Supplemental Online Content

Pouliopoulou DV, Macdermid JC, Saunders E, et al. Rehabilitation interventions for physical capacity and quality of life in adults with post–COVID-19 condition: a systematic review and meta-analysis. *JAMA Netw Open*. 2023; 6(9):e2333838
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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Study Protocol

PROSPERO
International prospective register of systematic reviews

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

A list of fields that can be edited in an update can be found here

1. * Review title.

Give the title of the review in English

Efficacy and safety of rehabilitation interventions in patients with post-COVID syndrome: a systematic review with meta-analysis

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

29/11/2022

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

28/01/2023

5. * Stage of review at time of this submission.

This field uses answers to initial screening questions. It cannot be edited until after registration.

Tick the boxes to show which review tasks have been started and which have been completed.

Update this field each time any amendments are made to a published record.

The review has not yet started: Yes

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Update this field each time any amendments are made to a published record.

The review has not yet started: Yes

Review stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Pavlos Bobos

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Bobos

7. * Named contact email.

Give the electronic email address of the named contact.

pbobos@uwo.ca

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

1151 Richmond Street

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+1-519-870-5145

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be

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Full title of the organisational affiliations for this review and website address if available. This field may be

completed as 'None' if the review is not affiliated to any organisation.

Western University

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Ms Dimitra Vasiliki Pouliopoulou. Western University
Ms Emily Saunders. Western University
Dr Joy MacDermid. Western University
Dr Erin Miller. Western University
Dr Sue Peters. Western University
Dr Trevor Birmingham. Western University
Dr Alison Rushton. Western University
Dr Pavlos Bobos. Western University

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

No funding was received to conduct this review

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Are rehabilitation interventions effective at improving aerobic and respiratory function and quality of life, in

patients diagnosed with long-covid?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

A systematic electronic search of the literature will be performed from January 2020 until December 2022, in PubMed, Scopus, CINAHL, and Clinical Trials Registry with no date restrictions. The following keywords will be used to identify potentially relevant studies: "covid-19", "long-covid", "post-covid", “sequelae”, "exercise", "exercise therapy", "rehabilitation", "physical activity", "physical therapy", "randomized controlled trials", "RCT". In addition, we will conduct a manual search of the reference lists of the included studies to identify any potential studies missed in the electronic search.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

The main condition being studied are patients suffering from Long covid syndrome as defined by The World Health Organization (WHO). The WHO defines Long COVID or post COVID syndrome as a case definition of “symptoms occurring three or more months after acute SARS-CoV-2 infection that last for at least two months and is not explainable by an alternative condition”.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

We will include randomized trials that include patients with Long COVID syndrome as defined by The World Health Organization (WHO). Studies that include interventions during acute care will be excluded.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

We will include studies that used aerobic, strength, conditioning and respiratory exercise interventions and treatment modalities. Studies that use a medication-only treatment will be excluded.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

The interventions in the control groups can be either usual/standard care or waitlist/control.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

We will only include randomised control trials. Studies that are self-controlled and do not include a control group will be excluded. Non-randomised, quasi-experimental and feasibility trials will be excluded. We will also exclude observational studies, case series, case reports and pilot studies.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

The main outcome will be performance-based aerobic function, measured with the 6-minute walking test. If similar measurements are used instead, such as a 3min-walking test or a 2-min walking test, we will extract the outcome measures and pool them using Standardised Mean Difference. The timepoint of the primary outcome will be directly post-intervention.

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

The effect measures for the main outsome will be the standardised mean differences (SMD) of change scores with 95% credible intervals. We will use OpenBUGS and STATA (Stata Statistical Software: Release 16, StataCorp LLC) to perform the meta-analysis.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

We will include long term performance-based aerobic function measured by the 6-minute walking test in our secondary outcomes. We will also include performance-based aerobic function measured by the 30-sec sit and stand test in both short and long-term follow-ups in our secondary outcomes. Other secondary outcomes will be patient-reported function, performance-based and patient reported respiratory function, Global Health Status and patient reported quality of life both in short and in long term follow-ups. If more than one effect measures are presented in a study for the same outcome, we will extract the one reported as the primary outcome in the study. We will also monitor adverse events and serious adverse events related to the interventions across all studies. Adverse events and non-adverse events unrelated to the interventions will not be included.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

The effect measures for performance-based and patient-reported aerobic function, respiratory function, Global Health Status and quality of life (continuous outcomes) will be the standardised mean differences (SMD) of change scores with 95% credible intervals. We will use OpenBUGS and STATA (Stata Statistical Software: Release 16, StataCorp LLC) to perform a meta-analysis using the standardised mean difference with 95% credible intervals. The effect measured for the adverse events (dichotomous outcome) will be the risk ratios with 95% credible intervals (CrIs).

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

The selection of individual studies will involve two independent reviewers who will perform a systematic electronic search of the databases. Two reviewers will identify potentially relevant articles, remove duplicates, and then screen titles and abstracts. The full text of any study marked include or uncertain will be obtained and the eligibility criteria will be applied. Two independent researchers will extract the data from the eligible included studies. Data extraction will include study, author, year, sample characteristics, intervention, comparison groups, aerobic function, respiratory function, Global Health Status, quality of life, and adverse or serious adverse events.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Two independent authors will assess the included RCTs for risk of bias (ROB). The ROB assessment will be performed using the Cochrane Risk of Bias tool. The ROB tool is based on 7 items, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The adequacy of each of the seven ROB domains will be rated as “low,” “unclear,” or “high” risk. We will summarize the assessment of ROB per study as Low ROB (if low ROB was judged for all the seven domains); as Unclear ROB (if unclear ROB was judged for one or more of the seven domains); and as High ROB (if high ROB was judged for one or more of the seven domains). The GRADE guidelines will be used to evaluate the certainty of evidence. The GRADE approach includes assessing ROB for study limitations, inconsistency, publication bias, imprecision, and indirectness. The rating of the quality of outcome across trials will be carried out to summarize the extent of our confidence (high, moderate, low, or very low).

