Respiratory Medicine

Pulmonary rehabilitation in sarcoidosis: a systematic review and meta-analysis

--Manuscript Draft--

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Abstract:	Background Exercise intolerance, muscle weakness, dyspnoea, and fatigue are frequent complications in symptomatic sarcoidosis patients. Pulmonary rehabilitation improves exercise capacity, symptoms, and quality of life in patients with chronic respiratory diseases. Our objective was to systematically determine the effects of pulmonary rehabilitation in patients with sarcoidosis. Methods A systematic review was conducted in seven databases. Studies that applied pulmonary rehabilitation in patients with sarcoidosis were reviewed. Two independent reviewers analysed the studies, extracted the data and assessed the quality of evidence. Results Of the 406 reports returned by the initial search, five articles reporting on 184 patients were included in the data synthesis. Two studies included multi-component exercise, one inspiratory muscle training, one a physical activity incentivisation programme, and one a telerehabilitation program. In the intervention group (IG), we found significant improvement in exercise capacity (SMD 1.65, 95%CI 0.45, 2.86 points, p=0.006). If we only analyse the studies that performed the six-minute walking test, the IG walked 40.3 (CI95% 20.3, 60.2) m higher than the control group (CG) (p<0.001). Additionally, the dyspnoea was reduced (MD -0.42 95%CI -0.75, -0.10, p=0.002). However, fatigue, quality of life and pulmonary function did not show any change. Conclusion Pulmonary rehabilitation could improve exercise capacity and dyspnoea perception in

	patients with sarcoidosis.
Response to Reviewers:	October 12th, 2023 Dear Editor, The revised version of the manuscript entitled “Pulmonary rehabilitation in sarcoidosis: a systematic review and meta-analysis (YRMED-D-23-00080) is currently being submitted to the Journal for consideration by the editor and reviewers. First of all, we would like to express our gratitude for the opportunity of submitting the current revised version of our manuscript. The material has been modified following your recommendations. At the end of this document, you will find the point-by-point responses to the reviewers. For a better location of the corrections, we highlighted with “tracked changes” the modified text in the manuscript. Finally, we appreciate the reviewers' comments that improved the revised manuscript's quality. We hope that the revised version of our manuscript has met the reviewer's and the editor´s expectations. Best regards, Dr. Jacobo Sellarés Hospital Clínic, Barcelona, Spain Reviewer 1Introduction Clear outline of the study context. The Cochrane Review of Dowman et al. regarding PR in ILD was cited (ref. 10), but I recommend citing the updated version of this review in 2021. https://pubmed.ncbi.nlm.nih.gov/34559419/ Response: Thank you very much for this comment. We revised the entire text and replaced the reference from Dowman et al 2014 with Dowman et al 2021. Reviewer 1Methods Clear outline of the used methods, procedures and data handling. Response: We sincerely appreciate your comment. We follow the Cochrane collaboration methodology. Reviewer 1Results Comprehensive outline of the results of the review. Response: Thanks for your appreciation Reviewer 1In lines 321-323 the heterogeneity of the training modalities in the selected studies is mentioned. I recommend to address this issue a little more. Especially regarding the main conclusion of this review it is important to reflect on this. What is the definition of the concept pulmonary rehabilitation used in this review? For example, the study of Karadalli et al. uses a unimodal intervention (IMT), other studies include multi-modal interventions (strength training, endurance training, breathing exercises, education, e.g.). Response: Thank you very much for this comment. We expanded the paragraph regarding the heterogeneity of the interventions (see lines 355-370). We agree with the reviewer that this aspect is relevant when writing the conclusions, so we soften the main conclusion in the abstract, also the conclusion at the beginning of the discussion, and at the final conclusions section. Reviewer 1Non randomized studies regarding PR or exercise training in sarcoidosis are not mentioned in the discussion section. Allthough, not randomized, the outcome of these studies may be of additional value in supporting the results of this review. Response: Thanks for this suggestion. We have included a paragraph that analyses several observational studies with even larger sample sizes, which showed benefits in the different outcomes included in this review (see lines 336-345). Reviewer 3 The metaanalysis prpposed by Sellares et coauthors is well-written and

	very interesting since it is focused on a crucial and unresolved issue in the framework of clinical management of patients with sarcoidosis. Standing that fatigue and muscle asthenia are among the most common symptoms reported by the patients and considering the ever-lasting lack of targeted drugs for the treatment of sarcoidosis, that, moreover, have always failed to improve this outcome, the evaluation of the potential effectiveness of PR is surely of interest, even though really few evidence are available on this topic, as the Authors underlined. Response: Thank you very much for your comment. We already addressed it. Reviewer 3 - did you have any data concerning the percentage of patients taking treatment (such as steroids o immunosuppressants) in study included in the metaanalysis?Thank you very much for this comment, we narratively added the information regarding the use of steroids (see lines 197-198). Of the 5 studies, 4 reported it, without finding significant differences between groups. We added this information in the results. - same question concerning the extrapulmonary localizations and/or the presence of sarcoid lung fibrosis, considering that both these aspects may significantly affect dyspnea and pulmonary functional parameters Response: Thanks for this suggestion. We reviewed the articles and added information regarding this in the results section (lines 201-206), in addition to a paragraph in the discussion (see lines 365-370). Reviewer 3 - SGRQ and K-bild were not originally designed as tools for evaluating the quality of life of patients with sarcoidosis: I think you should briefly underline this aspect in the Discussion and comment how this aspect may have influenced the lack of efficacy of PR on these specific outcomes. Response: Thanks for this suggestion. We added a statement regarding this issue, suggesting the use of specific tools for this outcome in this population, such as Sarcoidosis health questionnaire.

Barcelona, January 22th, 2022

Dear Editor,

We are submitting the manuscript entitled "**Pulmonary rehabilitation in sarcoidosis: a systematic review and meta-analysis**" for peer review at **Respiratory Medicine**. Here, we to determine the effects of pulmonary rehabilitation in exercise capacity, fatigue, dyspnoea, quality of life and pulmonary function patients with sarcoidosis.

It is well-known that pulmonary rehabilitation (PR) is a cornerstone of care for people with chronic respiratory diseases, that aims to improve exercise tolerance and quality of life. In interstitial lung diseases, it has been also demonstrated that PR is safe and improves exercise tolerance, quality of life and breathlessness. Additionally, in recent European Respiratory Society guidelines, PR has been recommended in patients with sarcoidosis to improve fatigue (conditional recommendation, low quality of evidence). However, it is not clear the global effect of this intervention in this specific condition. This is the first systematic review to explore this.

Health professionals can use this information to assess their patients or institutions when designing PR interventions. On the other hand, our results give valuable information to researchers in the design of their clinical protocols. Hence, we think that this manuscript is an excellent fit for the scope and standards of **Respiratory Medicine**, and we look forward to its peer review.

This manuscript has not been published or presented elsewhere in part or entirety and is not under consideration by another journal. We have read and

understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare.

All authors meet the authorship criteria, disclose all potential conflicts of interest, and release the copyright should the manuscript be accepted for publication.

We hope you will find the manuscript of interest.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

Dr. Jacobo Sellarés
Hospital Clínic de Barcelona
Spain

Table 1. Characteristics of the included studies

Author, year, country	Group	Subjects (M/F)	Age (years)	BMI (kg/m2)	FVC (%)	FEV_1 (%)	FEV_1/FVC (%)	DL_{CO} (%)
Karadalli et al, 2016 Turkey	Intervention	15 (5/10)	45.1 ± 8.1	27.0 ± 5.1	100.3 ± 11.3	93.3 ± 11.2	78.1 ± 6.2	77.8 ± 19.3
	Control	15 (6/9)	47.5 ± 12.9	29.3 ± 4.8	100.1 ± 21.9	95.9 ± 20.1	80.1 ± 5.2	87.3 ± 14.6
Naz et al, 2018 Turkey	Intervention	9 (3/6)	59 (52-64)*	30 (24-33)*	76 (66-90)*	73 (65-85)*	80 (65-81)*	45 (36-54)*
	Control	9 (3/6)	51 (45-57)*	26 (20-28)*	69 (44-81)*	64 (46-77)*	82 (78-87)*	52 (38-53)*
Drent et al, 2020 The Netherlands	Intervention	27 (13/14)	48 (26-72)**	27.1 ± 3.6	99.9 ± 16.3	91.0 ± 19.0	NR	79.6 ± 11.8
	Control	41 (10/31)	48 (29-73)**	27.9±5.3	94.8 ± 18.0	85.7 ± 21.8	NR	77.9 ± 18.9
Wallaert et al, 2020 France	Intervention	20 (10/10)	57.5 (48.0-63.5)*	28.4 (23.7-31.1)*	80.7 ± 18.2	66.8 ± 20.2	NR	56.8 ± 15.9
	Control	18 (7/11)	57.5 (49-65)*	27.3 (23.4-31.2)*	81.4 ± 18.2	61.1 ± 16.9	NR	62.7 ± 18.5
Cerdan de las Heras et al, 2022 Denmark	Intervention	15 (10/5)	56.1 ± 14.4	28.7 ± 4.5	93.1 ± 19.4	79.3 ± 16.4	87.1 ± 14.3	65.9 ± 15.9
	Control	15 (9/6)	51.6 ± 12.7	27.3 ± 4.9	84.7 ± 17.9	63.0 ± 23.9	75.9 ± 21.4	64.3 ± 17.2

