of persistent symptoms: 67.8% (n=8) in training group vs 16.2% (n=2) in control group after 4 weeks (p=0.013) SF-12, sub scores of mental components (MCS) and physical component (PCS): non-significant PHQ-9 (depressive symptoms): non-significant GAD-7 (anxiety symptoms):

	non-significant **Results from cardiopulmonary fitness and function** Improvement in exercise time: 80.34 s vs 20.83 s in favor of training group (p for group x time = 0.028) Improvement in maximum load (mean change, watt): 20.25 vs. 3.83 in favor of training group (p for group x time = 0.01) Peak VO_2 improved in the training group (mean change, mL/kg/Min): 4.64 vs –1.06 (p for group x time = 0.041) There were no significant differences in changes between groups for pulmonary function Additional outcomes reported
Limitations Noted	Small sample size; single-center; short duration (4 weeks) with no long-term follow-up; lack of stratified analysis for comorbidities; no detailed scale assessment of baseline exercise habits
Risk of bias	Moderate

Bassi et al. 2025

Author	Bassi et al. [3]
Year	2025
Country	India
Study design	Multicenter, double-blind, placebo-controlled, parallel-group randomised clinical trial (1:1 allocation).
Setting	8 hospitals across 6 states in India (5 private hospitals, 2 public hospitals, and 1 community outreach center).
Population	Adults with confirmed SARS-CoV-2 infection and persistent symptoms consistent with long covid. Participants had functional limitation (Post-Covid-19 Functional Status scale grade ≥2) and/or elevated inflammatory markers. Mean age 46 years; 60.4% female.
Inclusion Criteria	Confirmed SARS-CoV-2 infection; persistent symptoms after infection; PCFS score ≥2 and/or elevated inflammatory markers (hs-CRP >0.20 mg/dL or neutrophil-to-lymphocyte ratio >5); adult participants.
Exclusion Criteria	Indication for colchicine (e.g., arthritis, inflammatory bowel disease); gastrointestinal surgery or chronic diarrhea; conditions affecting colchicine absorption; pregnancy or breastfeeding; blood dyscrasias; severe renal impairment (eGFR <15 mL/min/1.73 m²).
Intervention Participants (n) Dropouts (n)	Colchicine 0.5 mg once daily (≤70 kg) or twice daily (>70 kg) for 26 weeks 177 At 26 weeks: 16 (161 analysed)
Control Participants (n) Dropouts (n)	Matching placebo tablets for 26 weeks 173 At 26 weeks: 19 (154 analysed)
Follow-up Timepoints	Baseline, 12 weeks, 26 weeks, and 52 weeks after randomisation
Outcomes Measured	Primary: Change in 6-minute walk test (6MWT) distance at 52 weeks Secondary: 6MWT at 12 and 26 weeks; quality of life (EQ-5D-5L); anxiety (GAD-7); depression (PHQ-9); dyspnea (Borg scale); maximal oxygen desaturation during 6MWT; fatigue (Chalder Fatigue scale); respiratory function (FVC, FEV1, FEV1/FVC); symptom count; adverse events
Results	**Mean change (SD) from baseline** (26-week data from modified intention-to-treat analysis, including randomised patients who had taken at least 1 dose of the trial medication, 12- and 52-week data not recorded by SBU)

	6MWT distance, meters: I: 25.34 (19.68) C: 17.17 (19.73) Mean difference (95% CI): 8.16 (−5.55 to 21.88) Maximal desaturation during 6MWT: I: −0.09 (0.49) C: 0.04 (0.49) Mean difference (95% CI): −0.13 (−0.57 to 0.32) Borg dyspnea score after completion of 6MWT: I: −1.24 (0.32) C: −1.27 (0.32) Mean difference (95% CI): 0.02 (−0.07 to 0.12) FEV1 (% predicted): I: −0.47 (1.98) C: 0.18 (2.00) Mean difference (95% CI): −0.64 (−4.44 to 3.15) EQ-5D-5L score: I: 0.07 (0.02) C: 0.08 (0.02) Mean difference (95% CI): −0.01 (−0.03 to 0.02) PHQ-9 score: I: −2.03 (0.43) C: −1.97 (0.43) Mean difference (95% CI): −0.06 (−0.59 to 0.47) GAD-7 score: I: −1.69 (0.37) C: −1.57 (0.37) Mean difference (95% CI): −0.11 (−0.59 to 0.36) Fatigue score: I: −0.70 (1.43) C: −1.13 (1.44) Mean difference (95% CI): 0.43 (−0.21 to 1.08) Self-reported symptom count: I: −2.10 (0.24) C: −2.32 (0.24) Mean difference (95% CI): 0.22 (−0.14 to 0.57)
Limitations Noted	Broad inclusion criteria capturing heterogeneous long-covid phenotypes; mild inflammatory state in many participants; long interval between infection and enrollment (median >1 year); underrepresentation of severe acute covid-19 survivors; potential influence of natural recovery. Participants with no follow-up data were excluded from analysis.
Risk of bias	Moderate

Berenguel Senén et al. 2024

Author	Berenguel Senén et al. [4]
Year	2024
Country	Spain
Study design Setting Population Follow up	Open label RCT Outpatient care Adults 18–65 years (mean 47 years, SD; 7.1, 73% female) with a history of covid-19 >12 weeks after infection and with asthenia and dyspnea on exertion After treatment, at 8 weeks
Intervention Participants (n) Drop-outs (n)	Therapeutic exercise training with both inhouse modality and a modality conducted at home with remote monitoring. Training was performed twice daily, six days a week for 8 weeks. 25 7
Control Participants (n) Drop-outs (n)	The control group received recommendations on physical exercise and healthy habits based on recommendations for the general population 25 6
Outcomes	**Primary outcome: change in peak VO2** I: Peak VO2 significantly improved by 15% after the TPEP (pre- vs postintervention: 24.9% vs 29.3% mL/kg/min; p<0.001) C: No significant changes in peak VO2 (pre- vs postintervention, 25.2 vs 24.8 mL/kg/min; p=0 .46) <u>Between group differences:</u> Peak VO2, mL/kg/min intervention 29.3 (SD 4.7) vs. control 25.5 (SD 7.7), p0<.001 **Secondary outcomes:** Quality of life scores <u>PCFS:</u> Intervention group 0 [0–1] vs control group 2 [0–2], p=0.015, in favour of active intervention <u>EQ5D-5L:</u> Intervention group 6 [6–7] vs control group 7 [6–10], p=0.01, in favour of active intervention <u>PHQ-9:</u> Intervention group 5 [4–9] vs control group 10 [5–14], p=0.03 in favour of active intervention <u>Neuromuscular capacity (load-velocity profiles for squat, bench press and pull down exercises)</u> Squat, p=0.43 Bench press, p=0.16 Pull down, p=0.02 in favour of active intervention Additional outcomes reported
Comments	Authors do not perform intention to treat analyses
Risk of bias	Moderate

Berube et al. 2023

Author	Berube et al. [5]
Year	2023
Country	Canada
Study design Setting Population Follow up	RCT, double-blind (triple?) Self-administration outside health care setting Adults (mean age 44.9±7.4 (intervention) and 44.5±10.1, 66% female) with previously confirmed COV covid-19 and persistent covid -19-related olfactory dysfunction (≥2 months, UPSIT) End of treatment / 12 weeks post allocation
Intervention Participants (n) Drop-outs (n)	Sniffing of four amber opaque glass vials, each containing an odor, twice daily for 12 weeks. Each session took 5 minutes and included a rotating exposure of each odor for 10 s, with 10 s rest intervals between each scent. 25 Lost to follow-up: 5 Excluded from analysis: 2
Control Participants (n) Drop-outs (n)	Sniffing of four amber opaque glass vials, containing odorless propylene glycole, twice daily for 12 weeks. Each session took 5 minutes and included a rotating exposure of each vial for 10 s, with 10 s rest intervals between each vial. 25 3
Outcomes	**Primary outcome** <u>UPSIT-40 score (range 0–40), higher = better, mean (SD):</u> I: pre = 24.3 (7.01) post = 35.8 (7.95) C: pre = 24.6 (5.58) post = 25.6 (6.13) We did not observe any significant effect of group or time, nor any interaction on the UPSIT scores, (rm ANOVA). The number of days between onset of OD and difference in UPSIT scores were significantly and positively correlated (r(40) = 0.38; p = 0.016). **Secondary outcomes** <u>Self-evaluation smell and taste sensitivity, VAS (range 0–10):</u> No effect of group was observed, but the interaction of group*time showed a trend (F(1,39) = 2.99; p = 0.091). <u>Presence of parosmia yes/no, (n):</u> After training, 14/19 participants from the trained group indicated parosmia, while this number was 21/22 in the placebo group (χ2 (1, 42) = 3.87, p = 0.049. <u>Quality of Life</u> Effect of time on quality of life impairment was observed (F(1,39) = 13.3; p = 0.001) No effect of group or interaction was observed I Nasal Obstruction Symptom Evaluation (NOSE), VAS (range “not a problem” to “severe problem”)
Comments	Effects on Nasal Obstruction Symptom Evaluation (NOSE) does not seem to be reported
Risk of bias	Moderate

Berry et al. 2025

Author	Berry et al. [6]
Year	2025
Country	Scotland, United Kingdom
Study design	Multicenter, parallel-group randomised clinical trial (1:1 allocation)
Setting	Queen Elizabeth University Hospital (Glasgow), Royal Infirmary (Glasgow), and Ninewells Hospital (Dundee), Scotland.
Population	Adults with confirmed covid-19 infection within the preceding 12 months and persistent symptoms; median age: 53.6 years; 62.7% female; 39.1% previously hospitalized for covid-19.
Inclusion Criteria	Confirmed covid-19 diagnosis (PCR, point-of-care test, lateral flow test, antibody test, or radiology); diagnosis within the past 12 months; persistent symptoms ≥4 weeks; categorized as community symptomatic (group A), post-hospital discharge with persistent symptoms (group B), or convalescing in hospital (group C).
Exclusion Criteria	Receiving inpatient physiotherapy after ICU stay; no expectation of being able to walk within 3 months; inability to provide informed consent; inability to comply with the study protocol; pregnancy.
Intervention Participants (n) Dropouts (n)	Personalized resistance exercise program for 3 months; including guidance document, exercise log, instructional videos and initial face-to-face consultation with exercise physiologist/therapist; follow-up support every 2 weeks via phone or video; exercises included chest press, rows, lateral raises, squats, lunges, calf raises; daily exercise targeting perceived exertion levels of 8–10. 117 22
Control Participants (n) Dropouts (n)	Usual care according to long covid clinical guidelines without additional research contact 116 16
Follow-up Timepoints	Baseline and 3 months after randomization
Outcomes Measured	<u>Primary:</u> Distance achieved during Incremental Shuttle Walk Test (ISWT) at 3 months Secondary: Spirometry (FVC, FEV1, peak flow), handgrip strength, Short Physical Performance Battery, Duke Activity Status Index, accelerometry-based physical activity, quality of life (EQ-5D-5L), anxiety/depression (PHQ-4), illness perception questionnaire, fatigue severity, dyspnea (MRC scale), hospitalization, adverse events, and post-exertional malaise
Results	Per protocol analysis at 3 months, median (IQR) **Primary outcome** <u>Incremental Shuttle Walk Test (ISWT) distance, meters:</u> I: 350 (200 to 528) C: 340 (195 to 465) Adjusted mean difference (95% CI): 36.5 (6.6 to 66.3); p =.02 **Secondary outcomes** <u>Spirometry, change in forced expiratory volume in 1 second, L:</u> I: 0.00 (−0.10 to 0.15) C: 0.00 (−0.10 to 0.10) Adjusted mean difference (95% CI): 0.00 (−0.13 to 0.14); NS <u>Physical function, change in handgrip strength, kg:</u> I: 2.5 (−0.8 to 5.8) C: 0.9 (−3.0 to 3.5) Adjusted mean difference (95% CI): 2.6 (0.9 to 4.2); p = .002 <u>Change in Short Physical Performance Battery (SPPB) score category:</u> Improvement, n (%): I: 25 (28.4) C: 13 (15.1)

	No change, n (%) I: 55 (62.5) C: 69 (80.2) Deterioration, n (%) I: 8 (9.1) C: 4 (4.7) Adjusted mean difference (95% CI): 1.7 (0.7 to 3.8); NS <u>Quality of life, change in EQ-5D-5L Health Utility score:</u> I: 0.01 (−0.02 to 0.21) C: 0.00 (−0.07 to 0.07) Adjusted mean difference (95% CI): 0.06 (0.01 to 0.11); p=.02 <u>Quality of life, change in EQ-5D-5L Visual Analogue scale:</u> I: 5.0 (0.0 to 15.0) C: 0.0 (−3.5 to 10.0) Adjusted mean difference (95% CI): 3.6 (−0.7 to 8.0); NS <u>Fatigue, change in Fatigue Severity score:</u> I: −4 (−13 to 1) C: 0 (−7 to 3) Adjusted mean difference (95% CI): −2.60 (−6.38 to 1.18); NS Additional outcomes reported <u>Safety:</u> No deaths occurred. Ten hospitalizations were recorded (mostly in the control group). No increase in post-exertional malaise and no serious adverse events related to the intervention.
Limitations	Outcome assessors aware of treatment allocation; exercise intervention unsupervised; adherence self-reported; control group had fewer contacts with research staff; study not powered for subgroup interaction analyses; no ITT-analysis
Risk of bias	Moderate

Besnier et al. 2025 & Gaudreau-Majeau et al. 2024

Author	Besnier et al. [7] Gaudreau-Majeau et al. [8] (Two articles reporting results from same study)
Year	2025 & 2024
Country	Canada
Study design	Randomised controlled trial (two-arm, parallel-group)
Setting	Centre ÉPIC, Montreal Heart Institute, Montreal, Quebec, Canada
Population	40 individuals with long covid; mean age 53; symptoms persisting ≥3 months post-infection; included fatigue, breathlessness, cognitive issues; 72% female in control group and 65% female in rehabilitation group
Inclusion criteria	Age ≥40 years; positive PCR test for SARS-CoV-2; persistent dyspnea and/or fatigue ≥3 months after infection; 1-point increase in dyspnea on Modified Medical Research Council scale compared to pre-infection period; no contraindication to exercise rehabilitation testing/training; able to give informed consent
Exclusion criteria	Pulmonary embolism; contraindications to cardiopulmonary stress tests/exercise training; severe exercise intolerance; significant myocardial ischemia or arrhythmia; severe pulmonary hypertension; severe respiratory disease; recent cardiovascular events; heart failure NYHA III/IV; kidney failure requiring dialysis
Intervention Participants (n) Drop-outs (n)	Rehabilitation group 8-week individualized, supervised cardiopulmonary rehabilitation (3 sessions/week of aerobic + resistance + daily inspiratory muscle training) 20 2 in Besnier et al; 5 in Gaudreau-Majeau et al
Control Participants (n) Drop-outs (n)	Control group maintained daily habits; rehabilitation offered after study completion. 20 3
Follow up time points	Baseline and 8 weeks post-intervention assessments (CPET, functional tests, quality of life questionnaires including SF-36, Post-Covid Functional Scale, Medical Research Council Breathlessness Scale, and symptom impact tools)
Outcomes Measured	<u>Primary:</u> Change in VO2 peak (mL/kg/min) via CPET <u>Secondary:</u> Submaximal CPET parameters (VE/VCO2 slope, ventilatory thresholds), functional tests (6-Min Walking Test, Timed Up and Go, Sit-to-Stand), quality of life (SF-36 physical and mental component scores), and symptom impact scales (personal, family, professional, social life, mood)
Results	Besnier et al: **Primary outcome** <u>VO_2 peak after 8 weeks (mL.kg.min):</u> 22.82 ± 5.57 vs 18.62 ± 3.77 in favor for rehabilitation group Effect corresponds to Hedge's g of 0.477 (p=0.003) (Several V02 outcomes, but VO_2 peak is highlighted by authors. Consistency in VO2 results.) **Secondary outcomes** <u>Spirometry:</u> FVC (L) no statistically significant differences between groups (p=0.350) <u>Physical functioning:</u> 6MWT (m): 548.9 ± 130.3 vs. 482.5 ± 81.1 at 8 weeks in favour of rehabilitation group. P=0.010 <u>TUG usual speed (seconds):</u> 6.99 ± 1.39 vs 8.22 ± 2.25 in favor of rehabilitation group (p=0.031) <u>TUG fast speed (seconds):</u> 5.56 ± 1.32 vs 6.26 ± 1.42 (p=0.066)

	Functional scales: PCFS category, trend towards improvement in rehabilitation group (p=0.063) MRC dyspnea scale, statistically significant improvement in rehabilitation group (p=0.43) Quality of life (SF-36): No statistically significant difference in physical functioning No statistically significant differences in Physical Component scale (PCS) and Mental Component Scale (MCS) Additional outcomes reported In each session, an adapted version of the Cotler's questionnaire was administered to assess postexertional malaise, PEM. --- Gaudreau-Majeau et al Primary outcomes Neuropsychological tests evaluating: - episodic memory - executive functions - processing speed - cognition (MoCA) - working memory - anxiety inventory, and - sleep quality (PSQI) All with no statistically significant differences at follow-up Symptoms of geriatric depression: 12.14 ± 8.55 vs 14.38 ± 7.88, p=0.015 Statistically significant improvements in rehabilitation group vs control Perceived stress (15.86 ± 8.31 vs 18.80 ± 10.28, p=0.002) Statistically significant improvements in rehabilitation group vs control Additional outcomes reported
Limitations Noted	Small sample size; predominantly Caucasian participants; short follow-up (8 weeks); lack of evaluation of alternative rehabilitation modalities; no stratified analysis for sex differences; potential variability from SARS-CoV-2 variants and vaccination status. Authors state that missing values were not imputed, and analysis was conducted on an intention-to-treat basis. It seems analysis was performed on complete cases only.
Risk of bias	Moderate

Busse et al. 2025

Author	Busse et al. [9]
Year	2025
Country	United Kingdom (England and Wales)
Study design	Pragmatic, multicentre, parallel-group randomised controlled trial
Setting	24 sites across England and Wales; NHS primary and secondary care services
Population	Adults ≥18 years with long covid symptoms ≥12 weeks; n=554; mean age 50; 72% women
Inclusion criteria	Age ≥18; ≥12 weeks long covid symptoms; GP consultation to rule out complications; able to consent
Exclusion criteria	Palliative/end-of-life care; hospitalised during acute covid; participation in another long covid trial
Interventions Participants (n) Dropouts (n)	'Listen' personalised self-management support (up to six 1:1 sessions via phone/video, delivered by trained practitioners + handbook where inclusivity considerations were integral) 277 67
Control Participants (n) Dropouts (n)	Usual NHS care (varied access to GP support, apps, or specialist long covid clinics) 277 77
Follow up time points	Baseline, 6 weeks (only health economic outcomes), 3 months
Outcomes Measured	Primary: Ox-PAQ Routine Activities scale at 3 months Secondary: Ox-PAQ Emotional Wellbeing & Social Engagement; SF-12 physical & mental health; Fatigue Impact Scale; General Self-Efficacy Scale; EQ-5D-5L; VAS; adverse events
Results	**Mean difference between groups at 3 months follow-up (95% confidence interval)** (Adjusted for site, baseline outcome score, age, gender, ethnic group, employment status, and the number of long covid symptoms at baseline) Ox-PAQ routine activities domain: –2.90 (–5.66 to –0.15) Ox-PAC emotional wellbeing domain: –5.89 (–8.99 to –2.79) Ox-PAC social engagement domain: –2.81 (–6.19 to 0.57) Fatigue Impact Scale overall: –8.65 (–1 2.79 to –4.52) EQ-5D-5L: 0.04 (0.00 to 0.07) VAS score (EQ-5D-5L): 2.72 (–0.80 to 6.24) Generalised self-efficacy scale (original scale + covid 4 items): 2.79 (1.66 to 3.93) SF-12 physical health: 0.48 (–0.74 to 1.71) SF-12 mental health: 2.85 (1.23 to 4.46) No serious adverse events were reported

	Domain scores from fatigue impact scale (cognitive, physical and social dimension) and generalized self-efficacy scale (original 10 items and covid 4 items) are also reported.. Results are also reported for mean difference between groups at 3 months follow-up adjusted for site and baseline outcome score.
Limitations Noted	Unblinded design; higher loss to follow-up; short follow-up period; limited ethnic diversity; self-referral may introduce bias; variable usual care pathways.
Risk of bias	Moderate

Calvache-Mateo et al. 2025

Author	Calvache-Mateo et al. [10]
Year	2025
Country	Spain
Study design	Single-blind, two-arm, parallel-group randomised controlled trial
Setting	Public health sciences faculty, University of Granada, Spain
Population	Adults ≥18 years with WHO-defined post- covid -19 condition and moderate–severe new-onset persistent pain (VAS ≥3.5). n=57 randomised (PIM n=27; control n=30). Majority female (~75%). Mean age ~ 45 years.
Inclusion criteria	Age ≥18 years; WHO-defined post- covid -19 condition; moderate or severe new-onset pain (VAS ≥3.5); pain not limited to a specific anatomical region.
Exclusion criteria	Pulmonary, cardiac, neurological, vascular or orthopedic disease limiting intervention; cognitive impairment (MoCA <26); SARS-CoV-2 reinfection; severe/critical acute covid -19; pre-existing chronic pain according to IASP; participation in other treatments or trials.
Interventions Participants (n) Drop-outs (n)	Pain Informed Movement (PIM) group: 8-week program with 2 supervised face-to-face sessions/week (1 group pain neuroscience education, 1 individual functional exercise + relaxation session, ~60 min each) plus 2 home sessions/week of prescribed exercises 30 3
Control Participants (n) Drop-outs (n)	Standard medical care and educational booklet; no supervised rehabilitation 30 0
Follow up time points	Baseline and post-intervention (8 weeks)
Outcomes Measured	Pain intensity and interference (Brief Pain Inventory); pain catastrophizing (PCS); kinesiophobia (Tampa Scale of Kinesiophobia); functionality (WHODAS 2.0).
Results	**Post-intervention MD (95% CI)** BPI Intensity: 2.84 (1.59 to 4.09) Interference: 3.10 (1.70 to 4.50) PCS Helplessness: 5.72 (2.89 to 8.54) Magnification: 2.56 (1.39 to 3.73) Rumination: 4.25 (2.53 to 5.97) Total: 12.52 (7.54 to 17.50) TSK 8.07 (5.38 to 10.76) WHODAS Communication: 2.13 (–1.24 to 5.50) Mobility: 3.33 (0.28 to 6.37) Self-Care: 0.95 (–0.87 to2.77) Interpersonal Relationships: 0.36 (–3.25 to 3.98) Home Life: 2.21 (–0.34 to 4.75) Work: 3.60 (–0.10 to 7.29) Social participation: 3.35 (–0.52 to 7.22) Total: 16.16 (2.28 to 30.03)

Limitations Noted	Small sample size; participants not blinded; lack of qualitative data; pain duration at baseline not measured; per-protocol analysis may overestimate effects.
Risk of bias	Moderate

Calvo-Paniagua et al. 2024

Author	Calvo-Paniagua et al. [11]
Year	2024
Country	Spain
Study design Setting Population Follow up	RCT Home-based tele-rehabilitation implemented by videoconference Adults 25–70 years (mean age about 49.4-50.8, women about 31.3-43.8%)) with moderate respiratory and/or functional impairments starting after the acute SARS-CoV-2 infection (mean duration after infection: 14.8 ± 1.7 months), at least 93% of oxygen saturation by pulse oximetry at rest on room air, n=64 Post-intervention and 1 and 3 months after post-intervention
Intervention Participants (n) Drop-outs (n)	A tele-rehabilitation program based on patient education, physical activity, airway clearing, and breathing exercise interventions, 18 sessions (40 minutes per session) in 7 weeks 32 0
Control Participants (n) Drop-outs (n)	Waitlist 32 0
Outcomes	**Primary outcome at post-intervention, mean change from baseline (95% CI)** Perceived physical exertion (MBDS): I: –7.6 (–8.1; –7.2) C: 0.0 (–0.6; 0.5) Group* time interaction (multivariate lineal general model): p<0.001 **Secondary outcomes, mean change from baseline at post-intervention (95% CI)** Health-related quality of life (SGRQ): I: 51.0 (–56.5; –45.6) C: 1.0 (–6.1; 8.0) Group* time interaction: p<0.001 6MWT test, walking distance (m): I: 126.5 (38.7; 214.3) C: –40.1 (–105.4; 25.1) Group* time interaction: p<0.001 Additional outcomes (oxygen saturation, heart rate, physical exertion severity) and follow-up times (1, and 3 months post-intervention) reported
Comments	Not fulfilling the WHO criteria completely but the average post-infection time was 14.8 ± 1.7 months
Risk of bias	Moderate

Campos et al. 2024

Author	Campos et al. [12]
Year	2024
Country	Brazil
Study design	Pragmatic randomised double-blind clinical trial
Setting	Dental clinic at Nove de Julho University, São Paulo, Brazil
Population	40 adult participants (18–64 years) (mean age: intervention 44 years; control 40 years) with persistent orofacial pain and/or tension-type headache >3 months post-covid-19 infection confirmed by RT-PCR; 34 participants analysed (per-protocol and ITT)
Inclusion criteria	Adults (18–64 years); confirmed SARS-CoV-2 infection by RT-PCR; recovered at least 30 days; persistent orofacial pain or tension-type headache for >3 months

Exclusion criteria	Neuropathy or headache types other than tension-type headache; physical or intellectual inability to complete questionnaires; illiteracy; diabetes; pacemaker; pregnancy; laser photosensitivity
Intervention Participants (n) Drop-outs (n)	VPBM group: 4 weekly sessions (30 min each) of vascular photobiomodulation (660 nm red laser, 100 mW) applied to radial artery using ECCO Reability device 14 2
Control Participants (n) Drop-outs (n)	Sham VPBM group: same protocol with inactive PBM device emitting conventional red light 20 4
Follow up time points	Baseline, weekly (VAS and BPI), and after 4 weeks (HIT-6, VAS, BPI) assessments
Outcomes Measured	Primary: Pain intensity (VAS; BPI) Secondary: Headache impact on activities (HIT-6); pain interference in walking, work, sleep, enjoyment of life
Results	**Primary outcome (ITT)** Pain intensity (BPI): No ITT-data reported Pain intensity (VAS): Significant reduction in both groups at end-of-treatment, but no statistically significant between-group difference (p = 0.189) **Secondary outcome (ITT)** Headache impact on activities (HIT-6): No significant between-group difference; p-value not reported (Per protocol results not tabulated by SBU)
Limitations Noted	Small sample size; convenience sample; short follow-up (4 weeks); first clinical trial of VPBM for post-covid-19 OFP and TTH; challenges in defining specific protocol; potential dropouts due to daily life factors The ITT analysis was limited to those 34 of the 40 included participants who underwent at least two of the four treatment sessions (data imputed using last observation carried forward).
Risk of bias	Moderate

Capin et al. 2022

Author Year Country Ref #	Capin et al. [13] 2022 USA [14]
Study design Setting Population Follow up	RCT Home environment/outside health care setting Adults (mean age 52 years, 47.7% female) discharged from hospital due to confirmed covid-19 (with and without ICU stay) 6 and 12 weeks
Intervention Participants (n) Drop-outs (n)	Multicomponent app-facilitated telerehabilitation program with e.g. physical exercises and lifestyle coaching, 12 individual sessions with licensed physical therapist during 9–10 weeks 29 1
Control Participants (n) Drop-outs (n)	No additional exercise equipment compared to material initially provided to both groups; educational handout about recovery from covid-19 and weekly check-in phone calls. 15 3
Outcomes	**Primary outcome:** <u>Feasibility (evaluated primarily by adherence and safety)</u> Adherence defined as percentage of 12 sessions attended, 9 sessions (75%) considered adherent. <u>Intervention group:</u> Adherence: 27/29 participants met the threshold of at least 75% adherence: 93% (95% CI, 77 to 99) (24 participants met 100 % adherence) Adverse events: Total of 29 AEs (17 moderate and 12 minor) among 11 individuals. Proportion experiencing any AE was smaller in intervention group compared to control group (38% vs 60%, p=0.21). <u>Control group:</u> Adverse events: From baseline to week 12: 1 hospitalisation (severe AE) 5 weeks after enrolment. Total of 17 AEs (1 severe, 4 moderate and 12 minor) in 9 individuals. No deaths or life-threatening AEs in either group. **Secondary outcomes** <u>Preliminary efficacy outcome measures: functional tests</u> (Performed remotely and facilitated by avatar in Health in Motion application, all models adjusted for treatment arm, visit, gender, age, BMI, duration of hospital stay and comorbidity index. Estimated change based on study population averages of male, age 53, BMI of 33, 5 days in the hospital and three comorbidities) <u>Physical function, 30 s chair stand (repetitions), change from baseline (95%CI):</u> Week 12: Intervention: 3.2 (1.8 to 4.6), p≤0.001 Control: 5.1 (3.2 to 7.0), p≤0.001 P-value for difference between groups: p=0.06 Additional outcomes on physical function reported
Comments	Assessor-blinded RCT
Risk of bias	Moderate

