LIVING SYSTEMATIC REVIEW OF THERAPEUTIC OPTIONS FOR POST-ACUTE AND POST-COVID19 CONDITION

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Living Systematic Review of Therapeutic Options for Post Acute or Post COVID-19 Condition

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This document includes the results of a rapid systematic review of current available literature. The information included in this review reflects the evidence as of the date posted in the document. In recognition of the fact that there are numerous ongoing clinical studies, PAHO will periodically update this review and corresponding recommendations as new evidence becomes available.

Contents

Acknowledgments

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Executive summary

Background

Post COVID-19 condition (PCC), also known as long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC), is the continuation or development of new symptoms in the period after acute infection with SARS-CoV-2. The World Health Organization (WHO) definition of PCC states that these symptoms should be present after three months of the initial SARS-CoV-2 infection and last for at least two months with no other explanation. While PASC definitions state that persistent or new symptoms need to be present 30 days after a documented SARS-COV-2 infection or the onset of COVID-19 symptoms, post COVID-19 condition or post-acute sequelae of SARS-CoV-2 infection (P-ACC) can affect anyone exposed to SARS-CoV-2, regardless of age or severity of acute infection. Many of the reported symptoms are debilitating and have a strong negative impact on mental health and quality of life. While most patients recover, some may experience multiple outcomes, with multiple organ systems affected simultaneously, including cardiovascular, mental, metabolic, renal, and others.

This review compiles the following evidence on potential therapeutic options for P-ACC. It includes all the identified clinical forms, symptoms, and manifestations of P-ACC for which an intervention was assessed in at least one randomized controlled trial (RCT). It is hoped this information will support investigators, policymakers, and prescribers navigate the flood of relevant data to ensure that management of P-ACC, at both the individual and population levels, is based on the best available knowledge. This resource will be continually updated as more research is released into public space.

Summary of evidence

All odd numbered tables (Table ES1 to ES15) present RCTs according to the reported P-ACC related organ/system affected and indicate the primary outcome measures used for each investigation and the level of certainty. The even numbered tables (Table ES2 to

ES16) summarize the status of evidence for the 74 potential therapeutic options for P-ACC for which studies were identified through this systematic review.

P-ACC-related asthenia or fatigue

Table ES1. List of RCTs on interventions for P-ACC-related asthenia or fatigue with primary outcome measures and certainty (n=39)

Intervention		Overall number of studies including the intervention, n=39	HRQL improvement (n of studies)	Overall symptom improvement (n of studies)	Fatigue improvement (n of studies)	Functional capacity improvement (n of studies)	Strength improvement (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Physical training		8	3		4	5	2		
Telerehabilitation	NEW	6	5		3	5			
Fermented food supplements		2		2					
Probiotics	NEW	2			2			1	
tDCS		2	1		2			1	
1_MNA		1			1	1			
Actovegin		1			1				
ADAPT_232 (adaptogens)		1			1				
Amygdala and Insula Retraining (AIR)		1	1		1				
Arginine_Vitamin C		1			1		1		
Aromatherapy		1	1		1				
AXA1125		1			1	1		1	
CCSA		1			1				
Cognitive behavioral therapy		1			1	1			
CQ10		1	1	1					
Creatine	NEW	1			1				
Cytoflavin		1			1				
Echinochrome A		1			1				
Enzimes_Probiotics		1			1				
Hydrogen (nasal)		1			1	1			
Immunodaat		1	1		1				
Mindfulness		1			1				
Phytochemicals		1	1		1				
Leronlimab		1		1					

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmful effect		
Uncertain effect		
No evidence or no estimable effect		

Table ES2. Summary of findings on potential therapeutic options for P-ACC-related asthenia or fatigue (n=24), as of 7 December 2023

	Intervention	Summary of findings
1	**1-MNA**	Uncertainty in potential benefits and harms. Further research is needed.
2	**Actovegin**	Actovegin may improve fatigue. However, certainty of the evidence was low. Further research is needed.
3	**ADAPT-232 (adaptogens)**	ADAPT-232 may not improve fatigue. However, certainty of the evidence was low. Further research is needed.
4	**Amygdala and Insula Retraining (AIR)**	Uncertainty in potential benefits and harms. Further research is needed.
5	**Arginine + Vitamin C**	Uncertainty in potential benefits and harms. Further research is needed.
6	**Aromatherapy**	Uncertainty in potential benefits and harms. Further research is needed.
7	**AXA1125**	AXA1125 may increase fatigue improvement but may not increase functional capacity improvement. However, certainty of the evidence was low. Further research is needed.
8	**CCSA**	Uncertainty in potential benefits and harms. Further research is needed.
9	**Coenzyme Q10**	Uncertainty in potential benefits and harms. Further research is needed.
10	**Cognitive behavioral therapy**	Cognitive behavioral therapy may increase fatigue improvement and functional capacity improvement. Further research is needed.
11	**Creatine**	Uncertainty in potential benefits and harms. Further research is needed.
12	**Cytoflavin**	Cytoflavin may not improve fatigue. However, certainty of the evidence was low. Further research is needed.
13	**Echinochrome A**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
14	**Enzymes + probiotics**	Enzymes + probiotics may improve fatigue. However, certainty of the evidence was low. Further research is needed.
15	**Fermented food supplements**	Uncertainty in potential benefits and harms. Further research is needed.
16	**Hydrogen (nasal)**	Uncertainty in potential benefits and harms. Further research is needed.
17	**Immunodaat**	Uncertainty in potential benefits and harms. Further research is needed.
18	**Leronlimab**	Uncertainty in potential benefits and harms. Further research is needed.
19	**Mindfulness**	Uncertainty in potential benefits and harms. Further research is needed.
20	**Phytochemicals**	Phytochemicals may improve fatigue and HRQL. However, certainty of the evidence was low. Further research is needed.
21	**Physical training**	Physical training may improve HRQL, strength and functional capacity. However, certainty of the evidence was low. Further research is needed.
22	**Probiotics**	Probiotics probably improve fatigue. The results on other important outcomes are uncertain. Further research is needed.
23	**Transcranial direct current stimulation (tDCS)**	tDCS may improve fatigue and HRQL and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.
24	**Telerehabilitation**	Telerehabilitation may improve fatigue and functional capacity. However, certainty of the evidence was low. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined 24 therapeutic options for P-ACC-related asthenia or fatigue.

• **Actovegin:** The results of one RCT suggest that actovegin may improve fatigue. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **ADAPT-232 (adaptogens):** The results of one RCT suggest that ADAPT-232 may not improve fatigue. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **AXA1125 (amino acids + N-acetylcysteine):** AXA1125 may increase fatigue improvement but may not increase functional capacity improvement. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Cytoflavin:** The results of one RCT suggest that cytoflavin may not improve fatigue. However, certainty of the evidence was low because of imprecision and risk of bias. Further research is needed.

• **Enzymes + probiotics:** The results of one RCT suggest that enzymes + probiotics may not improve fatigue. However, certainty of the evidence was low because of imprecision and risk of bias. Further research is needed.

• **Physical training:** The results of eight RCTs suggest that physical training may improve HRQL, strength, and functional capacity. However, certainty of the evidence was low because of imprecision and risk of bias. Two studies compared different training modalities but provided very low certainty evidence. Further research is needed.

• **Probiotics:** The results of two RCTs show that probiotics probably improve fatigue. However, its effects on other important outcomes are uncertain. Further research is needed.

• **Transcranial direct current stimulation (tDCS):** The results of two RCTs suggest that tDCS may improve fatigue and HRQL and may not increase adverse events. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Telerehabilitation:** The results of six RCTs suggest that telerehabilitation may improve fatigue and functional capacity. However, certainty of the evidence was low because of imprecision and risk of bias. Further research is needed.

P-ACC-related dyspnea

Table ES3. List of RCTs of interventions for P-ACC-related dyspnea with primary outcome measures and certainty (n=22)

Intervention		Overall number of studies including the intervention, n=22	HRQL improvement (n of studies)	Dyspnea improvement (n of studies)	Functional capacity improvement (n of studies)	Pulmonary function improvement (n of studies)	Radiological response (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Respiratory training	NEW	14	8	10	6	1			
ADAPT_232 (adaptogens)		1		1					
Albumin (inhaled)		1						1	
Antifibrotics		1			1				
Diaphragm release		1		1					
High dose steroids		1		1			1	1	1
Nebivolol		1		1					
Probiotics	NEW	1		1				1	
Treamid		1		1	1	1		1	

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmful effect		
Uncertain effect		
No evidence or no estimable effect		

Table ES4. Summary of findings on potential therapeutic options for P-ACC-related dyspnea (n=9), as of 7 December 2023

	Intervention	Summary of findings
1	**ADAPT-232 (adaptogens)**	ADAPT-232 may not improve dyspnea. However, certainty of the evidence was low. Further research is needed.
2	**Albumin (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
3	**Antifibrotics**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
4	**Diaphragm release**	Uncertainty in potential benefits and harms. Further research is needed.
5	**High dose steroids**	High dose steroids, compared to standard dose steroids, may not improve dyspnea and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.
6	**Nebivolol**	Uncertainty in potential benefits and harms. Further research is needed.
7	**Probiotics**	Probiotics may improve dyspnea. However, certainty of the evidence was low. Further research is needed.
8	**Respiratory training/rehabilitation**	Respiratory training/rehabilitation probably improves HRQL, dyspnea, and functional capacity
9	**Treamid**	Treamid may improve dyspnea and pulmonary function but may not improve functional capacity. Treamid may increase adverse events. However, certainty of the evidence was low. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined seven therapeutic options for P-ACC-related dyspnea.

• **ADAPT-232 (adaptogens):** The results of one RCT suggest that ADAPT-232 may not improve dyspnea. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **High dose steroids:** The results of one RCT suggest that high dose steroids (prednisone 40 mg a day) may not improve dyspnea compared to standard dose steroids (prednisone 10 mg a day). However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

• **Respiratory training/rehabilitation:** The results of 14 RCTs suggest that respiratory training probably improves HRQL, dyspnea and functional capacity.

• **Treamid:** The results of one RCT suggest that treamid may improve dyspnea and pulmonary function but may not improve functional capacity. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Probiotics:** The results of one RCT suggest that probiotics may improve dyspnea. However, certainty of the evidence was low because of imprecision. Further research is needed.

P-ACC-related neurocognitive symptoms or sleep disturbances

Table ES5. List of RCTs of interventions for P-ACC-related neurocognitive symptoms or sleep disturbances with primary outcome measures and certainty (n=13)

Intervention		Overall number of studies including the intervention, n=13	HRQL improvement (n of studies)	Overall symptom improvement (n of studies)	Cognitive improvement (n of studies)	Depression improvement (n of studies)	Sleep quality improvement (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Actovegin		1			1				
Celecoxib		1				1			
Donepezil	NEW	1			1				
Electrical stimulation		1							
Famotidine		1			1	1			
HBO		1	1		1	1			
Mindfulness		1				1			
Palmitoylethanolamide_Luteolin		1			1				
Physical training		1	1				1		
Probiotics	NEW	1			1		1		
taVNS		1							
tDCS		1			1				
Vortioxetine	NEW	1	1		1	1		1	

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmful effect		
Uncertain effect		
No evidence or no estimable effect		

Table ES6. Summary of findings on potential therapeutic options for P-ACC-related neurocognitive symptoms or sleep disturbances (n=13), as of 7 December 2023

	Intervention	Summary of findings
1	**Actovegin**	Actovegin may improve cognition. However, certainty of the evidence was low. Further research is needed.
2	**Celecoxib**	Uncertainty in potential benefits and harms. Further research is needed.
3	**Donepezil**	Uncertainty in potential benefits and harms. Further research is needed.
4	**Electric stimulation**	Uncertainty in potential benefits and harms. Further research is needed.
5	**Famotidine**	Famotidine may improve cognition. However, certainty of the evidence was low. Further research is needed
6	**Hyperbaric oxygen (HBO)**	HBO may improve HRQL. However, certainty of the evidence was low. Further research is needed.
7	**Mindfulness**	Uncertainty in potential benefits and harms. Further research is needed.
8	**Palmitoylethanolamide + Luteolin**	Uncertainty in potential benefits and harms. Further research is needed.
9	**Physical training**	Uncertainty in potential benefits and harms. Further research is needed.
10	**Probiotics**	Probiotics may improve cognition and sleep quality. However, certainty of the evidence was low. Further research is needed.
11	**Transcutaneous auricular vagus nerve stimulation (taVNS)**	Uncertainty in potential benefits and harms. Further research is needed.
12	**Transcranial direct current stimulation (tDCS)**	tCDS may not improve cognition. However, certainty of the evidence was low. Further research is needed.
13	**Vortioxetine**	Vortioxetine probably improves HRQL and may improve depression but may not improve cognition. Further research is needed

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined nine therapeutic options for PCC neurocognitive symptoms or sleep disturbances.

• **Actovegin:** The results of one RCT suggest that actovegin may improve cognition. However, certainty of the evidence was low because of risk of bias. Further research is needed.

• **Famotidine:** The results of one RCT suggest that famotidine may improve cognition. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Hyperbaric oxygen (HBO):** The results of one RCT suggest that HBO may improve HRQL. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Probiotics:** The results of one RCT suggest that probiotics may improve cognition and sleep quality. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Transcranial direct current stimulation (tDCS):** The results of one RCT suggest that tDCS may not improve cognition. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Vortioxetine** The results of one RCT shows that vortioxetine probably improves HRQL and may improve depression but may not improve cognition. However, certainty of the evidence was low because of imprecision for some of the outcomes. Further research is needed.

P-ACC-related olfactory and/or gustatory dysfunction

Table ES7. List of RCTs of interventions for P-ACC-related olfactory and/or gustatory dysfunction with primary outcome measures and certainty (n=19)

Intervention		Overall number of studies including the intervention, n=19	HRQL improvement (n of studies)	Overall symptom improvement (n of studies)	Olfactory symptoms improvement (n of studies)	Gustatory symptoms improvement (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Olfactory training		4			4			
Steroids		2			2	1		
Steroids (nasal)		2			2			1
ADAPT_232 (adaptogens)		1			1			
Alpha-lipoic acid	NEW	1			1			
Diode Laser		1				1		
DTPA		1			1			
EDTA		1			1			
Gabapentin		1			1			
Omega 3		1			1			
Palmitoylethanolamide_Luteolin		1			1			
Platelet-rich plasma	NEW	1			1			
Theophylline_nasal		1	1		1		1	
Vitamin A		1			1			

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmful effect		
Uncertain effect		
No evidence or no estimable effect		

Table ES8. Summary of findings on potential therapeutic options for P-ACC-related olfactory and/or gustatory dysfunction (n=14), as of 7 December 2023

	Intervention	Summary of findings
1	**ADAPT-232 (adaptogens)**	ADAPT-232 may not improve olfactory symptoms. However, certainty of the evidence was low. Further research is needed.
2	**Alpha-lipoic acid**	Uncertainty in potential benefits and harms. Further research is needed.
3	**Diode laser**	Uncertainty in potential benefits and harms. Further research is needed.
4	**EDTA**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
5	**Gabapentin**	Uncertainty in potential benefits and harms. Further research is needed.
6	**Olfactory training**	Olfactory training may improve olfactory symptoms. Further research is needed.
7	**Omega-3 fatty acids**	Uncertainty in potential benefits and harms. Further research is needed.
8	**Palmitoylethanolamide + Luteolin**	Palmitoylethanolamide + Luteolin may improve olfactory symptoms. However, certainty of the evidence was low. Further research is needed.
9	**Pentasodium diethylenetriamine pentaacetate (DTPA)**	Uncertainty in potential benefits and harms. Further research is needed.
10	**Platelet-rich plasma**	Uncertainty in potential benefits and harms. Further research is needed.
11	**Steroids (nasal)**	Uncertainty in potential benefits and harms. Further research is needed.
12	**Steroids**	Steroids may not improve olfactory nor gustatory symptoms. Further research is needed.
13	**Theophylline (nasal)**	Uncertainty in potential benefits and harms. Further research is needed.
14	**Vitamin A**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined nine therapeutic options for PCC olfactory and/or gustatory dysfunction.

• **ADAPT-232 (adaptogens):** The results of one RCT suggest that ADAPT-232 may improve olfactory symptoms. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Olfactory training:** The results of four RCTs suggest that olfactory training may improve olfactory symptoms. However, certainty of the evidence was low because of risk of bias and inconsistency. Further research is needed.

• **Palmitoylethanolamide + Luteolin:** The results of one RCT suggest that Palmitoylethanolamide + Luteolin may improve olfactory symptoms. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Steroids:** The results of two RCTs suggest that steroids may not improve olfactory nor gustatory symptoms. However, certainty of the evidence was low because of imprecision. Further research is needed.

P-ACC-related cardiovascular system symptoms

Table ES9. List of RCTs of interventions for P-ACC-related cardiovascular system symptoms with primary outcome measures and certainty (n=2)

Intervention	Overall number of studies including the intervention, n=2	HRQL improvement (n of studies)	Overall symptom improvement (n of studies)	Cardiac function improvement (n of studies)	Tachycardia improvement (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
HBO	1			1			
Ivabradine	1				1		

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmful effect		
Uncertain effect		
No evidence or no estimable effect		

Table ES10. Summary of findings on potential therapeutic options for P-ACC-related cardiovascular system symptoms (n=2), as of 7 December 2023

	Intervention	Summary of findings
1	**Hyperbaric oxygen**	Uncertainty in potential benefits and harms. Further research is needed.
2	**Ivabradine**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined two therapeutic options for P-ACC- related cardiovascular system symptoms.

• **The effects of assessed interventions are uncertain.**

P-ACC-related psychological distress

Table ES11. List of RCTs of interventions for P-ACC-related psychological distress with primary outcome measures and certainty (n=2)

Intervention	Overall number of studies including the intervention, n=2	HRQL improvement (n of studies)	Depression improvement (n of studies)	Post traumatic stress disorder improvement (n of studies)	Psychologic distress improvement (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
EMDR	1	1	1	1			
Virtual reality info	1		1				

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmful effect		
Uncertain effect		
No evidence or no estimable effect		

Table ES12. Summary of findings on potential therapeutic options for PCC psychological distress (n=2), as of 7 December 2023

	Intervention	Summary of findings
1	**Eye-movement desensitization and reprocessing (EMDR)**	Uncertainty in potential benefits and harms. Further research is needed.
2	**Virtual reality informational video**	Virtual reality informational video may improve depression, post-traumatic stress, and psychological distress. However, certainty of the evidence was low. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined one therapeutic option for PCC psychological distress.

• **Virtual reality informational video:** The results of one RCT suggest that virtual reality informational video may improve depression, post-traumatic stress, and psychological distress. However, certainty of the evidence was low because of imprecision. Further research is needed.

P-ACC-related thromboembolic risk

Table ES13. List of RCTs of interventions for P-ACC-related thromboembolic risk with primary outcome measures and certainty (n=1)

Intervention	Overall number of studies including the intervention, n=2	Mortality (n of studies)	HRQL improvement (n of studies)	VTE (symptomatic) (n of studies)	Major bleeding (n of studies)	Severe adverse events (n of studies)
Anticoagulants_Proph	2	2	1	2	2	

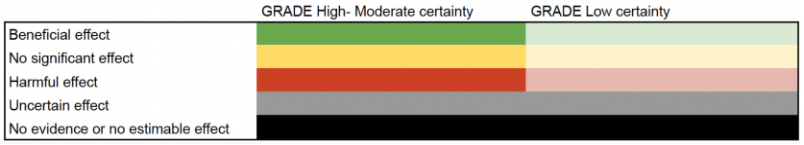


Table ES14. Summary of findings on potential therapeutic options for PCC thromboembolic risk (n=1), as of 7 December 2023

	Intervention	Summary of findings
1	**Anticoagulants (prophylactic dose)**	Anticoagulants may not have an important effect on mortality, VTE, major bleeding and HRQL. However, certainty of the evidence was low because of imprecision. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined one therapeutic option for PCC olfactory and/or gustatory dysfunction.

• **Anticoagulants:** The results of two RCTs suggest that anticoagulants (rivaroxaban and apixaban) may not have an important effect on mortality, HRQL, VTE or major bleeding. However, certainty of the evidence was low because of risk of imprecision. Further research is needed.

Pediatric inflammatory multisystem syndrome associated with SARS-CoV-2 (PIMS-TS)

Table ES13. List of RCTs of interventions for PIMS-TS with primary outcome measures and certainty (n=1)

Intervention	Overall number of studies including the intervention, n=1	Mortality (n of studies)	Time to discharge reduction (n of studies)	Respiratory support (n of studies)	Inotropics requirement (n of studies)	LVEF < 55% (n of studies)	Arrhythmia (n of studies)	VTE (symptomatic) (n of studies)	Major bleeding (n of studies)
Steroids	1		1	1	1	1	1	1	

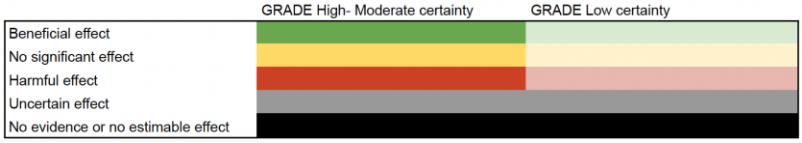


Table ES14. Summary of findings on potential therapeutic options for PCC thromboembolic risk (n=1), as of 7 December 2023

	Intervention	Summary of findings
1	**Steroids**	Steroids may reduce time to discharge and respiratory support requirements. However, certainty of the evidence was low for risk of bias and imprecision. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined one therapeutic option for PCC olfactory and/or gustatory dysfunction.