Abbreviations: BMI: Body mass index; DL_{CO}: Diffusing capacity for carbon monoxide; FEV_1: Forced expiratory volume during the first second; FVC: Forced vital capacity.
*median and interquartile range, **median and range

Table 2. Characteristics of pulmonary rehabilitation programs

Author, year	Duration and frequency	Type of intervention	Exercise capacity	Fatigue	Dyspnea	Quality of life	Pulmonary function	Respiratory muscles strength
Karadalli et al, 2016	30 min/d,7 days/week, for 6 weeks	Inspiratory muscle training at 40% of MIP	Δ6MWD** IG: 66.1 (44.3-88) CG: 11.6 (-10.2-33.5) ΔISWT** IG: 61.7 (32.0-91.2) CG: 16.2 (-14.5-46.8)	ΔFAS** IG:-8 (-14.4-(-2)); CG: -9.6 (-15.4-(-3.8))	ΔmMRC** IG:-1.1 (-1.3-(-0.8)); CG: -0.7 (-15.4-(-3.8))	ΔSGRQ** IG: -11.2 (-17.3-(-5.1)); CG: -9.4(-15.4-(-3.3))	ΔFEV_1** IG: 2.2 (-5.7-1.3); CG: 3.3 (-0.2-6.8) ΔFVC** IG: 2.5 (-1-6.1): CG: 3.5 (-0.1-7) $\Delta FEV_1/FVC$** IG: 0.2 (-1.4-1.9): CG: -0.5 (-2.1-1.1) ΔDLCO** IG: 2.2 (-2.2-6.7): CG: 3.4 (-1.3-8)	ΔMIP** IG: 45.9 (39.3-52.6); CG: 14.4 (7.7-21.1) ΔMEP** IG: 49.7 (39.3-60.2); CG: 21.7 (11.2-32.2)
Naz et al, 2018	12 w 2 times/w	Breathing exercises, endurance training, strength training for upper and lower limbs, and stretch- ing	Δ6MWD* IG: 40 (31-62) CG: -20 (-63-14)	ΔFSS* IG:-7 (-10-2); CG: 1 (0-4)	ΔmMRC* IG:-1 (-1.5-0); CG: 0 (0-0)	ΔSGRQ* IG: -19 (-25-1); CG: -11(-12-2)	ΔFEV_1* IG: 1 (-5-4); CG: -7 (-11-1) ΔFVC IG: 1 (-7-5): CG: -1 (-8-5) $\Delta FEV_1/FVC$ IG: 1 (-7-5): CG: -1 (-8-5) IG: -1(-3-2); CG:-4(-7-3) ΔDLCO IG: 7 (-1-12): CG: -2 (-6-14)	ΔMIP* IG: 6 (2-24); CG: 6 (-12-6) ΔMEP IG: 4 (-10-19); CG: -7 (-21-2)

Drent et al, 2020	3 months	Physical therapist-guided activity program. The coaching procedure included weekly action planning and feedback, modelling of behaviours and problem solving, and individual decision making, by email and/or telephone.	Δ6MWD IG: 28.7 ± 55.8 CG:4.7 ± 33.7 ΔVO_2max IG: 1.6 ± 2.6 CG:0.6 ± 2.4	ΔFAS IG: -3.7 ± 4.0 CG:-1.8 ± 5.3	NR	NR	ΔFEV_1 at baseline IG: 90.9 ± 20.9; CG: 85.7 ± 21.8 ΔFVC IG: 101.2 ± 19.4; CG: 94.8 ± 18.0 ΔDLCO IG: 77.2 ± 14.4; CG: 77.9 ± 18.9 IG: 79.6 ± 11.8; CG:77.9 ± 18.9	NR
Wallaert et al, 2020	2 months/ 3 times/w	Individual and group-based strengthening exercises, upper/lower limb training, and supervised endurance training. In addition, patients received training in resumption of daily life physical activity, therapeutic patient education, psychosocial support, and motivational communication, to facilitate health-related behavioral changes and self-management.	Δ6MST IG: 155 ± 45.3 CG: -27 ± 10.6 Δ6MST IG: -66.4 ± 85.4 CG: -27 ± 10.6	ΔFAS IG: -6.7 ± 4.95 CG: -2.0 ± 2.83	ΔmMRC* IG: 0 (0-1) CG: 0 (0-0)	NR	ΔFEV_1 (12-m)** IG-CG: 3.0 (-1.8-7.9) ΔFVC (12-m)** IG-CG: -2.3 (-7.3-2.6) ΔDLCO (12-m)** IG-CG: -2.8 (-10.2-4.6)	NR
Cerdan de Las Heras et al, 2022	3 months/ at least 60 m/w	Telerehabilitation group composed of video and chat-consultations with a physiotherapist and workout sessions with a virtual autonomous physiotherapist agent.	Δ6MWD IG-CG: 25.8 ± 21.9		ΔBorg scale IG-CG: 1.2 ± 0.5	ΔSGRQ-I IG-CG: -3.2 ± 8.9 ΔK-BILD IG-CG: 2.3 ± 2.6	ΔFVC IG-CG: 9.7 ± 7.0 ΔDLCO IG-CG: -17.6 ± 6.8	NR

Abbreviations: 6MST: Six-minute stepper test; 6MWD: Six-minute walking distance; DL_{CO}: Diffusing capacity for carbon monoxide; FAS: Fatigue assessment scale; FEV_1: Forced expiratory volume during the first second; FSS: Fatigue severity scale; FVC: Forced vital capacity; MIP: Maximum inspiratory pressure; mMRC: Modified medical research council; NR: Not reported. SGRQ: Saint George Respiratory questionnaire. *median + RIQ; ** mean + CI95%.

Figures legends:

Figure 1. Flowchart of the included studies

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 3. Forest plot for exercise capacity

Figure 4. Forest plot for six-minute walking distance (6MWD)

Figure 5. Forest plot for fatigue

Figure 6. Forest plot for dyspnoea

Figure 7. Forest plot for quality of life

Figure 8. Forest plot for carbon monoxide lung diffusing capacity (DL_{CO})

Figure 9. Forest plot for forced expiratory volume in the first second (FEV_1)

Highlights

- Exercise intolerance, dyspnoea, and fatigue are common in sarcoidosis patients.
- Pulmonary rehabilitation could improve exercise capacity in sarcoidosis patients.
- Pulmonary rehabilitation could improve symptoms in in sarcoidosis patients.

