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Published in:
Physical Therapy

DOI:
[10.1093/ptj/pzaa129](https://doi.org/10.1093/ptj/pzaa129)

Publication date:
2020

Document Version
Author accepted manuscript

[Link to publication in ResearchOnline](#)

Citation for published version (Harvard):

Rooney, S, Webster, A & Paul, L 2020, 'Systematic review of changes and recovery in physical function and fitness after severe acute respiratory syndrome–related Coronavirus infection: implications for COVID-19 rehabilitation', *Physical Therapy*, vol. 100, no. 10, pp. 1717-1729. <https://doi.org/10.1093/ptj/pzaa129>

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Systematic review of changes and recovery in physical function and fitness following Severe Acute Respiratory Syndrome-related Coronavirus (SARS-CoV) infection: Implications for COVID-19 rehabilitation

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Conflicts of interest: None

Funding: SR is funded by a Glasgow Caledonian University PhD Studentship; AW is funded by a grant award from the Multiple Sclerosis (MS) Society, UK. Multiple Sclerosis Society is a registered charity in England & Wales number 1139257 and in Scotland registered charity number SC041990

Word count: 4039

No. of tables: 2

No. of figures: 1

Abstract

Objectives: 1) Compare physical function and fitness outcomes in people infected with SARS-CoV to healthy controls; 2) quantify the recovery of physical function and fitness following SARS-CoV infection; 3) determine the effects of exercise following SARS-CoV infection.

Methods: Four databases (CINAHL, MEDLINE, ProQuest, and Web of Science Core Collections) were searched in April 2020 using keywords relating to SARS-CoV, physical function, fitness, and exercise. Observational studies or randomised controlled trials were included if they involved people following SARS-CoV infection and either assessed the change or recovery in physical function/fitness or evaluated the effects exercise post-infection.

Results: 10 articles were included in this review. Evidence from nine articles demonstrated that SARS-CoV patients had reduced levels of physical function and fitness post-infection in comparison to healthy controls. Furthermore, patients demonstrated incomplete recovery of physical function, with some experiencing residual impairments 1-2 years post-infection. Evidence from one randomised controlled trial found that a combined aerobic and resistance training intervention significantly improved physical function and fitness post-infection in comparison to a control group.

Conclusions: Physical function and fitness are impaired following SARS-CoV infection, and impairments may persist up to 1-2 years post-infection. Researchers and clinicians can use these findings to understand the potential impairments and rehabilitation needs of people recovering from the current COVID-19 outbreak. While one study demonstrated that exercise can improve physical function and fitness post-infection, further research is required to determine the effectiveness of exercise in people recovering from similar infections (e.g. COVID-19).

Impact statement: Considering the similarities in pathology and clinical presentation of SARS-CoV and COVID-19, it is likely that COVID-19 patients will present with similar impairments to physical function. Accordingly, research is required to measure the extent of functional impairments in COVID-19 cohorts. In addition, research should evaluate whether rehabilitation interventions such as exercise can promote post-infection recovery.

Keywords: Coronavirus; SARS; COVID-19; physical function; fitness; exercise

Introduction

In December 2019, the first case of novel coronavirus 2019 (COVID-19) was confirmed in Wuhan, Hubei Province, China;¹ since then, over **11.3 million cases have been confirmed globally (as of July 6th 2020)**, with the World Health Organisation declaring the current outbreak a pandemic.² The majority (80%) of people infected with COVID-19 present with mild-moderate disease characterised by a fever, persistent cough, and dyspnoea.³ However, more severe disease is experienced by 20% of people⁴ – particularly in those over 65 years old and with comorbidities such as cardiovascular disease, diabetes, and chronic respiratory disease.^{5,6} It is estimated that around 30% of people infected with COVID-19 will require hospitalisation,⁷ and of those hospitalised, 20% will be admitted to an Intensive Care Unit (ICU).³

During periods of critical illness and hospitalisation, it is common for people to experience a loss of physical function,⁸ which can be characterised by the development of new or worsening of existing impairments.⁹ Acquired changes to physical function during periods of hospitalisation and critical illness are more commonly experienced by those with more severe illness or existing comorbidities,⁸ and often lead to mobility disability and restrictions in activities of daily living.¹⁰ This decrease in physical functioning is thought to be attributed to prolonged periods of immobility, during which time people experience deconditioning (i.e. a reduction in physical fitness outcomes such as muscle strength or aerobic capacity),¹¹ or develop critical illness polyneuropathy and myopathy leading to impaired neuromuscular function.¹² Furthermore, in more severe cases, Acute Respiratory Distress Syndrome (ARDS) – which accounts for over 30% of COVID-19 related ICU admissions³ – also leads to deconditioning and long-term impairments in physical function.¹³

Therefore, considering the rising number of COVID-19 cases and the significant proportion of people that are hospitalised and require ICU care for management of the infection, it is likely that many people will require rehabilitation to promote recovery post-infection.¹⁴ Accordingly, it is important to understand the effect of COVID-19 on physical function and fitness in order to inform the design and assessment of rehabilitation interventions such as exercise, which has been demonstrated to improve physical function following critical illness by a **previous systematic review**.¹⁵

While there are currently no studies reporting the effect of COVID-19 on physical function and fitness, the importance of these outcomes to rehabilitation could be identified by

reviewing the impact of the Severe Acute Respiratory Syndrome-related Coronavirus (SARS-CoV) on physical function and fitness. SARS-CoV is a type of coronavirus which presents with similar symptoms to COVID-19 and caused a similar global outbreak of disease in 2003.¹⁶ While the reported cases of SARS-CoV were significantly lower than the current COVID-19 pandemic,¹⁷ a similar proportion of people infected with SARS-CoV were hospitalised and admitted to ICU;¹⁸ therefore, post-infection changes and recovery in physical function and fitness in people with COVID-19 may follow a similar pattern to those infected with SARS-CoV. Accordingly, this review aims to: 1) compare physical function and fitness outcomes in people infected with SARS-CoV to healthy controls; 2) quantify the recovery of physical function and fitness following SARS-CoV infection; 3) determine the effects of exercise on people following SARS-CoV infection.

Methods

Data sources and searches

A systematic review protocol was registered with the PROSPERO database in April 2020 (ID#: CRD42020182575). Searches were then conducted, on 28 April 2020, of the following databases from inception: CINAHL (via EBSCOhost), MEDLINE (via Ovid), ProQuest (Health & Medical Collection, Nursing & Allied Health Database, Coronavirus Research Database) and Web of Science Core Collections. Search strategies were comprised of keywords related to SARS-CoV, physical function, fitness, and exercise (Supplementary table 1) and were adapted for use in each different database. In addition, reference lists of included articles were hand searched to identify any additional articles.