Charoenporn et al. 2024

Author	Charoenporn et al. [15]
Year	2024
Country	Thailand
Study design	Randomised controlled trial (double-blind, placebo-controlled)
Setting	Thammasat University Hospital, Thailand
Population	80 adults aged 18–60 (mean age 34 years) with post-covid fatigue or neuropsychiatric symptoms ≥1 month and ≤12 months after covid-19; 77.5% female; mostly vaccinated
Inclusion criteria	Confirmed covid-19 within past 12 months using PCR or antigen testing; ≥1 post-covid symptom (fatigue, anxiety, depression, sleep disturbance, or cognitive impairment) starting within 3 months of infection and persisting ≥1 month; no residual common cold symptoms
Exclusion criteria	Pre-existing bipolar disorder, major depression, anxiety disorder, schizophrenia, or dementia; vitamin D supplementation in past month; serum 25(OH)D >50 ng/mL; serum calcium >10.5 mg/dL; pregnancy or lactation; contraindications to vitamin D
Intervention Participants (n) Drop-outs (n)	Vitamin D: 60,000 IU oral vitamin D2 weekly for 8 weeks (total 480,000 IU). Regular phone check-ins for adherence. 40 0
Control Participants (n) Drop-outs (n)	Placebo: starch capsule weekly for 8 weeks. Regular phone check-ins for adherence. 40 2 (missing blood outcomes; questionnaire data complete)
Follow up time points	Baseline, 4 weeks, and 8 weeks (end of intervention) assessments (fatigue, anxiety, depression, sleep quality, cognitive tests, inflammatory markers)
Outcomes Measured	Primary: Changes in fatigue (CFQ-11), anxiety/depression (DASS-21), sleep quality (PSQI), cognition (ACE-III, TMT-A and TMT-B) Secondary: Adverse events
Results	**Coefficients of adjusted between-group differences at 8 weeks** **Primary outcomes** Fatigue (CFQ-11): Statistically significant reduction in favor of intervention group: –3.5 (p=0.024) Depression (DASS-depression): No statistically significant difference, –1.7 (p=0.085) Anxiety (DASS-anxiety): Significant reduction in favor of intervention group, –2.0 (p=0.011) Sleep quality (PSQI): No statistically significant difference, –1.2 (p=0.052) Cognition (ACE-III): Statistically significant improvement in favor of intervention group, 2.1 (p=0.012) Cognition (TMT-A/B): No statistically significant difference, –6.9 (p=0.161) **Secondary outcomes** Adverse events: The incidence of adverse events was comparable between the treatment and control groups, with no reports of any serious adverse events
Limitations Noted	Small sample size; short follow-up (8 weeks); predominance of young female participants; use of vitamin D2 (less potent than D3); subacute and chronic PCS phases mixed; generalizability limited
Risk of bias	Low

Chen et al. 2022

Author	Chen et al. [16]
Year	2022
Country	China
Study design Setting Population Follow up	RCT Secondary care setting Participants (mean age 54.16±12.11 years (intervention) and 52.51±12.31 years (control)) were enrolled while hospitalized but according to inclusion criteria their condition also met discharge standards. Unclear time since covid-10 infection, thus not fulfilling WHO criteria for post covid-19. Inclusion criteria involved presence of "Qi deficiency" according to traditional Chinese medicine. 12 weeks
Intervention Participants (n) Drop-outs (n)	Chinese medicine Bufei Huoxue capsules, 4 capsules 3 times daily for 90 days 64 7 (ITT-analysis was performed on 64)
Control Participants (n) Drop-outs (n)	Placebo in same regimen as describe above 65 6 (but ITT-analysis on 65)
Outcomes	**Note:** outcomes do not seem to be calculated on all participants **Primary outcome** 6-min Walk Distance, mean difference (95% CI): 34.2 (11.7–56.8) p=0.0022 in favour of tested intervention **Secondary outcomes** Fatigue score (FAI), mean difference (95% CI): 17.8 (–29.5 to –6.2), p=0.0019 in favour of tested intervention St George's Respiratory Questionnaire, mean difference (95% CI): No overall significant difference was found between the two groups –2.4 (–5.8 to 1.0) p=0.1148 Borg Dyspnea Score: No overall significant difference was found between the two groups –0.1 (–0.5 to 0.2) p= 0.4801 Chinese medicine symptom complex score: No overall significant difference was found between the two groups 0.4 (–0.4 to 1.3) p=0.4723 Additional outcomes reported
Comments	Possible that active treatment was distinguishable from placebo. Inclusion criteria included categorizations according to traditional Chinese medicine.
Risk of bias	Moderate

Chung et al. 2023

Author	Chung et al. [17]
Year	2023
Country	China
Study design Setting Population Follow up	RCT, open-label Home environment/outside health care setting Adults aged ≥18 years with confirmed diagnosis of covid-19 and with persistent (≥3 months) of olfactory disorder (median age 36 years (IQR 26.0–43.0), 56% female, 100% mild disease). 4 weeks
Intervention 1 Participants (n) Drop-outs (n)	Combination group: Short-course (14 days) oral Vitamin A (25,000 IU soft gels) daily, in combination with OT (sequential exposures to four aromatic essential oils (lemon; eucalyptus; geranium; and cedarwood) delivered via aerosolisation diffuser units, 3 times/day for 4 weeks). During OT, study participants received 20 s of odorant exposures from each category, achieving aromatic stimulation for 80 s per treatment session. 10 1
Intervention 2 Participants (n) Drop-outs (n)	Standard care: OT only, as described above 11 3
Control Participants (n) Drop-outs (n)	Control group: No intervention received during the study period 5 5
Outcomes	**Primary outcome** Clinical improvements of olfactory function (improvement defined as a 2-point increase in BTT scores, measured differences in SIT scores): At end-of-treatment (4 weeks), a statistically significant difference was seen in mean BTT scores between groups (p<0.001). Mean BTT scores were significantly higher for the combination group compared to control, and compared to standard care groups: p<0.001, MD=4.4 (95% CI, 1.7 to 7.2); and p=0.009, MD=3.2 (95% CI, 0.5 to 5.9). There were no differences in BTT scores between standard care and control groups (p=0.229, MD=1.3, 95% CI, –0.9 to 3.4 Intragroup comparisons of BTT scores between baseline and end-of-treatment MD (95% CI): Mean differences of BTT scores were significantly higher for the combination group compared to control; p=0.002, MD=3.3 (CI, 1.0 to 5.6), and standard care; p=0.012, MD=2.3 (CI, 0.3 to 4.2). No difference was seen in the MD of BTT scores between baseline and end-of-treatment. **Secondary outcome:** Smell identification (SIT): There was a statistically significant difference in mean SIT scores between groups (p=0.043) at end-of-treatment. In the intragroup comparison, SIT scores were significantly higher in the combination group after treatment (p =0.009), but no differences were found in the standard care or control groups.
Comments	Small study
Risk of bias	Moderate

D'Ascanio et al. 2021

Author	D'Ascanio et al. [18]
Year	2021
Country	Italy
Study design Setting Population Follow up	RCT Outpatient care Adults aged 18–90 (mean age 42±14.1, 66.7% female) with a confirmed history of covid-19 and anosmia/hyposmia persisting ≥90 days after negative covid-19 nasopharyngeal swab. Severity of acute covid-19 infection not stated. 30 days
Intervention Participants (n) Drop-outs (n)	Olfactory training/stimulation through Sniffin' Sticks (2/day for 10 min, for 30 days) and daily treatment with PEA/Luteolin oral supplement 5 0
Control Participants (n) Drop-outs (n)	Olfactory training/stimulation through Sniffin' Sticks (2/day for 10 min, for 30 days) 7 0
Outcomes	<u>Change over time (T0–T1) in Sniffin scores (mean change)</u> I: 4 C: 2 The scores statistically significant different at T0 (p=0.01), but no statistical difference shown after 30 days (T1). (KW: p = 0.01)
Risk of bias	Moderate

da Silva et al. 2025

Author	da Silva et al. [19]
Year	2025
Country	Brazil
Study design	Multicenter, pilot, randomised, single-blind, parallel-group trial
Setting	Two centers in Brazil (Neuroscience and Motor Control Laboratory; Rehabilitation Service of Uberlândia); home-based smartphone intervention
Population	Adults ≥18 years with long covid and mild–moderate functional impairment (PCFS 1–3). Mean age ~34–36 years.
Inclusion criteria	Age ≥18 years; long covid symptoms >12 weeks; PCFS 1–3; education >9 years; able to complete smartphone-based tests independently.
Exclusion criteria	Dementia; psychiatric illness; substance abuse; severe somatic disease; severe exercise intolerance; non-adherence; unrelated motor/cognitive impairment.
Interventions Participants (n) Drop-outs (n)	Moderate-intensity physical training combined with smartphone-based cognitive tasks 15 sessions (50 min), 3×/week for 5 weeks: 49 5
Control Participants (n) Drop-outs (n)	Same moderate-intensity physical training protocol via recorded videos, without cognitive tasks 49 12
Follow up time points	Baseline and post-intervention (5 weeks)
Outcomes Measured	Sensorial CogScore4, cognitive performance via smartphone app: reaction time, reaction quality, decision time, decision quality, attention, impulsivity control.
Results	**Per protocol analysis, ANOVA group x time interaction** <u>Reaction time:</u> F (1,79) =0.97; p=0.327; η^2=0.012 <u>Decision time:</u> F (1,79) =1.53; p=0.220; η^2=0.019 <u>Reaction quality:</u>

	F (1,79) =0.13; p=0.720; η^2=0.002 Decision quality: F (1,79) =5.96; p=0.017; η^2=0.070 MD: 12.27 p= 0.017 Attention: F (1,79) =0.52; p=0.475; η^2=0.006 Impulsivity control: F (1,79) =0.12; P=0.734; η^2=0.001 Additional outcomes reported
Limitations Noted	Per protocol analysis; pilot sample size; short follow-up; no no-intervention control; expectation effects not controlled; limited assessment of far-transfer effects.
Risk of bias	Moderate

Dal Negro et al. 2022

Author	Dal Negro et al. [20]
Year	2022
Country	Italy
Study design Setting Population Follow up	RCT Cross-over Outpatient care Adults aged ≥18 years (mean age: 50.5±17.2 years, 62.5% female) with persistent dyspnea for 12–16 weeks after being defined “recovered” for covid-19 pneumonia One week after treatment
Intervention Participants (n) Drop-outs (n)	Nebivolol 2.5 mg once daily 8+8 (cross-over) 0
Control Participants (n) Drop-outs (n)	Placebo once daily 8+8 (cross-over) 0
Outcomes	Several clinical and lung function variables were investigated Nebivolol, but not placebo, improved: Pre post Vital capacity (44.1±8.6 vs. 51.9±9.0), p=0.003 Dyspnea score (2.5±0.8 vs. 0.6±0.3), p= 0.001 Additional outcomes reported
Comments	Small study
Risk of bias	Moderate

Daynes et al 2025

Author	Daynes et al. [21]
Year	2025
Country	United Kingdom
Study design	Single-blind, three-arm randomised controlled trial
Setting	University of Leicester and Northumbria University; specialist outpatient post-covid clinics
Population	Adults ≥18 years, previously hospitalised with covid-19; n=181 randomised; mean age 59; 55% male;
Inclusion criteria	≥18 years; hospitalised with confirmed covid-19; symptoms >12 weeks; functional impairment; diagnosed with post-covid-syndrome
Exclusion criteria	Contraindications to exercise; suspected alternative diagnoses (e.g., severe PEM/PESE, POTS); unstable comorbidities; completed rehab in prior 6 months
Intervention Participants (n) Drop-outs (n)	Face-to-face rehabilitation, twice weekly for 8 weeks including exercise, education and self-management strategies 56 11
Intervention Particpiants (n) Drop-outs (n)	Remote rehabilitation for 8 weeks, including exercise and self-directed symptom management advice 63 17
Control Participants (n) Drop-outs (n)	Usual care, individually tailored without exercise rehabilitation 62 2
Follow up time points	Baseline and 8 weeks post-intervention
Outcomes Measured	<u>Primary:</u> Incremental Shuttle Walking Test (ISWT) change <u>Secondary:</u> SPPB, 4-m gait speed, quadriceps strength, handgrip strength, EQ-5D-5L, PHQ-9, GAD-7, FACIT-FS, MoCA, DePaul Symptom Questionnaire, Dyspnoea-12, BPI
Results	Adjusted for age, sex, BMI, time since hospitalization, number of comorbidities, WHO severity index and recruiting site **Face to face rehabilitation vs usual care (n=56 vs n=63)** <u>ISWT,meter, mean (95% CI)</u> 52 (19 to 85) <u>SPPB, median (IQR)</u> 1.2 (–0.01 to 2.38) <u>4 MGS, ms^{-1}, mean (95% CI)</u> 0.12 (0.02 to 0.21) <u>Handgrip strength, kg, mean (95% CI)</u> 2.06 (0.07 to 4.18) <u>QMVC, kg, mean (95% CI)</u> 3.33 (–0.55 to 7.10) <u>EQ-5D-5L, utility index, mean (95% CI)</u> –0.02 (–0.11 to 0.07) <u>EQ-5D-5L, thermo-meter (VAS), mean (95% CI)</u> –1.08 (–7.65 to 5.46) <u>PHQ-9, mean (95% CI)</u> –0.41 (–1.08 to 1.91) <u>GAD-7 severity score, mean (95% CI)</u>

	–0.56 (–2.07 to 0.96) MoCA, mean (95% CI) 0.15 (–0.82 to 1.10) FACIT-FS, mean (95% CI) 2.93 (–0.31 to 6.16) Dyspnoea-12, mean (95% CI) –2.11 (–4.33 to 0.13) DSQ frequency, mean (95% CI) 1.05 (–7.00 to 7.11) DSQ severity, mean (95% CI) 0.22 (–1.43 to 1.88) **Remote rehabilitation vs usual care, n=62 vs n=63** ISWT, meter, mean (95% CI) 34 (1 to 66) SPPB, median (IQR) 1.5 (0.27 to 2.66) 4 MGS, ms^{-1}, mean (95% CI) 0.04 (–0.05 to 0.14) Handgrip strength, kg, mean (95% CI) –0.62 (–2.72 to 1.50) QMVC, kg, mean (95% CI) 3.35 (0.43 to 7.10) EQ-5D-5L, utility index, mean (95% CI) –0.05 (–0.14 to 0.04) EQ-5D-5L, thermo-meter, mean (95% CI) 0.97 (–7.38 to 5.73) PHQ-9, mean (95% CI) –0.52 (–1.02 to 2.02) GAD-7 severity score, mean (95% CI) –0.52 (–2.09 to 1.02) MoCA, mean (95% CI) 0.81 (–0.16 to 1.79) FACIT-FS, mean (95% CI) –1.75 (–4.97 to 1.57) Dyspnoea-12, mean (95% CI) 1.68 (–4.00 to –0.55) (SBU Comment: –1.68; the reported value of 1.68 appears to be a typo) DSQ frequency, mean (95% CI) –5.72 (–13.73 to 2.13) DSQ severity, mean (95% CI) –0.6 (–2.24 to 1.02)

Limitations Noted	Only hospitalised during acute Covid population; baseline differences due to access-based randomisation; some digital exclusion; no long-term follow-up; HRQoL tools may be insensitive; small immune substudy sample.
Risk of bias	Moderate

del Corral et al. 2023

Author	del Corral et al. [22]
Year	2023
Country	Spain
Study design Setting Population Follow up	RCT, with four groups Home based training Adult covid-19 survivors (71.6% female, 31.8% admitted to hospital, 5.7% admitted to ICU) with symptoms of fatigue and dyspnea for ≥2 months after covid-19 infection. 4, and 8 weeks post intervention. Only results of post intervention (8 weeks) tabulated.
Intervention Participants (n) Drop-outs (n)	Two groups of homebased inspiratory respiratory OR inspiratory and expiratory (device with resistance) training 40 min/day (split in 20-minute sessions) 6 times a week for 8 weeks. 22 + 22 1 + 1 in each group
Control Participants (n) Drop-outs (n)	Two groups of homebased SHAM (device without resistance) inspiratory respiratory OR inspiratory and expiratory training 40 min/day (split in 20-minute sessions) 6 times a week for 8 weeks. 22 + 22 1 +1 in each group
Outcomes	**Group x time interaction, mixed way ANOVA. Change from baseline values** <u>Health related quality of life (EQ-5D) with VAS of overall health:</u> There were statistically significant interactions between the time and group factors for HRQoL outcomes [EQ-5D-5L, index (F=2.459; p=0.031; h2=0.081) and VAS (F=3.373; p=0.004; h2 =0.108)] <u>Exercise tolerance:</u> There were no statistically significant interactions between the time and group factors for exercise tolerance. There were no statistically significant between-group differences for exercise tolerance. <u>Lung function:</u> The only lung function variable that showed a statistically significant group x time interaction was peak expiratory flow (PEF; F=3.612; p=0.003; h2 =0.114). <u>Cognitive and psychological status:</u> There were no statistically significant interactions between the time and group factors for the cognitive and psychological status outcomes Additional outcomes reported
Risk of bias	Low

Del Corral et al. 2025

Author	del Corral et al. [23]
Year	2025
Country	Spain
Study design	Randomised controlled trial (parallel, double-blind)
Setting	University Hospital 12 de Octubre, Madrid, Spain (Rehabilitation Department and Post-Covid Rehabilitation Unit)
Population	64 adults (mean age ~50 years; 64% female) with long-term post-covid-19 symptoms (fatigue, dyspnoea) persisting ≥3 months post-infection
Inclusion criteria	≥18 years old; confirmed SARS-CoV-2 by PCR; long-term post-covid symptoms ≥3 months; fatigue and dyspnoea;
Exclusion criteria	Underlying cardiopulmonary, neuromuscular, neurological, psychiatric, or cognitive conditions; contraindications to exercise; previous rehabilitation participation; lack of internet access
Intervention Participants (n) Drop-outs (n)	AE+RMT: 8-week aerobic exercise (50 min/session, 2×/week) plus home-based respiratory muscle training (3×/week, 40 min/session) with real device 32 2
Control Participants (n) Drop-outs (n)	AE+RMTsham group: same aerobic exercise plus sham RMT device. 32 3
Follow up time points	Baseline and 8 weeks post-intervention (end of program) assessments
Outcomes Measured	Primary: Health-related quality of life (EQ-5D-5L) and exercise tolerance (CPET; peak VO2) Secondary: Respiratory muscle strength (MIP, MEP, IME); lung function (spirometry, (DLCO); peripheral muscle strength (1-min (STS), handgrip), psychological status (HADS anxiety/depression)
Results	**Adjusted between-group difference at 8 weeks (95%CI); Cohen's d** **Primary outcomes** Health-related quality of life (EQ-5D-5L, index): No statistically significant difference 0.06 (−0.01 to 0.13); d=0.3 Health-related quality of life (EQ-5D-5L, VAS): No statistically significant difference 6.35 (−1.3 to14.0); d=0.4 Exercise tolerance (CPET; peak VO2): No statistically significant difference 0.4 (−0.5 to 1.3); d=0.2 **Secondary outcomes** Respiratory muscle strength (MIP): Statistically significant improvement in favor of intervention group 17.9 (10.4 to 25.4); d=1.2 Respiratory muscle strength (MEP): Statistically significant improvement in favor of intervention group 29.4 (17.7 to 41.1); d=1.3 Respiratory muscle strength (IME): Statistically significant improvement in favor of intervention group 9.0 (3.0 to 15.0); d=0.7 Lung function (spirometry): No statistically significant differences (FEV, FVC, FEV/FVC)

	(except for peak expiratory flow (PEF) which showed a statistically significant improvement in favor of intervention group, 0.6 (0.02 to 1.3); d=0.4) Peripheral muscle strength (1-min STS): No statistically significant differences 1.6 (−1.3 to 4.5); d=0.3 Peripheral muscle strength (handgrip): No statistically significant differences −0.2 (−2.2 to 1.8); d=0.1 Psychological status, anxiety (HADS-Anxiety): No statistically significant differences −0.04 (−1.5 to 1.4); d=0.1 Psychological status, depression (HADS-Depression): No statistically significant differences −0.2 (−1.5 to 1.2); d=0.1 Psychological status, distress (HADS-Total): No statistically significant differences) −0.3 (−2.7 to 2.2); d=0.1
Limitations Noted	Short duration (8 weeks); small sample size; single-center; limited generalizability to children or elderly; partial unblinding in some participants; no long-term follow-up
Risk of bias	Low

Di Stadio et al. 2022

Author	Di Stadio et al. [24]
Year	2022
Country	Italy
Study design Setting Population Follow up	RCT, multicenter, double-blind Self-administrated rehabilitation Outpatients aged 18–80 (65.4 % female, mean age 43.5 years) with confirmed history of covid-19 and anosmia/hyposmia persisting ≥ 6 months (confirmed with extended version of Sniffin' Sticks psychophysical test). No data provided on previous possible hospitalisation due to covid-19. 90 days
Intervention Participants (n) Drop-outs (n)	Daily treatment with oral supplement (PEA 700 mg + Lut 70 mg) as single dose, 5-10 minutes before breakfast plus olfactory training. Olfactory training entailed stimulation (Lemon, Rose, Eucalyptus, Cloves) 3 times per day for 6 minutes. 130 0
Control Participants (n) Drop-outs (n)	Olfactory training as noted for the intervention group + a daily placebo supplement therapy 55 0
Outcomes	Group comparisons Pre- and post- TDI scores (ANOVA): p<0.00001, F=13.23 – statistically significant differences Likelihood of recovery to normal TDI score (>31) at T3 (chi-square): Statistically significant differences favouring the intervention group, 56% resp. 10% respectively (p<0.00001). Only comparative results reported here. See study for more results from within the intervention- and control group.
Risk of bias	Moderate

Di Stadio et al. 2023

Author	Di Stadio et al. [25]
Year	2023
Country	Italy
Study design Setting Population Follow up	RCT, multicenter, double-blind study with four groups, one as active control Outpatient treatment Outpatients aged 18–80 (mean age 37–42 years, apx 59% female) with confirmed history of covid-19 and anosmia/hyposmia persisting ≥ 6 months (confirmed with extended version of Sniffin' Sticks psychophysical test). No data provided on previous possible hospitalisation due to covid-19. 90 days
Intervention Participants (n) Drop-outs (n)	3 groups: 1: Olfactory training + oral supplement (PEA 700 mg + Lut 70 mg) single dose once daily 2: Oral supplement (PEA 700 mg + Lut 70 mg) single dose once daily. No olfactory training 3: Oral supplement (PEA 700 mg + Lut 70 mg) single dose twice daily. No olfactory training Group 1: 100 Group 2: 50 Group 3: 50 Group 1: 24 Group 2: 2 Group 3: 10
Control Participants (n) Drop-outs (n)	Olfactory training as noted for the intervention group + a daily placebo supplement therapy 50 12
Outcomes	<u>Group comparisons:</u> Outcomes based on Snifn' Sticks identification test scores where patients were classified as having subclinical recovery (<3 points), clinically significant recovery (≥3 points), unchanged (0-point change), or worsened (≥1 point decrement) Combined therapy (umPEA–LUT + olfactory training group) resulted in significantly more recovery than the other regimens ($\chi 2$: $p < 0.00001$) Improvements of ≥3 points where observed in 89.2% (50 patients; double weighted in randomisation) receiving combined therapy group, 41.6% (20 patients) receiving um-PEA–LUT alone—once daily, 40% (16) patients) receiving um-PEA–LUT alone—twice daily, and 36.8% (14 patients) receiving olfactory training plus placebo
Comments	Analyses based only on participants with full follow-up data
Risk of bias	Moderate

Duffy et al. 2024

Author	Duffy et al. [26]
Year	2024
Country	USA
Study design	Randomised controlled trial (single-blinded)
Setting	Thomas Jefferson University Hospital and Monell Chemical Senses Center, Philadelphia, Pennsylvania, USA
Population	83 adults (mean age 50 ± 15 years; 71% female) with persistent olfactory dysfunction (OD) ≥6 months post-covid-19
Inclusion criteria	Adults ≥18 years; covid-19 positive (PCR or at-home test); OD duration ≥6 months; BSIT ≤8/12 or SCENTinel ≤40/100%
Exclusion criteria	Pre-existing OD (trauma, iatrogenic, idiopathic); active rhinosinusitis; skull-base tumors; malignancies; coagulopathies; thrombocytopenia; antiplatelet/blood thinning medication; nasal surgery during study period; pathology leading to obstruction of olfactory cleft
Intervention Participants (n) Drop-outs (n)	PRP group: three monthly topical applications of platelet-rich plasma (PRP)-coated Surgifoam to bilateral olfactory clefts 42 0
Control Participants (n) Drop-outs (n)	Placebo group: identical protocol using saline-coated Surgifoam 43 2
Follow up time points	Baseline; monthly assessments during 3 months of treatment; remote monthly follow-up from months 4 to 12
Outcomes Measured	<u>Primary:</u> Change in BSIT scores <u>Secondary:</u> SCENTinel odor intensity and Questionnaire of Olfactory Disorders—Negative Statements (QOD-NS) for quality of life
Results	I: n=42 C: n=41 <u>Smell identification (changes in BSIT scores from baseline):</u> PRP-group experienced a significant increase in scores compared to placebo from month 1 to months 5, 6, 7, 8, 9, and 12 ($p < 0.05$ for all) <u>Smell identification (total BSIT scores):</u> Despite a greater improvement in BSIT scores from baseline, total BSIT scores were similar between the two groups throughout the study ($p = 0.264$) <u>Odor intensity (SCENTinel odor intensity):</u> No significant differences between groups over time or from baseline ($p > 0.05$) <u>Quality of life (change in QOD-NS from baseline):</u> No statistically significant difference between groups <u>Adverse events:</u> None observed
Limitations Noted	Use of BSIT (lower fidelity than Sniffin Sticks); subjective SCENTinel measures; significant attrition during remote follow-up; short follow-up period; small sample size; lack of threshold/discrimination testing
Risk of bias	Moderate

Dwiputra et al. 2024

Author	Dwiputra et al. [27]
Year	2024
Country	Indonesia
Study design	Randomised controlled trial (single-blind)
Setting	National Cardiovascular Center Harapan Kita (NCCHK), Jakarta, Indonesia
Population	46 adults with long covid and cardiovascular comorbidities; mean age ~55 years; 52% male; symptoms persisting >30 days post-covid-19 diagnosis
Inclusion criteria	History of positive covid-19 infection confirmed by a PCR test; persistent symptoms ≥30 days; cardiovascular comorbidities (hypertensive heart disease, coronary artery disease (CAD), heart failure, congenital heart disease, post-operative cardiac surgeries)
Exclusion criteria	Chronic obstructive pulmonary disease, stroke, severe musculoskeletal impairment (e.g., fracture, amputation, severe lower extremity arthritis)
Intervention Participants (n) Drop-outs (n)	Intervention group: Home-based breathing and chest mobility exercises 3×/week for 12 weeks plus home-based cardiac rehabilitation (brisk walking 5×/week, 30 min). 23 1
Control Participants (n) Drop-outs (n)	Control group: Home-based cardiac rehabilitation only (brisk walking 5×/week, 30 min). 23 2
Follow up time points	Baseline and post-intervention (12 weeks) assessments
Outcomes Measured	Primary: Cardiorespiratory functional capacity (6-MWT; PEFR; PCF; predicted VO2 peak) Secondary: EuroQoL
Results	**Between-group difference (95% CI) at 12 weeks** **Primary outcomes:** Cardiopulmonary functional status 6-MWT distance: Statistically significant improvement in favor of intervention group 52.39 (4.81 to 99 96) PEFR, L/min: Statistically significant improvement in favor of intervention group 91.30 (8.61 to 173.99) PCF, L/min: Statistically significant improvement in favor of intervention group 99.56 (19.91 to 179.21) Predicted VO2 peak, mUkg/min: No statistically significant difference between groups **Secondary outcomes:** Quality of life (EuroQoL score, %): No statistically significant difference between groups Major cardiovascular events: None observed related to the study Adverse effects: None observed related to the study Additional outcomes reported
Limitations Noted	Remote monitoring limited exercise supervision; VO2 peak were estimated, not measured via CPET; resource constraints; single-center; modest sample size
Risk of bias	Moderate

Elgayar et al. 2025

Author	Elgayar et al. [28]
Year	2025
Country	Egypt
Study design	Parallel-group, single-center, prospective, randomised controlled trial
Setting	Physical therapy unit, Al Mahalla Al Kobra Chest Hospital, Egypt
Population	Men aged 40–60 years with chronic post-covid-19 pulmonary fibrosis (PC19-PF)
Inclusion criteria	Male sex; age 40–60 years; mild–moderate PC19-PF (grade 1–3); moderate-to-severe prior covid-19 (WHO-CPS 4–9); fibrosis >6 months; MRC dyspnea grade 1–3; BMI 18.5–29.9 kg/m²
Exclusion criteria	Other chronic chest disease; unstable cardiovascular disease; smoking; oxygen therapy; neurological or musculoskeletal disorders affecting exercise; other medical contraindications
Intervention Participants (n) Drop-outs (n)	AE + DBE: treadmill aerobic exercise (30–45 min, 55–70% HRmax) + diaphragmatic breathing, 3×/week for 12 weeks 20 1
Intervention Participants (n) Drop-outs (n)	RE + DBE: resistance exercises at 55–65% 1RM + diaphragmatic breathing, 3×/week for 12 weeks 20 0
Intervention Participants (n) Drop-outs (n)	AE/RE + DBE: combined aerobic (55–70% HRmax) and resistance (55–65% 1RM) exercise + DBE, 3×/week for 12 weeks 20 0
Control Participants (n) Drop-outs (n)	Diaphragmatic breathing exercise only 20 1
Follow up time points	Baseline and post-intervention (12 weeks)
Outcomes Measured	<u>Primary:</u> Ventilatory function (FVC, DLCO) <u>Secondary:</u> Fibrosis grade (CT), exercise capacity (estimated VO_2max), dyspnea (MRC scale), quality of life (SF-12 PCS and MCS)
Results	**AE + DBE vs control, MD (95% CI):** <u>FVC (%):</u> 5.1 (1.1 to 9.1) <u>Est VO_2max:</u> 13.9 (8.4 to 19.4) <u>MRC:</u> –1.2 (–1.9 to –0.5) <u>SF-12, PCS:</u> 7.4 (2.9 to 12) <u>SF-12, MCS:</u> 8 (3 to 13) **RE + DBE vs control, MD (95% CI)** <u>FVC (%):</u> –0.2 (–4.1 to 3.7) <u>Est VO_2max:</u> 4.4 (1 to 9.9) <u>MRC:</u> –0.5(–0.9 to –0.1)

