Bilaga till rapport

Insatser vid postcovid och andra närliggande tillstånd och syndrom – en kartläggning
Treatment and rehabilitation interventions for post-COVID and other related conditions and syndromes –a systematic mapping of studies
Rapport 379 (2024)

Bilaga 4 Tabell över inkluderade studier

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Postcovid

Author	*Berenguel Senén*
Year	*2024*
Country	*Spain*
Ref #	*[1]*
Study design	*Open label RCT*
Setting	*Outpatient care*
Population	*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*
Follow up	*After treatment, at 8 weeks*
Intervention	*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.*
Participants (n)	*25*
Drop-outs (n)	*7*
Comparison	*The control group received recommendations on physical exercise and healthy habits based on recommendations for the general population*
Participants (n)	*25*
Drop-outs (n)	*6*
Outcomes	*<u>Primary endpoint:</u> change in peak VO2* *Interventions group: peak VO2 significantly improved by 15% after the TPEP (pre- vs postintervention, 24.9% vs 29.3% mL/kg/min; p<0.001)* *Control group: showed no significant changes in peak VO2 (pre- vs postintervention, 25.2 vs 24.8 mL/kg/min; p=0 .46)* *Between group differences:* *Peak VO2, mL/kg/min intervention 29.3 (SD 4.7) vs. control 25.5 (SD 7.7), p0<.001* *<u>Secondary endpoints:</u>* *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* *Neuromuscular capacity:* *evaluated using load-velocity profiles for squat, bench press and pull down exercises* *<u>Squat</u>, p=0.43* *<u>Bench press</u>, p=0.16* *<u>Pull down</u>, p=.02 in favour of active intervention* *Additional outcomes were reported*
Comments	*Authors do not perform intention to treat analyses*
Risk of bias	*Moderate*

Author	*Berube*
Year	*2023*
Country	*Canada*
Ref #	*[2]*
Study design	*RCT, double-blind (triple?)*
Setting	*Self-administration outside health care setting*
Population	*Adults (mean age 44.9±7.4 (intervention) and 44.5±10.1, 66% female) with previously confirmed COVID-19 and persistent COVID-19-related olfactory dysfunction (≥2 months, UPSIT)*
Follow up	*End of treatment / 12 weeks post allocation*
Intervention	*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.*
Participants (n)	*25*
Drop-outs (n)	*Lost to follow-up: 5 Excluded from analysis: 2*
Comparison	*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.*
Participants (n)	*25*
Drop-outs (n)	*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>* *We did not observe an effect of group, 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>* *We observed an effect of time (F(1,39) = 13.3; p = 0.001) on quality of life impairment but no effect of group or interaction* *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*

Author	*Calvo-Paniagua*
Year	*2024*
Country	*Spain*
Ref #	*[3]*
Study design	*RCT*

Setting	*Home-based tele-rehabilitation implemented by videoconference*
Population	*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*
Follow up	*Post-intervention and 1 and 3 months after post-intervention*
Intervention	*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*
Participants (n)	*32*
Drop-outs (n)	*0*
Comparison	*Waitlist*
Participants (n)	*32*
Drop-outs (n)	*0*
Outcomes	*Primary outcome at post-intervention, mean change from baseline (95% CI):* *<u>Perceived physical exertion (MBDS):</u>* *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):* *<u>Health-related quality of life (SGRQ):</u>* *I: 51.0 (−56.5; −45.6)* *C: 1.0 (−6.1; 8.0)* *Group* time interaction: p<0.001* *<u>6MWT test, walking distance (m):</u>* *I: 126.5 (38.7; 214.3)* *C: −40.1 (−105.4; 25.1)* *Group* time interaction: p<0.001oxygen saturation,* *Additional outcomes (oxygen saturation, heart rate, physical exertion severity) and follow-up times (1, and 3 months post-intervention) were reported*
Comments	*Not fulfilling the WHO criteria completely but the average post-infection time was 14.8 ± 1.7 months*
Risk of bias	*Moderate*

Author	*Capin*
Year	*2022*
Country	*USA*
Ref #	*[4]*
Study design	*RCT*
Setting	*Home environment/outside health care setting*
Population	*Adults (mean age 52 years, 47.7% female) discharged from hospital due to confirmed COVID-19 (with and without ICU stay)*
Follow up	*6 and 12 weeks*
Intervention	*Multicomponent app-facilitated telerehabilitation program with e.g. physical exercises and lifestyle coaching, 12 individual sessions with licensed physical therapist during 9–10 weeks*
Participants (n)	*29*
Drop-outs (n)	*1*
Comparison	*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*

Participants (n) Drop-outs (n)	*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* *See study for additional outcomes on physical function.*
Comments Risk of bias	*Assessor-blinded RCT* *Moderate*

Author Year Country Ref #	*Chen* *2021* *China* *[5]*
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	*Chinese medicine Bufei Huoxue capsules, 4 capsules 3 times daily for 90 days.*

Participants (n) Drop-outs (n)	*64* *7 (ITT-analysis was performed on 64)*
Comparison 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: 34.2 (11.7–56.8) p=0.0022 in favour of tested intervention* *Secondary outcomes:* *Fatigue score (FAI):* *17.8 (–29.5 to –6.2), p=0.0019 in favour of tested intervention* *St George's Respiratory Questionnaire:* *–2.4 (–5.8 to 1.0) p=0.1148* *Borg Dyspnea Score:* *–0.1 (-0.5 to 0.2) p= 0.4801* *Chinese medicine symptom complex score:* *0.4 (–0.4 to 1.3) p=0.4723* *Additional outcomes were reported.*
Comments Risk of bias	*Possible that active treatment was distinguishable from placebo. Inclusion criteria included categorizations according to traditional Chinese medicine.* *Moderate*

Author Year Country Ref #	*Chung* *2023* *China* *[6]*
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*

Comparison	*Control group:*
	No intervention received during the study period
Participants (n)	*5*
Drop-outs (n)	*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*

Author	*DalNegro*
Year	*2022*
Country	*Italy*
Ref #	*[7]*
Study design	*RCT Cross-over*
Setting	*Outpatient care*
Population	*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*
Follow up	*One week after treatment*
Intervention	*Nebivolol 2.5 mg once daily*
Participants (n)	*8+8 (cross-over)*
Drop-outs (n)	*0*
Comparison	*Placebo once daily*
Participants (n)	*8+8 (cross-over)*
Drop-outs (n)	*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*

	More outcomes are reported in the article
Comments	*Small study*
Risk of bias	*Moderate*

Author	*D'Ascanio*
Year	*2021*
Country	*Italy*
Ref #	*[8]*
Study design	*RCT*
Setting	*Outpatient care*
Population	*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.*
Follow up	*30 days*
Intervention	*Olfactory training/stimulation through Sniffin' Sticks (2/day for 10 min, for 30 days) and daily treatment with PEA/Luteolin oral supplement*
Participants (n)	*5*
Drop-outs (n)	*0*
Comparison	*Olfactory training/stimulation through Sniffin' Sticks (2/day for 10 min, for 30 days).*
Participants (n)	*7*
Drop-outs (n)	*0*
Outcomes	*Change over time (T0–T1) in Sniffin scores (mean change)* *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)*
Comments	
Risk of bias	*Moderate*

Author	*DelCorral*
Year	*2023*
Country	*Spain*
Ref #	*[9]*
Study design	*RCT, with four groups*
Setting	*Home based training*
Population	*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.*
Follow up	*4, and 8 weeks post intervention. Only results of post intervention (8 weeks) tabulated.*
Intervention	*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.*
Participants (n)	*22 + 22*
Drop-outs (n)	*1 + 1 in each group*
Comparison	*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.*
Participants (n)	*22 + 22*
Drop-outs (n)	*1 +1 in each group*
Outcomes	*Group x time interaction, mixed way ANOVA. Change from baseline values.* *Health related quality of life (EQ-5D) with VAS of overall health*

	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.* *There were additional outcomes reported.*
Comments Risk of bias	 *Low*

Author Year Country Ref #	*Di Stadio* *2022* *Italy* *[10]*
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*
Comparison Participants (n) Drop-outs (n)	*Olfactory training as noted for the intervention group + a daily placebo supplement therapy* *55* *0*
Outcomes	*Group comparisons:* *<u>Pre- and post- TDI scores (ANOVA):</u>* *p<0.00001, F=13.23 – statistically significant differences* *<u>Likelihood of recovery to normal TDI score (>31) at T3 (chi-square):</u>* *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.*
Comments Risk of bias	 *Moderate*

Author Year Country	*Di Stadio* *2023* *Italy*

Ref #	*[11]*
Study design	*RCT, multicenter, double-blind study with four groups, one as active control*
Setting	*Outpatient treatment*
Population	*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.*
Follow up	*90 days*
Intervention	*Three 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.*
Participants (n)	*Group 1: 100; group 2: 50; group 3: 50*
Drop-outs (n)	*Group 1: 24; group 2: 2; group 3: 10*
Comparison	*Olfactory training as noted for the intervention group + a daily placebo supplement therapy*
Participants (n)	*50*
Drop-outs (n)	*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 (χ2: p < 0.00001)* *Improvements of ≥3 points where observed in 89.2% (50 patients; double weighted in randomization) 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 on based only on participates with full follow data.*
Risk of bias	*Moderate*

Author	*Elhamrawy*
Year	*2023*
Country	*Egypt*
Ref #	*[12]*
Study design	*RCT, 3-arm*
Setting	*Supervised exercise sessions*
Population	*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*
Follow up	*Post-treatment*
Intervention 1	*Four 60-minute sessions of Tai Chi exercises weekly for 12 weeks*
Participants (n)	*18*
Drop-outs (n)	*0*
Intervention 2	*Four supervised 60-minute aerobic training sessions weekly for 12 weeks*
Participants (n)	*18*
Drop-outs (n)	*0*
Comparison	*Maintaining their usual ADLs*
Participants (n)	*18*

Drop-outs (n)	*0*
Outcomes	*<u>Hand grip strength:</u>* *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* *<u>Fatigue severity scale:</u>* *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:</u>* *Mean difference (SE) in number of repetitions between groups* *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:</u>* *Mean difference (SE) in number of repetitions between groups* *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:</u>* *Mean difference (SE)* *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:</u>* *Mean difference (SE) in number of steps between groups* *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*
Comments Risk of bias	 *Low*

Author	*Espinoza-Bravo*
Year	*2023*
Country	*Spain*
Ref #	*[13]*
Study design	*RCT*
Setting	*Home-based exercise programmes instructed by a mobile phone application*
Population	*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*
Follow up	*8 weeks*
Intervention	*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*

Participants (n) Drop-outs (n)	*24* *3*
Comparison 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 Risk of bias	*Not completely fulfilling the WHO criteria but an average of 17.4 months had passed since infection in the sample* *Moderate*

Author	*Fan*

Year	*2021*
Country	*China*
Ref #	*[14]*
Study design	*RCT, single-blind*
Setting	*Online/mobile phone intervention and counselling clinic at hospital*
Population	*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.*
Follow up	*6 months*
Intervention	*Narrative exposure therapy (NET, Schauer et al., 2011) and personalised psychological treatment. NET for 1–2 sessions/week for 8 weeks, 90~120 min.*
Participants (n)	*56*
Drop-outs (n)	*0*
Comparison	*Personalised psychological interventions based on the participants' symptoms (1 session/week, 40-60 min)*
Participants (n)	*55*
Drop-outs (n)	*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)*
Comments	
Risk of bias	*Moderate*