Study selection

Both randomised controlled trials and observational studies (with either a cross-sectional or prospective design) that included adults who had been infected with SARS-CoV were eligible for this review. Furthermore, studies were also required to meet one of the following criteria: 1) assess physical function or physical fitness in people following SARS-CoV infection in comparison to a healthy control group using an objective measurement; 2) longitudinally assess physical function or physical fitness in people following SARS-CoV infection using an objective measurement; 3) evaluate the

effects of an exercise intervention following SARS-CoV infection either as a standalone intervention or as part of a rehabilitation programme. Only full-text articles published in English were included in this review; grey literature and conference abstracts were excluded.

After removing duplicate articles, search results were exported to **Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia)**. The title and abstracts of all articles were then screened against the eligibility criteria by one reviewer (SR). Subsequently, two reviewers (SR, AW) independently screened full texts of all remaining articles for eligibility, and disagreements were resolved through consensus in consultation with a third reviewer (LP) if required.

Data extraction and quality assessment

Data extraction was completed independently by one reviewer (SR) using a standardised data extraction form. Data that was extracted from all studies included: study details (author, year of publication, study design, location of study) and participant demographics (sample size, age, gender, time since infection, duration of hospitalisation, comorbidities). Furthermore, either the outcome measures used to assess physical function/fitness and time-points of assessment, or details of the exercise intervention (type, duration, frequency, intensity, control group) and effect were also extracted.

Methodological quality of included studies was assessed by two reviewers (SR, AW) using either the PEDro scale for randomised controlled trials¹⁹ or the NIH quality assessment tool for observational cohort and cross-sectional studies.²⁰ Quality assessment was completed independently, and any discrepancies between reviewers were resolved through consensus in consultation with a third reviewer (LP) if required. No studies were excluded based on the result of the quality assessment.

Data synthesis and analysis

The results of the included studies were analysed through separate narrative syntheses corresponding to the aims of this systematic review. Firstly, descriptive values of physical function and fitness outcomes were compared to normative control data reported in each

study in order to determine the difference in physical function/fitness following SARS-CoV infection. These results were compared between studies which include the same outcome measures to determine consistency of the results. Secondly, longitudinal descriptive data was synthesised to determine the extent of recovery in physical function and fitness at various time-points following infection. The mean/median change in physical function/fitness over time (either in comparison to control values or baseline data) determined the rate and magnitude of recovery post-infection. Lastly, for randomised controlled trials, individual study estimates of treatment effects (size and direction) were presented in order to determine the effects of exercise post-infection.

Results

Results of the search

After removing duplicates, the title and abstracts of 377 articles were screened against the eligibility criteria and 363 were excluded primarily as the studies did not include people infected with SARS-CoV (n=161) or the articles were grey literature (n=105). The full-texts of the remaining 14 articles were then screened for eligibility, and four were excluded as two articles which described observational studies did not include a measure of physical function or fitness, one article included a single measure of physical function but did not compare values to healthy controls, and one article was a conference abstract. Accordingly, 10 articles²¹⁻³⁰ were included in this systematic review (Figure 1).

Figure 1 near here

Study design

Of the included articles, six reported the results of cohort studies investigating longitudinal changes in physical function (Table 1),^{22,23,26,28-30} three described the results of cross-sectional studies investigating the difference in physical function and fitness in comparison to healthy controls (Table 1),^{21,25,27} and one reported the results of a randomised controlled trial investigating the effects of an exercise intervention following SARS-CoV infection (Table 2).²⁴ The results of one cohort study were reported across four articles— Hui et al.²², Hui et

al.²³, and Hui et al.²⁹ include the same cohort of participants at various time-points post-infection, and Ngai et al.³⁰ reports results from a sub-group of this cohort who completed all assessments up to 24-months post-infection. The majority of studies were conducted in Asia (Hong Kong, n=4;^{22-26,29,30} Singapore, n=1;²¹ Taiwan, n=1²⁷), with only one study conducted outside of Asia (Canada, n=1).²⁸

Table 1 near here

Table 2 near here

The overall methodological quality of the included articles is described in **Tables 2 and 3**, and a detailed description of each item response is provided in Supplementary **tables 2 and 3**. The total number of items adequately addressed on the NIH quality assessment tool ranged from 6²⁷-10²². Most studies had clearly defined and consistent eligibility criteria, recruited at least 50% of the eligible population, and used valid and reliable outcome measures to quantify physical function/fitness. However, only five studies controlled for confounding variables such as age,^{22,23,25,26,30} and only two studies had a loss to follow-up of less than 20%.^{22,28} The randomised controlled trial by Lau et al.²⁴ scored nine on the PEDro scale; due to the nature of the intervention, neither the participants nor therapists were blinded to treatment allocation.

Participants

Across the observational studies, a total of 516 people infected with SARS-CoV were included with sample sizes ranging from 13-171. **Participants were included in each study at various times post-infection, with studies including participants at 3 months post-infection onset (i.e. 3 months since the initial presentation of symptoms related to the infection),^{22,23,26,29,30} or 2 weeks,²⁵ 3 months,^{21,28} and 14 months post-discharge (which relates to discharge from hospital in all cases).²⁷** The mean duration of hospitalization ranged from 20.4²¹-28.2³⁰ days, and 8%²⁷-28%²² of participants required admission to ICU with the exception of the study by Li et al.²⁶, where all participants were admitted to ICU since the purpose of this study was to investigate people with ARDS caused by SARS-CoV.

The proportion of participants with pre-existing medical conditions before SARS-CoV infection ranged from 8%²⁷-56%²¹ across studies.

The sample size of the randomised controlled trial by Lau et al.²⁴ was 133, of which 71 were assigned to the exercise intervention group and 62 were assigned to the control group. Participants were recruited two weeks post-hospital discharge and were a sub-group of participants from the study by Lau et al.²⁵ who had impaired physical function at baseline. The mean duration of hospitalization for the intervention and control group was 23.2±11.3 days and 22.1±10.9 days respectively.