• **Steroids:** The results of one RCT suggest that steroids may reduce time to discharge and respiratory support requirements. However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

P-ACC prophylaxis

Table ES15. List of RCTs of interventions for P-ACC prophylaxis with primary outcome measures and certainty (n=9)

Intervention		Overall number of studies including the intervention, n=9	Mortality (n of studies)	HRQL improvement (n of studies)	P-ACC (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Fluvoxamine		2			2		
Budesonide + Mouthwash	NEW	1			1		
CP		1			1		
Ivermectin		1			1		
Leflunomide		1			1		1
Metformin		1			1		
Remdesivir		1	1		1		
Saline + Mouthwash	NEW	1			1		

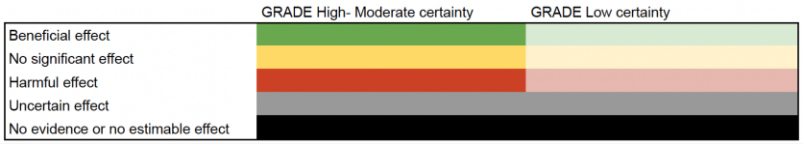


Table ES16. Summary of findings on potential therapeutic options for P-ACC prophylaxis (n=8), as of 7 December 2023

	Intervention	Summary of findings
1	**Budesonide + Saline + Mouthwash**	Uncertainty in potential benefits and harms. Further research is needed.
2	**Convalescent plasma**	Convalescent plasma may not reduce P-ACC. However, certainty of the evidence was low. Further research is needed.
3	**Fluvoxamine**	Fluvoxamine may not reduce P-ACC. However, certainty of the evidence was low. Further research is needed.
4	**Ivermectine**	Ivermectin may not reduce P-ACC. However, certainty of the evidence was low. Further research is needed.

	Intervention	Summary of findings
5	**Leflunomide**	Leflunomide may not reduce P-ACC. However, certainty of the evidence was low. Further research is needed.
6	**Metformin**	Metformin may reduce P-ACC. However, certainty of the evidence was low. Further research is needed.
7	**Remdesivir**	Remdesivir may not reduce P-ACC. However, certainty of the evidence was low. Further research is needed.
8	**Saline + Mouthwash**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined six therapeutic options for PCC olfactory and/or gustatory dysfunction.

• **Metformin:** The results of one RCT suggest that metformin may reduce P-ACC. However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

• **Ivermectin:** The results of one RCT suggest that ivermectin may reduce P-ACC. However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

• **Convalescent plasma:** The results of one RCT suggest that convalescent plasma may not reduce P-ACC. However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

• **Remdesivir:** The results of one RCT suggest that remdesivir may not reduce P-ACC. However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

• **Leflunomide:** The results of one RCT suggest that leflunomide may not reduce P-ACC. However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

• **Fluvoxamine:** The results of two RCTs suggest that fluvoxamine may not reduce P-ACC. However, certainty of the evidence was low because of imprecision. Further research is needed.

Changes since previous edition

• **Creatine for P-ACC related fatigue or asthenia:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Telerehabilitation for P-ACC related fatigue or asthenia:** New evidence included not affecting results interpretation and/or certainty of the evidence judgments.

• **Saline + Mouthwash for P-ACC prophylaxis:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Budesonide + Mouthwash for P-ACC prophylaxis:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Alpha-lipoic acid for P-ACC-related olfactory and/or gustatory dysfunction:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Donepezil for P-ACC-related neurocognitive symptoms:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Respiratory training for P-ACC-related dyspnea:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Platelet-rich plasma for P-ACC-related olfactory and/or gustatory dysfunction:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Vortioxetine for P-ACC-related neurocognitive symptoms:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Probiotics for P-ACC related fatigue or asthenia:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Probiotics for P-ACC related neurocognitive symptoms:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Probiotics for P-ACC related dyspnea:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

Concluding remarks

• The Pan American Health Organization (PAHO) is continually monitoring ongoing research on any possible therapeutic options. As evidence emerges, PAHO will immediately assess and update its position, particularly as it applies to any special population subgroups such as children, expectant mothers, and those with immune conditions.

• PAHO is also mindful of the emerging differential impact of PCC on ethnic and minority groups and is continuously seeking data that could help in mitigating excess risk of severe illness or death in minority subgroups. These groups are plagued by social and structural inequities that bring to bear a disproportionate burden of COVID-19 illness.

• The safety of the patient suffering from COVID-19 is a key priority to improve the quality of care in the provision of health services.

• Adequately designed and reported clinical trials are crucial for the practice of evidence-based medicine. Most of the research to date on PCC has very poor methodology that is hidden and very difficult to validate. Greater transparency and better designed studies are urgently needed.

Systematic review of therapeutic options for post-acute or post COVID-19 condition (P-ACC)

Background

Post COVID-19 condition (PCC), also known as long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC), is the continuation or development of new symptoms in the period after acute infection with SARS-CoV-2 *(1–4)*. The World Health Organization (WHO) definition of PCC states that these symptoms should be present after three months of the initial SARS-CoV-2 infection and last for at least two months with no other explanation *(1, 2)*. While PASC definitions state persistent or new symptoms need to be present 30 days after a documented SARS-COV-2 infection or the onset of COVID-19 symptoms (*3, 4*). Post COVID-19 condition or post-acute sequelae of SARS-CoV-2 infection (P-ACC) can affect anyone exposed to SARS-CoV-2, regardless of age or severity of acute infection. Many of the reported symptoms are debilitating and have a strong negative impact on mental health and quality of life *(5)*. While most patients recover, some may experience multiple outcomes, with multiple organ systems affected simultaneously, including cardiovascular, mental, metabolic, renal, and others *(3, 6)*. Recommendations for the management of patients with PCC are continuously being developed and need to evolve as evidence of interventions effects becomes available (*7*).

In this review, we compiled the following evidence on potential therapeutic options for P-ACC. We included all the identified clinical forms, symptoms, and manifestations of P-ACC for which an intervention was assessed in at least one randomized controlled trial (RCT). We hope this information will support investigators, policymakers, and prescribers navigate the flood of relevant data to ensure that management of P-ACC, at both the individual and population levels, is based on the best available knowledge. We will endeavor to continually update this resource as more research is released into the public space.

Methods

We used the Living OVerview of Evidence (L·OVE; available from: https://iloveevidence.com) platform to identify studies for inclusion in this review. This platform is a system that maps PICO (Patient–Intervention–Comparison–Outcome) questions to a repository developed by Epistemonikos Foundation. This repository is continuously updated through searches in electronic databases, preprint servers, trial registries, and other resources relevant to COVID-19. The latest version of the methods, the total number of sources screened, and a living flow diagram and report of the project is updated regularly on the L·OVE website *(8)*.

Search strategy

We systematically searched in L·OVE for COVID-19. The search terms and databases covered are described on the L·OVE search strategy methods page (available from: https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?question_domain=undefined&section=methods). The repository is continuously updated, and the information is transmitted in real time to the L·OVE platform. It was last checked for this review on 3 November2023. The searches covered the period from the inception date of each database, and no study design, publication status, or language restriction was applied.

Study selection

The results of the searches in the individual sources were de-duplicated by an algorithm that compares unique identifiers (database identification number, digital object identifier [DOI], trial registry identification number), and citation details (i.e., author names, journal, year of publication, volume, number, pages, article title, and article abstract). Then, the information matching the search strategy was sent in real time to the L·OVE platform, where at least two authors independently screened the titles and abstracts yielded against the inclusion criteria. We obtained the full reports for all titles that appeared to meet the inclusion criteria or required further analysis and then decided about their inclusion.

Inclusion criteria

We aimed to find all available RCTs for potential therapeutic interventions for P-ACC with study designs that included head-to-head comparisons, or control groups with no intervention or a placebo. Target patient populations included both adults and children with persistent, or new, symptoms or clinical manifestations after acute COVID-19. We used the term Post Acute or Post COVID-19 condition (P-ACC) to refer to the population included in our review (studies reporting on patients with persistent or new symptoms after acute COVID-19 independently of the time of onset of those symptoms) *(1–4)*. We focused on comparative effectiveness studies that provide evidence on outcomes of crucial importance to patients (mortality, health-related quality of life [HRQL], and disease-specific symptoms).

Living evidence synthesis

An artificial intelligence algorithm deployed in the Coronavirus/COVID-19 topic of the L·OVE platform provides instant notification of articles with a high likelihood of being eligible. The authors review them, decide upon inclusion, and update the living web version of the review accordingly. If meta-analytical pooling is possible from retrieved evidence, we will do this to derive more precise estimates of effect and derive additional statistical power. No electronic database search restrictions were imposed.

For any meta-analytical pooling, if and when data allow, we pool all studies and present the combined analysis with relative and absolute effect sizes. To assess interventions' absolute effects, we applied relative effects to baseline risks (risks with no intervention). For baseline risks we used the mean risk in the control groups from included RCTs. For continuous outcomes, when possible, we calculated relative and absolute effects by estimating the proportion of patients with important improvement or deterioration following published guidance *(9)*.

For result interpretations and imprecision assessment we used a minimally contextualized approach that considers whether the 95% confidence interval (CI) includes the null effect, or, when the point estimate is close to the null effect, whether the 95% CI lies within the

boundaries of small but important benefit and harm that corresponds to every outcome assessed *(10, 11)*.

We used the following absolute effects thresholds to define important benefits and harms: Mortality, +/-1%; HRQL improvement, +/-2%; Overall symptom improvement, +/-5%; Functional capacity improvement, +/-5%; Strength improvement, +/-5%; Fatigue improvement, +/-5%; Pulmonary function improvement, +/-10%; Radiological response, +/-10%; Cognitive improvement, +/-5%; Depression improvement, +/-5%; Olfactory symptoms improvement, +/-5%; Gustatory symptoms improvement, +/-5%; Tachycardia improvement, +/-5%; Venous thromboembolism (VTE) (symptomatic), +/-3%; Post-traumatic stress disorder improvement, +/-5%; Psychological distress improvement, +/-5%; Major bleeding, +/-3%; Severe adverse events, +/-3%; Adverse events, +/-5%; Time to discharge reduction, +/-4%; Respiratory support requirement +/-2%; Inotropic requirement +/-2%; Left ventricular ejection fraction deterioration (LVEF <55%) +/-5%; Arrhythmia +/-5%; P-ACC, +/-3%.

For some interventions when we found significant heterogeneity, we performed subgroup analysis considering: 1) risk of bias (high/moderate vs low risk of bias); and 2) intervention characteristics (e.g., different doses or administration schemes). When we observed significant differences between subgroups, we presented individual subgroups' estimates of effect and certainty of the evidence assessment.

A risk of bias assessment was applied to RCTs focusing on randomization, allocation concealment, blinding, attrition, or other biases relevant to the estimates of effect (Table 1) *(12)*. The GRADE approach was used to assess the certainty of the body of evidence for every comparison on an outcome basis *(13)*.

Study selection, data extraction, and risk of bias assessment were performed, independently and in parallel, by two reviewers. Discrepancies were resolved by discussion.

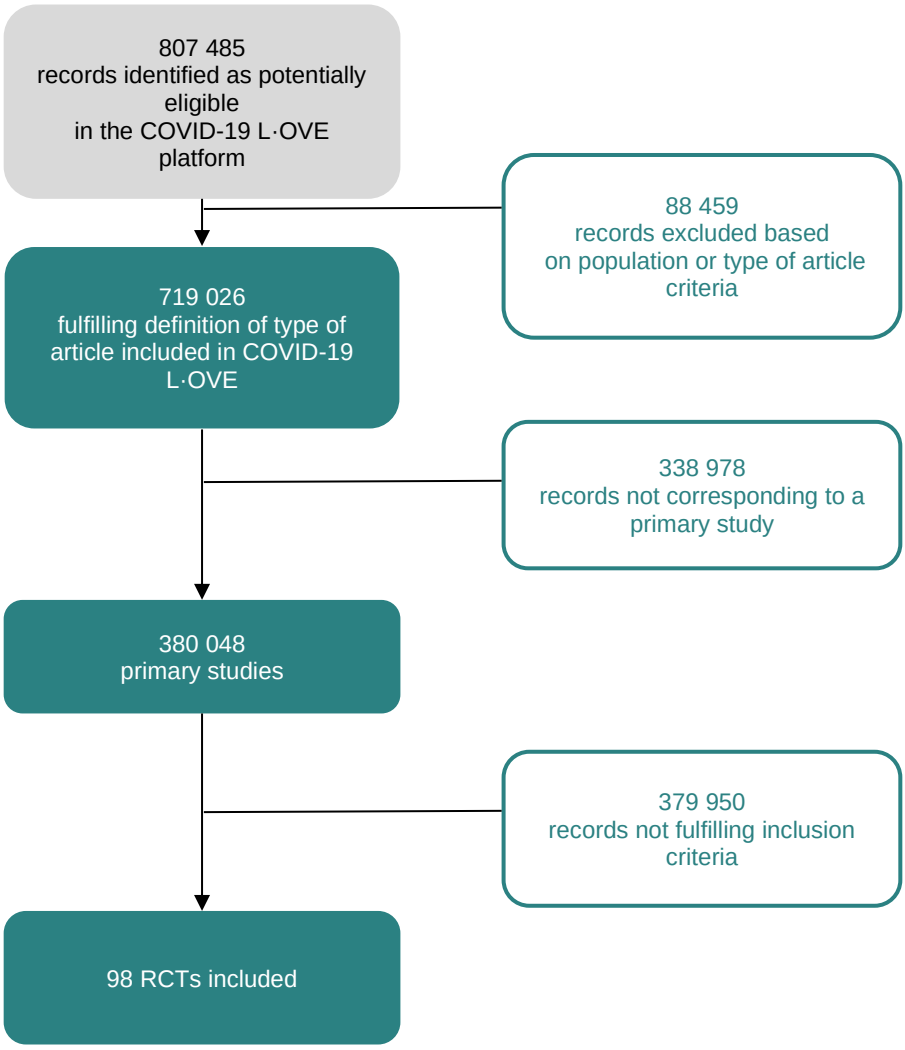
We used MAGIC authoring and publication platform (available from: https://app.magicapp.org/) to generate the tables summarizing our findings, which are included in Annex 1.

Results

Studies identified and included

The study identification and selection process is shown in Figure 1. A total of 89 RCTs were selected for inclusion. A list of excluded studies is available upon request.

Figure 1. Study identification and selection process



Risk of bias

Overall, our risk of bias assessment for the limited reported RCTs found high risk of bias due to suboptimal randomization, allocation concealment, and blinding (as well as other methodological and reporting concerns). Most RCTs were also very small in size and had small event numbers. The methods were very poor overall, and the reporting was suboptimal. In general, follow-up was short. The risk of bias assessment of each RCT is presented in Table 1.

Table 1. Risk of bias of included RCTs

Study	Risk-of-bias arising from randomization process	Risk-of-bias due to deviations from the intended interventions	Risk-of-bias due to missing outcome data	Risk-of-bias in measurement of the outcome	Risk-of-bias in selection of the reported result	Overall Risk-of-bias judgement	
						Mortality	HRQL, symptom specific outcomes
Vaira LA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RC 4-7-2020 (Abdelalim AA et al)	High	Some Concerns	Low	Some Concerns	Low	High	High
Di Stadio	High	Some Concerns	Low	Some Concerns	Low	High	High
Chudzik M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CITADEL	High	Some Concerns	Low	Some Concerns	Low	High	High
MICHELLE	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Zilberman-Itskovich	Low	Low	Low	Low	Low	Low	Low
Botek M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Jadhav KP et al	High	Some Concerns	Low	Some Concerns	Low	High	High
COLDSTER	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Oliver-Mas	Low	Low	Low	Low	Low	Low	Low
Nambi	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Di Stadio_2	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Hansen	Low	Low	Low	Low	Low	Low	Low
Tosato	High	Some Concerns	Low	Some Concerns	Low	High	High
Rathi	High	Some Concerns	Low	Some Concerns	Low	High	High
Bazdyrev	Low	Low	Low	Low	Low	Low	Low
King	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ICU-VR	High	Some Concerns	Low	Some Concerns	Low	High	High
ENO Breathe	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Pires	High	Some Concerns	Low	Some Concerns	Low	High	High
McNarry	High	Some Concerns	Low	Some Concerns	Low	High	High
Srinivasan	High	Some Concerns	Low	Some Concerns	Low	High	High
Kharaeva_Moderate	High	Some Concerns	Low	Some Concerns	Low	High	High
Kharaeva_Severe	High	Some Concerns	Low	Some Concerns	Low	High	High
Gaylis	High	Some Concerns	Low	Some Concerns	Low	High	High
Karosanidze	Low	Low	Low	Low	Low	Low	Low
Badran	Low	Low	Low	Low	Low	Low	Low
COVANOS	Low	Some Concerns	Low	Some Concerns	Low	Low	High
RECOVER	High	Some Concerns	Low	Some Concerns	Low	High	High
Kutashov	High	Some Concerns	Low	Some Concerns	Low	High	High
Vallier	High	Some Concerns	Low	Some Concerns	Low	High	High
Swissped RECOVERY	Low	Some Concerns	Low	Some Concerns	Low	Low	High
UK Phyto-V	High	Some Concerns	Low	Some Concerns	Low	High	High
Rodriguez-Blanco	High	Some Concerns	Low	Some Concerns	Low	High	High
COVID-OUT - Metformin	Low	Low	High	Low	Low	High	High
COVID-OUT - Ivermectin	Low	Low	High	Low	Low	High	High
COVID-OUT - Fluvoxamine	Low	Low	High	Low	Low	High	High
Santana	Low	Low	Low	Low	Low	Low	Low
CSSC-004	Low	Low	Some Concerns	Low	Low	Low	Some Concerns
Deshpande	High	Some Concerns	Low	Some Concerns	Low	High	High
Dal Negro	High	Some Concerns	Low	Some Concerns	Low	High	High
InsCOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Rutkowski	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SOLIDARITY - Finland	Low	Low	Low	Low	Low	Low	Low
Hawkins	Low	Low	Low	Low	Low	Low	Low
Schepens	Low	Low	Low	Low	Low	Low	Low
Kusumawardani	High	Some Concerns	Low	Some Concerns	Low	High	High
SCENT2	Low	Low	Low	Low	Low	Low	Low
Hausswirth	High	Some Concerns	Low	Some Concerns	Low	High	High
Versace	High	Low	Low	Low	Low	High	High
ACTIV-4C	Low	Low	Low	Low	Low	Low	Low
Simpson	High	Some Concerns	Low	Some Concerns	Low	High	High
Stavrou	High	Some Concerns	Low	Some Concerns	Low	High	High
Zulbaran-Rojas	High	Some Concerns	Low	Some Concerns	Low	High	High
Kalayeh	High	Some Concerns	Low	Some Concerns	Low	High	High
DEFEAT-COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Kerget	High	Some Concerns	Low	Some Concerns	Low	High	High
Farahani	Low	Low	Low	Low	Low	Low	Low
Finnigan	Low	Low	Low	Low	Low	Low	Low
Longobardi	Low	Some Concerns	Low	Some Concerns	Low	Low	High

Kuut	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Shabaan	Low	Low	Low	Low	Low	Low	Low
RECOVE	High	Some Concerns	Low	Some Concerns	Low	High	High
Del Corral	Low	Low	Low	Low	Low	Low	Low
Imam	High	Some Concerns	Low	Some Concerns	Low	High	High
Nagy	High	Some Concerns	Low	Some Concerns	Low	High	High
Ibrahim	High	Some Concerns	Low	Some Concerns	Low	High	High
Samper-Pardo	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Momtazmanesh	Low	Low	Low	Low	Low	Low	Low
Leitman	Low	Low	Low	Some Concerns	High	High	High
Brichetti	Low	Low	Low	Low	Low	Low	Low
Lerner	Low	Low	Low	Low	Low	Low	Low
Rasmussen	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Caprioli	Low	Low	Low	Low	Low	Low	Low
Nambi_2	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Chung	High	Some Concerns	Low	Some Concerns	Low	High	High
Toussaint	High	Some Concerns	Low	Some Concerns	Low	High	High
Oliveira	High	Some Concerns	Low	Some Concerns	Low	High	High
Da Silva	Low	Low	Low	Low	Low	Low	Low
Tanhan	High	Some Concerns	Low	Some Concerns	Low	High	High
TERECO	Low	Low	Low	Low	Low	Low	Low
Ansari	High	Some Concerns	Low	Some Concerns	Low	High	High
Hautefort	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Ampio	High	Some Concerns	Low	Some Concerns	Low	High	High
GRACE	Low	Low	High	Low	Low	High	High
Mirenayat	High	Some Concerns	Low	Some Concerns	Low	High	High
Espinoza-Bravo	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Senén	High	Some Concerns	Low	Some Concerns	Low	High	High
COVEMERALD	High	Some Concerns	Low	Some Concerns	Low	High	High
Abdelazim	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Tanashyan	Low	Low	Low	Low	Low	Low	Low
Ogonowska-Slodownik	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Alsharidah	High	Some Concerns	Low	Some Concerns	Low	High	High
Slankamenac	High	Some Concerns	Low	Some Concerns	Low	High	High
Jing	High	Some Concerns	Low	Some Concerns	Low	High	High
Figueiredo	Low	Low	Low	Low	Low	Low	Low
Pooladgar	High	Some Concerns	Low	Some Concerns	Low	High	High
Hashemi	High	Some Concerns	Low	Some Concerns	Low	High	High
Evman	Low	Some Concerns	Low	Some Concerns	Low	Low	High
McIntyre	Low	Low	Low	Low	Low	Low	Low
RECOVERY	Low	Low	High	Low	Low	High	High

Main findings

P-ACC-related asthenia or fatigue

Actovegin

See Summary of findings Table A1, Annex 1

We identified one RCT including 444 participants in which Actovegin was compared against standard of care. Our results showed:

- Actovegin may improve fatigue, relative risk (RR) 1.84 (95% CI 1.59 to 2.14); risk difference (RD) 39.7% (95% CI 27.7% to 56.3%); Low certainty ⊕⊕◯◯

ADAPT-232 (adaptogens)

See Summary of findings Table A2, Annex 1

We identified one RCT including 99 participants in which ADAPT-232 was compared against standard of care. Our results showed:

- ADAPT-232 may not improve fatigue, relative risk (RR) 1.02 (95% CI 0.84 to 1.24); risk difference (RD) 1.6% (95% CI –12.6% to 18.9%); Low certainty ⊕⊕◯◯

Cytoflavin

See Summary of findings Table A3, Annex 1

We identified one RCT including 200 patients in which cytoflavin was compared against standard of care. Our results showed:

- Cytoflavin may not improve fatigue, RR 1.02 (95% CI 0.98 to 1.06); RD 2.1% (95% CI –1.9% to 6.2%); Low certainty ⊕⊕◯◯

Enzymes + probiotics

See Summary of findings Table A4, Annex 1

We identified one RCT including 200 patients in which enzymes + probiotics were compared against standard of care. Our results showed:

- Enzymes + probiotics may improve fatigue, RR 6.07 (95% CI 3.79 to 9.71); RD 76% (95% CI 41.8% to 85%); Low certainty ⊕⊕◯◯