Author	*Figueiredo*
Year	*2024*
Country	*Brazil*
Ref #	*[15]*
Study design	*RCT, double-blind*
Setting	*Outpatient care, self-administration*
Population	*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	*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*
Participants (n)	*64*
Drop-outs (n)	*15*
Comparison	*Olfactory training as above + placebo*
Participants (n)	*64*
Drop-outs (n)	*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*
Comments	
Risk of bias	*Moderate*

Author	*Finnigan*
Year	*2023*
Country	*UK*
Ref #	*[16]*
Study design	*RCT, double-blind*
Setting	*Outpatient care, self-administration*
Population	*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*
Follow up	*28 days post start of treatment*
Intervention	*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*
Participants (n)	*21*
Drop-outs (n)	*0*
Comparison	*Placebo administered in the same way as the active substance*
Participants (n)	*20*
Drop-outs (n)	*0*
Outcomes	*Primary outcome was change in phosphocreatine rate – not tabulated here.* *Other outcomes:* *CFQ-11 Total fatigue Likert score (range 0-33) at 28 days, change from baseline, mean (SD):* *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* *6-minute walk test (MWT) distance in meters, mean (SD):* *I: 25.57 (54.0)* *C: 25.3 (12.1)* *p>0.05 (ns) (MD not reported)* *Adverse events, number of patients:* *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*

Author	*Hansen*
Year	*2023*
Country	*Denmark*

Ref #	*[17]*
Study design	*RCT, cross-over. Washout period 4 weeks.*
Setting	*Primary care setting. Patients were recruited from a specialized post-covid condition outpatient clinic*
Population	*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).*
Follow up	*End of treatment. 4 weeks after treatment.*
Intervention	*CoQ10 capsules in five 100-mg doses per day for 6 weeks*
Participants (n)	*121*
Drop-outs (n)	*2*
Comparison	*placebo capsules containing soy oil for 6 weeks*
Participants (n)	*121*
Drop-outs (n)	*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*
Comments	
Risk of bias	*Low*

Author	*Hosseinpoor*
Year	*Iran*
Country	*2022*
Ref #	*[18]*
Study design	*RCT*
Setting	*Outpatient care setting*
Population	*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)*
Follow up	*14 and 28 days after treatment*
Intervention	*one puff of 0.05% wt/vol mometasone furoate (Raha Company, Iran) intranasal spray on each side twice per day for 4 weeks*
Participants (n)	*40*
Drop-outs (n)	*5*
Comparison	*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*

Participants (n)	*40*
Drop-outs (n)	*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 were reported*
Comments	
Risk of bias	*Low*

Author	*Ibrahim*
Year	*2023*
Country	*Saudi Arabia*
Ref #	*[19]*
Study design	*Block RCT*
Setting	*Outpatient setting*
Population	*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)*
Follow up	*End of treatment (10 weeks)*
Intervention	*Moderate intensity aerobic exercises 4 times per week for 10 weeks*
Participants (n)	*24*
Drop-outs (n)	*0*
Intervention	*Low intensity aerobic exercises 4 times per week for 10 weeks*
Participants (n)	*24*
Drop-outs (n)	*0*
Comparison	*Medical care and advice*
Participants (n)	*24*
Drop-outs (n)	*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*
Comments	
Risk of bias	*Low*

Author	*Jimeno-Almazan*
Year	*2022*
Country	*Spain*
Ref #	*[20]*
Study design	*VO_2-max stratified RCT*
Setting	*University medical center*
Population	*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*
Follow up	*End of treatment (8 weeks)*
Intervention	*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*
Participants (n)	*19*
Drop-outs (n)	*Not mentioned*
Comparison	*WHO guidelines: Support for Rehabilitation: Self-Management after COVID-19 Related Illness, see comment*
Participants (n)	*20*
Drop-outs (n)	*Not mentioned*
Outcomes	*Primary outcome:* *<u>PCFS post treatment mean (SD)</u>* *I: 1.1 (1.2)* *C: 1.8 (1.1)* *Group effect: p=0.033, ηp^2=0.15 (ANOVA)* *Other reported outcomes:* *<u>Pulmonary function:</u> FVC (L), %FVC, FEV-1 (L), %FEV-1, FEV-1/FVC, FEV25-75% (L·s−1), MVV (L), %MVV* *<u>Quality of life and fatigue:</u> SF-12 (PA), SF-12 (MH), mMRC, CFQ-11 (bimodal), CFQ-11 (Likert), FSS, DSQ-14, PCSF* *<u>Anxiety and depression:</u> GAD-7, PHQ-9* *<u>Cardiovascular fitness:</u> VO_2max (ml/kg/min), Final RPE 6–20, Final HR (b·m−1)* *<u>Muscular strength:</u> 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*

Author	*Jimeno-Almazan*
Year	*2023*
Country	*Spain*
Ref #	*[21]*
Study design	*VO_2-max stratified RCT*
Setting	*Outpatient care setting*
Population	*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*
Follow up	*End of treatment (8 weeks)*
Intervention	*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*
Participants (n)	*21*
Drop-outs (n)	*1*
Intervention	*Inspiratory muscle training (RM): inspiratory muscle training protocol with PowerBreath Classic Heath Series mechanic threshold devices*
Participants (n)	*17*
Drop-outs (n)	*0*
Intervention	*Concurrent training as above plus inspiratory muscle training as above (CTRM)*
Participants (n)	*25*
Drop-outs (n)	*2*
Comparison	*Advised to follow WHO guidelines: "Support for Rehabilitation: Self-Management after COVID-19-Related Illness"*
Participants (n)	*20*
Drop-outs (n)	*0*
Outcomes	*Main outcomes:* *Cardiorespiratory fitness, measured as:* *<u>VO_2max</u>* *Following the 8 wk-intervention period, no significant differences between groups were detected in the estimated VO_2max ($P > 0.05$).* *Muscle strength:* *<u>Lower body maximal and submaximal strength (squat 1RM and MPVALL)</u>* *Between groups effects not reported* *<u>Upper body submaximal strength (Bench Press MPVALL)</u>* *Authors report significant interaction for upper body submaximal strength (Bench Press MPVALL) ($P < 0.05$) for CT and CTRM groups.* *<u>Dominant hand grip strength</u>* *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 wk-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 [20].*
Risk of bias	*Moderate*

Author	*Kerget*
Year	*2023*
Country	*Turkey*
Ref #	*[22]*
Study design	*RCT*
Setting	*Outpatient care*
Population	*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*
Follow up	*12 weeks post start of treatment*
Intervention	*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*
Participants (n)	*15*
Drop-outs (n)	*0*
Comparison	*Nintedanib (an antifibrotic agent, off-label use), oral tablets 300 mg/day*
Participants (n)	*15*
Drop-outs (n)	*0*
Outcomes	*<u>6-minute walk test (MWT) distance in meters, mean change from baseline (SD):</u>* *I: 29.8 (27.2)* *C: 70 (48.4)* *P<0.05* *<u>Forced vital capacity (FVC), liters, mean change from baseline (SD):</u>* *I: 0.2 (0.3)* *C: 0.4 (0.3)* *P=0.17* *<u>Forced expiratory volume (FEV), liters, mean change from baseline (SD):</u>* *I: 0.2 (0.3)* *C: 0.2 (0.2)* *P=0.66* *<u>Heart rate, mean change from baseline (SD):</u>* *I: −12.9 (11.6)* *C: 10.2 (7.4)* *P=0.46* *<u>S02, finger tip saturation:</u>* *I: 5.6 ± 4.8* *C: 10.6 ± 4.1* *P=0.005* *<u>Adverse events, number of patients:</u>* *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*
Comments	

Risk of bias	*Moderate*

Author	*Kerling*
Year	*2024*
Country	*Germany*
Ref #	*[23]*
Study design	*RCT*
Setting	*Outpatient care*
Population	*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.*
Follow up	*After treatment (3 months)*
Intervention	*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)*
Participants (n)	*35*
Drop-outs (n)	*5*
Comparison	*Asked to continue with their current lifestyle and everyday activities*
Participants (n)	*37*
Drop-outs (n)	*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)*

	<u>VC predicted (%) mean difference (95% CI) between groups over time</u> *–0.08 (–3.69 to 3.52)*
Comments	
Risk of bias	*Moderate*

Author	*Klirova*
Year	*2024*
Country	*Czech Republic*
Ref #	*[24]*
Study design	*RCT, double-blind*
Setting	*Medical facility*
Population	*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.*
Follow up	*8 weeks*
Intervention	*Transcranial direct current stimulation (tDCS)*
Participants (n)	*17*
Drop-outs (n)	*1*
Comparison	*Sham-tDCS*
Participants (n)	*18*
Drop-outs (n)	*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*
Comments	
Risk of bias	*Moderate*

Author	*Kogel*
Year	*2023*
Country	*Germany*
Ref #	*[25]*
Study design	*RCT*

Setting	*Outpatient training program*
Population	*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	*Follow up after intervention (4 weeks) and after 3 and 6 months.*
Intervention	*4 weeks of two to three times weekly personalized strength endurance training.*
Participants (n)	*29*
Drop-outs (n)	*9 (at 6 months follow up)*
Comparison	*Care as usual, with no restrictions on exercise.*
Participants (n)	*28*
Drop-outs (n)	*8 (at 6 month follow up)*
Outcomes	*There were various significant between group effects at the assessment after 4 week intervention, not tabulated here.* *Outcomes at 3 and 6 monhts :* *Strenings measurements* *Cardiopulmonary* *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)* *After 3 months:* *no significant differences between the groups in any of the questionnaires or subdomains.* *At 6 months:* *The subdomain of psychological quality of life (MQOL) was significantly better in the exercise group than in the control group (exercise 29±9 vs. control 25±9, p<0.05)* *Physical activity* *The total physical activity per week was significantly greater in the exercise group than in the control group assessed with GPAQ (exercise 1280±1192 vs. control 644±554, p<0.05)* *Additional outcomes were reported*
Comments	
Risk of bias	*Moderate*

Author	*Kuut*
Year	*2023*
Country	*The Netherlands*
Ref #	*[26]*
Study design	*RCT*
Setting	*Online intervention*
Population	*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*
Follow up	*19 weeks, 6 months*
Intervention	*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*
Participants (n)	*57*

Drop-outs (n)	*11*
Comparison	*Care as usual*
Participants (n)	*57*
Drop-outs (n)	*4*
Outcomes	***Primary outcome:*** *Fatigue Mean (SE) at T0, T1, T2:* *(Higher score on CIS-fatigue-scale indicates more severe fatigue, ≥35 indicates severe fatigue)* *CBT: 47.8 (0.7), 30.6 (1.4), 31.5 (1.7)* *CAU: 47.0 (0.8), 39.9 (1.4), 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):* *Physical functioning (self-rated, SF-35 PF): 7.1 (2.9 to 11.3), P=0.001* *Social functioning (WSAS score): −6.6 (−9.1 to −4.2), P<0.001* *Somatic symptoms (PHQ-15): −2.0 (−2.9 to −1.0), P<0.001* *Problems concentrating (CIS-conc): −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.*
Comments **Risk of bias**	*Moderate*

Author	*Lasheen*
Year	*2023*
Country	*Egypt*
Ref #	*[27]*
Study design	*RCT, double-blind*
Setting	*Outpatient care, self-administration*
Population	*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*
Follow up	*End of treatment / 2 months post-allocation*
Intervention	*Corticosteroids, 8 doses over 2 months (twice weekly) injected in the olfactory mucosa*
Participants (n)	*20*
Drop-outs (n)	*0*
Comparison	*Placebo injections (saline)*
Participants (n)	*20*
Drop-outs (n)	*0*
Outcomes	*QOD-NS (range 0-51) post-intervention, mean (SD)* *I: 7.60 (8.91)* *C: 12.40 (12.00)*