Physical function and fitness in comparison to healthy controls

All of the observational studies included in this review compared measures of physical function or fitness in people with SARS-CoV to healthy controls (Table 1). Of these studies, four measured physical function,^{22,23,25,26,28-30} and two measured physical fitness.^{21,27} Physical fitness was quantified according to maximum oxygen consumption (VO_{2max}) during cardiopulmonary exercise testing;^{21,27} All studies that measured physical function used the Six-minute Walk Test (6MWT).^{22,23,25,26,28-30}

Physical fitness was found to be impaired in people infected with SARS-CoV in the study by Ong et al.²¹ which reported that VO_{2max} values were 78.6%±17.0% less in those with SARS-CoV compared to normative reference values at 3 months post hospital discharge. Ong et al.²¹ also reported that none of the exercise tests in people infected with SARS-CoV were limited by pulmonary or ventilatory function. Conversely, the study by Su et al.²⁷ found no significant difference in VO_{2max} between people with SARS-CoV and healthy controls; although, this study recruited participants who had been discharged from hospital for significantly longer (14 months vs. 3 months) and had a smaller sample size (n=13 vs. n=46) in comparison to the study by Ong et al.²¹

Across the studies which measured physical function, all reported a reduction in 6MWT performance following SARS-CoV infection. In the cross-sectional study by Lau et al.²⁵, 6MWT distance was found to be significantly lower in people infected with SARS-CoV compared to healthy controls 2 weeks post hospital discharge. Similarly, Tansey et al.²⁸ and Li et al.²⁶ found that 6MWT distance in people infected with SARS-CoV was 67%-81% of that recorded for healthy controls at 3 months post hospital discharge – this reduction was

found to be greatest among those who had received mechanical ventilation.²⁶ Impaired physical function was also shown to persist long-term following SARS-CoV infection, as Li et al.²⁶ and Tansey et al.²⁸ found that 6MWT distance in people infected with SARS-CoV was 74%-83% of that recorded for healthy controls at 12 months post hospital discharge, and Hui et al.^{23,29} found that 6MWT distance was significantly lower in those infected with SARS-CoV at 12-months **post-infection onset** (with the exception of males aged 41-60) and 24 months **post-infection onset**.³⁰

Recovery of physical function and fitness

Of the cohort studies measuring recovery post-infection, all measured changes in physical function using the 6MWT.^{22,23,26,28-30} Assessments were conducted at 3, 6, and 12 months either **post-infection onset**^{22,23,26,29,30} or post hospital discharge;²⁸ however, Ngai et al.³⁰ also performed measurements at 18 and 24 months **post-infection onset**. No study included in this review assessed longitudinal changes in fitness following SARS-CoV infection.

Initial short-term recovery of physical function following SARS-CoV infection was demonstrated by the studies included in this review, as most studies found that 6MWT distance increased between 3-6 months **post-infection onset**,^{22,23,26,29,30} with the exception of the study by Tansey et al. which recorded no change.²⁸ However, although the 6MWT increased at 6 months, Li et al.²⁶ reported that values were still 72%-79% of that recorded for healthy controls. Following the first 6-months **post-infection onset**, Li et al.²⁶ reported that no further change in 6MWT distance was recorded. Similarly, Hui et al.^{23,29} also reported that no significant change in 6MWT distance was found between 3 and 12 months **post-infection onset**, indicating that there was minimal long-term recovery of physical function post-infection. Furthermore, in the sub-group analysis of the cohort initially described by Hui et al.²², Ngai et al.³⁰ also found that no change in 6MWT was found between 3-24 months **post-infection onset**.

Effects of exercise following SARS-CoV infection

The randomised controlled trial by Lau et al.²⁴ investigated the effect of a 6-week exercise intervention on physical function, physical fitness, and quality of life following SARS-CoV infection. Participants received 2 sessions weekly which lasted 60-90 minutes and included

30-45 minutes of aerobic exercise at 60-70% of predicted maximal heart rate, and resistance training targeting the upper and lower limbs. Participants in the control group received advice about general exercise and weekly telephone conversations with a physiotherapist.

Following the 6-week intervention, Lau et al. reported that both 6MWT distance and VO_{2max} (measured sub-maximally using the Chester Step Test) increased in the exercise intervention group. Furthermore, the mean difference in 6MWT distance and VO_{2max} recorded for the exercise group was significantly greater than the change recorded in the control group ($77.4 \pm 71.3m$ vs. $20.7 \pm 98.6m$ and 3.6 ± 5.4 ml/kg/min vs. 1.0 ± 7.3 ml/kg/min respectively).

Therefore, these results indicate that exercise improves 6MWT and VO_{2max} in people who have been infected with SARS-CoV. However, no significant difference was found in muscle strength or quality of life between the exercise and control groups.

Discussion

The evidence presented in this review highlights the long-term impact of SARS-CoV infection on physical function and fitness. Evidence from a small number of studies demonstrates that, following SARS-CoV infection, patients have reduced levels of physical function and fitness in comparison to healthy controls. Furthermore, while an increase in physical function is noted within the first 6 months **following infection onset**, recovery is incomplete and people with SARS-CoV may experience residual impairments in physical function 1-2 years after the infection. Therefore, this highlights the need for rehabilitation interventions to promote physical recovery of people following SARS infection. Evidence from one randomised controlled trial suggests that exercise may promote recovery in physical function and fitness in people infected with SARS-CoV.²⁴ However, further evidence is required to determine the effectiveness of rehabilitation interventions, such as exercise, in promoting recovery post-infection – particularly during the current outbreak of COVID-19 in which similar patterns of impairments and recovery in physical function may be experienced.

The mechanisms leading to impaired physical function following SARS-CoV infection are likely multifactorial and arise as a consequence of the infection, prolonged hospitalisation, and/or immobility.³¹ For example, during periods of immobility due to critical illness, around 25% of patients develop significant muscle weakness – particularly of the lower limb muscle groups involved in functional mobility.³² This acquired weakness may be attributed to a

decrease in muscle cross-sectional area and muscle fibre size,^{33,34} or a reduction in type II muscle fibres.³⁵ In addition, up to 50% of people admitted to ICU may develop critical illness myopathy or neuropathy leading to a reduction in motor unit recruitment and force generating capacity of the muscle.¹² Alongside changes in muscle function, lower levels of aerobic capacity are associated with reduced physical function and independence during activities of daily living.³⁶ As identified through this review, people infected with SARS-CoV demonstrate decreased VO_{2max} independent of pulmonary and ventilatory function; thus, deconditioning and decreased levels of cardiorespiratory fitness may also account for the reductions in physical function post-infection. Furthermore, post-viral fatigue, which was reported in 40% of people following SARS-CoV infection,³⁷ may also contribute to reduced physical function due to increased perception of effort during functional tasks.³⁸

Importantly, the proposed mechanisms contributing to impaired physical function are not unique to SARS-CoV infection and may be experienced by all causes of critical illness and hospitalisation.³⁹ These mechanisms may also cause impairments to physical function in people infected with COVID-19 – particularly considering the number of people currently hospitalised and admitted to ICU with COVID-19.^{3,7} Accordingly research is required to measure physical function in people following COVID-19 infection to determine whether similar impairments are experienced post-infection, and to quantify the prevalence and severity of any changes to physical function.