Figure 1

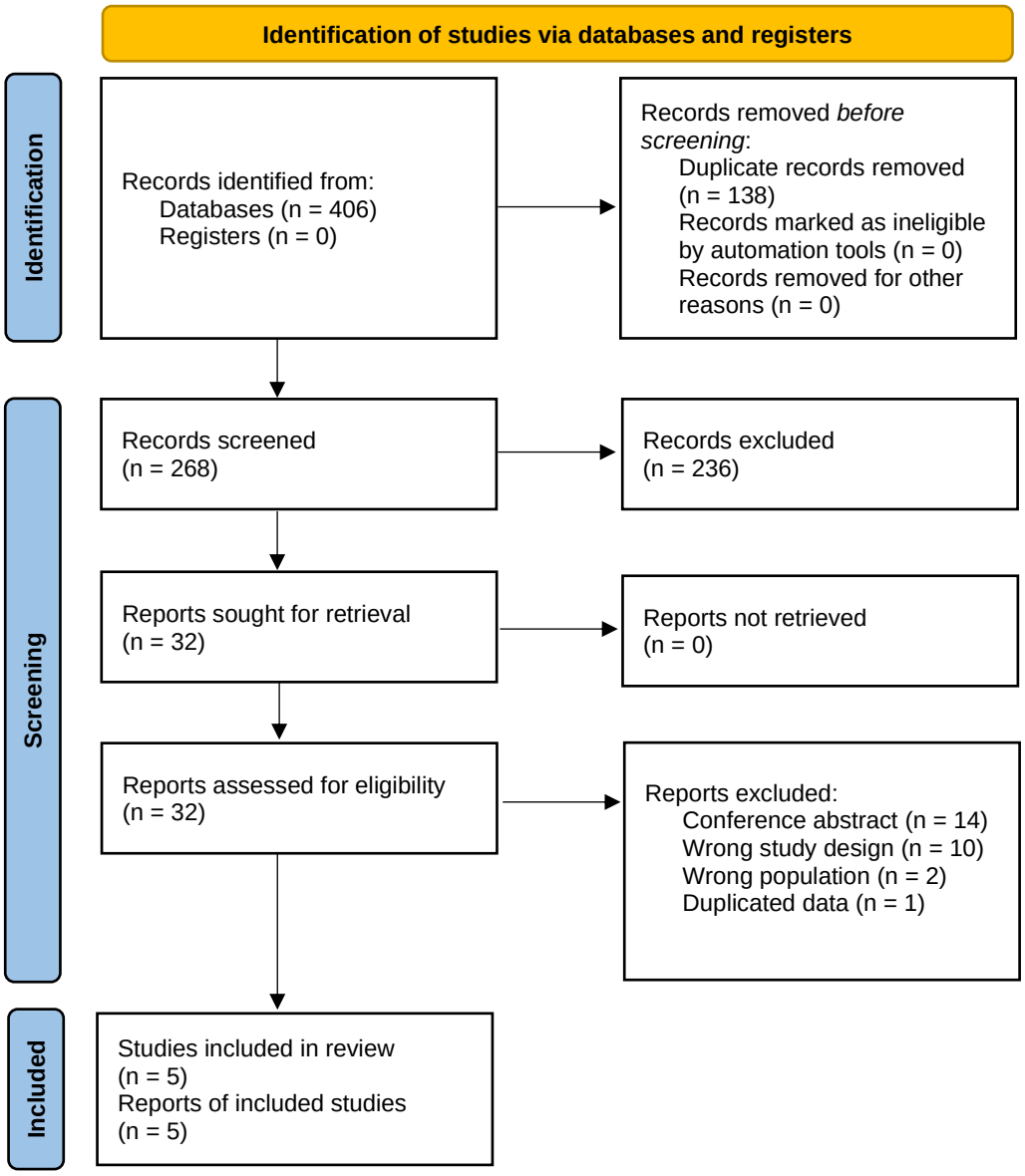

Identification of studies via databases and registers
Identification
Records identified from:
Databases (n = 406)
Registers (n = 0)
Records removed *before screening*:
Duplicate records removed (n = 138)
Records marked as ineligible by automation tools (n = 0)
Records removed for other reasons (n = 0)
Screening
Records screened
(n = 268)
Records excluded
(n = 236)
Reports sought for retrieval
(n = 32)
Reports not retrieved
(n = 0)
Reports assessed for eligibility
(n = 32)
Reports excluded:
Conference abstract (n = 14)
Wrong study design (n = 10)
Wrong population (n = 2)
Duplicated data (n = 1)
Included
Studies included in review
(n = 5)
Reports of included studies
(n = 5)

Figure 2

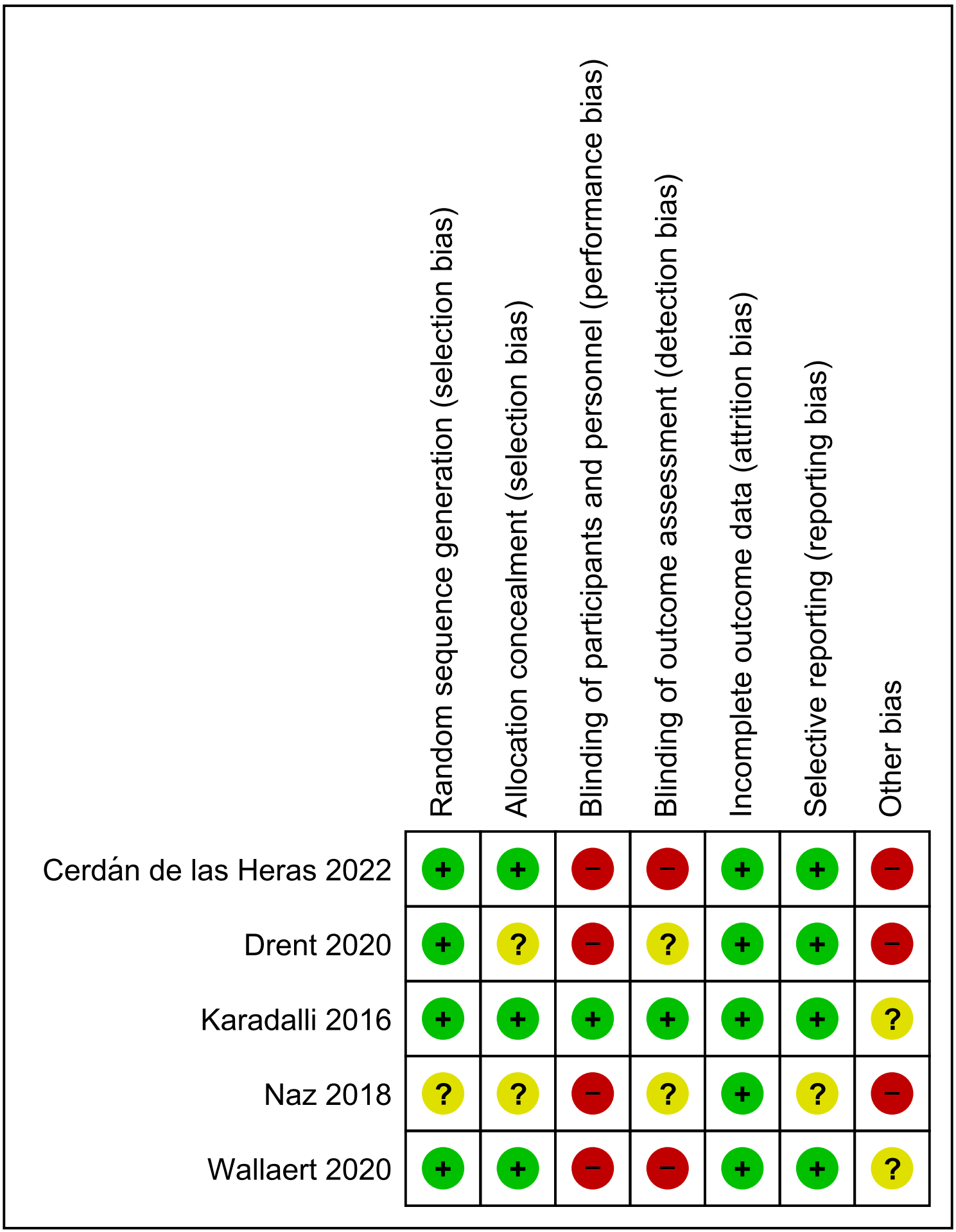

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Cerdán de las Heras 2022
Drent 2020
Karadalli 2016
Naz 2018
Wallaert 2020

Figure 3

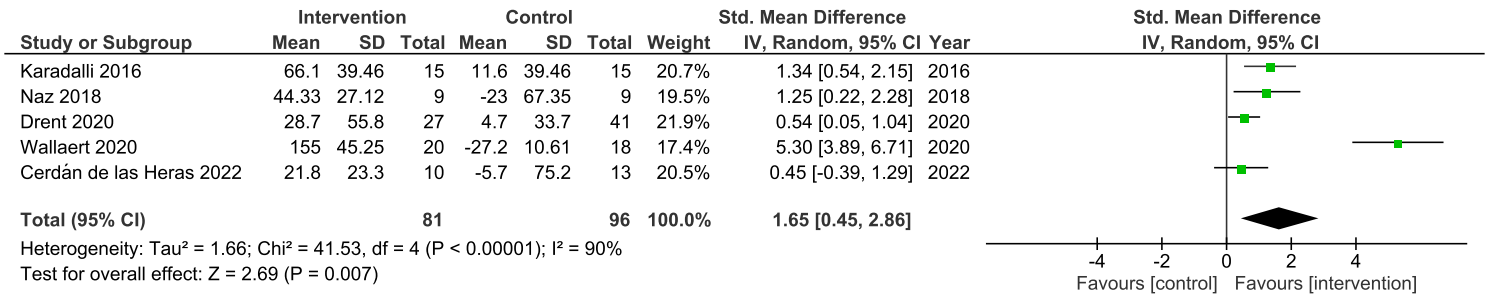

Intervention
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Karadalli 2016 66.1 39.46 15 11.6 39.46 15 20.7% 1.34 [0.54, 2.15] 2016
Naz 2018 44.33 27.12 9 -23 67.35 9 19.5% 1.25 [0.22, 2.28] 2018
Drent 2020 28.7 55.8 27 4.7 33.7 41 21.9% 0.54 [0.05, 1.04] 2020
Wallaert 2020 155 45.25 20 -27.2 10.61 18 17.4% 5.30 [3.89, 6.71] 2020
Cerdán de las Heras 2022 21.8 23.3 10 -5.7 75.2 13 20.5% 0.45 [-0.39, 1.29] 2022
Total (95% CI) 81 96 100.0% 1.65 [0.45, 2.86]
Heterogeneity: Tau² = 1.66; Chi² = 41.53, df = 4 (P < 0.00001); I² = 90%
Test for overall effect: Z = 2.69 (P = 0.007)
-4
-2
0
2
4
Favours [control]
Favours [intervention]