	SF-12, PCS: 3.5 (1 to 8) SF-12, MCS: 4.2 (0.7 to 9.2) **AE/RE + DBE vs control, MD (95% CI)** FVC (%): 3.3 (0.6 to 7.3) Est VO_2max: 9.1 (3.6 to 14.6) MRC: –1 (–1.9 to –0.2) SF-12, PCS: 7.4 (2.8 to 11.9) SF-12, MCS: 8.4 (3.3 to 13.4)
Limitations Noted	Male-only sample; single-center design; assessors not blinded for some outcomes; VO_2max estimated rather than directly measured; short-term follow-up only.
Risk of bias	Moderate

Elhamrawy et al. 2023

Author Year Country	Elhamrawy et al. [29] 2023 Egypt
Study design Setting Population Follow up	RCT, 3-arm Supervised exercise sessions Adults aged ≥60 years (mean age 65.7±3.6 (I1), 66.2±3.8 (I2) and 66.3±4 (control), 35.2% female) with covid-19 with mild-to-moderate symptoms according to PCFS; 18 ≥3 months post-recovery Post-treatment
Intervention 1 Participants (n) Drop-outs (n)	Four 60-minute sessions of Tai Chi exercises weekly for 12 weeks 18 0
Intervention 2 Participants (n) Drop-outs (n)	Four supervised 60-minute aerobic training sessions weekly for 12 weeks 18 0
Control Participants (n) Drop-outs (n)	Maintaining their usual ADLs 18 0
Outcomes	Hand grip strength, mean difference (SE) in kg between groups Tai Chi vs control: –5.7 (1.2), p= 0.0001 Aerobic training vs control: –3.2 (0.7), p= 0.0001 Tai Chi vs aerobic training: –2.5 (1.2), p=0.0435 Fatigue severity scale, mean difference (SE) between groups Tai Chi vs control: 4.8 (1.4), p= 0.001 Aerobic training vs control:

	6 (1.2), p= 0.0001 Tai Chi vs aerobic training: –1.2 (1), p=0.2491 <u>30-second arm curls test, mean difference (SE) in number of repetitions between groups</u> Tai Chi vs control: –4.3 (0.5), p= 0.0001 Aerobic training vs control: –5.3 (0.3), p= 0.0001 Tai Chi vs aerobic training: 1 (0.4), p= 0.0235 <u>30-second chair stands test, mean difference (SE) in number of repetitions between groups:</u> Tai Chi vs control: –4 (0.4), p= 0.0001 Aerobic training vs control: –4.4 (0.5), p= 0.0001 Tai Chi vs aerobic training: 0.4 (0.4), p= 0.3618 <u>8-Foot up and go test, mean difference (SE):</u> Tai Chi vs control: 1.1 (0.2), p= 0.0001 Aerobic training vs control: 1 (0.2), p= 0.0001 Tai Chi vs aerobic training: 0.1 (0.2), p= 0.6021 <u>2-minute step test, mean difference (SE) in number of steps between groups:</u> Tai Chi vs control: –7.8 (1.8), p= 0.0001 Aerobic training vs control: –6.4 (1.3), p= 0.0001 Tai Chi vs aerobic training: –1.3 (1.8), p=0.4689
Risk of bias	Low

Espinoza-Bravoet al. 2023

Author	Espinoza-Bravo et al. [30]
Year	2023
Country	Spain
Study design Setting Population Follow up	RCT Home-based exercise programmes instructed by a mobile phone application Adults aged 20–60 years (mean age 42.4 (SD 6.5) years; 79.1 % women) having a diagnosis of covid-19 confirmed by PCR or an antigen test, the presence of at least 1 of certain persistent symptoms (fatigue, dyspnea, or functional limitation) for at least 6 weeks after infection, n=48 8 weeks
Intervention Participants (n) Drop-outs (n)	Functional exercise programme consisting of low-intensity strengthening exercise protocol for large muscle groups with increasing difficulty, 4–6 exercises per session, 25–40 minutes per week for 8 weeks. 24 3
Control Participants (n) Drop-outs (n)	Aerobic exercise programme consisting of a progressive low-intensity walking protocol with weekly load adjustments, 25–45 minutes per week for 8 weeks 24 2
Outcomes	**Primary outcome at post-intervention, pre-post MD (95% CI)** <u>Fatigue (FAS):</u> AE: −5.1 (−10.3 to 0.1) FE: −6.7 (−11.9 to −1.3) ns **Secondary outcomes:** <u>Activities of daily living (LCADL):</u> AE: −5.6 (−11.4 to 0.2) FE: −0.9 (−4.9 to 6.7) ns <u>30s standing test (repetitions):</u> AE: 1.2 (−1.0 to 3.4) FE: 2.6 (0.3 to 4.9) ns <u>Stress, PSS</u> AE: −6.2 (−10.3 to −2.1) FE: −4.9 (−9.1 to 0.8) ns <u>Depression (HADS-D):</u> AE: −2.0 (−4.8 to 0.4) FE: −0.5 (−3.0 to 2.0) ns <u>Anxiety (HADS-A):</u> AE. −1.0 (−3.1 to 1.2) FE: −0.1 (−2.3 to 2.1) ns <u>Quality of life (EQ-5D-5L):</u> AE: 0.1 (−0.1 to 0.2) FE: 0.1 (−0.2 to 0.2) ns <u>Global impression of change (PGIC), mean (SE):</u> AE: 4.0 (1.1) FE: 3.1 (1.5) P= 0.042, favouring FE

Comments	Not completely fulfilling the WHO criteria but an average of 17.4 months had passed since infection in the sample
Risk of bias	Moderate

Fan et al. 2021

Author	Fan et al. [31]
Year	2021
Country	China
Study design Setting Population Follow up	RCT, single-blind Online/mobile phone intervention and counselling clinic at hospital covid-19 patients (mean age 46±12.34 years, 62% female, 79% with mild symptoms) near discharge stage from hospital with positive screening results for posttraumatic stress symptoms (PTSS) Not fulfilling WHO criteria for post covid-19 (long covid) but sufficiently long follow-up. 6 months
Intervention Participants (n) Drop-outs (n)	Narrative exposure therapy (NET, Schauer et al., 2011) and personalised psychological treatment. NET for 1–2 sessions/week for 8 weeks, 90~120 min 56 0
Control Participants (n) Drop-outs (n)	Personalised psychological interventions based on the participants' symptoms (1 session/week, 40-60 min) 55 0
Outcomes	Effect of NET on PTSS (PCL-C) (time x group interaction, rm ANOVA): PCL-C: significant ($F_{1,109}$=36.300, p<0.001), effect size: 0.143 (ηp 2) Effect of NET on depression (SDS), anxiety (SAS), and sleep quality (PSQI), (time x group interaction, rm ANOVA): SDS: not significant ($F_{1,109}$=0.957, p=0.329), effect size: 0.004 (ηp 2) SAS: not significant ($F_{1,109}$= 0.740, p=0.390), effect size: 0.003 (ηp 2) PSQI: not significant ($F_{1,109}$=0.124, p=0.011), effect size: 0.011 (ηp 2)
Risk of bias	Moderate

Farrell et al. 2025

Author	Farrell et al. [32]
Year	2025
Country	USA
Study design	Single-center, randomised, double-blind, placebo-controlled clinical trial
Setting	Washington University in St Louis USA
Population	Adults aged 18–70 years with persistent covid-19–induced parosmia ≥6 months after infection. 57 enrolled; 48 randomised (SGB n=32; placebo n=16). Median age 45 years; 81% female. 47 completed 1-month follow-up; 46 completed 3-month follow-up.
Inclusion criteria	Age 18–70 years; covid-19 infection ≥6 months prior; self-reported parosmia; English proficiency; screening DisODOR score ≥40 and ≥25 at injection visit.
Exclusion criteria	Pre-COVID olfactory dysfunction; conditions affecting olfaction or nerve function; current olfactory therapies; contraindications to stellate ganglion block; prior SGB; anticoagulant use; allergy to local anesthetics.
Intervention Participants (n) Drop-outs (n)	SGB: ultrasound-guided unilateral stellate ganglion block with 6–8 mL mepivacaine 1% 32 2
Control Participants (n) Drop-outs (n)	Saline injection 16 0
Follow up time points	Baseline; 1 month; 3 months post-injection
Outcomes Measured	Primary: Proportion of responders (≥15-point decrease in DisODOR score) Secondary: DisODOR change; CGI-I and CGI-S; UPSIT; olfaction catastrophizing (OCS); anxiety and depression (HADS); long-COVID symptoms (LCQ); treatment satisfaction; safety
Results	**3 months post-injection** Proportion difference between groups (95% CI) Responders: –6 (–32 to 23) CGI smell loss: Slightly to much better: –6 (–32 to 23) About the same: 19 (–10 to 44) Slightly to much worse: –13 (–30 to 8) Median difference between groups (95% CI) DisODOR: –1.0 (–14 to 17) LCQ total: 0.0 (–5 to 1) OCS score: 1.0 (–7 to 8) HADS anxiety: 0.0 (–2 to 4) HADS depression: 1.0 (–2 to 4)

Limitations Noted	Per protocol-analysis; early termination due to futility; smaller sample than planned; strong placebo response; single-center design; reliance on patient-reported outcomes; lack of objective parosmia measures.
Risk of bias	Moderate

Fernandez et al. 2025

Author	Fernandez et al. [33]
Year	2025
Country	Belgium
Study design	Randomised controlled trial (parallel two-group design) evaluating psychoeducational interventions for cognitive complaints in long covid
Setting	University and hospital centers in Belgium (Université de Liège, Université Libre de Bruxelles, and associated clinical departments).
Population	Adults with long covid experiencing cognitive complaints. 130 randomised. 122 included in analysis (63 cognitive intervention; 59 affective intervention). Mean age 47 ± 10 years; 69.7% female.
Inclusion Criteria	Aged between 18 and 70, reported cognitive complaints (top 20% of dissatisfied functioning on the BRIEF-A (Behaviour Rating Inventory of Executive Function) or MMQ (Multifactorial Memory Questionnaire) questionnaires), they have poor objective performance and at least one SARS-CoV-2 infection at least 3 months prior to study confirmed by a PCR, antigen test or by a healthcare professional.
Exclusion Criteria	Individuals with pre-existing neurological, cognitive or psychiatric disorders were excluded.
Intervention Participants (n) Drop-outs (n)	Cognitive-focused psychoeducation group; four 90-minute psychoeducational sessions. 65 2
Intervention Participants (n) Drop-outs (n)	Affective-focused psychoeducation group: four 90-minute psychoeducational sessions 65 6
Follow-up Timepoints	Baseline, 2 months post-intervention, and 8 months post-intervention.
Outcomes Measured	<u>Primary:</u> Subjective cognitive complaints; Behaviour Rating Inventory of Executive Function (BRIEF-A) and Multifactorial Memory Questionnaire (MMQ) <u>Secondary:</u> RBANS (Repeatable Battery for the Assessment of Neuropsychological Status), BVMT-R (Brief Visuospatial Memory Test Revised), TAP (Test of Attentional Performance), D2-R, Stroop, Brown-Peterson and fluency tasks, MFIS-21, PSQI, OQ-45 QLSI, EQ-5D-5L, WPAI
Results	2 months post intervention <u>BRIEF:</u> AI: 133.9 (±28.3) CI: 134.6 (±23.5) <u>MMQ composite score:</u> AI: 99.8 (±25) CI: 105.2 (±20.8)
Limitations Noted	Relatively short intervention (four sessions); improvements may require longer treatment; lack of untreated control group; reliance partly on self-reported outcomes.
Risk of bias	Moderate

Figueiredo et al. 2024

Author	Figueiredo et al. [34]
Year	2024
Country	Brazil
Study design Setting Population	RCT, double-blind Outpatient care, self-administration Adults aged 18–65 years (I: mean age 38.2 ± 11.3 years, 79.6% female; C: mean age 39.9 ± 13.3 years, 84.3% female) with previous confirmed SARS-CoV-2 infection (I: 93.9% mild disease; C: 93.9% mild disease) and olfactive disorder lasting ≥3 months, as well as smell loss confirmed by CCCRC test score <6.0 12 weeks
Intervention Participants (n) Drop-outs (n)	Olfactory training (kit with 4 odorants (rose, eucalyptus, lemon, cloves) to be sniffed twice a day for apx 10 s each) + alpha-lipoic acid: 300 mg tablet twice a day 64 15
Control Participants (n) Drop-outs (n)	Olfactory training as above + placebo 64 13
Outcomes	Olfactory function (CCCRC score, mean±SD) I (n=49): 2.7±1.5 (baseline) 4.6±1.3 (12 weeks) p-value (within group) <0.001 C (n=51): 2.9±1.4 (baseline) 4.3±1.6 (12 weeks) p-value (within group) <0.001 p-value between groups: p=0.63 Olfactory function (VAS score, median [IQR] I (n=49): 2.5 [0–5] (baseline) 6 [4–8] (12 weeks) p-value (within group) < 0.001 C (n=51): 3 [1–5] (baseline) 6.5 [5–8] (12 weeks) p-value (within group) < 0.001 p-value between groups: p=0.97
Risk of bias	Moderate

Finnigan et al. 2023

Author Year Country	Finnigan et al. [35] 2023 United Kingdom
Study design Setting Population Follow up	RCT, double-blind Outpatient care, self-administration Adults aged 18–64 years (43.6 years, range 24–56; 68% female) with fatigue-dominant long covid (total fatigue (bimodal) score of ≥8 on CFQ-11) and post-exertional skeletal muscle phosphocreatine recovery rate constant [τPCr] >50 s 28 days post start of treatment
Intervention Participants (n) Drop-outs (n)	Oral AXA1125 (an endogenous metabolic modulator) 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 h between consecutive doses 21 0
Control Participants (n) Drop-outs (n)	Placebo administered in the same way as the active substance 20 0
Outcomes	Primary outcome was change in phosphocreatine rate – not tabulated here **Other outcomes** <u>CFQ-11 Total fatigue Likert score (range 0–33) at 28 days, change from baseline, mean (SD):</u> I: –5.25 (5.49) C: –2.25 (2.92) Least square MD (95% CI): –4.30 (–7.14 to –1.47), p=0.0039 <u>6-minute walk test (MWT) distance in meters, mean (SD)</u>: I: 25.57 (54.0) C: 25.3 (12.1) p>0.05 (ns) (MD not reported) <u>Adverse events, number of patients:</u> I: 11 (52%) C: 4 (20%)
Comments	Industry-funded study with some of the authors being employed and having options in the funding company
Risk of bias	Low

Geng et al. 2024

Author	Geng et al. [36]
Year	2024
Country	USA
Study design	Randomised controlled trial (double-blind, placebo-controlled)
Setting	Stanford University, USA
Population	155 adults with post-acute sequelae of SARS-CoV-2 infection (PASC); mean age ~45 years; females 59%; diverse demographic (Asian, Black, Hispanic, White); symptomatic ≥3 months post-covid
Inclusion criteria	Adults ≥18 years; with confirmed prior SARS-CoV-2 infection; persistent symptoms consistent with PASC; symptoms lasting ≥3 months post-infection; weight greater than 40 kg; estimated glomerular filtration rate of 60 mL/min or higher
Exclusion criteria	Pregnancy or breastfeeding; severe liver disease; SARS-CoV-2 infection, and use of SARS-CoV-2-specific treatment within 30 days of randomisation; SARS-CoV-2 vaccination within 28 days, or other vaccine within 14 days of randomisation, or medications that interact with study drug
Intervention Participants (n) Drop-outs (n)	Nirmatrelvir-ritonavir: 300 mg nirmatrelvir + 100 mg ritonavir twice daily for 15 days 102 4
Control Participants (n)	Placebo: matching placebo regimen + 100 mg ritonavir twice daily for 15 days. 53

Drop-outs (n)	4
Follow up time points	Baseline, and thereafter at several time points until 10 weeks post-randomisation
Outcomes Measured	Primary: Change in pooled PASC symptom severity scores (fatigue, brain fog, body aches, cardiovascular symptoms, shortness of breath, gastro-intestinal symptoms) at 10 weeks measured using Likert scales from 0 to 3 Secondary: Symptom severity at different time points, symptom burden and relief, patient global measures, Patient-Reported Outcomes Measurement Information System (PROMIS) measures, sit-to-stand test change from baseline, PGIS and PGIC. Safety: adverse events
Results	**Primary outcome** Change in pooled PASC symptom severity scores at 10 weeks: No statistically significant difference between groups at 10 weeks, adjusted for baseline severity **Secondary outcomes** Symptom severity at different time points during 15 weeks: No consistent patterns to distinguish NMV/r from PBO/r groups Symptom burden and relief: No statistically significant differences in proportion of participants experiencing relief at 5, 10, and 15 weeks; alleviation at 10 weeks; or time to relief of each core symptom and the most bothersome symptom Patient global measures and PROMIS measures: Changes from baseline in PGIS and PGIC scores at 2, 5, 10, and 15 weeks and PROMIS scales for physical function, fatigue, dyspnea, and cognitive abilities showed no statistically significant between-group difference at 10 week Sit-to-stand test change from baseline: No significant between-group differences at 10 weeks Adverse events: Rates were similar in NMV/r and PBO/r groups and mostly of low grade
Limitations Noted	Single-center; modest sample size; follow-up limited to 10 weeks; heterogeneous symptom presentation; lack of biomarker data; findings may not generalize to severe or hospitalized covid-19 cases
Risk of bias	Low

Gupta et al. 2022

Author	Gupta et al. [37]
Year	2022
Country	USA
Study design	Phase 2 randomised clinical trial (triple-blinded, placebo-controlled)
Setting	Conducted virtually; participants from Missouri and Illinois, USA
Population	51 adults (mean age 46 ± 13 years; 71% female) with chronic olfactory dysfunction 3–12 months after suspected covid-19 infection
Inclusion criteria	Adults with olfactory dysfunction 3–12 months after suspected COVID-19; University of Pennsylvania Smell Identification Test (UPSIT) ≤33 (men) or ≤34 (women)
Exclusion criteria	History of olfactory dysfunction before covid-19; nasal polyps; prior sinonasal or skull base surgery; neurodegenerative disease; prior seizures; arrhythmia; pregnancy; breastfeeding; current theophylline or methylxanthine use; allergy to theophylline; other contraindications
Intervention Participants (n) Drop-outs (n)	Treatment group: Saline nasal irrigation (SNI) with 400 mg theophylline twice daily for 6 weeks. 26 4

Control Participants (n) Drop-outs (n)	Control group: SNI with placebo (lactose powder) twice daily for 6 weeks. 25 2
Follow up time points	Baseline, 3 weeks, and 6 weeks assessments
Outcomes Measured	Primary: Clinical Global Impression-Improvement (CGI-I) scale responders (≥slightly better). Secondary: UPSIT score changes; Questionnaire for Olfactory Disorders (QOD) Adverse effects
Results	**Primary outcome** CGI-I scale responders (≥slightly better): 13 (59%) participants in the theophylline arm, compared with 10 (43%) in the placebo arm (absolute difference between groups: 15.6% (95% CI –13.2 to 44.5)) **Secondary** UPSIT score changes: Not statistically significantly different between the two study arms QOD: Change in score on each of the 4 QOL assessments related to smell loss was not different between the study arms Adverse effects: Similar between groups at 6 weeks, no severe adverse effects
Limitations Noted	Virtual design limited physical examinations; small sample size; many participants correctly guessed placebo; short follow-up (6 weeks); did not collect vaccination status; inconclusive efficacy findings
Risk of bias	Low

Guttuso et al. 2024

Author	Guttuso et al. [38]
Year	2024
Country	USA
Study design	Randomised clinical trial (double-blind, placebo-controlled) with subsequent open-label dose-finding study
Setting	University at Buffalo, New York, USA (neurology clinic)
Population	52 participants (58% male; mean age 58.5 years) with post–covid-19 condition (PCC) fatigue or cognitive dysfunction >4 weeks post infection; all self-reported positive covid-19 test; symptoms persisted >6 months for ~10%
Inclusion criteria	Positive covid-19 test; bothersome fatigue or cognitive dysfunction >4 weeks post infection; FSS-7 or BFSS score ≥28; BDI-II score <29; no conditions known to cause fatigue or cognitive dysfunction prior to covid-infection; no tobacco/THC use >6 months; not pregnant or nursing
Exclusion criteria	History of lithium use; psychoactive/steroid medication change within 30 days; fibromyalgia, chronic fatigue syndrome, rheumatoid arthritis, or other fatigue/cognitive dysfunction conditions; applying for disability for PCC
Intervention Participants (n) Drop-outs (n)	Lithium aspartate 10–15 mg/day for 3 weeks 26 2 (Data from open-label phase and dose-finding phase not extracted by SBU)
Control Participants (n) Drop-outs (n)	Placebo for 3 weeks 26 0
Follow up time points	Baseline, 3 weeks
Outcomes Measured	Primary: Change in combined FSS-7 and BFSS scores Secondary:

	Insomnia Severity Index, Generalized Anxiety Disorder Scale-2, Beck Depression Inventory-II, Short-Form-12 Health Survey (SF-12) physical/mental scores
Results	**Primary outcome:** Between-group difference at 3 weeks (95% CI) Change in combined FSS-7 and BFSS scores: Not statistically significantly different between groups –3.6 (–16.6 to 9.5) **Secondary outcomes:** Insomnia Severity Index: Not statistically significantly different between groups –1.6 (–5.5 to 2.3) Generalized Anxiety Disorder Scale-2: Not statistically significantly different between groups 0.6 (–0.5 to 1.8) BDI-II: Not statistically significantly different between groups 0.4 (–3.5 to 4.2) SF-12, Physical Component Score: Not statistically significantly different between groups 0.9 (–4.8 to 6.6) SF-12, Mental Component Score: Not statistically significantly different between groups 2.2 (–3.3 to 7.6) Additional outcomes reported
Limitations Noted	Small sample size; short follow-up; lack of biomarker assessment; preliminary nature of findings; findings not definitive on efficacy of higher doses
Risk of bias	Low

Hansen et al. 2023

Author	Hansenet al. [39]
Year	2023
Country	Denmark
Study design Setting Population Follow up	RCT, cross-over. Washout period 4 weeks. Primary care setting. Patients were recruited from a specialized post-covid condition outpatient clinic Adults (median age 49, range 22–70, 74.8% female), >2 persisting symptoms 12 weeks after confirmed covid-19 (15.1% admitted to hospital during acute covid-19 infection). End of treatment. 4 weeks after treatment.
Intervention Participants (n) Drop-outs (n)	CoQ10 capsules in five 100-mg doses per day for 6 weeks 121 2
Control Participants (n) Drop-outs (n)	Placebo capsules containing soy oil for 6 weeks 121 2
Outcomes	Change in the number and/or severity of post-covid-condition-related symptoms after six weeks of CoQ10 treatment or placebo, compared to baseline, measured as a symptom score and a health index On average, the symptom scores were reduced by 5.18 points (95% CI, 3.40 to 6.95) after the six-week treatment with CoQ10, compared to a reduction of 4.04 points (95% CI to 2.13; 5.96) after receiving placebo. After adjusting for sequence and period, the mean difference

	in the change in symptom scores between CoQ10 and placebo was –1.18 (95% CI, −3.54 to 1.17) (p = 0.32). The estimated mean improvement in health index score was 0.04 (95% CI, 0.02 to 0.06) and 0.03 (95% CI, 0.006 to 0.05) after six weeks of CoQ10 treatment or placebo, respectively. After adjusting for period and sequence effect in the linear mixed-effects model, the estimated difference was 0.01 (95% CI, −0.02 to 0.04), which was not statistically significant (p = 0.40). The mean difference in symptom scores between baseline and week six was −5.85 points (95% CI, −8.21 to −3.48; p < 0.001), indicating that the participants in both arms improved significantly regardless of the treatment regimen in the first treatment period. Change in total symptom score in each of the seven clusters of the PCC-specific questionnaire were calculated as a post-hoc analysis
Risk of bias	Low

He et al. 2024

Author	He et al. [40]
Year	2024
Country	China
Study design	Pilot randomised controlled trial (parallel, prospective)
Setting	Renmin Hospital of Wuhan University, Department of Respiratory and Critical Care Medicine, Wuhan, China
Population	73 adults with post-acute sequelae of covid-19 (PASC) after Omicron infection; median age ~68–71 years; persistent symptoms ≥20 weeks; mixed comorbidities (hypertension, diabetes, CHD, etc.)
Inclusion criteria	Adults aged 18–80 years with confirmed omicron SARS-CoV-2 infection (Dec 2022–Jan 2023); consistent with NICE definition of PASC; stable medical condition; no significant changes in treatment over the last three months
Exclusion criteria	Acute SARS-CoV-2 infection within 4 weeks; pregnancy; menstruating; acute physical disease (e.g., myocardial infarction, stroke); severe liver dysfunction; bleeding disorders; allergy to anticoagulants; epilepsy; hemochromatosis; toxic diffuse goiter; severe anemia (<90 g/L hemoglobin)
Intervention Participants (n) Drop-outs (n)	O3-MAH group: Major ozone autohemotherapy daily for 7 days + conventional treatment. 38 3
Control Participants (n) Drop-outs (n)	Conventional group: Conventional therapy (inhaled bronchodilators, oral antitussives/mucolytics, nebulized corticosteroids/anticholinergics) for 7 days. 39 1
Follow up time points	Baseline and post-treatment (7 days) assessments; no long-term follow-up
Outcomes Measured	<u>Primary:</u> Symptom score (sore throat, cough, expectoration, nasal congestion and/or runny nose, shortness of breath, chest tightness, chest pain, palpitations, headache, fatigue, insomnia, loss of smell and taste, and loss of appetite), 6-minute walk distance (6MWD), lung function: Forced vital capacity (FVC), Forced expiratory volume in one second (FEV1), tidal volume (VT)
Results	**Between group differences at end-of-treatment (at 7 days)** <u>Symptom score:</u> Statistically significant improvement in favor of intervention group Md (IQR) 3 (2, 4) vs 4 (3, 7), p = 0.0478 <u>6MWD, meters:</u> Not statistically significantly different between groups p = 0.2633 <u>6MWD, % of expected distance:</u>

	Statistically significantly better in the O3-MAH group Md (IQR) 95.97 (93.04, 101.63) vs 89.65 (80.50, 98.17), p = 0.0032 <u>Lung function:</u> FVC, L/min: Not statistically significantly different between groups, p = 0.7400 <u>FEV1, L/min:</u> Not statistically significantly different between groups, p = 0.9013 <u>VT, L:</u> Statistically significantly better in the O3-MAH group Md (IQR) 0.77 (0.63, 0.98) vs 0.61 (0.415, 0.84), p = 0.0374 Additional outcomes reported No participant indicated treatment-related symptoms nor adverse events
Limitations Noted	Per protocol-analysis; single-center; open-label (no blinding); short follow-up; small sample size; variable baseline inflammation; lack of stratified analysis by severity; no long-term outcomes
Risk of bias	Moderate

Hohberger et al. 2025

Author	Hohberger et al. [41]
Year	2025
Country	Germany
Study design	Prospective, exploratory, placebo-controlled, double-blind, randomised phase IIa clinical trial with cross-over. Only data before crossover are included
Setting	Department of Ophthalmology, Universitätsklinikum Erlangen (UKER), Erlangen, Germany -
Population	Adults aged 18–80 years with WHO-defined post-covid syndrome, fatigue as major symptom, ≥3 PCS symptoms persisting ≥3 months, and seropositivity for GPCR functional autoantibodies. n=30 randomised (rovunaptabin n=14; placebo n=16). Mean age ~40 years; ~67% male
Inclusion criteria	Age 18–80 years; documented SARS-CoV-2 infection; PCS symptoms ≥3 months; clinically relevant fatigue (Bell score ≤60); ≥3 PCS symptoms; seropositivity for GPCR-fAAbs; informed consent
Exclusion criteria	Use of anticoagulants; long-term COVID-related organ damage; other medical causes of fatigue (e.g. MS, anaemia); obstructive sleep apnoea; BMI ≥30 kg/m²; acute severe heart or lung disease; malignancy; pregnancy or breastfeeding; interfering medications; eye diseases
Intervention Participants (n) Drop-outs RCT (n) Drop-outs crossover (n)	Single intravenous infusion of rovunaptabin 1350 mg in 50 mL NaCl 0.9% over 75–90 minutes at day 0. 14 1 0
Control Participants (n) Drop-outs (RCT) (n) Drop-outs (crossover (n)	Matching placebo infusion (50 mL NaCl 0.9%) over 75–90 minutes. 16 0 1
Follow up time points	Baseline (day 0); days 1–2; weeks 1, 2, and 4; cross-over at day 42; follow-up at days 43, 44, 49, 56, 70, and end of study at day 91
Outcomes Measured	<u>Primary:</u> Treatment-emergent adverse events (TEAEs) up to day 28 (co-primary to day 70) <u>Secondary:</u> Fatigue (FACIT-Fatigue, Chalder Fatigue Scale); fatigue severity (Bell score, FSS); quality of life (SF-36); ME/CFS diagnosis (CCC); exercise capacity (6MWT); post-exertional malaise (DSQ-PEM); GPCR-fAAb neutralisation