As highlighted by the studies included in this review, recovery of physical function following SARS-CoV is incomplete with impairments persisting up to 1-2 years **post-infection onset**. Greater levels of impairment in physical function after 12 months were found in those patients who required mechanical ventilation during hospitalisation,²⁶ indicating that the severity of infection may be associated with poorer recovery post-infection. Promoting recovery of physical function in people with SARS-CoV should be a key target of post-infection management, as long-term physical function and quality of life were shown to be positively correlated in people with SARS-CoV, indicating that lower levels of physical function post-infection are associated with poorer quality of life.^{23,26} In addition, two studies which found incomplete recovery of physical function reported that only 80-83% of people had returned to work 12-months **following infection onset**.^{28,30} Accordingly, the evidence presented in this review highlights the need for rehabilitation to promote recovery of physical function following SARS infection – particularly in those hospitalised with severe infections.

In order to design effective rehabilitation strategies, the selection of intervention type and dose must be specific to key functional impairments. As physical function and fitness were demonstrated to be impaired following SARS-CoV infection, exercise – which aims to improve or maintain aspects of physical fitness and function⁴⁰ – may be an appropriate rehabilitation intervention to address these impairments. Indeed, evidence from one study found that a combined aerobic and resistance training intervention improved 6MWT distance and VO_{2max} by approximately 13% and 3% within the first 2-months post hospital discharge following SARS-CoV infection.²⁴ This evidence is in line with findings from **a Cochrane review where a small number of studies reported that exercise may improve physical function following critical illness.**¹⁵ However, despite the potential beneficial effect of exercise, there is a lack of evidence to support its use for people with SARS-CoV infection as only one study evaluating the effects of exercise was identified by this review. In addition, the safety of exercise following SARS-CoV is unclear, as this study did not report whether any adverse events occurred.

Implications for COVID-19 rehabilitation

Due to the large cohort of COVID-19 survivors, and considering the physical complications of hospitalisation and ICU admission, it is anticipated that there will be a large demand for rehabilitation to promote post-infection recovery.^{14,41} Accordingly, COVID-19 rehabilitation strategies have been recently published.^{42,43} However, the impact of COVID-19 on outcomes such as physical function and fitness and how these outcomes will recover over time is currently unclear. Considering the similarities in pathology and clinical presentation of SARS-CoV and COVID-19, it is anticipated that people with COVID-19 will experience similar impairments to physical function and fitness described in this review. **Although, due to the disparity in COVID-19 infection and death rates among minority ethnic groups – particularly in the UK and USA –⁴⁴ it is unclear whether the findings from the SARS-CoV literature is generalizable to all COVID-19 patients across varying demographic and cultural profiles. Therefore, routine recording of such demographic data should be done post-infection to guide rehabilitation strategies by identifying patient cohorts who may be at greater risk of developing post-infection impairments in function.**

While rehabilitation interventions are required for COVID-19 patients, this review highlights that there is lack of studies investigating the effects of exercise following SARS infection.

Therefore, further research is required to evaluate the effects of exercise in people with COVID-19 to determine whether exercise can promote post-infection recovery. Particular focus should be given to the type and dose of exercise required to elicit beneficial effects post-infection, and how exercise prescription should be modified at various time points post-infection to optimise the recovery of function (e.g. inpatient vs. outpatient rehabilitation). In addition, consideration should also be given to the mode of exercise delivery to ensure safety and effectiveness of the intervention; for example online exercise programmes may offer a practical solution to limit the exposure of health care practitioners and patients to COVID-19,⁴⁵ although face-to-face sessions may be required in some instances to achieve the prescribed exercise dosage.

Finally, although this review focused on physical function and fitness, it is important to consider other potential symptoms of COVID-19 – such as severe fatigue, depression, and cognitive dysfunction – that may impact these outcomes and the effectiveness of rehabilitation. Viral infection is suggested to contribute to the development of chronic fatigue syndrome,⁴⁶ and it was estimated that 27% of people fulfilled the diagnostic criteria for chronic fatigue syndrome following SARS-CoV infection;³⁷ thus, people with COVID-19 may also experience high levels of post-infection fatigue. In addition, cognitive dysfunction such as delirium,⁴⁷ and chronic psychological impairments such as depression and post-traumatic stress disorder may also be experienced during periods of critical illness and ICU care.⁴⁸ **Accordingly, future studies should evaluate the consequences of COVID-19 across psychological and cognitive domains and determine how these outcomes influence the recovery of physical function; these findings can then inform the design and delivery of tailored rehabilitation interventions which consider the impact of symptoms such as fatigue on recovery.**

Limitations

There are important limitations to consider when interpreting the results of this review. Firstly, only one outcome measure (6MWT) was used by the included studies to quantify physical function. 6MWT performance is shown to be dependent upon levels of cardiorespiratory fitness;⁴⁹ therefore it is unclear whether other measures of physical function that require less aerobic capacity – such as the timed up and go or timed 10m walk test – would demonstrate similar patterns of impairment post-infection. In addition, while the

number of confirmed SARS-CoV case was reported to be 8096, the total number of participants included by the studies in this review only accounts for 8% of this population.¹⁷ Consequently, it is unclear whether the results of this review are representative of the entire SARS-CoV population. Furthermore, due to the small number of studies and variability in timing of outcome measurements, it was not possible to perform a meta-analysis. Lastly, as this review only focussed on the effects of exercise, it is unclear whether other rehabilitation interventions have similar effects on post-infection recovery.

Conclusions

Evidence from this review highlights that physical function and fitness are reduced in people following SARS-CoV infection. Furthermore, recovery of physical function is incomplete with impairments persisting 1-2 years post-infection. Due to the similarities in pathology and the significant number of people admitted to hospital and ICU, it is likely that people with COVID-19 will experience similar impairments to physical function and fitness. Therefore, rehabilitation interventions are required to promote recovery post-infection. While exercise may improve physical function post-infection, only one study has evaluated the effects of exercise in a SARS-CoV population. Accordingly, research is required to understand the effects of COVID-19 on physical function and fitness, and determine whether exercise can promote post-infection recovery.