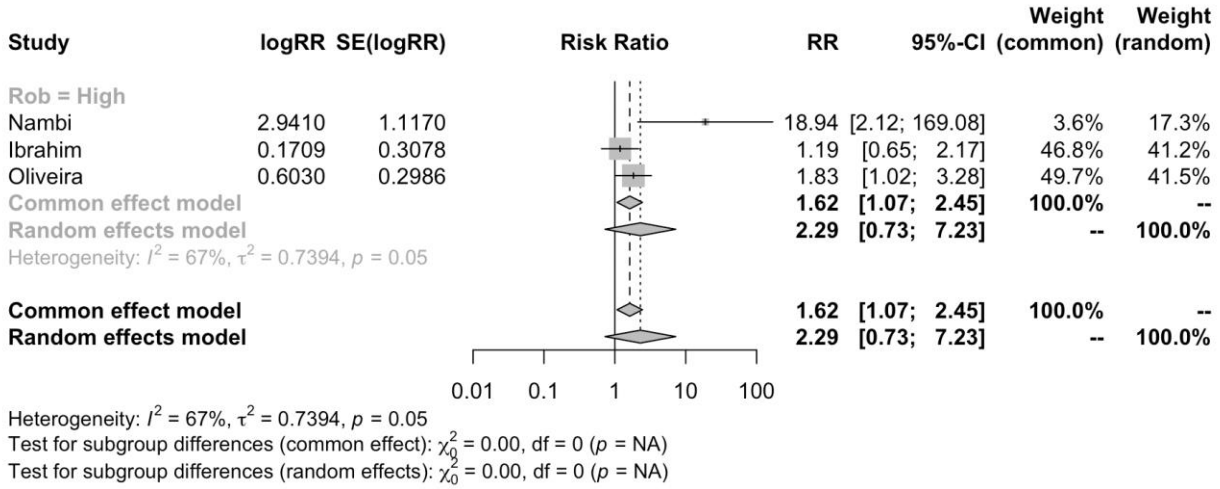
Physical training

See Summary of findings Table A30, Annex 1

We identified six RCTs including 304 patients in which physical training was compared against standard of care. Our results showed:

- Physical training may improve HRQL, 1.62 (95% CI 1.07 to 2.45); RD 21.1% (95% CI 2.4% to 49.2%); Low certainty ⊕⊕◯◯
- Physical training may improve fatigue, RR 4.66 (95% CI 1.96 to 11.09); RD 44.4% (95% CI 11.7% to 87.9%); Low certainty ⊕⊕◯◯
- Physical training may improve functional capacity, RR 1.81 (95% CI 1.23 to 2.65); RD 17.4% (95% CI 4.9% to 35.4%); Low certainty ⊕⊕◯◯
- Physical training may improve strenght, RR 3.13 (95% CI 1.02 to 9.55); RD 11.3% (95% CI 0.1% to 45.4%); Low certainty ⊕⊕◯◯

Figure 1. HRQL improvement in RCTs comparing physical training with standard of care for treatment of patients with P-ACC-related asthenia/fatigue



Phytochemicals

See Summary of findings Table A5, Annex 1

We identified one RCT including 147 patients in which phytochemicals were compared against standard of care. Our results showed:

- Phytochemicals may improve HRQL, RR 1.33 (95% CI 1.03 to 1.71); RD 18% (95% CI 1.8% to 39%); Low certainty ⊕⊕◯◯
- Phytochemicals may improve fatigue, RR 1.24 (95% CI 0.95 to 1.62); RD 13.1% (95% CI -2.5% to 33.5%); Low certainty ⊕⊕◯◯

Transcranial direct current stimulation (tDCS)

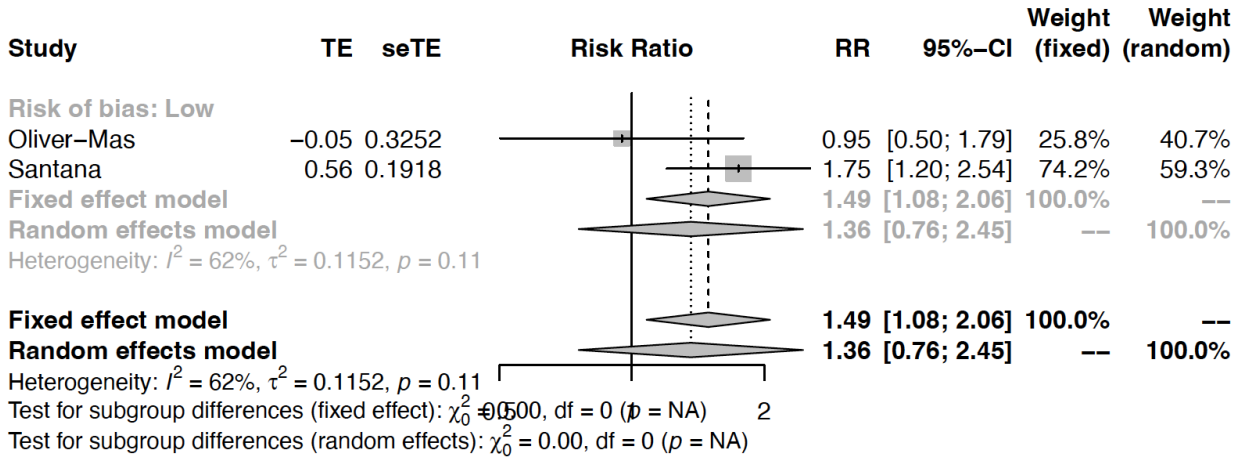
See Summary of findings Table A6, Annex 1

We identified two RCTs including 117 patients in which tDCS was compared against standard of care. Our results showed:

- tDCS may improve fatigue, RR 1.36 (95% CI 0.76 to 2.45); RD –16.9% (95% CI –11.2% to 53%); Low certainty ⊕⊕◯◯ (see figure 2.)

- tDCS may improve HRQL, RR 1.37 (95% CI 1.09 to 1.71); RD –26% (95% CI –6.7% to 30%); Low certainty ⊕⊕◯◯
- tDCS may not increase adverse events, RR 0.83 (95% CI 0.26 to 2.73); RD –3.4% (95% CI –15.5% to 36%); Low certainty ⊕⊕◯◯

Figure 2. Fatigue in RCTs comparing tDCS with standard of care for treatment of patients with P-ACC-related asthenia/fatigue



AXA1125

See Summary of findings Table A27, Annex 1

We identified one RCT including 41 participants in which AXA1125 was compared against standard of care. Our results showed:

- AXA1125 may improve fatigue, RR 1.07 (95% CI 0.79 to 1.44); RD 5.1% (95% CI –16.6% to 34.5%); Low certainty ⊕⊕◯◯
- AXA1125 may not improve functional capacity, RR 0.87 (95% CI 0.51 to 1.48); RD -8.1% (95% CI –30% to 29.3%); Low certainty ⊕⊕◯◯

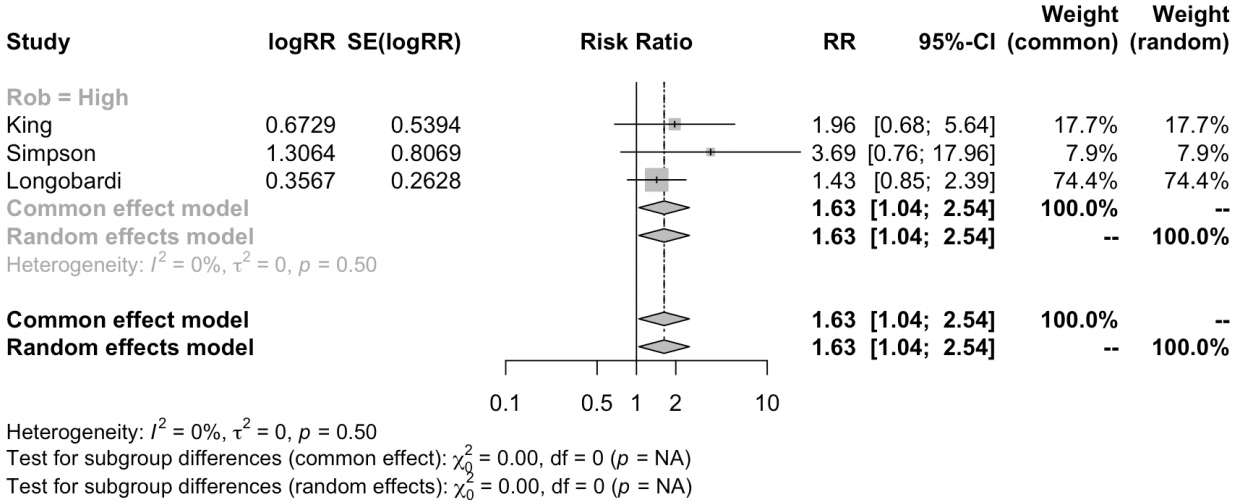
Telerehabilitation

See Summary of findings Table A28, Annex 1

We identified six RCTs including 294 participants in which telerehabilitation was compared against standard of care. In addition, we identified one study in which synchronous and asynchronous telerehabilitation strategies were compared. Our results showed:

- Telerehabilitation may improve fatigue, RR 1.63 (95% CI 1.04 to 2.54); RD 19.1% (95% CI 1.2% to 46.8%); Low certainty ⊕⊕◯◯ (see figure 3.)
- Telerehabilitation may improve functional capacity, RR 1.47 (95% CI 1.19 to 1.82); RD 20.7% (95% CI 8.4% to 36.2%); Low certainty ⊕⊕◯◯

Figure 3. Fatigue in RCTs comparing telerehabilitation with standard of care for treatment of patients with P-ACC-related asthenia/fatigue



Cognitive behavioral therapy

See Summary of findings Table A29, Annex 1

We identified one RCT including 114 participants in which cognitive behavioral therapy was compared against standard of care. Our results showed:

- Behavioral therapy may improve fatigue, RR 2.2 (95% CI 1.35 to 3.58); RD 31.6% (95% CI 9.2% to 68%); Low certainty ⊕⊕◯◯
- Behavioral therapy may improve functional capacity, RR 1.37 (95% CI 1.08 to 1.73); RD 22.4% (95% CI 4.8% to 44.7%); Low certainty ⊕⊕◯◯

Probiotics

See Summary of findings Table A34, Annex 1

We identified two RCT including 436 participants in which probiotics were compared against standard of care. Our results showed:

- Probiotics probably improve fatigue, RR 1.53 (95% CI 1.23 to 1.89); RD –20.2% (95% CI 8.8% to 33.9%); Moderate certainty ⊕⊕⊕◯

P-ACC-related dyspnea

ADAPT-232 (adaptogens)

See summary of findings Table A7 in Annex 1

We identified one RCT including 99 patients in which ADAPT-232 was compared against standard of care. Our results showed:

- ADAPT-232 may not improve dyspnea, RR 1 (95% CI 0.94 to 1.06); RD 0% (95% CI –5.4% to 5.7%); Low certainty ⊕⊕◯◯

High dose steroids

See Summary of findings Table A9, Annex 1

We identified one RCT including 130 patients in which high dose steroids (prednisone 40 mg a day) was compared against standard dose steroids (prednisone 10 mg a day). Our results showed:

- High dose steroids may not improve dyspnea, RR 1 (95% CI 0.87 to 1.15); RD 0% (95% CI –11% to 13%); Low certainty ⊕⊕◯◯
- High dose steroids may not increase adverse events, RR 0.92 (95% CI 0.75 to 1.13); RD –6.2% (95% CI –19.3% to 10%); Low certainty ⊕⊕◯◯

Probiotics

See Summary of findings Table A35, Annex 1

We identified one RCT including 285 participants in which probiotics were compared against standard of care. Our results showed:

- Probiotics probably improve dyspnea, RR 1.28 (95% CI 1.05 to 1.54); RD 14.8% (95% CI 2.9% to 29.1%); Low certainty ⊕⊕◯◯

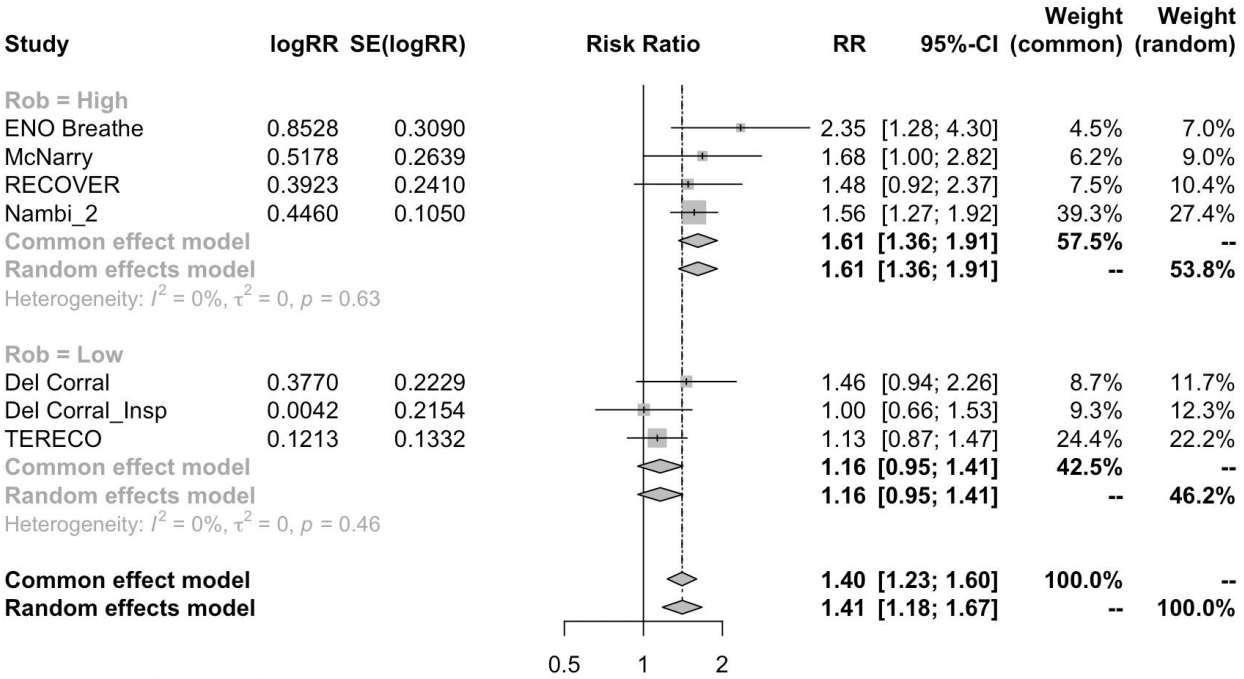
Respiratory training/rehabilitation

See Summary of findings Table A10, Annex 1

We identified eleven RCTs including 686 patients in which different modalities of respiratory training/rehabilitation were compared with standard of care. In addition, we identified two studies that compared home based respiratory training vs. inpatient respiratory training, two studies comparing VR respiratory training vs. conventional respiratory training and one study that compares incentive spirometry vs. conventional respiratory training. Our results showed:

- Respiratory training/rehabilitation probably improves HRQL RR 1.41 (95% CI 1.18 to 1.67); RD 22.3% (95% CI 9.8% to 36.5%); Moderate certainty ⊕⊕⊕◯ (see Figure 4)
- Respiratory training/rehabilitation probably improves dyspnea, RR 2.44 (95% CI 1.33 to 4.49); RD 41.4% (95% CI 9.5% to 58.6%); Moderate certainty ⊕⊕⊕◯
- Respiratory training/rehabilitation may improve functional capacity, RR 1.34 (95% CI 1.11 to 1.62); RD 17.1% (95% CI 5.5% to 31.1%); Moderate certainty ⊕⊕⊕◯

Figure 4. HRQL in RCTs comparing respiratory training/rehabilitation with standard of care for treatment of patients with P-ACC-related dyspnea.



Treamid

See Summary of findings Table A11, Annex 1

We identified one RCT including 59 patients in which treamid was compared with standard of care. Our results showed:

- Treamid may improve dyspnea, RR 1.96 (95% CI 0.9 to 4.25); RD 21.7% (95% CI –2.3% to 73.7%); Low certainty ⊕⊕◯◯
- Treamid may improve functional capacity, RR 1.1 (95% CI 0.64 to 1.9); RD 0.4% (95% CI 16.2% to 39.8%); Low certainty ⊕⊕◯◯
- Treamid may increase adverse events, RR 1.19 (95% CI 0.56 to 2.5); RD 5.5% (95% CI –12.7% to 43.6%); Low certainty ⊕⊕◯◯

P-ACC-related neurocognitive symptoms or sleep disturbances

Actovegin

See Summary of findings Table A12, Annex 1

We identified one RCT including 44 patients in which actovegin was compared with standard of care. Our results showed:

- Actovegin may improve cognition, RR 1.19 (95% CI 1.06 to 1.33); RD 12.7% (95% CI 4.2% to 22.3%); Low certainty ⊕⊕◯◯

Famotidine

See Summary of findings Table A31, Annex 1

We identified one RCT including 50 patients in which famotidine was compared with standard of care. Our results showed:

- Famotidine may improve cognition, RR 1.33 (95% CI 1.05 to 1.69); RD 24.6% (95% CI 3.7% to 51.1%); Low certainty ⊕⊕◯◯
- It is uncertain if famotidine improves depresion, RR 3.71 (95% CI 0.83 to 16.6); RD 20.6% (95% CI -1.3% to 92.4%); Very low certainty ⊕◯◯◯

Hyperbaric oxygen (HBO)

See Summary of findings Table A13, Annex 1

We identified one RCT including 73 patients in which HBO was compared with standard of care. Our results showed:

- HBO may improve HRQL, RR 1.3 (95% CI 0.84 to 2); RD 13.9% (95% CI –7.4% to 46.9%); Low certainty ⊕⊕◯◯

Transcranial direct current stimulation (tDCS)

See Summary of findings Table A14, Annex 1

We identified one RCT including 47 patients in which tDCS was compared with standard of care. Our results showed:

- tDCS may not improve HRQL, RR 0.59 (95% CI 0.33 to 1.05); RD –27.5% (95% CI –44.8% to 3.4%); Low certainty ⊕⊕◯◯

Vortioxetine

See Summary of findings Table A33, Annex 1

We identified one RCT including 149 patients in which vortioxetine was compared with standard of care. Our results showed:

- Vortioxetine probably improve HRQL, RR 1.35 (95% CI 1.03 to 1.77); RD 17% (95% CI 1.4% to 39%); Moderate certainty ⊕⊕⊕◯
- Vortioxetine may not improve cognition, RR 0.97 (95% CI 0.74 to 1.28); RD –1.6% (95% CI –15.3% to 16.5%); Low certainty ⊕⊕◯◯
- Vortioxetine may improve depression, RR 1.43 (95% CI 0.97 to 2.12); RD 14.8% (95% CI –1.1% to 38.3%); Low certainty ⊕⊕◯◯

Probiotics

See Summary of findings Table A36, Annex 1

We identified one RCT including 369 patients in which probiotics were compared with standard of care. Our results showed:

- Probiotics may improve cognition, RR 1.56 (95% CI 1.17 to 2.09); RD 15.1% (95% CI 4.5% to 29.2%); Low certainty ⊕⊕◯◯

- Probiotics may improve sleep quality, RR 1.32 (95% CI 1.05 to 1.65); RD 27% (95% CI 8.6% to 17.5%); Low certainty ⊕⊕◯◯

P-ACC-related olfactory and/or gustatory dysfunction

ADAPT-232 (adaptogens)

See Summary of findings Table A15, Annex 1

We identified one RCT including 99 patients in which ADAPT-232 was compared with standard of care. Our results showed:

- ADAPT-232 may not improve olfactory symptoms, RR 0.89 (95% CI 0.79 to 1.01); RD –10.3% (95% CI –20.5% to 1.4%); Low certainty ⊕⊕◯◯

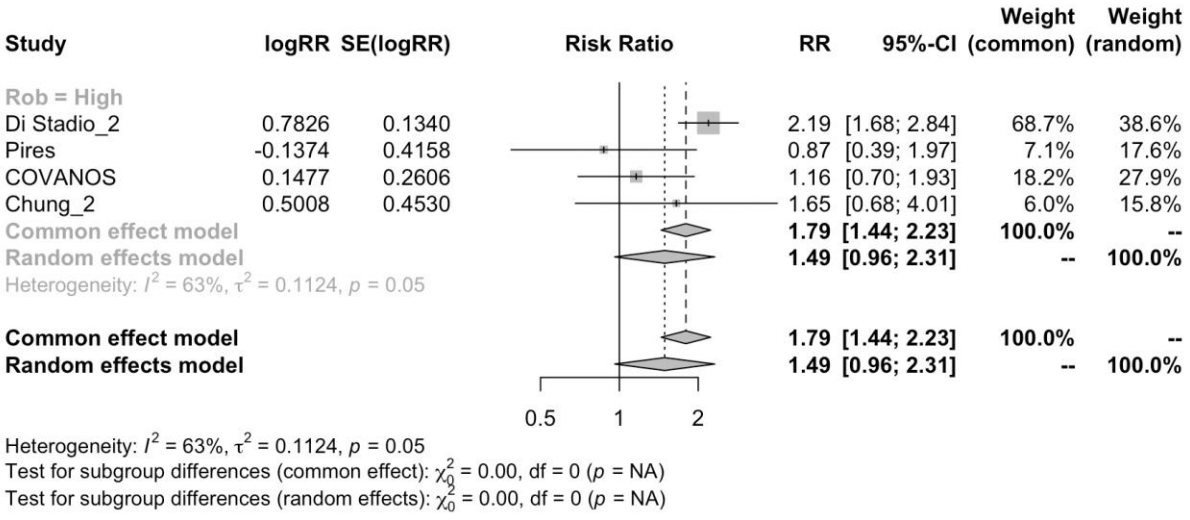
Olfactory training

See Summary of findings Table A32, Annex 1

We identified four RCTs including 308 patients in which olfactory training was compared with standard of care. Our results showed:

- Olfactory training may improve olfactory symptoms, RR 1.49 (95% CI 0.96 to 2.31); RD 20% (95% CI –1.6% to 53.6%); Low certainty ⊕⊕◯◯

Figure 5. Olfactory symptoms in RCTs comparing olfactory training with standard of care for treatment of patients with P-ACC-related olfactory and/or gustatory dysfunction.