Figure 4

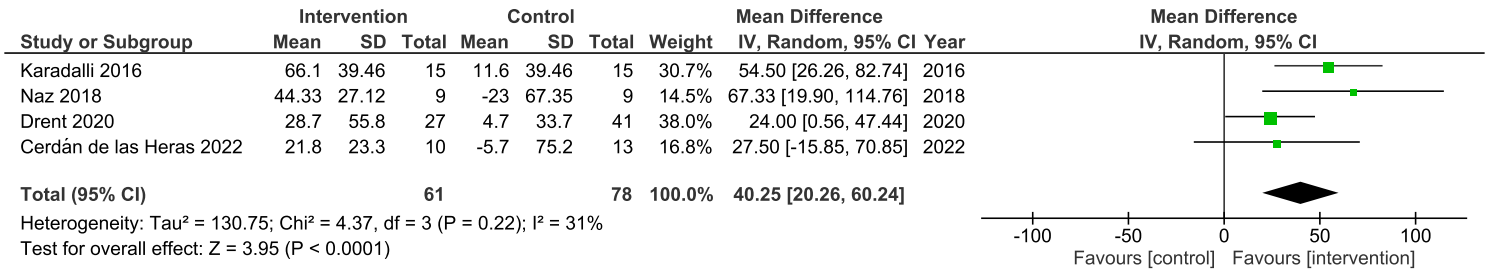

Intervention
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Karadalli 2016 66.1 39.46 15 11.6 39.46 15 30.7% 54.50 [26.26, 82.74] 2016
Naz 2018 44.33 27.12 9 -23 67.35 9 14.5% 67.33 [19.90, 114.76] 2018
Drent 2020 28.7 55.8 27 4.7 33.7 41 38.0% 24.00 [0.56, 47.44] 2020
Cerdán de las Heras 2022 21.8 23.3 10 -5.7 75.2 13 16.8% 27.50 [-15.85, 70.85] 2022
Total (95% CI) 61 78 100.0% 40.25 [20.26, 60.24]
Heterogeneity: Tau² = 130.75; Chi² = 4.37, df = 3 (P = 0.22); I² = 31%
Test for overall effect: Z = 3.95 (P < 0.0001)
-100
-50
0
50
100
Favours [control]
Favours [intervention]

Figure 5

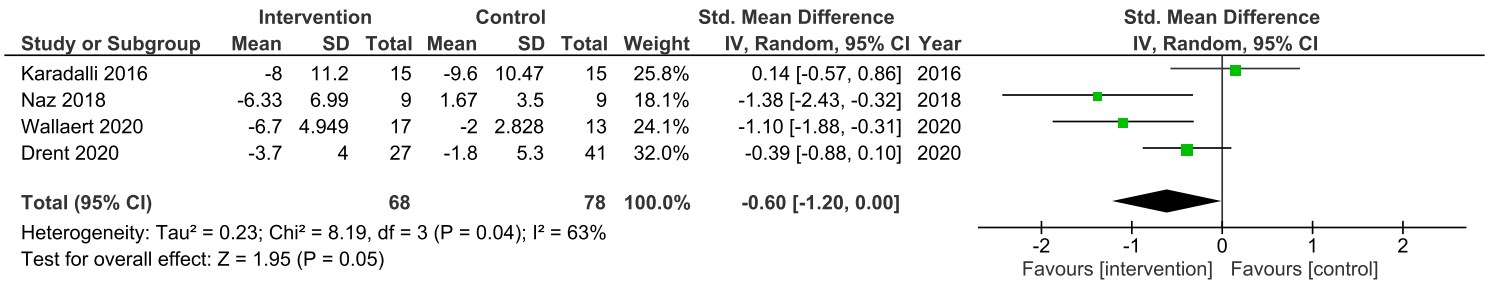

Intervention
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Karadalli 2016 -8 11.2 15 -9.6 10.47 15 25.8% 0.14 [-0.57, 0.86] 2016
Naz 2018 -6.33 6.99 9 1.67 3.5 9 18.1% -1.38 [-2.43, -0.32] 2018
Wallaert 2020 -6.7 4.949 17 -2 2.828 13 24.1% -1.10 [-1.88, -0.31] 2020
Drent 2020 -3.7 4 27 -1.8 5.3 41 32.0% -0.39 [-0.88, 0.10] 2020
Total (95% CI) 68 78 100.0% -0.60 [-1.20, 0.00]
Heterogeneity: Tau² = 0.23; Chi² = 8.19, df = 3 (P = 0.04); I² = 63%
Test for overall effect: Z = 1.95 (P = 0.05)
-2
-1
0
1
2
Favours [intervention]
Favours [control]

Figure 6

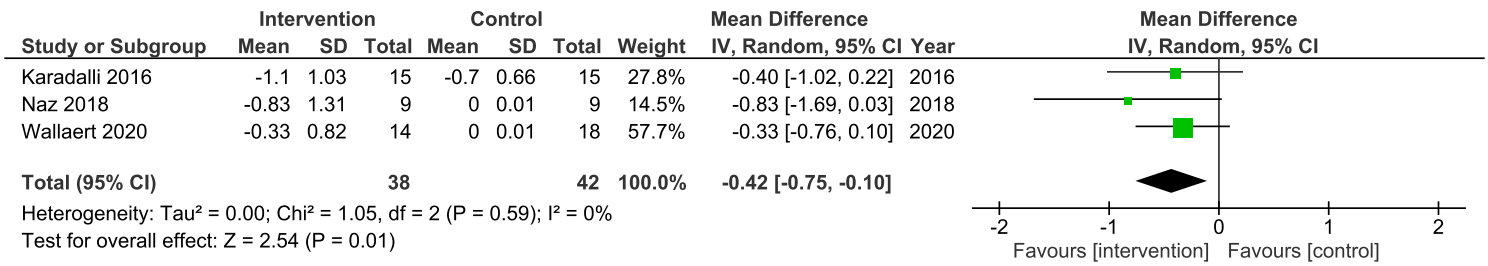

Intervention
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Karadalli 2016 -1.1 1.03 15 -0.7 0.66 15 27.8% -0.40 [-1.02, 0.22] 2016
Naz 2018 -0.83 1.31 9 0 0.01 9 14.5% -0.83 [-1.69, 0.03] 2018
Wallaert 2020 -0.33 0.82 14 0 0.01 18 57.7% -0.33 [-0.76, 0.10] 2020
Total (95% CI) 38 42 100.0% -0.42 [-0.75, -0.10]
Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 2.54 (P = 0.01)
-2
-1
0
1
2
Favours [intervention]
Favours [control]

Figure 7

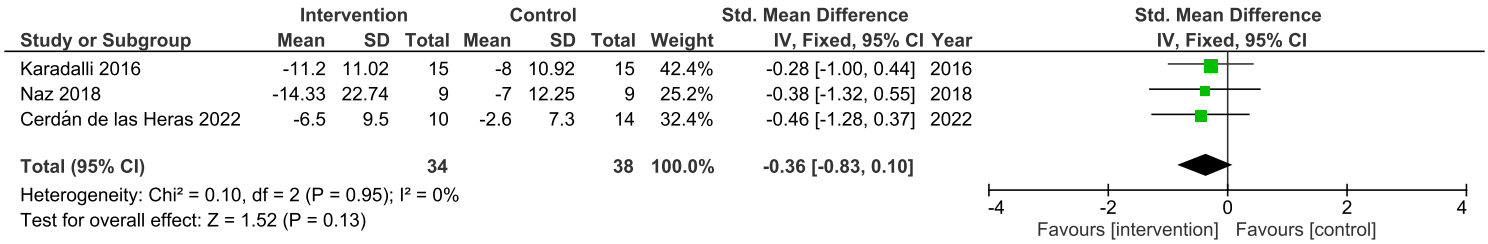

Intervention
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI Year
IV, Fixed, 95% CI
Karadalli 2016 -11.2 11.02 15 -8 10.92 15 42.4% -0.28 [-1.00, 0.44] 2016
Naz 2018 -14.33 22.74 9 -7 12.25 9 25.2% -0.38 [-1.32, 0.55] 2018
Cerdán de las Heras 2022 -6.5 9.5 10 -2.6 7.3 14 32.4% -0.46 [-1.28, 0.37] 2022
Total (95% CI) 34 38 100.0% -0.36 [-0.83, 0.10]
Heterogeneity: Chi² = 0.10, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.52 (P = 0.13)
-4
-2
0
2
4
Favours [intervention]
Favours [control]