References

1. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med*. 2020;382(13):1199-1207.
2. World Health Organisation. Coronavirus disease (COVID-19): Situation report - 168. Geneva, Switzerland: World Health Organisation; 2020.
3. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med Infect Dis*. 2020;34:1-13.
4. World Health Organisation. Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19). Geneva, Switzerland: World Health Organisation; 2020.
5. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: A model-based analysis. *Lancet Infect Dis*. 2020;3099(20):1-9.
6. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481
7. European Centre for Disease Prevention and Control. Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK – eighth update. Solna, Sweden: European Centre for Disease Prevention and Control;2020.
8. Rawal G, Yadav S, Kumar R. Post-intensive care syndrome: An overview. *J Transl Int Med*. 2017;5(2):90-92.
9. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: Report from a stakeholders' conference. *Crit Care Med*. 2012;40(2):502-509.
10. Barnato AE, Albert SM, Angus DC, Lave JR, Degenholtz HB. Disability among elderly survivors of mechanical ventilation. *Am J Respir Crit Care Med*. 2011;183(8):1037-1042.

11. Herridge MS, Moss M, Hough CL, et al. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. *Intensive Care Med.* 2016;42(5):725-738.
12. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: A systematic review. *Intensive Care Med.* 2007;33(11):1876-1891.
13. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med.* 2011;364(14):1293-1304.
14. Simpson R, Robinson L. Rehabilitation following critical illness in people with COVID-19 infection. *Am J Phys Med Rehabil.* 2020. [In press].
15. Connolly B, Salisbury L, O'Neill B, et al. Exercise rehabilitation following intensive care unit discharge for recovery from critical illness. *Cochrane Database Syst Rev.* 2015;2015(6):CD008632.
16. Peiris JS, Lai ST, Poon LL, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet.* 2003;361(9366):1319-1325.
17. World Health Organisation. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. Geneva, Switzerland: World Health Organisation; 2020.
18. Manocha S, Walley KR, Russell JA. Severe acute respiratory distress syndrome (SARS): A critical care perspective. *Crit Care Med.* 2003;31(11):2684-2692.
19. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther.* 2003;83(8):713-721.
20. NIH National Heart, Lung, and Blood Institute. Quality assessment tool for observational cohort and cross-sectional studies. Available online at: <https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort>. 2014. Accessed April 6th 2020.

21. Ong K, Ng A, Lee L, et al. Pulmonary function and exercise capacity in survivors of severe acute respiratory syndrome. *Eur Respir J*. 2004;24(3):436-442.
22. Hui DS, Joynt GM, Wong KT, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. *Thorax*. 2005;60(5):401-409.
23. Hui DS, Wong KT, Ko FW, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. *Chest*. 2005;128(4):2247-2261.
24. Lau HM, Ng GY, Jones AY, Lee EW, Siu EH, Hui DS. A randomised controlled trial of the effectiveness of an exercise training program in patients recovering from severe acute respiratory syndrome. *Aust J Physiother*. 2005;51(4):213-219.
25. Lau HM, Lee EW, Wong CN, Ng GY, Jones AY, Hui DS. The impact of severe acute respiratory syndrome on the physical profile and quality of life. *Arch Phys Med Rehabil*. 2005;86(6):1134-1140.
26. Li TS, Gomersall CD, Joynt GM, Chan DPS, Leung P, Hui DSC. Long-term outcome of acute respiratory distress syndrome caused by severe acute respiratory syndrome (SARS): An observational study. *Crit Care Resusc*. 2006;8(4):302-308.
27. Su M, Hsieh Y, Wang Y, Lin A, Chung Y, Lin M. Exercise capacity and pulmonary function in hospital workers recovered from severe acute respiratory syndrome. *Respiration*. 2007;74(5):511-516.
28. Tansey CM, Louie M, Loeb M, Gold WL, et al. One-year outcomes and health care utilization in survivors of severe acute respiratory syndrome. *Arch Intern Med*. 2007;167(12):1312-20.
29. Hui DSC, Wong KT, Antonio GE, Tong M, Chan DP, Sung JJY. Long-term sequelae of SARS: Physical, neuropsychiatric, and quality-of-life assessment. *Hong Kong Med J*. 2009;15(Suppl 8):21-23.

30. Ngai JC, Ko FW, Ng SS, To K, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology*. 2010;15(3):543-550.
31. Parry SM, Puthuchearu ZA. The impact of extended bed rest on the musculoskeletal system in the critical care environment. *Extrem Physiol Med*. 2015;4(16):1-8.
32. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: A prospective multicenter study. *JAMA*. 2002;288(22):2859-2867.
33. Puthuchearu ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness. *JAMA*. 2013;310(15):1591-1600.
34. Parry SM, El-Ansary D, Cartwright MS, et al. Ultrasonography in the intensive care setting can be used to detect changes in the quality and quantity of muscle and is related to muscle strength and function. *J Crit Care*. 2015;30(5):1-14.
35. Topp R, Ditmyer M, King K, Doherty K, Hornyak J. The effect of bed rest and potential of prehabilitation on patients in the intensive care unit. *AACN Clin Issues*. 2002;13(2):263-276.
36. Arnett SW, Laity JH, Agrawal SK, Cress ME. Aerobic reserve and physical functional performance in older adults. *Age Ageing*. 2008;37(4):384-389.
37. Lam MH, Wing YK, Yu MW, et al. Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: Long-term follow-up. *Arch Intern Med*. 2009;169(22):2142-2147.
38. Ross SD, Estok RP, Frame D, Stone LR, Ludensky V, Levine CB. Disability and chronic fatigue syndrome: A focus on function. *Arch Intern Med*. 2004;164(10):1098-1107.
39. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. *N Engl J Med*. 2014;370(17):1626-1635.
40. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. *Public Health Rep*. 1985;100(2):126-131.