Palmitoylethanolamide + Luteolin

See Summary of findings Table A16, Annex 1

We identified one RCT including 130 patients in which palmitoylethanolamide + luteolin was compared with standard of care. Our results showed:

- Palmitoylethanolamide + luteolin may improve olfactory symptoms, RR 3.11 (95% CI 1.47 to 6.66); RD 35.5% (95% CI 7.8% to 83.3%); Low certainty ⊕⊕◯◯

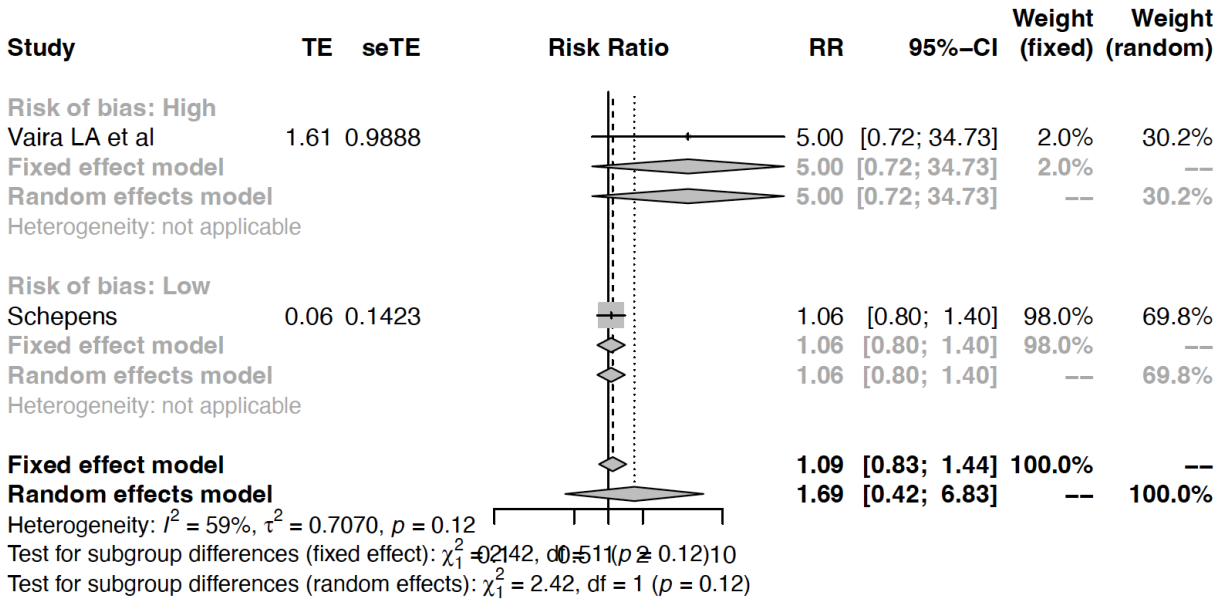
Steroids

See Summary of findings Table A17, Annex 1

We identified two RCTs including 131 patients in which steroids were compared with standard of care. Our results showed:

- Steroids may not improve olfactory symptoms, RR 1.09 (95% CI 0.83 to 1.44); RD 3.3% (95% CI –6.2% to 16.1%); Low certainty ⊕⊕◯◯ (figure 5)
- Steroids may not improve gustatory symptoms, RR 1.01 (95% CI 0.67 to 1.53); RD 0.5% (95% CI –14.6% to 23.3%); Low certainty ⊕⊕◯◯

Figure 6. Olfactory symptoms in RCTs comparing steroids with standard of care for treatment of patients with P-ACC-related olfactory and/or gustatory dysfunction.


Study
TE
seTE
Risk Ratio
RR
95%–CI
Weight (fixed)
Weight (random)
Risk of bias: High
Vaira LA et al 1.61 0.9888 5.00 [0.72; 34.73] 2.0% 30.2%
Fixed effect model 5.00 [0.72; 34.73] 2.0% --
Random effects model 5.00 [0.72; 34.73] -- 30.2%
Heterogeneity: not applicable
Risk of bias: Low
Schepens 0.06 0.1423 1.06 [0.80; 1.40] 98.0% 69.8%
Fixed effect model 1.06 [0.80; 1.40] 98.0% --
Random effects model 1.06 [0.80; 1.40] -- 69.8%
Heterogeneity: not applicable
Fixed effect model 1.09 [0.83; 1.44] 100.0% --
Random effects model 1.69 [0.42; 6.83] -- 100.0%
Heterogeneity: I^2 = 59%, τ^2 = 0.7070, p = 0.12
Test for subgroup differences (fixed effect): χ^2_1 = 2.42, df = 1 (p = 0.12)
Test for subgroup differences (random effects): χ^2_1 = 2.42, df = 1 (p = 0.12)

P-ACC-related cardiovascular system symptoms

The effects of the assessed interventions are uncertain.

P-ACC-related psychological distress

Virtual reality (VR) informational video

See Summary of findings Table A18, Annex 1

We identified one RCT including 89 patients in which a virtual reality-based (VR) intervention was compared with standard of care. Our results showed:

- VR informational video may improve depression, RR 1.21 (95% CI 0.95 to 1.54); RD 14% (95% CI –3.7% to 36.7%); Low certainty ⊕⊕◯◯
- VR informational video may improve post-traumatic stress, RR 1.18 (95% CI 0.98 to 1.42); RD 13.8% (95% CI –1.5% to 32.3%); Low certainty ⊕⊕◯◯
- VR informational video may improve psychological distress, RR 1.49 (95% CI 1.08 to 2.05); RD 25.5% (95% CI 4.1% to 55.1%); Low certainty ⊕⊕◯◯

P-ACC-related thromboembolic risk

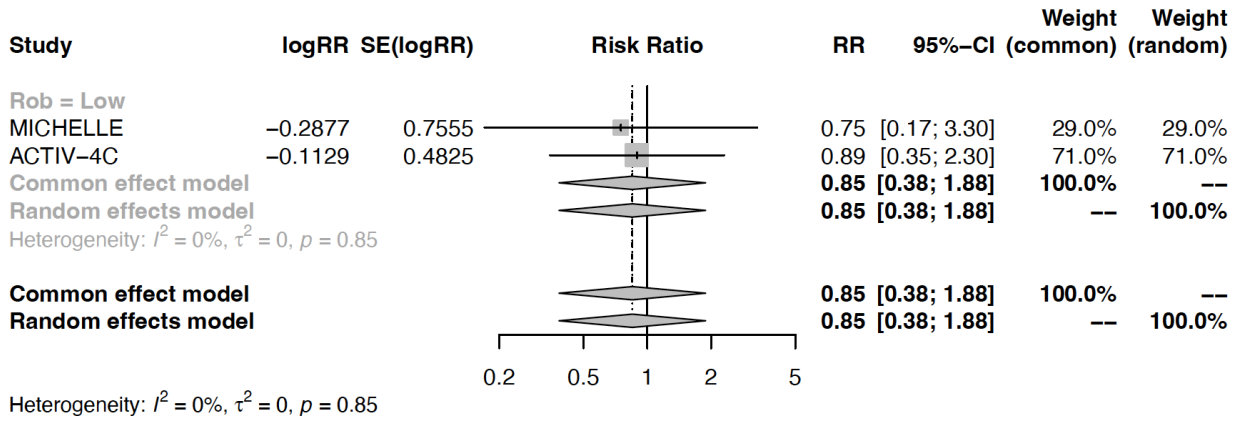
Anticoagulants

See Summary of findings Table A19, Annex 1

We identified two RCTs including 1535 patients with COVID-19 after hospitalization in which anticoagulants in prophylactic dose were compared with standard of care. Our results showed:

- Anticoagulants may not have an important effect on mortality, RR 0.85 (95% CI 0.38 to 0.88); RD -0.3% (95% CI –1.2% to 1.8%); Low certainty ⊕⊕◯◯ (Figure 6)
- Anticoagulants may not have an important effect on RR 0.99 (95% CI 0.78 to 1.24); Low certainty ⊕⊕◯◯
- Anticoagulants may not have an important effect on VTE, RR 1 (95% CI 0.29 to 3.45); RD 0% (95% CI –2.3% to 7.9%); Low certainty ⊕⊕◯◯ (based on low RoB studies)
- Anticoagulants may not have an important effect on VTE, RR 2.01 (95% CI 0.18 to 22.1); RD 0.1% (95% CI –0.1% to 1.2%); Low certainty ⊕⊕◯◯

Figure 7. Mortality in RCTs comparing anticoagulants with standard of care for treatment of patients with COVID-19 after hospitalization.



Pediatric inflammatory multisystem syndrome associated with SARS-CoV-2 (PIMS-TS)

Steroids

See Summary of findings Table A20, Annex 1

We identified one RCT including 75 patients in which systemic steroids were compared with intravenous immunoglobulins (IVIG). Our results showed:

- Steroids may reduce time to discharge, RR 1.09 (95% CI 0.88 to 1.39); RD 4.5% (95% CI -6% to 19.5%); Low certainty ⊕⊕◯◯
- Steroids may reduce respiratory support requirements, RR 0.49 (95% CI 0.27 to 0.89); RD -28.2% (95% CI -40.5% to -5.9%); Low certainty ⊕⊕◯◯

P-ACC prophylaxis

Metformin

See Summary of findings Table A21, Annex 1

We identified one RCT including 1125 patients in which metformin was compared with standard of care. Our results showed:

- Metformin may reduce P-ACC, RR 0.59 (95% CI 0.39 to 0.88); RD -4.3% (95% CI -6.4% to -1.2%); Low certainty ⊕⊕◯◯

Ivermectin

See Summary of findings Table A22, Annex 1

We identified one RCT including 739 patients in which metformin was compared with standard of care. Our results showed:

- Metformin may reduce P-ACC, RR 0.99 (95% CI 0.61 to 1.62); RD 0% (95% CI -1.7% to 2.6%); Low certainty ⊕⊕◯◯

Convalescent plasma

See Summary of findings Table A23, Annex 1

We identified one RCT including 882 patients in which metformin was compared with standard of care. Our results showed:

- Convalescent plasma may not reduce P-ACC, RR 0.93 (95% CI 0.77 to 1.12); RD -2.4% (95% CI -7.9% to -4.2%); Low certainty ⊕⊕◯◯

Remdesivir

See Summary of findings Table A24, Annex 1

We identified one RCT including 181 patients in which metformin was compared with standard of care. Our results showed:

- Remdesivir may not reduce P-ACC, RR 1.06 (95% CI 0.53 to 2.13); RD 0.8% (95% CI -6.9% to -16.4%); Low certainty ⊕⊕◯◯

Leflunomide

See Summary of findings Table A25, Annex 1

We identified one RCT including 172 patients in which leflunomide was compared with standard of care. Our results showed:

- Leflunomide may not reduce P-ACC, RR 1.28 (95% CI 0.92 to 1.77); RD 11.2% (95% CI -3.2% to 31.1%); Low certainty ⊕⊕◯◯

Fluvoxamine

See Summary of findings Table A26, Annex 1

We identified two RCTs including 680 patients in which fluvoxamine was compared with standard of care. Our results showed:

- Fluvoxamine may not reduce P-ACC, RR 0.99 (95% CI 0.81 to 1.21); RD -0.4% (95% CI -8.4% to 9.3%); Low certainty ⊕⊕◯◯

Full description of included studies

Tables 2 to 10 list all the identified studies that were included in this systematic review by intervention and P-ACC-related organ system affected. The treatments are arranged in alphabetical order. Study or author names, publication status, patient populations, interventions, sources of bias, outcomes, effect sizes, and certainty are listed for each study.

Table 2. Description of included studies and interventions effects for P-ACC-related asthenia or fatigue

1-MNA **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Chudzik et al. *(14)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 30 days of acute COVID-19). 25 assigned to 1-MNA 58 mg a day and 25 assigned to standard of care.	Median age 49.5, male 32%, hypertension 14%, diabetes 2%	Not reported (NR)	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** Very low certainty ⊕◯◯◯ **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Actovegin Actovegin may improve fatigue. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Kutashov et al. (*15*); Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after NR days of acute COVID-19). 222 assigned to Actovegin 1200 mg a day for 60 days and 222 assigned to standard of care.	Mean age 67.6, male 31.98%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** RR 1.84 (95% CI 1.59 to 2.14); RD 39.7% (95% CI 27.7.6% to 53.6%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

ADAPT-232 (adaptogens)

ADAPT-232 may not improve fatigue. However, certainty of the evidence was low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
Karosanidze et al. *(16)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 30 days of acute COVID-19). 49 assigned to ADAPT-232 (adaptogens) 60 mL a day for 14 days and 50 assigned to standard of care.	Mean age 48.9, male 14%	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** RR 1.02 (95% CI 0.84 to 1.24); RD 1.6% (95% CI –12.6% to 18.9%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Amygdala and Insula Retraining (AIR)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
Toussaint et al *(17);* Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 84 days of acute COVID-19). 50 assigned to Amygdala and Insula Retraining (AIR) 40 to 60 minutes a day and 50 assigned to standard of care.	Mean age 43.6	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** Very low certainty ⨁◯◯◯ **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⨁◯◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Arginine + Vitamin C

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					

Tosato et al. *(18)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 28 days of acute COVID-19). 23 assigned to Arginine + Vitamin C 1.66 g/500 mg for 28 days and 23 assigned to standard of care.	Mean age 50.5 ± 14, male 34.8%, interval between COVID-19 and enrolment 254 days, hospitalization during COVID-19 56.5%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** No information **Strength improvement:** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Severe adverse events:** No information
Aromatherapy **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					

Hawkins et al *(19)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 150 days of acute COVID-19). 20 assigned to Aromatherapy Twice a day for 14 days and 20 assigned to standard of care.	Male 0%	NR	Low risk of bias	**HRQL improvement:** Very low certainty ⨁◯◯◯ **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⨁◯◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
AXA1125 (amino acids + N-acetylcysteine) **AXA1125 may increase fatigue improvement but may not increase functional capacity improvement. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Finnigan et al *(20)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 84 days of acute COVID-19). 21 assigned to AXA1125 33.9 gr twice a day for 4 weeks and 20 assigned to standard of care.	Mean age 43.6, male 31.7%,	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** RR 1.07 (95% CI 0.79 to 1.44);

					RD 5.1% (95% CI –16.6% to 34.5%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** RR 0.87 (95% CI 0.51 to 1.48); RD -8.1% (95% CI –30% to 29.3%); Low certainty ⊕⊕◯◯ **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
CCSA (ethylmethylhydroxypyridine, trimethylhydrosinium propionate and succinate acid anion) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Tanashyan et al *(21)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 84 days of acute COVID-19). 15 assigned to CCSA 5 ml a day for 10 days and 15 assigned to standard of care.	Mean age 35, male 20%	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** No

					information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Coenzyme Q10 (CQ10) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Hansen et al. *(22)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 84 days of acute COVID-19). 59 assigned to coenzyme Q10 500 mg a day for 6 weeks and 60 assigned to standard of care.	Median age 49, male 25.2%, obesity 33.6%, interval between COVID-19 and enrolment 288.55 days, hospitalization during COVID-19 15.1%	NR	Low risk of bias	**HRQL improvement:** Very low certainty ⨁◯◯◯ **Overall symptom improvement:** Very low certainty ⨁◯◯◯ **Fatigue improvement:** No information **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Cognitive behavioral therapy **Cognitive behavioral therapy may increase fatigue improvement and functional capacity improvement. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Kuut et al. *(23);* Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 84 days of acute COVID-19). 57 assigned to Cognitive behavioral therapy for 17 weeks and 57 assigned to standard of care.	Mean age 46, male 27%, interval between COVID-19 and enrolment 188 days, hospitalization during COVID-19 11.5%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** RR 2.2 (95% CI 1.35 to 3.58); RD 31.6% (95% CI 9.2% to 68%); Low certainty ⨁⨁◯◯ **Functional capacity improvement:** RR 1.37 (95% CI 1.08 to 1.73); RD 22.4% (95% CI 4.8% to 44.7%); Low certainty ⨁⨁◯◯ **Strength improvement:** No information **Adverse events:** No information **Severe adverse**

					events: No information
Creatine **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Slankamenac et al *(24)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 0 to 84 days of acute COVID-19). 6 assigned to Creatine 4 gr a day for 6 months and 6 assigned to standard of care.	Mean age 27.5, male 50%	NR	High risk of bias Notes: Concealment of allocation and blinding probably inapropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⨁◯◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Cytoflavin **Cytoflavin may not improve fatigue. However, certainty of the evidence was low. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
CITADEL trial *(25)*, Putilina et al.; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 30 to 90 days of acute COVID-19). 50 assigned to cytoflavin 2 tablets a day for 25 days and 50 assigned to standard of care.	Mean age 40.4 ± 12, male 57%, hypertension 38%, diabetes 4%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** RR 1.02 (95% CI 0.98 to 1.06); RD 2.1% (95% CI –1.9% to 6.2%); Low certainty ⨁⨁◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Echinochrome A

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
Brichetti et al *(26)* Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 84 days of acute COVID-19). 24 assigned to Echinochrome A and 22 assigned to standard of care.	Age between 18 and 60, male 40%,	NR	Low risk of bias Notes:	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⨁◯◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Enzymes + probiotics

Enzymes + probiotics may improve fatigue. However, certainty of the evidence was low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					

Rathi et al. *(27)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after acute COVID-19). 100 assigned to enzymes + probiotics ImmunoSEB (500 mg/capsule) + ProbioSEB CSC3 (5 billion CFUs /capsule) and 100 assigned to standard of care.	Mean age 41.2 ± 13, male 63.5%, interval between COVID-19 and enrolment 19.5 days, one comorbidity 14.5%	NR	High risk of bias Notes: Concealment of allocation and blinding probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** RR 6.07 (95% CI 3.79 to 9.71); RD 76% (95% CI 41.8% to 85%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Fermented food supplements **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Kharaeva et al. *(28)*; Peer reviewed; 2022	Patients with P-ACC after moderate infection (asthenia or fatigue after acute COVID-19). 68 assigned to fermented food supplements 14 g	Age 38–69, male 51.5%, hypertension 36.1%, diabetes 15.5%, chronic lung disease 14.4%, obesity 19.6%, hospitalization during COVID-19 46.4%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** Very low certainty

	twice a day for 20 days and 29 assigned to standard of care.				⊕◯◯◯ **Fatigue improvement:** No information **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Kharaeva et al. *(28)*; Peer reviewed; 2022	Patients with P-ACC after severe infection (asthenia or fatigue after 0 days of acute COVID-19). 64 assigned to fermented food supplements 14 g twice a day for 20 days and 27 assigned to standard of care.	Age 36–65, male 47.2%, diabetes 28.6%, chronic lung disease 20.9%, asthma 3.3%, chronic heart disease 37.5%, obesity 40.6%, hospitalization during COVID-19 41.8%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Hydrogen (nasal)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					

Botek et al. *(29)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 21 to 35 days of acute COVID-19). 26 assigned to hydrogen (nasal) 300 mL/min for 14 days and 24 assigned to standard of care.	Mean age 40, male 52%, interval between COVID-19 and enrolment 25 days	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** Very low certainty ⊕◯◯◯ **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Immunodaat **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					

Deshpande trial *(30)*; Preprint; 2022	Patients with post COVID-19 condition. 26 assigned to Immunodaat 500 mg a day for 30 days and 28 assigned to standard of care.	Mean age 38.9, male 59.4%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** Very low certainty ⨁◯◯◯ **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⨁◯◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Leronlimab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Gaylis et al. *(31)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 90 days of acute COVID-19). 27 assigned to Leronlimab 700 mg a week for 8 weeks and 26 assigned to standard of care.	NR	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** Very low certainty ⨁◯◯◯ **Fatigue improvement:** No information

					Functional capacity improvement: No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Mindfulness training **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Hausswirth et al *(32);* Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 90 days of acute COVID-19). 17 assigned to a mindfulness based intervention (Rebalance®) 2 to 3 sessions (30 min) a week for 4 weeks and 17 assigned to standard of care.	Mean age 47.9, male 26.5%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⨁◯◯◯ **Functional capacity improvement:** No information **Strength**

					improvement: No information **Adverse events:** No information **Severe adverse events:** No information
Physical training **Physical training may improve HRQL, strength and functional capacity. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Nambi et al. *(33)*; Peer reviewed; 2022	Patients with P-ACC (sarcopenia after acute COVID-19). 36 assigned to aerobic training (high intensity) and 37 assigned to aerobic training (standard intensity).	Mean age 63.5, male 100%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** RR 1.62 (95% CI 1.07 to 2.45); RD 21.1% (95% CI 2.4% to 49.2%); Low certainty ⊕⊕◯◯ **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** RR 1.81 (95% CI 1.23 to 2.65); RD 17.4% (95% CI 4.9% to 35.4%); Low certainty ⊕⊕◯◯ **Strength improvement:** RR 3.13 (95% CI 1.02 to 9.55); RD 11.3% (95% CI
Rodriguez-Blanco et al. *(34)* Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 40 days of acute COVID-19). 24 assigned to endurance training rehabilitation (ETR) (10 breathing and strength-based exercises) for 14 days, and 24 assigned to standard of care.	Mean age 40.7, male 22.91%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
RECOVE trial *(35)* Jimeno-Almazán et al; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 84 days of acute COVID-19). 43 assigned to physical training 3 days a week for 8	Mean age 45.3 ± 8, male 31%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

	weeks and 20 assigned to standard of care.				0.1% to 45.4%); Low certainty ⊕⊕◯◯ **Adverse events:** No information **Severe adverse events:** No information
Ibrahim et al. *(36)* Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after acute COVID-19). 24 assigned to physical training 4 times a week for 10 weeks and 24 assigned to standard of care.	Mean age 63, male 39.6%, diabetes 81.2%, chronic lung disease 66.6%, CHD 83.3%, cancer 12.5%,	NR	High risk of bias Notes: Concealment of allocation and blinding probably inappropriate.	
Rasmussen et al *(37)* Peer reviewed; 2022	Patients with post COVID-19 condition. 14 assigned to Aerobic training (high intensity) three time a week for 12 weeks and 14 assigned to standard of care.	Mean age 57.3 ± 10, male 67.9%, interval between COVID-19 and enrolment 42 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	
Oliveira et al;*(38)* Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after acute COVID-19). 31 assigned to physical training 60-minutes, twice-weekly for 12 weeks and 28 assigned to standard of care.	Mean age 52.3 ± 11.9, male 42.4%, hypertension 44.1%, diabetes 10.6%, CHD 13.6%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Ogonowska-Slodownik et al *(39)*; Peer reviewed; 2022	Pediatric patients with post COVID-19 condition (asthenia or fatigue after acute COVID-19). 48 assigned to Physical training twice a week, 45 minutes for 8 weeks and 26 assigned to standard of care.	Mean age 10.8, male 41.9%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	