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

For data synthesis we will use OpenBUGS (version 3.2.3, Cambridge, UK) and STATA (Stata Statistical Software: Release 16, StataCorp LLC). We will perform a pair-wise Bayesian random-effects meta-analyses using the normal likelihood to compare rehab interventions versus usual care, waitlist or no intervention using standardized mean difference with 95% credible intervals for continuous outcomes and risk ratio with 95% credible Intervals for binary ones. If meta-analysis is not possible, we will present the results in a narrative format. We will provide descriptive statistics of the patient groups, interventions, outcomes, and adverse effects of treatments. We will report all results using the intention-to-treat principle (the sample randomized in the study). If trials report standard error, we will transform it into standard deviation. For missing values such as standard deviation, we will use the following methods: 1. We convert 95% Confidence Intervals or Standard Error to Standard Deviation; 2. Digitizer software — Digitize a scanned graph or chart into (x, y)-data, will be used when data was presented in graphic form (http://www.digitizeit.de/). To facilitate analysis, data imputation rules will be used when necessary. We will assess small study effects with Harbord test and we will investigate the presence of publication bias with funnel plots. In the presence of publication bias we will impute the missing studies to account for publication bias in the meta-analysis. We will compare the observed and the imputed studies by using the non-parametric “trim and fill” method. We will use contour-enhanced funnel plot to assess if imputed studies fall in the region of statistical significance.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

Heterogeneity will be assessed with tau squared statistic (?2). In the presence of substantial heterogeneity in the meta-analysis, we planned to perform separate univariate meta-regressions to quantify factors that may contribute to substantial heterogeneity. We prespecified the following factors: allocation concealment, time of follow-up and length of inpatient stay.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness

No

Diagnostic

No

Epidemiologic

No

Individual patient data (IPD) meta-analysis

No

Intervention

No

Living systematic review

No

Meta-analysis

Yes

Methodology

No

Narrative synthesis

No

Network meta-analysis

No

Pre-clinical

No

Prevention

No

Prognostic

No

Prospective meta-analysis (PMA)

No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
Yes

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
Yes

For COVID-19 registrations please tick all categories that apply. Doing so will enable your record to appear in area-specific searches

Chinese medicine
Diagnosis
Epidemiological
Genetics
Health impacts
Immunity

Long COVID
Mental health
PPE
Prognosis
Public health intervention
Rehabilitation
Service delivery
Transmission
Treatments
Vaccines
Other

Crime and justice

No

Dental

No

Digestive system

No

Ear, nose and throat

No

Education

No

Endocrine and metabolic disorders

No

Eye disorders

No

General interest

No

Genetics

No

Health inequalities/health equity

No

Infections and infestations

Yes

International development

No

Mental health and behavioural conditions

No

Musculoskeletal

No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
Yes

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
Yes

Respiratory disorders
Yes

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse

No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Canada

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

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International prospective register of systematic reviews

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.

Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

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eTable 1. Research strategy

MEDLINE, Feb 10th 2023

1	**COVID-19/ or SARS-CoV-2/**	**215156**
2	"Physical and Rehabilitation Medicine"/ or Rehabilitation Research/ or Rehabilitation/	21606
3	("long covid*" or "post covid*" or "long-covid*" or "post-covid*" or "covid* sequela*").tw.	7677
4	Physical Therapy Modalities/	40348
5	Exercise Therapy/	48171
6	2 or 4 or 5	105687
7	("physical therapy" or "physiotherapy" or "rehabilitation" or "exercise").tw.	504861
8	6 or 7	545923
9	1 or 3	218382
10	8 and 9	4194
11	Randomized Controlled Trial/ or Clinical Trial/	908100
12	("RCT" or "randomised control* trial" or "randomized control* trial" or "feasibility" or "pilot" or "trial").tw.	1764982
13	11 or 12	1764982
14	10 and 13	508

eMethods. Models

eBUGS code. Fixed and random-effects model

Fixed-effect model

```
model {
            for(i in 1:ns)
            {
            mu[i] ~ dnorm(0,.0001)
            for (k in 1:2) {
                  r[i,k] ~ dbin(p[i,k],n[i,k])
                  logit(p[i,k]) <- mu[i] + d[k]
            }
      }
d[1]<- 0
d[2] ~ dnorm(0,.0001)
or <- exp(d[2])
prob.harm <- step(d[2])
}
```

Random-effects Model

```
model {
for(i in 1:ns) {
      delta[i,1] <- 0
      mu[i] ~ dnorm(0,.0001)
      for (k in 1:2) {
                  r[i,k] ~ dbin(p[i,k],n[i,k])
                  logit(p[i,k]) <- mu[i] + delta[i,k]
      }
      delta[i,2] ~ dnorm(d[2], tau)
}
d[1]<- 0
d[2] ~ dnorm(0,.0001)
sd ~ dunif(0,2)
tau <- pow(sd,-2)
or <- exp(d[2])
prob.harm <- step(d[2])
}
```

eTable 2. Excluded studies – reasons for exclusion

Study	Reason for exclusion
Abodonya 2021[1]	Wrong study design
Achabaeva 2022[2]	Wrong intervention
Ahmed 2021[3]	Wrong study design
Al-Aly 2021[4]	Wrong study design
Al Chikhanie 2021[5]	Wrong study design
Besnier 2022[6]	protocol only
Betschart 2021[7]	Wrong study design
Bodrova 2020[8]	Wrong intervention
Bragin 2021[9]	Wrong intervention
Brame 2022[10]	Wrong patient population
Cahalan 2022[11]	Wrong study design
Calabrese 2021[12]	Wrong study design
Calvo-Paniagua 2022[13]	Wrong study design
Corna 2022[14]	Wrong patient population
Dalbosco-Salas 2021[15]	Wrong study design
Eross 2020[16]	Wrong study design
Gloeckl 2021[17]	Wrong study design
Hawkins 2022[18]	Wrong intervention
Hermann 2020[19]	Wrong study design
Kaisinova 2021[20]	full text not available
Kim 2022[21]	Wrong comparator
Kortianou 2022[22]	Wrong study design
Kuut 2021[23]	protocol only
Li 2020[24]	Wrong patient population
Liu 2021[25]	Wrong intervention
Liu 2021[26]	Wrong patient population
Llurda-Almuzara 2022[27]	Wrong patient population
Lu 2021[28]	Wrong intervention
Luo 2022[29]	Wrong intervention
Martin 2021[30]	Wrong study design
Mayer 2021[31]	Wrong study design
Michler 2022[32]	Wrong study design
Mukand 2022[33]	Wrong study design
Nagy 2022[34]	Wrong comparator
Nambi 2022[35]	Wrong comparator
Orlova 2022[36]	Wrong intervention
Palau 2022[37]	missing data
Pehlivan 2022[38]	missing data
Piquet 2021[39]	Wrong study design
Plaza 2022[40]	Wrong study design
Sharma 2022[41]	missing data
Shogenova 2021[42]	Wrong patient population
Spruit 2020[43]	Wrong study design
Srinivasan 2021[44]	Wrong intervention
Szczegielniak 2021[45]	Wrong study design
Tang 2021[46]	Wrong study design
Toulgui 2022[47]	Wrong study design
Tsutsui 2021[48]	Wrong study design
Udina 2021[49]	Wrong study design
Vallier 2023[50]	Wrong comparator