Figure 8

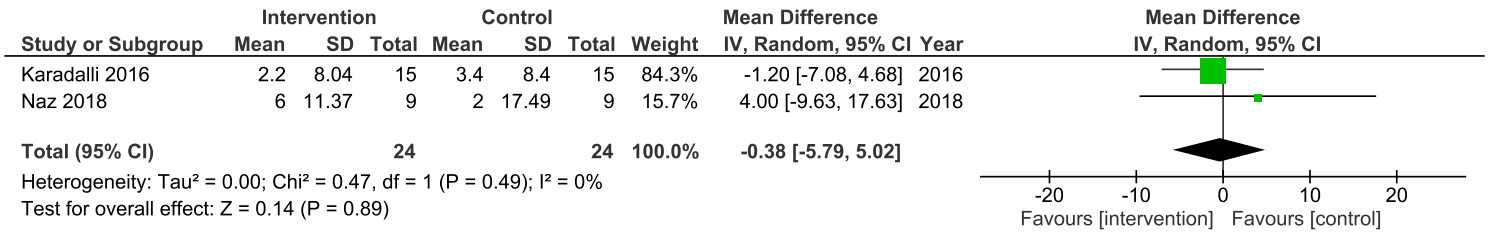
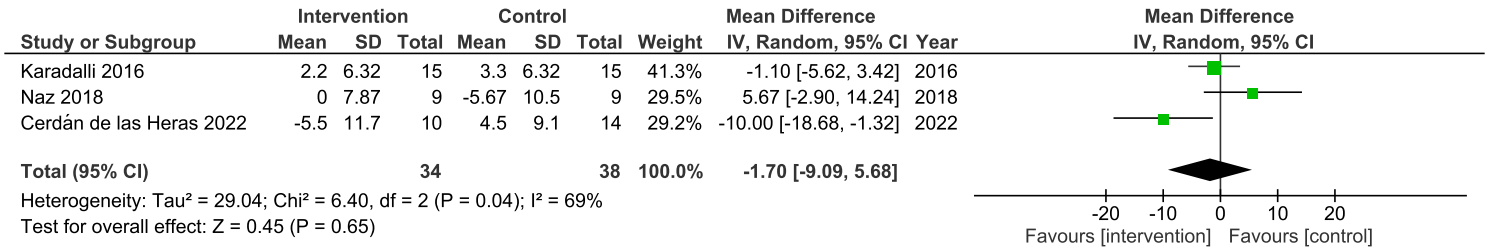

Intervention
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Karadalli 2016 2.2 8.04 15 3.4 8.4 15 84.3% -1.20 [-7.08, 4.68] 2016
Naz 2018 6 11.37 9 2 17.49 9 15.7% 4.00 [-9.63, 17.63] 2018
Total (95% CI) 24 24 100.0% -0.38 [-5.79, 5.02]
Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)
-20
-10
0
10
20
Favours [intervention]
Favours [control]

Figure 9


Intervention
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Karadalli 2016 2.2 6.32 15 3.3 6.32 15 41.3% -1.10 [-5.62, 3.42] 2016
Naz 2018 0 7.87 9 -5.67 10.5 9 29.5% 5.67 [-2.90, 14.24] 2018
Cerdán de las Heras 2022 -5.5 11.7 10 4.5 9.1 14 29.2% -10.00 [-18.68, -1.32] 2022
Total (95% CI) 34 38 100.0% -1.70 [-9.09, 5.68]
Heterogeneity: Tau² = 29.04; Chi² = 6.40, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 0.45 (P = 0.65)
-20 -10 0 10 20
Favours [intervention] Favours [control]

Authors` contributions

XAR: Conceptualisation, formal analysis, methodology, reviewing procedure and data extraction, writing (original draft, review and editing). **RTC**: Conceptualisation, formal analysis, methodology, reviewing procedure and data extraction, writing (original draft, review and editing). **EC**: Conceptualisation, reviewing procedure and data extraction, writing (review and editing). **EGS**: Conceptualisation, formal analysis, writing (original draft, review and editing). **LSN**: Conceptualisation, reviewing procedure and data extraction, writing (review and editing). **JF**: Conceptualisation, formal analysis, writing (review and editing). **FH**: Conceptualisation, formal analysis, writing (review and editing). **MRC**: Formal analysis, writing (review and editing). **IB**: Conceptualisation, supervision, formal analysis, writing (review and editing). **JS**: Conceptualisation, supervision, formal analysis, writing (review and editing).

Pulmonary rehabilitation in sarcoidosis: a systematic review and meta-analysis

Short title: Pulmonary rehabilitation in sarcoidosis

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ABSTRACT

Background: Exercise intolerance, muscle weakness, dyspnoea, and fatigue are frequent complications in symptomatic sarcoidosis patients. Pulmonary rehabilitation improves exercise capacity, symptoms, and quality of life in patients with chronic respiratory diseases. Our objective was to systematically determine the effects of pulmonary rehabilitation in patients with sarcoidosis.

Methods: A systematic review was conducted in seven databases. Studies that applied pulmonary rehabilitation in patients with sarcoidosis were reviewed. Two independent reviewers analysed the studies, extracted the data and assessed the quality of evidence.

Results: Of the 406 reports returned by the initial search, five articles reporting on 184 patients were included in the data synthesis. Two studies included multi-component exercise, one inspiratory muscle training, one a physical activity incentivisation programme, and one a telerehabilitation program. In the intervention group (IG), we found significant improvement in exercise capacity (SMD 1.65, 95%CI 0.45, 2.86 points, p=0.006). If we only analyse the studies that performed the six-minute walking test, the IG walked 40.3 (CI95% 20.3, 60.2) m higher than the control group (CG) (p<0.001). Additionally, dyspnoea score was reduced (MD -0.42 95%CI -0.75, -0.10, p=0.002). However, fatigue, quality of life and pulmonary function did not show any change.

Conclusion: Pulmonary rehabilitation could improve exercise capacity and dyspnoea perception in patients with sarcoidosis.

Keywords: Pulmonary rehabilitation; Sarcoidosis; Exercise capacity; Dyspnoea; Fatigue; Quality of life

Abbreviations: 6MST: Six-minute stepper test; 6MWD: Six-minute walking distance; 6MWT: Six-minute walking test; ATS: American Thoracic Society; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CRD: Chronic respiratory diseases; DL_{CO}: Carbon monoxide lung diffusing capacity; ERS: European respiratory society; FAS: Fatigue assessment scale; FEV_1: Forced expiratory volume in the first second; FSS: fatigue severity scale; FVC: Forced vital capacity; ILD: Interstitial lung disease; INPLASY: International Platform of Registered Systematic Review and Meta-analysis Protocols; IQR: Interquartile range; K-BILD; King's brief interstitial lung disease questionnaire; MD: Mean difference; mMRC: Modified medical research council; PR: Pulmonary rehabilitation; QoL: Quality of life; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROM: Patient reported outcome measures; RCT: Randomised controlled trials; SGRQ: Saint George Respiratory Questionnaire; SMD: Standard mean difference; WASOG: World Association for Sarcoidosis and Other Granulomatous Disorders.

Introduction

Sarcoidosis is a systemic disease of unknown aetiology characterised by the infiltration of various organs by non-necrotising granulomas [1]. Near 40% of patients with sarcoidosis experience the disease as a chronic condition [2]. In a survey performed in 1842 sarcoidosis patients, quality of life and physical function were rated as the most important outcomes, even over other items such as pulmonary function tests and blood tests [3]. Exercise intolerance, muscle weakness, and fatigue are frequent chronic problems in symptomatic sarcoidosis patients [4]. However, patients with sarcoidosis can still have symptoms that result in a reduced quality of life (QoL), even after clinical signs of the disease have disappeared. These symptoms may include fatigue and exercise limitation [5,6]. Fatigue can affect up to 70% of patients [7], and current medical therapies have limited effect in its improvement [8].

It is well-known that pulmonary rehabilitation (PR) is a cornerstone of care for people with chronic respiratory diseases (CRD) that aims to improve exercise tolerance and quality of life [9]. In interstitial lung diseases (ILD), it has also been demonstrated that PR is safe and improves exercise tolerance, quality of life and breathlessness [10]. In recent European Respiratory Society (ERS) guidelines [8], PR has been recommended in patients with sarcoidosis to improve fatigue (conditional recommendation, low quality of evidence). However, it is not clear the global effect of this intervention in this specific condition. Accordingly, the objective of this systematic review was to determine the effects of PR in patients with sarcoidosis.