41. Stam HJ, Stucki G, Bickenbach J. Covid-19 and post intensive care syndrome: A call for action. *J Rehabil Med.* 2020;52(4):1-4.
42. Phillips M, Turner-Stokes L, Wade D, Walton K. Rehabilitation in the wake of covid-19 - A phoenix from the ashes. British Society of Rehabilitation Medicine:2020. Available online at: <https://www.bsrm.org.uk/downloads/covid-19bsrmissue1-published-27-4-2020.pdf>. Accessed July 4th 2020
43. Thomas P, Baldwin C, Bissett B, et al. Physiotherapy management for COVID-19 in the acute hospital setting: Clinical practice recommendations. *J Physiother.* 2020;66(2):73-82.
44. Pan D, Sze S, Minhas JS, Bangash MN, Pareek N, Divall P, et al. The impact of ethnicity on clinical outcomes in COVID-19: A systematic review. *EClinicalMedicine.* 2020;23:1-8.
45. Lee A. COVID-19 and the Advancement of Digital Physical Therapist Practice and Telehealth. *Phys Ther.* 2020. [In press].
46. Rasa S, Nora-Krukle Z, Henning N, et al. Chronic viral infections in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *J Transl Med.* 2018;16(268):1-25.
47. Wilcox ME, Brummel NE, Archer K, Ely EW, Jackson JC, Hopkins RO. Cognitive dysfunction in ICU patients: Risk factors, predictors, and rehabilitation interventions. *Crit Care Med.* 2013;41(9):81-98.
48. Jackson JC, Pandharipande PP, Girard TD, et al. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: A longitudinal cohort study. *Lancet Respir Med.* 2014;2(5):369-379.
49. Burr JF, Bredin SS, Faktor MD, Warburton DE. The 6-minute walk test as a predictor of objectively measured aerobic fitness in healthy working-aged adults. *Phys Sportsmed.* 2011;39(2):133-139.

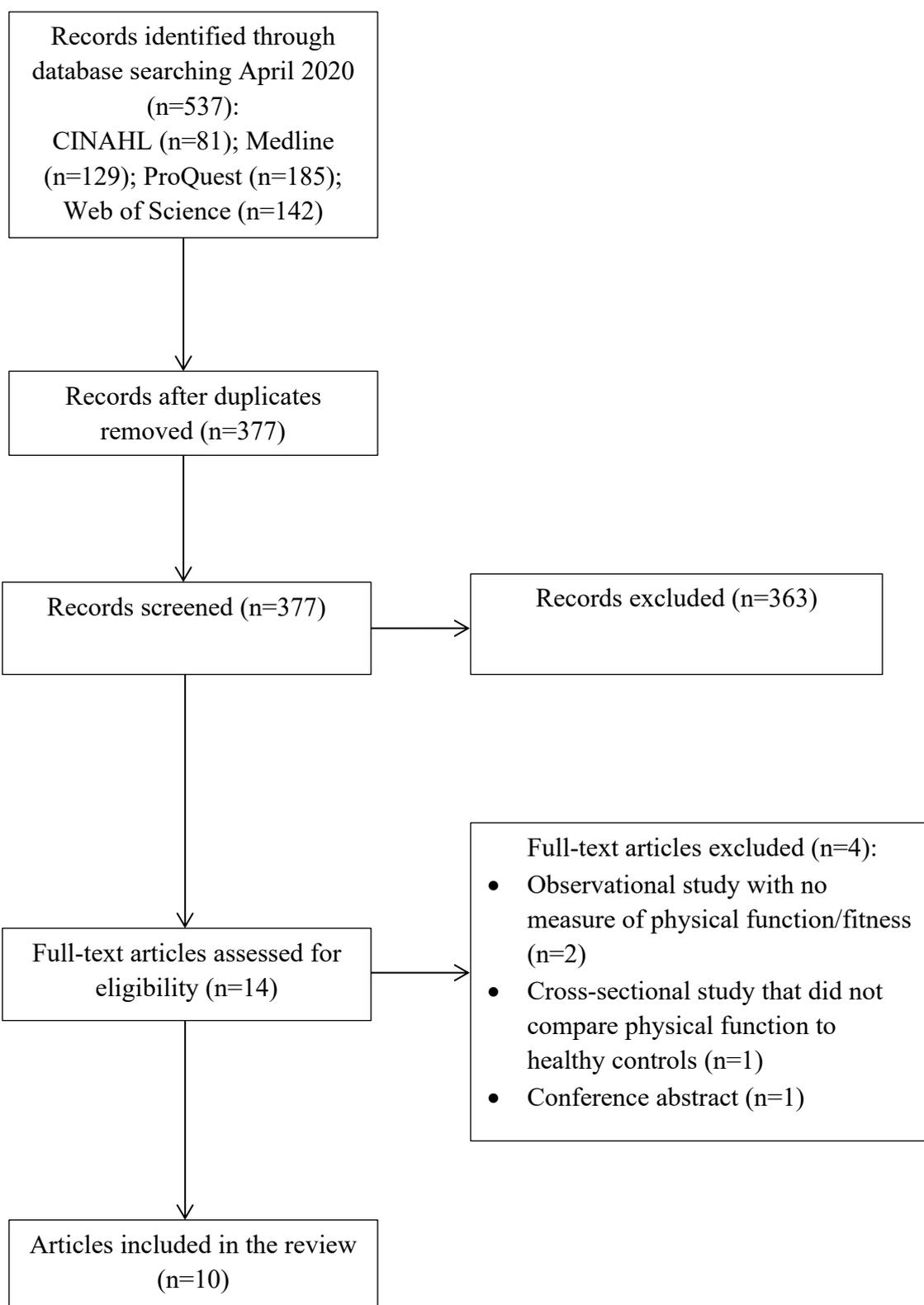


Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram

Table 1 – Cross-sectional and longitudinal studies measuring the change or recovery in physical function and fitness

Study, design, location, quality	Participant demographics	Control demographics	Physical function/fitness outcome measure	Timing of assessment	Main findings*
Ong et al., 2004 ²¹ Cross-sectional Singapore NIH = 7	N = 46 (34 F/12 M) Age (mean ± SD) = 37.3±10.7 Time since infection onset = NR Duration of hospitalisation (mean ± SD), days = 20.4±17.3 ICU admission = 22% Mechanical ventilation = 15% Pre-existing medical condition = 56%	N = 95 (47 F/48 M) Age (mean ± SD) = 42.4 ± 12.4	Aerobic capacity (VO _{2max}): Symptom limited CPET using lower-limb cycle ergometer and gas exchange measurement; testing protocol of 10 W/min	3 months post hospital discharge	<u>VO_{2max} (mL/kg/min): 20.3±5.1 (mean % of normative value -78.6±17.0)</u>
Hui et al., 2005; ²² Hui et al., 2005; ²³ Hui et al., 2009 ²⁹ Cohort study Hong Kong NIH = 10; 9; 8	N = 110 (66 F/44 M) Age (mean ± SD) = 35.6±9.8 Time since infection onset = NR Duration of hospitalisation (mean ± SD), days = 22.0±13.9 ICU admission = 28% Mechanical ventilation = 6% Pre-existing medical condition = 15%	N = 538 (F/M NR) Age = NR	6MWT (m)	3, 6, 12 months post infection onset	<u>6MWT distance</u> 3 months: 464±83m 6 months: 502±95m 12 months: 511±90m (3 months to 12 months, p<0.01) <u>Mean difference (95% CI) at 12 months vs. healthy controls</u> Age 21-30: M = -113 (-145, -81), p<0.01 F = -84 (-131, -37), p<0.01 Age 31-40: M = -84 (-132, -36), p<0.05 F = -92 (-121, -62), p<0.05

