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## **A Systematic Review of Physical Activity and Physical Fitness in Sarcoidosis.**

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## Abstract

Individuals with sarcoidosis are at risk of deconditioning and heightened non-communicable diseases through decreased muscle strength and physical activity. This systematic review analysed published data to provide an overview of the **associations of physical activity and physical fitness with sarcoidosis**.

A systematic search of PubMed and ScienceDirect, was conducted in April 2021 following PRISMA guidelines, to determine the **association** of sarcoidosis with levels of physical activity and fitness. Experimental studies of patients with sarcoidosis where **cardio-respiratory** capacity, physical activity and/or muscle strength were measured were selected.

Twenty-one trials with 1442 participants met the inclusion criteria. Studies (published between 1986-2018) found reduced **cardio-respiratory capacity (n=17)**, **physical activity levels (n=2)** and muscle strength (**n=8**) within sarcoidosis patients, with those experiencing fatigue affected more than non-fatigued.

Physical activity is reduced in sarcoidosis compared to normative values, including sedentary healthy individuals. In addition, muscle strength and **cardio-respiratory capacity / fitness** are reduced, with individuals affected by fatigue. Three clinical exercise-intervention trials demonstrated improved muscle strength and six-minute walk distance alongside decreased fatigue ratings. The deconditioning effects of sarcoidosis, in addition to associated symptoms, can be overcome/improved by exercise. Further well-designed trials with exercise prescription are needed to establish standardised exercise recommendations specific to sarcoidosis.

*Keywords: Sarcoidosis, Interstitial Lung Disease, Exercise Rehabilitation, Muscle Strength, Physical Activity, Fatigue, Exercise Prescription,*

## **Introduction**

Physical activity and, by extension, exercise should be a key component of everyone's life for numerous well-documented health reasons, including improved quality of life and reduced risk of non-communicable diseases [1]. The need for physical activity and/or exercise as a consequence of chronic disease(s) is amplified due to its ability to reduce symptoms and therefore improve the health of individuals [2]. However, within individuals experiencing chronic disease, specifically interstitial lung diseases (ILD) such as asthma, Chronic Obstructive Pulmonary Disease (COPD) and sarcoidosis [3, 4, 5], physical activity has been recorded at lower levels when compared with healthy counterparts, despite the known public health benefits for both healthy and chronically ill populations [6, 7]. For example; regular physical activity within COPD patients has been shown to reduce not just admissions to hospital, but also all-cause mortality, as well as specifically, respiratory mortality [8], while physical inactivity is the fourth biggest killer across the world's population [9].

Sarcoidosis is a non-caseating granulomatous disease [10], a condition that involves the inflammation of organs and tissues [11]. The granulomas form as a result of lymphocyte cells clustering together [12]. Up to 90% of sarcoidosis cases are pulmonary; however the condition can affect numerous other locations, such as the liver, heart and skin [13]. Despite sarcoidosis affecting a significant number of people globally (sarcoidosis affects 1 in 10,000 in the UK [14]) and being second only to asthma in young adults for respiratory diseases [15], there is a dearth of research into the condition, as well as a limited understanding of non-pharmacological treatments to alleviate the primary and secondary symptoms. Unfortunately, the typical sarcoidosis symptoms including fatigue, dyspnoea and chronic cough [16, 17], often lead to decreased levels of physical activity and the negative side effects associated with this, such as sarcopenia or cachexia [18], and as such the symptoms have been suggested as being pivotal within the deconditioning process [19]. The loss of muscle mass and strength is also a major

problem in sarcoidosis [17] as this leads to reduced quality of life caused by an impairment of day-to-day functional abilities such as stair climbing or carrying shopping. High levels of fatigue and decreased lung function [17, 20, 21] cause greater relative exertion during physical tasks such as stair climbing or walking [22], which aids in the faster progression of the deconditioning process and thus compounds the above [23]. It is worth noting however, that within healthy adolescent males, vigorous physical activity was positively associated with body muscle strength in the lower body [24]. Despite these findings [24], it is unclear whether this trend is consistent across all demographics such as age, fitness level and disease severity [25]. Although, physical activity and exercise, as well as muscle strength due to its relevance to physical health, have a growing body of knowledge in relation to sarcoidosis [26], still much remains unknown, including the effect of sarcoidosis on muscle in terms of strength and mass, the mechanism behind any changes and the extent to which these can be directly attributed to sarcoidosis, rather than other compounding factors such as reduced physical activity.