Results	Day 28, Participants with at least 1 TEAE, n (%) I: 6 (43) C: 3 (19) **Statistically significant results: mean difference (95% CI)** FACIT: 2.91 (0.17 to 5.56) Bell score: 7.54 (3.43 to 11.64) FSS: –0.43 (–0.75 to –0.11) SF36-Vitality: 6.65 (3.38 to 9.93) SF36-General health: 4.86 (1.04 to 8.67) SF36-Social functioning: 6.46 (0.31 to 12.61) SF36-Mental component: 2.73 (0.19 to 5.28) Chalder Fatigue Scale, other subscales of SF-36, 6MWT and DSQ-PEM: Results not statistically significant
Limitations Noted	Small sample size; exploratory phase IIa design; self-reported outcomes only; lack of established biomarkers beyond GPCR-fAAbs; limited generalisability to broader PCS populations.
Risk of bias	Moderate

Hosseinpoor et al. 2022

Author Year Country Ref #	Hosseinpoor et al. [42] Iran 2022 [43]
Study design Setting Population Follow up	RCT Outpatient care setting Non-hospitalized adult patients (mean age 32.2 (intervention), 34.9 (control), 64.3% female) who had persistent anosmia or severe microsmia >4 weeks due to covid-19. Not completely fulfilling WHO criteria for post covid-19 (long covid) 14 and 28 days after treatment
Intervention Participants (n) Drop-outs (n)	One puff of 0.05% wt/vol mometasone furoate (Raha Company, Iran) intranasal spray on each side twice per day for 4 weeks 40 5
Control Participants (n) Drop-outs (n)	One puff of 0.65% wt/vol sodium chloride nasal spray on each side (Decosalin, Raha Company, Iran) was administered to the patients in the placebo group twice daily for 4 weeks 40 5
Outcomes	<u>The Iran Smell Identification Test (Iran-SIT):</u> Changes in Smell Test (Iran-SIT) score between baseline and 4 weeks; mean (SD) I: 10.08 (4.22) C: 6.57 (3.62) p<0.001 <u>Olfactory dysfunction, evaluated with visual analog scale (VAS, 0–10, higher = better)</u> Changes in VAS score between baseline and 4 weeks; mean (SD) I: 4.66 (2.36) C: 2.66 (2.26) p=0.001 Frequence of anosmia and severe or mild microsmia at baseline and 2 and 4 weeks. Non-significant between group results at all time periods. No side effects were noted in the placebo and intervention groups of the study Additional outcomes reported
Risk of bias	Low

Ibrahim et al. 2023

Author	Ibrahim et al. [44]
Year	2023
Country	Saudi Arabia
Study design Setting Population Follow up	Block RCT Outpatient setting Adults aged 60–80 (mean 62.6, 56.9% female, 23.6% with mild illness, 37.3% pneumonia, 37.5% severe penumonia) Not completely fulfilling WHO criteria for post covid-19 (long covid) End of treatment (10 weeks)
Intervention Participants (n) Drop-outs (n)	Moderate intensity aerobic exercises 4 times per week for 10 weeks 24 0
Intervention Participants (n) Drop-outs (n)	Low intensity aerobic exercises 4 times per week for 10 weeks 24 0
Control Participants (n) Drop-outs (n)	Medical care and advice 24 0
Outcomes	**Primary outcomes** <u>6-MWT, magnitude of change pre and post 10 weeks. Mean (SD), 95% CI:</u> Moderate intensity: 26.67 (13.21), 21.09 to 32.24 Low intensity: 14.71 (7.07), 11.72 to 17.69 Comparison group: 0.63 /3.33), –0.78 to 2.03 p= <0.01 <u>PCFS, magnitude of change pre and post 10 weeks. Mean (SD), 95% CI:</u> Moderate intensity: –1.58 (0.50), –1.80 to–1.37 Low intensity: –1.38 (0.65), –1.65 to –1.10 Comparison group: –0.63 (0.71), –0.93 to –0.32 p= <0.01 **Secondary outcomes** 1-min STS, 36 subscales, HADS
Risk of bias	Low

Jing et al. 2025

Author	Jing et al. [45]
Year	2025
Country	China
Study design	Multicenter, randomised, double-blind, placebo-controlled clinical trial
Setting	Five centers in China, including Hubei Provincial Hospital of Traditional Chinese Medicine, Huangshi Hospital of Traditional Chinese Medicine, Wuhan Third Hospital, Jingmen First People's Hospital, Wuhan Integrated TCM & Western Medicine Hospital
Population	Discharged convalescent covid-19 patients with CT-confirmed pulmonary fibrosis. n=142 randomised (FZHY n=72; placebo n=70); mean age ~58 years; <50% male. The diagnostic criteria for suspected and diagnosed covid-19 cases were based on the Diagnosis and Treatment Guideline for covid-19 (Trial seventh Edition) released by the National Health Commission of the People's Republic of China
Inclusion criteria	Confirmed covid-19; discharged and RNA-negative; CT evidence of pulmonary fibrosis; age 18–70 years; informed consent
Exclusion criteria	Previous lung surgery; mechanical ventilation dependence; chronic lung disease (e.g. COPD); severe cardiac disease; diseases affecting survival; resting heart rate >120 beats/min; systolic blood pressure >180 mmHg and diastolic blood pressure >100 mmHg; severe obesity (BMI >30); pregnancy/breastfeeding; participation in other trials; poor compliance
Interventions Participants (n) Drop-outs (n)	Fuzheng Huayu (FZHY) herbal extraction tablets 1.6 g orally, three times daily for 24 weeks, plus vitamin C and respiratory rehabilitation 72 6

Control Participants (n) Drop-outs (n)	Matching placebo tablets on same schedule, plus vitamin C and respiratory rehabilitation 70 7
Follow up time points	Baseline; weeks 4, 8, 12, 16, 20; primary endpoint at 24 weeks with full analysis set
Outcomes Measured	Primary: Regression rate of pulmonary fibrosis on HRCT; pulmonary function (FVC, FEV1, FEV1/FVC) Secondary: 6-minute walk distance; pulmonary inflammation regression; clinical symptoms; quality of life (QOL-BREF); depression (PHQ-9); anxiety (GAD-7); adverse events
Results	**Results at 24 weeks** Regression rate of pulmonary fibrosis FZHY group (n= 72): 48/72, 66.7% Placebo group (n=70): 33/70, 47.1% p= 0.019 Disappearance rate of shortness of breath FHZY group (n=42): 81% Placebo group: (n=41): 80.5% p=0.957 Disappearance rate of fatigue FHZY group (n=33): 63.3% Placebo group (n=29): 72.4 % p=0.456 (cough, insomnia, sweating, poor appetite, and diarrhea are also reported) QOL-BREF score, mean (SD): subjective perception of quality of life FZHY group (n=63): 3.7 (0.65) Placebo group (n=62): 3.7 (0.56) p=0.737 QOL-BREF score, mean (SD): subjective feeling of health status FZHY group (n=63): 3.3 (0.86) Placebo group (n=62): 3.3 (0.78) p=0.642 QOL-BREF score, mean (SD): physical health FZHY group (n=63): 69.8 (13.59) Placebo group (n=62): 68.4 (10.51) p=0.542 QOL-BREF score, mean (SD): psychological health FZHY group (n=63): 70.5 (15.98) Placebo group (n=62): 71.1 (12.30) p=0.813 QOL-BREF score, mean (SD): social relationships FZHY group (n=63): 63.2 (15.26) Placebo group (n=62): 65.0 (10.40) p=0.452 QOL-BREF score, mean (SD): environment FZHY group (n=63): 67.5 (12.60) Placebo group (n=62): 69.1 (10.29) p=0.442

	PHQ-9 score, mean (SD): FZHY group (n=63): 2.7 (4.05) Placebo group (n=62): 2.6 (2.67) p=0.807 GAD-7 score, mean (SD): FZHY group (n=63): 2.3 (3.79) Placebo group (n=62): 1.6 (2.37) p=0.214 After 24 weeks of treatment, both the FZHY and placebo groups demonstrated a trend toward improved performance in the 6-min walk test; however, this difference was not statistically significant. Adverse events: FHZY group (n=72) Abnormal liver function, renal dysfunction, abnormal ECG, urinary leukocytosis, dyslipidemia and hyperglycemia Placebo group (n=70) Abnormal liver function, renal dysfunction, abnormal ECG, urinary leukocytosis, increased C-reactive protein, leukocytosis and back pain
Limitations Noted	Limited pulmonary function testing due to infection risk; semi-quantitative CT scoring; sample size not adjusted during trial; predominantly early-pandemic unvaccinated population; limited generalizability to newer variants.
Risk of bias	Moderate

Jimeno-Almazan et al. 2022

Author	Jimeno-Almazan et al. [46]
Year	2022
Country	Spain
Study design Setting Population Follow up	VO_2-max stratified RCT University medical center Non-hospitalised adults (45.2±9.5 years, 74.4% female) with confirmed covid-19 and a chronic symptomatic phase, lasting >12 weeks from onset of symptoms End of treatment (8 weeks)
Intervention Participants (n) Drop-outs (n)	Training 3 days/week for 8 weeks: 2 days of resistance training combined with moderate intensity variable training and 1 day of light intensity continuous training 19 Not mentioned
Control Participants (n) Drop-outs (n)	WHO guidelines: Support for Rehabilitation: Self-Management after covid-19 Related Illness, see comment 20 Not mentioned
Outcomes	**Primary outcome** PCFS post treatment mean (SD) I: 1.1 (1.2) C: 1.8 (1.1) Group effect: p=0.033, ηp^2=0.15 (ANOVA) **Other reported outcomes** Pulmonary function: FVC (L), %FVC, FEV-1 (L), %FEV-1, FEV-1/FVC, FEV25-75% (L·s−1), MVV (L), %MVV Quality of life and fatigue: SF-12 (PA), SF-12 (MH), mMRC, CFQ-11 (bimodal), CFQ-11 (Likert), FSS, DSQ-14, PCSF Anxiety and depression: GAD-7, PHQ-9

	Cardiovascular fitness: VO_2max (ml/kg/min), Final RPE 6–20, Final HR (b·m−1) Muscular strength: Sit-to-stand (s), Handgrip (kg), BP-50% 1RM (m·s−1), HSQ-50% 1RM (m·s−1), Leg extension (N)
Comments	WHO guidelines: support for rehabilitation involves recommendation of aerobic exercise for 20-30 minutes 5 times a week.
Risk of bias	Moderate

Jimeno-Almazan et al. 2023

Author	Jimeno-Almazanet al. [47]
Year	2023
Country	Spain
Study design Setting Population Follow up	VO_2-max stratified RCT Outpatient care setting Non-hospitalised adults (45.3±8.0 years, 68.8% female) with confirmed covid-19 and a chronic symptomatic phase, lasting >12 weeks from onset of symptoms End of treatment (8 weeks)
Intervention 1 Participants (n) Drop-outs (n)	Concurrent training (CT): a three-days-a-week concurrent training routine: two days of resistance training followed by moderate intensity variable training and one day of a monitored autonomous light intensity continuous training 21 1
Intervention 2 Participants (n) Drop-outs (n)	Inspiratory muscle training (RM): inspiratory muscle training protocol with PowerBreath Classic Heath Series mechanic threshold devices 17 0
Intervention 3 Participants (n) Drop-outs (n)	Concurrent training as above plus inspiratory muscle training as above (CTRM) 25 2
Control Participants (n) Drop-outs (n)	Advised to follow WHO guidelines: “Support for Rehabilitation: Self-Management after covid-19-Related Illness” 20 0
Outcomes	**Primary outcomes** Cardiorespiratory fitness, measured as VO_2max at end of treatment (8 weeks): No significant differences between groups in estimated VO_2max ($P > 0.05$) Muscle strength: lower body maximal and submaximal strength (squat 1RM and MPVALL) Between groups effects not reported Muscle strength: upper body submaximal strength (Bench Press MPVALL) Authors report significant interaction for upper body submaximal strength (Bench Press MPVALL) ($P < 0.05$) for CT and CTRM groups Dominant hand grip strength No inter- or intragroup interactions were found for the dominant hand grip strength **Secondary outcomes** PCFS, mMRC <2, PHQ9 <10, GAD7 <10, FSS <4, CFS <18, SF-12 PA, SF-12 MH, number of symptoms, frequency of 10 specific symptoms. After 8 week-intervention period, no significant differences between groups were detected in the mMRC (dyspnea), GAD-7 (anxiety), PCFS (functional status), and SF-12 PA and MH (health-related quality of life). Additional outcomes reported
Comments	Study uses same study protocol as [48].
Risk of bias	Moderate

Kaczmarczyk et al. 2024

Author	Kaczmarczyk et al. [49]
Year	2024
Country	Poland
Study design	Randomised controlled trial (parallel, intervention vs. control)
Setting	Józef Piłsudski University of Physical Education in Warsaw, Poland
Population	51 older adults (≥65 years). Mean age ~69–75 years. Both sexes. Post-covid survivors (average 9 months since onset). 92% vaccinated. Infection described as mild for 33%, moderate for 51%, severe for 10%, very severe for 6%.
Inclusion criteria	≥65 years old; positive RT-PCR or antibody test for SARS-CoV-2 in last 3–12 months; at least one post-covid symptom (e.g., fatigue, weakness, dizziness, headache, memory issues, exercise intolerance, depression); medically screened for exacerbations of post-exercise symptoms, able to participate in resistance training
Exclusion criteria	<65 years; active cardiac disease; oxygen desaturation <95% for more than 1 min; autonomic dysfunction (orthostatic intolerance); serious health conditions (e.g., cancer)
Interventions Participants (n) Drop-outs (n)	Resistance training program: twice weekly, 60 min sessions, 8 weeks. Exercises: incline bench press, 45° leg press, latissimus pull-down, trunk crunch, T-Bar row, leg extension, leg curl. Intensity: 70% of 1RM, 3 sets × 12 reps. Warm-up 15 min. 28 2
Control Participants (n) Drop-outs (n)	Continued usual physical activity without modifications 23 3
Follow up time points	Baseline and post-intervention (8 weeks) assessments
Outcomes Measured	Muscle strength (isometric, isokinetic); Functional performance (Timed Up and Go, Chair Stand Tests: 5STS, CS-30); Self-reported post-covid symptoms
Results	**Group (control, intervention) x Testing session (before, after):** <u>TUG (seconds):</u> F (1,42) = 3.06 p = 0.0876 η^2 = 0.068 <u>Chair test 5STS (seconds):</u> F (1,42) = 8.49 p = 0.0057 η^2 = 0.168 <u>Chair test CS-30 (No. of repetitions):</u> Z = 4.65 p = 0.0001 R = 0.806 Additionally, muscle strength reported in several tests Percentage of post-covid symptoms reported for intervention group
Limitations Noted	Small sample size; intervention group already high functioning; no systematic tracking of symptoms in control group; reliance on gym equipment may limit generalizability Short intervention duration; limited diet control; lack of biochemical data; small sample size; no non-COVID control group; generalizability limited to elderly adults
Risk of bias	Moderate

Kaddoussi et al. 2024

Author	Kaddoussi et al. [50]
Year	2024
Country	Tunisia
Study design	Randomised controlled trial (single-blinded)
Setting	Outpatient departments of pulmonology and physical medicine & rehabilitation, Fattouma Bourguiba Hospital, Monastir, Tunisia
Population	36 adult long-covid-19 patients (LC19Ps) with persistent dyspnoea ≥3 months post-diagnosis; mean age 52–53 years; mix of sexes; comorbidities include diabetes, hypertension; excluded active smokers; varying lung injury extents on CT
Inclusion criteria	Confirmed covid-19; age >18; persistent dyspnoea ≥3 months post-diagnosis; mMRC dyspnoea score ≥2
Exclusion criteria	Pre-existing chronic lung diseases (asthma, COPD, lung cancer); moderate/advanced heart failure; mobility-limiting conditions; active cigarette/narghile smokers; contraindications to 6MWT or spirometry; missed sessions or evaluations
Intervention Participants (n) Drop-outs (n)	Ambulatory cardiopulmonary rehabilitation program (CPRP) – 18 sessions over 6 weeks including warm-up, aerobic treadmill training, resistance exercises, respiratory exercises, therapeutic education 24 4
Control Participants (n) Drop-outs (n)	Usual care/sedentary activity 12 2
Follow up time points	Baseline (pre-CPRP) and post-CPRP (6 weeks); additional 2-week evaluation phase pre- and post-intervention
Outcomes Measured	Primary: 6-minute walk distance (6MWD) Secondary: Dyspnoea (Borg, mMRC), spirometry (FEV1, FVC), heart rate (rest and end), SpO2, 6-minute walk work (6MWW). Minimal clinically important difference (MCID) defined as 30 m for 6MWD and 1 point for mMRC
Results	**Post-CPRP** I: n=20 C: n=10 6MWD (m): IG significantly increased by 168 ± 99 m vs. CG's 5 ± 45 m (exceeded MCID of 30 m) Dyspnoea reduction: IG improved mMRC by –1.5 ± 0.8 (MCID: 1), CG by –0.1 ± 0.3. IG improved Borg by –3.5 ± 2.0, CG by –1.3 ± 1.5 Resting heart rate: IG decreased by –9 ± 9 bpm, CG change was 1 ± 7 bpm Spirometry: Small improvements in IG (FEV1, FVC), but no statistical or clinical difference compared to CG Safety: No patients stopped during 6MWT, no side effects noted Abnormal 6MWD percentage: IG decreased from 100% to 75%, CG unchanged at 80%

Limitations Noted	Single-center; small sample size; short follow-up (6 weeks); no post-6MWT blood pressure or recovery SpO2 measured; no bronchodilator tests; limited equipment (no plethysmography or diffusion capacity tests); no waist circumference data; results may not generalize to other populations
Risk of bias	Moderate

Kerling et al. 2024

Author	Kerling et al. [51]
Year	2024
Country	Germany
Study design Setting Population Follow up	RCT Outpatient care Volunteers ≥18 years (mean age 46.2 (SD 11.2) years, 67,7% women) with a continuing impairment of physical or mental health after covid-19 (detection by polymerase chain reaction) infection with a fatigue assessment scale (FAS) score of 22 points. After treatment (3 months)
Intervention Participants (n) Drop-outs (n)	Individually designed exercise plan recommending 150 min of moderate physical activity per week (60–75% of the maximum heart rate measured during the incremental exercise test) 35 5
Control Participants (n) Drop-outs (n)	Asked to continue with their current lifestyle and everyday activities 37 5
Outcomes	**Primary outcome** V̇O2peak (ml/min/kg) mean difference (95% CI) between groups over time: –0.6 (–1.8 to 0.8) **Secondary outcomes** FAS mean difference (95% CI) between groups over time: 0.3 (–2.6 to 3.9) SF-36 MCS mean difference (95% CI) between groups over time: –3.0 (–8.5 to 2.5) SF-36 PCS mean difference (95% CI) between groups over time: 1.2 (–2.7 to 5.1) HADS-D depression mean difference (95% CI) between groups over time: 1.0 (–0.7 to 2.8) HADS-D anxiety mean difference (95% CI) between groups over time: 0.2 (–1.4 to 1.6) WAI mean difference (95% CI) between groups over time: 1.0 (–1.9 to 3.8) FEV1 (l) mean difference (95% CI) between groups over time: –0.05 (–0.18 to 0.07) FEV1 predicted (%) mean difference (95% CI) between groups over time: 1.69 (–2.00 to 5.39) VC (l) mean difference (95% CI) between groups over time: 0.00 (–0.15 to 0.16) VC predicted (%) mean difference (95% CI) between groups over time: –0.08 (–3.69 to 3.52)
Risk of bias	Moderate

Kerget et al. 2023

Author	Kerget et al. [52]
Year	2023
Country	Turkey
Study design Setting Population Follow up	RCT Outpatient care Adults aged >18 (60% female, 62.6±8.1 years (intervention) and 68.4±9.8 years (control)) with confirmed covid-19, presented with symptoms, having fibrosis secondary to covid-19 on radiological imaging, not requiring intubation and mechanical ventilation during acute covid-19 12 weeks post start of treatment
Intervention Participants (n) Drop-outs (n)	Pirfenidone (an antifibrotic agent, off-label use) oral tablets, 600 mg/day the first week, 1200 mg/day the second week, and 1800 mg/day the third week 15 0
Control Participants (n) Drop-outs (n)	Nintedanib (an antifibrotic agent, off-label use), oral tablets 300 mg/day 15 0
Outcomes	6-minute walk test (MWT) distance in meters, mean change from baseline (SD): I: 29.8 (27.2) C: 70 (48.4) P<0.05 Forced vital capacity (FVC), liters, mean change from baseline (SD): I: 0.2 (0.3) C: 0.4 (0.3) P=0.17 Forced expiratory volume (FEV), liters, mean change from baseline (SD): I: 0.2 (0.3) C: 0.2 (0.2) P=0.66 Heart rate, mean change from baseline (SD): I: −12.9 (11.6) C: 10.2 (7.4) P=0.46 S02, finger tip saturation: I: 5.6 ± 4.8 C: 10.6 ± 4.1 P=0.005 Adverse events, number of patients: Diarrhea: I: 0, C: 12 (80%) Nausea-vomiting: I: 1 (6.6%), C: 10 (66.6%) Loss of appetite: I: 1 (6.6%), C: 4 (26.6%) Rash: I: 1 (6.6%) C: 0 Photosensitivity: I: 1 (6.6%), C: 0
Risk of bias	Moderate

Khodabakhshian et al. 2025

Author	Khodabakhshian et al. [53]
Year	2025
Country	Iran
Study design	Randomised controlled trial (double-blind)
Setting	Kashan University of Medical Sciences, Kashan, Iran
Population	52 adults with persistent fatigue ≥6 weeks after acute covid-19; mean age ~37 years; majority female (approx. 86% in intervention group, 64% in sham group)
Inclusion criteria	Age 18–65; Iranian nationality; persistent fatigue (Chalder Fatigue Scale >4); PCR confirmed covid-19 ≥6 weeks prior; physician-approved treatment completion
Exclusion criteria	Acute severe disease; chronic diseases (anemia, MS, cancer, psychiatric disorders); pregnancy or breastfeeding; BMI >40 kg/m²; covid-19 complications (e.g., thromboembolism); mechanical ventilation during acute covid-19; auricular health problems; acupressure/acupuncture in prior 3 months; medication/substance abuse; complementary therapy use
Intervention Participants (n) Drop-outs (n)	Intervention group: Auriculotherapy with Vaccaria seeds on six fatigue-related ear points for 4 weeks, pressed twice daily (60 presses/session, 5 days/week). Weekly replacements of seeds/tapes 26 4
Control Participants (n) Drop-outs (n)	Sham group: Adhesive tape without seeds on same points; no pressing. Weekly replacements of seeds/tapes. 26 4
Follow up time points	Baseline (T0), immediately post-intervention (T1, 4 weeks), and 4 weeks after intervention (T2, 8 weeks total) assessments using Chalder Fatigue Scale
Outcomes Measured	<u>Primary:</u> Fatigue score (Chalder Fatigue Scale; CFS) <u>Secondary:</u> None specified; adverse events (itching, allergic reactions) monitored.
Results	**ITT-results (adjusted for financial status and history of hospitalization due to covid-19)** <u>Fatigue score (CFS):</u> Repeated-measures ANOVA revealed a significant time-group interaction for fatigue $F(2,50)=6.978$; $p=0.008$
Limitations Noted	Single-center; modest sample size; high proportion of female/educated participants (generalizability limited); possible placebo effects from sham adhesive tapes; lack of biomarker confirmation; short follow-up; potential misclassification due to PCR sensitivity
Risk of bias	Moderate

Kim et al. 2025

Author	Kim et al. [54]
Year	2025
Country	USA
Study design	Randomised, double-blind, placebo-controlled pilot clinical trial
Setting	Duke Rhinology Clinics, Duke University School of Medicine, Durham, North Carolina, USA.
Population	Adults ≥18 years with persistent smell loss ≥3 months after COVID-19 infection confirmed by Smell Identification Test (SIT). Fifteen participants were randomised in the pilot trial. Thirteen participants were included in the final analysis.
Inclusion Criteria	Adults aged ≥18 years with post-COVID smell loss for more than 3 months confirmed using the Smell Identification Test (SIT)
Exclusion Criteria	Pregnancy or lactation; febrile illness within 1 week; treatment with another investigational drug within 3 months; active sinonasal disease (e.g., rhinosinusitis or nasal polyps); allergy to study drug or materials; glaucoma; inability to consent
Intervention Participants (n) Drop-outs (n)	Endoscopic placement of dissolvable sponge delivering topical beclomethasone (84 mcg/0.3 mL per side) into the olfactory cleft. Treatment repeated after 2 weeks. 7 1
Control Participants (n) Drop-outs (n)	Placebo group received identical endoscopic placement of dissolvable sponge delivering saline. 8 1
Follow-up Timepoints	Baseline, 1 month after treatment, and 3–4 months after treatment
Outcomes Measured	Primary: Improvement in Smell Identification Test (SIT) score, defined as ≥4-point increase (minimal clinically important difference) Secondary: Questionnaire on Olfactory Dysfunction (QOD), and safety assessed by adverse event monitoring and nasal endoscopic examination
Results	**Olfactory function – smell identification (SIT)** At 1 month: Improvement (ΔSIT ≥4) in 66.7% (4/6) of participants in intervention group vs 28.6% (2/7) in placebo group (p=0.28) At 3 months: Improvement in 66.7% of participants in intervention group vs 42.9% in placebo group (p=0.50) Secondary QOD: Data not reported Safety: No adverse events were reported
Limitations	Small pilot sample size; not powered to detect efficacy; short follow-up duration; participants predominantly female; findings require confirmation in larger trials; per protocol analysis
Risk of bias	Moderate

Kjellberg et al. 2025

Author	Kjellberg et al. [55]
Year	2025
Country	Sweden
Study design	Randomised, placebo-controlled, double-blind, parallel-group phase II trial
Setting	Hyperbaric outpatient clinic, Karolinska University Hospital, Stockholm, Sweden
Population	Adults 18–60 years, previously healthy (ASA I–II), diagnosed with long covid; n=80 randomised (40 HBOT, 40 placebo); 81% women; mean age 41
Inclusion criteria	Age 18–60; symptoms ≥12 weeks; ICD-10 U09.9 diagnosis; previously healthy (ASA I–II); working/studying pre-COVID; informed consent
Exclusion criteria	Pregnancy; ASA ≥III before post-covid; RAND-36 PF or RP >70; diabetes; hypertension (pre-COVID); HBOT contraindications; participation in another trial; cognitive/language barriers
Intervention Participants (n) Drop-outs (n)	HBOT; 100% O_2 at 2.4 ATA, 90 min, 2× 5-min air breaks 40 2 (Received sham treatment due to error: 1)
Control Participants (n) Dropouts (n)	Medical air at 1.34→1.2 ATA for 90 min with similar breaks 40 8
Follow up time points	Baseline, 6 weeks (end of treatment), 13 weeks (primary endpoint), 26 weeks, 52 weeks
Outcomes Measured	Primary: RAND-36 PF and RP change at 13 weeks Secondary: 6MWT, 30s CST, EQ-5D-5L, endothelial function (RHI) Exploratory: long-term RAND-36, symptom tracking, AEs (severity, relation to IMP)
Results	**ITT-analysis at 13 weeks, I: n=40, C: n=39, mean change from baseline (SD)** RAND-36 – physical functioning: I: 9 (18.68) C: 8.59 (16.02) RAND-36 – role limitations due to physical health: I: 6.25 (20.22) C: 3.85 (16.76) 6MWT: I: 15.92 (79.63) C: 23.23 (49.60) 30 seconds CST: I: 0.28 (2.77) C: 0.71 (2.30) EQ-5D-5L index: I: 0.05 (0.21) C: 0.10 (0.19) EQ-5D VAS: I: 5.35 (15.57) C: 6.13 (15.28) Results are also reported at 26 and 52 weeks
Limitations Noted	Small sample size; dose may be insufficient (10 sessions); population highly symptomatic and not representative; severe PEM limited treatment frequency; possible placebo physiological effects; imbalance due to extremely low RAND-36 RP baseline scores; one death in placebo group.
Risk of bias	Low