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Comments	
Risk of bias	*Moderate*

Author	*Lau*
Year	*2024*
Country	*China*
Ref #	*[28]*
Study design	*Double blinded RCT*
Setting	*Outpatient setting*
Population	*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.*
Follow up	*3 and 6 months*
Intervention	*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*
Participants (n)	*232*
Drop-outs (n)	*28 (at 6 month follow up)*
Comparison	*Placebo, which consisted of low dose vitamin C 1 mg twice daily*
Participants (n)	*231*
Drop-outs (n)	*32 (at 6 month follow up)*
Outcomes	*Primary outcome:* *<u>Symptoms assessed with PACSQ-14 (OR, 95% CI):</u>* *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:* *<u>Quality of life (VAS at 6 months, aided by trained interviewers, mean (SD))</u>* *SIM01: 76.0 (SD 12.0)* *Placebo: 74.5 (12.3)* *p=0.17* *<u>Physical activity (IPAC at 6 months, median (IQR)):</u>* *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, 956.0–3290.0* *p=0.37* *Additional results were reported*
Comments	*Although blinded, it is likely that participants may have realized their group allocation.*
Risk of bias	*Moderate*

Author	*Lerner*
Year	*2023*
Country	*United States*

Ref #	*[29]*
Study design	*RCT*
Setting	*Primary care setting*
Population	*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.*
Follow up	*6 weeks*
Intervention	*Daily capsules of 2000 mg omega-3 fatty acid supplementation.*
Participants (n)	*70*
Drop-outs (n)	*13*
Comparison	*Placebo*
Participants (n)	*69*
Drop-outs (n)	*9*
Outcomes	*Primary outcome:* *<u>Change in BSIT score between-group difference at 6 weeks, 95% CI:</u>* *−0.43 (−1.13 to 0.27), as SMD: 0.228 (−0.15 to 0.59), p=0.221* *<u>Quality of life (modified brief QOD-NS survey):</u>* *No significant difference over time in the two groups (β=0.004, p =0.96)* *Secondary outcome:* *<u>SNOT-22 (Sino-Nasal Outcome Test-22):</u>* *No significant difference between groups over time (β =0.1605, p=0.462)*
Comments	*No ITT-analyses.*
Risk of bias	*Moderate*

Author	*Li*
Year	*2021*
Country	*China*
Ref #	*[30]*
Study design	*RCT, multicenter*
Setting	*Home-based, outside health care setting*
Population	*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 completely fulfilling WHO criteria for post COVID-19 (long covid)*
Follow up	*~28 weeks*
Intervention	*Unsupervised home-based 6-weekexercise programme comprising breathing control and thoracic expansion, aerobic exercise and LMS exercise, delivered via smartphone, and remotely monitored with heart rate telemetr.*
Participants (n)	*59*
Drop-outs (n)	*23*
Comparison	*Short education at baseline.*
Participants (n)	*61*
Drop-outs (n)	*5*
Outcomes	*Functional exercise capacity:* *<u>Adjusted between-group difference in change in 6MWD from baseline (treatment effect):</u>* *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)*
Comments Risk of bias	 *Moderate*

Author Year Country Ref #	*Longobardi* *2023* *Brazil* *[31]*
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*
Comparison 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
Comments	
Risk of bias	*Moderate*

Author	*McGregor*
Year	*2023*
Country	*UK*
Ref #	*[32]*
Study design	*Multicenter RCT*
Setting	*Home-based online-delivered intervention*
Population	*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*
Follow up	*3, 6 and 12 months*
Intervention	*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*
Participants (n)	*298*
Drop-outs (n)	*82*
Comparison	*Usual care (a single online session of advice and support)*
Participants (n)	*287*
Drop-outs (n)	*61*
Outcomes	*Outcomes at 3 months, adjusted MD (95% CI):* *Primary outcome:* *<u>Health related quality of life, PROPr score:</u>* *0.03 (0.01 to 0.05), P=0.02* *Secondary outcomes:* *<u>Fatigue, PROPr subscale score:</u>* *2.50 (1.19 to 3.81), P<0.001* *<u>HADS anxiety:</u>* *0.29 (–0.37 to 0.94), P=0.38* *<u>HADS depression:</u>* *0.46 (–0.14 to 1.05), P=0.13* *<u>Physical activity, IPAQ-SF (MET min/week):</u>* *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 were reported*
Comments	
Risk of bias	*Måttlig*

Author	*McIntyre*
Year	*2023*
Country	*Canada*
Ref #	*[33]*

Study design	*RCT, double-blind*
Setting	*Primary care*
Population	*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*
Follow up	*8 weeks*
Intervention	*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*
Participants (n)	*75*
Drop-outs (n)	*7*
Comparison	*Placebo*
Participants (n)	*74*
Drop-outs (n)	*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	
Risk of bias	*Moderate*

Author	*McNarry*
Year	*2021*
Country	*United Kingdom*
Ref #	*[34]*
Study design	*RCT*
Setting	*Primary care setting*

Population	*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.*
Follow up	*8 weeks*
Intervention	*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.*
Participants (n)	*224*
Drop-outs (n)	*113*
Comparison	*"Usual care" waitlist control*
Participants (n)	*57*
Drop-outs (n)	*20*
Outcomes	*Health-related quality of life (K-BILD total score):* *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).*
Comments	
Risk of bias	*Moderate*

Author	*Momtazmanesh*
Year	*2023*
Country	*Iran*
Ref #	*[35]*
Study design	*RCT, double-blind*
Setting	*Self-administration outside health care setting*
Population	*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)*
Follow up	*6 and 12 weeks*
Intervention	*Famotidine (40 mg, twice daily for 12 weeks)*
Participants (n)	*29*
Drop-outs (n)	*7 (Week 6: 5, week 12: 2)*
Comparison	*Placebo*
Participants (n)	*29*
Drop-outs (n)	*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.*
Comments Risk of bias	 *Moderate*

Author Year Country Ref #	*Navas-Otero* *2024* *Spain* *[36]*
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*
Comparison 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:* *Quality of life (EQ-5D VAS). The dimensions assessed:* • *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*

	Disability (WHODAS 2.0): *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* *The impairment in functioning (WSAS):* *Of five subscales tested, none showed a statistically significant finding.* *Total score for WSAS, p for group comparison =0.978*
Comments Risk of bias	*Multiple testings and no correction* *Moderate*

Author Year Country Ref #	*Ogonowska-Slodownik* *2023* *Poland* *[37]*
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*
Comparison Participants (n) Drop-outs (n)	*LAND - Land based aerobic exercises twice a week, 45 min per session, for eight weeks* *29* *6*
Comparison 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:* *<u>PedsQL children mean difference (95% CI) between groups post intervention</u>* *4.3 (-2.8 to 11.5)* *<u>PedsOL parent mean difference (95% CI) between groups post intervention</u>* *7.2 (0.9 to 13.5)* *Additional outcomes were reported*
Comments Risk of bias	*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 randomization.* *Moderate*

Author Year Country Ref #	*Ojeda* *2024* *Spain* *[38]*
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*
Comparison 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.* *the 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?''*
Comments	
Risk of bias	*Moderate*

Author	*Okan*
Year	*2022*
Country	*Turkey*
Ref #	*[39]*
Study design	*RCT*
Setting	*Outpatient clinic and telerehabilitation in home environment*
Population	*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*
Follow up	*5 weeks*
Intervention	*Breathing exercises (respiratory control, pursed lip breathing, and diaphragmatic breathing exercises) 3/day for 5 weeks (one session performed via telemedicine each week).*
Participants (n)	*26*
Drop-outs (n)	*0*
Comparison	*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.*
Participants (n)	*26*
Drop-outs (n)	*0*
Outcomes	*Functional capacity* *<u>Group x time interaction 6MWT:</u>* *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* *<u>Group x time interaction FEV1 %:</u>* *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)* *<u>Group x time interaction FVC %:</u>* *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) *<u>Group x time interaction FEV1/FVC %:</u>* *Difference not significant* *<u>Group x time interaction MVV %:</u>* *(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.*
Comments Risk of bias	 *Moderate*

Author Year Country Ref #	*Oliver-Mas* *2023* *Spain* *[40]*
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*
Comparison Participants (n) Drop-outs (n)	*Sham tDCS* *24* *0*
Outcomes	*Primary outcome:* *<u>Change in fatigue, rm ANOVA, time x group interaction</u>* *MFIS-total: not significant ($F_{(2,82)}$=1.730, p=0.184)* *MFIS-physical: <u>significant, favouring intervention</u> ($F_{(2,82)}$=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): <u>significant, favouring intervention ($F_{(2,82)}$</u>=3.447, p=0.036)* *Executive function (Stroop – IG) and 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.*
Comments Risk of bias	 *Moderate*

Author Year	*Palau* *2022*

Country	*Spain*
Ref #	*[41]*
Study design	*RCT*
Setting	*Home based inspiratory muscle training (IMT) program.*
Population	*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.*
Follow up	*12 weeks, approximately*
Intervention	*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.*
Participants (n)	*13*
Drop-outs (n)	*0*
Comparison	*Usual care including baseline visit.*
Participants (n)	*13*
Drop-outs (n)	*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 endpoint:* *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 were reported.*
Comments	
Risk of bias	*Moderate*

Author	*Pleguezuelos*
Year	*2024*
Country	*Spain*
Ref #	*[42]*
Study design	*RCT, single blinded*
Setting	*Outpatients setting*
Population	*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.*
Follow up	*15 weeks (also evaluated at 3 months and 12 months (detraing)*
Intervention	*A supervised homebased telerehabilitation program combining aerobic and strength exercises three times weekly for 15 weeks.*
Participants (n)	*75*
Drop-outs (n)	*9*

Comparison	*No supervised telerehabilitation. Participants in control group were asked to carry out their routine daily life activities*
Participants (n)	*75*
Drop-outs (n)	*10*
Outcomes	*Primary outcome:* *Cardiopulmonary exercise test performed on ergometric bicycle (several tests performed)* *Exercise capacity (exercise time in seconds):* *An intervention × time interaction effect was detected (p=0.001) in favour of intervention* *Peak oxygen uptake (V02):* *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 were reported*
Comments	
Risk of bias	*Moderate*

Author	*Philip*
Year	*2022*
Country	*UK*
Ref #	*[43]*
Study design	*RCT*
Setting	*Outpatient setting.*
Population	*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)*
Follow up	*6 weeks.*
Intervention	*The English National Opera Breathe programme, breathing retraining using singing techniques (6 weeks, online).*
Participants (n)	*74*
Drop-outs (n)	*16*
Comparison	*Care as usual*
Participants (n)	*76*
Drop-outs (n)	*5*
Outcomes	*Primary outcome:* *Change in HRQoL, baseline – end of 6-week course, assessed by SF-36, MHC and PHC score* *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).* *VAS for breathlessness (running):* *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*

Author	*Rasmussen*
Year	*2023*
Country	*Denmark*
Ref #	*[44]*
Study design	*Investigator blinded RCT*
Setting	*Outpatient*
Population	*Persons (mean age 57.2 (SD 10) years, 32% women) previously hospitalized for laboratory confirmed SARS-CoV-2, but no specific symptoms were required.*
Follow up	*12 weeks*
Intervention	*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*
Participants (n)	*14*
Drop-outs (n)	*1*
Comparison	*Standard care*
Participants (n)	*14*
Drop-outs (n)	*1; 4 participants engaged in exercise program*
Outcomes	*The primary outcome was left ventricular mass measured with MRI, not reported here.* *Secondary outcomes included:* *<u>Lung function, measured with with spirometry.</u>* *There were no statistically significant differences in between group comparisons for predictive values of FEV1, FVC, TLC and RV.* *<u>Functional capacity and HRQoL</u>, 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.* *<u>Strength testing</u>* *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.* *<u>Physical activity level</u>* *Posture and physical activity behaviors are measured using three axial accelerometer-based physical activity monitors.* *<u>Step counts per day</u> and <u>time spent at moderate/ high activity level</u> changed in the HIIT group from baseline. However, time spent being inactive concurrently decreased in the HIIT group compared with the control group (ns).* *Several additional outcomes were reported*
Comments	
Risk of bias	*Moderate*