Espinoza-Bravo et al *(40)*; Preprint; 2022	Patients with post COVID-19 condition (asthenia or fatigue after acute COVID-19). 21 assigned to functional training 5 times a week for 4 weeks and 22 assigned to aerobic training 5 times a week for 4 weeks.	Mean age 42.4, male 21%,	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** Very low certainty ⊕◯◯◯ **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Phytochemicals

Phytochemicals may improve fatigue and HRQL. However, certainty of the evidence was low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
UK Phyto-V trial *(41)* Thomas et al; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after acute COVID-19). 74 assigned to phytochemicals one capsule a day	Mean age 53, male 56%, obesity 35%, interval between COVID-19 and enrolment 108 days, hospitalization during COVID-19 63%	NR	High risk of bias Notes: Concealment of allocation and blinding probably inappropriate.	**HRQL improvement:** RR 1.33 (95% CI 1.03 to 1.71); RD 18% (95% CI 1.8% to 39%); Low certainty ⊕⊕◯◯

	and 73 assigned to standard of care.				**Overall symptom improvement:** No information **Fatigue improvement:** RR 1.24 (95% CI 0.95 to 1.62); RD 13.1% (95% CI -2.5% to 33.5%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Probiotics **Probiotics probably improve fatigue. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Caprioli et al *(42)* Preprint; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 28 days of acute COVID-19). 19 assigned to VSL#3 2 sachets twice a day for 4 weeks and 19 assigned to standard of care.	Mean age 54.1 ± 7.9, male 52.6%, interval between COVID-19 and enrolment 756 days, hospitalization during COVID-19 57.9%	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** RR 1.53 (95% CI

RECOVERY trial *(43)*; Lau et al; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 28 days of acute COVID-19). 196 assigned to Probiotics Two sachets a day for 6 months and 202 assigned to standard of care.	Mean age 49.4, male 34.6%, hypertension 14.3%, diabetes 8.6%, asthma 1.3%, CHD 5%, CKD 1.9%, interval between COVID-19 and enrolment 112 days, hospitalization during COVID-19 14.3%	Vaccinated 69.1%	High risk of bias Notes: Significant loss to follow-up	1.23 to 1.89); RD –20.2% (95% CI 8.8% to 33.9%); Moderate certainty ⨁⨁⨁◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Severe adverse events:** No information
Transcranial direct current stimulation (tDCS) **tDCS may improve fatigue and HRQL, and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Oliver-Mas et al. *(44)*; Preprint; 2022	Patients with P-ACC (asthenia or fatigue after 180 days of acute COVID-19). 23 assigned to transcranial direct current stimulation (tDCS) 1 session a week for 8 weeks and 24 assigned to standard of care.	Mean age 45.6, male 21.3%, hypertension 12.8%, diabetes 4.3%, interval between COVID-19 and enrolment 620 days, hospitalization during COVID-19 14.9%	NR	Low risk of bias	**HRQL improvement:** RR 1.37 (95% CI 1.09 to 1.71); RD –26% (95% CI –6.7% to 30%); Low certainty ⨁⨁◯◯ **Overall symptom improvement:** No information
Santana et al *(45);* Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 90 days of acute COVID-19). 35 assigned to	Mean age 53, male 35.7%, hypertension 17.1%, diabetes 14.3%, chronic lung disease 5.7%, CHD 7.1%, , hospitalization during	NR	Low risk of bias	**Fatigue improvement:** RR 1.36 (95% CI 0.76 to 2.45); RD –16.9% (95% CI –11.2% to 53%); Low certainty ⨁⨁◯◯

	transcranial direct current stimulation (tDCS) 10 sessions and 35 assigned to standard of care.	COVID-19 25.7%			**Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** RR 0.83 (95% CI 0.26 to 2.73); RD –3.4% (95% CI –15.5% to 36%); Low certainty ⊕⊕◯◯) **Severe adverse events:** No information
Telerehabilitation **Telerehabilitation may improve fatigue and functional capacity. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
King et al. *(46)*; Preprint; 2022	Patients with P-ACC (asthenia or fatigue after 110 days of acute COVID-19). 11 assigned to telerehabilitation twice weekly for 10 weeks and 10 assigned to standard of care.	Mean age 48.5 ± 13, male 47.6%, interval between COVID-19 and enrolment 366 days, hospitalization during COVID-19 19%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** Very low certainty ⊕◯◯◯ **Overall symptom improvement:** No information **Fatigue improvement:** RR 1.63 (95% CI 1.04 to 2.54); RD 19.1% (95% CI 1.2% to 46.8%); Low certainty ⊕⊕◯◯ **Functional capacity**
Simpson et al *(47)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 14 days of acute COVID-19). 15 assigned to telerehabilitation 45 to 60 min sessions,	Mean age 58 ± 12, male 58%, interval between COVID-19 and enrolment 14 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

	twice a week for 4 weeks and 12 assigned to standard of care.				**improvement:** RR 1.47 (95% CI 1.19 to 1.82); RD 20.7% (95% CI 8.4% to 36.2%); Low certainty ⊕⊕◯◯ **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Longobardi et al. *(48);* Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 84 days of acute COVID-19). 21 assigned to home physical training 3 times a week for 16 weeks and 20 assigned to standard of care.	Mean age 61, male 50%, hypertension 56%, diabetes 36%, chronic lung disease 16%, CHD 20%, obesity 28%, interval between COVID-19 and enrolment 159 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	
Samper-Pardo et al. *(49)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 84 days of acute COVID-19). 52 assigned to Telerehabilitation through specificaly designed app for 12 weeks and 48 assigned to standard of care.	Mean age 48.3 ± 9.26, male 20%, hypertension %, diabetes %, chronic lung disease %, asthma %, CHD %, CKD %, cancer %, obesity %, interval between COVID-19 and enrolment days, hospitalization during COVID-19 %	Corticosteroids %, remdesivir %, hydroxychloroquine %, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma %; Vaccinated %	High risk of bias Notes: Non-blinded study which might have introduced bias.	
Da Silva et al. *(50)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after acute COVID-19). 28 assigned to Telerehabilitation three time a week for 8 weeks and 29 assigned to standard of care.	Mean age 55 ± 11, male 56%, diabetes 42%, chronic lung disease 16%, CHD 65%, obesity 60%	NR	Low risk of bias	
Alsharidah et al *(51)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 0 days of acute COVID-19). 24 assigned to Telerehabilitation 3 times a week for 6 weeks and 24 assigned to	Mean age 23, male 0%,	NR	High risk of bias Notes: Concealment of allocation and blinding probably inapropriate.	

	standard of care.				
Tanhan et al. *(52)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 0 days of acute COVID-19). 16 assigned to synchronous telerehabilitation three day a week and 16 assigned to asynchronous telerehabilitation	Mean age 54, male 46.9%, interval between COVID-19 and enrolment 49 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** Very low certainty ⊕◯◯◯ **Overall symptom improvement:** No information **Fatigue improvement:** No information **Functional capacity improvement:** Very low certainty ⊕◯◯◯ **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Table 3. Description of included studies and interventions effects for P-ACC-related dyspnea.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
ADAPT-232 (adaptogens) **ADAPT-232 may not improve fatigue. However, certainty of the evidence was low. Further research is needed.**					
RCT					
Karosanidze et al. *(16)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 30 days of acute COVID-19). 49 assigned to ADAPT-232 (adaptogens) 60 mL a day for 14 days and 50 assigned to standard of care.	Mean age 48.9, male 14%	NR	Low risk of bias	**HRQL improvement:** No information **Dyspnea improvement:** RR 1 (95% CI 0.94 to 1.06); RD 0% (95% CI –5.4% to 5.6%); Low certainty ⨁⨁◯◯ **Functional capacity improvement:** No information **Pulmonary function improvement:** No information **Radiological response:** No information **Adverse events:** No information **Severe adverse events:** No information
Albumin (inhaled) **Uncertainty in potential benefits and harms. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
Ampio trial; Other; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 28 days of acute COVID-19). 15 assigned to albumin (inhaled) and 16 assigned to standard of care.	Mean age 52.1 ± 13, male 43.8%	NR	High risk of bias Notes: Concealment of allocation and blinding probably inapropriate.	**HRQL improvement:** No information **Dyspnea improvement:** No information **Functional capacity improvement:** No information **Pulmonary function improvement:** No information **Radiological response:** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Severe adverse events:** No information

Antifibrotics

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					

Kerget et al *(53)*; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 84 days of acute COVID-19). 15 assigned to pirfenidone 600 to 1800 mg a day for 3 months and 15 assigned to nintendanib 300 mg a day for 3 months	Mean age 65.6, male 40%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Dyspnea improvement:** No information **Functional capacity improvement:** Very low certainty ⊕◯◯◯ **Pulmonary function improvement:** No information **Radiological response:** No information **Adverse events:** No information **Severe adverse events:** No
Diaphragm release **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Nagy et al; *(54)*; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities acute COVID-19). 26 assigned to diaphragm release three sessions a week for 6 weeks and 26 assigned to standard of care.	Mean age 40	NR	High risk of bias Notes: Concealment of allocation and blinding probably inapropriate.	**HRQL improvement:** No information **Dyspnea improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** No information

					Pulmonary function improvement: No information **Radiological response:** No information **Adverse events:** No information **Severe adverse events:** No information
Nebivolol **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Dal Negro et al *(55)*; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 84 days of acute COVID-19). 8 assigned to Nebivolol 2.5 mg a day and 8 assigned to standard of care.	Mean age 50.5 ± 17.2, male 63%	NR	High risk of bias Notes: Concealment of allocation and blinding probably inappropriate.	**HRQL improvement:** No information **Dyspnea improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** No information **Pulmonary function improvement:** No information **Radiological response:** No information **Adverse events:** No information **Severe adverse**

					events: No
Probiotics **Probiotics may improve dyspnea. However certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
RECOVERY trial *(43)*; Lau et al; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 28 days of acute COVID-19). 196 assigned to Probiotics Two sachets a day for 6 months and 202 assigned to standard of care.	Mean age 49.4, male 34.6%, hypertension 14.3%, diabetes 8.6%, asthma 1.3%, CHD 5%, CKD 1.9%, interval between COVID-19 and enrolment 112 days, hospitalization during COVID-19 14.3%	Vaccinated 69.1%	High risk of bias Notes: Significant loss to follow-up	**HRQL improvement:** No information **Dyspnea improvement:** RR 1.28 (95% CI 1.05 to 1.54); RD 14.8% (95% CI 2.9% to 29.1%); Moderate certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Pulmonary function improvement:** No information **Radiological response:** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Severe adverse events:** No
Respiratory training/rehabilitation **Respiratory training probably improves HRQL, dyspnea and functional capacity**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
ENO Breathe trial *(56)*, Philip et al.; Peer reviewed; 2022	Patients with P-ACC (dyspnea and/or lung radiological abnormalities after 30 days of acute COVID-19). 58 assigned to ENO Breathe 6-week program and 71 assigned to standard of care.	Mean age 49.5 ± 12, male 17.3%, interval between COVID-19 and enrolment 320 days, hospitalization during COVID-19 17.3%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** RR 1.41 (95% CI 1.18 to 1.67); RD 22.3% (95% CI 9.8% to 36.5%); Moderate certainty ⨁⨁⨁◯ **Dyspnea improvement:** RR 2.44 (95% CI 1.33 to 4.49); RD 41.4% (95% CI 9.5% to 71.3%); Moderate certainty ⨁⨁⨁◯ **Functional capacity improvement:** RR 1.34 (95% CI 1.11 to 1.62); RD 17.1% (95% CI 5.5% to 31.1%); Moderate certainty ⨁⨁⨁◯ **Pulmonary function improvement:** Very low certainty ⨁◯◯◯ **Radiological response:** No information
McNarry et al. *(57)*; Peer reviewed; 2022	Patients with P-ACC (dyspnea and/or lung radiological abnormalities after acute COVID-19). 37 assigned to inspiratory muscle training 3 sessions a week for 8 weeks and 37 assigned to standard of care.	Mean age 46.6 ± 12, male 12.8%, interval between COVID-19 and enrolment 270 days	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate. Intention-to-treat (ITT) analysis for primary outcome not available.	
Srinivasan et al. *(58)*; Peer reviewed; 2022	Patients with P-ACC (dyspnea and/or lung radiological abnormalities after acute COVID-19). 24 assigned to respiratory training 3 times a day for 6 weeks and 24 assigned to standard of care.	NR	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Rodriguez-Blanco et al; *(34)* Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 40 days of acute COVID-19). 24 assigned to respiratory training (10 breathing and strength-based exercises) for 14 days, and 24 assigned to standard of care.	Mean age 40.7, male 22.91%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Adverse events:** No information **Severe adverse events:** No
InsCOVID trial *(59)*; Palau et al; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 90 days of acute COVID-19). 13 assigned to inspiratory muscle training twice a day for 12 weeks and 13 assigned to standard of care.	Mean age 50.4 ± 12.2, male 58%, hypertension 12%, interval between COVID-19 and enrolment 362 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	
RECOVER trial. *(60)*, Romanet et al.; Preprint; 2022	Patients with P-ACC (dyspnea and/or lung radiological abnormalities after 90 days of acute COVID-19). 27 assigned to endurance training rehabilitation (ETR) two (1 h) sessions per week for 10 weeks and 33 assigned to standard of care.	Mean age 58.2, male 61.6%, diabetes 36.7%, chronic lung disease 8.3%, chronic heart disease 5%, cancer 5%, interval between COVID-19 and enrolment 173 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
RECOVE trial *(35)*; Jimeno-Almazán et al; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 84 days of acute COVID-19). 40 assigned to respiratory training	Mean age 45.3 ± 8, male 31%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

	twice a day for 8 weeks and 20 assigned to standard of care.				
Del Corral et al *(61)* Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 84 days of acute COVID-19). 44 assigned to Respiratory training home-based, 40 minutes a day, 6 days a week for 8 weeks and 44 assigned to standard of care.	Mean age 46.4, male 28.5%, interval between COVID-19 and enrolment 350.7 days, hospitalization during COVID-19 31.8%	Corticosteroids 5.7%	Low risk of bias	
Nambi et al *(62)* Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 28 days of acute COVID-19). 68 assigned to Home pulmonary rehabilitation four time a week for 8 weeks and 68 assigned to standard of care.	Mean age 48, male 47.8%, hypertension 30.1%, chronic lung disease 5.9%, CHD 8%, obesity 15.4%,	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	
TERECO trial *(63)*; Li et al; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 0 days of acute COVID-19). 55 assigned to home pulmonary rehabilitation 3 to 4 sessions a week for	Mean age 50.6 ± 10.98, male 44.5%, hypertension 21.9%, diabetes 13.6%, chronic lung disease 5.9%, CHD 7.6%, obesity 15.3%, interval between COVID-19 and enrolment 71 days, hospitalization during COVID-19 100%	NR	Low risk of bias Notes:	

	6 weeks and 50 assigned to standard of care.				
Mirenayat et al *(64)*; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 7 days of acute COVID-19). 26 assigned to Respiratory training Twice a day for 4 weeks and 26 assigned to standard of care.	Mean age 50.02, male 55.7%,	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Senén trial *(65)*; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 84 days of acute COVID-19). 18 assigned to Respiratory training 2 daily sessions, 6 days a week for 8 weeks and 19 assigned to standard of care.	Mean age 47 ± 7.1, male 27%, hypertension 14%, diabetes 0%, chronic lung disease 8%, CKD 0%, interval between COVID-19 and enrolment 359 days	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Hashemi et al *(66)*; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after COVID-19). 35 assigned to Home pulmonary rehabilitation two sessions a day, 3 to 4 times a week for 4 weeks and 35 assigned to	Median age 43.5, male 45.3%, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

	standard of care.				
Vallier et al; *(67)* Peer reviewed; 2022	Patients with P-ACC (dyspnea and/or lung radiological abnormalities after acute COVID-19). 8 assigned to home pulmonary rehabilitation four times a week for 4 weeks and 9 assigned to inpatient rehabilitation four times a week for 4 weeks	Mean age 54.8 ± 16, male 70.6%, interval between COVID-19 and enrolment 141 days, hospitalization during COVID-19 76.5%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** Very low certainty ⊕◯◯◯ **Dyspnea improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** Very low certainty ⊕◯◯◯ **Pulmonary function improvement:** No information **Radiological response:** No information **Adverse events:** No information **Severe adverse events:** No information
Simpson et al *(47)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 14 days of acute COVID-19). 15 assigned to telerehabilitation 45 to 60 min sessions, twice a week for 4 weeks and 12 assigned to standard of care.	Mean age 58 ± 12, male 58%, interval between COVID-19 and enrolment 14 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Rutkowski et al *(68)*; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after of acute COVID-19). 18 assigned to VR respiratory training five sessions a week for 3 weeks and 14	Mean age 57.8 ± 4.9, male 37.5%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** No information **Dyspnea improvement:** Very low certainty ⊕◯◯◯ **Functional capacity**

	assigned to conventional respiratory training.				**improvement:** Very low certainty ⊕◯◯◯ **Pulmonary function improvement:** No information **Radiological response:** No information **Adverse events:** No information **Severe adverse events:** No information
Stavrou et al *(69)*; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 60 days of acute COVID-19). 10 assigned to VR respiratory training and 10 assigned to standard of care.	Mean age 53.9, male 80%, interval between COVID-19 and enrolment 60 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Kusumawardani et al *(70)*; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after acute COVID-19). 10 assigned to incentive spirometry 5 times a day for four weeks and 10 assigned to conventional respiratory training.	Mean age 46, male 65%, hypertension 5%, diabetes 5%, obesity 55%, interval between COVID-19 and enrolment 22.5 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Dyspnea improvement:** No information **Functional capacity improvement:** No information **Pulmonary function improvement:** Very low certainty ⊕◯◯◯ **Radiological response:** No information **Adverse events:** No information **Severe adverse events:** No information

Steroids (high dose)

High dose steroids may not improve dyspnea and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
COLDSTER trial *(71)*; Dhooria et al; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 21 to 49 days of acute COVID-19). 65 assigned to High dose steroids Prednisone 40 mg a day descending progressively to 10 mg a day for 6 weeks and 65 assigned to standard of care.	Mean age 57, male 68%, one commorbiditie 73%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** No information **Dyspnea improvement:** RR 1 (95% CI 0.87 to 1.15); RD 0% (95% CI –11.1% to 12.7%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Pulmonary function improvement:** No information **Radiological response:** Very low certainty ⊕◯◯◯ **Adverse events:** RR 0.92 (95% CI 0.75 to 1.13); RD –6.2% (95% CI –19.3% to 10%); Low certainty ⊕⊕◯◯ **Severe adverse events:** Very low certainty ⊕◯◯◯

Treamid

Treamid may improve dyspnea and pulmonary function, but may not improve functional capacity. Treamid may increase adverse events. However, certainty of the evidence was low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
Bazdyrev et al. *(72)*; Peer reviewed; 2022	Patients with P-ACC (dyspnea and/or lung radiological abnormalities after acute COVID-19). 29 assigned to treamid 50 mg a day for 28 days and 30 assigned to standard of care.	Mean age 55 ± 11, male 44.1%	NR	Low risk of bias	**HRQL improvement:** No information **Dyspnea improvement:** RR 1.96 (95% CI 0.9 to 4.25); RD 21.7% (95% CI –2.3% to 73.7%); Low certainty ⨁⨁◯◯ **Functional capacity improvement:** RR 1.10 (95% CI 0.64 to 1.90); RD 4.3% (95% CI –16.2% to 39.8%); Low certainty ⨁⨁◯◯ **Pulmonary function improvement:** RR 2.48 (95% CI 1 to 6.17); RD 24.7% (95% CI 0% to 86.1%); Low certainty ⨁⨁◯◯ **Radiological response:** Very low certainty ⨁◯◯◯ **Adverse events:** RR 1.19 (95% CI 0.56 to 2.50); RD –5.5% (95% CI –12.7% to 43.6%); Low certainty ⨁⨁◯◯ **Severe adverse events:** No

					information

Table 4. Description of included studies and interventions effects for PCC neurocognitive symptoms or sleep disturbances

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
Actovegin **Actovegin may improve cognition. However, certainty of the evidence was low. Further research is needed.**					
RCT					
Kutashov et al *(15)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after NR days of acute COVID-19). 222 assigned to Actovegin 1200 mg a day for 60 days and 222 assigned to standard of care.	Mean age 67.6, male 31.98%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Cognitive improvement:** RR 1.19 (95% CI 1.06 to 1.33); RD 12.7% (95% CI 4.2% to 22.3%); Low certainty ⊕⊕◯◯ **Depression improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Celecoxib **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					

Ansari trial *(73)*; Peer reviewed; 2022	Patients with post COVID-19 condition (depression after 20 days of acute COVID-19). 31 assigned to celecoxib 200 mg a day for 6 weeks and 31 assigned to standard of care.	Mean age 27.8, male 61%, hypertension 11.3%, interval between COVID-19 and enrolment 87.5 days,	Corticosteroids 25.8%, remdesivir 11.3%,	High risk of bias Notes: Concealment of allocation and blinding probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Cognitive improvement:** No information **Depression improvement:** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Severe adverse events:** No information
Donepezil **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Pooladgar et al *(74)*; Peer reviewed; 2022	Patients with post COVID-19 condition (neurocognitive symptoms after 30 days of acute COVID-19). 10 assigned to Donepezil 5 mg for 12 weeks and 15 assigned to standard of care.	Mean age 44.5, male 36%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Cognitive improvement:** Very low certainty ⊕◯◯◯ **Depression improvement:** No information **Adverse events:**

					No information **Severe adverse events:** No information
Electric stimulation **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Zulbaran-Rojas et al *(75)*; Peer reviewed; 2022	Patients with post COVID-19 condition (neurocognitive after acute COVID-19). 10 assigned to Electrical stimulation and 8 assigned to standard of care.	Mean age 51.7, male 27.8%, hypertension 44.4%, diabetes 33.3%, interval between COVID-19 and enrolment 299 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Cognitive improvement:** No information **Depression improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Famotidine **Famotidine may improve cognition. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					