Klirova et al. 2024

Author Year Country	Klirova et al. [56] 2024 Czech Republic
Study design Setting Population Follow up	RCT, double-blind Medical facility Adults aged 18–75 years (70% female, mean age 42.2 ±10.5); covid-19 negativity at the time of pre-study entry; symptom duration >1 month after detection of covid-19; FIS score ≥40; presence of neuropsychiatric symptoms of PASC (A-PASC, minimum total score ≥25); possible psychopharmacological medication on a stable dose for ≥4 weeks. 8 weeks
Intervention Participants (n) Drop-outs (n)	Transcranial direct current stimulation (tDCS) 17 1
Control Participants (n) Drop-outs (n)	Sham-tDCS 18 1
Outcomes	**At 8 week follow-up (time x condition intergroup differences, LS mean difference, Sidak-corrected)** <u>Fatigue (FIS total score changes):</u> tDCS vs sham: 11.3 (95% CI, −11.7 to 34.4), t=1.31, p_{corr}=0.7 – not significant Sham: −27.1 (95% CI, −45.2 to −9.1), t=4.40, p_{corr}<0.001 Active: −15.8 (95% CI, −33.7 to 2.1), t=2.59, p_{corr}=0.13 <u>Anxiety (GAD-7 self-assessment score changes):</u> tDCS vs sham: 0.33 (95% CI, −4.02 to 4.67), p=1.000 – not significant <u>Depression (PHQ-9 self-assessment score changes):</u> tDCS vs sham: 0.88 (95% CI, −3.29 to 5.04), p=0.997 – not significant <u>Quality of life (AQoL−6D total score changes):</u> tDCS vs sham: −3.23 (95% CI, −12.25 to 5.79), p=0.939 – not significant See study for domain specific results within FIS and AQoL−6D
Risk of bias	Moderate

Knopman et al. 2026

Author	Knopman et al. [57]
Year	2026
Country	USA
Study design	Multicenter, 5-arm, phase 2 randomised clinical trial
Setting	22 clinical trial sites across the United States. Interventions were delivered remotely via telehealth.
Population	378 individuals were screened, resulting in 328 adult participants ≥18 years with cognitive symptoms following SARS-CoV-2 infection persisting ≥12 weeks (long covid); 73,5% female
Inclusion Criteria	Age ≥18 years; prior SARS-CoV-2 infection; persistent cognitive complaints for ≥12 weeks; PROMIS Cognitive Function Short Form T-score <40.
Exclusion Criteria	Preexisting cognitive disorders before COVID-19 infection; neuropsychiatric or medical conditions that could complicate assessment; use of psychoactive medications prescribed for long-COVID cognitive symptoms; other exclusionary clinical conditions.
Intervention 1 Participants (n) Drop-outs (n) Intervention 2 Participants (n) Drop-outs (n) Intervention 3 Participants (n) Drop-outs (n)	Adaptive computerized cognitive training – BrainHQ - targeting memory, attention, and processing speed; 30 min/session, 5 sessions per week for 10 weeks 67 5 Cognitive-behavioral rehabilitation – PASC-Cognitive Recovery (PASC-CoRE) + BrainHQ: structured cognitive rehabilitation program including attention regulation, goal management training, and fatigue management (9 group sessions 1.5h/session + 3 individual sessions 30 min per session) combined with BrainHQ training 66 3 Active transcranial direct current stimulation (tDCS) + BrainHQ: tDCS (2.0 mA, 30 min/session) targeting the dorsolateral prefrontal cortex combined with BrainHQ cognitive training 66 11
Control 1 Participants (n) Drop-outs (n) Control 2 Participants (n) Drop-outs (n)	4Active comparator – unstructured online puzzles and games (30 min/session), 5 sessions per week for 10 weeks 64 3 Sham tDCS stimulation combined with BrainHQ cognitive training 65 6
Follow-up Timepoints	Baseline, mid-intervention (≈35 days), end of intervention (≈70 days), and 3-month follow-up after completion of the intervention
Primary Outcome	Modified Everyday Cognition Scale 2 (ECog2) assessing self-reported cognitive function.
Secondary Outcomes	PROMIS cognitive function, fatigue, sleep, depression and anxiety; neuropsychological tests (Auditory Verbal Learning Test, Symbol Digit Modalities Test, Digit Vigilance Test, lexical and semantic fluency, NIH Toolbox Flanker Test)
Results	**At end-of-intervention (other time-points not tabulated by SBU):** No intervention demonstrated statistically significant benefit on the primary outcome compared with the active comparator Adjusted differences in mean ECog2 change were approximately 0.0 to 0.1 across comparisons All groups showed modest improvements in self-reported cognition and secondary outcomes over time <u>Safety:</u>

	No serious adverse events attributable to the interventions were reported One minor thermal injury occurred under a tDCS electrode Overall interventions were considered safe
Limitations Noted	Trial entry was based on subjective cognitive symptoms, and over one-half of the participants did not have performance-based impairment; partly unblinded (participants assigned to PASC-CoRE were aware of their treatment, participants assigned to receive tDCS treatment were blinded to active or sham stimulations)
Risk of bias	Moderate

Kogel et al. 2023

Author	Kogel et al. [58]
Year	2023
Country	Germany
Study design Setting Population Follow up	RCT Outpatient training program Participants, aged ≥18 years (mean age 42.7 (SD 13.4) years, 61% women) were recruited from a post covid clinic. Parti cants should have sustained fatigue (defined as >50 points with four or more dimensions affected on the MFI-20-questionnaire) at a minimum of 6 weeks after a covid-19. The mean age was 42.7±13.4 years and 61% were females. Follow up after intervention (4 weeks) and after 3 and 6 months.
Intervention Participants (n) Drop-outs (n)	4 weeks of 2–3 times weekly personalized strength endurance training 29 9 (at 6 months follow up)
Control Participants (n) Drop-outs (n)	Care as usual, with no restrictions on exercise 28 8 (at 6 month follow up)
Outcomes	There were various significant between group effects at the assessment after 4 week intervention (not tabulated here) Strength measurement and cardiopulmonary testing; fatigue (assessed with Multidimensional Fatigue Inventory-20), quality of life (assessed with McGill Quality of Life Questionnaire (MQOL)); functional status (assessed with Post-Covid-19 Functional Status (PCFS)) **Outcomes after 3 months** No significant differences between groups in any of the questionnaires or subdomains **Outcomes at 6 months** Psychological quality of life (MQOL): Significantly better in exercise group compared to control group (exercise 29±9 vs control 25±9, p<0.05) Total physical activity per week, assessed with GPAQ: Significantly greater in exercise group compared to control group (exercise 1280±1192 vs control 644±554, p<0.05) Additional outcomes reported
Risk of bias	Moderate

Kuut et al. 2023

Author Year Country	Kuut et al. [59] 2023 The Netherlands
Study design Setting Population Follow up	RCT Online intervention Adults aged ≥18 (mean age 45.7±12.4 (intervention) and 46.0±12.9 (control), 72.8% female, 89% non-hospitalised during initial infection) with severe fatigue (≥35 on the CIS-fatigue) and limitations in physical functioning (≤65 on physical functioning subscale of SF-36) and/or social functioning (≥10 on WSAS) following COVID-19 infection 19 weeks, 6 months
Intervention Participants (n) Drop-outs (n)	CBT for fatigue post COVID-19 infection (Fit after COVID), blended intervention developed by adapting existing CBT protocols for severe fatigue in long-term medical conditions 57 11
Control Participants (n) Drop-outs (n)	Care as usual 57 4
Outcomes	**Primary outcome** <u>Fatigue Mean (SE) at T0, T1, T2:</u> (Higher score on CIS-fatigue-scale indicates more severe fatigue, ≥35 indicates severe fatigue) CBT: T0 = 47.8 (0.7) T1 = 30.6 (1.4) T2 = 31.5 (1.7) CAU: T0 = 47.0 (0.8) T1 = 39.9 (1.4) T2 = 39.9 (1.7) Overall between-group difference, Mean (95% CI): −8.8 (−11.9 to −5.8), p<0.001 Cohen's d of the overall effect: 0.69 **Secondary outcomes** Overall between-group difference, Mean (95% CI) <u>Physical functioning (self-rated, SF-35 PF):</u> 7.1 (2.9 to 11.3), P=0.001 <u>Social functioning (WSAS score):</u> −6.6 (−9.1 to −4.2), P<0.001 <u>Somatic symptoms (PHQ-15):</u> −2.0 (−2.9 to −1.0), P<0.001 <u>Problems concentrating (CIS-conc):</u> −5.1 (−6.9 to −3.4), P<0.001 All significant results represent mean difference based on two follow-up timepoints and were all in favour of CBT. Eight adverse events were recorded during CBT, and 20 during CAU. No serious adverse events were recorded.
Risk of bias	Moderate

Lasheen et al. 2023

Author	Lasheen et al. [60]
Year	2023
Country	Egypt
Study design Setting Population Follow up	RCT, double-blind Outpatient care, self-administration Adults (21 to 56 years, mean 33 vs 32 years), 55% women, with olfactory dysfunction (anosmia, hyposmia, or parosmia) >3 months post-covid-19, with complete recovery from COVID-19, n=40 End of treatment / 2 months post-allocation
Intervention Participants (n) Drop-outs (n)	Corticosteroids, 8 doses over 2 months (twice weekly) injected in the olfactory mucosa 20 0
Control Participants (n) Drop-outs (n)	Placebo injections (saline) 20 0
Outcomes	QOD-NS (range 0–51) post-intervention, mean (SD): I: 7.60 (8.91) C: 12.40 (12.00) ns
Risk of bias	Moderate

Lau et al. 2024

Author	Lau et al. [61]
Year	2024
Country	China
Study design Setting Population Follow up	Double blinded RCT Outpatient setting Adults aged ≥18 (mean age about 49 years, females about 65%) with laboratory verified SARS-CoV-2 infection with at least one post acute covid 19 symptom (according to PACSQ-14) for ≥4 weeks. Thus, participants did not fully fulfil the WHO-criteria. 3 and 6 months
Intervention Participants (n) Drop-outs (n)	Oral synbiotic preparation (SIM01, with 20 billion colony forming units of three bacterial strains: B adolescentis, B bifidum, and B longum) administrated as sachets twice daily 232 28 (at 6 month follow up)
Control Participants (n) Drop-outs (n)	Placebo, which consisted of low dose vitamin C 1 mg twice daily 231 32 (at 6 month follow up)
Outcomes	**Primary outcome** Symptoms assessed with PACSQ-14 (OR, 95% CI): At 6 months, a significantly higher proportion of individuals who received SIM01 had alleviations in - fatigue (2.273, 1.520 to 3.397), p=0.0001 - memory loss (1.967, 1.271 to 3.044), p=0.0024 - difficulty in concentration (2.644, 1.687–4.143), p<0.0001 - gastrointestinal upset (1.995, 1.304–3.051, p=0.0014 - general unwellness (2.360, 1.428–3.900, p=0.0008) compared with placebo, after adjusting for multiple comparisons **Secondary outcomes** Quality of life (VAS at 6 months, aided by trained interviewers, mean (SD)): SIM01: 76.0 (SD 12.0) Placebo: 74.5 (12.3) p=0.17 Physical activity (IPAC at 6 months, median (IQR)): Post-hoc analysis showed no significant difference in total metabolic equivalent of task minutes/week between the two groups

	SIM01: 1646.3 (IQR 815.6–2899.5) Placebo: 1902.0 (IQR 956.0–3290.0) p=0.37 Additional outcomes reported
Comments	Although blinded, it is likely that participants may have realized their group allocation.
Risk of bias	Moderate

León-Herrera et al. 2024

Author	León-Herrera et al. [62]
Year	2024
Country	Spain
Study design	Randomised clinical trial (blind, parallel groups)
Setting	Spanish long-covid associations; online multimodal rehabilitation program with videoconferences and Moodle platform
Population	134 participants (mean age ~49 years; 84% female) with persistent symptoms ≥3 months post-covid; members of Spanish long-covid collectives
Inclusion criteria	Adults aged 18–80; persistent covid symptoms ≥3 months; member of Spanish long-covid associations; no alternative diagnosis
Exclusion criteria	Serious uncontrolled medical conditions; concurrent rehabilitation or psychotherapy; participation in another trial within 6 months; pregnancy/lactation; suicide risk; significant medical, psychological, or social issues preventing participation
Intervention Participants (n) Drop-outs (n)	Usual care plus online multimodal program (8 weekly 1.5h sessions via videoconference + Moodle resources) covering physical activity, respiratory rehabilitation, cognitive rehabilitation, diet, sleep hygiene, emotional management, meditation; community participation 67 5
Control Participants (n) Drop-outs (n)	Usual care 67 5
Follow up time points	Baseline and 3 months post-intervention assessments
Outcomes Measured	<u>Primary:</u> Quality of life (SF-36 physical and mental health scores) <u>Secondary:</u> Persistent symptoms, cognitive function (MoCA), lower limb strength (Sit-to-Stand), anxiety/depression (HADS), sleep (ISI), self-efficacy, health literacy, patient activation
Results	**Per protocol-analysis at 3 months post-intervention, I: n=62, C: n=62, mean change from baseline (SD)** <u>SF-36 Physical Health:</u> I: 1.97 (8.77) vs C: 1.38 (6 83), p = 0.678 <u>SF-35 Mental Health:</u> I: 1.98 (8.87) vs C: –1.26 (8 99), p= 0.046 <u>Number of persistent symptoms:</u> I: 0.73 (4.41) vs C: –0.27 (31 7), p = 0.514 <u>MoCA:</u> I: 0.53 (2.26) vs

	C: 0.42 (2.83), p= 0.807 Sit-to-Stand Test: I: 0.58 (2.76) vs C: 0.29 (2.98), p = 0.094 HADS: I: –1 .87 {6.24) vs C: –0. 1 0 {5.59), p = 0.098 ISI: I: –1 1 9 (5.82) vs C: –0.52 {5.20), p = 0.496 Self-efficacy: I: –0.85 (8.85) vs C: 0.77 (6.19), p = 0.953
Limitations Noted	Per protocol-analysis; participants unblinded; differences in baseline symptoms; adherence variability; predominantly female sample; reinfections/relapses during program; short-term follow-up (3 months)
Risk of bias	Moderate

Lerner et al. 2023

Author	Lerner et al. [63]
Year	2023
Country	USA
Study design Setting Population Follow up	RCT Primary care setting Adults aged ≥18 (78.6% female, IG: mean age 41.5±14.6, CG: mean age 40.7±12.7) with self-reported new-onset olfactory dysfunction and clinically suspected or laboratory-confirmed SARS-CoV-2 infection. No data provided on previous possible hospitalisation due to covid-19 Not completely fulfilling WHO criteria for post covid-19, but authors do themselves consider the study population to demonstrate persistent covid-related OD 6 weeks
Intervention Participants (n) Drop-outs (n)	Daily capsules of 2000 mg omega-3 fatty acid supplementation 70 13
Control Participants (n) Drop-outs (n)	Placebo 69 9
Outcomes	**Primary outcomes** Change in BSIT score between-group difference at 6 weeks, 95% CI: −0.43 (−1.13 to 0.27), as SMD: 0.228 (−0.15 to 0.59), p=0.221 Quality of life (modified brief QOD-NS survey): No significant difference over time in the two groups (β=0.004, p =0.96) **Secondary outcomes** SNOT-22 (Sino-Nasal Outcome Test-22): No significant difference between groups over time (β =0.1605, p=0.462)
Comments	No ITT-analyses
Risk of bias	Moderate

Li et al. 2022

Author	Li et al. [64]
Year	2022
Country	China
Study design Setting Population Follow up	RCT, multicenter Home-based, outside health care setting Adults aged 18–75 years (55.5% female, mean age: 50.6 years) discharged after inpatient treatment for covid-19 (68.1% not severe, 86.6% oxygen support or non-invasive ventilation), with a mMRC dyspnoea score of 2–3. Not fulfilling WHO criteria for post covid-19 (long covid) completely ~28 weeks
Intervention Participants (n) Drop-outs (n)	Unsupervised home-based 6-week exercise programme comprising breathing control and thoracic expansion, aerobic exercise and LMS exercise, delivered via smartphone, and remotely monitored with heart rate telemetry 59 23
Control Participants (n) Drop-outs (n)	Short education at baseline 61 5
Outcomes	**Functional exercise capacity** Adjusted between-group difference in change in 6MWD from baseline (treatment effect): Post-treatment (6 weeks): 65.45 m (95% CI, 43.80 to 87.10; p<0.001) Follow-up (apx 28 weeks): 68.62 m (95% CI, 46.39 to 90.85; p<0.001) **Perceived dyspnoea** mMRC perceived dyspnoea, to favourable outcome (mMRC=0): Post-treatment (6 weeks): 1.46 (95% CI, 1.17 to 1.82; p=0.001) Follow-up (apx 28 weeks): 1.22 (95% CI, 0.92 to 1.61; p= 0.162) **Health-related quality of life** SF-12 PCS (higher scores indicating better health): Post-treatment (6 weeks): 3.79 (95% CI, 1.24 to 6.35; p=0.004) Follow-up (apx 28 weeks): 2.69 (95% CI, 0.06 to 5.32; p= 0.045) SF-12 MCS (higher scores indicating better health): Post-treatment (6 weeks): 2.18 (95% CI, –0.54 to 4.90; p= 0.116) Follow-up (apx 28 weeks): 1.99 (95% CI, –0.81 to 4.79; p= 0.164)
Risk of bias	Moderate

Longobardi et al. 2023

Author	Longobardi et al.
Year	2023
Country	Brazil
Study design Setting Population Follow up	RCT, single-blind Primary care/home-based Survivors (mean age 60.8±7.1 years (intervention) and 61.2±7.7 (control), 50% female) of severe/critical covid-19 (5±1 months after intensive care unit discharge) 16 weeks post study start (end of treatment)
Intervention Participants (n) Drop-outs (n)	A home-based semi-supervised exercise training programme, 3 sessions a week for 16 weeks 25 4
Control Participants (n) Drop-outs (n)	Standard of care including general advice for a healthy lifestyle 25 5
Outcomes	**Post-intervention between-group differences, adjusted MD (95% CI)** SF-36 physical functioning: 16.8 (5.8 to 27.9), p=0.005, favours intervention

	SF-36 general health 17.4 (1.8 to 33.1) p=0.024, favours intervention Cardiorespiratory fitness, time to exhaustion (s) 81.6 (–58.9 to 222.2) p=0.406 Pulmonary function, FEV (L) –0.16 (–0.77 to 0.44) p=0.881 Handgrip strength, kg 2.42 (–6.33 to 11.15) p= 0.879 Also reported: self-reported presence of persistent symptoms (no significant differences), several additional outcomes
Risk of bias	Moderate

Lukkunaprasit et al. 2024

Author	Lukkunaprasit et al.
Year	2024
Country	Thailand
Study design	Randomised controlled trial (double-blind, placebo-controlled)
Setting	College of Pharmacy, Rangsit University, Thailand
Population	66 participants (mean age ~41 years; majority female) with persistent long covid symptoms ≥4 weeks post-infection; most had mild initial covid-19 illness
Inclusion criteria	Thai adults ≥20 years; confirmed covid-19 (antigen or PCR test) ≥4 weeks prior; at least one long covid symptom verified by physician; willing to complete study procedures
Exclusion criteria	Current/suspected pneumonitis, chronic obstructive pulmonary disease, chronic lung diseases, chronic renal disease, cardiovascular diseases, cerebrovascular diseases, congenital heart diseases, psychotic disorders, hepatitits, cirrhosis, immunodeficiency disorders, positive THC test, pregnancy/breastfeeding, warfarin or benzodiazepine use, hypersensitivity to intervention, participation in other trials, other conditions interfering with participation
Intervention Participants (n) Drop-outs (n)	Clears-belong Plus (CPE): combined plant extract 4500 mg/day (1500 mg 3 times daily) (Citrus aurantifolia, Tiliacora triandra, Cannabis sativa, Alpinia galanga, Piper nigrum) for 7 days 33 2
Control Participants (n) Drop-outs (n)	Identical placebo 33 11
Follow up time points	Post-intervention (Day 8), and safety follow-up calls up to Day 14
Outcomes Measured	Primary: Change in CRP levels and total symptom score (0–57 scale): not reported by SBU. Secondary: Full recovery (symptom score=0), improvement in symptoms, HRQOL (EQ-5D-5L utility and VAS scores), adverse events
Results	**Post treatment (day 8)** Total symptom score, median (IQR) CPE: 5 (3, 8) Placebo: 8 (3, 11) EQ-5D-5L, utility score, median (IQR) CPE: 0.96 (0.94, 1.00) Placebo: 1.00 (0.96, 1.00) EQ-5D-5L, VAS score, median (IQR) CPE: 90 (85, 95)

	Placebo: 95 (85, 95) Any moderate to severe symptoms RR (95% CI): 0.57 (0.35 to 0.91) Moderate to severe fatigue RR (95 % CI): 0.25 (0.08 to 0.81) Moderate to severe PEM RR (95% CI): 0.35 (0.16 to 0.78) Adverse events (n) CPE: 31 Placebo: 33
Limitations Noted	Small sample size; short duration (7 days); new unvalidated symptom questionnaire; high placebo dropout (unblinding risk); low adherence rates; exclusion of many comorbidities limits generalizability
Risk of bias	Moderate

Maritescu et al. 2024

Author	Maritescu et al. [65]
Year	2024
Country	Romania
Study design	Randomised controlled trial (single-masked, outcome assessor blinded)
Setting	Pulmonary Rehabilitation Center, Clinical Hospital of Infectious Diseases and Pulmonology 'Victor Babes', Timisoara, Romania
Population	61 adults aged 54–74 years with long-term covid-19 symptoms (moderate to severe dyspnea and fatigue) persisting ≥3 months post-infection
Inclusion criteria	Confirmed covid-19 via RT-qPCR or antibody test; moderate/severe dyspnea and fatigue lasting ≥3 months post-infection; age 18–75; stable medical condition; no recent exacerbations or hospitalizations in past 3 months
Exclusion criteria	Severe comorbid conditions (heart disease, stroke, neurodegenerative diseases, acute illnesses); major surgery or hospitalization within past 6 months; severe psychiatric/cognitive disorders; active respiratory infections; immunocompromised status; severe mobility impairments; high alcohol or substance abuse
Intervention Participants (n) Drop-outs (n)	21-day pulmonary rehabilitation (aerobic, strength, breathing exercises) + daily 20-min progressive muscle relaxation sessions 35 4
Control Participants (n) Drop-outs (n)	21-day pulmonary rehabilitation (aerobic, strength, breathing exercises) 35 5
Outcomes Measured	Primary: Mental health (GHQ-12, PHQ-9, GAD-7) and sleep quality (PSQI). Secondary: Lung function (FVC, FEV1), exercise capacity (6MWT).
Results	The group receiving PR+PMR showed greater improvement in mental health (GHQ-12), depression (PHQ-9), anxiety (GAD-7), and sleep quality (PSQI) compared to PR alone ($p<0.0001$ for all comparisons). No significant difference in exercise capacity improvement between groups ($p=0.1711$)
Limitations Noted	Per protocol-analysis; single-center; small sample size (61 participants); short intervention (21 days); older adult population limits generalizability; no long-term follow-up to assess sustainability of improvements
Risk of bias	Moderate

McGregor et al. 2024

Author	McGregor et al. [66]
Year	2024
Country	United Kingdom
Study design Setting Population Follow up	Multicenter RCT Home-based online-delivered intervention Adults (26–86 years, mean 56 years, 52% women) discharged from NHS hospitals at least three months previously after covid-19 and with ongoing physical and/or mental health sequelae, n=585 3, 6 and 12 months
Intervention Participants (n) Drop-outs (n)	Rehabilitation Exercise and psychological support (REGAIN) programme, consisting of weekly home based, live, supervised, group exercise and psychological support sessions (1 h each) delivered online for 8 weeks 298 82
Control Participants (n) Drop-outs (n)	Usual care (a single online session of advice and support) 287 61
Control	Outcomes at 3 months, adjusted MD (95% CI) **Primary outcome** Health related quality of life, PROPr score: 0.03 (0.01 to 0.05), P=0.02 **Secondary outcomes** Fatigue, PROPr subscale score: 2.50 (1.19 to 3.81), P<0.001 HADS anxiety: 0.29 (−0.37 to 0.94), P=0.38 HADS depression: 0.46 (−0.14 to 1.05), P=0.13 Physical activity, IPAQ-SF (MET min/week): 1.66 (1.14 to 2.41), P=0.01 The effect on health related quality of life (PROPr score) was sustained at 12 months Additional outcomes reported
Risk of bias	Moderate

McIntyre et al. 2024

Author	McIntyre et al. [67]
Year	2024
Country	Canada
Study design Setting Population Follow up	RCT, double-blind Primary care Adults (mean age 43.65±12.26 in intervention group, 44.94±12.03 in control group, 65.8% female) with a history of confirmed SARS-CoV-2 infection who met WHO-defined 19 criteria for PCC 8 weeks
Intervention Participants (n) Drop-outs (n)	Vortioxetine (multimodal antidepressant). Participants aged 18–65 years: 10 mg/day week 1–2, 20 mg/day week 3–8. Participants aged 65+: 5 mg/day during week 1–2, 10mg/day week 3–8 75 7
Control Participants (n) Drop-outs (n)	Placebo 74 1
Outcomes	<u>Cognitive function (DSST total score)</u> Between-group analysis (unadjusted) did not show a significant difference in the overall change in cognitive function: MD (SE): 0,157 (0,171); 95% CI, –0.179 to 0.492; p=0.361 In the fully adjusted model, a significant treatment × time interaction was observed in favour of vortioxetine with baseline CRP as a moderator (p=0.012) A significant improvement in DSST scores were observed in vortioxetine versus placebo treated participants in those whose baseline CRP was above the mean (p=0.045) <u>Depressive symptoms (QIDS-SR16 total score)</u> A significant treatment x time interaction, $\chi 2=4.837$, p=0.028 was observed after adjusting for age, sex, education, and baseline QIDS-SR-16 total score Significant group ($\chi 2=4.653$, p=0.031) and time ($\chi =49.184$, p<0.001) effects were also observed A significant between-group difference was also observed: MD (SEM)=–1.516 (0.679), 95% CI,–2.847 to –0.185, p = 0.026 <u>HRQoL (WHO-5 total score)</u> A significant treatment x time interaction, $\chi 2=7.893$, p = 0.005 was observed after adjusting for age, sex, education, and baseline WHO-5 total score Significant group ($\chi 2$ 11 = 8.675, p = 0.003) and time ($\chi 2 = 29.69$, p < 0.001) effects were also observed, indicating that participants' WHO-5 scores significantly improved over time and at significantly different rates within each treatment group A significant between-group difference was observed: MD (SEM)=2.356 (0.807), 95% CI, 0.774 to 3.938, p=0.004
Comments	Additional publications based on study reported above, reporting on additional research questions and outcomes not relevant for this SBU-report, have been published in 2024 [68] [69]
Risk of bias	Moderate

McNarry et al. 2021

Author	McNarry et al. [70]
Year	2021
Country	United Kingdom
Study design Setting Population Follow up	RCT Primary care setting Adults (mean age 46.6±12.2 years; 88% female) recovering from self-reported covid-19 (9.0±4.2 months post-acute infection) with breathlessness. No data provided on previous possible hospitalisation due to covid-19. 8 weeks
Intervention Participants (n) Drop-outs (n)	Inspiratory Muscle Training, 3 unsupervised sessions/week for 8 weeks, with a handheld inspiratory flow resistive device that wirelessly syncs to a mobile device via an App to provide graphical biofeedback. 224 113
Control Participants (n) Drop-outs (n)	"Usual care" waitlist control 57 20
Outcomes	<u>Health-related quality of life (K-BILD total score):</u> No between-group difference post-intervention I: 58.2±12.3 C: 59.5±12.4 p<0.05 See study for additional results on several secondary outcomes on respiratory function (no significant between-group differences post-intervention based on ITT-analysis)
Risk of bias	Moderate

Melián-Ortíz et al. 2025

Author	Melián-Ortíz et al. [71]
Year	2025
Country	Spain
Study design	Triple-blind randomised controlled pilot trial
Setting	Clinical University of the Faculty of Nursing and Physiotherapy Salus Infirmorum, Pontifical University of Salamanca, Madrid Campus, Spain
Population	Women diagnosed with post-covid-19 condition for >1 year; n=16 completed intervention (EG n=9; CG n=7); mean age 46.1 years; recruited via AMACOP patient association.
Inclusion criteria	Women diagnosed with post-covid-19 condition for >1 year; presence of central sensitization symptoms.
Exclusion criteria	Age <18 or >60; previous spinal surgery or trauma; pregnancy; fibromyalgia diagnosis; pacemaker or drug-dispensing electronic implanted pump; skin sensitivity disorders.
Intervention Participants (n) Drop-outs (n)	Active superficial neuromodulation (NESA XSIGNAL®). Total scheduled sessions: 15 over 2 months, alternating days (3×/week). Protocol included programs P1, P5, P6, P7, P8 with varying session durations 9 0
Control Participants (n) Drop-outs (n)	Placebo device. Total scheduled sessions: 15 over 2 months, alternating days (3×/week). Protocol included programs P1, P5, P6, P7, P8 with varying session durations 9 2
Follow up time points	Baseline (T0), mid-intervention (T1), post-intervention (T2)
Outcomes Measured	Mechanical sensitization: PPT at C5–C6, D5–D6, and tibialis anterior; Heart rate variability (SDNN, rMSSD); resting heart rate; Salivary cortisol levels; Fatigue (MFIS); Sleep quality (PSQI); Quality of life (SF-36: 8 domains)
Results	**Post-intervention (T2), per protocol-analysis, I: n=9, C: n=7, Mean (SD)** <u>PPT C5–C6 vertebral level (kg):</u>