Author	*Romanet*
Year	*2023*
Country	*France*
Ref #	*[45]*
Study design	*Open assessor blinded multicenter RCT*
Setting	*Outpatient program setting*
Population	*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)*
Follow up	*12 weeks*
Intervention	*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.*
Participants (n)	*27*
Drop-outs (n)	*0 (4 chose standard physiotherapy during follow up)*
Comparison	*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.*
Participants (n)	*33*
Drop-outs (n)	*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.* *Mean difference (95% CI) between-groups at 90 days:* *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).* *Mean difference (95% CI) between-groups at 90 days:* *mMRC: –0.76 (–1.21 to –0.30), 0.001, in favour of intervention* *Measurement of HRQoL (SF-12) at 90 days* *SF-12 total score: 8.24, 95% CI (0.22 to 16.25), p=0.14, in favour of intervention* *Additional outcomes were reported*
Comments	
Risk of bias	*Moderate*

Author	*Samper-Pardo*
Year	*2023*
Country	*Spain*
Ref #	*[46]*
Study design	*RCT, open-label*
Setting	*Primary health care*
Population	*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.*
Follow up	*3 months*
Intervention	*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
Participants (n)	*52*
Drop-outs (n)	*7*
Comparison	*Treatment as usual established by their general practitioner*
Participants (n)	*48*
Drop-outs (n)	*6*
Outcomes	*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)*
Comments Risk of bias	*Moderate*

Author	*Sánchez-Milá*
Year	*2023*
Country	*Spain*
Ref #	*[47]*
Study design	*RCT*
Setting	*Primary care setting*
Population	*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*
Follow up	*Mid-term (15 days) and after treatment (31 days)*
Intervention	*Respiratory treatment based on inspiratory muscle training using PowerBreathe for 31 days*
Participants (n)	*103*
Drop-outs (n)	*3*
Comparison	*Treatment based on traditional diaphragmatic exercises prescribed in various respiratory conditions for 31 days*
Participants (n)	*104*
Drop-outs (n)	*4*
Outcomes	*Main outcomes:* *<u>FVC (liters) post treatment, mean (SD):</u>* *I: 4.0255 (0.10994)* *C: 3.5408 (0.08307)* *p < 0.001 (based on group x time effect)* *<u>FEV1 (liters) post treatment, mean (SD):</u>* *I: 3.6177 (0.31406)* *C: 2.9529 (0.08729)* *p < 0.001 (based on group x time effect):* *<u>FEV1/FVC (%) post treatment, mean (SD):</u>* *I: 73.2897 (3.57746)* *C: 69.9542 (1.17489)* *p < 0.001 (based on group x time effect)* *<u>PEFR (liters/min) post treatment, mean (SD):</u>* *I: 8.0926 (0.21457)* *C: 7.5725 (0.24420)* *p < 0.001 (based on group x time effect)* *<u>FIVC (liters) post treatment, mean (SD):</u>* *I: 2.3745 (0.22702)* *C: 2.0859 (0.11724)* *p < 0.001 (based on group x time effect)* *<u>MIP cmH2O post treatment, mean (SD):</u>* *I: 91.1064 (4.67964)* *C: 79.3713 (3.73998)* *p < 0.001 (based on group x time effect)* *Other outcomes:* *<u>Systolic pressure (mmHg) post treatment, mean (SD):</u>*

	I: 122.29 (4.680) *C: 133.94 (3.250)* *p < 0.001 (based on group x time effect)* *<u>Dyastolic pressure (mmHg) post treatment, mean (SD):</u>* *I: 72.49 (43.82)* *C: 78.69 (6.324)* *p < 0.001 (based on group x time effect)* *<u>Dyspnea Borg post treatment, mean (SD):</u>* *I: 1.03 (0.784)* *C: 3.02 (0.791)* *p < 0.001 (based on group x time effect)* *<u>Lower limbs borg post treatment, mean (SD):</u>* *I: 1.00 (0.816)* *C: 1.58 (1.093)* *p = 0.002 (based on group x time effect)* *<u>Oxygen Saturation (mmHg) post treatment, mean (SD):</u>* *I: 97.52 (1.141)* *C: 97.62 (1.117)* *p = 0.841 (based on group x time effect)* *<u>Cardiac Frequency (BPM) post treatment, mean (SD):</u>* *I: 86.16 (2.505)* *C: 85.93 (2.571)* *p = 0.969 (based on group x time effect)* *<u>6MWD (meters) post treatment, mean (SD):</u>* *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 randomization*
Risk of bias	*Moderate*

Author	*Santana*
Year	*2023*
Country	*Brazil/USA*
Ref #	*[48]*
Study design	*RCT, double-blind*
Setting	*Department of Rehabilitation at University Medical Center*
Population	*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.*
Follow up	*5 weeks*
Intervention	*3 mA HD-tDCS targeting left primary motor cortex (M1), 30 min paired with individually tailored rehabilitation program.* *2 sessions/week over 5 weeks.*
Participants (n)	*35*
Drop-outs (n)	*0*
Comparison	*Sham HD-tDCS paired with rehabilitation program*
Participants (n)	*35*

Drop-outs (n)	*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-bref)* *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)*
Comments Risk of bias	

Author Year Country Ref #	*Schepens* *2022* *The Netherlands* *[49]*
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*
Comparison Participants (n) Drop-outs (n)	*Placebo capsules once daily for 10 days* *57* *1*
Outcomes	*Outcomes at 12 weeks:* *Sniffin' Sticks test TDI score (range 1-48), mean (SD)* *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* *Taste Strip Test total score (range 0-16), mean (SD)*

	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* *Adverse events, number of events:* *I: 3* *C:0*
Comments Risk of bias	 *Low*

Author	*Shamohammadi*
Year	*2021*
Country	*Iran*
Ref #	*[50]*
Study design	*RCT, double-blind*
Setting	*Primary care/ home-based*
Population	*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.*
Follow up	*3 months post study start*
Intervention	*Tadalafil, 5 mg daily for 3 months*
Participants (n)	*35*
Drop-outs (n)	*3*
Comparison	*Placebo*
Participants (n)	*35*
Drop-outs (n)	*5*
Outcomes	*<u>International Index of Erectile Function (IIEF-5), MD change from baseline</u>* *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*

Author	*Tosato*
Year	*2022*
Country	*Italy*
Ref #	*[51]*
Study design	*RCT, single-blind*
Setting	*Post-acute COVID-19 outpatient clinic*
Population	*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.*
Follow up	*28 days*
Intervention	*Oral supplementation 1.66 g L-arginine plus 500 mg liposomal vitamin C, 2/day for 28 days*
Participants (n)	*25*
Drop-outs (n)	*2*
Comparison	*Placebo*
Participants (n)	*25*
Drop-outs (n)	*2*
Outcomes	*<u>Distance walked on the 6 min walk test (median (IQR) change from baseline)</u>* *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 m; effect size=0.56* *See study for more results on secondary outcomes: handgrip strength, flow-mediated dilation, and fatigue persistence*
Comments	
Risk of bias	*Moderate*

Author	*Yan*
Year	*2023*
Country	*US*
Ref #	*[52]*
Study design	*RCT*
Setting	*Outpatient setting.*
Population	*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.*
Follow up	*4 and 12 weeks. Only 12-weeks results are reported below.*
Intervention	*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.*
Participants (n)	*18*
Drop-outs (n)	*4*
Comparison	*Three intranasal injections with placebo (sterile saline) bilaterally in the same locations as in the intervention group.*
Participants (n)	*12*
Drop-outs (n)	*12*
Outcomes	*Primary outcome:* *<u>Change in TDI using Sniffin' Sticks, results between groups:</u>* *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:* *<u>Responder rate at 3 months (where a responder was defined as a clinically significant improvement on Sniffin' Sticks TDI score, ≥5.5 points):</u>* *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))* *<u>VAS:</u> 0.88, (95% CI, –0.38 to 2.15), p=0.167* *Additional outcomes were reported*
Comments Risk of bias	 *Moderate*

Author Year Country Ref # Authour Year Country Ref #	*Zilberman-Itskovich* *2022* *Israel* *#1251* *Leitman* *2023* *Israel* *[53]*
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.* *<u>HBOT protocol:</u>* *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*
Comparison Participants (n) Drop-outs (n)	*<u>Sham protocol:</u>* *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)* *<u>Cognitive assessment</u>:* *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))* *<u>Quality of life (SF-36):</u>* *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* *<u>Olfactory and gustatory function:</u>* *No significant group-by-time interactions.* *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=<u>not</u> significant)* *<u>Cardiac function:</u>* *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) were non-significant*
Comments Risk of bias	*Cardiac function outcomes are reported in a separate publication (Leitman et al 2023, #1278)* *Low for cognitive and most other outcomes,Some concerns for cardiac outcomes*

POTS – Posturalt ortostatiskt takykardisyndrom, POTS

Author Year Country Ref #	*Arnold* *2013* *US* *[54]*
Study design Setting Population Follow up	*RCT, double-blind cross-over between drugs* *Tertiary care center* *12 females with POTS (diagnosis according to Freeman R et al, 2011) and 7 matched female controls* *1 day*
Intervention Participants (total n) Drop-outs (total n)	*Single low dose of propranolol (20 mg) with ≥2 washout days between intervention and control* *(See study for secondary objective: high-dose propranolol (80 mg), equipotent metoprolol (100 mg), and placebo on VO_2max in a separate cohort of 5 patients with POTS).* *19 (POTS=12, healthy=7)* *1 (POTS)*
Comparison	*Placebo with ≥2 washout days between intervention and control*
Allocated to placebo first (n)	*POTS=4* *Healthy=2*

Outcomes	*Maximal exercise capacity determined by exercise test performed on semi-recumbent bicycle 1 hour after receiving intervention/placebo (VO_2 measured at rest and at graded exercise to maximal effort reaching peak oxygen consumption; VO_2max)* *All exercise measures, including VO_2max and peak HR, were similar between groups following placebo, suggesting exercise capacity was not impaired in POTS:* *Propranolol (20 mg) improved VO_2max in patients with POTS (24.5±0.7 placebo vs 27.6±1.0 mL/min/kg propranolol; p=0.024), but not in healthy subjects.* *The increase in VO_2max in POTS was associated with attenuated peak heart rate responses (142±8 bpm with propranolol vs 165±4 bpm with placebo; p=0.005) and improved stroke volume (81±4 mL with propranolol vs 67±3 mL with placebo; p= 0.013).*
Comments Risk of bias	 *Moderate*