Methods

Protocols and registration

We reported a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. The review was registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY202230046).

Criteria for considering studies in this review

We included randomised and quasi-randomised controlled trials (RCTs) of patients with a confirmed diagnosis of sarcoidosis based on the American Thoracic Society (ATS), ERS and World Association for Sarcoidosis and Other Granulomatous Disorders (WASOG). In addition, studies that evaluated the effects of PR in patients with sarcoidosis were eligible. We excluded editorials, review articles, systematic reviews, meta-analyses and case reports, all articles that did not follow the guidelines for sarcoidosis diagnosis, and PR programmes less than four weeks. The search strategy was based on the PICO model (population: patients with sarcoidosis; intervention: pulmonary rehabilitation; control: no intervention or placebo; and outcome: exercise capacity, fatigue, dyspnoea, pulmonary function, quality of life, respiratory muscle strength).

Search strategies and data resources

We reviewed the Embase, PubMed/MEDLINE, Web of Science, CINAHL, Cochrane Register of Clinical Trials (CENTRAL), Scopus, and SciELO databases on March 14, 2022, and updated on January 15, 2023. We conducted the searches with the followings terms: (((Pulmonary rehabilitation) OR (respiratory rehabilitation) OR

(exercise) OR (physical training) OR (aerobic training) OR (strength training) OR (interval training)) AND ((sarcoidosis)) AND ((Exercise Tolerance) OR (Exercise Capacity) OR (Cardiorespiratory Fitness) OR (Oxygen Consumption) OR (Physical Fitness) OR (Aerobic Capacity) OR (Six-minute walk test) OR (6MWT) OR (Cardiopulmonary Exercise Test) OR (Shuttle walking test) OR (SWT) OR (Distance walked))). We imposed no language or publication restrictions. The terms selected were combined using Boolean logical operators (OR, AND, NOT). We also conducted a manual search of the references included in the selected articles. All references were analysed in Rayyan web software [12].

Reviewing procedure and data extraction

The selected references were reviewed independently. First, the titles and abstracts were reviewed by two investigators (XAR, LSN), and references deemed not relevant were excluded. Second, the full text of the references selected in the previous step was checked against the eligibility criteria (XAR, LSN). A third reviewer (RTC) solved any disagreement at any phase. Finally, additional unpublished data were requested from the study's authors when possible.

Two investigators (XAR, RTC) extracted the data independently and in duplicate using a standardised protocol and reporting forms. The following information was extracted from each included study: design, population characteristics, pulmonary function, characteristics of the intervention (duration, frequency, and type of exercise), and outcomes (exercise capacity, quality of life, respiratory muscle strength, fatigue,

dyspnoea and pulmonary function tests). If some relevant data were not in the article, the authors were contacted to request the information.

Methodological quality assessment

An assessment of the methodological quality of the primary articles was carried out using the Cochrane Collaboration tool for assessing the risk of bias [13]. The tool included seven items: generation of a random sequence, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective of reports and other biases. For each item, the risk of bias for the study was rated according to three categories: low, high, or unclear risk of bias. Two reviewers (RTC, LSN) independently assessed the risk of bias of the studies. A third author (XAR) was consulted for discrepancies that could not be resolved.

Data synthesis and analysis

We reported summaries of the association between the outcomes for each study in terms of mean differences (MD) or standard mean differences (SMD) using Review Manager 5 (RevMan, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). In addition, we compared absolute values and obtained combined measurements of the effect of each primary outcome through meta-analysis with a random-effect model due to the expected heterogeneity between studies [13]. Statistical heterogeneity was measured with the I^2 statistic and classified as low (I^2 < 25%), moderate (I^2 = 25–50%), or high (I^2 > 50%) [13].The overall certainty of evidence was assessed independently by two reviewers (RTC, LSN) using the GRADE approach [14]. Disagreements were solved by consensus.

Results

Study selection

The initial search yielded 406 potential references. In total, 138 duplicate records were deleted. We screened 268 titles and abstracts and excluded 236 records that did not meet our inclusion criteria. Thirty-two of these were assessed as full text. All studies that did not fulfil all the predefined criteria were excluded, and their bibliographic details were listed with the specific reason for exclusion. Of these, 14 were excluded for conference abstract, 10 for wrong study design, two for wrong population, and one for duplicated data. Ultimately, five studies met the criteria for eligibility and were included in the review [15–19]. The flow chart of the study selection process is shown in Figure 1.

Characteristics of the included studies

Two studies were conducted in Turkey [15,16], one in France [17], one in The Netherlands [18], and one in Denmark [19]. All studies were published after 2016. The characteristics of included studies are shown in Table 1. Two studies included multicomponent exercise [15,17], one inspiratory muscle training [16], one physical activity incentive programme [18], and one a telerehabilitation program [19].

Participants

In total, 184 patients with sarcoidosis were included (86 in the intervention group and 98 in the control group). Sample sizes varied between 18 and 68 participants [15,18]. The studies included 108 (59%) females and 76 (41%) males with mean age varied

between 45.1 ± 8.1 and 59 (IQR 52-64) years old [15,16]. The body mass index (BMI) varied between 26 (IQR 20-28) and 30 (IQR 24-33) kg/m^2 [15]. The forced vital capacity (FVC) varied between 69 (44-81)% and 100.3 ± 11.3% [15,16], and diffusing capacity for carbon monoxide (DL_{CO}) varied between 45 (IQR 36-54)% and 87.3 ± 14.6% [15,16]. Four studies reported the use of steroids without significant differences between groups, 36 in the IG (50.7%) and 35 in the CG (42.2%) [15,17–19]. Regarding the stage of sarcoidosis, four studies reported it [15,16,18,19], one study reported patients in stage 1 and 2 [16], one study reported patients in stage 3 and 4 [15], and two studies reported patients in all stages [18,19]. Regarding extrapulmonary involvement, four articles reported on it [16–19]. One author reported no involvement in other organs [16], one author reported that there was neither cardiac nor neurological involvement [18], one author reported that only two patients (one in each group) presented heart involvement [17], and one author reported compromise in multiple systems [19]. The characteristics of the included studies are shown in Table 1.

Characteristics of training

Two of the selected articles performed multicomponent exercise that included endurance training and strength exercises [15,17]. The duration was between 8 and 12 weeks [15,17], and the frequency varied between twice and three times per week [15,17]. One of the articles was based on inspiratory muscle training that was performed at 40% of maximum inspiratory pressure (MIP), 30 min/day, seven days/w for six weeks [16], and the other study conducted a physical therapist-guided activity programme [18]. The coaching procedure included weekly action planning and

feedback, modelling of behaviours and problem-solving, and individual decision-making by email and/or telephone [18]. One study was performed through telerehabilitation composed of video and chat consultations with a physiotherapist and workout sessions with a virtual autonomous physiotherapist agent [19]. The details of the training programmes are shown in Table 2.

Methodological quality assessment

All studies had a high or unclear risk of bias in at least one domain. All studies claimed to be randomised [15–19]. However, not all of them explained how the randomisation was performed. One study reported was double-blinded [16], and only one study reported that researchers and outcome assessments were blinded [16]. All studies had a low risk in attrition bias [15–19]. Four studies had a low risk of selection reporting [16–19]. Finally, no studies had a low risk of other potential sources of bias (Figure 2).

Main findings

Exercise capacity: Five studies evaluated the exercise capacity as outcome (Table 2) [15–19]. These studies compared 81 patients in the intervention group (IG) versus 96 patients in the control group (CG). Four studies measured the six-minute walking distance (6MWD) [15,16,18,19], and one study used the six-minute stepper test (6MST) [17]. The analysis showed a significative difference in favour of IG with an SMD of 1.65 (CI95% 0.45, 2.86), p=0.007. The heterogeneity of the comparison was high (I^2 = 90%) (Figure 3). If we only analyse the studies that performed the six-minute walking test (6MWT), the IG walked 40.3 (CI95% 20.3, 60.2) m longer than the CG (p<0.001) (Figure 4). The heterogeneity was moderate (I^2 = 31%). The certainty of

evidence, according to the GRADE methodology, was very low for exercise capacity and low for 6MWD.

Fatigue: Four studies evaluated fatigue as an outcome (Table 2) [15–18]. These studies compared 68 patients in the IG versus 78 patients in CG. Two studies measured the fatigue assessment scale (FAS) [17,18], and two studies used a fatigue severity scale (FSS) [15,16]. The result did not show a significative difference between groups (SMD -0.60 (CI95% -1.20, 0.00, p=0.05). The heterogeneity of the comparison was high (I^2 = 67%) (Figure 5). Therefore, the certainty of evidence according to the GRADE methodology was low.