Momtazmanesh et al *(76);* Peer reviewed; 2022	Patients with post COVID-19 condition (neurocognitive after 20 days of acute COVID-19). 25 assigned to famotidine 80 mg a day and 25 assigned to standard of care.	Mean age 36.3, male 54%, hypertension 12%, diabetes 4%, CHD 2%, cancer 8%, obesity 22%, interval between COVID-19 and enrolment 29 days, hospitalization during COVID-19 100%	Corticosteroids 16%, remdesivir 84%	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Cognitive improvement:** RR 1.33 (95% CI 1.05 to 1.69); RD 24.6% (95% CI 3.7% to 51.1%); Low certainty ⊕⊕◯◯ **Depression improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Hyperbaric oxygen (HBO) **HBO may improve HRQL. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					

Zilberman-Itskovich et al. *(77)*; Peer reviewed; 2022	Patients with P-ACC (neurocognitive symptoms after 90 days of acute COVID-19). 37 assigned to HBO 1 session a day for 40 days and 36 assigned to standard of care.	Mean age 48, male 39.7%, hypertension 8.2%, diabetes 2.7%, chronic lung disease 0%, asthma 4.1%, cancer 0%, obesity 27.4%, interval between COVID-19 and enrolment 165 days, hospitalization during COVID-19 16.4%	NR	Low risk of bias	**HRQL improvement:** RR 1.30 (95% CI 0.84 to 2); RD 13.9% (95% CI –7.4% to 46.9%); Low certainty ⨁⨁◯◯ **Overall symptom improvement:** No information **Cognitive improvement:** Very low certainty ⨁◯◯◯ **Depression improvement:** Very low certainty ⨁◯◯◯ **Adverse events:** No information **Severe adverse events:** No information
Mindfulness training **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Hausswirth et al *(32)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 90 days of acute COVID-19). 17 assigned to a mindfulness based intervention (Rebalance®) 2 to	Mean age 47.9, male 26.5%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Cognitive improvement:** No

	3 sessions (30 min) a week for 4 weeks and 17 assigned to standard of care.				information **Depression improvement:** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Severe adverse events:** No information
Palmitoylethanolamide + luteolin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Versace et al *(78);* Peer reviewed; 2022	Patients with post COVID-19 condition (neurocognitive after acute COVID-19). 17 assigned to Palmitoylethanolamide + Luteolin 1400/400mg a day for 8 weeks and 17 assigned to standard of care.	Mean age 50.8, male 35.3%	NR	High risk of bias Notes: pseudo-randomized	**HRQL improvement:** No information **Overall symptom improvement:** No information **Cognitive improvement:** Very low certainty ⊕◯◯◯ **Depression improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Physical training

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
Kalayeh et al *(79)*; Preprint; 2022	Patients with post COVID-19 condition (sleep disturbances after 84 days of acute COVID-19). 17 assigned to endurance training rehabilitation (ETR) Three times a week for eight weeks and 15 assigned to standard of care.	Mean age 25, male 100%, interval between COVID-19 and enrolment 165 days,	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** Very low certainty ⨁◯◯◯ **Overall symptom improvement:** No information **Cognitive improvement:** No information **Depression improvement:** No information **Sleep quality improvement:** Very low certainty ⨁◯◯◯ **Adverse events:** No information **Severe adverse events:** No information

Probiotics

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					

RECOVERY trial *(43)*; Lau et al; Peer reviewed; 2022	Patients with post COVID-19 condition (neurocognitive symptoms after 28 days of acute COVID-19). 196 assigned to Probiotics Two sachets a day for 6 months and 202 assigned to standard of care.	Mean age 49.4, male 34.6%, hypertension 14.3%, diabetes 8.6%, asthma 1.3%, CHD 5%, CKD 1.9%, interval between COVID-19 and enrolment 112 days, hospitalization during COVID-19 14.3%	Vaccinated 69.1%	High risk of bias Notes: Significant loss to follow-up	**HRQL improvement:** No information **Overall symptom improvement:** No information **Cognitive improvement:** RR 1.56 (95% CI 1.17 to 2.09); RD 15.1% (95% CI 4.5% to 29.2%); Low certainty ⊕⊕◯◯ **Depression improvement:** No information **Sleep quality improvement:** RR 1.32 (95% CI 1.05 to 1.65); RD 27% (95% CI 8.6% to 17.5%) **Adverse events:** Very low certainty ⊕◯◯◯ **Severe adverse events:** No information
Transcutaneous auricular vagus nerve stimulation (taVNS) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Badran et al. *(80)*; Preprint; 2022	Patients with P-ACC (neurocognitive symptoms after acute COVID-19). 6 assigned to transcutaneous	Mean age 48.5 ± 11.3, male 33.3%	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information

	auricular vagus nerve stimulation (taVNS) 2 (1 h) sessions a day for 4 weeks and 6 assigned to standard of care.				**Cognitive improvement:** No information **Depression improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Transcranial direct current stimulation (tDCS) **tDCS may not improve fatigue and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Oliver-Mas et al. *(44)*; Preprint; 2022	Patients with P-ACC (asthenia or fatigue after 180 days of acute COVID-19). 23 assigned to transcranial direct current stimulation (tDCS) 1 session a week for 8 weeks and 24 assigned to standard of care.	Mean age 45.6, male 21.3%, hypertension 12.8%, diabetes 4.3%, interval between COVID-19 and enrolment 620 days, hospitalization during COVID-19 14.9%	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Cognitive improvement:** RR 0.59 (95% CI 0.33 to 1.05); RD –27.5% (95% CI –44.8% to 3.4%); Low certainty ⊕⊕◯◯ **Depression improvement:** No information **Adverse events:** No information **Severe adverse events:** No

					information
Vortioxetine **Vortioxetine probably improves HRQL and may improve depression but may not improve cognition. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
McIntyre et al *(81)*; Peer reviewed; 2022	Patients with post COVID-19 condition (neurocognitive symptoms after 84 days of acute COVID-19). 75 assigned to vortioxetine 5 to 20 mg a day for 8 weeks and 74 assigned to standard of care.	Mean age 44.3, male 34%,	NR	Low risk of bias	**HRQL improvement:** RR 1.35 (95% CI 1.03 to 1.77); RD 17% (95% CI 1.4% to 39%); Moderate certainty ⨁⨁⨁◯ **Overall symptom improvement:** No information **Cognitive improvement:** RR 0.97 (95% CI 0.74 to 1.28); RD –1.6% (95% CI –15.3% to 16.5%); Low certainty ⨁⨁◯◯ **Depression improvement:** RR 1.43 (95% CI 0.97 to 2.12); RD 14.8% (95% CI –1.1% to 38.3%); Low certainty ⨁⨁◯◯ **Adverse events:** Very low certainty ⨁◯◯◯ **Severe adverse**

					events: No information

Table 5. Description of included studies and interventions effects for PCC olfactory and/or gustatory dysfunction

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
ADAPT-232 (adaptogens) **ADAPT-232 may not improve olfactory symptoms. However, certainty of the evidence was low. Further research is needed.**					
RCT					
Karosanidze et al. *(16)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 30 days of acute COVID-19). 49 assigned to ADAPT-232 (adaptogens) 60 mL a day for 14 days and 50 assigned to standard of care.	Mean age 48.9, male 14%	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** RR 0.89 (95% CI 0.79 to 1.01); RD –10.3% (95% CI –20.5% to 1.4%); Low certainty ⊕⊕◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Alpha-lipoic acid **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					

Figueiredo et al *(82)*; Peer reviewed; 2022	Patients with post COVID-19 condition (Olfactory and/or gustatory dysfunction after 84 days of acute COVID-19). 49 assigned to Alpha-lipoic acid 600 mg a day for 12 weeks and 51 assigned to standard of care.	Mean age 39, male 18%,	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** Very low certainty ⨁◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Diode laser **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Shabaan et al;*(83)*; Peer reviewed; 2022	Patients with post COVID-19 condition (Olfactory and/or gustatory dysfunction after 28 days of acute COVID-19). 18 assigned to Diode laser 6-minute session and 18 assigned to standard of care.	Mean age 41.5, male 22.2%, hospitalization during COVID-19 22.2%	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** Very low certainty ⨁◯◯◯ **Gustatory symptoms improvement:** No information

					Adverse events: No information **Severe adverse events:** No information
EDTA (Ethylene Diamine Tetra Acetic Acid) **The effects of gabapentin fatty acids are uncertain. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Abdelazim et al *(84)*; Peer reviewed; 2022	Patients with post COVID-19 condition (olfactory and/or gustatory dysfunction after 168 days of acute COVID-19). 25 assigned to EDTA 0.1 ml for 3 months and 25 assigned to standard of care.	Mean age 40.5, male 38%, hypertension 16%, diabetes 22%, asthma 6%, enrolment 180 days, hospitalization during COVID-19 %	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** Very low certainty ⊕◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Gabapentin **The effects of gabapentin fatty acids are uncertain. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**

RCT					
GRACE trial *(85)*; Mahadev et al; Peer reviewed; 2022	Patients with post COVID-19 condition (olfactory and/or gustatory dysfunction after 84 days of acute COVID-19). 18 assigned to gabapentin 900 to 3600 mg a day for 4 weeks and 26 assigned to standard of care.	Mean age 43, male 25%	NR	High risk of bias Notes: Significant lost to follow-up	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** Very low certainty ⊕◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Olfactory training

Olfactory training may improve olfactory symptoms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
Di Stadio et al. *(86)*; Peer reviewed; 2022	Patients with P-ACC (olfactory and/or gustatory dysfunction after 180 days of acute COVID-19). 76 assigned to olfactory training and 88 assigned to standard of care.	Mean age 40.7, male 27.6%, hypertension 1.7%, diabetes 0%, chronic heart disease 5.2%	Steroids 44%, vitamins 20.7%, alpha lipoic/nicetile 26.7%	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms**

Pires et al. *(87)*; Preprint; 2022	Patients with P-ACC (olfactory and/or gustatory dysfunction after 30 days of acute COVID-19). 26 assigned to advanced olfactory training with 8 essential oils: rose, eucalyptus, clove and lemon, citronella, mint, vanilla and cedarwood and 54 assigned to standard of care.	Mean age 37.6, male 35%	Steroids (nasal) 23.8%	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**improvement:** Very low certainty ⊕◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
COVANOS trial *(88)*, Lechner et al; Peer reviewed; 2022	Patients with P-ACC (olfactory and/or gustatory dysfunction after 30 days of acute COVID-19). 25 assigned to olfactory training for 12 weeks and 26 assigned to standard of care.	Mean age 44, male 13.8%, hypertension 8.9%, diabetes 1.1%, chronic lung disease 0%, asthma 12.6%, chronic heart disease 0%, cancer 2.1%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	
Chung et al. *(89);* Peer reviewed; 2022	Patients with post COVID-19 condition (Olfatory or gustatory disfunction after 84days of acute COVID-19). 8 assigned to olfactory training thrice daily for 4 weeks and 5 assigned to standard of care.	Mean age 52.5, male 30.7%, cancer 15.4%, interval between COVID-19 and enrolment 154 days,	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Omega-3 Fatty Acids

The effects of omega 3 fatty acids are uncertain. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					

Lerner et al *(90)* Peer reviewed; 2022	Patients with post COVID-19 condition (Olfactory and/or gustatory dysfunction after acute COVID-19). 57 assigned to Omega 3 2000 mg a day and 60 assigned to standard of care.	Mean age 41, male 21.4%	Corticosteroids 6.6%	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** Very low certainty ⊕◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Palmitoylethanolamide + Luteolin

Palmitoylethanolamide + Luteolin may improve olfactory symptoms. However, certainty of the evidence was low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
Di Stadio et al; *(86)* Peer reviewed; 2023	Patients with post COVID-19 condition (Olfactory and/or gustatory dysfunction after 180 days of acute COVID-19). 94 assigned to Palmitoylethanolamide + Luteolin 700/70 mg a day and 36 assigned to standard of care.	Mean age 40.4 ± , male 46.2%, hypertension 2.3%, diabetes 0%	NR	High risk of bias Notes: Concealment of allocation and blinding probably inapropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** RR 3.11 (95% CI 1.47 to 6.66); RD 35.5% (95% CI 7.8% to 83.3%); Low certainty ⊕⊕◯◯

					Gustatory symptoms improvement: No information **Adverse events:** No information **Severe adverse events:** No information
Pentasodium diethylenetriamine pentaacetate (DTPA) **The effects of DTPA are uncertain. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Imam et al;*(91);* Peer reviewed; 2022	Patients with post COVID-19 condition (Olfactory and/or gustatory dysfunction after 0 days of acute COVID-19). 33 assigned to DTPA 2% nasal spray, three times a day for one month and 33 assigned to standard of care.	Mean age 39.4, male 42.4%, hypertension 22.7%, diabetes 22.7%, asthma 7.6%, interval between COVID-19 and enrolment 97 days,	Corticosteroids 27.3%	High risk of bias Notes: Concealment of allocation and blinding probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** Very low certainty ⊕◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Platelet-rich plasma

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
Evman et al *(92)*; Peer reviewed; 2022	Patients with post COVID-19 condition (Olfactory and/or gustatory dysfunction after 365 days of acute COVID-19). 12 assigned to Platelet-rich plasma 1 ml once and 13 assigned to standard of care.	Mean age 32.6, male 48%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** Very low certainty ⊕◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** Very low certainty ⊕◯◯◯

Steroids (nasal)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					

RC 4-7-2020 trial *(93)*, Abdelalim et al.; Peer reviewed; 2022	Patients with P-ACC (olfactory and/or gustatory dysfunction after acute COVID-19). 50 assigned to Mometasone 2 puffs (100 µg) once daily in each nostril for 3 weeks and 50 assigned to standard of care.	Mean age 29, male 46%, hypertension 14%, diabetes 16%, hospitalization during COVID-19 31%	Steroids 13%	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** Very low certainty ⊕◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** Very low certainty ⊕◯◯◯
Hautefort et al *(94)*; Peer reviewed; 2022	Patients with post COVID-19 condition (Olfactory and/or gustatory dysfunction after 30 days of acute COVID-19). 62 assigned to budesonide 2 mg a day for 30 days and 61 assigned to standard of care.	Mean age 40.3, male 32.5%, hypertension %, diabetes 1.6%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	

Steroids

Steroids may not improve olfactory nor gustatory symptoms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
Vaira et al *(95)*; Peer reviewed; 2022	Patients with P-ACC (olfactory and/or gustatory dysfunction after acute COVID-19). 9 assigned to prednisone 1 mg/kg a day and 9 assigned to standard of care.	Mean age 42.1, male 38.8%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** RR 1.09 (95% CI 0.83 to 1.44); RD 3.3% (95% CI –6.2% to 16.1%); Low certainty
Schepens et al *(96)*; Peer reviewed; 2022	Patients with post COVID-19 condition (Olfactory and/or gustatory dysfunction after 28	Median age 49, male 36.5%, interval between COVID-19 and enrolment 56 days	Vaccinated 79.1%	Low risk of bias	

	days of acute COVID-19). 57 assigned to Prednisone 40 mg a day for 10 days and 56 assigned to standard of care.				⊕⊕◯◯ **Gustatory symptoms improvement:** RR 1.01 (95% CI 0.67 to 1.53); RD 0.5% (95% CI –14.6% to 23.3%); Low certainty ⊕⊕◯◯ **Adverse events:** No information **Severe adverse events:** No information
Theophylline (nasal) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
SCENT2 trial *(97)*; Gupta et al; Peer reviewed; 2022	Patients with post COVID-19 condition (Olfactory and/or gustatory dysfunction after 90 days of acute COVID-19). 26 assigned to Theophylline (nasal) 400 mg twice a day for 6 weeks and 25 assigned to standard of care.	Mean age 44.7, male 29.4%, interval between COVID-19 and enrolment 387 days	NR	Low risk of bias	**HRQL improvement:** Very low certainty ⊕◯◯◯ **Overall symptom improvement:** No information **Olfactory symptoms improvement:** Very low certainty ⊕◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse**

					events: Very low certainty ⊕◯◯◯
Vitamin A **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Chung et al *(89);* Peer reviewed; 2022	Patients with post COVID-19 condition (Olfactory and/or gustatory dysfunction after 84 days of acute COVID-19). 9 assigned to Vitamin A 25000 IU for 14 days and 8 assigned to standard of care.	Mean age 42 ± 35.3, male %, hypertension 5.9%, diabetes 0%, cancer 0%,	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** Very low certainty ⊕◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Table 6. Description of included studies and interventions effects for PCC cardiovascular system symptoms

Hyperbaric oxygen Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Leitman et al. *(98)* Peer reviewed; 2022	Patients with post COVID-19 condition (cardiological symptoms after 60 days of acute COVID-19). 16 assigned to HBO five sessions per week for two months and 13 assigned to standard of care.	Mean age 47, male 41.7%, hypertension 10%, chronic lung disease 5%, CHD 1.7%, interval between COVID-19 and enrolment 158 days, hospitalization during COVID-19 13.3%	NR	High risk of bias Notes: Post-Hoc analysis based on a surrogate marker of cardiac function	**HRQL improvement:** No information **Overall symptom improvement:** No information **Cardiac function improvement:** Very low certainty ⊕◯◯◯ **Tachycardia improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Ivabradine Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					

Jadhav et al. *(99)*; Peer reviewed; 2022	Patients with P-ACC (cardiovascular symptoms after 0 to 14 days of acute COVID-19). 25 assigned to Ivabradine 5 to 10 mg and 25 assigned to standard of care.	Mean age 48.8 ± 7.66	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Tachycardia improvement:** Very low certainty ⨁◯◯◯ **Adverse events:** No information **Severe adverse events:** No information

Table 7. Description of included studies and interventions effects for PCC psychological distress

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
Eye-movement desensitisation and reprocessing (EMDR) **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
COVEMERALD trial *(100)*; Bates et al; Peer reviewed; 2022	Patients with post COVID-19 condition (psychological distress after 84 days of acute COVID-19). 11 assigned to EMDR up to eight 60 to 90 minutes sessions and 12 assigned to standard of care.	Mean age 58 ± 15.3, male 61.5%, CHD 15.4%, CKD 3.8%, cancer 3.8%, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** Very low certainty ⨁◯◯◯ **Depression improvement:** Very low certainty ⨁◯◯◯ **Post-traumatic stress improvement:** Very low certainty ⨁◯◯◯ **Psychological distress improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Virtual reality informational video **Virtual reality informational video may improve depression, post-traumatic stress, and psychological distress. However, certainty of the evidence was low. Further research is needed.**					
RCT					

ICU-VR trial *(101)*, Vlake et al.; Peer reviewed; 2022	Patients with P-ACC (psychological distress after 90 days of acute COVID-19). 45 assigned to virtual reality 14-minute informational video session once and 44 assigned to standard of care.	Mean age 60, male 36%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Depression improvement:** RR 1.21 (95% CI 0.95 to 1.54); RD 14% (95% CI –3.7% to 36.7%); Low certainty ⊕⊕◯◯ **Post-traumatic stress improvement:** RR 1.18 (95% CI 0.98 to 1.42); RD 13.8% (95% CI –1.5% to 32.3%); Low certainty ⊕⊕◯◯ **Psychological distress improvement:** RR 1.49 (95% CI 1.08 to 2.05); RD 25.5% (95% CI 4.1% to 55.1%); Low certainty ⊕⊕◯◯ **Adverse events:** No information **Severe adverse events:** No information

Table 8. Description of included studies and interventions effects for P-ACC-related thromboembolic risk

Anticoagulants (prophylactic dose) **Anticoagulants may not have an important effect on mortality, VTE, major bleeding and HRQL. However, certainty of the evidence was low because of imprecision. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and**

					GRADE certainty of the evidence
RCT					
MICHELLE trial *(102)*, Ramacciotti et al.; Peer reviewed; 2022	Patients with P-ACC (at increased risk of VTE after acute COVID-19). 159 assigned to rivaroxaban 10 mg a day for 35 days and 159 assigned to standard of care.	Mean age 57.1, male 60%, interval between COVID-19 and enrolment 8 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias to symptoms, VTE and adverse events outcomes.	**Mortality:** RR 0.85 (95% CI 0.38 to 0.88); RD -0.3% (95% CI –1.2% to 1.8%); Low certainty ⨁⨁◯◯ **HRQL improvement:** RR 0.99 (95% CI 0.78 to 1.24); Low certainty ⨁⨁◯◯ **VTE (symptomatic):** RR 1 (95% CI 0.29 to 3.45); RD 0% (95% CI –2.3% to 7.9%); Low certainty ⨁⨁◯◯ **Major bleeding:** RR 2.01 (95% CI 0.18 to 22.1); RD 0.1% (95% CI –0.1% to 1.2%); Low certainty ⨁⨁◯◯ **Severe adverse events:** No information
ACTIV-4C trial *(103)*; Wang et al; Peer reviewed; 2022	Patients with post COVID-19 condition (thromboembolic events after 0 days of acute COVID-19). 607 assigned to Apixaban 5 mg a day for 30 days and 610 assigned to standard of care.	Median age 54, male 50.5%, hypertension 46.7%, diabetes 28.3%, chronic lung disease 6.1%, asthma 13.7%, CHD 5.6%, interval between COVID-19 and enrolment 0 days, hospitalization during COVID-19 100%	NR	Low risk of bias	

Table 9. Description of included studies and interventions effects for PIMS-TS

Steroids Steroids may reduce time to discharge and respiratory support requirements. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Swissped RECOVERY trial *(104)*; Welzel et al; Peer reviewed; 2022	Patients with PIMS-TS. 37 assigned to methylprednisolone 10 mg/kg a day for 3 days and 38 assigned to IVIG 2 gr/kg once	Mean age 9.1, male 75%, underlying chronic disease 11%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**Mortality:** No information **Time to discharge reduction:** RR 1.09 (95% CI 0.88 to 1.39); RD 4.5% (95% CI -6% to 19.5%); Low certainty ⨁⨁◯◯ **Respiratory support:** RR 0.49 (95% CI 0.27 to 0.89); RD -28.2% (95% CI -40.5% to -5.9%); Low certainty ⨁⨁◯◯ **Inotropic requirements:** Very low certainty ⨁◯◯◯ **LVEF <55%:** Very low certainty ⨁◯◯◯ **Arrhythmia:** Very low certainty ⨁◯◯◯ **VTE:** Very low certainty ⨁◯◯◯ **Major bleeding:** No information

Table 10. Description of included studies and interventions effects for P-ACC prophylaxis