Therefore, better understanding of the **association** between sarcoidosis and physical activity, **fitness** and muscle strength, alongside other associated factors such as **cardio-respiratory capacity**, lung function and heightened inflammation that may induce changes, may help to improve the treatment and guidance available to sarcoidosis patients and thus lead to improved health status and quality of life. A review of all currently available research on physical activity, **fitness, cardio-respiratory capacity** and muscle strength relating to sarcoidosis is therefore required, with the aim of drawing insight and defining future directions for new research and potential treatment strategies for the condition. The purpose of this systematic review, therefore, was to analyse published data to provide an overview of **how levels of physical activity and physical fitness are associated with sarcoidosis.**

## **Methods**

### *Data Sources and Searches*

Standardised systematic review methodology based on PRISMA [27, 28] was utilised throughout this review. A search of PubMed and Science Direct was conducted in April 2021 and all duplicate documents found were removed from the results. Additionally, a hand search of the reference lists of articles included in the final analysis that were identified via the database search was conducted, as were the first twenty “related articles” of those included database search articles on PubMed. A hand search of other reviews, commentaries, letters, PhD dissertations, and reference lists of original articles was also conducted. The search terms chosen to aid this review were constructed based on the PICOT framework (Population, intervention, comparison, outcome, time; [28]). Terms utilised included: “Sarcoidosis” OR “Pulmonary”, AND “Physical Activity” OR “Rehabilitation”, OR “Exercise Prescription”, OR “Exercise Training”, OR “Muscle Strength”, OR “Aerobic”, “Aerobic Capacity”, OR “Cardiopulmonary Exercise Testing (CPET)”, OR “Handgrip”, OR “Isokinetic dynamometry”.

### *Study Selection*

Inclusion criterion included sarcoidosis being researched individually and not as part of a wider group such as interstitial lung disease (ILD), exercise testing of sarcoidosis participants including aerobic, muscle strength and physical activity and included both real-world data (i.e. accelerometer) and questionnaires (i.e. international physical activity questionnaire (IPAQ)).

Exclusion criterion extended to mixed ILD studies, lack of exercise testing, case studies and other systematic reviews/meta-analysis as well as use of inspiratory muscle training (IMT).

The reviewer was not blinded to study authors, institutions or journals of publication. If a

decision on the relevance of a paper could not be made from the title and abstract, full text was obtained and checked.

#### *Data Extraction, Synthesis and Analysis*

Data extraction was carried out via two Microsoft Office tables, and studies were placed in order of publication year. The data extraction results were summarised into two structured tables one focussing on research with rehabilitation programmes and the other including those measuring exercise, physical activity and muscle strength. Meta-analysis was not performed due to the differences between the studies.

## Results

### *Summary of Studies*

In total, 1089 studies were identified following the literature search (Figure 1). Of these studies, 21 articles were included within the review following record screening and having met the inclusion criteria. A total of 1442 sarcoidosis participants were included with studies ranging from 14 – 160 participants (Table 1; Table 2). Of the 21 studies considered, 17 measured lung function, 17 conducted a form of cardiopulmonary exercise testing (CPET; six-minute walk test (6MWT), symptom linked bicycle test etc.), eight assessed muscle strength, eight evaluated fatigue and, two considered physical activity levels within pulmonary sarcoidosis through direct measurement, utilising an accelerometer [4, 5]. Three studies also looked at depression/depressive symptoms [4, 5, 34], and three studies used healthy matched controls alongside sarcoidosis participants [4, 29, 30], while three evaluated the effects of rehabilitation treatment programmes [31, 32, 34; Table 2]. **The suggested degree of impaired capacity that sarcoidosis patients may experience, and the degree of proposed improvement obtained with exercise training in light of such studies is schematically illustrated in Figure 2.**