Author	*Coffin*
Year	*2012*
Country	*US*
Ref #	*[55]*
Study design	*RCT, single-blind cross-over*
Setting	*University specialist care center*
Population	*Patients aged ≥ 18 years (86.7% female; 37±12 years) that met criteria for POTS having ≥6-month history of symptoms in the absence of an additional chronic disorder known to cause orthostatic intolerance and in the absence of prolonged bed rest.*
Follow up	*2 and 4 hrs*
Intervention Participants (n)	*Desmopressin (DDAVP) 0.2 mg* *30*
Comparison	*Placebo (on separate days)*
Outcomes	*<u>Standing HR (mean bpm, SD) pre and post study drug administration (p<0.05 was considered significant):</u>* *DDAVP: 111.8±17.8 (pre); 101.9±14.5 (2 hrs); 102.0±15.9 (4 hrs)* *Placebo: 117.1±16.0 (pre); 109.2±17.4 (2 hrs); 106.8±16.1 (4 hrs)* *p-value (between drugs): 0.070 (pre); 0.001 (2 hrs); 0.006 (4 hrs)* *rm ANOVA: P_{drug}<0.001* *<u>Seating HR (mean bpm, SD) pre and post study drug administration (p<0.05 was considered significant):</u>* *DDAVP: 85.1±13.5 (pre); 80.4±13.3 (2 hrs); 82.9±13.8 (4 hrs)* *Placebo: 85.1±13.5 (pre); 84.0±14.0 (2 hrs); 84.7±13.3 (4 hrs)* *p-value (between drugs): 0.414 (pre); 0.034 (2 hrs); 0.219 (4 hrs)* *rm ANOVA: P_{drug}0.048* *See study for additional results on Delta (Standing-Seated) HR, Standing SBP, Sitting SBP, Delta (Standing-Sitting) SBP, and Symptom score (au).*
Comments Risk of bias	 *Moderate*

Author	*Gamboa*
Year	*2015*
Country	*US*

Ref #	*[56]*
Study design	*RCT, single-blind cross-over*
Setting	*University specialist care center*
Population	*Patients aged ≥18 years (96% female, 30±2 years) who met criteria for POTS: HR rise ≥30 bpm within 10 min of standing or head-up tilt (HUT); absence of orthostatic hypotension (fall in BP ≥20/10 mm Hg); symptoms ≥6 months; and absence of medications or additional chronic disorders known to cause tachycardia. All patients were non-smokers, not pregnant, nor endurance-trained athletes*
Follow up	*10 minutes*
Intervention	*Increased inspiratory resistance with an impedance threshold device (ITD)*
Participants (n)	*37*
Drop-outs (n)	*11*
Comparison	*Sham*
Outcomes	*<u>Heart rate (bpm) after 10 minutes of HUT, n=26 (mean±SEM, p-value=paired t-test):</u>* *I: 102±4* *C: 109±4* *p=0.007* *<u>Stroke volume (mL) after 10 min of HUT, n=26 (mean±SEM, p-value=paired t-test):</u>* *I: 35±2* *C: 31±2* *p=0.026* *<u>Mean arterial pressure mm Hg after 10 min of HUT, n=26 (mean±SEM, p-value=paired t-test):</u>* *I: 84±2* *C: 83±2* *p=0.164* *<u>Total peripheral resistance (dyne×sec×cm^{-5}) after 10 min of HUT, n=26 (mean±SEM, p-value=paired t-test):</u>* *I: 2109±138* *C: 2082±104* *p= 0.750* *See study for additional secondary outcome results on cardiac output, systolic and diastolic blood pressure after 10 min of HUT (both not significant), and all outcome measures mentioned above in supine position*
Comments	
Risk of bias	*Moderate*

Author	*Green*
Year	*2013*
Country	*US*
Ref #	*[57]*
Study design	*RCT, single-blind cross-over*
Setting	*University specialist care center*
Population	*Patients aged ≥18 years (92.6% female, 34±9 years) who met criteria for POTS (developing symptoms of orthostatic intolerance, accompanied by HR rise ≥30 bpm within 10 min of standing, in absence of orthostatic hypotension (fall in BP ≥20/10 mm Hg). All had symptoms ≥6 months and absence of additional chronic disorders known to cause orthostatic intolerance.*
Follow up	*2 and 4 hrs*
Intervention	*Atomoxetine 40 mg*

Participants (n) Drop-outs (n)	*27* *0*
Comparison	*Placebo (on separate days)*
Outcomes	*<u>Standing HR (mean bpm±SD) pre and post study drug administration:</u>* *Atomoxetine: 110±18 (pre); 121±17 (2 hrs); 117±14 (4 hrs)* *Placebo: 114±17 (pre); 105.5±15.0 (2 hrs); 104±16 (4 hrs)* *p-value (between drugs): 0.204 (pre); 0.001 (2 hrs); 0.001 (4 hrs)* *rm ANOVA: P_{drug}<0.002* *(P<0.05 considered significant for ANOVA and P<0.0125 was considered significant for the post-hoc hemodynamic t-tests)* *<u>Seating HR (mean bpm±SD) pre and post study drug administration:</u>* *Atomoxetine: 86±10 (pre); 89±13 (2 hrs); 89±12 (4 hrs)* *Placebo: 84±12 (pre); 79±10 (2 hrs); 78±11 (4 hrs)* *p-value (between drugs): 0.334 (pre); <0.001 (2 hrs); <0.001 (4 hrs)* *rm ANOVA: P_{drug}<0.001* *(P<0.05 considered significant for ANOVA and P<0.0125 was considered significant for the post-hoc hemodynamic t-tests)* *See study for additional results on Delta (Standing-Seated) HR, Standing SBP, Sitting SBP, Delta (Standing-Sitting) SBP, and Symptom score (au).*
Comments Risk of bias	 *Moderate*

Author Year Country Ref #	*Green* *2014* *US* *[58]*
Study design Setting Population Follow up	*RCT, single-blind cross-over* *University specialist care center* *Patients aged ≥18 years (92.3% female, 32±9 years) who met criteria for POTS (developing symptoms of orthostatic intolerance, accompanied by HR rise ≥30 bpm within 10 min of standing, in absence of orthostatic hypotension (fall in BP ≥20/10 mm Hg). All had symptoms for at least 6 months and absence of additional chronic disorders known to cause orthostatic intolerance.* *4 hrs*
Intervention Participants (n) Drop-outs (n)	*Melatonin (oral 3 mg)* *78* *0*
Comparison	*Placebo (on separate days)*
Outcomes	*<u>Standing HR (mean bpm±SEM, 95% CI) after study drug administration:</u>* *Melatonin-Placebo:* *<u>Change at 2 hrs:</u> –4.1±1.7 (95% CI, −7.5 to −0.7), p=0.017* *<u>Change at 4 hrs:</u> –4.5±1.7 (95% CI, −7.9 to −1.1), p=0.009* *(p<0.05 was considered significant)* *<u>Seated HR (mean bpm±SEM, 95% CI) after study drug administration:</u>* *Melatonin-Placebo:* *<u>Change at 2 hrs:</u> –3.4±1.5 (95% CI, −6.2 to −0.5), p=0.021* *<u>Change at 4 hrs:</u> –2.4±1.3 (95% CI, −5.0 to 0.22), p=0.073* *(p<0.05 was considered significant)*

	See study for additional results on Delta (Standing-Seated) HR, Standing SBP, Sitting SBP, Delta (Standing-Sitting) SBP, and Symptom score (au).
Comments	
Risk of bias	*Moderate*

Author	*Kpaeyeh*
Year	*2014*
Country	*US*
Ref #	*[59]*
Study design	*RCT, single-blind cross-over*
Setting	*University specialist care center*
Population	*Patients aged ≥18 years (88.9% female, 32±10 years) who met criteria for POTS (increase in HR ≥ 30 bpm with standing in the absence of orthostatic hypotension)*
Follow up	*4 hrs*
Intervention	*Modafinil (100 mg)*
Participants (n)	*54*
Drop-outs (n)	*0*
Comparison	*Placebo (given on separate days, 31 patients received placebo on first day)*
Outcomes	*Standing HR (mean bpm±SD) pre and post study drug administration:* *Modafinil: 112±14 (pre); 105±16 (4 hrs)* *Placebo: 113±14 (pre); 101±16 (4 hrs)* *p-value (between drugs): 0.575 (pre); 0.139 (4 hrs)* *rm ANOVA: P_{drug}=0.328* *(p≤0.05 considered statistically significant)* *Seated HR (83 ±12 bpm vs 84±11 bpm; p=0.763) at 4 hrs post administration were both similar between the modafinil and the placebo group.* *See study for additional results on orthostatic change in HR, standing SBP, seated SBP, orthostatic change in SBP, and symptom score (VOSS).*
Comments	*Unclear for how long patients had been showing symptoms prior to study participation.*
Risk of bias	*Moderate*

Author	*Mar*
Year	*2014*
Country	*US*
Ref #	*[60]*
Study design	*RCT, double-blind cross-over*
Setting	*University specialist care center*
Population	*Patients aged ≥18 years (95% female, 39±9 years) who met criteria for POTS (developed symptoms of orthostatic intolerance accompanied by HR rise of >30 beats/min within 10 min of standing in absence of orthostatic hypotension (a fall in BP of >20/10 mmHg)). All patients had ≥6-month history of symptoms in absence of additional chronic disorder known to cause orthostatic intolerance, and in absence of prolonged bed rest.*
Follow up	*2, 4 hrs*
Intervention	*Sertraline (50 mg)*
Participants (n)	*39*
Drop-outs (n)	*0*
Comparison	*Placebo (on different random day)*

Outcomes	*<u>Standing HR (mean bpm±SD) pre and post study drug administration:</u>* *Sertraline: 115±17 (pre); 108±16 (2 hrs); 102±17 (4 hrs)* *Placebo: 117±17 (pre); 107±20 (2 hrs); 106±21 (4 hrs)* *p-value (between drugs): 0.312 (pre); 0.913 (2 hrs); 0.167 (4 hrs)* *(p<0.05 considered statistically significant)* *<u>Seating HR (mean bpm±SD) pre and post study drug administration:</u>* *Sertraline: 89±12 (pre); 82±11 (2 hrs); 80±12 (4 hrs)* *Placebo: 86±12 (pre); 80±10 (2 hrs); 80±12 (4 hrs)* *p-value (between drugs): 0.165 (pre); 0.166 (2 hrs); 0.912 (4 hrs)* *(p<0.05 considered statistically significant)* *See study for additional results on Delta (Standing-Seated) HR, Standing SBP, Sitting SBP, Delta (Standing-Sitting) SBP, and Symptom score (au).*
Comments Risk of bias	 *Moderate*

Author Year Country Ref #	*Moon* *2018* *South Korea* *[61]*
Study design Setting Population Follow up	*RCT, open label* *University specialist care center* *Patients(all ages) who fulfilled HR criteria for POTS and following criteria: (1) HR increment ≥ 30 bpm (or ≥ 40 bpm in patients aged 12–19) within 10 min after standing; (2) presence of considerable orthostatic intolerance symptoms, defined by OIQ score ≥ 10; and (3) no overt cause of tachycardia (eg acute blood loss, prolonged bed rest, hyperthyroidism, or tachycardia-promoting medications).* *1, 3 months*
Intervention	*<u>Propranolol (P):</u> starting dose of 10 mg 2/day; dosage increase was allowed up to 20 mg 2/day after 1 month, according to clinician's discretion* *<u>Bisoprolol (B)</u>: starting dose of 2.5 mg 1/day; dosage increase was allowed up to 5 mg 1/day after 1 month, according to clinician's discretion* *<u>Pyridostigmine (PS):</u> starting dose of 30 mg 2/day, maintained for 3 months*
Participants (Total n) Drop-outs (Total n)	*103* *26*
Intervention groups (n=after drop-out) Total n (male:female)	*Group 1: P only (n=19)* *Group 2: B only (n=17)* *Group 3: P + PS (n=18)* *Group 4: B + PS (n=23)* *77 (26:41)*
Outcomes	*<u>Symptom score (OIQ) reduction after 1 and 3 months of medical treatment:</u>* *Group 1 – Δ baseline$_{P\ only}$: −6.3±5.6 (1 month); −12.0±5.7 (3 months)* *Group 2 – Δ baseline$_{B\ only}$: −4.8±4.7 (1 month); −10.9±6.9 (3 months)* *Group 3 – Δ baseline$_{P+PS}$: −6.3±4.7 (1 month); −10.1±4.0 (3 months)* *Group 4 – Δ baseline$_{P+PS}$: −6.4±7.1 (1 month); −10.0±5.1 (3 months)* *Δ baseline$_{Total}$: − 6.0±5.6 (1 month); −10.7±5.4 (3 months)*