Vink 2020[51]	Wrong study design
Wang 2020[52]	Wrong study design
Xiong 2020[53]	Wrong study design
Zilberman-Itskovich 2022[54]	Wrong intervention

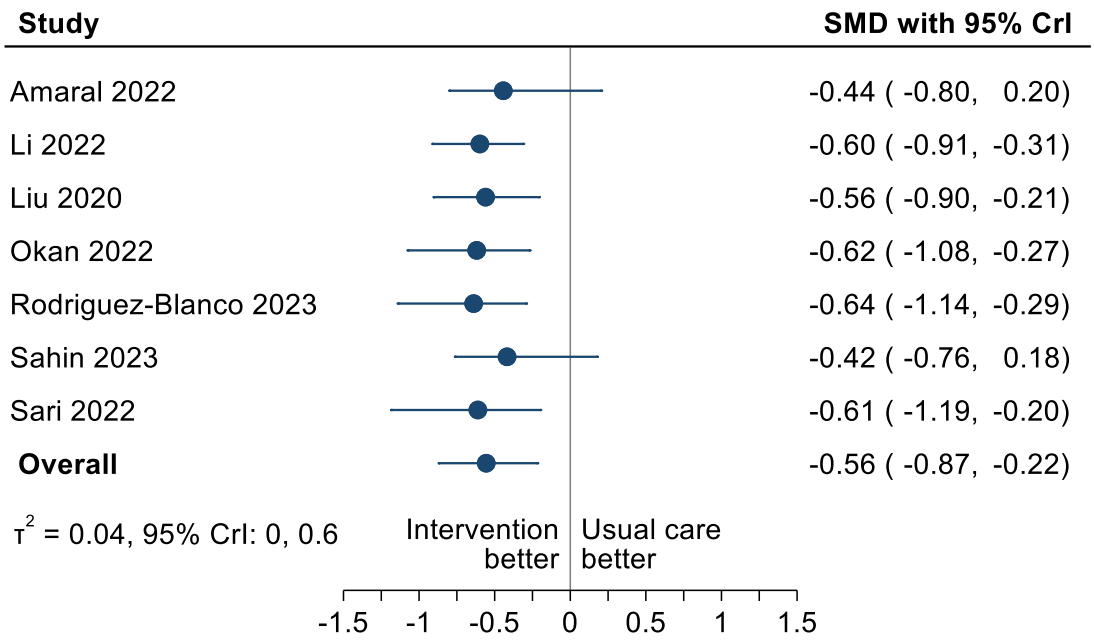
eTable 3. Tidier

	TiDiER checklist item											
Author	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Amaral 2022[55]	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	x	x
Capin 2022[56]	✓	✓	✓	✓	✓	✓	✓	x	x	NA	✓	✓
de Corral 2022[57]	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	x	x
de Souza[58]	✓	✓	x	x	x	x	✓	x	x	NA	x	x
Jimeno-Almazan 2022[59,60]	✓	✓	x	✓	✓	✓	✓	✓	✓	NA	✓	x
Li 2022[61]	✓	✓	x	x	✓	✓	✓	x	✓	NA	x	x
Liu 2022[62]	✓	✓	✓	✓	x	✓	x	✓	✓	NA	x	x
McNarry 2022[63]	✓	✓	✓	✓	x	✓	✓	✓	✓	NA	x	✓
Okan 2022[64]	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	x	✓
Phillip 2022[65]	✓	✓	✓	✓	✓	✓	✓	✓	x	NA	x	✓
Rodriguez-Blanco 2023[66]	✓	✓	✓	✓	✓	✓	✓	✓	x	NA	x	x
Romanet 2022[67]	✓	✓	x	✓	✓	x	x	✓	x	NA	x	✓
Sari 2023[68]	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	x	✓
Sahin 2023[69]	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓	✓

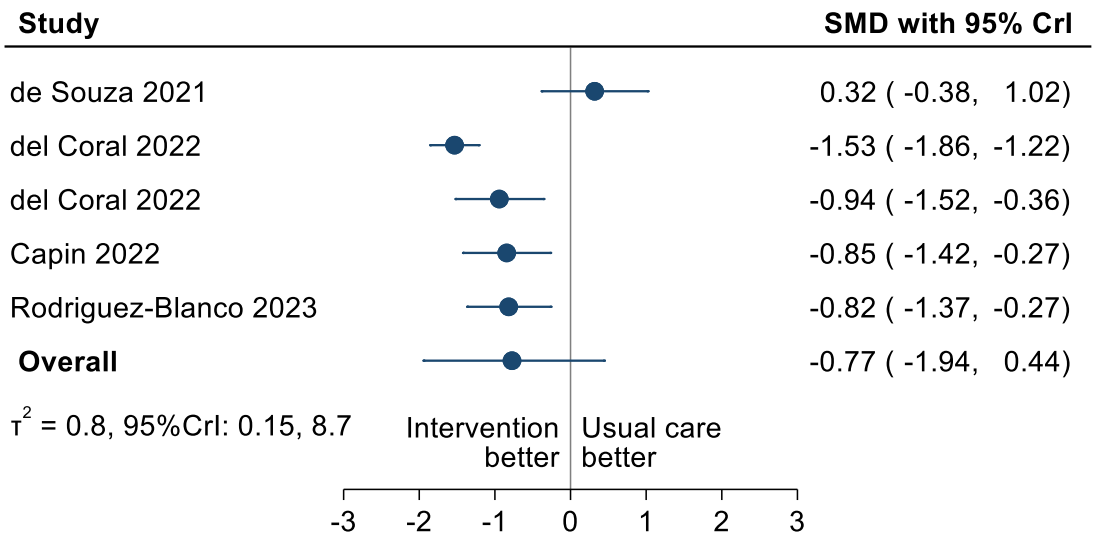
1. Brief name
2. Why (rationale, theory, goal)
3. Materials used in intervention (physical or informational)
4. Procedures (activities, processes)
5. Intervention providers
6. Modes of delivery (e.g. face-to-face, virtual, individual or group)
7. Location of intervention
8. When and how much (number of sessions, time period, schedule and dose)
9. Details of tailoring
10. Modifications to intervention
11. Planned adherence and fidelity assessment
12. Actual adherence and fidelity