### *Exercise Testing*

Some form of exercise testing was conducted in 17 of the studies (Table 1; Table 2). Exercise testing included standardised testing such as the six-minute walk test, modified shuttle test, symptom limited bicycle test and symptom limited maximal exercise test (peak  $\dot{V}O_2$ ) but some studies reported as generic “cardiopulmonary exercise test”. Limitations of many of the studies were that most lacked detailed descriptive methods of how the exercise test was conducted beyond providing a name, and potential confounding factors that could not be standardised which included warm-up protocol, nutrition intake prior to testing and verbal encouragement



frequency. Additionally, across the evaluated studies, the outcomes of the exercise testing were measured in different ways thereby increasing the difficulty of determining any trends in the findings. Overall, it can be deemed that pulmonary sarcoidosis negatively affects exercise performance and impairs gas exchange but the extent to which this occurs, and the specific impact is unclear.

### *Physical Activity*

Only two studies measured physical activity, with both using accelerometers to assess movement patterns [4, 5]. The first study, [5] compared age, gender and race-matched sarcoidosis and healthy patients and found sarcoidosis patients to be less physically active and experiencing more fatigue than non-sarcoidosis patients. The second study [4] found physical activity to be reduced in fatigued sarcoidosis patients when compared with non-fatigued sarcoidosis patients and reduced in both fatigued and non-fatigued sarcoidosis patients when compared to a healthy control population (Table 1). While the mechanism(s) behind this remain unclear, fatigue was found to be associated with reduced physical activity [4] and participants grouped as fatigued following a self-reported questionnaire recorded lower physical activity than their non-fatigued peers. Additionally, confounding factors were alluded to, but never fully explained, likely due to shortcomings in the body of knowledge, as previously discussed in relation to exercise testing.

### *Muscle Strength*

Of the eight studies associated with measurement of muscle strength, elbow flexor muscle strength and quadricep peak torque [4, 26, 31, 32, 33] received the most attention, although hamstring peak torque and handgrip strength were also measured and reported within one [33]

and two studies [4, 32], respectively (Table 1). Three different methods (Isokinetic dynamometry, back and leg dynamometer and MicroFET) were generally used to measure muscle strength. This means that some discrepancies between the findings can be expected, however there was much more consistency in these reported variables than observed in the exercise testing. Muscle strength was shown to be reduced in comparison to general population reference values for those with sarcoidosis across all of the eight studies. Marcellis *et al.* [33] found quadricep peak torque (QPT) was reduced by 21.3% and 18% respectively, after a two year follow-up, compared against normative values. However, studies exploring efficacy of rehabilitation [31, 32, 34] suggest a possibility of reversing this trend within the defined population. Fatigue has been associated with this detrimental symptom of reduced muscle strength within sarcoidosis patients, for example [4] found fatigued participants scored significantly lower than their non-fatigued counter-parts although other confounding factors have not been effectively determined. All rehabilitation studies [31, 32, 34] showed statistically significant improvements to fatigue scores (FAS and fatigue severity scale; FSS) and six-minute walk distance (6MWD), in addition to their respected muscle strength scores, quadricep [31], leg strength [34] and elbow flexion percentage [32], despite differing approaches to rehabilitation.

## 1 Discussion

2 This systematic review identified 21 studies that investigated the influence and levels of  
3 physical fitness, physical activity and muscle strength on people with sarcoidosis.