	ANOVA among Groups 1 to 4; p= 0.811 (1 month); 0.635 (3 months) *See study for additional results on depression (BDI-II), QoL (SF-36; SF-36 PCS; and SF-36 MCS), maximal HR increment, and number of patients who satisfied HR criteria of POTS after 1 month and 3 months.*
Comments	*No placebo, no ITT-analysis*
Risk of bias	*Moderate*

Author	*Raj*
Year	*2005*
Country	*US*
Ref #	*[62]*
Study design	*RCT, single-blind cross-over*
Setting	*University specialist care center*
Population	*Patients (82,4% female, 37±11 years) with POTS (symptoms of orthostatic intolerance accompanied by heart rate rise ≥30 bpm (or rate that exceeded 120 bpm) within first 10 minutes of standing or head-up tilt in the absence of orthostatic hypotension (a fall in blood pressure of >20/10 mm Hg) and with an elevated standing norepinephrine value (>2.81 nmol/L [475 pg/mL]). All patients had ≥6-month history of symptoms in absence of other chronic debilitating disorder or prolonged bed rest, free of medications that could impair autonomic tone, and had not been taking fludrocortisone for ≥5days before testing.*
Follow up	*4 hrs*
Intervention	*Pyridostigmine, an acetylcholinesterase inhibitor (30 mg orally)*
Participants (n)	*17*
Drop-outs (n)	*2*
Comparison	*Placebo*
Outcomes	*<u>Standing HR (mean bpm±SD) pre and post study drug administration:</u>* *Pyridostigmine: 119±16 (pre); 100±16 (2 hrs); 104±16 (4 hrs) – rm ANOVA P<0.001* *Placebo: 120±14 (pre); 111±14 (2 hrs); 109±17 (4 hrs) – rm ANOVA P<0.001* *p-value$_{Pyridostigmine\ vs\ placebo}$: 0.722 (pre); 0.001 (2 hrs); 0.160 (4 hrs)* *<u>Sitting HR (mean bpm±SD) pre and post study drug administration:</u>* *Pyridostigmine: 87±11 (pre); 80±18 (2 hrs); 81±14 (4 hrs) – rm ANOVA P=0.293* *Placebo: 87±10 (pre); 86±13 (2 hrs); 86±13 (4 hrs) – rm ANOVA P=0.833* *p-value$_{Pyridostigmine\ vs\ placebo}$: 0.815 (pre); 0.070 (2 hrs); 0.011 (4 hrs)* *Rm ANOVA: P<0.05 considered statistically significant. p-value$_{Pyridostigmine\ vs\ placebo}$: <0.025 was deemed to be significant.* *See study for additional results on Delta (Standing-Sitting) HR, Standing SBP, Sitting SBP, Delta (Standing-Sitting) SBP, and Symptom score (au).*
Comments	*Unclear for how long patients had been showing symptoms prior to study participation.*
Risk of bias	*Moderate*

Author	*Smith*
Year	*2020*
Country	*US*
Ref #	*[63]*
Study design	*RCT, single-blind cross-over*
Setting	*University specialist care center*

Population	*Female patients aged ≥18 (32±2 years) with POTS (≥6-month history of orthostatic symptoms accompanied by HR increase of ≥30 bpm within 10 min of standing, in absence of orthostatic hypotension (decrease in BP ≥20/10 mm Hg) or alternative conditions known to cause postural tachycardia).*
Follow up	*2 hrs*
Intervention	*Abdominal compressions (40 mm Hg applied with an inflatable binder for ~2 minutes before standing)*
Participants (n)	*19* *(18 completed the 3 treatment arms of the primary objective (placebo, propranolol, and placebo combined with abdominal compression)*
Drop-outs (n)	*1*
Comparisons	*Placebo and Propranolol, 20 mg (on separate days)*
Outcomes	*<u>Standing HR (mean bpm±SEM) pre and post study interventions:</u>* *Abdominal compressions + placebo: 111±5 (pre); 96±4* (2 hrs)* *Placebo: 109±3 (pre); 98±4 (2 hrs)* *Propranolol: 106±3 (pre); 81±2** (2 hrs)* *<u>Sitting HR (mean bpm±SEM) pre and post study interventions:</u>* *Abdominal compressions + placebo: 80±3 (pre); 77±3* (2 hrs)* *Placebo: 79±2 (pre); 76±3 (2 hrs)* *Propranolol: 80±3 (pre); 65±2** (2 hrs)* **P<0.05 vs propranolol, rm ANOVA adjusted for multiple comparisons using Bonferroni correction.* ***P<0.05 vs placebo* *See study for additional results on Delta (Standing-Sitting) HR, Standing SBP, Sitting SBP, Delta (Standing-Sitting) SBP, and Symptom score (au).*
Comments	
Risk of bias	*Moderate*

Author	*Taub*
Year	*2021*
Country	*US*
Ref #	*[64]*
Study design	*RCT, double-blind cross-over*
Setting	*University cardiology clinic*
Population	*Patients aged 18–65, (95.5% female) with POTS, classified by: 1) symptoms upon standing; 2) increase in heart rate ≥30 beats/min upon postural change from recumbent to upright position within 10 min of standing; and 3) absence of orthostatic hypotension. Hyperadrenergic POTS, a subtype of POTS, is defined as an elevation in NE >600 pg/ml upon standing and a systolic BP increase of >10 mm Hg when standing upright for 10 min. A positive HUTT test (heart rate ≥30 beats/min) and NE (≥600 pg/ml) were required for study enrollment.*
Follow up	*2,5 months*
Intervention	*Ivabradine (5 mg 2/day) followed by 1 week washout*
Participants (n)	*10*
Drop-outs (n)	*4*
Comparisons	*Placebo followed by 1 week washout*
Participants (n)	*16*
Drop-outs (n)	*0*
Outcomes	*<u>Effect of ivabradine on standing HR (mean bpm±SD), n=22:</u>*

N=22	*Baseline: 95.1±16.8* *Ivabradine: 77.9±9.3* *Placebo: 94.2±16.2* *p-value$_{between\ placebo\ and\ ivabradine}$: 0.001 (statistically significant p < 0.05)* *Cohen's D: 1.05 (95% CI, 0.544 to 1.58)* *<u>Effect of ivabradine on supine HR (mean bpm±SD), n=22:</u>* *Baseline: 73.6±11.7* *Ivabradine: 64.9±6.5* *Placebo: 77.5±12.8* *p-value$_{between\ placebo\ and\ ivabradine}$: 0.001 (statistically significant p < 0.05)* *Cohen's D: 1.26 (95% CI, 0.706 to 1.820)* *See study for additional results on delta (standing vs supine) HR, change in self-reported QOL (SF-36), and changes in plasma NE levels.*
Comments	*Although double-blinded many patients noticed significant differences and suspected that they were on ivabradine- Unclear for how long patients had been showing symptoms prior to study participation.*
Risk of bias	*Moderate*

Author	*Wheatley-Guy*
Year	*2023*
Country	*US*
Ref #	*[65]*
Study design	*RCT*
Setting	
Population	*Adult patients (95.5% female, 35±11 years) with POTS, classified by: 1) symptoms upon standing; 2) increase in heart rate ≥30 beats/min upon postural change from recumbent to upright position within 10 min of standing; and 3) absence of orthostatic hypotension. Hyperadrenergic POTS, a subtype of POTS, is defined as an elevation in NE >600 pg/ml upon standing and a systolic BP increase of >10 mm Hg when standing upright for 10 min. A positive HUTT test (heart rate ≥30 beats/min) and NE (≥600 pg/ml) were required for study enrollment.*
Follow up	*3 months*
Intervention	*Semi-supervised exercise treatment (ET) consisting of 3 aerobic sessions/week, starting on semi-recumbent modalities for most and progressed to upright modalities (upright bike or treadmill) as tolerated. The ET group received an in-person consultation and 8 supervised exercise sessions (weekly for 1 month and then biweekly for 2 months).*
Participants (n)	*31*
Drop-outs (n)	*5*
Comparisons	*The SOC group followed recommendations of their primary neurologist or cardiologist for managing treatment of their symptoms. 1 participant had a medication change during intervention period. 2 participants received an exercise consultation and the same exercise program, but no supervised exercise sessions. One completed physical therapy.*
Participants (n)	*29*
Drop-outs (n)	*6*
Outcomes N=22	*<u>Average change in VO_{2PEAK} from baseline to 3 months post (mL/min/kg, least-square means, 95% CI):</u>* *I: 3.42 (2.61 to 4.23)* *C: −0.2 (−1.08 to 0.68)* *p<0.0001* *<u>Change in peak workload from baseline to 3 months post (watts, least-square means, 95% CI):</u>*

	I: 19.0 (12.8 to 25.2) *C: 0.2 (−6.5 to 7.0)* *p=0.0002* *<u>Symptom improvement from baseline to 3 months post (COMPASS 31$_{TOTAL}$, least mean square difference, 95% CI):</u>* *I: −11.38 (−15.38 to −7.38)* *C: −6.49 (−10.58 to −2.4)* *p=0.0925* *See study for several additional results on change in exercise tolerance markers, symptom subscale- and functional ability scores.*
Comments	*Unclear for how long patients had been showing symptoms prior to study participation.*
Risk of bias	*Moderate*

ME CFS / kroniskt trötthetssyndrom

Author	*Fluge*
Year	*2019*
Country	*Norway*
Ref #	*[66]*
Study design	*RCT, double-blind, multicentre*
Setting	*5 hospitals*
Population	*ME/CFS according to Canadian consensus criteria, n=152*
Follow up	*24 months post study start*
Intervention	*Rituximab, 500 mg/m2 of body surface area, 2 infusions 2 weeks apart, followed by 4 maintenance infusions with a fixed dose of 500 mg at 3, 6, 9, and 12 months*
Participants (n)	*77*
Drop-outs (n)	*0*
Comparison	*Placebo*
Participants (n)	*75*
Drop-outs (n)	*1*
Outcomes	*<u>Between-group differences at 16 to 21 months follow-up, MD (95% CI)</u>* *Fatigue score (range 0-6): −0.06 (−0.51 to 0.39), p=0.79* *Function level (range 0-6): −0.68 (−5.90 to 4.54), p=0.31* *SF-36 PF score: 0.42 (−8.12 to 8.96), p=0.52* *SF-36 PCS score: −0.21 (−3.18 to 2.77), p=0.27* *Fatigue Severity Scale score: −0.07 (−3.21 to 3.08) p=0.68* *Mean steps per 24 hrs: −127 (−1004 to 749), p=0.58* *<u>Serious adverse events</u>* *I: 31 events in 20 patients* *C: 16 events in 14 patients*
Comments	*One of the study authors is mentioned as inventor in the patent of the intervention*
Risk of bias	*Low*