	I: 1.87 (0.78) C: 1.92 (1.76) <u>PPT D5–D6 dorsal level:</u> I: 2.27 (0.91) C: 2.37 (2.59) <u>PPI tibialis anterior:</u> I: 3.34 (1.26) C: 2.13 (1.56) <u>Heart rate (bpm):</u> I: 82.22 (10.69) C: 77.29 (10.93) <u>PSQI:</u> I: 9.22 (6.04) C: 8.14 (3.29) <u>MFIS:</u> I: 51.78 (22.94) C: 51.99 (16.39) <u>SF-36:</u> Physical function I: 50.49 (28.89) C: 63.75 (20.06) Physical role I: 25.00 (35.36) C: 9.76 (19.01) Body pain I: 36.00 (21.82) C: 50.48 (20.67) General health I: 28.78 (12.23) C: 33.19 (14.23) Vitality I: 31.67 (10.16) C: 24.81 (14.65) Social function I: 47.22 (39.41) C: 51.67 (39.81) Emotional role I: 48.15 (47.46) C: 60.00 (40.55) Mental health I: 52.88 (24.25) C: 63.35 (19.44)
Limitations Noted	Per protocol-analysis; insufficient sample size (pilot instead of full RCT); recruitment challenges; no correction for multiple comparisons; potential placebo effects; small number of participants limiting statistical power.
Risk of bias	Moderate

Mogensen et al. 2025

Author	Mogensen et al. [72]
Year	2025
Country	Denmark
Study design	Randomised, placebo-controlled, investigator-blinded single-center trial
Setting	Department of Otorhinolaryngology, Head & Neck Surgery & Audiology, , Rigshospitalet, Copenhagen Denmark
Population	Adults ≥18 years with COVID-19–related olfactory dysfunction >12 weeks. Median age 49 years; 71% female; majority with hyposmia ± parosmia.
Inclusion criteria	Adults ≥18 years; confirmed COVID-19 (PCR); anosmia/hyposmia ± parosmia diagnosed by Sniffin' Sticks TDI test; olfactory dysfunction >12 weeks; ability to understand Danish.
Exclusion criteria	Other causes of olfactory dysfunction (sinonasal disease, neurological disease); abnormal rhinoscopy; inability to understand Danish; non-compliance.
Intervention Participants (n) Drop-outs (n)	Twice-daily classical olfactory training with 4 essential oils (orange, lavender, clove, peppermint) for 12 weeks. All participants recorded adherence in diaries and received weekly reminders. 32 7
Control Participants (n) Drop-outs (n)	Identical twice-daily protocol using odor-free oils in identical containers. All participants recorded adherence in diaries and received weekly reminders. 33 9
Follow up time points	Baseline and 12-week follow-up
Outcomes Measured	Primary: Change in Sniffin' Sticks TDI total score (threshold, discrimination, identification). Secondary: Subjective olfactory function (NRS 0–10); quality of life related to olfactory dysfunction (NRS).
Results	**Per protocol-analysis** TDI score at 12 weeks, median (IQR): I: 28.50 (21.63 to 30.50) C: 25.25 (19.94 to 28.69) Subjective olfactory function, NRS, median (IQR): I: 5 (4.00 to 7.50) C: 7 (4.00 to 9.00) Self-rated QoL, NRS, median (IQR): I: 4.00 (3.00 to 7.50) C: 4 (2.25 to 7.00)
Limitations Noted	Per protocol-analysis; unable to blind most participants due to residual olfactory function; higher than expected dropout; study may be underpowered; high proportion with long-duration dysfunction; high prevalence of parosmia; adherence self-reported; limited generalizability to early-phase olfactory dysfunction.
Risk of bias	Moderate

Momtazmanesh et al. 2023

Author	Momtazmanesh et al. [73]
Year	2023
Country	Iran
Study design Setting Population Follow up	RCT, double-blind Self-administration outside health care setting Patients aged 18–65 (mean age 37.32±9.59 (intervention) and 35.16±8.24 (control), 46% female) with a history of covid-19-related hospitalisation, and at least 20 days since onset, and 7 days since last day of symptoms; MMSE ≤23 or MoCa ≤22. Not completely fulfilling WHO criteria for post covid-19) 6 and 12 weeks
Intervention Participants (n) Drop-outs (n)	Famotidine (40 mg, twice daily for 12 weeks) 29 7 (Week 6: 5, week 12: 2)
Control Participants (n) Drop-outs (n)	Placebo 29 7 (Week 6: 5, week 12: 2)
Outcomes	Changes in cognitive function from baseline to week 12 (MMSE; mean (SD)) I = 4.96 (2.34) C = 2.68 (1.52) MD (95% CI): 2.28 (1.16 to 3.4), t=4.091, p<0.001 Rm GLM analysis showed a significant effect for treatment (F = 8.97, p-value = 0.004) and time × treatment (F = 11.00, p-value <0.001) Assessment of cognitive function (MoCA; mean (SD)) I = 5.76 (1.74) C = 2.92 (1.44) MD (95% CI): 2.84 (1.93 to 3.75), t=6.288, p<0.001 Rm GLM analysis showed a significant effect for treatment (F = 13.36, p-value = 0.001) and time × treatment (F = 20.5, p-value <0.001) Assessment of depression symptoms (HAM-D; mean (SD)) I = −2.16 (1.46) C = −1.24 (1.23) MD (95% CI): −0.92 (−1.69 to −0.15), t= −2.403, p=0.020 Rm GLM analysis showed a significant effect for time (F = 65.28, p-value <0.001) and time × treatment (F = 5.13, p-value = 0.014) but not for treatment on changes of HAM-D scores. Assessment of anxiety symptoms (HAM-A; mean (SD)) I = − 0.8 (1.19) C = − 0.2 (0.5) MD (95% CI): −0.60 (−1.12 to−0.07), t= −2.324, p=0.027 Rm GLM analysis indicated that time (F = 12.15, p:< 0.001) and time × treatment (F = 4.27, p-value = 0.031) had significant effects on changes of HAM-A scores.
Risk of bias	Moderate

Murano et al. 2025

Author	Murano et al. [74]
Year	2025
Country	Italy
Study design	Two-arm randomised controlled trial with repeated measures
Setting	Department of Anesthesia and Critical Care, General Hospital in Lecco, Italy
Population	Covid-19 ICU survivors. Mean age ~60; 65.6% male.
Inclusion criteria	1) New-onset anxiety, depression or insomnia after SARS-CoV-2 infection and ICU stay, and chronic pain after SARS-CoV-2 infection and ICU stay; 2) ICU hospitalization in 2021–2022 for covid-19; 3) >18 years old; 4) On drug therapy for anxiety/depression/insomnia or chronic pain; 5) No pre-covid history of these symptoms.
Exclusion criteria	1) Undergoing CBT prior to covid-19; 2) <18 years; 3) chronic cancer pain; 4) not on current drug therapy; 5) pre-existing anxiety, depression, insomnia, or pain before infection; 6) inability to understand/follow protocol.
Intervention Participants (n) Dropouts (n)	8-week MBSR program, 2 hours/week, group format (4–9 per group), homework 20–45 min/day, led by trained psychologists/nurses. 52 5
Control Participants (n) Dropouts (n)	Usual care with drug therapy, treatment and evaluations 53 10
Follow up time points	Baseline, 6 months, and 12 months after MBSR program completion
Outcomes Measured	Primary: Chronic pain intensity and interference (Brief Pain Inventory – Short Form). Secondary: Anxiety (HADS-A), Depression (HADS-D), Insomnia (Insomnia Severity Index). Additional: Concurrent symptom clusters (pain, anxiety, depression, insomnia).
Results	**Per protocol-analysis at 12 months** BPI-SF subscales <u>Pain on average, mean (SD):</u> I: 2.55 (0.90) C: 3.04 (1.29) p= 0.051 <u>Pain right now, mean (SD):</u> I: 1.65 (1.36) C: 1.67 (1.04) p= 0.919 <u>Pain interference with general activity, mean (SD):</u> I: 1.81 (1.07) C: 2.04 (1.74) p= 0.507 Other pain interference measures are also reported <u>HADS-anxiety, mean:</u> I: 10.88 C: 13.41 t = –5.167 p< 0.001 <u>HADS-depression, mean:</u> I: 9.67 C: 10.69 t= –2.458 p= 0.018 Results at 6 months are also reported

Limitations Noted	Per protocol-analysis; did not reach planned sample size; monocentric design; self-administered outcome tools; 3 patients lost at 12-month follow-up; possible expectation bias; effects may not persist to 12 months.
Risk of bias	Moderate

Navas-Otero et al. 2024

Author	Navas-Otero et al. [75]
Year	2024
Country	Spain
Study design Setting Population Follow up	RCT, singel-blind Outpatient care Participants (>18 years) recruited from a regional long covid association with a diagnosis of long covid-19 syndrome (mean age apx 43–44 years, apx 80% female; average time since infection apx 18–20 months). Thus, population likely fulfilling the WHO criteria. 6 weeks
Intervention Participants (n) Drop-outs (n)	A lifestyle adjustment program, based on symptom monitoring and recognition of symptomatology and on the other hand, adaptation and functional improvement 27 0
Control Participants (n) Drop-outs (n)	Control group. The control group intervention received the standard medical care, plus a leaflet with information about the main long covid-19 symptoms 27 0
Outcomes	Outcome measures: <u>Quality of life (EQ-5D VAS), dimensions assessed:</u> - Mobility, p for group comparison =0.74 - Self-Care p for group comparison =0.004, in favour of active intervention - Daily Living p for group comparison =0.749 - Pain/Discomfort p for group comparison =0.660 - Anxiety/Depression, p for group comparison =0.009 in favour of active intervention - EQ-D5 VAS, p for group comparison =0.085 <u>Disability (WHODAS 2.0):</u> Of seven subscales tested, one showed a statistically significant finding in favour of active intervention: - Selfcare p for group comparison =0.014 - Total score WHODAS, p for group comparison =0.495 <u>The impairment in functioning (WSAS):</u> Of five subscales tested, none showed a statistically significant finding. Total score for WSAS, p for group comparison =0.978
Comments	Multiple testings and no correction
Risk of bias	Moderate

Nerli et al. 2024

Author	Nerli et al. [76]
Year	2024
Country	Norway
Study design	Randomised clinical trial (pragmatic, parallel-group)
Setting	Single referral center in South-Eastern Norway Regional Health Authority
Population	310 patients with mild to moderate post-covid-19 condition; mean age 43 years; 72% female; symptoms ≥3 months; functional disability interrupting normal activities
Inclusion criteria	Age ≥16; confirmed covid-19 (PCR or antigen); persistent symptoms ≥3 months; functional disability interrupting normal activities
Exclusion criteria	Other chronic illness explaining symptoms; sustained organ damage (heart, lung, neurological disorders); bedridden; insufficient Norwegian language skills
Intervention Participants (n) Dropouts (n)	Intervention group: Brief outpatient rehabilitation program (2–8 encounters, 2–6 weeks apart) based on Cognitive Activation Theory of Stress (CATS); physicians and physiotherapists trained in cognitive and behavioral approaches 154 29
Control Participants (n) Dropouts (n)	Care as usual 156 54
Follow up time points	Baseline (T0), post-intervention (T1), and 12 months after inclusion (T2)
Outcomes Measured	<u>Primary:</u> Physical function (SF-36 Physical Function Subscale) <u>Secondary:</u> SF-36 subscales (vitality, general health, social function, etc.), return to work self-efficacy, fatigue, postexertional malaise, breathlessness, cognitive difficulties, sleep problems, anxiety, depression, smell/taste abnormalities <u>Safety outcomes:</u> Healthcare contacts, hospital admissions, novel diseases, worsening symptoms, work ability, suicidality
Results	ITT-analysis with multiple imputation of missing values. Results adjusted for baseline values of each effectiveness end point <u>SF-36 subscores, T2 (12 months after inclusion), MD (95% CI):</u> - Physical function: 9.0 (4.0 to 13.9) - Role limitations due to physical problems: 14.9 (3.6 to 26.2) - Bodily pain: 2.4 (−1.0 to 5.8) - General health: 7.6 (1.2 to 13.9) - Vitality: 7.6 (2.3 to 13.0) - Social functioning: 14.0 (7.2 to 20.8) - Role limitations due to emotional problems: 17.4 (4.4 to 30.4) - Mental health: 6.6 (3.3 to 9.9) <u>Return to work self-efficacy, T2, MD (95% CI):</u> - 0.4 (0.1 to 0.7) <u>Symptoms, T2, MD (95% CI):</u> - Fatigue: −2.4 (−4.2 to −0.7) - Post-exertional malaise: −12.4 (−19.8 to −5.1) - Breathlessness: −0.4 (−0.6 to −0.2) - Cognitive difficulties: −0.3 (−0.5 to −0.1) - Sleep problems: 4.8 (2.3 to 7.4) - Anxiety symptoms: −0.9 (−1.6 to −0.2) - Depressive symptoms: −1.2 (−1.9 to −0.5) - Smell and/or taste abnormalities: −0.1 (−0.4 to 0.2) Results at T1 (post intervention) also reported in study

	For SF-36, physical function subscore, a difference of 10 points was considered clinically significant.
Limitations Noted	Single-center design; lack of blinding (possible placebo effects); moderately impaired, mostly nonhospitalized participants (limits generalizability); attention imbalance between groups; no sham intervention; patient-reported outcomes only; potential missing data bias
Risk of bias	Moderate

Ogonowska-Slodownik et al. 2023

Author	Ogonowska-Slodownik et al. [77]
Year	2023
Country	Poland
Study design Setting Population Follow up	RCT Outpatient care Children 10 to 12 years old with symptoms typical of post covid-19 condition, including fatigue and shortness of breath/respiratory issues, at least one month after an initial covid-19 infection. After treatment (8 weeks)
Intervention Participants (n) Drop-outs (n)	AQUA - Aquatic aerobic exercises twice a week, 45 min per session, for eight weeks 27 2
Control 1 Participants (n) Drop-outs (n)	LAND - Land based aerobic exercises twice a week, 45 min per session, for eight weeks 29 6
Control 2 Participants (n) Drop-outs (n)	CONTROL – no exercise 30 4
Outcomes	**Primary outcomes** VO2 max [ml/kg/min] mean difference (95% CI) between groups post intervention 2.9 (–1.5 to 7.4) HR max [beats/min] mean difference (95% CI) between groups post intervention 1.8 (–6.9 to 10.6) VE [L/min] mean difference (95% CI) between groups post intervention 0.9 (–8.5 to 10.2) OUES [L/min] mean difference (95% CI) between groups post intervention 0.04 (–0.3 to 0.4) OUES [ml/kg/min] mean difference (95% CI) between groups post intervention 2.7 (–2.3 to 7.8) RER mean difference (95% CI) between groups post intervention 0.003 (–0.02 to 0.03) CFSQ mean difference (95% CI) between groups post intervention 1.2 (–3.6 to 6.1) **Secondary outcomes** PedsQL children mean difference (95% CI) between groups post intervention 4.3 (–2.8 to 11.5) PedsOL parent mean difference (95% CI) between groups post intervention 7.2 (0.9 to 13.5) Additional outcomes reported
Comments	A third group named control was included but participants were not identified the same way as for the other groups, nor were they included in the randomisation.
Risk of bias	Moderate

Okan et al. 2022

Author	Okan et al. [78]
Year	2022
Country	Turkey
Study design Setting Population Follow up	RCT Outpatient clinic and telerehabilitation in home environment Adults aged ≥18 years (44.6% female, mean age: 48.9 (intervention), 52.2 (control)) who had been previously (2 months prior) treated for covid-19 pneumonia in hospital (9% ICU admitted) Not completely fulfilling WHO criteria for post covid-19 5 weeks
Intervention Participants (n) Drop-outs (n)	Breathing exercises (respiratory control, pursed lip breathing, and diaphragmatic breathing exercises) 3/day for 5 weeks (one session performed via telemedicine each week) 26 0
Control Participants (n) Drop-outs (n)	A brochure explaining breathing exercises as above. The first practice session was performed face-to-face in hospital environment, similar to the intervention group. Patients recommended to practice a 20 to 30-minute light-intensity walk five times/week 26 0
Outcomes	**Functional capacity** Group x time interaction 6MWT: 95% CI: 1.254–9.631, F=31.324, p3<0.001; pη2=0.646 Significant difference with large* estimated impact magnitude (two-way mixed-effect ANOVA analysis with post-hoc Bonferroni correction) **Pulmonary function** Group x time interaction FEV1 %: 95% CI: 0.220–4.357, F=11.939, p3=0.001; pη2=0.193 Significant difference with large* estimated impact magnitude (two-way mixed-effect ANOVA analysis with post-hoc Bonferroni correction) Group x time interaction FVC %: 95% CI: 0.221–3.568, F=13.815, p3=0.001; pη2=0.216 Significant difference with large* estimated impact magnitude (two-way mixed-effect ANOVA analysis with post-hoc Bonferroni correction) Group x time interaction FEV1/FVC %: Difference not significant Group x time interaction MVV %: 95% CI: 3.212–7.250, F=27.979, p3<0.001, pη2=.537) Significant difference (two-way mixed-effect ANOVA analysis with post-hoc Bonferroni correction) *The value was considered: - small if it was 0.01≤η2<0.06 - moderate if it was 0.06≤η2<0.14, and - large if it was ≥0.14
Risk of bias	Moderate

Ojeda et al. 2024

Author	Ojeda et al. [79]
Year	2024
Country	Spain
Study design Setting Population Follow up	RCT, single-blind Primary care setting Adult survivors (aged 65 (56−71) years, 73.5% male) from critically severe (confirmed) covid-19 infection with at least one of the following inclusion criteria: 1) APACHE II score >14, 2) ICU stay >10 days, 3) acquired weakness in ICU, 4) delirium during ICU admission 6 months
Intervention Participants (n) Drop-outs (n)	A follow up program, patient education on post-intensive care syndrome and pain, and a psychological intervention based on Rehm's self-control model in patients with abnormal depression scores (≥8) in the Hospital Anxiety and Depression Scale (HADS) at the baseline visit 51 8
Control Participants (n) Drop-outs (n)	Care as usual (follow-up appointments with their referring physicians (primary care physicians or specialists not directly involved in study). No preventive psychological intervention was administered to the patients as part of study. 51 8
Outcomes	**Quality of life** <u>EQ VAS – intervention group; control group; p-value:</u> Baseline: 70 (60 to 80); 75 (60 to 80); p=0.56 3-month: 70 (63 to 80); 78 (60 to 80); p=0.6 – adjusted p-value: >0.99 6-month: 80 (65 to 90); 80 (60 to 90); p=0.69 – adjusted p-value: >0.99 <u>EQ 5D/5L – intervention group; control group; p-value:</u> Baseline: 0.8 (0.6 to 0.9); 0.8 (0.6 to 0.9); p=0.18 3-month: 0.9 (0.7 to 1); 0.8 (0.6 to 0.9); p=0.72 – adjusted p-value: >0.99 6-month: 0.9 (0.7 to 1); 0.8 (0.6 to 1); p=0.09 – adjusted p-value: 0.86 <u>Pain (BPI – first question*) intervention group; control group; p-value:</u> Baseline: 24 (53); 28 (55); p>0.99 3-month: 20 (54); 23 (52); p>0.99 – adjusted p-value: >0.99 6-month: 20 (47); 21 (49); p>0.99 – adjusted p-value: >0.99 <u>Anxiety HADS-A intervention group; control group; p-value:</u> Baseline: 6 (12); 9 (20); p=0.4 3-month: 8 (22); 7 (16); p=0.56 – adjusted p-value: >0.99 6-month: 7 (16); 7 (17); p>0.99 – adjusted p-value: >0.99 <u>Depression HADS-D intervention group; control group; p-value:</u> Baseline: 5 (10); 6 (13); p=0.51 3-month: 5 (14); 9 (21); p=0.6 – adjusted p-value: >0.99 6-month: 5 (12); 9 (22); p=0.6 – adjusted p-value: >0.99 See study for additional results on BPI-SF average pain item, BPI-SF interference score, DN4, PCS, PTSD Checklist (PCL-5) *''Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain?''
Risk of bias	Moderate

Oliver-Mas et al. 2023

Author	Oliver-Mas et al. [80]
Year	2023
Country	Spain
Study design Setting Population Follow up	RCT, double-blind Medical facility Patients (mean age 45.66±9.49 years, 78.72% female) with post-covid fatigue (MFIS>50), 19% previously hospitalised 1 month
Intervention Participants (n) Drop-outs (n)	Transcranial direct current stimulation (tDCS), 8 sessions (2 mA) á 20 minutes 24 0
Control Participants (n) Drop-outs (n)	Sham tDCS 24 0
Outcomes	**Primary outcome** Change in fatigue, rm ANOVA, time x group interaction: MFIS-total: not significant ($F_{(2,82)}$=1.730, p=0.184) MFIS-physical: significant, favouring intervention ($F_{(2,82)}$=3.517, p=0.034) MFIS-cognitive: not significant ($F_{(2,82)}$=0.55, p=0.496) MFIS-psychosocial: not significant ($F_{(2,82)}$=1.730, p=0.184) **Secondary outcomes** Depression (BDI-II): significant, favouring intervention ($F_{(2,82)}$=3.447, p=0.036) Executive function (Stroop – IG): non-significant results Quality of life (EuroQoL-5D – VAS): non-significant results All the adverse events reported were mild and transient, with no differences between the active stimulation and sham stimulation groups
Risk of bias	Moderate

Oliver-Mas et al. 2025

Author	Oliver-Mas et al. [81]
Year	2025
Country	Spain
Study design	Randomised parallel comparative feasibility trial (double-blind)
Setting	Department of Neurology, Hospital Clínico San Carlos, Madrid, Spain
Population	Adults with post-covid condition and clinically significant fatigue. n=67 randomised. Mean age 47.8 years; ~81% female; mean symptom duration ~32 months.
Inclusion criteria	Confirmed covid-19 infection ≥6 months prior; WHO-defined post-covid condition; clinically significant fatigue (MFIS ≥38); native Spanish proficiency; written informed consent.
Exclusion criteria	Neurological disorders or systemic diseases affecting fatigue; active psychiatric disorders affecting fatigue/cognition; history of stroke, traumatic brain injury or meningitis; current treatment with radiotherapy or chemotherapy for cancer; drug use; other conditions with potential impact on fatigue; history of substance abuse; contraindication for tDCS.
Interventions Participants (n) Dropouts (n)	M1 + Cognitive Training (M1+CT): Anodal tDCS over left primary motor cortex (2 mA, 20 min/session) combined with adaptive computerized cognitive training; 15 sessions 33 2
Control Participants (n) Drop-outs (n)	DLPFC + Cognitive Training (DLPFC+CT): Anodal tDCS over left dorsolateral prefrontal cortex (2 mA, 20 min/session) combined with the same adaptive cognitive training; 15 sessions. 34 2
Follow up time points	Baseline (T0); post-treatment (T1); 1-month follow-up (T2)
Outcomes Measured	Primary: Physical fatigue (Fatigue Severity Scale – FSS)

	Secondary: Modified Fatigue Impact Scale (MFIS total, physical, cognitive); ecological momentary assessment of fatigue; cognition (attention, working memory, processing speed, executive function, memory); depression (BDI-II); anxiety (STAI); sleep quality (PSQI); pain (Brief Pain Inventory); quality of life (EuroQoL-5D); feasibility and safety.
Results	ANOVA group effect: F (p-value) - FSS: 0.508 (0.479) - MFIS-total: 0.535 (0.467) - MFIS-physical: 1.360 (0.248) - MFIS-cognitive: 0.033 (0.856) - BDI-II: 0.633 (0.429) - PSQI: 1.188 (0.280) - STAI-state: 0.009 (0.923) - BPI-intensity: 0.087 (0.770) - BPI-functionality: 0.104 (0.748) - EuroQoL-5D: 0.562 (0.456) No significant time-per-group interaction was found in any cognitive test.
Limitations Noted	No sham or usual-care control group; inability to isolate effects of tDCS vs cognitive training; short follow-up duration (1 month); relatively small sample size; generalizability may be limited.
Risk of bias	Low

Palau et al. 2022

Author	Palau et al. [82]
Year	2022
Country	Spain
Study design Setting Population Follow up	RCT Home based inspiratory muscle training (IMT) program. Symptomatic adult aged >18 (median age 50.4±12.2, 42% female) with a previous admission due to SARS-CoV-2 pneumonia and at least 3 months after discharge. 12 weeks, approximately
Intervention Participants (n) Drop-outs (n)	Base line physiotherapist assessment and education in home-based inspiratory training program consisting of twice daily 20 min inspiratory resistance training of 25%–30% of measured maximal inspiratory pressure for 12 weeks 13 0
Control Participants (n) Drop-outs (n)	Usual care including baseline visit 13 0
Outcomes	**Primary outcome** Average change from baseline in mean peak VO_2: At 3 months, the mean of peakVO_2 was higher in those in the IMT group (22.2mL/kg/min; 95% CI, 21.3 to 23.2 vs 17.8mL/kg/min; 95% CI, 16.8 to 18.7; p<0.001) **Secondary outcome** Included dimensions in the Quality of life EQ-5D-3L tool: A significant improvement in usual activities (−0.31, 95% CI, −0.54 to −0.07, p=0.013) and anxiety/depression (−0.53, 95% CI, −0.67to −0.40, p<0.001) dimensions was found in IMT group with no significant changes in the usual care group. IMT resulted in a non-significant improvement in both groups' mobility, self-care and pain/discomfort dimensions. A significant change in the patient's self-rated health on the vertical VAS dimension in the IMT group (21.1, 95% CI, 12.9to 29.4, p<0.001) Additional outcomes reported
Risk of bias	Moderate

Philip et al. 2022

Author	Philip et al. [83]
Year	2022
Country	United Kingdom
Study design Setting Population Follow up	RCT Outpatient setting Participants recovering from covid-19 (mean age 49 (SD 12) years, 81% women) with ongoing breathlessness, with or without anxiety, ≥4 weeks after symptom onset (the study population, thus, does not fulfil the WHO-criteria for post covid-19) 6 weeks.
Intervention Participants (n) Drop-outs (n)	The English National Opera Breathe programme, breathing retraining using singing techniques (6 weeks, online) 74 16
Control Participants (n) Drop-outs (n)	Care as usual 76 5
Outcomes	**Primary outcomes** <u>Change in HRQoL, baseline – end of 6-week course, assessed by SF-36, MHC and PHC score</u> Compared to usual care, ENO Breathe was associated with an improvement in MHC score (regression coefficient 2.42 (95% CI, 0.03 to 4.80), p=0.047), but not PHC score (0.60, –1.33 to 2.52, p=0·54). <u>VAS for breathlessness (running):</u> Favoured ENO Breathe participation: –10.48 (–17.23 to –3.73), p=0.0026 No other statistically significant between-group differences in any other secondary outcome were observed
Comments	The study population does not fulfil the WHO-criteria for post covid-19
Risk of bias	Moderate

Pleguezuelos et al. 2024

Author	Pleguezuelos et al. [84]
Year	2024
Country	Spain
Study design Setting Population Follow up	RCT, single blinded Outpatients setting Participants recruited from hospital care (apx 57–73% hospitalized, apx 30–42% in ICU), aged >18 years, (mean age about 54 (SD 11) years, about 21% women) with confirmed previous acute covid-19 infection, and presenting post-covid symptoms. The group did NOT fulfil the WHO-criteria at the time of inclusion. 15 weeks (also evaluated at 3 months and 12 months (detraing)
Intervention Participants (n) Drop-outs (n)	A supervised homebased telerehabilitation program combining aerobic and strength exercises three times weekly for 15 weeks 75 9
Control Participants (n) Drop-outs (n)	No supervised telerehabilitation. Participants in control group were asked to carry out their routine daily life activities 75 10
Outcomes	**Primary outcome** Cardiopulmonary exercise test performed on ergometric bicycle (several tests performed) <u>Exercise capacity (exercise time in seconds):</u> An intervention × time interaction effect was detected (p=0.001) in favour of intervention <u>Peak oxygen uptake (V02):</u>

	No intervention × time interaction effect or main intervention effect was observed in the relative V̇O2peak (p>0.05) Power output (Watts): In power output (Figure 3C), an intervention × time interaction effect was found (p<0.001) Mechanical efficiency: In delta efficiency an intervention × time interaction effect was detected (p=0.001) Additional outcomes reported.
Risk of bias	Moderate