4 The key findings of the review are decreased levels of **cardio-respiratory** exercise capacity,  
5 physical activity and muscle strength within the sarcoidosis population compared to a healthy  
6 population or predicted normative data. Those patients experiencing daily symptoms of fatigue  
7 demonstrated greater impairment than non-fatigued sarcoidosis patients (Table 1).  
8 Unfortunately, there is yet to be an extensive range of controlled and standardised research **of**  
9 patients with pulmonary sarcoidosis that focusses on exercise, from which clear outcomes can  
10 be utilised for treatment guidelines and to optimise the future direction of research. However,  
11 key findings from the available literature relating to exercise and sarcoidosis, emphasise the  
12 requirement for further research that aims to overcome these constraints.

13 All 21 studies recorded some sign of impairment as recorded by the variables tested in terms  
14 of **cardio-respiratory capacity (n=17)**, physical activity (n=2) and muscle strength (**n=8**)  
15 (Tables 1 & 2). Most prevalent were the reduction in lung function [39], and by extension  $\dot{V}O_2$   
16 peak [43], and reduced distance within the six-minute walk test [33] or other exercise test  
17 performance outcome such as modified shuttle walk test [41] and  $\dot{V}O_2$  max [37]. The lack of  
18 consensus between the studies in terms of the choice of exercise tests, led to discrepancies  
19 across the research and reduced the ability to form clear conclusions as different exercise tests  
20 have varying benefits and constraints, although there was consistent evidence, regardless of the  
21 test used, of physiological and functional decrements in patients suffering from sarcoidosis [41,  
22 45]. One issue across the current literature is the lack of understanding or explanation of the  
23 mechanisms associated with the findings in comparison to predicted and normative values,  
24 where the research reported thus far lacks sufficient depth in the analysis of the findings.

25 Furthermore, as it stands, it is unknown how the reported improvements would compare to  
26 healthy untrained individuals undergoing the same or similar exercise training/treatment due  
27 to the lack of a control/comparison group within the research, as well as the complexities of  
28 sarcoidosis and its effect on each individual patient. Fatigue has been associated with reduced  
29 physical activity within numerous populations such as cancer patients and elderly patients,  
30 whilst reduced physical activity is associated with physical deconditioning which causes  
31 reduced exercise capacity. For example, Kallianos *et al.* [22] found cardio-respiratory capacity  
32 to be limited yet the mechanism(s) responsible for this impairment were not investigated  
33 despite the researchers noting both ventilatory and cardiocirculatory factors which may be  
34 attributed to the exercise limitation. However, impaired diffusing capacity of the lungs and/or  
35 increased dead space related to pulmonary hypertension were considered as possible reasons  
36 for ventilatory factors. Impaired defusing capacity may result in a knock-on detrimental effect  
37 on the delivery of oxygen, Sietsema *et al.* [36] found impairment of oxygen delivery and  
38 utilisation within sarcoidosis participants with normal lung function. Those who recorded  
39 abnormal oxygen consumption responses patterns (nine participants) had echocardiographic  
40 studies undertaken due to the association with cardiovascular disease. Five participants at rest  
41 or during exercise recorded right ventricular systolic dysfunction with four of them also  
42 showing hypertrophy of the right ventricular. However, another factor may be impaired  
43 utilisation of oxygen at the muscle due to granulomatous lesions, which was not investigated  
44 [36]. Furthermore, contradictory findings surrounding the diffusing capacity of the lungs for  
45 carbon monoxide (DLCO) were reported, with the DLCO suggested as a good predictor of the  
46 absence of pulmonary gas exchange impairment [43] despite Marcellis *et al.* [40] suggesting  
47 that pulmonary gas exchange impairment occurs at maximal exercise in a substantial number  
48 of the participants, despite normal resting DLCO. The reasons for these observed differences  
49 remain unknown but could be associated with the lack of consistency in the disease states