NA: not applied

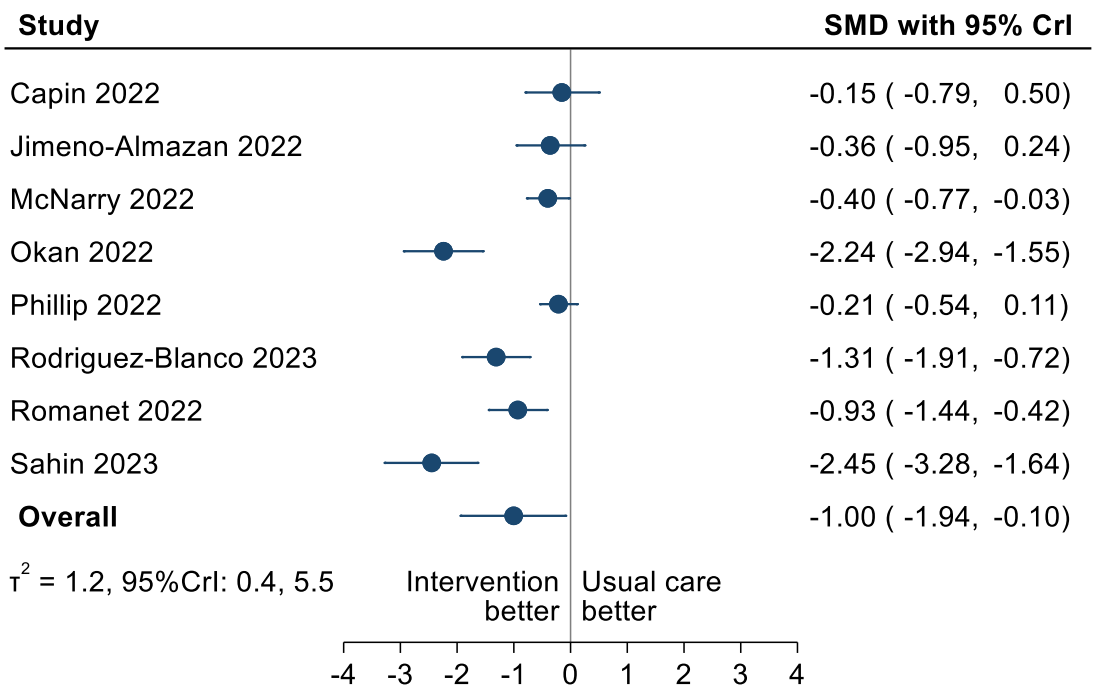
eFigure 1. Caterpillar plot for exercise capacity



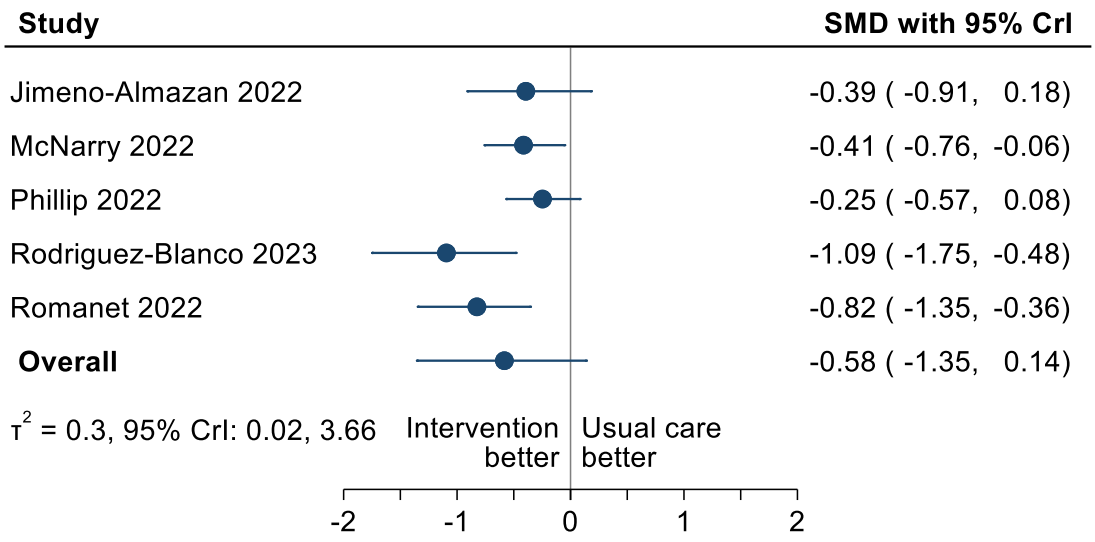
eFigure 2. Caterpillar plot for lower limb muscle function