					<p>Age 41-50: M = -81 (-160, -29), p>0.05 F = -74 (-136, -12), p<0.05</p> <p>Age 51-60: M = -129 (-1727, 1469), p>0.05 F = -133 (-206, -58), p<0.01</p>
<p>Lau et al., 2005²⁵ Cross-sectional Hong Kong NIH = 7</p>	<p>N = 171 (111 F/60 M) Age (mean ± SD) = 37.36±12.65 Time since infection onset (mean ± SD), days = 81.79±18.46 Duration of hospitalisation (mean ± SD), days = 21.79±9.93 ICU admission = 14% Mechanical ventilation = NR Pre-existing medical condition = NR</p>	<p>N = 548 (226 F/322 M) Age (mean ± SD) = 37.8±10.9</p>	6MWT (m)	2 weeks post hospital discharge	<p><u>6MWT distance vs. healthy controls</u> Age 20-29: SARS = 644.37±86.10; C = 698.00±76.00; p<0.01 Age 30-39: SARS = 623.53±91.22; C = 698.00±76.00; p<0.01 Age 40-49: SARS = 563.90±84.17; C = 635±57.00; p<0.01 Age 50-59: SARS = 517.88±91.62; C = 635.00±57.00; p<0.01 Age >60: SARS = 430.29±130.07; C = 512.00±79.00; p<0.01</p>
<p>Li et al., 2006²⁶ Cohort Study Hong Kong NIH = 9</p>	<p>N = 59 (25 F/34 M) Age (mean ± SD) = 47±16 Time since infection onset = NR Duration of hospitalisation (median (IQR)), days = 31 (20-54) ICU admission = 100% Mechanical ventilation = 46% Pre-existing medical condition = 17%</p>	<p>N = NR Age = NR</p>	6MWT (m)	3, 6, and 12 months post infection onset	<p><u>6MWT distance (mean % of normative value)</u> 3 months: Ventilated = 400±90 (67%); Non-ventilated = 475±94 (72%) 6 months: Ventilated = 451±91 (72%); Non-ventilated = 524±107 (79%) 12 months: Ventilated = 461±140 (74%); Non-ventilated = 523±95 (79%)</p> <p><u>Change in 6MWT distance</u> 3 months vs. 6 months: Ventilated, p<0.05; Non-ventilated, p<0.01 6 months vs. 12 months: Ventilated,</p>

					p>0.05; Non-ventilated, p>0.01
Su et al., 2007 ²⁷ Cross-sectional Taiwan NIH = 6	N = 13 (10 F/ 3M) Age (mean ± SD) = 31.4±4.8 Time since infection onset = NR Duration of hospitalisation (mean ± SD), days = 20.77±11.43 ICU admission = 8% Mechanical ventilation = 8% Pre-existing medical condition = 8%	N = 14 (F/M NR) Age = NR	Aerobic capacity (VO _{2max}): Symptom limited CPET using lower-limb cycle ergometer and gas exchange measurement; testing protocol NR	14 months post hospital discharge	VO _{2max} (mL/kg/min) vs. healthy controls SARS = 26.3±83.4; C = 27.9±86.0; p>0.05
Tansey et al., 2007 ²⁸ Cohort study Canada NIH = 9	N = 117 (78 F/ 39M) Age (median (IQR)) = 42 (33-51) Time since infection onset = NR Duration of hospitalisation (median (IQR)), days = 14 (8-19) ICU admission = 16% Mechanical ventilation = 9% Pre-existing medical condition = 9%	N = 290 (173 F/117 M) Age (range) = 40-80	6MWT (m)	3, 6, 12 month post hospital discharge	<u>Median (IQR) 6MWT distance, % of normative value</u> 3 months: 483 (396-552), 81% 6 months: 487 (447-553), 81% 12 months: 488 (448-555), 83%
Ngai et al., 2010 ³⁰ Cohort study Hong Kong NIH = 9	N = 55 (36 F/19 M) Age (mean ± SD) = 44.4±13.2 Time since infection onset = NR Duration of hospitalisation (mean ± SD), days = 28.2±25.2 ICU admission = 22% Mechanical ventilation = 7%	N = 538 (F/M NR) Age = NR	6MWT (m)	3, 6, 12, 18, 24 months post infection onset	<u>6MWT distance</u> 3 months: 439.0±89.1m 6 months: 460.1±102.8m (vs. 3 months, p<0.05) 12 months: 464.7±101.9m 18 months: 466.3±91.0m 24 months: 462.6±120.0m (3 months to 24 months, p>0.05)

	Pre-existing medical condition = NR			<u>Mean difference (95% CI) at 24 months vs. healthy controls</u> Age 21-30: M = -109 (-231.1, 13.1), p>0.05 F = -104 (-175.6, -32.4), p<0.01 Age 31-40: M = -135 (-241.3, -55.7), p<0.01 F = -90 (-155.9, -24.1), p<0.01 Age 41-50: M = -73 (-174.9, 29.9), p>0.05 F = -82 (-125.4, -38.6), p<0.001 Age 51-60: M = -213 (-290., -4.3), p<0.01 F = -161.0 (-326.0, 2.4), p>0.05
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* Values presented as mean ± SD unless stated otherwise

Abbreviations: 6MWT, 6-minute walk test; C, Control group; CPET, Cardiopulmonary exercise testing; F, Female; ICU, Intensive Care Unit; M, Male; NIH, NIH Quality assessment tool for observational cohort and cross-sectional studies; NR, Not reported; SARS, Severe acute respiratory syndrome related Coronavirus; VO_{2max}, Maximum oxygen consumption

Table 2 – Details of the randomised controlled trial investigating the effects of exercise post SARS-CoV infection