50 within this condition. Despite the lack of understanding regarding the mechanisms of the  
51 observed alterations to **cardio-respiratory capacity**, lung function, physical activity and muscle  
52 strength, key findings which may aid in directing future work are those of the various exercise  
53 parameters ( $\dot{V}O_2$  max, gas exchange, total lung capacity, exercise heart rate response) that were  
54 typically more detrimentally affected as the radiographic stage increased [36, 37]. **Further**  
55 **research is also required to understand to what degree exercise capacity is reduced/limited in**  
56 **sarcoidosis and how much this limit is due to fatigue caused by the sarcoidosis and therefore**  
57 **what potential can be improved beyond the exercise capacity at the onset of the symptoms. Due**  
58 **to the complexities of the disease and how it presents itself from patient to patient, it is likely**  
59 **that there is a varying degree of detrimental impact on exercise capacity between the disease**  
60 **itself and the symptoms of fatigue, which would vary at an individual patient level.**  
61 **Furthermore, the effects of the disease and the symptoms of fatigue are likely to also be further**  
62 **complicated and impacted on whether sarcoidosis is currently active within a patient or not.**

63

#### 64 *Fatigue*

65 A factor that became prominent within this review, despite not being a primary search term,  
66 was fatigue. Fatigue has been recognised as a major symptom within pulmonary sarcoidosis  
67 [17] and has been reported to occur in up to 70% of cases [4]. Fatigue is compounded by the  
68 secondary effects it has, such as decreased quality of life [4, 40] and psychological distress [4].  
69 This is likely, in part, caused by the isolating effect of fatigue, and worsened by the lack of a  
70 physical manifestation for others to see. Korenromp *et al.* [4] found fatigue to be a chronic  
71 symptom within sarcoidosis, despite clinical remission, associated with reduced muscle  
72 strength and physical activity in comparison to both healthy control and self-reported non-  
73 fatigued pulmonary sarcoidosis participants. However in contrast, Zieleznik *et al.* [42] found

74 fatigue not to correlate with lung function or distance covered within the six-minute walk test.  
75 In addition to this, Saligan [5] found sedentary healthy controls scored statistically significantly  
76 lower fatigue ratings ( $P < 0.01$ ) than the sarcoidosis group and had a higher daily energy  
77 expenditure (1748 kcal) than fatigued sarcoidosis patients (1324 kcal). The control group also  
78 outperformed on the six-minute walk test. It is worth noting, however, despite the control group  
79 being age, gender and ethnicity matched, they were not matched for body mass index (BMI)  
80 or body composition, which is a key limitation within the research, as body composition  
81 differences (i.e. the muscle mass of participants) may in part explain the differences between  
82 daily energy expenditure [46].

83 However, much like the mechanisms behind the reduction in exercise performance, the  
84 understanding of the mechanisms behind fatigue remain unknown. Strookappe *et al.* [26] states  
85 fatigue within sarcoidosis is multifaceted and as such, further research needs to be conducted  
86 to understand these diverse effects and their implications. Despite this, the three rehabilitation  
87 interventions [31, 32, 34] found that the exercise programmes significantly improved fatigue,  
88 by scores of 2.7 and 4.2 respectively, via the fatigue assessment scale (FAS) [31, 32] and 7, via  
89 the fatigue severity scale (FSS) [34].

90

### 91 *Physical Activity*

92 Physical inactivity even within healthy populations has been shown to be a complex and a  
93 serious issue [47]. Research into physical activity is severely limited within pulmonary  
94 sarcoidosis at present [4, 5], despite the known benefits for the general population including  
95 decreased levels of non-communicable diseases as well as lower risk of depression [48],  
96 although physical activity within sarcoidosis has been associated with fatigue [4] as a  
97 confounding factor. Garcia-Aymerich *et al.* [49] found even COPD patients with low self-