Polat et al. 2025

Author	Polat et al. [85]
Year	2025
Country	Türkiye
Study design	Single-center, randomised, assessor-blinded controlled trial
Setting	Department of Physical Medicine and Rehabilitation, Sivas Cumhuriyet University, tertiary university hospital, Türkiye.
Population	79 adults aged 18–65 years with post-covid-19 condition (PCC) diagnosed ≥90 days after PCR-confirmed covid-19 infection and experiencing PCC symptoms for at least 8 weeks.
Inclusion Criteria	Age 18–65 years; PCR-confirmed covid-19 infection ≥90 days earlier; persistent PCC symptoms for ≥8 weeks.
Exclusion Criteria	History of hospitalization for covid-19 with severe complications; pneumonia or organ failure; recent myocardial infarction or orthopedic surgery within 2 years; uncontrolled cardiovascular disease; chronic respiratory diseases; fibromyalgia syndrome; neurological diseases; inability to mobilize.
Intervention Participants (n) Drop-outs (n)	Virtual Reality Exercise Group (VRG): semi-immersive motion-controlled video game–based VR exercise (Xbox Kinect Sports Rivals); 30–45 minutes, 3 times/week for 8 weeks under physiotherapist supervision. 39 2
Control Participants (n) Drop-outs (n)	Conventional Exercise Group (CTG); supervised conventional exercise including moderate-intensity aerobic (bicycle ergometer), strength training, stretching, and neuromuscular balance exercises; 30–45 minutes, 3 times/week for 8 weeks. 40 3
Follow-up Timepoints	Baseline and post-intervention at 8 weeks
Primary Outcome	Pain intensity measured using the Visual Analog Scale (VAS, 0–10 cm, higher = worse pain)
Secondary Outcomes	Fatigue Severity Scale (FSS), Hospital Anxiety and Depression Scale (HADS-A and HADS-D), quality of life using SF-12 (physical and mental components), and functional exercise capacity measured by the 6-Minute Walk Test (6MWT).
Results	**Mean difference (95% CI) at 8 weeks** Pain intensity (VAS): −1.37 (−1.73 to −1.00), p <0.001 Fatigue (FSS): −4.19 (−6.99 to −1.39), p=0.004 Anxiety (HADS-A): 0.16 (−0.45 – 0.78), p=0.601 Depression (HADS-D): −1.16 (−2.02 to −0.31), p=0.009 Functional exercise capacity (6MWT-meters): +9.9 (−4.6 to 24.4), p=0.175

	Quality of life (SF-12 Physical): −0.18 (−3.97 to 3.61), p=0.926 Quality of life (SF-12 Mental): −2.10 (−6.91 – 2.72), p=0.388 Safety: No adverse events or post-exertional symptom exacerbation were reported. Participants tolerated both exercise programs well.
Limitations noted	Per protocol analysis; single-center study; restricted generalizability to those with severe disease; short follow-up time; PEM not assessed with standardized instrument
Risk of bias	Moderate

Rana et al. 2025

Author	Rana et al. [86]
Year	2025
Country	India
Study design	Double-blind randomised placebo-controlled feasibility trial (two parallel arms)
Setting	D. N. De Homoeopathic Medical College & Hospital, Kolkata, West Bengal, India
Population	60 adults (aged 18–65) with post-covid-19 conditions (symptoms ≥3 months); 76.7% female in IHMP group, 56.7 % in control group
Inclusion criteria	Confirmed SARS-CoV-2 infection; ≥3 months from onset; symptoms lasting ≥2 months; literate adults; able to consent
Exclusion criteria	Pneumonia, SpO2 <95%, abnormal labs (liver enzymes, lipid profile, urea, creatinine, blood sugar), hypertension ≥140/90 or hypotension <90/60, chronic diseases (uncontrolled diabetes, heart, liver, kidney disease), malignancy, psychiatric illness, COPD/asthma, concurrent other treatments, pregnancy/lactation, substance abuse, prior homeopathy within 6 months, concurrent trial participation
Intervention Participants (n) Drop-outs (n)	IHMP group: Individualized homeopathic medicines (Natrum muriaticum, Pulsatilla nigricans, Rhus toxicodendron, Calcarea carbonica, etc.) in centesimal potencies (6c, 30c, 200c, 1000c) plus concomitant care for 3 months. Standard non-pharmacological advice. 30 1
Control Participants (n) Drop-outs (n)	Placebo group: Identical-looking placebo globules plus concomitant care for 3 months. Standard non-pharmacological advice. 30 2
Follow up time points	Baseline, monthly assessments up to 3 months
Outcomes Measured	Primary: Post-covid-19 symptoms checklist score. Secondary: Measure Yourself Medical Outcomes Profile v2 (MYMOP-2) scores (symptom 1, symptom 2, activity difficulty, well-being). Feasibility metrics: recruitment (34%), retention (95%), attrition (5%)
Results	**ITT analysis, missing data imputed through linear regression** Post covid-19 symptom checklist scores, MD (SE): Total symptom score: –4.2 (0.4) MYMOP-2 scores: - Symptom 1: –2.4 (0.3) - Symptom 2: –2.4 (0.4) - Difficulty in activity: –2.3 (0.3) - Feeling of well-being: –1.8 (0.3) - Profile score: –2.2 (0.3) Results are also reported after 1 and 2 months
Limitations Noted	Feasibility design; small sample size; short trial duration (3 months); single center; use of rescue remedies during unrelated acute events (potential confounding); predominance of female participants; no long-term follow-up
Risk of bias	Moderate

Rasmussen et al. 2023

Author	Rasmussen et al. [87]
Year	2023
Country	Denmark
Study design Setting Population Follow up	Investigator blinded RCT Outpatient Persons (mean age 57.2 (SD 10) years, 32% women) previously hospitalized for laboratory confirmed SARS-CoV-2, but no specific symptoms were required. 12 weeks
Intervention Participants (n) Drop-outs (n)	High-intensity interval training (HIIT) program with three 38 minutes supervised and individualized work out sessions including every week on bicycle ergometer with the aim to improve cardiorespiratory fitness 14 1
Control Participants (n) Drop-outs (n)	Standard care 14 1; 4 participants engaged in exercise program
Outcomes	The primary outcome was left ventricular mass measured with MRI, not reported here **Secondary outcomes** Lung function, measured with with spirometry: There were no statistically significant differences in between group comparisons for predictive values of FEV1, FVC, TLC and RV Functional capacity and HRQoL,measured with Post-Covid-19 functional scale PCFC: In terms of PCFS, similar proportions reported no functional limitations (PFCS 0) at baseline. At follow-up, this proportion had almost doubled in the HIIT group, whereas the proportion in the standard care group was similar as baseline Strength testing Upper and lower body strength were assessed by one-repetition maximum tests (the maximum amount of weight that can be lifted once with proper form through full range of motion, 1RM) in chest press- and leg press machines. Wmax and leg press 1RM increased similarly in both groups, whereas chest press 1RM was improved in the intervention group only, and there were no notable between group changes in body composition Physical activity level Posture and physical activity behaviors are measured using three axial accelerometer-based physical activity monitors Step counts per day and time spent at moderate/ high activity level changed in the HIIT group from baseline. However, time spent being inactive concurrently decreased in the HIIT group compared with the control group (ns) Additional outcomes reported
Risk of bias	Moderate

Redel et al. 2024

Author	Redel et al. [88]
Year	2024
Country	Netherlands
Study design	Randomised, double-blind, placebo-controlled trial
Setting	Franciscus Gasthuis & Vlietland Hospital, Rotterdam, Netherlands
Population	72 adults aged 18–70 years with long covid (persistent symptoms ≥3 months) within 12 months of SARS-CoV-2 infection; median age ~48 years; 62.5% female
Inclusion criteria	PCR-confirmed SARS-CoV-2 infection; at least two long covid symptoms per WHO criteria; symptoms <1 year; aged 18–70
Exclusion criteria	ICU admission for covid-19; abnormal chest radiograph or pulmonary function test; current acute covid-19; systemic immunological disorders; psychiatric disorders; use of immune-modulatory drugs; pregnancy or lactation; milk allergy
Intervention Participants (n) Dropouts (n)	Lactoferrin 1200 mg/day (600 mg twice daily) orally for 6 weeks + usual care (physiotherapy/psychological support as needed) 36 4
Control Participants (n) Dropouts (n)	Identical appearance placebo capsules twice daily for 6 weeks + usual care 36 3
Follow up time points	Baseline (T0), 6 weeks (T6), and 12 weeks (T12) post-randomisation assessments
Outcomes Measured	<u>Primary:</u> Fatigue (Fatigue Assessment Scale) <u>Secondary:</u> Anxiety and depression (HADS), cognitive failure (CFQ), muscle strength (handgrip, sit-to-stand), laboratory parameters (ferritin, transferrin saturation, CK, etc.)
Results	<u>Fatigue</u> No significant difference between intervention group (lactoferrin) and control group (placebo) at 6 or 12 weeks No differences between groups on secondary outcomes at 6 or 12 weeks <u>Adverse effects:</u> Mild and similar between groups
Limitations Noted	Single-center; relatively small sample size; concurrent other therapies (physiotherapy, occupational therapy) may confound results; short follow-up; potential placebo/Hawthorne effect; no pre-long-covid baseline data; uncertain dose/frequency adequacy
Risk of bias	Low

Rodríguez-Morán et al. 2024

Author	Rodríguez-Morán et al. [89]
Year	2024
Country	Mexico
Study design	Open-label randomised controlled clinical trial
Setting	Mexican Social Security Institute, Durango, Mexico
Population	60 adults (mean age 52.8 ± 12.6 years) with hypomagnesemia, vitamin D deficiency, and mild-to-moderate depression related to long-covid; confirmed covid-19 diagnosis via PCR; symptoms persisting ≥12 weeks
Inclusion criteria	Adults >30 years; confirmed covid-19 (PCR); hypomagnesemia (sMg<1.8 mg/dL); vitamin D deficiency (25-OH vit D <30 ng/mL); mild-to-moderate depression (BDI 11-30) persisting ≥12 weeks
Exclusion criteria	Pregnancy; use of antidepressants or magnesium/vitamin D supplements in past 90 days
Intervention Participants (n) Dropouts (n)	Magnesium chloride 1300 mg (382 mg elemental magnesium) + Vitamin D 4000 IU daily for 4 months. Supplements administered post-breakfast 30 0
Control Participants (n) Dropouts (n)	Vitamin D 4000 IU daily for 4 months. Supplements administered post-breakfast 30 1
Follow up time points	Baseline and 4 months post-intervention assessments (BDI, serum magnesium, vitamin D, metabolic parameters)
Outcomes Measured	Primary: Beck Depression Inventory (BDI) score (improvement defined as BDI <11). Secondary: Serum magnesium and vitamin D levels; metabolic parameters (glucose, triglycerides, HDL-c). Adverse events (mild gastrointestinal symptoms) monitored.
Results	Beck Depression Inventory (BDI) scores (assumed to report mean ± SD): I: 9.2 ± 7.5 C: 21.6 ± 9.1 p: 0.006 Adverse events (mild, no withdrawals), n: I: 6 C: 3
Limitations Noted	Per protocol-analysis; open-label design; lack of placebo control; small sample size; no pre-COVID baseline BDI scores; conducted at single center
Risk of bias	Moderate

Romanet et al. 2023

Author	Romanet et al. [90]
Year	2023
Country	France
Study design Setting Population Follow up	Open assessor blinded multicenter RCT Outpatient program setting Population (mean age 58 (SD 12) years, women 38%) with persistent respiratory symptoms after CARDS. Participants fulfilled WHO criteria for post covid-19 (long covid) 12 weeks
Intervention Participants (n) Drop-outs (n)	Exercise training rehabilitation (ETR) including both endurance and strength training for pulmonary rehabilitation,2 x 60 minutes per week for 12 weeks. Power intensity was adjusted according to each participant's progress until the target heart rate and dyspnea were reached 27 0 (4 chose standard physiotherapy during follow up)
Control Participants (n) Drop-outs (n)	Standard usual care during the 90 days and received standard physiotherapy at the rate of 2 x 30 min sessions per week for 10 weeks 33 0 (3 chose endurance training during follow up)
Outcomes	**Primary outcome** Measurement of dyspnea in its 3 dimensions, as assessed by the difference in the multidimensional dyspnea profile (MDP) score <u>Mean difference (95% CI) between-groups at 90 days:</u> MDP total score: –18.61 (–27.78 to –9.44), p<0.0001, in favour of intervention. Breathing discomfort: –1.74 (–2.81 to –0.67), p=0.0006, in favour of intervention. Sensory dimension: –9.92 (–14.67 to –5.18), p<0.0001, in favour of intervention. **Secondary outcomes** Measurement of functional dyspnoea (mMRC scale) <u>Mean difference (95% CI) between-groups at 90 days:</u> <u>mMRC:</u> –0.76 (–1.21 to –0.30), 0.001, in favour of intervention <u>Measurement of HRQoL (SF-12) at 90 days:</u> <u>SF-12 total score:</u> 8.24, 95% CI (0.22 to 16.25), p=0.14, in favour of intervention Additional outcomes reported
Risk of bias	Moderate

Samper-Pardo et al. 2023 & Leon Herrera et al. 2025

Author	Samper-Pardo et al. [91]
Year	2023
Country	Spain (3 month data)
Author	Leon-Herrera et al. [92]
Year	2025
Country	Spain (6 month data)
Study design Setting Population Follow up	RCT, open-label Primary health care Adults aged ≥18 (80% female, mean age 48.28±9.26) with confirmed covid-19 diagnosis >12 weeks prior and with persistent long covid symptoms. 3 months [46] and 6 months [Leon-Herrera 2025 (#1023)]
Intervention Participants (n) Drop-outs (n)	ReCOVery APP (with rehabilitative content and attended three sessions on motivational methodology, APP management, and strengthening of their personal constructs; health literacy, self-efficacy, and personal activation), in addition to treatment as usual established by their general practitioner 52 7
Control Participants (n) Drop-outs (n)	Treatment as usual established by their general practitioner 48 6
Outcomes	Samper Pardo et al **Primary outcome** Quality of life <u>SF-36 Physical health, 3 month follow-up – baseline, mean (SD):</u> I: 4.56 (12.14) C: 8.02 (14.38) p=0.234 CI (–9.20 to 2.28) <u>SF-36 Mental health, 3 month follow-up – baseline, mean (SD):</u> I: 5.07 (16.10) C: 3.20 (18.27) p=0.615 CI (–5.49 to 9.23) **Secondary outcomes** <u>Cognitive domains (memory, attention, language, or working memory measured with MoCA), 3 month follow-up – baseline, mean (SD):</u> I: 0.91 (4.24) C: 0.30 (2.87) p=0.439 CI (–0.93 to 2.14) <u>Physical functioning (30 s Sit-to-stand test) 3 month follow-up – baseline, mean (SD):</u> I: 0.32 (2.24) C: –0.28 (4.84) p= 0.806 CI (–1.36 to 1.06) <u>Affective status (measured with HADS) 3 month follow-up – baseline, mean (SD):</u> I: –0.28 (4.84) C: –1.21 (6.17) p=0.441 CI (–1.45 to 3.30) <u>Sleep quality (measured with ISI) 3 month follow-up – baseline, mean (SD):</u>

	I: –0.54 (5.35) C: –1,47 (5.94) p=0.449 CI (–1.50 to 3.36) --- Leon-Herrera et al, 6 month follow-up **Primary outcomes** Physical health (measured with SF-36) mean difference (SD) post-pre: I: 5.33 (14.03) C: 7.50 (17.37) P: 0.541 Mental health (SF-measured with SF-36) mean difference (SD) post-pre: I: 14.48 (19.85) C: 11.87 (19.92) P=0.559 **Secondary outcomes** Cognitive impairment (measured with MoCA) mean difference (SD) post-pre: I: 2.41 (3.49) C: 1.28 (2.34) P=0.097 Physical functioning (measured with 30 s Sit-to.stand-test) mean difference (SD) post-pre: I: 1.31 (2.70) C: 1.74 (4.26) P= 0.600 Affective state (measured with HADS) mean difference (SD) post-pre: I: –2.14 (4.68) C: –1.97 (5.11) P=0.878 Sleep quality (measured with ISI) mean difference (SD) post-pre: I: 1.52 (6.38) C: –0.68 (5.20 P=0.096
Risk of bias	Moderate

Sánchez-Milá et al. 2023

Author	Sánchez-Milá et al. [93]
Year	2023
Country	Spain
Study design Setting Population Follow up	RCT Primary care setting Adults 18–65 years (mean age in treatment group 1: 24 (14 SD) years, in treatment group 2: 40 (SD 22) years, women about 50%), >5 months since medically diagnosed covid-19 with symptoms such as dyspnea or fatigue Mid-term (15 days) and after treatment (31 days)
Intervention Participants (n) Drop-outs (n)	Respiratory treatment based on inspiratory muscle training using PowerBreathe for 31 days 103 3
Control Participants (n) Drop-outs (n)	Treatment based on traditional diaphragmatic exercises prescribed in various respiratory conditions for 31 days 104 4
Outcomes	**Primary outcomes** FVC (liters) post treatment, mean (SD): I: 4.0255 (0.10994) C: 3.5408 (0.08307) p < 0.001 (based on group x time effect) FEV1 (liters) post treatment, mean (SD): I: 3.6177 (0.31406) C: 2.9529 (0.08729) p < 0.001 (based on group x time effect): FEV1/FVC (%) post treatment, mean (SD): I: 73.2897 (3.57746) C: 69.9542 (1.17489) p < 0.001 (based on group x time effect) PEFR (liters/min) post treatment, mean (SD): I: 8.0926 (0.21457) C: 7.5725 (0.24420) p < 0.001 (based on group x time effect) FIVC (liters) post treatment, mean (SD): I: 2.3745 (0.22702) C: 2.0859 (0.11724) p < 0.001 (based on group x time effect) MIP cmH2O post treatment, mean (SD): I: 91.1064 (4.67964) C: 79.3713 (3.73998) p < 0.001 (based on group x time effect) **Secondary outcomes** Systolic pressure (mmHg) post treatment, mean (SD): I: 122.29 (4.680) C: 133.94 (3.250) p < 0.001 (based on group x time effect) Dyastolic pressure (mmHg) post treatment, mean (SD): I: 72.49 (43.82) C: 78.69 (6.324) p < 0.001 (based on group x time effect) Dyspnea Borg post treatment, mean (SD):

	I: 1.03 (0.784) C: 3.02 (0.791) p < 0.001 (based on group x time effect) Lower limbs borg post treatment, mean (SD): I: 1.00 (0.816) C: 1.58 (1.093) p = 0.002 (based on group x time effect) Oxygen Saturation (mmHg) post treatment, mean (SD): I: 97.52 (1.141) C: 97.62 (1.117) p = 0.841 (based on group x time effect) Cardiac Frequency (BPM) post treatment, mean (SD): I: 86.16 (2.505) C: 85.93 (2.571) p = 0.969 (based on group x time effect) 6MWD (meters) post treatment, mean (SD): I: 595.44 (46.302) C: 603.26 (50.572) p = 0.203 (based on group x time effect)
Comments	Considerate age difference between group despite randomisation
Risk of bias	Moderate

Sánchez-Milá et al. 2024

Author	Sanchez Milá et al. [94]
Year	2024
Country	Spain
Study design	Randomised clinical trial (controlled experimental study)
Setting	Catholic University of Avila, Spain (NEUMUSK Group Research, Department of Physiotherapy)
Population	200 university students with post-covid-19 symptoms >5 months; aged 18–45 years; complaints of dyspnea, fatigue, and loss/reduction of smell and taste
Inclusion criteria	Medically diagnosed covid-19 via PCR; >5 months post-infection; symptoms of dyspnea; loss or decrease of smell and taste; age 18–45 years
Exclusion criteria	Severe exercise intolerance; ischemia during low-intensity exercise; severe pulmonary hypertension; severe covid-19 symptoms; recent cardiovascular events; cancer; muscular or severe neurological diseases
Intervention Participants (n) Dropouts (n)	31-day home-based rehabilitation program combining inspiratory training (PowerBreathe Plus device (30 breaths/day, 5 mins), aerobic walking exercise for 40 mins/day at 60-75% max heart rate, and olfactory/gustatory training with specified odours and tastes daily (onion, detergent, sugar, salt, orange juice, coffee). 105 5
Control Participants (n) Dropouts (n)	No therapy for 31 days 104 4
Follow up time points	Baseline (day 1), mid-treatment (day 2 for dyspnea scores), and post-treatment (day 31) assessments
Outcomes Measured	Primary: Respiratory outcomes (FVC, FEV1/FVC ratio, PImax); dyspnea scores (modified Borg scale, MMRC) Secondary: Neurological outcomes (Singapore Smell and Taste Questionnaire scores for smell and taste)
Results	Intervention group showed significant improvement compared to control in: - FVC (p<.001) - FEV1/FVC ratio (p<0.01) - Peak Inspiratory Pressure (p<0.01)

	- Dyspnea MBS and MMRC scales (p<0.01) - Olfactory and gustatory scores in SSTQ (p<0.01) No significant improvement in FEV1 Effect sizes were medium to large
Limitations Noted	Single-center; limited to university-aged adults (18–45); no long-term follow-up; lack of pre-covid baseline data; reliance on self-reported olfactory/gustatory scores; non-supervised home exercises (potential adherence issues)
Risk of bias	Moderate

Santana et al 2023

Author	Santana et al. [95]
Year	2023
Country	Brazil/USA
Study design Setting Population Follow up	RCT, double-blind Department of Rehabilitation at University Medical Center Adults aged 18–80 years (mean age 51.63±15.87 (intervention) and 54.46±19.01 (control), 64.3% female) with diagnosis of PASC-related fatigue, followed in an outpatient clinic, 73% home-isolated with symptoms in acute phase. 5 weeks
Intervention Participants (n) Drop-outs (n)	3 mA HD-tDCS targeting left primary motor cortex (M1), 30 min paired with individually tailored rehabilitation program, 2 sessions/week over 5 weeks 35 0
Control Participants (n) Drop-outs (n)	Sham HD-tDCS paired with rehabilitation program 35 0
Outcomes	Fatigue severity, assessed by MFIS-scale: The intervention group had significantly greater reduction in fatigue compared to sham at the end of the 5-week intervention. Mean group difference: 14.03; effect size: 1.2 (95% CI, 7.78 to 20.28; p<.001) MFIS-subscales: Reduction in fatigue was found in both cognitive (mean group difference: 8.29; effect size: 1.1, 95% CI, 3.56 to 13.01; p< .001) and psychosocial subscales (mean group difference: 2.37; effect size 1.2, 95% CI, 1.34 to 3.40; p< .001). No difference was observed between groups on physical fatigue (mean group difference: 0.71 points; effect size 0.1 (95% CI, 4.47 to 5.90; p=.09)). Anxiety (HAM-A): Favoures intervention group (mean group difference: 4.88; effect size: 0.9 (95% CI, 1.93 to 7.84; p<.001)) Quality of life (WHOQOL-brief): Favoures intervention group (mean group difference: 14.80; effect size: 0.7; (95% CI, 7.87 to 21.73; p<.001)) Pain (MPQ): No significant difference between groups (mean group difference: 0.74; no effect size (95% CI, 3.66 to 5.14; p=.09) The proportion of clinically improved participants was significantly larger in the intervention group compared to sham group (77.14% vs 45.71%; NNT ¼ 3; odds ratio ¼ 0.24; 95% CI, 0.08e0.70; P<.001)
Risk of bias	Moderate

Sawano et al. 2025

Author	Sawano et al. [96]
Year	2025
Country	USA
Study design	Phase 2, decentralised, double-blind, randomised, placebo-controlled trial
Setting	Decentralised trial across 28 of the 48 contiguous US states; remote participation with home delivery of study medication and local laboratory testing
Population	Adults ≥18 years with documented prior SARS-CoV-2 infection and long covid symptoms starting within 4 weeks of infection and persisting ≥12 weeks. n=100 randomised (nirmatrelvir–ritonavir n=49; placebo–ritonavir n=51). Mean age 42.3 years; 66% female.
Inclusion criteria	Age ≥18 years; documented SARS-CoV-2 infection; long covid symptoms persisting ≥12 weeks; symptom onset within 4 weeks of acute infection; ability to participate in a decentralised digital trial.
Exclusion criteria	Use of nirmatrelvir–ritonavir within previous 2 months; acute medical illness such as SARS-CoV-2 infection within past 2 weeks; active liver disease; renal impairment; immunocompromise; pregnancy; use of strong CYP3A4 inducers or CYP3A4-dependent medications.
Intervention Particpants (n) Drop-outs (n)	Nirmatrelvir–ritonavir group: nirmatrelvir 300 mg + ritonavir 100 mg orally twice daily for 15 days 49 5
Control Participants (n) Control (n)	Placebo–ritonavir group: matching placebo tablets + ritonavir 100 mg orally twice daily for 15 days 51 3
Follow up time points	Baseline; day 15; day 28 (primary endpoint); week 6
Outcomes Measured	<u>Primary:</u> Change in PROMIS-29 Physical Health Summary Score from baseline to day 28. <u>Secondary:</u> PROMIS-29 Mental Health Summary Score; PROMIS-Preference score; cognitive function (PROMIS v2.0); symptom burden (GSQ-30); COVID Core Outcome Measures for Recovery score; quality of life (EQ-5D-5L, EQ-VAS); PGI-S; PGI-C; safety and adverse events.
Results	**Day 28, difference in mean change from baseline (95% CI) between groups** <u>PROMIS:</u> - PROMIS-29 Physical Health Summary Score: –0.53 (–2.46 to 1.40) - PROMIS-29 Mental Health Summary Score: 0.42 (–1.81 to 2.65) - PROMIS-Preference Score: 0.00 (–0.05 to 0.05) - Results for domains of PROMIS-29 are also reported - PROMIS version 2.0 Cognitive Function Short Form 6a: –0.73 (–3.28 to 1.82) <u>Modified GSQ-30 score:</u> –3.43 (–9.37 to 2.50) <u>COVID Core Outcome Measures for Recovery score:</u> –0.07 (–0.39 to 0.26) <u>EQ-5D-5L:</u> –0.02 (–0.89 to 0.85) <u>EQ-VAS:</u> 3.76 (–1.91 to 9.44) <u>PGI-S:</u> –0.00 (–0.42 to 0.42) <u>PGI-C:</u> 0.09 (–0.34 to 0.53)

Limitations Noted	Small phase 2 sample; short treatment duration; lack of long covid–specific validated outcome tool; digital recruitment may limit representativeness; limited power to detect changes in individual symptoms; possible unmasking due to dysgeusia.
Risk of bias	Moderate

Schepens et al. 2022

Author	Schepens et al. [97]
Year	2022
Country	The Netherlands
Study design Setting Population Follow up	RCT, double-blind Self-administration outside health care setting Adults >18 years old (median age 49 years (IQR 41–57, range 20–78), 63.5% female) with persistent (>4 weeks) olfactory disorders within 12 weeks after confirmed covid-19 12 weeks post start of treatment
Intervention Participants (n) Drop-outs (n)	Oral prednisolone, 40 mg capsules once daily for 10 days 58 1
Control Participants (n) Drop-outs (n)	Placebo capsules once daily for 10 days 57 1
Outcomes	**Outcomes at 12 weeks** <u>Sniffin' Sticks test TDI score (range 1–48), mean (SD):</u> I: 28.8 (24–30.9) C: 26.8 (23.6–29.3) MD (95% CI): –1.5 (–3.0 to 0.25), p=0.10 <u>Taste Strip Test total score (range 0–16), mean (SD)</u>: I: 11 (9–13) C: 11 (9.3–13) MD (95% CI): 0.00 (–1.00 to 1.00), p=0.50 <u>Olfactory Disorders Questionnaire, total score (range 0.13–1.00), mean (SD):</u> I: 0.4 (0.3–0.5) C: 0.4 (0.3–0.6) MD (95% CI): 0.00 (–0.06 to 0.06), p= 0.89 <u>Sense of smell, VAS (range 0–10), mean (SD):</u> I: 3.6 (1.0–5.8 C: 3.2 (1.8–6.5) MD (95% CI): 0.3 (–0.9 to 1.3), p=0.53 <u>Sense of taste, VAS (range 0–10), mean (SD):</u> I: 5.0 (2.0–7.8) C: 5.6 (2.3–7.6) MD (95% CI): 0.1 (–1.00 to 1.3), p=0.80 <u>Trigeminal sensations, VAS (range 0–10), mean (SD):</u> I: 5.3 (2.4–7.9) C: 5.1 (2.9–7.4) MD (95% CI): –0.2 (–1.3 to 1.00), p=0.76 <u>Adverse events, number of events:</u> I: 3 C:0
Risk of bias	Low

Shamohammadi et al. 2022

Author	Shamohammadi et al. [98]
Year	2022
Country	Iran
Study design Setting Population Follow up	RCT, double-blind Primary care/ home-based Men aged 30–50 (mean age 41.37±2.34 (intervention) and 39.23±2.45 (control)), outpatients with ED following recovery from covid-19 without acute respiratory distress syndrome and with negative PCR test. 3 months post study start
Intervention Participants (n) Drop-outs (n)	Tadalafil, 5 mg daily for 3 months 35 3
Control Participants (n) Drop-outs (n)	Placebo 35 5
Outcomes	International Index of Erectile Function (IIEF-5), MD change from baseline: Erectile function p=0.001, favours intervention Overall satisfaction p=0.001, favours intervention Additional subscales are reported
Comments	Clinical relevance uncertain
Risk of bias	Low