Author	*Gotaas*
Year	*2021*
Country	*Norway*

Ref #	*[67]*
Study design	*RCT*
Setting	*A multidisciplinary outpatient fatigue clinic*
Population	*Participants (mean age between 32 and 37 in groups, women between 70% to 91% in groups) with ME/CFS according to the CDC 1994 criteria, n=236. Examination of a subsample of the population revealed that approximately 83% also fulfilled the Canada criteria.*
Follow up	*16 (and 52 weeks) post study start*
Intervention	*a) Individual standard CBT, 16 weekly sessions, plus a booster session 4 weeks later* *b) Individual interpersonal personality-oriented CBT (I-CBT), 8 weekly sessions, plus a booster session 4 weeks later*
Participants (n)	*CBT: 76, I-CBT: 76*
Drop-outs (n)	*At 16 weeks: CBT: 24, I-CBT: 19 (calculated from table 5)*
Comparison	*Waiting list control for 16 weeks*
Participants (n)	*78*
Drop-outs (n)	*At 16 weeks: 16 (calculated from table 5)*
Outcomes	*<u>Between-group differences at post-intervention (16-18 weeks from baseline)</u>* *<u>CFQ, MD (95% CI)</u>* *CBT vs waiting-list: 5.9 (0.5 to 10.5) p = 0.03* *I-CBT vs waiting-list: 4.8 (−0.4 to 9.9) p = 0.07* *<u>SF-36 PF score, MD (95% CI)</u>* *CBT vs waiting-list, 14.2 (7.9 to 20.4) p < 0.001* *I-CBT vs waiting-list SF-36 PF score: 6.8 (0.5 to 13.2) p = 0.036* *<u>SF-36 mental health subscore</u>* *CBT vs waiting list: significant difference (effect not specified in numbers)* *I-CBT vs waiting list: ns* *<u>CGI, participants with positive change vs. negative or minimum change post-score, OR (95% CI)</u>* *CBT vs waiting-list: 5.5 (1.9 to 16.3), p = 0.002* *I-CBT vs waiting-list: 4.1 (1.4 to 12.1), p = 0.011*
Comments	*52 weeks follow-up is reported for CBT and I-CBT but not for waiting list group*
Risk of bias	*Moderate*

Author	*Joseph*
Year	*2022*
Country	*US*
Ref #	*[68]*
Study design	*RCT, double-blind*
Setting	*A cardiopulmonary exercise laboratory*
Population	*Participant (mean age 40 (SD 14) years, women 39%) with ME/CFS according to National Academy of Medicine criteria (chronic fatigue for > 6 months, postexertional malaise, unrefreshing sleep, plus one additional minor criteria) n=45*
Follow up	*50 minutes after administration*
Intervention	*Pyridostigmine, 60 mg oral dose taken after performing an iCPET*
Participants (n)	*23*
Drop-outs (n)	*0*

Comparison	*Placebo taken after performing an iCPET*
Participants (n)	*22*
Drop-outs (n)	*0*
Outcomes	*Between-group differences at 50 min follow-up iCPET, MD (95% CI)* *Peak VO_2, mL/min:* *–53.6 (–105.2 to –2.0) p=0.043, favours intervention* *Modified Borg fatigue scale:* *0.8 (–1.5 to –0.1), p=0.038, favours intervention* *Borg dyspnea scale,* *n.s p=0.147* *Authors also report outcomes for Peak – rest VO_2, Peak Qc, Peak rest Qc, Peak RAP, Peak rest RAP, Peak PAWP, Peak stroke volume, Peak (Ca-vO2)/[Hb], VE/VCO2*
Comments	*Very short follow-up time (50 minutes) limits the assessment of clinically relevant effects*
Risk of bias	*Moderate*

Author	*Nilsson*
Year	*2017*
Country	*Sverige*
Ref #	*[69]*
Study design	*RCT*
Setting	*Outpatient setting.*
Population	*Participants had a mean age of 45.3 (SD 13.6) and 47.9 (SD 9.8) in intervention and control group, respectively; 84% women). Patients were diagnosed with ME according to the Fukuda and the International Consensus Criteria (ICC). Participants had long (approximately 7-10 years) history of symptoms.*
Follow up	*6 weeks*
Intervention	*Experimental drug compound (−)-OSU6162 (a novel drugs that modulate primarily dopaminergic and serotonergic transmission) was administrated for two-week treatment.*
Participants (n)	*26*
Drop-outs (n)	*0*
Comparison	*Placebo, in a similar way that's described above*
Participants (n)	*26*
Drop-outs (n)	*1*
Outcomes	*Primary outcome:* *Mental fatigue measured with MFS and CGI-C-scale* *Secondary outcomes:* *Results on the FF scale (the FibroFatigue scale), Beck Depression Inventory (BDI) and pain visual analogue scale (VAS)* *Results:* *At follow-up, week 6 (4 weeks after end of treatment), the MFS score did not differ from baseline level for any group and mean CGI-C score had returned to level of unchanged (score 4) in both groups.* *No difference between treatment groups could be detected at any time point (p-values for difference between treatments >0.1).*

	Outcomes were also reported for shorter follow-up periods.
Comments	
Risk of bias	*Low/moderate*

Author	*Pinxsterhuis*
Year	*2017*
Country	*Norway*
Ref #	*[70]*
Study design	*Two armed RCT*
Setting	*Outpatient setting*
Population	*Participants had a mean age of about 44 years, women 81.8% and 94.4% in compared groups. Participants met with CDC and Canada diagnostic criteria. Patients were recruited from a variety of sources including healthcare professionals, waiting lists for the patient education program at our hospital, and patient organizations for chronic fatigue syndrome.*
Follow up	*6 and 12 months*
Intervention	*A self-management program. A three-day training program was conducted by a peer counsellor and an occupational therapist after participation. The training program involved coping with their illness and dealing with health care professionals and significant others*.
Participants (n)	*73*
Drop-outs (n)	*14 at 12 months follow-up*
Comparison	*Care as usal*
Participants (n)	*73*
Drop-outs (n)	*14 at 12 months follow-up*
Outcomes	*<u>Results at 6 months follow-up, differences in change means.</u>* *Physical functioning using the SF-36 questionnaire:* *Intervention group 0.6 (−2.9, 4.0) vs control group 4.3 (−0.4, 8.9), p=0.21* *Fatigue severity scale* *Intervention group −0.2 (−1.7, 1.3) vs control group −2.7 (−4.7, −0.7), p= 0.039* *Self-efficacy* *Intervention group 0.4 (−0.4, 1.1) vs control group −0.8 (−1.5, −0.0), p= 0.039* *Illness cognition questionnaire – acceptance* *Intervention group 0.9 (0.3, 1.6) vs control group 1.1 (0.4, 1.7), p=0.85* *<u>Results at 12 months follow-up, differences in change means.</u>* *Physical functioning using the SF-36 questionnaire:* *Intervention group 0.8 (−4.2, 5.7) vs control group −0.3 (−5.4, 4.9) p=0.76* *Fatigue severity scale* *Intervention group 0.4 (−1.4, 2.2) vs control group −1.4 (−3.0, 0.1), p=0.13* *Self-efficacy* *Intervention group −0.2 (−1.1, 0.7) vs control group −0.5 (−1.2, 0.1), p=0.55* *Illness cognition questionnaire – acceptance*

	Intervention group 0.7 (0.1, 1.4) vs control group 0.5 (−0.1, 1.1), p= 0.68 *Additional outcomes were reported.*
Comments Risk of bias	*Not based on ITT-analyses* *Moderate*

Author Year Country Ref #	*Witham* *2015* *Great Britain* *[71]*
Study design Setting Population Follow up	*RCT* *Outpatient care.* *Participants had a mean age of 48.1 (SD 12.0) and 50.7 (SD 13.1) in compared groups. Proprtion women 72% and 80% in compared groups. Participants were recruited from the via advertising in the ME Research UK* *magazine and through local ME patient support groups. Participants fulfilled both Fukuda and Canada criteria for ME and had and serum 25OHD level<75 nmol/L.* *6 months*
Intervention Participants (n) Drop-outs (n)	*100,000 units of oral vitamin D3 at study start and at 2 and 4 months.* *25*
Comparison Participants (n) Drop-outs (n)	*Placebo with similar administration as described above.* *25*
Outcomes	*Primary outcome:* *Arterial stiffness (not tabulated here as it was not part of PICO)* *Secondary outcomes:* *Several secondary outcomes, including fatigue (assessed with The Piper fatigue scale). Neither the total score nor the subscales resulted in a statistically significant treatment effect.* *Additional outcomes were reported, mainly vascular outcome measures.*
Comments Risk of bias	 *Moderate*

PANS /PANDAS

Author Year Country Ref #	*Murphy* *2015* *US* *[72]*
Study design Setting Population Follow up	*RCT* *Outpatient setting* *Youth between 4 and 13 years of age with a history of recent (but not necessarily sudden and severe) onset of OCD and/or tics and symptom duration ≤ 6 months)* *End of treatment (30 days)*
Intervention	*Cefdinir 14mg/kg per day in two daily doses (max 600mg) for a total of 30 days*

Participants (n) Drop-outs (n)	*10* *1*
Comparison Participants (n) Drop-outs (n)	*Placebo (matched for taste, color, and consistency to cefdinir suspension) for a total of 30 days* *11* *0*
Outcomes	*Primary outcomes: (between-group differences)* *Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)* *Differences were not statistically significant* *Yale Global Tic Severity Scale (YGTSS)* *Differences were not statistically significant* *Secondary outcomes: (between-group differences)* *Clinical Global Impression-Severity Scale (CGI-S OCD)* *Differences were not statistically significant* *Clinical Global Impression-Severity Scale (CGI-S tics)* *Differences were not statistically significant* *No serious adverse events reported.* *Parent ratings of Swanson, Nolan, and Pelham–IV Parent Scale (SNAP-IV) AND Tourette's Disorder Scale (TODS) are also reported.*
Comments Risk of bias	 *Low*

Systematisk översikt

Author Year Country Ref #	*Johnsson* *2020* *Sweden* *[73]*
Study design Included studies Population	*Systematic review* *4 RCT* *3 NRSI* *All studies from US* *Children (<18 years) with symptoms corresponding to the research condition of PANS*
Intervention	*Anti-inflammatory, antibacterial or immunomodulating treatments, including cyclooxygenase (COX) inhibitors, glucocorticoids, antibiotics, immunoglobulins, therapeutic plasma exchange, rituximab, and inhibitors of tumour necrosis factor (TNF)*
Comparison	*No anti-inflammatory, antibacterial or immunomodulatory treatment*
Outcome	*CY-BOCS was measured in 4 RCTs, none were statistically significant.* *CGI-S or CGI-I was measured in 3 RCTs, one was statistically significant.* *YGTSS was measured in two RCTs, none were statistically significant.* *CGAS was measured in three RCTs, none were statistically significant.* *Complications were reported in 3 RCTs.* *Other outcomes were reported in individual studies.* *HRQL according to validated scales:* *None of the included studies investigated potential effects of the interventions regarding HRQL.* *Level of functioning*

	It is uncertain whether antibiotic or immunomodulatory treatment improves the level of functioning in children with symptoms that correspond to PANS – GRADE: ⊕◯◯◯ (very low quality of evidence). (Penicillin, azithromycin in 2 RCT, intravenous globulins (IVIG) and plasma exchange in 1 RCT) *<u>Symptom change (reported by patients, caregivers and care staff)</u>* *It is uncertain whether anti-inflammatory, antibiotic or immunomodulatory treatment improves symptoms in children with symptoms that correspond to PANS – GRADE: ⊕◯◯◯ (very low quality of evidence).* *(2 cross-sectional studies on anti-inflammatory treatment, 2 RCTs and 1 before/after study on antibiotics, and 2 RCTs on immunomodulatory treatment)* *<u>Complications</u>* *Anti-inflammatory and antibiotic drugs as well as IVIG can probably result in adverse reactions as listed in the SPC – GRADE ⊕⊕⊕◯ (moderate quality of evidence), and plasma exchange may result in complications – GRADE ⊕⊕◯◯ (low quality of evidence), in children with symptoms that correspond to PANS.* *3 RCTs and 2 cross-sectional studies).*
Comments Risk of bias	*This review is based on seven studies with major risk of bias and problems regarding directness and precision* *Low*