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
Budesonide + Saline + Mouthwash **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Jing et al *(105)*; Peer reviewed; 2022	Patients with COVID-19. 120 assigned to Budesonide (nasal spray)+ Saline (nasal irrigation) once a day + Mouthwash four times a day and 140 assigned to standard of care.	Mean age 66, male 37.2%	NR	High risk of bias Notes: Concealment of allocation and blinding probably inapropriate.	**Mortality:** No information **HRQL improvement:** No information **P-ACC:** Very low certainty ⨁◯◯◯ **Adverse events:** No information **Severe adverse events:** No information
Convalescent plasma **Convalescent may not reduce P-ACC. However, certainty of the evidence was low. Further research is needed.**					
RCT					
CSSC-004 trial *(106)*; Kelly et al; Preprint; 2022	Patients with mild to moderate COVID-19. 445 assigned to convalescent plasma 250 ml once and 437 assigned to standard of care.	Median age 43, male 42.6%, hypertension 23.5%, diabetes 8.2%, obesity 16%,	Vaccinated 22%	High risk of bias Notes: Significant loss to follow-up	**Mortality:** No information **HRQL improvement:** No information **P-ACC:** RR 0.93 (95% CI 0.77 to 1.12); RD -2.4% (95% CI -7.9% to 4.2%); Low certainty ⨁⨁◯◯

					Adverse events: No information **Severe adverse events:** No information
Fluvoxamine **Fluvoxamine may not reduce P-ACC. However, the certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
COVID-OUT trial *(107)*; Bramante et al; Preprint; 2022	Patients with mild to moderate COVID-19. 298 assigned to Fluvoxamine 50 mg once followed by 100 mg a day for 14 days and 297 assigned to standard of care.	Median age 44.5, male 45.8%, hypertension 26.9%, diabetes 1.1%, obesity 47.2%,	Corticosteroids 1.5%, monoclonal antibodies 4.2%; Vaccinated 56.4%	High risk of bias Notes: Significant loss to follow-up	**Mortality:** No information **HRQL improvement:** No information **P-ACC:** RR 0.99 (95% CI 0.81 to 1.21); RD -0.4% (95% CI -8.4% to 9.3%); Low certainty ⊕⊕◯◯ **Adverse events:** No information **Severe adverse events:** No information
Farahani et al. *(108)*; Peer reviewed; 2022	Patients with post COVID-19 condition (P-ACC prophylaxis after 0 days of acute COVID-19). 42 assigned to Fluvoxamine 100 mg a day for 10 days and 43 assigned to standard of care.	Mean age 38.5, male 51.2%, hypertension 15.3%, diabetes 6.5%, CHD 11.6%,	Vaccinated 100%	Low risk of bias	
Ivermectin **Ivermectin may not reduce P-ACC. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
COVID-OUT - Ivermectin trial *(107)*; Bramante	Patients with mild to moderate COVID-19. 377	Median age 45.5, male 44%, hypertension 26.7%,	Corticosteroids 1.5%, monoclonal antibodies 4.2%;	High risk of bias Notes: Significant	**Mortality:** No information

et al; Preprint; 2022	assigned to Ivermectin 390-470 mcg/kg per day for 3 days and 361 assigned to standard of care.	diabetes 2%, obesity 48.8%	Vaccinated 52.2%	loss to follow-up	**HRQL improvement:** No information **P-ACC:** RR 0.99 (95% CI 0.61 to 1.62); RD 0% (95% CI -1.7% to -2.6%); Low certainty ⨁⨁◯◯ **Adverse events:** No information **Severe adverse events:** No information
Leflunomide **Leflunomide may not reduce P-ACC. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
DEFEAT-COVID trial *(109)*; Kralj-Hans et al; Peer reviewed; 2022	Patients with moderate to severe COVID-19). 81 assigned to leflunomide 100 mg/day for 3 days followed by 20 mg/day for 7 days and 91 assigned to standard of care.	Mean age 55.8, male 67%, diabetes 22%, chronic lung disease 12%, CHD 39%, cancer 3%, obesity 4%, interval between COVID-19 and enrolment 0 days, hospitalization during COVID-19 100%	Corticosteroids 95%, remdesivir %, hydroxychloroquine 47%, tocilizumab 2.3%,	High risk of bias Notes: Non-blinded study which might have introduced bias.	**Mortality:** No information **HRQL improvement:** No information **P-ACC:** RR 1.28 (95% CI 0.92 to 1.77); RD 11.2% (95% CI -3.2% to 31.1%); Low certainty ⨁⨁◯◯ **Adverse events:** No information **Severe adverse events:** Very low certainty ⨁◯◯◯
Metformin **Metformin may reduce P-ACC. However, certainty of the evidence was low. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
COVID-OUT - Metformin trial *(107)*; Bramante et al; Preprint; 2022	Patients with mild to moderate COVID-19. 564 assigned to metformin 1500 mg a day for 14 days and 561 assigned to standard of care.	Median age 45.5, male 45.3%, hypertension 22.8%, diabetes 1.6%, obesity 47.4%	Steroids 1.5%, remdesivir %, monoclonal antibodies 4.2%; Vaccinated 55.6%	High risk of bias Notes: Significant loss to follow-up	**Mortality:** No information **HRQL improvement:** No information **P-ACC:** RR 0.59 (95% CI 0.39 to 0.88); RD -4.3% (95% CI -6.4% to -1.2%); Low certainty ⨁⨁◯◯ **Adverse events:** No information **Severe adverse events:** No information
Remdesivir **Remdesivir may not reduce P-ACC. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
SOLIDARITY - Finland trial *(110)*; Nevalainen et al; Peer reviewed; 2022	Patients with post COVID-19 condition (P-ACC prophylaxis after 0 days of acute COVID-19). 98 assigned to Remdesivir 200 mg once followed by 100 mg a day for 10 days and 83 assigned to standard of care.	Mean age 58.4, male 60.2%, diabetes 22.1%, hospitalization during COVID-19 100%	Corticosteroids 71.8%	Low risk of bias	**Mortality:** Very low certainty ⨁◯◯◯ **HRQL improvement:** No information **P-ACC:** RR 1.06 (95% CI 0.53 to 2.13); RD 0.8% (95% CI -6.9% to 16.4%); Low certainty ⨁⨁◯◯

					Adverse events: No information **Severe adverse events:** No information
Nasal saline + Mouthwash **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Jing et al *(105)*; Peer reviewed; 2022	Patients with COVID-19. 119 assigned to Saline (nasal irrigation and spray) once a day + Mouthwash four times a day and 140 assigned to standard of care.	Mean age 66, male 37.2%	NR	High risk of bias Notes: Concealment of allocation and blinding probably inapropriate.	**Mortality:** No information **HRQL improvement:** No information **P-ACC:** Very low certainty ⨁◯◯◯ **Adverse events:** No information **Severe adverse events:** No information

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Annex 1. Summary of findings tables

Summary of findings Table A1.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: Actovegin
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	 Actovegin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Fatigue improvement	Relative risk: 1.54 (CI 95% 1.59 - 2.14) Based on data from 444 participants in 1 study Follow up 90 days	**471** per 1000	**725** per 1000 Difference: **254 more per 1000** (CI 95% 278 more - 537 more)	**Low** Due to very serious risk of bias[1]	Actovegin may improve fatigue

1. **Risk of Bias: very serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: no serious.** 95% CI include important benefits and harms.

Summary of findings Table A2.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: ADAPT-232
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	ADAPT-232		
Fatigue improvement	Relative risk 1.02 (95% CI 0.84 to 1.24) Based on data from 99 participants in 1 study Follow-up 21 days	**800** per 1000	**816** per 1000 Difference: **16 more per 1000** (95% CI 128 fewer to 192 more)	**Low** Due to very serious imprecision[1]	Adapt-232 may have little or no difference on fatigue improvement

1. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A3.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: Cytoflavin
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	Cytoflavin		
Fatigue improvement[a]	Relative risk 1.02 (95% CI 0.98 to 1.06) Based on data from 200 participants in 1 study Follow-up 25 days	**979** per 1000	**999** per 1000 Difference: **20 more per 1000** (95% CI 20 fewer to 21 more)	**Low** Due to serious risk of bias, Due to serious imprecision[b]	Cytoflavin may have little or no difference on fatigue improvement

a. Decrease in 12 units of the MFI score.
b. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.

Summary of findings Table A4.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: Enzymes + probiotics
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	Enzymes + probiotics		
Fatigue improvement	Relative risk 6.07 (95% CI 3.71 to 9.71) Based on data from 200 participants in 1 study Follow-up 25 days	**150** per 1000	**911** per 1000 Difference: **761 more per 1000** (95% CI 407 more to 850 more)	**Low** Due to serious risk of bias, Due to serious imprecision[a]	Enzymes + probiotics may increase fatigue improvement

a. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.

Summary of findings Table A5.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: Phytochemicals
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Phytochemicals		
HRQL improvement	Relative risk: 1.33 (CI 95% 1.03 - 1.71) Based on data from 147 participants in 1 study Follow up 30 days	**543** per 1000	**722** per 1000 Difference: **179 more per 1000** (CI 95% 16 more - 386 more)	**Low** Due to serious risk of bias, Due to serious imprecision[1]	Phytochemicals may increase HRQL improvement
Fatigue improvement	Relative risk: 1.24 (CI 95% 0.95 - 1.62) Based on data from 147 participants in 1 study Follow up 30 days	**539** per 1000	**668** per 1000 Difference: **129 more per 1000** (CI 95% 27 fewer - 334 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Phytochemicals may increase fatigue improvement

1. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Low number of patients.
2. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Low number of patients.

Summary of findings Table A6.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: Transcranial direct current stimulation (tDCS)
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Transcranial direct current stimulation (tDCS)		
Fatigue improvement	Relative risk: 1.36 (CI 95% 0.76 - 2.45) Based on data from 117 participants in 2 studies Follow up 32.5 days	**468** per 1000	**636** per 1000 Difference: **168 more per 1000** (CI 95% 112 fewer - 672 more)	**Low** Due to very serious imprecision[1]	Transcranial direct current stimulation (tdcs) may have little or no difference on fatigue improvement
HRQL improvement	Relative risk: 1.37 (CI 95% 1.09 - 1.71) Based on data from 70 participants in 1 study Follow up 35 days	**705** per 1000	**966** per 1000 Difference: **261 more per 1000** (CI 95% 63 more - 295 more)	**Low** Due to very serious imprecision[2]	Transcranial direct current stimulation (tdcs) may improve HRQL
Adverse events	Relative risk: 0.83 (CI 95% 0.26 - 2.73) Based on data from 47 participants in 1 study Follow up 30 days	**208** per 1000	**173** per 1000 Difference: **35 fewer per 1000** (CI 95% 154 fewer - 360 more)	**Low** Due to very serious imprecision[3]	Transcranial direct current stimulation (tdcs) may have little or no difference on adverse events

1. **Imprecision: very serious.** 95% CI include important benefits and harms;
2. **Imprecision: very serious.** 95% CI include important benefits and harms;
3. **Imprecision: very serious.** 95% CI include important benefits and harms;

Summary of findings Table A7.

Population: Patients with P-ACC-related dyspnea
Intervention: ADAPT-232
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	ADAPT-232		
Dyspnea improvement	Relative risk 1.0 (95% CI 0.94 to 1.06) Based on data from 99 participants in 1 study Follow-up 21 days	**980** per 1000	**980** per 1000 Difference: **0 fewer per 1000** (95% CI 59 fewer to 20 more)	**Low** Due to very serious imprecision[a]	ADAPT-232 may have little or no difference on dyspnea improvement

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A8.

Population: Patients with P-ACC-related dyspnea
Intervention: Endurance training
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Endurance training	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
HRQL improvement[a]	Relative risk 1.48 (95% CI 0.92 to 2.37) Based on data from 60 participants in 1 study Follow-up 21 days	**441** per 1000	**980** per 1000 Difference: **0 fewer per 1000** (95% CI 59 fewer to 20 more)	**Low** Due to serious risk of bias, Due to serious imprecision[b]	Endurance training may increase HRQL improvement
Dyspnea improvement[c]	Relative risk 2.03 (95% CI 0.98 to 4.21) Based on data from 60 participants in 1 study Follow-up 21 days	**236** per 1000	**980** per 1000 Difference: **0 fewer per 1000** (95% CI 59 fewer to 20 more)	**Low** Due to serious risk of bias, Due to serious imprecision[d]	Endurance training may increase dyspnea improvement

a. Increment of 7 units in the SF-12 scale.
b. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.
c. Increment of 7 units in the SF-12 scale.
d. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.

Summary of findings Table A9.

Population: Patients with P-ACC-related dyspnea
Intervention: High dose steroids (i.e., prednisone 40 mg a day)
Comparator: Standard dose steroids (i.e., prednisone 10 mg a day)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard dose steroids	 High dose steroids	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Dyspnea improvement	Relative risk 1.0 (95% CI 0.87 to 1.15) Based on data from 130 participants in 1 study Follow-up 42 days	**862** per 1000	**862** per 1000 Difference: **0 fewer per 1000** (95% CI 112 fewer to 129 more)	**Low** Due to serious risk of bias, Due to serious imprecision[a]	High dose steroids may have little or no difference on dyspnea improvement
Radiological response	Relative risk 1.33 (95% CI 0.69 to 2.59) Based on data from 60 participants in 1 study Follow-up 21 days	**185** per 1000	**246** per 1000 Difference: **61 more per 1000** (95% CI 57 fewer to 294 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[b]	We are uncertain whether high dose steroids increases or decreases radiological response
Adverse events	Relative risk 0.92 (95% CI 0.75 to 1.13) Based on data from 60 participants in 1 study Follow-up 21 days	**769** per 1000	**707** per 1000 Difference: **62 fewer per 1000** (95% CI 192 fewer to 100 more)	**Low** Due to serious risk of bias, Due to serious imprecision[c]	High dose steroids may have little or no difference on adverse events
Severe adverse events	Relative risk 3.0 (95% CI 0.32 to 28.09) Based on data from 60 participants in 1 study Follow-up 21 days	**15** per 1000	**45** per 1000 Difference: **30 more per 1000** (95% CI 10 fewer to 406 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[d]	We are uncertain whether high dose steroids increases or decreases severe adverse events

a. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.
b. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** 95% CI includes important benefits and harms.
c. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.
d. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A10.

Population: Patients with P-ACC-related dyspnea
Intervention: Respiratory training/rehabilitation
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Respiratory training	**Certainty of the Evidence** (Quality of evidence)	**Summary**
HRQL improvement	Relative risk: 1.41 (CI 95% 1.18 - 1.67) Based on data from 644 participants in 8 studies Follow up 90 days	**493** per 1000	**695** per 1000 Difference: **202 more per 1000** (CI 95% 89 more - 330 more)	**Moderate** Due to serious risk of bias[1]	Respiratory training probably increases HRQL improvement
Functional capacity improvement	Relative risk: 1.34 (CI 95% 1.11 - 1.62) Based on data from 451 participants in 6 studies Follow up 120 days	**502** per 1000	**673** per 1000 Difference: **171 more per 1000** (CI 95% 55 more - 311 more)	**Moderate** Due to serious risk of bias[2]	Respiratory probably increases functional capacity improvement
Dyspnea improvement	Relative risk: 2.44 (CI 95% 1.33 - 4.49) Based on data from 649 participants in 10 studies Follow up 79 days	**287** per 1000	**700** per 1000 Difference: **413 more per 1000** (CI 95% 95 more - 713 more)	**Moderate** Due to serious risk of bias[3]	Respiratory training probably increases dyspnea improvement
Pulmonary function improvement	Relative risk: 12.8 (CI 95% 1.65 - 99.5) Based on data from 26 participants in 1 studies Follow up 90 days	**66** per 1000	**845** per 1000 Difference: **779 more per 1000** (CI 95% 43 more - 6501 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether respiratory training increases or decreases pulmonary function improvement

2. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias;
3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
4. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias;
5. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** 95% CI include important benefits and harms;

Summary of findings Table A11.

Population: Patients with P-ACC-related dyspnea
Intervention: Treamid
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Treamid	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Functional capacity improvement	Relative risk 1.1 (95% CI 0.64 to 1.9) Based on data from 59 participants in 1 study Follow-up 28 days	**445** per 1000	**490** per 1000 Difference: **45 more per 1000** (95% CI 160 fewer to 401 more)	**Low** Due to very serious imprecision[a]	Treamid may have little or no difference on functional capacity improvement
Dyspnea improvement	Relative risk 1.96 (95% CI 0.9 to 4.25) Based on data from 59 participants in 1 study Follow-up 28 days	**227** per 1000	**445** per 1000 Difference: **218 more per 1000** (95% CI 23 fewer to 738 more)	**Low** Due to very serious imprecision[b]	Treamid may increase dyspnea improvement
Pulmonary function improvement	Relative risk 2.48 (95% CI 1.0 to 6.17) Based on data from 59 participants in 1 study Follow-up 28 days	**167** per 1000	**414** per 1000 Difference: **247 more per 1000** (95% CI 0 fewer to 863 more)	**Low** Due to very serious imprecision[c]	Treamid may increase pulmonary function improvement
Adverse events	Relative risk 1.19 (95% CI 0.56 to 2.5) Based on data from 59 participants in 1 study Follow-up 28 days	**290** per 1000	**345** per 1000 Difference: **55 more per 1000** (95% CI 128 fewer to 435 more)	**Low** Due to very serious imprecision[d]	Treamid may increase adverse events

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.
b. **Imprecision: very serious.** 95% CI includes important benefits and harms.
c. **Imprecision: very serious.** 95% CI includes important benefits and harms.
d. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A12.

Population: Patients with P-ACC-related neurocognitive symptoms or sleep disturbances
Intervention: Actovegin
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Actovegin		
Cognitive improvement	Odds ratio: 1.19 (CI 95% 1.06 - 1.33) Based on data from 444 participants in 1 study	**673** per 1000	**710** per 1000 Difference: **37 more per 1000** (CI 95% 13 more - 384 fewer)	**Low** Due to very serious risk of bias[1]	Actovegin may improve cognition

1. **Risk of Bias: very serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Indirectness: serious.** Non appropriately established MID; **Imprecision: no serious.** 95% CI include important benefits and harms.

Summary of findings Table A13.

Population: Patients with P-ACC-related neurocognitive symptoms or sleep disturbances
Intervention: Hyperbaric oxygen (HBO)
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	HBO	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
HRQL improvement	Relative risk 1.3 (95% CI 0.84 to 2.0) Based on data from 73 participants in 1 study	**469** per 1000	**610** per 1000 Difference: **141 more per 1000** (95% CI 75 fewer to 469 more)	**Low** Due to very serious imprecision[a]	HBO may increase HRQF improvement
Cognitive improvement	Odds ratio 2.84 (95% CI 1.09 to 7.37) Based on data from 73 participants in 1 study	**667** per 1000	**850** per 1000 Difference: **183 more per 1000** (95% CI 19 more to 22 more)	**Very low** Due to extremely serious imprecision, Due to serious indirectness[b]	We are uncertain whether HBO increases or decreases cognitive improvement
Depression improvement	Odds ratio 35.9 (95% CI 2.72 to 474.6) Based on data from 73 participants in 1 study Follow-up 28 days	**681** per 1000	**987** per 1000 Difference: **306 more per 1000** (95% CI 172 more to 312 more)	**Very low** Due to extremely serious imprecision, Due to serious indirectness[c]	We are uncertain whether HBO increases or decreases depression improvement

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.
b. **Indirectness: serious.** Non appropriately established minimal important difference (MID). **Imprecision: extremely serious.** 95% CI includes important benefits and harms.
c. **Indirectness: serious.** Non appropriately established MID. **Imprecision: extremely serious.** 95% CI includes important benefits and harms.

Summary of findings Table A14.

Population: Patients with P-ACC-related neurocognitive symptoms or sleep disturbances
Intervention: Transcranial direct current stimulation (tDCS)
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	Transcranial direct current stimulation (tDCS)		
Cognitive improvement	Relative risk 0.59 (95% CI 0.33 to 1.05) Based on data from 47 participants in 1 study Follow-up 30 days	**667** per 1000	**394** per 1000 Difference: **273 fewer per 1000** (95% CI 447 fewer to 33 more)	**Low** Due to very serious imprecision[a]	tDCS may have little or no difference on cognitive improvement

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A15.

Population: Patients with P-ACC-related olfactory and/or gustatory dysfunction
Intervention: ADAPT-232
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	ADAPT-232		
Olfactory symptoms improvement	Relative risk 0.89 (95% CI 0.79 to 1.01) Based on data from 99 participants in 1 study Follow-up 21 days	**960** per 1000	**854** per 1000 Difference: **106 fewer per 1000** (95% CI 202 fewer to 10 more)	**Low** Due to very serious imprecision[a]	ADAPT-232 may have little or no difference on olfactory symptoms

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A16.

Population: Patients with P-ACC-related olfactory and/or gustatory dysfunction
Intervention: Palmitoylethanolamide + Luteolin
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Palmitoylethanolamide + Luteolin		
Olfactory symptoms improvement	Relative risk: 3.13 (CI 95% 1.47 - 666.0) Based on data from 130 participants in 1 study Follow up 90 days	**167** per 1000	**523** per 1000 Difference: **356 more per 1000** (CI 95% 78 more - 833 more)	**Low** Due to very serious imprecision[1]	Palmitoylethanolamide + luteolin may increase olfactory symptoms improvement

1. **Imprecision: very serious.** 95% CI include important benefits and harms;

Summary of findings Table A17.

Population: Patients with P-ACC-related olfactory and/or gustatory dysfunction
Intervention: Steroids
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Steroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Olfactory symptoms improvement	Relative risk: 1.09 (CI 95% 0.83 - 1.44) Based on data from 131 participants in 2 studies Follow up 52 days	**365** per 1000	**398** per 1000 Difference: **33 more per 1000** (CI 95% 62 fewer - 161 more)	**Low** Due to very serious imprecision[1]	Steroids may have little or no difference on olfactory symptoms
Gustatory symptoms improvement	Relative risk: 1.01 (CI 95% 0.67 - 1.53) Based on data from 113 participants in 1 study Follow up 84 days	**443** per 1000	**447** per 1000 Difference: **4 more per 1000** (CI 95% 146 fewer - 235 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Steroids may have little or no difference on gustatory symptoms

1. **Imprecision: very serious.** Low number of patients, Wide confidence intervals.
2. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Low number of patients.