98 reported physical activity levels had lower hospital admissions and mortality rates than those  
99 reporting very low levels. Low was classified as engaging in light physical activity including  
100 walking or biking for less than two hours per week, while very low was classed as sedentary  
101 activities such as sitting during working hours and no leisure time activity, jogging or cycling  
102 [49]. Many factors influencing physical inactivity are understood but implementing changes to  
103 improve physical activity over a sustained period of time remains difficult [9]. Interestingly,  
104 Egan *et al.* [50] found despite pulmonary rehabilitation in COPD patients improving exercise  
105 capacity, physical activity remained unchanged from baseline. The combination of a chronic  
106 disease coupled with, in some cases, severe fatigue, is likely to only increase the difficulty in  
107 achieving the desired behavioural changes. Korenromp *et al.* [4] found higher levels of physical  
108 activity on weekdays for both fatigued and non-fatigued sarcoidosis participants than on  
109 weekends, however fatigued participants showed a bigger drop in physical activity levels on  
110 the weekends compared to their non-fatigued peers. This indicates that those sarcoidosis  
111 patients' having to work might have increased physical activity levels through occupational  
112 activity compared to those who do not, although job status, hours, or industry occupation were  
113 not recorded within the study. A limitation of Saligan's [5] study was the exclusion of recording  
114 physical activity on weekends opting for three consecutive days during the week therefore  
115 leading to a more limited view than Korenromp *et al.* [4] study.

116

### 117 *Muscle Strength*

118 Muscle strength is associated with functional limitations [51]. Handgrip strength is a useful  
119 indicator of quality of life in the elderly [52] as well as young adults [53], and it is also  
120 correlated with mobility [53] and with lower functional scores [54]. A number of studies  
121 demonstrated a reduction in muscle strength within pulmonary sarcoidosis [4, 5, 33]. Marcellis

122 *et al.* [40] found reductions at both baseline, and follow-up against normative values, for elbow  
123 flexor muscle strength (reduction of 6.7 and 14.6 %), quadriceps peak torque (reduction of 21.3  
124 and 18 %) and hamstrings peak torque (reduction of 13.5 and 12.4 %). In contrast, Strookappe  
125 *et al.* [26] found elbow flexor muscle strength to be  $100.5 \pm 20.4\%$  of the predicted value using  
126 normative data for a healthy population. Handgrip strength also showed mixed results ranging  
127 from 81% to 96.8% predicted [26] and thus highlights again the complexity and variability of  
128 the condition and the need for more detailed research addressing the differing severities of the  
129 condition.

130 It would be beneficial to have comparable data through use of a standardised method for testing  
131 muscle strength in sarcoidosis. **Although it is lower limb muscle function that is a limiting**  
132 **factor for ambulatory activity, handgrip strength has been demonstrated to be a good predictor**  
133 **of whole body muscular strength and endurance and therefore can be considered a beneficial**  
134 **measurement technique for evaluation of populations who may not be able to complete more**  
135 **strenuous tests [55].** This review also found both isokinetic dynamometry [33], back and leg  
136 dynamometer [34] and microFET [31, 32] were utilised within the current literature, **which**  
137 **may be more functionally relevant for physical activity levels.** Muff *et al.* [56] found the  
138 different methods correlated strongly within healthy adults for knee extensor and flexor muscle  
139 strength however a limitation of the microFET is the flexor/extensor ratio with correlations  
140 against the isokinetic ranging from -0.04 to 0.46. Again, the research stopped short of providing  
141 answers relating to the mechanisms by which muscle strength is affected by pulmonary  
142 sarcoidosis, nevertheless, Marcellis *et al.* [31], Strookappe *et al.* [32] and Naz *et al.* [34] did  
143 show significant improvements in muscle strength following completion of their intervention  
144 programmes. Participants within Marcellis *et al.*'s [31] study demonstrated quadricep strength  
145 lift ability increased by 10.7kg compared to baseline, Naz *et al.*, [34] showed a median  
146 improvement of 10kg for leg strength while Strookappe *et al.* [32] recorded a 7.2% increase in



147 elbow flexor muscle strength. Based on this, it can be suggested that deconditioning as a  
148 consequence of a sarcoidosis-induced decrease in physical activity, plays a key role in the  
149 reduction of muscle strength.