Dyspnoea: Four studies evaluated dyspnoea as outcome (Table 2) [15–17,19]. These studies compared 38 patients in the IG versus 42 patients in CG. Three studies measured the modified Medical research council (mMRC) scale, and one the Borg scale during the 6MWT [19]. We only pooled the studies that measure dyspnoea at rest. The result showed a significative difference in favour of IG with an MD of -0.42 (CI95% -0.75, -0.10), p=0.01. The heterogeneity of the comparison was low (I^2 = 0%) (Figure 6). The certainty of evidence according to the GRADE methodology was low.

Quality of life: Three studies examined the quality of life (Table 2) [15,16,19]. In all studies, the instrument used was the Saint George Respiratory Questionnaire (SGRQ), and one used the King's Brief Interstitial Lung Disease Questionnaire (K-BILD) [19]. These studies compared 34 participants in the IG versus 38 participants in the CG. Both groups had similar punctuation (SMD -0.36; 95%CI -0.83, 0.10; p=0.13). The heterogeneity of the comparison was low (I^2 = 0%) (Figure 7). The certainty of evidence according to the GRADE methodology was low.

Pulmonary function: Two studies examined the DL_{CO} post-intervention (Table 2) [15,16]. These studies compared 24 participants in the IG versus 24 participants in the CG. Both groups had similar values (MD -0.38; 95%CI -5.79, 5.02; p=0.89). The heterogeneity of the comparison was low (I^2 = 0%) (Figure 8). Three studies examined the forced expiratory volume during the first second (FEV_1) post-intervention (Table 2) [15,16]. These studies compared 34 participants in the IG versus 38 participants in the CG. Both groups had similar value (MD 1.70; 95%CI -9.09, 5.68; p=0.65). The heterogeneity of the comparison was high (I^2 = 69%) (Figure 9). Therefore, the certainty of evidence according to the GRADE methodology was very low for both DL_{CO} and FEV_1.

Discussion

This systematic review shows that pulmonary rehabilitation could improve exercise capacity and dyspnoea in patients with sarcoidosis. In the case of fatigue and quality of life, there was no change despite a clear trend towards improvement in the IG. In pulmonary function, there was neither improvement nor deterioration.

The present study demonstrates that pulmonary rehabilitation programmes in patients with sarcoidosis, primarily based on exercise interventions, effectively improve exercise capacity similar to that observed in other CRD [20,21]. Four out of five studies used the 6MWT [15,16,18,19]. 6MWD has been shown to be independently associated with mortality in CRD, meaning the shorter distance, the worse prognosis.[22,23] In sarcoidosis, the use of 6MWD has been little explored as a prognostic factor; however, decreased 6MWD has been associated with decreased survival in patients with sarcoidosis-associated pulmonary hypertension [24].

Therefore, exercise capacity is a variable of interest that shows clinical improvement and potentially impacts the prognosis of this disease. When analysing the studies that only performed the 6MWT, we observe that the change is 40 meters, one-third longer than the minimal clinically important difference (MCID) established close to 30 meters by the ATS/ERS [25]. Taking this into consideration, sarcoidosis patients could be classified after rehabilitation programs into responders.

An important aspect to consider in a PR programme are the symptoms. In this case, dyspnoea showed significant improvement. These results align with what has been reported in other CRD [10,26]; however, this change did not reach the MCID for this scale, which is a decrease of 1 point [27]. Although it is widely used in PR, mainly as a discriminative tool to characterise populations or stratify patients with respiratory diseases [28], this scale may not be specific enough to detect moderate changes due to limitations in the low number of levels [27].

Fatigue is a very common symptom in sarcoidosis (reported in up to 90% of patients) and is strongly associated with a reduction in QoL [29,30]. Although differences are not statistically significant, there is a clear trend towards improvement. Furthermore, it is not always related to sarcoidosis-induced organ involvement and can persist for many years, even in patients with clinical remission [31]. In patients with sarcoidosis, in any scenario, it is mandatory to assess fatigue using validated scales [8]. The study of fatigue seems to be a valuable parameter to evaluate response to the PR programme in these patients and shows the importance of studying and evaluating symptoms or patient reported outcome measures (PROMs) in the follow-up.[8]

We found no improvement in quality of life. While the included studies individually improved this PROM, the meta-analysis did not, contrary to what has been reported in other CRD, such as chronic obstructive pulmonary disease (COPD) or ILD [20,21]. There was a trend towards statistical significance, but probably the presence of a heterogeneous population with a wide standard deviation, the small number of articles, and the small sample size may explain that the quality of life in these patients did not improve in the meta-analysis. An important point is that patients from all the studies had a BMI >25, that is, overweight, and one of them even had an IG with obesity [32,33]; an noteworthing point to consider is that it has been identified as a potential risk factor for sarcoidosis, which could influence the results of exercise capacity tests, and, naturally, one's perception of their quality of life. It's crucial to emphasize that both the K-BILD and SGRQ questionnaires were not originally designed to assess the quality of life in patients with sarcoidosis. Therefore, future studies should employ dedicated questionnaires tailored for this specific population, such as the Sarcoidosis Health Questionnaire [34]. This aspect could have contributed to the ineffectiveness of PR in achieving these particular outcomes.

Lung function parameters did not improve at the end of the PR programme, but they did not deteriorate either. The condition of being a progressive fibrotic lung disease may explain why lung function did not improve or may even have functionally deteriorated with a decrease in FVC and DL_{CO} values.[35,36]

In the article selection process, several studies were not considered because they did not have a control group [37–39]. However, it is important to emphasize that observational studies have shown benefits of PR. Lingner et al, conducted a study in 296 patients with sarcoidosis (average age 49.1 ± 9.7 years, 47% female, average

vital capacity 87.0 ± 20.6 predicted), showing that a 3-week program improved 6MWD by almost 40 meters, in addition to showing an improvement in HRQoL, dyspnoea, fatigue, anxiety and depression [37]. These results were also reported by Guber et al, who conducted a 12-week study in 52 subjects with sarcoidosis, showing an increase in physical capacity, dyspnoea, and HRQoL. Particularly, subjects with FEV_1/FVC <70% showed a greater increase in 6MWD [38].

The studies included in the systematic review used different training protocols such as aerobic exercise, IMT or incentives for physical activity through all training protocols proved to be effective. The most recent study included in this review used a telerehabilitation program [19]. Telerehabilitation programs have shown to be just as effective as face-to-face programs and superior to non-intervention, making it a good alternative, especially in the face of pandemics such as COVID-19 [40]. It is, therefore, the case that the different elements of PR programmes can work in different settings and that, finally, there is more than one intervention tool that clinicians can choose according to their local reality. On the other hand, the articles selected included unimodal or multimodal interventions with complementary strategies included in PR programs as education or breathing exercises. Without a doubt, if we analyse each of these types of training, it would not be possible to carry out meta-analysis. These aspects are very common in PR studies so it must be considered when we analyse these results.

Undoubtedly, an important factor to evaluate the response to exercise is muscle quality, with the use of steroids being a factor that affects. Although the studies that reported the use of steroids, not find significant differences between them [15,17–19].

Another important factor is the state of the cardiovascular and respiratory system. Most studies reported no or few patients with cardiac involvement [17,19] and although the number of patients with respiratory involvement was not reported, the analysis of lung function allows us to estimate that they did have significant compromise on lung volumes [15] and particularly in diffusion capacity [17,19]. However, the studies did not report differences between the groups regarding these two systems.

Our study has limitations. First, we were very strict in some search terms since we only considered patients with sarcoidosis. On the other hand, all studies were performed in Europe, and it would be interesting to see if these results could be replicated in places with different resources. Moreover, population characterisation included little information on comorbidities that may be present in a significant number of patients [41]. Complications such as pulmonary hypertension or other cardiorespiratory diseases can play an essential role in limiting exercise capacity and the presence of fatigue, and they are not even mentioned.

Conclusion

Pulmonary rehabilitation could improve exercise capacity and dyspnoea in patients with sarcoidosis. Future research is needed with a larger number of patients focused on patients' reported outcomes to optimise the decision-making in clinical practice. Nevertheless, the data shown in this systematic review could be a useful starting point.

Author Contributions

All listed authors contributed to the study. In particular, XAR: Conceptualisation, formal analysis, methodology, reviewing procedure and data extraction, writing (original draft,

review and editing). RTC: Conceptualisation, formal analysis, methodology, reviewing procedure and data extraction, writing (original draft, review and editing). EC: Conceptualisation, reviewing procedure and data extraction, writing (review and editing). EGS: Conceptualisation, formal analysis, writing (original draft, review and editing). LSN: Conceptualisation, reviewing procedure and data extraction, writing (review and editing). JF: Conceptualisation, formal analysis, writing (review and editing). FH: Conceptualisation, formal analysis, writing (review and editing). MRC: Formal analysis, writing (review and editing). IB: Conceptualisation, supervision, formal analysis, writing (review and editing). JS: Conceptualisation, supervision, formal analysis, writing (review and editing).