Summary of findings Table A18.

Population: Patients with P-ACC-related psychological distress
Intervention: Virtual reality informational video
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Virtual informational video		
Depression improvement	Relative risk 1.21 (95% CI 0.95 to 1.54) Based on data from 89 participants in 1 study Follow-up 90 days	**682** per 1000	**825** per 1000 Difference: **143 more per 1000** (95% CI 34 fewer to 368 more)	**Low** Due to serious risk of bias, Due to serious imprecision[a]	Virtual reality informational video may increase depression improvement
Post-traumatic stress disorder improvement	Relative risk 1.18 (95% CI 0.98 to 1.42) Based on data from 89 participants in 1 study Follow-up 90 days	**773** per 1000	**912** per 1000 Difference: **139 more per 1000** (95% CI 15 fewer to 227 more)	**Low** Due to serious risk of bias, Due to serious imprecision[b]	Virtual reality informational video may increase post-traumatic stress disorder improvement
Psychologic distress improvement	Relative risk 1.49 (95% CI 1.08 to 2.05) Based on data from 89 participants in 1 study Follow-up 90 days	**523** per 1000	**779** per 1000 Difference: **256 more per 1000** (95% CI 42 more to 549 more)	**Low** Due to serious risk of bias, Due to serious imprecision[c]	Virtual reality informational video may increase psychological distress improvement

a. **Risk of bias: serious. Imprecision: serious.** Low number of patients.
b. **Risk of bias: serious. Imprecision: serious.** Low number of patients.
c. **Risk of bias: serious. Imprecision: serious.** Low number of patients.

Summary of findings Table A19.

Population: Patients with P-ACC-related thromboembolic risk
Intervention: Anticoagulants
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Anticoagulants	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
HRQL improvement	Relative risk: 0.99 (CI 95% 0.78 - 1.24) Based on data from 1217 participants in 1 study Follow up 90 days			**Low** Due to very serious imprecision[1]	Anticoagulants may have little or no difference on HRQL
VTE	Relative risk: 1.0 (CI 95% 0.29 - 3.45) Based on data from 1535 participants in 2 studies Follow up 32.5 days	**32** per 1000	**32** per 1000 Difference: **0 fewer per 1000** (CI 95% 23 fewer - 78 more)	**Low** Due to very serious imprecision[2]	Anticoagulants may have little or no difference on VTE
Mortality	Relative risk: 0.85 (CI 95% 0.38 - 1.88) Based on data from 1535 participants in 2 studies Follow up 32.5 days	**20** per 1000	**17** per 1000 Difference: **3 fewer per 1000** (CI 95% 12 fewer - 18 more)	**Low** Due to very serious imprecision[3]	Anticoagulants may have little or no difference on mortality
Major bleeding	Relative risk: 2.01 (CI 95% 0.18 - 22.1) Based on data from 1535 participants in 2 studies Follow up 32.5 days	**1** per 1000	**2** per 1000 Difference: **1 more per 1000** (CI 95% 1 fewer - 21 more)	**Low** Due to very serious imprecision[4]	Anticoagulants may have little or no difference on major bleeding

1. **Imprecision: very serious.** Low number of patients, Wide confidence intervals.
2. **Imprecision: very serious.** Low number of patients, Wide confidence intervals.
3. **Imprecision: very serious.** Low number of patients, Wide confidence intervals.
4. **Imprecision: very serious.** Low number of patients, Wide confidence intervals.

Summary of findings Table A20.

Population: Patients with PIMS-TS
Intervention: Steroids
Comparator: IVIG

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** IVIG	Steroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Time to discharge time reduction[1]	Relative risk: 1.09 (CI 95% 0.88 - 1.39) Based on data from 75 participants in 1 study Follow up 28	**500** per 1000	**545** per 1000 Difference: **45 more per 1000** (CI 95% 60 fewer - 195 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Steroids may decrease time to discharge
Respiratory support	Relative risk: 0.49 (CI 95% 0.27 - 0.89) Based on data from 75 participants in 1 study Follow up 28	**553** per 1000	**271** per 1000 Difference: **282 fewer per 1000** (CI 95% 404 fewer - 61 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[3]	Steroids may decrease respiratory support requirements
Inotropic requirements	Relative risk: 0.68 (CI 95% 0.35 - 1.32) Based on data from 75 participants in 1 study Follow up 28	**395** per 1000	**269** per 1000 Difference: **126 fewer per 1000** (CI 95% 257 fewer - 126 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to very serious imprecision[4]	We are uncertain whether steroids increases or decreases inotropic requirements
Left ventricular fraction deterioration	Relative risk: 0.57 (CI 95% 0.21 - 1.54) Based on data from 75 participants in 1 study Follow up 28	**237** per 1000	**135** per 1000 Difference: **102 fewer per 1000** (CI 95% 187 fewer - 128 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to very serious imprecision[5]	We are uncertain whether steroids increases or decreases LVEF deterioration
Arrhythmia	Relative risk: 2.05 (CI 95% 0.19 - 21.7) Based on data from 75 participants in 1 study Follow up 28	**26** per 1000	**53** per 1000 Difference: **27 more per 1000** (CI 95% 21 fewer - 538 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to very serious imprecision[6]	We are uncertain whether steroids increases or decreases Arrhythmias
Venous thromboembolic events	Relative risk: 0.34 (CI 95% 0.01 - 8.14) Based on data from 75 participants in 1 study Follow up 28	**39** per 1000	**13** per 1000 Difference: **26 fewer per 1000** (CI 95% 39 fewer - 278 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to very serious imprecision[7]	We are uncertain whether steroids increases or decreases VTE

1. Proportion of patients discharged on day 6.
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Wide confidence intervals.
3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Wide confidence intervals.
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Wide confidence intervals.
5. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Wide confidence intervals.

6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Wide confidence intervals.
7. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Wide confidence intervals.

Summary of findings Table A21.

Population: Patients with COVID-19
Intervention: Metformin to prevent P-ACC
Comparator: SOC

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Metfomin to prevent P-ACC		
P-ACC	Relative risk: 0.59 (CI 95% 0.39 - 0.88) Based on data from 1125 participants in 1 study Follow up 300 days	**105** per 1000	**62** per 1000 Difference: **43 fewer per 1000** (CI 95% 64 fewer - 13 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[1]	Metformin may reduce P-ACC

1. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Low number of patients.

Summary of findings Table A22.

Population: Patients with COVID-19
Intervention: Ivermectin to prevent P-ACC
Comparator: SOC

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Ivermectin to prevent P-ACC		
P-ACC	Relative risk: 0.99 (CI 95% 0.61 - 1.62) Based on data from 738 participants in 1 study Follow up 300 days	**105** per 1000	**104** per 1000 Difference: **1 fewer per 1000** (CI 95% 41 fewer - 65 more)	**Low** Due to serious risk of bias, Due to serious imprecision[1]	Ivermectin may not reduce P-ACC

1. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Low number of patients.

Summary of findings Table A23.

Population: Patients with COVID-19
Intervention: Convalescent plasma to prevent P-ACC
Comparator: SOC

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	CP to prevent P-ACC		
P-ACC	Relative risk: 0.93 (CI 95% 0.77 - 1.12) Based on data from 882 participants in 1 study Follow up 90 days	**343** per 1000	**319** per 1000 Difference: **24 fewer per 1000** (CI 95% 79 fewer - 41 more)	**Low** Due to serious risk of bias, Due to serious imprecision[1]	Convalescent plasma may not reduce P-ACC

1. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Low number of patients.

Summary of findings Table A24.

Population: Patients with COVID-19
Intervention: Remdesivir to prevent P-ACC
Comparator: SOC

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Remdesivir to prevent P-ACC		
Mortality	Relative risk: 0.85 (CI 95% 0.25 - 2.83) Based on data from 181 participants in 1 study Follow up 365 days	**60** per 1000	**51** per 1000 Difference: **9 fewer per 1000** (CI 95% 45 fewer - 110 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision	We are uncertain whether remdesivir to prevent p-acc increases or decreases mortality
P-ACC	Relative risk: 1.06 (CI 95% 0.53 - 2.13) Based on data from 181 participants in 1 study Follow up 365 days	**145** per 1000	**154** per 1000 Difference: **9 more per 1000** (CI 95% 68 fewer - 164 more)	**Low** Due to serious risk of bias, Due to serious imprecision	Remdesivir may not reduce P-ACC

1. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** Low number of patients, Wide confidence intervals.
2. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Low number of patients.

Summary of findings Table A25.

Population: Patients with COVID-19
Intervention: Leflunomide to prevent P-ACC
Comparator: SOC

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Leflunomide to prevent P-ACC		
P-ACC	Relative risk: 1.28 (CI 95% 0.92 - 1.77) Based on data from 172 participants in 1 study Follow up 90 days	**407** per 1000	**521** per 1000 Difference: **114 more per 1000** (CI 95% 33 fewer - 313 more)	**Low** Due to serious risk of bias, Due to serious imprecision[1]	Remdesivir may not reduce P-ACC
Severe adverse events	Relative risk: 1.76 (CI 95% 0.81 - 3.85) Based on data from 214 participants in 1 study Follow up 90 days	**82** per 1000	**144** per 1000 Difference: **62 more per 1000** (CI 95% 16 fewer - 234 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether remdesivir to prevent p-acc increases or decreases mortality

1. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Low number of patients.
2. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** Low number of patients, Wide confidence intervals.

Summary of findings Table A26.

Population: Patients with COVID-19
Intervention: Fluvoxamine to prevent P-ACC
Comparator: SOC

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Fluvoxamine to prevent P-ACC		
P-ACC	Relative risk: 0.99 (CI 95% 0.81 - 1.21) Based on data from 680 participants in 2 studies Follow up 192 days	**444** per 1000	**440** per 1000 Difference: **4 fewer per 1000** (CI 95% 84 fewer - 93 more)	**Low** Due to very serious imprecision[1]	Fluvoxamine may not reduce P-ACC

5. **Imprecision: very serious.** Wide confidence intervals.

Summary of findings Table A27.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: AXA1125
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	AXA1125	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Fatigue improvement	Relative risk: 1.07 (CI 95% 0.79 - 1.44) Based on data from 41 participants in 1 study Follow up 28 days	**780** per 1000	**835** per 1000 Difference: **55 more per 1000** (CI 95% 164 fewer - 343 more)	**Low** Due to very serious imprecision[1]	Axa1125 may increase fatigue improvement
Functional capacity improvement	Relative risk: 0.87 (CI 95% 0.51 - 1.48) Based on data from 41 participants in 1 study Follow up 28 days	**607** per 1000	**528** per 1000 Difference: **79 fewer per 1000** (CI 95% 297 fewer - 291 more)	**Low** Due to very serious imprecision[2]	Axa1125 may not increase functional capacity improvement
Adverse events	Relative risk: 2.62 (CI 95% 1.0 - 6.89) Based on data from 41 participants in 1 study Follow up 28 days	**200** per 1000	**524** per 1000 Difference: **324 more per 1000** (CI 95% 0 fewer - 800 more)	**Very low** Due to extremely serious imprecision[3]	We are uncertain whether axa1125 improves or worsen adverse events

1. **Imprecision: very serious.** 95% CI include important benefits and harms.
2. **Imprecision: very serious.** 95% CI include important benefits and harms.
3. **Imprecision: ~extreme_serious.** 95% CI include important benefits and harms.

Summary of findings Table A28.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: Telerehabilitation
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Telerehabilitation	**Certainty of the Evidence** (Quality of evidence)	**Summary**
HRQL improvement	Relative risk: 1.47 (CI 95% 0.88 - 2.44) Based on data from 253 participants in 5 studies Follow up 61.6 days	**338** per 1000	**497** per 1000 Difference: **159 more per 1000** (CI 95% 41 fewer - 487 more)	**Very low** Due to very serious imprecision, Due to serious risk of bias[1]	We are uncertain whether telerehabilitation increases or decreases hrql improvement
Fatigue improvement	Relative risk: 1.63 (CI 95% 1.04 - 2.54) Based on data from 89 participants in 3 studies Follow up 79 days	**304** per 1000	**636** per 1000 Difference: **168 more per 1000** (CI 95% 112 fewer - 672 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Telerehabilitation may increase fatigue improvement
Functional capacity improvement	Relative risk: 1.47 (CI 95% 1.19 - 1.82) Based on data from 267 participants in 5 studies Follow up 73 days	**441** per 1000	**648** per 1000 Difference: **207 more per 1000** (CI 95% 84 more - 362 more)	**Low** Due to serious risk of bias, Due to serious imprecision[3]	Telerehabilitation may increase functional capacity improvement

1. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** 95% CI include important benefits and harms, Wide confidence intervals;
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Low number of patients;
3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** 95% CI include important benefits and harms, Low number of patients;

Summary of findings Table A29.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: Cognitive behavioral therapy
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Cognitive behavioral therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Fatigue improvemen	Relative risk: 2.2 (CI 95% 1.35 - 3.58) Based on data from 114 participants in 1 studies Follow up 119 days	**263** per 1000	**636** per 1000 Difference: **168 more per 1000** (CI 95% 112 fewer - 672 more)	**Low** Due to serious risk of bias, Due to serious imprecision[1]	Cognitive behavioral therapy may increase fatigue improvement
Functional capacity improvement	Relative risk: 1.37 (CI 95% 1.08 - 1.73) Based on data from 114 participants in 1 studies Follow up 119 days	**614** per 1000	**841** per 1000 Difference: **227 more per 1000** (CI 95% 49 more - 448 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Cognitive behavioral therapy may increase functional capacity improvement

1. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Low number of patients;
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** 95% CI include important benefits and harms, Low number of patients;

Summary of findings Table A30.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: Physical training
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Physical training	**Certainty of the Evidence** (Quality of evidence)	**Summary**
HRQL improvement[1]	Relative risk: 1.62 (CI 95% 1.07 - 2.47) Based on data from 180 participants in 3 studies Follow up 70 days	**340** per 1000	**551** per 1000 Difference: **211 more per 1000** (CI 95% 24 more - 500 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Physical training may increase HRQL improvement
Functional capacity improvement[3]	Relative risk: 1.81 (CI 95% 1.23 - 2.65) Based on data from 226 participants in 5 studies Follow up 56 days	**393** per 1000	**711** per 1000 Difference: **318 more per 1000** (CI 95% 90 more - 648 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Physical training may increase functional capacity improvement
Fatigue improvement[5]	Relative risk: 2.1 (CI 95% 0.8 - 5.02) Based on data from 213 participants in 4 studies Follow up 38.5 days	**121** per 1000	**254** per 1000 Difference: **133 more per 1000** (CI 95% 24 fewer - 486 more)	**Low** Due to serious risk of bias, Due to very serious imprecision[6]	Uncertainty about interventions effects
Strength improvement[7]	Relative risk: 3.13 (CI 95% 1.02 - 9.55) Based on data from 132 participants in 2 studies Follow up 70 days	**53** per 1000	**166** per 1000 Difference: **113 more per 1000** (CI 95% 1 more - 453 more)	**Low** Due to very serious imprecision, Due to serious imprecision[8]	We are uncertain whether cognitive behavioral therapy increases or decreases strength improvement

1. Decrease in 12 units of the MFI score
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Low number of patients;
3. Decrease in 12 units of the MFI score
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** 95% CI include important benefits and harms, Low number of patients;
5. Decrease in 12 units of the MFI score
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Low number of patients, Wide confidence intervals;
7. Decrease in 12 units of the MFI score
8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Low number of patients;

Summary of findings Table A31.

Population: Patients with P-ACC-related neurocognitive symptoms or sleep disturbances
Intervention: Famotidine
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Famotidine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Cognitive improvement	Relative risk: 1.33 (CI 95% 1.05 - 1.69) Based on data from 50 participants in 1 study	**739** per 1000	**983** per 1000 Difference: **244 more per 1000** (CI 95% 37 more - 510 more)	**Low** Due to very serious imprecision[1]	Famotidine may improve cognition
Depression improvement	Relative risk: 3.71 (CI 95% 0.83 - 16.6) Based on data from 50 participants in 1 study	**76** per 1000	**282** per 1000 Difference: **206 more per 1000** (CI 95% 13 fewer - 926 more)	**Very low** Due to extremely serious imprecision[2]	We are uncertain whether famotidine increases or decreases depression improvement

1. **Indirectness: serious.** Non appropriately established MID; **Imprecision: very serious.** Low number of patients;
2. **Indirectness: serious. Imprecision: ~extremely_serious.** 95%CI includes important benefits and harms,

Summary of findings Table A32.

Population: Patients with P-ACC-related olfactory and/or gustatory dysfunction
Intervention: Olfactory training
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Olfactory training		
Olfactory symptoms improvement	Relative risk: 1.49 (CI 95% 0.96 - 2.31) Based on data from 308 participants in 4 studies Follow up 59.5 days	**409** per 1000	**609** per 1000 Difference: **200 more per 1000** (CI 95% 16 fewer - 536 more)	**Low** Due to serious risk of bias, Due to serious inconsistency[1]	Olfactory training may increase olfactory symptoms improvement

1. **Risk of Bias: serious. Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.;

Summary of findings Table A33.

Population: Patients with P-ACC-related neurocognitive symptoms or sleep disturbances
Intervention: Vortioxetine
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Vortioxetine	**Certainty of the Evidence** (Quality of evidence)	**Summary**
HRQL improvement	Relative risk: 1.35 (CI 95% 1.03 - 1.77) Based on data from 149 participants in 1 studies Follow up 56 days	**508** per 1000	**686** per 1000 Difference: **178 more per 1000** (CI 95% 15 more - 391 more)	**Moderate** Due to serious imprecision[1]	Vortioxetine probably improves HRQL
Cognitive improvement	Relative risk: 0.97 (CI 95% 0.74 - 1.28) Based on data from 149 participants in 1 studies Follow up 56 days	**579** per 1000	**562** per 1000 Difference: **17 fewer per 1000** (CI 95% 151 fewer - 162 more)	**Low** Due to very serious imprecision[2]	Vortioxetine may not improve cognition
Depresion improvement	Relative risk: 1.43 (CI 95% 0.97 - 2.12) Based on data from 149 participants in 1 studies Follow up 56 days	**343** per 1000	**490** per 1000 Difference: **147 more per 1000** (CI 95% 10 fewer - 384 more)	**Low** Due to very serious imprecision[3]	Vortioxetine may improve depresion
Adverse events	Relative risk: 1.2 (CI 95% 0.86 - 1.66) Based on data from 149 participants in 1 studies Follow up 56 days	**446** per 1000	**535** per 1000 Difference: **89 more per 1000** (CI 95% 62 fewer - 294 more)	**Very low** Due to extremely serious imprecision[4]	We are uncertain whether vortioxetine improves or worsen adverse events

1. **Imprecision: serious.** Low number of patients;
2. **Indirectness: serious.** Non appropriately established MID; **Imprecision: very serious.** Low number of patients;
3. **Imprecision: very serious.** 95%CI includes important benefits and harms, ;
4. **Imprecision: extremely serious.** 95%CI includes important benefits and harms, ;

Summary of findings Table A34.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: Vortioxetine
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	 Probiotics	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Fatigue improvement	Relative risk: 1.53 (CI 95% 1.23 - 1.89) Based on data from 436 participants in 2 studies Follow up 98 days	**381** per 1000	**583** per 1000 Difference: **202 more per 1000** (CI 95% 88 more - 339 more)	**Moderate** Due to serious risk of bias[1]	Probiotics probably improves fatigue
Adverse events	Relative risk: 0.88 (CI 95% 0.51 - 1.51) Based on data from 463 participants in 1 studies Follow up 168 days	**108** per 1000	**95** per 1000 Difference: **13 fewer per 1000** (CI 95% 53 fewer - 55 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether probiotics improves or worsen adverse events

1. **Risk of Bias: serious. Imprecision: no serious.** 95% CI include important benefits and harms;
2. **Risk of Bias: serious. Imprecision: very serious.** 95% CI include important benefits and harms;

Summary of findings Table A35.

Population: Patients with P-ACC-related related dyspnea
Intervention: Probiotics
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Probiotics	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Dyspnea improvement	Relative risk: 1.28 (CI 95% 1.05 - 1.54) Based on data from 285 participants in 1 studies Follow up 168 days	**537** per 1000	**687** per 1000 Difference: **150 more per 1000** (CI 95% 27 more - 290 more)	**Low** Due to serious risk of bias, Due to serious imprecision[1]	Probiotics may improve dyspnea
Adverse events	Relative risk: 0.88 (CI 95% 0.51 - 1.51) Based on data from 463 participants in 1 studies Follow up 168 days	**108** per 1000	**95** per 1000 Difference: **13 fewer per 1000** (CI 95% 53 fewer - 55 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether probiotics improves or worsen adverse events

1. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up; **Imprecision: serious.** 95% CI include important benefits and harms;
2. **Risk of Bias: serious. Imprecision: very serious.** 95% CI include important benefits and harms;

Summary of findings Table A36.

Population: Patients with P-ACC-related neurocognitive symptoms or sleep disturbances
Intervention: Probiotics
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Probiotics	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Congnitive improvement	Relative risk: 1.56 (CI 95% 1.17 - 2.09) Based on data from 369 participants in 1 studies Follow up 168 days	**269** per 1000	**420** per 1000 Difference: **151 more per 1000** (CI 95% 46 more - 293 more)	**Low** Due to serious risk of bias, Due to serious imprecision[1]	Probiotics may improve cognition
Sleep quality improvement	Relative risk: 1.56 (CI 95% 1.17 - 2.09) Based on data from 369 participants in 1 studies Follow up 168 days	**269** per 1000	**420** per 1000 Difference: **151 more per 1000** (CI 95% 46 more - 293 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Probiotics may improve cognition
Adverse events	Relative risk: 1.32 (CI 95% 1.05 - 1.65) Based on data from 305 participants in 1 studies Follow up 168 days	**270** per 1000	**356** per 1000 Difference: **86 more per 1000** (CI 95% 14 more - 176 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether probiotics improves or worsen adverse events

1. **Risk of Bias: serious. Imprecision: serious.** Low number of patients;
2. **Risk of Bias: serious. Imprecision: serious.** Low number of patients;
3. **Risk of Bias: serious. Imprecision: very serious.** 95% CI include important benefits and harms;

This review compiles the evidence on potential therapeutic options for post COVID-19 condition (PCC). Included are all the identified clinical forms, symptoms and manifestations of PCC for which an intervention was assessed in at least one randomized controlled trial.