150

### 151 *Exercise Rehabilitation*

152 Although exercise-based rehabilitation also referred to as pulmonary rehabilitation [57] is  
153 known to be beneficial within COPD and asthma, there is a shortage of research into its effect  
154 on sarcoidosis. McCarthy *et al.*'s [58] systematic review found rehabilitation improved quality  
155 of life and exercise capacity in addition to dyspnoea and fatigue within COPD with the  
156 improvements clinically significant. It is worth noting however, no difference has been  
157 attributed between exercise only programs and more complex pulmonary rehabilitation  
158 programmes based on the current body of knowledge. At present, only three studies have  
159 investigated exercise as a potential rehabilitation strategy to improve the symptoms and quality  
160 of life of sarcoidosis patients [31, 32, 34]. These three studies showed promising results with  
161 improvements in quality of life, muscle strength and exercise performance, as measured via  
162 six-minute walk test, as well as reductions in self-reported fatigue. Additionally, Marcellis *et*  
163 *al.* [31] recorded an initial 72.2% continuation rate of a similar exercise programme following  
164 completion of the study, which highlights the value placed on the programme and the results  
165 by the participants themselves. Unfortunately, no follow-up to check on the outcome measures  
166 or exercise adherence was implemented within any of the studies, barring Marcellis *et al.* [31].  
167 However, Forkan *et al.* [59] found prescribed home exercise programs had a 37% adherence  
168 for elderly people with impaired balance, with time since discharge not found to affect  
169 adherence within the population, where no difference was reported between those discharged  
170 12 or 24 months prior. It is worth noting all three studies [31, 32, 34] had differing

171 methodologies for the exercise programme; Marcellis *et al.* [31] evaluated a 13-week  
172 programme featuring both aerobic (60% maximal walking speed of 6MWT via  
173 treadmill/cycling on an ergometer) and resistance training (40% multiple-repetition maximum,  
174 increasing 3% weekly, 8-10 reps, 3 sets) for one hour three times a week, whereas Strookappe  
175 *et al.* [32] used an intervention consisting of one hour twice a week involving aerobic exercise  
176 at 50-60% peak work calculated from the steep-ramp test and resistance training of 3 sets  
177 consisting of 15-20 reps with the weight set by participants own 13-15 rating on Borg RPE per  
178 session. By contrast, Naz *et al.* [34] used an intervention involving two sessions a week on a  
179 12-week programme, involving both aerobic (walking and cycling, 15 mins continuously at  
180 80% speed of 6MWT and 70% estimated work rate via the 6MWT, increasing within symptom  
181 tolerance when goals met) and resistance training (selected through 4-6 rating on the modified  
182 Borg scale, starting at 8 reps and progressing to 10, once participant would achieve 1-2 reps on  
183 top of this, workload increased by 2-10%). All strategies produced statistically significant  
184 improvements, and therefore suggests that a cross-section of exercise modalities and intensities  
185 could improve physical performance in patients with sarcoidosis.

186

### 187 *Future Directions*

188 The results of this systematic review can help to direct future research. Due to the lack of  
189 knowledge and evidence regarding sarcoidosis and physical activity / fitness, this review has  
190 helped to identify key areas for future research, as well as highlighting the potential benefits of  
191 fitness and physical activity for patients with sarcoidosis. One vital factor requiring further  
192 research is the efficacy of exercise and physical activity as a potential rehabilitation option  
193 beyond current pharmacological routes, based on the promising outcomes reported thus far [31,  
194 32, 34]. Additionally, a future aim should be to identify and create optimised non-

195 pharmacological treatment plans, ideally personalised to each individual, due to the evidence  
196 of the complex, varied and individual nature of the condition and in keeping with other trends  
197 within the healthcare sector [59]. To achieve these aims, research will need to be conducted to  
198 explore the specific mechanisms behind the reduction of muscle strength, lung function and  
199 exercise performance, as well as any other associated confounding variables such as fatigue  
200 [61] and impaired heart rate response to exercise [62]. There is a need to identify and  
201 understand trends in fatigue and lifestyle factors with the aim to utilise this information to  
202 improve quality of life and develop strategies to address resulting factors such as impaired gas  
203 exchange and heart rate. Collectively, such work could enable creation of a standardised set of  
204 exercise tests for aerobic capacity and muscle strength within sarcoidosis, that could be used  
205 to assess and inform treatment strategies, as currently the wide range of tests employed make  
206 it difficult to draw clear conclusions.