Post-sepsis

Author Year Country Ref #	*Gawlytta* *2022* *Germany* *[74]*
Study design Setting Population Follow up	*RCT, open-label* *Location-independent online-intervention* *We included dyads (k) comprising of a previously ICU-admitted patient (≥18 years) treated for sepsis for >5 days and ICU-discharged >1month ago together with spouse (≥18 years, married or cohabited). A patient-spouse dyad was included if at least one presented a presumptive PTSD diagnosis (PTSD checklist for DSM-5 (PCL-5) ≥33) associated with the life-threatening event. Overall: 48% female, aged (median (Q1, Q3) 55 (47, 62) years.* *3, 6 and 12 months (only for intervention group), comparison between groups is post-treatment/waiting (5 weeks)*
Intervention Participants (n) Drop-outs (n)	*Internet-based cognitive-behavioural writing therapy (iCBT), 2 x 50 min internet-based writing assignments/week x 5 weeks (10 essays in total). After completion of each assignment, the therapist provided individual feedback and further writing instructions to the participant. The treated participant also received a supportive letter from his/her respective partner.* *k=12, n=16* - *ICU patient only (k = 6)* - *Spouse only (k = 2)* - *Both patient and spouse (k = 4)* *7*
Comparison Participants (n)	*Waitlist (5 weeks of waiting) followed by iCBT, but without a supportive letter from their spouses.* *k = 13, n = 18* - *ICU patient only (k = 6)* - *Spouse only (k = 2)*

	- *Both patient and spouse (k = 5)*
Drop-outs (n)	*2*
Outcomes	*<u>Difference in pre–post change of PTSD symptom severity score (PCL-5), mean difference (95% CI):</u>* *There was no evidence for difference between the intervention and the control group:* *−0.96 (−5.88 to 3.97)* *p=0.703* *<u>Between-group effect sizes (Cohen´s d, standardised mean differences, 95% CI) for changes from baseline to 5 weeks after randomisation (end of treatment/waiting time):</u>* *PTSD symptom severity (PCL-5):* *ITT(best-case/worst-case): –0.14 (–0.81 to 0.54)* *ITT(MICE): 0.48 (–0.21 to 1.16)* *Psychological distress (BSI-18):* *ITT(best-case/worst-case): 0.04 (–0.64 to 0.71)* *ITT(MICE): 0.51 (–0.17 to 1.20)* *Health-related quality of life (EQ-5D-5L):* *ITT(best-case/worst-case): –0.25 (–0.93 to 0.42)* *ITT(MICE): 0.09 (–0.58 to 0.77)* *See study for more secondary outcome results on relationship satisfaction, remission at the end of treatment/waiting time, and dyadic concordance in treatment effects*
Comments Risk of bias	 *Moderate*

Author Year Country Ref #	*Schmidt* *2016* *Germany* *[75]*
Study design Setting Population Follow up	*RCT, multicenter (9 units), non-blinded* *Primary care* *Adult patients aged ≥18 years (mean age 61.6±14.4, 33.8% females), survivors of severe sepsis or septic shock.* *6, 12 months*
Intervention Participants (n) Drop-outs (n)	*12-month primary care management intervention based on the Chronic Care Model, which core components including case management focusing on pro-active patient symptom monitoring, clinical decision support for the PCP, and training for both patients and their PCPs in evidence-based care.* *148* *41*
Comparison Participants (n) Drop-outs (n)	*Care as usual from their PCPs (including periodic contacts, referrals to specialists and prescription of medication and therapeutic aids, at quantities comparable to those for other populations with multiple chronic conditions) without additional information or monitoring.* *143* *48*
Outcomes	*A primary-care-focused team-based intervention did not improve mental HRQoL or impact PCP care compared with usual care-* *<u>Change in mental HRQoL (MCS-SF36) between ICU discharge and 6 months post-ICU (95% CI):</u>*

	I: 3.79 score points (1.05 to 6.54) *C: 1.64 score points (1.22 to 4.51)* *Mean treatment effect: 2.15 (–1.79 to 6.09), p=0.28* *(all data n=200 patients (n=104 intervention, n=96 control) These results were unchanged in several sensitivity analyses.* *Change in mental HRQoL (MCS-SF36) between ICU discharge and 12 months post-ICU (mean of the change score (SD):* *I: 3.7 (13.4)* *C: 2.3 (12.6)* *Estimated treatment effect (95% CI): 1.4 (–2.4 to 5.2), p=0.47* *Results from a 24-month follow-up study by the same author [76]:* *At 24 months, there was no difference between groups (MCS-SF36)* *I (mean (SD)): 3.1 (13.9)* *C (mean (SD)): 1.1 (13.6)* *p=0.36*
Comments Risk of bias	*Moderate*

Post-influensa

No studies included.

Förkortningar

ADLs = Activities of daily living; **AE** = Adverse events; **apx** = approximately; **A-PASC** = Post-COVID-19 Symptoms Assessment Questionnaire; **AQoL-6D** = Assessment of Quality of life—six dimensions; **ATA** = Atmospheres absolute (pressure); **BP** = Blood pressure; **bpm** = Beats per minute; **BDI-II** = Beck depression inventory; **BPI** = Brief pain inventory; **BSI-18** = Behavioural symptoms inventory-18 global score index; **BTT** = Butanol threshold test; **C** = Control; **CARDS** = COVID-19-associated Acute Respiratory Distress Syndrome; **CAU** = Care as usual; **CCCRC test score** = Connecticut Chemosensory Clinical Research Center test score; **CES-D** = Center for Epidemiological Studies Depression Scale; **CG** = Control group; **CGI**= Clinical Global Impression Scale; **CGI-C** = Clinical global impression of change; **CIS-conc** = Concentration subscale of Checklist individual strength; **CIS-fatigue** = Fatigue severity subscale of the Checklist Individual Strength; **COMPASS 31** = Composite Autonomic Symptom Score; **CRP** = C-reactive protein; **DDAVP** = Desmopressin; **DN4** = Douleur Neuropathique en 4 Questions; **DSC** = Dynamic Susceptibility Contrast; **DSST** = Digit Symbol Substitution Test; **DTI** = Diffusion Tensor Imaging; **ED** = Erectile dysfunction; **ET** = Exercise therapy; **EQ-5D-5L** = EuroQol-5 dimension-5-Level group; **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; **FVC** = Forced vital capacity; **GAD-7**: Generalized Anxiety Disorder 7-item scale; **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; **HUTT** = Head-up tilt table test; **HR** = Heart rate; **hrs** = Hours; **HRQoL** = Health-related quality of life; **I** = Intervention; **iCEPT** = Invasive cardiopulmonary exercise test; **ICU** = Intensive care unit; **IG**= Intervention group; **IIEF-5** = International Index of Erectile Function; **IPAC** = International Physical Activity Questionnaire; **IQR** = Interquartile range; **ISI** = Insomnia Severity Index; **ITT** = Intention to treat; **K-BILD** = King's Brief Interstitial Lung Disease questionnaire; **KW** = Kruskal-Wallis test; LCADL = **London Chest Activity of Daily Living Scale**; **LS MD** = Least squares mean difference; **LUT** = Luteolin; **m** = Meter; **MCS** = Mental Component Summary score of Short Form-36 Health Survey (SF-36); **MD** = Mean difference; **MDBS** = Modified Borg Dyspnea Scale; **MFIS** = Modified fatigue impact scale; **MICE** = Multiple imputation by chained equations; **MMSE** = Mini Mental State Examination; **mMRC** = Modified British Medical Research Council dyspnoea scale; **MMV** = Maximal voluntary ventilation;

MoCa = Montreal Cognitive Assessment; **MPQ** = McGill pain questionnaire; **MRI** = Magnetic Resonance Imaging; **N/n** = Antal; **NE** = Norepinephrine; **ηp 2** = Partial eta-squared effect size; **NP-PASC** = Neuropsychiatric Post-acute sequelae of Sars-CoV-2 infection; **NRSI** = Non-randomized studies of interventions; **ns**=Not statistically significant; **OD** = Olfactory dysfunction*;* **OIQ** = Orthostatic intolerance questionnaire*;* **OR** = Odds ratio; **OT** = Olfactory training*;* **PASC** = Post-acute sequelae of Sars-CoV-2 infection; **PACSQ-14** = Post-acute COVID-19 syndrome 14-item improvement questionnaire*;* **PCC** = Post-covid(-19) conditions; **PCFS** = Post-COVID-19 functional Status scale; **PCL-C** = Post-traumatic Stress Disorder (PTSD) Checklist: Civilian; **PCL-5** = Posttraumatic Stress Disorder Checklist (version 5); **PCR** = Polymerase chain reaction; **PCS** = Pain Catastrophizing Scale; **PEA** = Palmitoylethanolamide; **PGIC** = Patient Global Impression of Change; **PHQ-9** = Patient Health Questionnaire; **PHQ-15** = Patient Health Questionnaire; **PICO** = Framework for structuring a research question by defining the Population, Intervention, Control and Outcomes; **QIDS-SR-16** = Quick Inventory of Depressive Symptomatology; **QOD-NS** = Questionnaire of olfactory disorder-negative statement; **QoL** = Quality of Life; **POTS**=Postural tachycardia syndrome; **PQSI** = Pittsburgh Sleep Quality Index; **PSP** = Primary care physician; **PSS** = Perceived Stress Scale; **PTSD checklist** = Post-traumatic stress disorder checklist; **PTSS** = Post-traumatic stress symptoms; **RAND SF-36** = RAND 36 Item Short Form Health Survey SF-36; **RCT** = Randomised controlled trial; **Rm ANOVA** = Repeated measures ANOVA; **RT-PCR** = Reverse transcription polymerase chain reaction; **RV**=Residual Volume, **s** = second(s); **SAS** = Self-rating Anxiety Scale; **SBP** = Systolic blood pressure; **SD** = Standard deviation; **SDS** = Self-rating Depression Scale; **SE** = Standard error; **SEM** = Standard error of mean; **SF-36** = Short form health survey-36; **SF-12** = Short form health survey-12; **SF-12 MCS** = Short form health survey-12 Mental component score; **SF-12 PCS** = Short form health survey-12 Physical component score; **SGRQ** = St George's Respiratory Questionnaire; **SIT** = Smell identification test; **SOC** = Standard of care; **SPC** = Summary of products characteristics; **Stroop – IG**: Stroop interference – index of golden; **TDI score** = Sum of results obtained for odour Threshold, Discrimination, and Identification; **tDCS** = Transcranial direct current stimulation; **TLC**=Total Lung Capacity; **Tph** = Tukey post-hoc test; **TSPP** = Tetrasodium Pyrophosphate; **UPSIT** =University of Pennsylvania Smell Identification Test; **VAS** = Visual analogue scale; **VO_2** = Oxygen uptake; **VO_{2PEAK}** = Peak oxygen consumption; **WHO-5** = The World Health Organisation- Five Well-Being Index; **WHODAS 2.0** = World Health Organization Disability Assessment Schedule; **WHOQOL-brief** = The World Health Organization Quality of Life Brief Version; **WSAS** = Work and Social Adjustment Scale; **6MWD** = 6 minute walking distance test; **6MWT** = 6 minute walking test

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