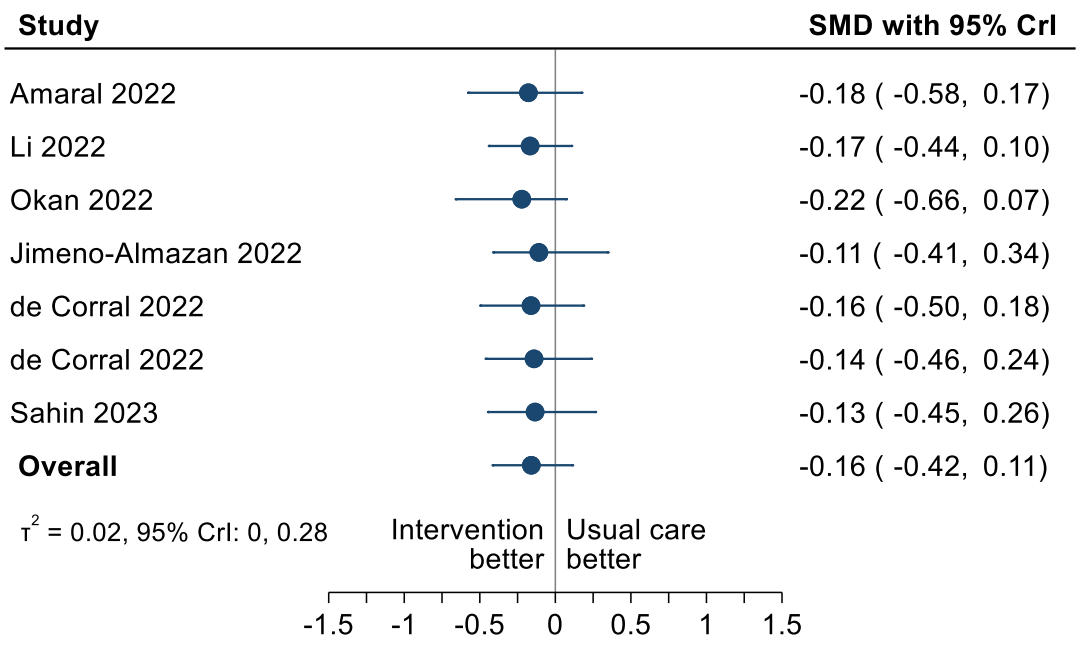
eFigure 3. Caterpillar plot for dyspnea



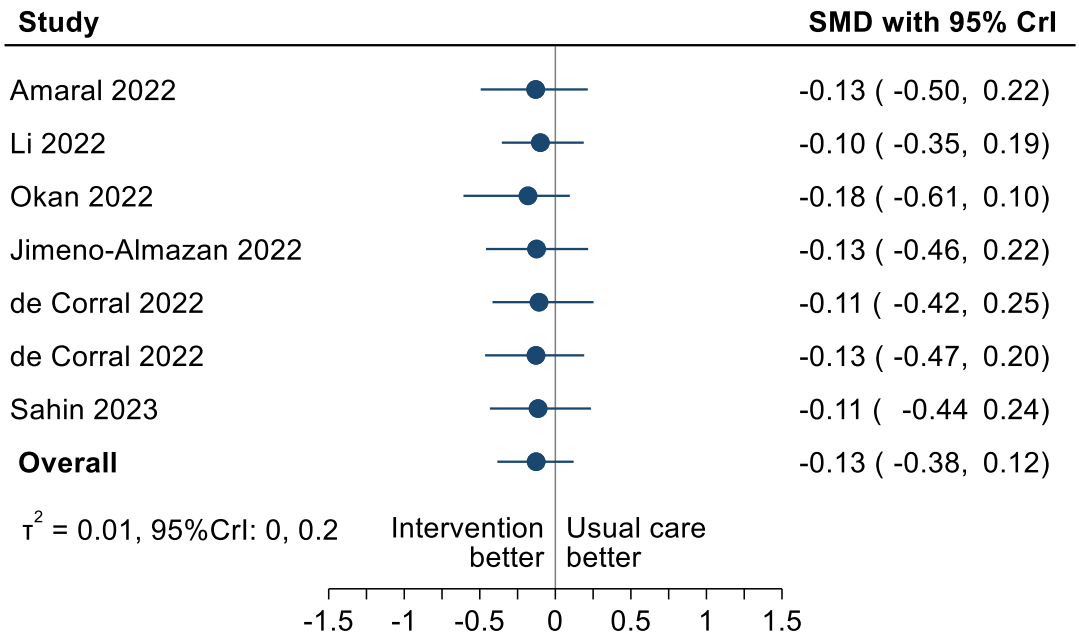
eFigure 4. Sensitivity analysis for dyspnea (allocation concealment)



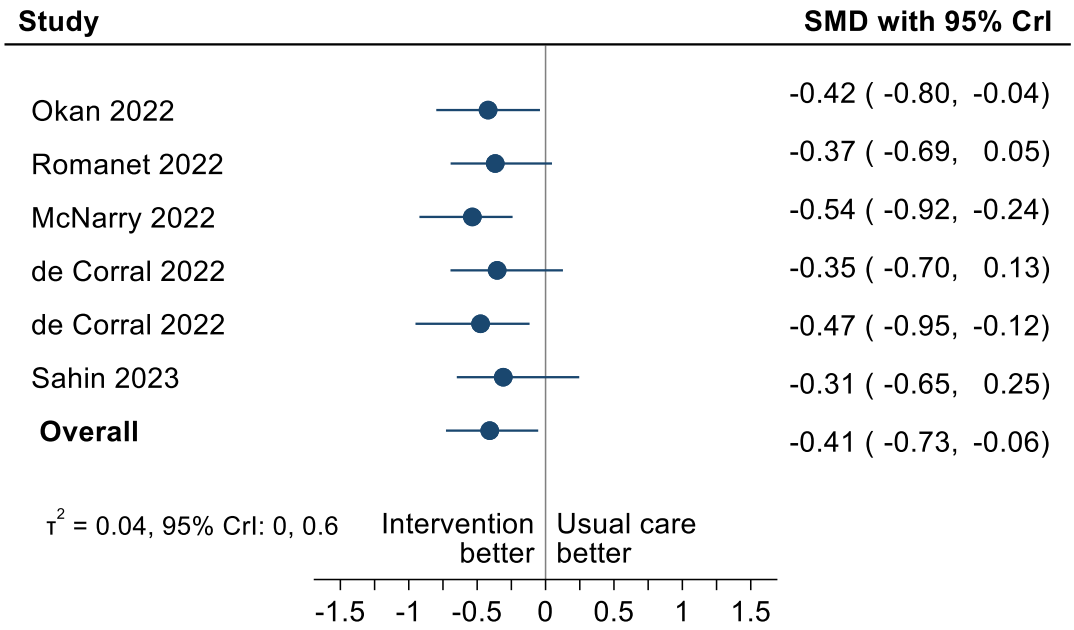
eFigure 5. Caterpillar plot for respiratory function (FEV1)