Sharma et al 2024

Author	Sharma et al. [99]
Year	2024
Country	India
Study Design	Randomised controlled trial
Setting	Outpatient Department of Physiotherapy, India
Population	38 participants with long covid; age 25–60 years; both sexes
Inclusion criteria	RT-PCR confirmed covid-19; age 25–60; long covid symptoms ≥2 months; dyspnoea, fatigue or exertion symptoms
Exclusion criteria	Cardiovascular, neurological, diabetes, hypertension, recent trauma/surgery, pregnancy, respiratory/cognitive impairments
Intervention Participants (n) Dropouts (n)	Comprehensive rehabilitation (aerobic, strength, balance, flexibility, breathing, education) 6 weeks 19 0
Control Participants (n) Dropouts (n)	Breathing exercises only 19 0
Follow up time points	6 weeks
Outcomes Measured	6MWT (functional capacity), Fatigue Severity Scale, EQ-5D-5L (quality of life), dyspnoea, RPE
Results	**Post treatment** FSS mean (SD): I: 21.31 (6.69) C: 30.63 (8.36) P= 0.006 EQ-5D-5L mean (SD): I: 0.74 (0.09) C: 0.65 (0.15)

	P=0.007 EQ VAS mean (SD): I: 71.31 (8.63) C: 61.84 (4.45) P=0.002 6MWD mean (SD): I: 469.00 (45.11) C: 414.43 (33.97) P<0.0001
Limitations Noted	Single centre; small sample size; no long-term follow-up; outcome assessor not blinded
Risk of bias	Moderate

Tosato et al. 2022

Author	Tosato et al. [100]
Year	2022
Country	Italy
Study design Setting Population Follow up	RCT, single-blind Post-acute covid-19 outpatient clinic Adults aged 20–60 (median age 50.5 (IQR 14.0), 65.2% female) with previous covid-19 infection with persistent fatigue (Response “most or all the time” to item seven on CES-D), 56.5% previously hospitalised. 28 days
Intervention Participants (n) Drop-outs (n)	Oral supplementation 1.66 g L-arginine plus 500 mg liposomal vitamin C, 2/day for 28 days 25 2
Control Participants (n) Drop-outs (n)	Placebo 25 2
Outcomes	Distance walked on the 6 min walk test (median (IQR) change from baseline) I: +30.0 (40.5) m C: +0.0 (75.0) m p=0.001 Mean difference=50 m (95% CI, 20.0 to 80.0); effect size=0.56 See study for more results on secondary outcomes: handgrip strength, flow-mediated dilation, and fatigue persistence
Risk of bias	Moderate

Tryfonos et al 2024

Author	Tryfonos et al. [101]
Year	2024
Country	Sweden
Study design	Randomised crossover clinical trial
Setting	Karolinska University Hospital and Karolinska Institutet, Sweden
Population	31 adults with PCC; mean age ~47 years; 76% female; persistent symptoms ≥3 months post-SARS-CoV-2 infection; no prior hospitalization; no significant comorbidities 31 healthy controls were also recruited
Inclusion criteria	Age 18–64; laboratory-confirmed SARS-CoV-2 infection; persistent postexertional malaise ≥3 months; no prior hospitalization; no history of cardiovascular/respiratory disease or somatic symptom disorder; symptom onset after March 2020
Exclusion criteria	Presence of chronic illnesses explaining symptoms; organ damage; insufficient Norwegian language skills (not applicable here); pregnancy not specified
Intervention Participants (n) Dropouts (n)	High intensity interval training (HIIT) 26 to 30 (order of type of training not specified) 0 to 4 (not specified at which training session participants discontinued)
Intervention Participants (n) Dropouts (n)	Moderate-intensity continuous training (MICT) 26 to 30 (order of type of training not specified) 0 to 4 (not specified at which training session participants discontinued)
Intervention Participants (n) Dropouts (n)	Strength training (ST) 26 to 30 (order of type of training not specified) 0 to 4 (not specified at which training session participants discontinued)
Follow up time points	Baseline, immediately after exercise, and 48 hours post-exercise for each intervention
Outcomes Measured	Postexertional symptoms as assessed by VAS for 10 symptoms (fatigue, muscle pain, joint pain, fever, chills, lymph node discomfort, sore throat, headache, memory, and concentration), Multidimensional Fatigue Inventory; Profile of Mood States; Somatic and Psychological Health Report.
Results	**Results at 48 hours post-exercise** <u>Fatigue VAS 0–10, median (IQR):</u> HIIT:6.0 (4.0 to 8.0) MICT: 4.5 (2.8 to 7.0) ST: 5.0 (4.0 to 7.0) <u>MFI Total, median (IQR):</u> HIIT: 66.0 (56.5, 76.0) MICT: 66.5 (57.2, 73.8) ST: 64.0 (54.5, 70.0) <u>POMS Total Mood Disturbance, median (IQR):</u> HITT: 32.0 (13.5, 49.0) MICT: 33.5 (18.5, 52.8) ST: 28.0 (16.0, 45.5) <u>SPHERE SOMA, median (IQR):</u> HIIT: 6.5 (4.2, 10.0) MICT: 6.5 (4.2, 9.0) ST: 6.0 (4.0, 9.8) <u>SPHERE PHYSH, median (IQR):</u> HIIT: 1.0 (0.0, 2.8) MICT: 1.0 (0.0, 3.0) ST: 0.0 (0.0, 2.0) Subscales and other results are also reported

Limitations Noted	Small sample size; single-center; 48-hour follow-up may miss delayed symptom peaks; predominantly female sample; absence of pre-COVID baseline muscle data; applicability limited to nonhospitalized PCC without comorbidities
Risk of bias	Moderate

Vernon et al. 2025

Author	Vernon et al. [102]
Year	2025
Country	USA
Study design	Single-center, randomised, double-blind, controlled clinical trial
Setting	Bateman Horne Center, Salt Lake City, Utah, USA
Population	Adults aged 18–65 years with WHO-defined long covid, experiencing moderate to severe fatigue and post-exertional malaise. Majority female (~71%). Mean age ~ 45 years.
Inclusion criteria	WHO-defined long covid; suspected, probable, or confirmed SARS-CoV-2 infection; moderate–severe fatigue and PEM; access to smartphone and internet; ability to comply.
Exclusion criteria	Uncontrolled medical or psychiatric illness; recent stimulant or oxaloacetate use; pregnancy or breastfeeding; significant recent head trauma; BMI >40.
Intervention Participants (n) Drop-outs (n)	Oxaloacetate (OAA) group: Oral oxaloacetate 2,000 mg/day (four 500 mg capsules daily) for 42 days. 35 2
Control Participants (n) Drop-outs (n)	Matching placebo (rice flour) 2,000 mg/day for 42 days 34 5
Follow up time points	Baseline (Day 1), Day 21, Day 42
Outcomes Measured	<u>Primary:</u> Fatigue reduction (Chalder Fatigue Questionnaire). <u>Secondary:</u> Symptom burden (DSQ-SF), quality of life (RAND-36). Exploratory: Cognitive performance (DANA Brain Vital), upright activity time (UP Time), safety.
Results	**Day 42** <u>CFQ total score: mean change (SE):</u> I: −7.36 ± 1.40 C: −6.63 ± 1.38 p=0.710 <u>RAND-36 (SF-36): mean change (SE):</u> Physical function I: 46 (3.7) C: 53 (4.2) p= 0.22 Role physical I: 10 (2.2) C: 18 (2.4) p=0.25 Energy I: 21 (2.1) C: 30 (2.2) p=0.11 Pain I: 53 (3.5) C: 57 (3.9) p=0.49

	Emotion I: 58 (3.2) C: 63 (3.6) p=0.28 Role emotional I: 38 (3.1) C: 47 (3.4) p=0.43 Social function I: 36 (3.0) C: 40 (3.1) p=0.57 General health I: 33 (2.8) C: 34 (2.8) p=0.80 <u>DSQ-SF scores:</u> No statistically significant difference between groups <u>UP Time:</u> No statistically significant differences between groups <u>DANA Brain Vital, percent change</u> PRT I: 14.1% C: –1.4% p= 0.011 GNG I: 10.0% C: 0.9% p=0.017 SRT: No between-group difference (p=0.091) Total cognitive efficiency I: 10.7% I: –0.04% p=0.007
Limitations Noted	Modest sample size; short intervention duration; single-center design; CFQ may lack sensitivity; no biological markers; limited generalizability; number of participants analysed not reported.
Risk of bias	Moderate

Volckaerts et al. 2025

Author	Volckaerts et al. [103]
Year	2025
Country	Belgium
Study design	Prospective, pragmatic, two-centre, parallel-group randomised controlled trial
Setting	Two hospitals in Belgium (Antwerp University Hospital and Ziekenhuis Oost-Limburg) with rehabilitation delivered by primary care physiotherapists.
Population	Adults ≥18 years with confirmed COVID-19 infection more than 6 weeks earlier and persistent long-COVID symptoms (fatigue, dyspnoea, or reduced functional status).
Inclusion Criteria	Confirmed COVID-19 infection >6 weeks earlier and persistent symptoms defined by CAT ≥10, mMRC ≥2, CIS-fatigue ≥36, or PCFS ≥2.
Exclusion Criteria	Cognitive, hearing, visual, neurological or musculoskeletal conditions; had more than eight physiotherapy sessions due to long covid complaints, and any in the past 12 weeks before randomisation; neurological disorders that impact respiratory function; organ transplantation in the past or near future; active malignancy or (maintenance) treatment for active malignancy or curatively treated malignancy within the past year.
Intervention Participants (n) Drop-outs (n)	Pulmonary Rehabilitation (PR): 12-week stepwise pulmonary rehabilitation programme in primary care with 36 individual physiotherapy sessions (3 sessions/week, ~30 min), including education, endurance training, strength training, breathing exercises, inspiratory muscle training, lifestyle coaching. 39 7
Control Participants (n) Drop-outs (n)	Usual care with no pulmonary rehabilitation during the intervention period. 37 6
Follow-up Timepoints	Assessments at baseline, 6 weeks, 12 weeks (end of intervention), 24 weeks, and questionnaires at 36 weeks.
Primary Outcome	Change in functional exercise capacity measured by the 6-minute walk distance (6MWD) from baseline to 12 weeks.
Secondary Outcomes	CIS-fatigue score, COPD Assessment Test (CAT), EQ-5D-5L quality of life, daily step counts (accelerometer), maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), handgrip strength, Nijmegen questionnaire, Hospital Anxiety and Depression Scale (HADS), and dyspnoea (mMRC).
Results	**Adjusted ITT-analysis of mean difference (95% CI) at 12 weeks (end-of-study)** (Results from other follow-up times not tabulated by SBU) <u>Functional exercise capacity (6MWD, meters):</u> 38.81 (18.17 to 59.45), p <0.001 <u>COPD Assessment Test (CAT, points):</u> –3.60 (–6.28 to –0.92), p=0.009 <u>CIS-fatigue score (points):</u> –7.65 (–12.74 to –2.57), p=0.004 <u>Maximal inspiratory pressure (MIP, cmH2 O):</u> 9.90 (1.30 to 18.49), p=0.025 <u>Maximal expiratory pressure (MEP, cmH2 O):</u> 12.62 (0.33 to 24.92), p=0.044 <u>EQ-5D-5L VAS (points):</u> 2.51 (–6.10 to 11.11), p= 0.563 <u>Nijmegen questionnaire (points):</u> –3.79 (–7.14 to –0.44), p= 0.027 <u>HADS anxiety (points):</u> –1.34 (–2.75 to 0.08), p=0.063

	HADS depression (points): –0.95 (–2.26 to 0.36) p=0.150 Safety: Eight adverse events were reported (four post-exertional malaise, two musculoskeletal issues, one nausea, one atypical chest pain) and one unrelated serious adverse event (sepsis) Additional outcomes reported
Limitations Noted	Modest sample size, which reduces precision and reproducibility of the findings; indication of limited sensitivity of the EQ-5D-5L to capture long covid-specific burden; individuals with a high symptom burden or experiencing PEM likely chose not to participate due to concerns about the intensive nature of the programme; no validated questionnaire was used to screen for PEM. Note that results are adjusted for covariates, several models are available.
Risk of bias	Moderate

Yan et al. 2023

Author	Yan et al. [104]
Year	2023
Country	USA
Study design Setting Population Follow up	RCT Outpatient setting. Participants (mean age 44.1 years±14.0, 50% female) with PCR–confirmed diagnosis of severe acute covid-19 with objective olfactory dysfunction between 6–12 months after acute infection. 4 and 12 weeks. Only 12-weeks results are reported below.
Intervention Participants (n) Drop-outs (n)	Three intranasal injections with platlet rich plasma at two sites within the olfactory cleft along the superior septum, posterior to the head of the middle turbinate 18 4
Control Participants (n) Drop-outs (n)	Three intranasal injections with placebo (sterile saline) bilaterally in the same locations as in the intervention group 12 12
Outcomes	**Primary outcome** Change in TDI using Sniffin' Sticks, results between groups: Total change in TDI: 3.67 95%CI (0.05 to 7.29), p=0.047 T score: 0.07 95%CI (–1.71 to 1.85), p=0.935 D score: 2.40 95%CI (0.80 to 4.00), p= 0.004 I score: 1.12 95%CI (–0.76 to 3.00) p=0.239 **Secondary outcomes** Responder rate at 3 months: (where a responder was defined as a clinically significant improvement on Sniffin' Sticks TDI score, ≥5.5 points) By completion of trial the responder rate was 8.3% in the placebo arm (1 of 12) compared to 57.1% (8 of 14) of subjects in the PRP arm (OR 12.5 (95% exact bootstrap CI, 2.2–116.7)) VAS: 0.88, (95% CI, –0.38 to 2.15), p=0.167 Additional outcomes reported
Risk of bias	Moderate

Yasacı et al. 2025

Author	Yasacı et al. [105]
Year	2025
Country	Turkey
Study design	Single-blind randomised controlled trial (prospective)
Setting	Gaziosmanpaşa Training and Research Hospital, Istanbul, Turkey
Population	64 adults with Post-Covid-19 Syndrome (PCS) (32 in telerehabilitation group, 32 in control group); mean age 56 years; 47% female; symptoms ≥3 months; persistent dyspnea, pain, and functional limitations
Inclusion criteria	Diagnosis of PCS by specialist; dyspnea score 2–3 on mMRC scale; age ≥18; ability to follow directions; access to technological facilities
Exclusion criteria	SpO2 <92% at rest, systolic BP <90 mmHg, diastolic BP <60 mmHg, asthma/COPD, other lung diseases
Interventions Participants (n) Drop-outs (n)	Telerehabilitation group: 6-week supervised TR program (2 sessions of 45 minutes/week) including breathing, relaxation, range-of-motion, walking, and squatting exercises; monitored via video conferencing. Intensity monitored on RPE scale. 32 0
Control Participants (n) Drop-outs (n)	Unsupervised home exercise with same protocol 32 4
Follow up time points	Baseline and post-intervention (6 weeks) assessments
Outcomes Measured	Primary: Dyspnea (mMRC), pain intensity (NPRS), functional capacity (5-TST) Secondary: Sleep quality (PSQI), anxiety and depression (HADS)
Results	**Per protocol analysis, Difference in mean change between groups, mean (95% CI)** mMRC: 0.8 (0.5 to 1.1), p = 0.001 Pain intensity (NPRS): 0.8 (0.3 to 1.4), p = 0.006 5-TST (seconds): 2.3 (0.9 to 3.8), p = 0.001 PSQI: 1.0 (0.2 to 1.9), p = 0.018 HADS-anxiety: 1.28 (0.4 to 2.1), p = 0.001 HADS-depression: 0.5 (–0.1 to 1.1) p = 0.124
Limitations Noted	Per protocol-analysis; single-center; small sample size; moderate severity only (excluded severe cases); short follow-up (6 weeks); open-label to patients (only assessors blinded); self-reported adherence; no biomarker data; limited generalizability
Risk of bias	Moderate

Zha et al. 2024

Author	Zha et al. [106]
Year	2024
Country	China
Study design	Randomised controlled trial (single-blind, prospective)
Setting	Renmin Hospital of Wuhan University, Wuhan, China
Population	98 adults aged 18–70 years with post-acute sequelae of covid-19 (PASC) after Omicron BA.5; symptoms of dyspnea and fatigue ≥12 weeks; median symptom duration ~22 weeks; 33 males, 62 females
Inclusion criteria	Confirmed covid-19 Omicron BA.5 (Dec 2022–Jan 2023); persistent symptoms ≥12 weeks; dyspnea and fatigue; age 18–70 years; any gender; informed consent
Exclusion criteria	Acute covid-19 in past 12 weeks; pregnancy/lactation; acute illness; recent MI (within the last three months), unstable angina, acute stroke (within the last six months); stage III hypertension; decompensated chronic renal failure; severe extracranial blood flow disorders; congenital heart/great vessel abnormalities; intellectual/mental disability; hypoxia intolerance
Interventions Participants (n) Drop-outs (n)	IHE: Intermittent hypoxia exposure (5-min hypoxia alternating with 5-min normoxia, repeated five times/day, 10–12% O2) + routine therapy (e.g. inhaled bronchodilators and nebulized corticosteroids/anticholinergics as needed) for ≥7 days (median = 10 days) 49 2
Control Participants (n) Drop-outs (n)	NE: Normoxia exposure + routine therapy (e.g. inhaled bronchodilators and nebulized corticosteroids/anticholinergics as needed) for ≥7 days (median = 10 days). 49 1
Follow up time points	Baseline and post-intervention (after ≥7 days) assessments; no long-term follow-up
Outcomes Measured	Primary: 6-minute walk distance (6MWD), spirometry (VT, FVC, FEV1, FEV1/FVC), Borg Dyspnea Scale, mMRC, Fatigue Assessment Scale (FAS), Chalder Fatigue Scale-11 (CFQ-11). Secondary: Adverse events, subjective improvement (dyspnea, fatigue), impact of IHE duration (<10 vs ≥10 days)
Results	**Per protocol analysis, Change at post-intervention (after ≥7 days)** 6MWD (meters): median (IQR): IHE: 47.0 (30.0, 61.0) NE: 23.5 (11.5, 33.0) V_T: median (IQR): IHE: 0.3 (0.2, 0.5) NE: 0.0 (–0.1, 0.2) FVC: median (IQR): IHE: 0.2 (0.1, 0.4) NE: 0.1 (0.0, 0.3) FVC % pred: median (IQR): IHE: 6.1 (4.2, 10.6) NE: 3.2 (–0.9, 8.8) FEV_1: median (IQR): IHE: 0.1 (0.1, 0.3) NE: 0.1 (0.0, 0.2) FEV_1 % pred: median (IQR): IHE: 5.3 (4.1 to 9.9) NE: 2.1 (–0.8 to 6.9) Borg Dyspnea Scale: median (IQR): IHE: 1.0 (0.0, 1.0) NE: 0.0 (0.0 to 1.0)

	mMRC: median (IQR): IHE: 0.0 (0.0, 1.0) NE: 0.0 (0.0, 0.0) FAS: median (IQR): IHE: 15.5 (13.0, 18.0) NE: 6.0 (5.0, 7.8) CFQ-11: median (IQR): IHE: 6.0 (4.0, 8.0) NE: 4.0 (2.0, 5.0) **Subjective assessment of symptoms** Improvement in dyspnea: n (%): IHE: 36 (76.6) NE: 19 (39.6) Improvement in fatigue: n (%): IHE: 39 (83.0) NE: 15 (31.3) No severe adverse events. 87.2% in IHE group and 79.2% in NE group experienced sleepiness
Limitations Noted	Per protocol-analysis; small sample size; short duration (7–15 days); single-center; no biomarker analysis; focus on dyspnea/fatigue only (other PASC symptoms not assessed); lack of long-term follow-up
Risk of bias	Moderate

Zilberman-Itskovich et al. 2022 & Leitman et al. 2023

Author	Zilberman-Itskovich et al. [107]
Year	2022
Country	Israel
Author	Leitman et al. [108]
Year	2023
Country	Israel
Study design Setting Population Follow up	RCT, double-blind Medical facility Adults ≥18 years (mean age 48.4±10.6 years (intervention) and 47.8±8.5 years (control), 60.3% females) with persistent cognitive symptoms affecting quality of life >3 months following confirmed covid-19 infection (16% previously hospitalised during acute phase of infection) 1–3 weeks after last treatment session
Intervention Participants (n) Drop-outs (n)	HBOT in a multi-place Starmed-2700 chamber (HAUX, Germany), 40 daily sessions, 5 sessions per week within a 2-month-period. HBOT protocol: 100% oxygen by mask at 2ATA for 90 min, 5-minute air breaks every 20 min. Compression/decompression rates 1.0 m/min. 40 3
Control Participants (n) Drop-outs (n)	Sham protocol: 21% oxygen by mask at 1.03 ATA for 90 min. To mask controls, the chamber pressure was raised up to 1.2 ATA during the first 5 minutes along with circulating air noise, followed by decompression (0.4 m/min) to 1.03 ATA during next 5 minutes 39 3
Outcomes	**Results presented as Cohen's d net effect size and p-value (p<0.05 was considered significant)**

	Cognitive assessment: • Cognitive score: d=0.495, p=0.038 (significant) • Attention: d=0.477, p=0.045 • Executive function: d=0.463, p=0.052 (significant) • Memory: d=0.111, p=0.636 • Information processing speed: d= 0.303, p=0.200 • Motor skills: d=0.338, p=0.154 • (Mindstreams computerized cognitive testing battery (NeuroTrax Corporation, Bellaire, TX)) Quality of life (SF-36): • Physical functioning: d=–0.269, p=0.254 • Physical limitations: d=0.546, p=0.023 (significant) • Emotional limitations: d=0.215, p=0.361 • Energy: d=0.522, p=0.029 (significant) • Emotional wellbeing: d=0.459, p=0.054 • Social function: d=0.391, p=0.099 • Pain domain: d=0.254, p=0.281 • General health domain: d=0.338, p=0.153 Olfactory and gustatory function: No significant group-by-time interactions. Cardiac function: Global longitudinal strain (GLS), %: d=0.245, p=0.041 Other cardiac outcomes (Global Work Index, Global Constructive Work, Global Wasted Work, Global Work Efficacy): Non-significant See study for additional results on sleep quality (PSQI, Global=significant), psychological symptoms (BSI-18, Total=significant), pain (BPI, Pain interference=significant), pulmonary function (spirometry=not significant)
Comments	Cardiac function outcomes are reported in a separate publication (Leitman et al 2023, #1278)
Risk of bias	Low for cognitive and most other outcomes, Moderate for cardiac outcomes

Abbreviations

ACE-III	Addenbrooke's Cognitive Examination-III (cognitive assessment tool)
ADLs	Activities of daily living
AE	Aerobic exercise / Adverse events
A-PASC	Post-COVID-19 symptoms assessment questionnaire
apx	approximately
AQoL-6D	Assessment of quality of life—six dimensions
ATA	Atmospheres absolute (pressure)
AT	Anaerobic threshold
BDI	Beck Depression Inventory
BDI-II	Beck Depression Inventory-II
BFSS	Brief Fatigue Severity Scale
BMI	Body mass index
BP	Blood pressure
BPI	Brief Pain Inventory
bpm	Beats per minute
BSI-18	Behavioural Symptoms Inventory-18 global score index
BSIT	Brief Smell Identification Test
BTT	Butanol threshold test
C	Control
CAD	Coronary artery disease
CARDS	COVID-19-associated acute respiratory distress syndrome
CATS	Cognitive activation theory of stress

CAU	Care as usual
CBT	Cognitive behavioural therapy
CCCRC test score	Connecticut Chemosensory Clinical Research Center test score
CES-D	Centre for Epidemiological Studies Depression Scale
CFQ	Cognitive Failures Questionnaire
CFQ-11	Chalder Fatigue Scale-11 (fatigue assessment)
CG	Control group
CGI	Clinical Global Impression Scale
CGI-C	Clinical global impression of change
CGI-I	Clinical Global Impression–Improvement (scale)
CHD	Coronary heart disease
CIS-conc	Concentration subscale of Checklist Individual Strength
CIS-fatigue	Fatigue severity subscale of the Checklist Individual Strength
CK	Creatine kinase
COPD	Chronic obstructive pulmonary disease
COMPASS 31	Composite Autonomic Symptom Score
CPE	Clears-belong Plus (plant extract combination)
CPET	Cardiopulmonary exercise test
CPRP	Cardiopulmonary rehabilitation programme
CRP	C-reactive protein
CS-30	Chair stand test (30 seconds)
DASS-21	Depression Anxiety Stress Scales-21
DDAVP	Desmopressin

DLCO	Diffusing capacity of the lungs for carbon monoxide
DN4	Douleur Neuropathique en 4 Questions
DSC	Dynamic susceptibility contrast
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSST	Digit Symbol Substitution Test
DTI	Diffusion tensor imaging
ED	Erectile dysfunction
EQ-5D-5L	EuroQol 5-Dimension 5-Level (quality of life questionnaire)
ET	Exercise therapy
FAI	Fatigue Assessment Inventory
FAS	Fatigue Assessment Scale
FEV	Forced expiratory volume
FEV1	Forced expiratory volume in the first second
FIS	Fatigue Impact Scale
FSS	Fatigue severity scale
FSS-7	Fatigue Severity Scale-7
FVC	Forced vital capacity
GAD-7	Generalised Anxiety Disorder 7-item scale
GHQ-12	General Health Questionnaire-12
GLM	General linear model
GPAQ	WHO Global Physical Activity Questionnaire
h	Hour(s)
HADS	Hospital Anxiety and Depression Scale

HADS-A	Hospital Anxiety and Depression Scale – anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale – depression subscale
HAM-A	Hamilton anxiety rating scale
HBOT	Hyperbaric oxygen treatment
HIIT	High-intensity interval training
HIT-6	Headache Impact Test-6
HR	Heart rate
HRmax	Maximum heart rate
HRQoL	Health-related quality of life
hrs	Hours
HUTT	Head-up tilt table test
I	Intervention
ICU	Intensive care unit
IG	Intervention group
IHE	Intermittent hypoxia exposure
IHMP	Individualised homeopathic medicine protocol
IIEF-5	International Index of Erectile Function
IME	Inspiratory muscle endurance
iCEPT	Invasive cardiopulmonary exercise test
IPAC	International Physical Activity Questionnaire
IQR	Interquartile range
ISI	Insomnia Severity Index
ITT	Intention-to-treat (analysis)

JNMCH	Jawaharlal Nehru Medical College and Hospital
K-BILD	King's Brief Interstitial Lung Disease questionnaire
KW	Kruskal–Wallis test
LCADL	London Chest Activity of Daily Living Scale
LC19Ps	Long-COVID-19 patients
LS MD	Least squares mean difference
LUT	Luteolin
m	Metre
MCS	Mental Component Summary score of Short Form-36 Health Survey (SF-36)
MD	Mean difference
MDBS	Modified Borg Dyspnoea Scale
MEP	Maximal expiratory pressure
MFIS	Modified fatigue impact scale
MI	Myocardial infarction
MICE	Multiple imputation by chained equations
MICT	Moderate-intensity continuous training
MIP	Maximal inspiratory pressure
MMSE	Mini Mental State Examination
MMV	Maximal voluntary ventilation
MoCA	Montreal Cognitive Assessment
MRC	Medical Research Council
mMRC	Modified Medical Research Council (dyspnoea scale)
MS	Multiple sclerosis

MYMOP-2	Measure Yourself Medical Outcomes Profile version 2
NCCHK	National Cardiovascular Center Harapan Kita
NE	Normoxia exposure
NMV/r	Nirmatrelvir-ritonavir
NPRS	Numeric Pain Rating Scale
NYHA	New York Heart Association (heart failure classification)
O3-MAH	Ozone major autohaemotherapy
OD	Olfactory dysfunction
OFP	Orofacial pain
PASC	Post-acute sequelae of SARS-CoV-2 infection
PBO/r	Placebo-ritonavir
PCF	Peak cough flow
PCFS	Post-COVID Functional Scale
PCR	Polymerase chain reaction
PCS	Physical Component Score/Scale; also Post-COVID-19 syndrome
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PEM	Post-exertional malaise
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9 (depression screening)
PMR	Progressive muscle relaxation
POMS	Profile of Mood States

PPP	Per protocol population
PR	Pulmonary rehabilitation
PROMIS	Patient-Reported Outcomes Measurement Information System
PRP	Platelet-rich plasma
PSQI	Pittsburgh Sleep Quality Index
QOD	Questionnaire of Olfactory Disorders
QOD-NS	Questionnaire of Olfactory Disorders—Negative Statements
QOL	Quality of life
RCT	Randomised controlled trial
RM	Repetition maximum (e.g., 1RM = one repetition maximum)
RMT	Respiratory muscle training
RPE	Rating of perceived exertion
RR	Relative risk
RT-PCR	Reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SE	Standard error
SF-12	Short Form-12 Health Survey
SF-36	Short Form-36 Health Survey (quality of life questionnaire)
SNI	Saline nasal irrigation
SpO2	Oxygen saturation (peripheral)
SPHERE	Somatic and Psychological Health Report
SSTQ	Singapore Smell and Taste Questionnaire

ST	Strength training
STS	Sit-to-stand (test)
THC	Tetrahydrocannabinol
TMT-A	Trail Making Test Part A
TMT-B	Trail Making Test Part B
TR	Telerehabilitation
TTH	Tension-type headache
TUG	Timed Up and Go (test)
UPSIT	University of Pennsylvania Smell Identification Test
VAS	Visual analogue scale
VO2	Oxygen consumption (volume of oxygen)
VPBM	Vascular photobiomodulation
VT	Tidal volume
WHO	World Health Organization
5STS	5-repetition Sit-to-Stand test
6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
6MWW	6-Minute Walk Work

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