Author, date, location	Participants	Intervention	Control	Outcome measures	Main findings
Lau et al., 2005 ²⁴ Hong Kong PEDro = 9	N = 133 (88 F/45 M) Age (mean ± SD): I = 35.9±9.3; C = 38.3±11.2 Time since infection onset = NR Duration of hospitalisation (mean ± SD), days: I = 23.2±11.3; C = 22.1±10.9 ICU admission = NR Mechanical ventilation = NR Pre-existing medical condition = NR	Exercise programme: 6 weeks; 2x supervised sessions/week; 60-90 minutes 30-45 minutes aerobic exercise (60-70% HRmax); resistance training 3 sets of 10–15 repetition maximum load	Educational session about general exercise and weekly telephone calls with a physiotherapist	6MWT; VO _{2max} (Chester Step Test); SF-36; MVIC of gluteus maximum, deltoids, and hand-grip (hand-held dynamometry) 0, 6 weeks	<u>Mean±SD change at 6 weeks</u> 6MWT (m) : I = 77.4±71.3; C = 20.7±98.6; p<0.05 VO_{2max} (ml/kg/min) : I = 3.6±5.4; C = 1.0±7.3; p<0.05 MVIC gluteus maximus (kgf) : I = 10.4±12.3; C = 8.8±14.7; p>0.05 MVIC deltoids (kgf) : I = 7.5±6.1; C = 5.5±10.1; p>0.05 Right hand grip (kgf) : I = 4.7±6.0; C = 1.7±5.2; p<0.05 Left hand grip (kgf) : I = 4.2±5.9; C = 2.2±4.8; P<0.05 SF-36 (PF) : I = 3.7±18.4; C = 3.7±16.1; p>0.05 SF-36 (RP) : I = 14.4±40.2; C = 14.6±37.2; p>0.05 SF-36 (RE) : I = 1.9±38.2; C = 8.9±42.0; p>0.05 SF-36 (P) : I = 0.0±24.9; C = -5.0±24.1; p>0.05 SF-36 (SF) : I = 12.9±22.8; C = 14.2±24.2; p>0.05 SF-36 (GH) : I = -0.8±17.5; C = -2.5±18.6; p>0.05 SF-36 (MH) : I = -1.6±11.7; C = -0.3±16.9; p>0.05 SF-36 (V) : I = 1.3±18.0; C = 2.5±14.2; p>0.05

Abbreviations: 6MWT, 6-minute walk test; C, Control groups; F, Female; HRmax, Maximum heart rate; GH, General Health subscale; I, Intervention; ICU, Intensive Care Unit; M, Male; MH, Mental Healthy subscale; NR, Not reported; p, Bodily Pain subscale; PF, Physical Function sub-scale; RE, Role Emotional subscale; RP, Role Physical subscale; SF-36, Medical Outcomes Survey Short Form 36 questionnaire; SF, Social Functioning subscale; V, Vitality subscale; VO_{2max}, Maximum oxygen consumption

Supplementary table 1 – Search strategy

Database	Search terms
CINAHL (n=81); Medline (n=129); ProQuest (n=185); Web of Science (n=142)	(“Coronavirus” or “severe acute respiratory syndrome” or “Severe Acute Respiratory Syndrome-related Coronavirus” or “SARS” or “SARS-CoV” or “COVID-19” or “SARS-CoV-2” or “COVID19” or “novel coronavirus” or “coronavirus 2019” or “ COVID19” or “COVID 19”) AND (“physical fitness” or “maxim* oxygen consumption” or “maxim* oxygen uptake” or “cardiopulmonary exercise testing” or “cardiopulmonary exercise test” or “CPET” or “VO2-max” or “VO2max” or “VO2-peak” or “VO2peak” or “aerobic capacity” or “maxim* aerobic capacity” or “cardiopulmonary fitness” or “6MWT” or “6 minute walk test” or “muscle strength” or “maxim* voluntary contraction” or “maxim* muscle contraction” or “muscle function” or “mechanical muscle function” or “muscle power” or “explosive strength” or “rate of force development” or “physical function*” or “decondition*” or “disability” or “gait” or “walking” or “sit to stand” or “exercise” or “exercise therap*” or “exercise movement technique*” or “resistance training” or “aerobic exercise*” or “rehab*”)

Supplementary table 2 – Quality assessment of observational studies using the NIH quality assessment tool for observational cohort and cross-sectional studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Ong et al. ²¹	1	1	1	1	0	1	0	N/A	1	N/A	1	0	N/A	0
Hui et al. ²²	1	1	1	1	0	1	1	N/A	1	N/A	1	0	1	1
Hui et al. ²³	1	1	1	1	0	1	1	N/A	1	N/A	1	0	0	1
Lau et al. ²⁵	1	1	1	1	0	1	0	N/A	U	N/A	1	0	N/A	1
Li et al. ²⁶	1	1	1	1	0	1	1	N/A	1	N/A	1	0	U	1
Su et al. ²⁷	1	1	1	1	0	1	0	N/A	U	N/A	1	0	N/A	0
Tansey et al. ²⁸	1	1	1	1	0	1	1	N/A	1	N/A	1	0	1	0
Hui et al. ²⁹	1	1	1	1	0	1	1	N/A	1	N/A	1	0	0	0
Ngai et al. ³⁰	1	1	1	1	0	1	1	N/A	1	N/A	1	0	0	1

Notes: 1, yes; 0, no; N/A, not applicable; U, Unclear

Q1, Was the research question or objective in this paper clearly stated; Q2, Was the study population clearly specified and defined; Q3, Was the participation rate of eligible persons at least 50%; Q4, Were all the subjects selected or recruited from the same or similar populations (including the same time period)/were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants; Q5, Was a sample size justification, power description, or variance and effect estimates provided; Q6, For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured; Q7, Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed; Q8, For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable); Q9, Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants; Q10, Was the exposure(s) assessed more than once over time; Q11, Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants; Q12, Were the outcome

assessors blinded to the exposure status of participants; Q13, Was loss to follow-up after baseline 20% or less; Q14, Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)

Supplementary table 3 – Quality assessment of randomised controlled trials using the PEDro scale

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Lau et al. ²⁴	1	1	1	1	0	0	1	1	1	1	1

Notes: 1, yes; 0, no

Q1, eligibility criteria were specified; Q2, subjects were randomly allocated to groups; Q3, allocation was concealed; Q4, the groups were similar at baseline regarding the most important prognostic indicators; Q5, there was blinding of all subjects; Q6, there was blinding of all therapists who administered the therapy; Q7, there was blinding of all assessors who measured at least one key outcome; Q8, measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; Q9, all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by “intention to treat”; Q10, the results of between-group statistical comparisons are reported for at least one key outcome; Q11, the study provides both point measures and measures of variability for at least one key outcome