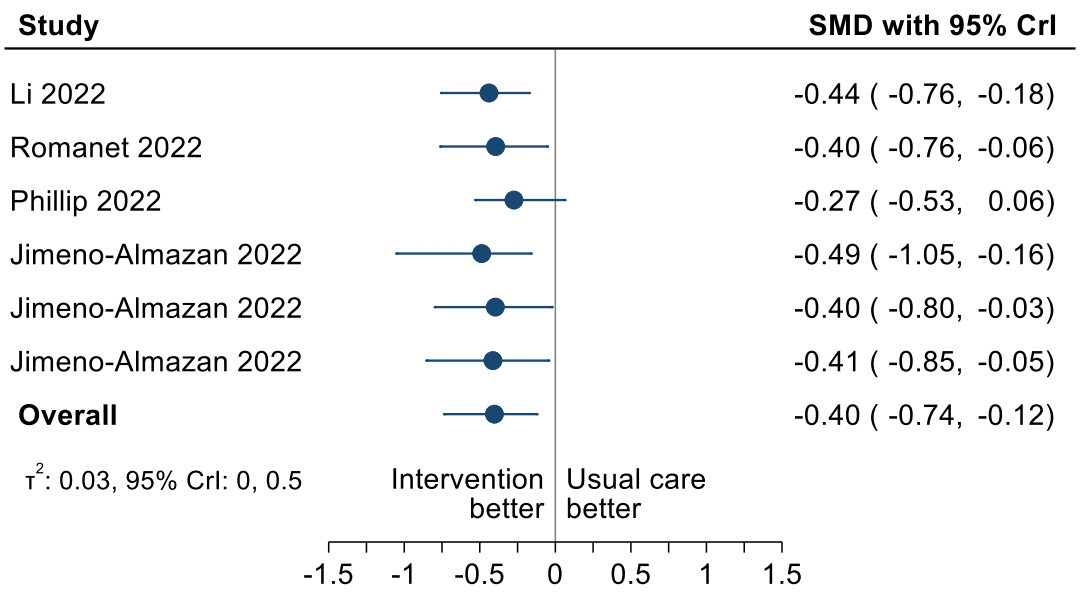
eFigure 6. Caterpillar plot for respiratory function (FVC)



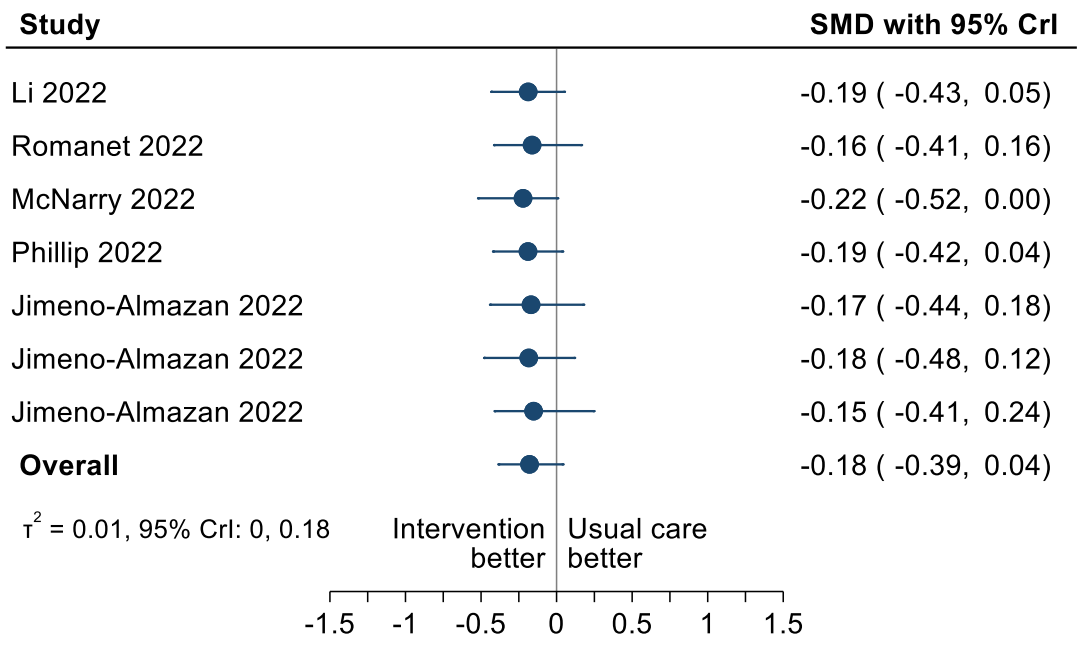
eFigure 7. Caterpillar plot for quality of life outcomes



eFigure 8. Caterpillar plot of physical health outcomes



eFigure 9. Caterpillar plot for mental health outcomes



eTable 4. Adverse events Results

	Odds Ratio			Heterogeneity	
Model	**Median**	**95% CrI**	**Probability of AEs**	**Median**	**95% CrI**
Fixed Effect	1.45	0.65, 3.40	82%	-	-
Random Effects	1.68	0.32, 9.94	75%	0.30	0.07, 117.70

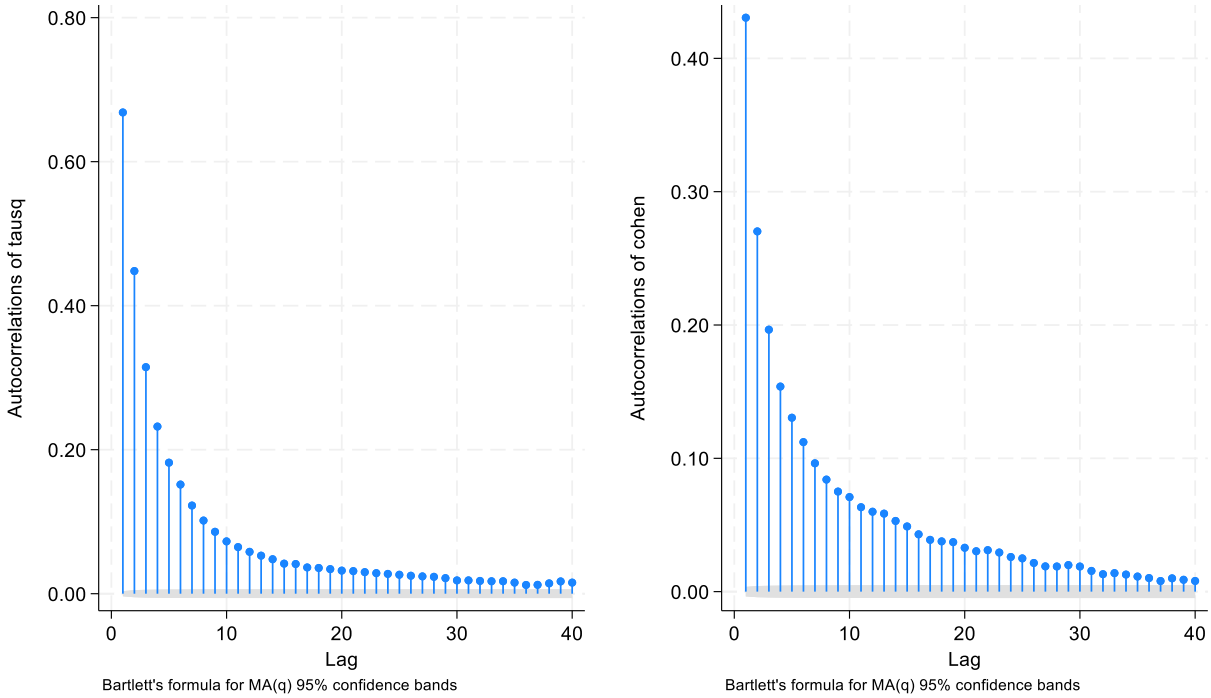
eTable 5: Model fit and model comparison for adverse events