Conflict of interests

None

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Table 1. Characteristics of the included studies

Author, year, country	Group	Subjects (M/F)	Age (years)	BMI (kg/m2)	FVC (%)	FEV_1 (%)	FEV_1/FVC (%)	DL_{CO} (%)
Karadalli et al, 2016 Turkey	Intervention	15 (5/10)	45.1 ± 8.1	27.0 ± 5.1	100.3 ± 11.3	93.3 ± 11.2	78.1 ± 6.2	77.8 ± 19.3
	Control	15 (6/9)	47.5 ± 12.9	29.3 ± 4.8	100.1 ± 21.9	95.9 ± 20.1	80.1 ± 5.2	87.3 ± 14.6
Naz et al, 2018 Turkey	Intervention	9 (3/6)	59 (52-64)*	30 (24-33)*	76 (66-90)*	73 (65-85)*	80 (65-81)*	45 (36-54)*
	Control	9 (3/6)	51 (45-57)*	26 (20-28)*	69 (44-81)*	64 (46-77)*	82 (78-87)*	52 (38-53)*
Drent et al, 2020 The Netherlands	Intervention	27 (13/14)	48 (26-72)**	27.1 ± 3.6	99.9 ± 16.3	91.0 ± 19.0	NR	79.6 ± 11.8
	Control	41 (10/31)	48 (29-73)**	27.9±5.3	94.8 ± 18.0	85.7 ± 21.8	NR	77.9 ± 18.9
Wallaert et al, 2020 France	Intervention	20 (10/10)	57.5 (48.0-63.5)*	28.4 (23.7-31.1)*	80.7 ± 18.2	66.8 ± 20.2	NR	56.8 ± 15.9
	Control	18 (7/11)	57.5 (49-65)*	27.3 (23.4-31.2)*	81.4 ± 18.2	61.1 ± 16.9	NR	62.7 ± 18.5
Cerdan de las Heras et al, 2022 Denmark	Intervention	15 (10/5)	56.1 ± 14.4	28.7 ± 4.5	93.1 ± 19.4	79.3 ± 16.4	87.1 ± 14.3	65.9 ± 15.9
	Control	15 (9/6)	51.6 ± 12.7	27.3 ± 4.9	84.7 ± 17.9	63.0 ± 23.9	75.9 ± 21.4	64.3 ± 17.2

Abbreviations: BMI: Body mass index; DL_{CO}: Diffusing capacity for carbon monoxide; FEV_1: Forced expiratory volume during the first second; FVC: Forced vital capacity.
*median and interquartile range, **median and range

Table 2. Characteristics of pulmonary rehabilitation programs

Author, year	Duration and frequency	Type of intervention	Exercise capacity	Fatigue	Dyspnea	Quality of life	Pulmonary function	Respiratory muscles strength
Karadalli et al, 2016	30 min/d,7 days/week, for 6 weeks	Inspiratory muscle training at 40% of MIP	Δ6MWD** IG: 66.1 (44.3-88) CG: 11.6 (-10.2-33.5) ΔISWT** IG: 61.7 (32.0-91.2) CG: 16.2 (-14.5-46.8)	ΔFAS** IG:-8 (-14.4-(-2)); CG: -9.6 (-15.4-(-3.8))	ΔmMRC** IG:-1.1 (-1.3-(-0.8)); CG: -0.7 (-15.4-(-3.8))	ΔSGRQ** IG: -11.2 (-17.3-(-5.1)); CG: -9.4(-15.4-(-3.3))	ΔFEV_1** IG: 2.2 (-5.7-1.3); CG: 3.3 (-0.2-6.8) ΔFVC** IG: 2.5 (-1-6.1): CG: 3.5 (-0.1-7) $\Delta FEV_1/FVC$** IG: 0.2 (-1.4-1.9): CG: -0.5 (-2.1-1.1) ΔDLCO** IG: 2.2 (-2.2-6.7): CG: 3.4 (-1.3-8)	ΔMIP** IG: 45.9 (39.3-52.6); CG: 14.4 (7.7-21.1) ΔMEP** IG: 49.7 (39.3-60.2); CG: 21.7 (11.2-32.2)
Naz et al, 2018	12 w 2 times/w	Breathing exercises, endurance training, strength training for upper and lower limbs, and stretch- ing	Δ6MWD* IG: 40 (31-62) CG: -20 (-63-14)	ΔFSS* IG:-7 (-10-2); CG: 1 (0-4)	ΔmMRC* IG:-1 (-1.5-0); CG: 0 (0-0)	ΔSGRQ* IG: -19 (-25-1); CG: -11(-12-2)	ΔFEV_1* IG: 1 (-5-4); CG: -7 (-11-1) ΔFVC IG: 1 (-7-5): CG: -1 (-8-5) $\Delta FEV_1/FVC$ IG: 1 (-7-5): CG: -1 (-8-5) IG: -1(-3-2); CG:-4(-7-3) ΔDLCO IG: 7 (-1-12): CG: -2 (-6-14)	ΔMIP* IG: 6 (2-24); CG: 6 (-12-6) ΔMEP IG: 4 (-10-19); CG: -7 (-21-2)

Drent et al, 2020	3 months	Physical therapist-guided activity program. The coaching procedure included weekly action planning and feedback, modelling of behaviours and problem solving, and individual decision making, by email and/or telephone.	Δ6MWD IG: 28.7 ± 55.8 CG:4.7 ± 33.7 ΔVO_2max IG: 1.6 ± 2.6 CG:0.6 ± 2.4	ΔFAS IG: -3.7 ± 4.0 CG:-1.8 ± 5.3	NR	NR	ΔFEV_1 at baseline IG: 90.9 ± 20.9; CG: 85.7 ± 21.8 ΔFVC IG: 101.2 ± 19.4; CG: 94.8 ± 18.0 ΔDLCO IG: 77.2 ± 14.4; CG: 77.9 ± 18.9 IG: 79.6 ± 11.8; CG:77.9 ± 18.9	NR
Wallaert et al, 2020	2 months/ 3 times/w	Individual and group-based strengthening exercises, upper/lower limb training, and supervised endurance training. In addition, patients received training in resumption of daily life physical activity, therapeutic patient education, psychosocial support, and motivational communication, to facilitate health-related behavioral changes and self-management.	Δ6MST IG: 155 ± 45.3 CG: -27 ± 10.6 Δ6MST IG: -66.4 ± 85.4 CG: -27 ± 10.6	ΔFAS IG: -6.7 ± 4.95 CG: -2.0 ± 2.83	ΔmMRC* IG: 0 (0-1) CG: 0 (0-0)	NR	ΔFEV_1 (12-m)** IG-CG: 3.0 (-1.8-7.9) ΔFVC (12-m)** IG-CG: -2.3 (-7.3-2.6) ΔDLCO (12-m)** IG-CG: -2.8 (-10.2-4.6)	NR
Cerdan de Las Heras et al, 2022	3 months/ at least 60 m/w	Telerehabilitation group composed of video and chat-consultations with a physiotherapist and workout sessions with a virtual autonomous physiotherapist agent.	Δ6MWD IG-CG: 25.8 ± 21.9		ΔBorg scale IG-CG: 1.2 ± 0.5	ΔSGRQ-I IG-CG: -3.2 ± 8.9 ΔK-BILD IG-CG: 2.3 ± 2.6	ΔFVC IG-CG: 9.7 ± 7.0 ΔDLCO IG-CG: -17.6 ± 6.8	NR

Abbreviations: 6MST: Six-minute stepper test; 6MWD: Six-minute walking distance; DL_{CO}: Diffusing capacity for carbon monoxide; FAS: Fatigue assessment scale; FEV_1: Forced expiratory volume during the first second; FSS: Fatigue severity scale; FVC: Forced vital capacity; MIP: Maximum inspiratory pressure; mMRC: Modified medical research council; NR: Not reported. SGRQ: Saint George Respiratory questionnaire. *median + RIQ; ** mean + CI95%.

Figures legends:

Figure 1. Flowchart of the included studies

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 3. Forest plot for exercise capacity

Figure 4. Forest plot for six-minute walking distance (6MWD)

Figure 5. Forest plot for fatigue

Figure 6. Forest plot for dyspnoea

Figure 7. Forest plot for quality of life

Figure 8. Forest plot for carbon monoxide lung diffusing capacity (DL_{CO})

Figure 9. Forest plot for forced expiratory volume in the first second (FEV_1)