Summary	Fixed effect model	Random effects model
Posterior mean residual deviances	35.18	25.58
Posterior mean deviances	40.91	33.17
Effective number of parameters	5.73	7.60
Deviance information criteria (DIC)	46.65	40.77

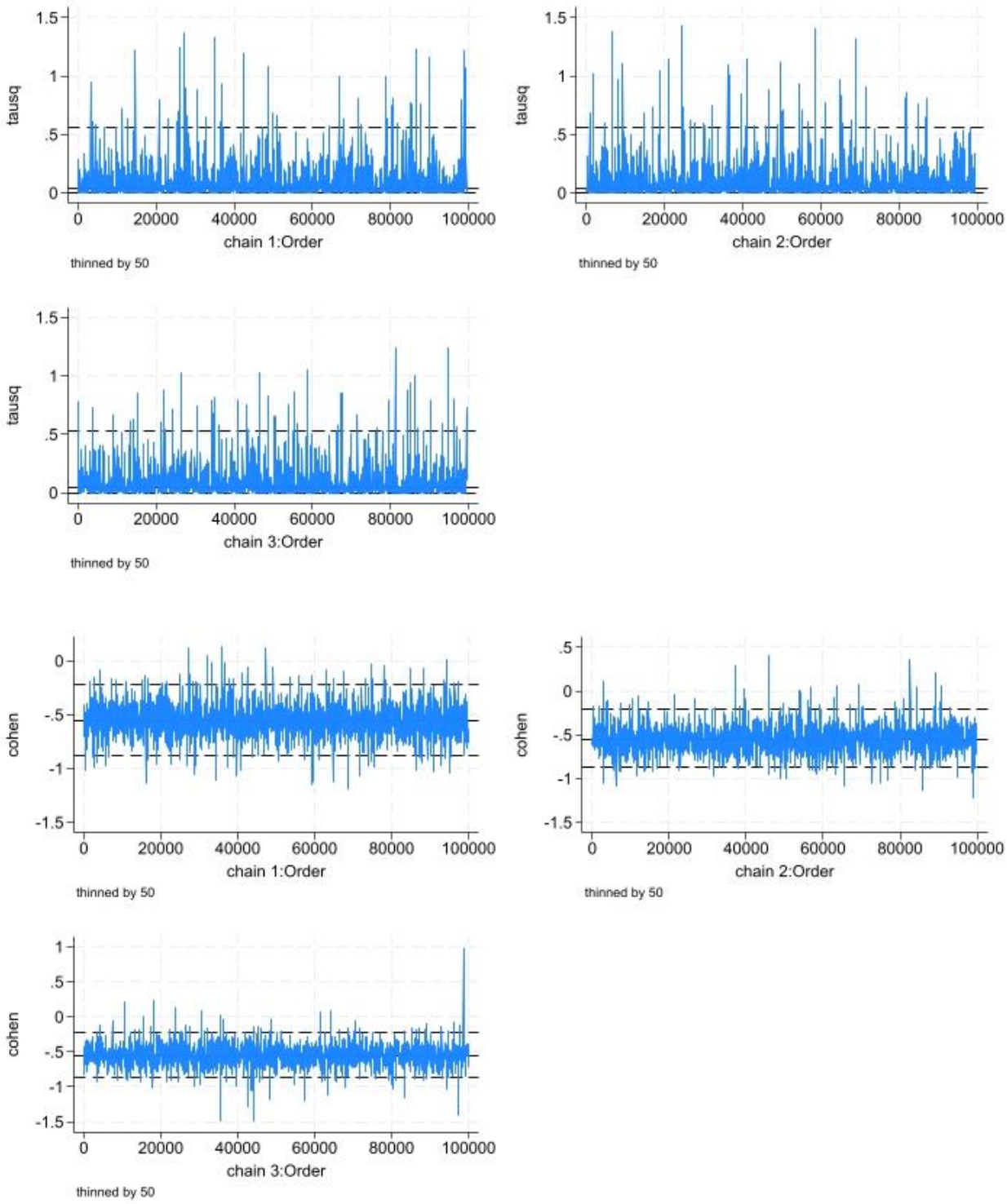
eTable 6: Publication bias

Outcome	SE	P value
Functional aerobic capacity	1.93	0.71
Functional lower limb muscle strength and endurance	2.09	0.25
Dyspnoea	5.01	0.13
Respiratory Function – FEV1	2.54	0.97
Respiratory Function – FVC	2.85	0.88
Quality of life – Overall	3.87	0.60
Quality of life – Physical Health	2.50	0.66
Quality of life – Mental Health	2.44	0.87
Adverse Events	52.26	0.07

eFigure 10. Autocorrelation



eFigure 11. Trace plot



eTable 7. Sensitivity analysis

6MWT				
Study	**median**	**95% CrI**	**Pr_Sup**	**Pr_MID**
Amaral 2022	-0.51	(-0.80, -0.01)		
Li 2022	-0.59	(-0.86, -0.33)		
Liu 2020	-0.56	(-0.85, -0.27)		
Okan 2022	-0.59	(-0.96, -0.31)		
Rodriguez-Blanco 2023	-0.60	(-1.00, -0.32)		
Sahin 2023	-0.49	(-0.77, -0.00)		
Sari 2022	-0.59	(-1.01, -0.26)		
Total effect estimate	**-0.56**	**(-0.81, -0.31)**	**100.0%**	**97.7%**
τ^2	0.01	(0.00, 0.20)		

STS				
Study	**median**	**95% CrI**	**Pr_Sup**	**Pr_MID**
de Souza 2021	0.18	(-0.54, 0.90)		
del Coral 2022	-1.51	(-1.83, -1.18)		
del Coral 2022	-0.93	(-1.49, -0.37)		
Capin 2022	-0.85	(-1.39, -0.29)		
Rodriguez-Blanco 2023	-0.83	(-1.35, -0.28)		
Total effect estimate	**-0.79**	**(-1.50, -0.02)**	**98%**	**92%**
τ^2	-0.92	(-2.50, 0.86)		

Dyspnoea				
Study	**median**	**95% CrI**	**Pr_Sup**	**Pr_MID**
Capin 2022	-0.19	(-0.82, 0.45)		
Jimeno-Almazan 2022	-0.38	(-0.97, 0.21)		
McNarry 2022	-0.41	(-0.77, -0.05)		
Okan 2022	-2.18	(-2.88, -1.50)		
Phillip 2022	-0.22	(-0.54, 0.10)		
Rodriguez-Blanco 2023	-1.30	(-1.89, -0.72)		
Romanet 2022	-0.93	(-1.44, -0.42)		
Sahin 2023	-2.36	(-3.18, -1.56)		
Total effect estimate	**-0.99**	**(-1.75, -0.28)**	**99%**	**97%**
τ^2	0.79	(0.26, 2.92)		

FEV1				
Study	**median**	**95% CrI**	**Pr_Sup**	**Pr_MID**
Amaral 2022	-0.17	(-0.49, 0.13)		
Li 2022	-0.16	(-0.42, 0.09)		
Okan 2022	-0.19	(-0.55, 0.07)		
Jimeno-Almazan 2022	-0.13	(-0.40, 0.23)		
de Corral 2022	-0.16	(-0.45, 0.14)		
de Corral 2022	-0.15	(-0.42, 0.16)		
Sahin 2023	-0.14	(-0.41, 0.18)		
Total effect estimate	-0.16	(-0.39, 0.08)	**91%**	**11%**
τ^2	**0.01**	**(0.00, 0.11)**		

FVC				
Study	**median**	**95% CrI**	**Pr_Sup**	**Pr_MID**
Amaral 2022	-0.13	(-0.43, 0.16)		
Li 2022	-0.11	(-0.35, 0.15)		
Okan 2022	-0.16	(-0.50, 0.10)		
Jimeno-Almazan 2022	-0.12	(-1.39, -0.29)		
de Corral 2022	-0.11	(-0.39, 0.19)		

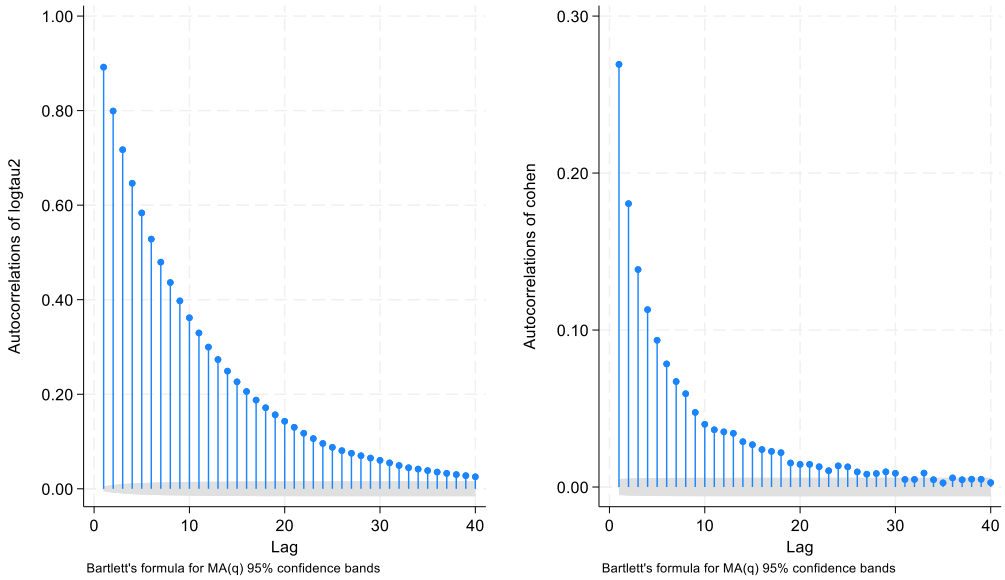
de Corral 2022	-0.13	(-0.42, 0.15)		
Sahin 2023	-0.12	(-0.40, 0.17)		
Total effect estimate	**-0.13**	**(-0.36, 0.10)**	**86%**	**7%**
τ^2	0.01	(0.00, 0.10)		

QoL				
Study	**median**	**95% CrI**	**Pr_Sup**	**Pr_MID**
Okan 2022	-0.42	(-0.73, -0.10)		
Romanet 2022	-0.39	(-0.67, -0.04)		
McNarry 2022	-0.49	(-0.83, -0.23)		
de Corral 2022	-0.39	(-0.68, -0.00)		
de Corral 2022	-0.45	(-0.82, -0.15)		
Sahin 2023	-0.36	(-0.65, 0.08)		
Total effect estimate	**-0.41**	**(-0.66, -0.15)**	**100%**	**82%**
τ^2	0.01	(0.00, 0.19)		

PHC				
Study	**median**	**95% CrI**	**Pr_Sup**	**Pr_MID**
Li 2022	-0.42	(-0.71, -0.18)		
Romanet 2022	-0.39	(-0.70, -0.11)		
Phillip 2022	-0.32	(-0.55, -0.01)		
Jimeno-Almazan 2022	-0.44	(-0.89, -0.17)		
Jimeno-Almazan 2022	-0.39	(-0.72, -0.09)		
Jimeno-Almazan 2022	-0.40	(-0.76, -0.10)		
Total effect estimate	**-0.40**	**(-0.65, -0.17)**	**100%**	**81%**
τ^2	0.01	(-2.50, 0.86)		

MHC				
Study	**median**	**95% CrI**	**Pr_Sup**	**Pr_MID**
Li 2022	-0.19	(-0.41, 0.03)		
Romanet 2022	-0.17	(-0.40, 0.10)		
McNarry 2022	-0.21	(-0.47, 0.00)		
Phillip 2022	-0.19	(-0.40, 0.02)		
Jimeno-Almazan 2022	-0.17	(-0.41, 0.11)		
Jimeno-Almazan 2022	-0.18	(-0.44, 0.08)		
Jimeno-Almazan 2022	-0.16	(-0.39, 0.15)		
Total effect estimate	-0.18	(-0.37, 0.02)	**97%**	**11%**
τ^2	**0.01**	**(0.00, 0.08)**		

eFigure 12 Sensitivity analysis – Autocorrelation plot



eFigure 13 Sensitivity analysis – Trace plot