207

208 In conclusion, sarcoidosis has been shown to have a detrimental effect on various factors  
209 related to physical activity and fitness such as lung function, quality of life, **cardio-respiratory**  
210 **capacity** and physical activity levels, to name a few. The mechanisms behind these negative  
211 effects are complex and remain unclear. However, this review has also highlighted evidence  
212 suggesting that many of the negative effects of sarcoidosis can be reversed with appropriate  
213 exercise regimens. The deconditioning effects of sarcoidosis, in addition to associated  
214 symptoms, can be overcome/improved by exercise and there is a need for further in-depth  
215 studies exploring these features and their mechanisms as well as greater focus on exercise  
216 rehabilitation for improved patient care.

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218 **Table 1.** Exercise Capacity, Physical Activity and Muscle Strength studies within Sarcoidosis.

References	Participants (N=)	Age/Gender Mean age or Range (yrs)	Factors studied	Main Findings	Summary of Findings
Athos <i>et al.</i> [35]	39  Male = 12 Female = 27	Mean: 39 Range: 21-75	<ul style="list-style-type: none"> <li>• Lung Function (FVC, FEV<sub>1</sub>, MVV, DLCO).</li> <li>• Exercise Capacity (Incremental symptom limited exercise test (<math>\dot{V}O_2</math>))</li> <li>• Dyspnoea (MRC)</li> </ul>	<ul style="list-style-type: none"> <li>• Pulmonary limitation to exercise occurred in 29% (stage 0 &amp; 1) and 95% (stage 2 &amp; 3).</li> <li>• <math>\dot{V}O_2</math> was not reported.</li> <li>• 89% reported dyspnoea.</li> </ul>	<ul style="list-style-type: none"> <li>• Severe abnormalities of gas exchange occurred more frequently from submaximal exercise studies.</li> <li>• No single test or combination of lung function, arterial blood gas, or pulmonary symptom tests could precisely predict pulmonary limitation to exercise.</li> </ul>
Sietsema <i>et al.</i> [36]	20  Male = 6 Female = 14	Mean: 43 Range: 24-58	<ul style="list-style-type: none"> <li>• Lung function (FVC)</li> <li>• Exercise capacity (Symptom limited maximal exercise testing (peak <math>\dot{V}O_2</math>))</li> <li>• Heart rate</li> </ul>	<ul style="list-style-type: none"> <li>• Forced vital capacity averaged 88±12% of predicted value.</li> <li>• 11 of 20 patients failed to reach &gt; 80% of predicted maximum <math>\dot{V}O_2</math>, although all but 3 of them met criteria for maximal or near-maximal effort.</li> <li>• 7 of the 11 had one or more abnormal <math>\dot{V}O_2</math> response to exercise.</li> </ul>	<ul style="list-style-type: none"> <li>• Impairment in the rate of delivery and utilisation of oxygen during exercise, despite normal lung functions.</li> <li>• Reduced maximal exercise capacity, abnormal efficiency of pulmonary gas exchange.</li> <li>• Exertional symptoms and their absence predicted neither normal or abnormal results of exercise testing.</li> </ul>
Medinger <i>et al.</i> [37]	48	Mean: 41	<ul style="list-style-type: none"> <li>• Lung function (FEV<sub>1</sub>, FVC),</li> <li>• Exercise Capacity (6min</li> </ul>	<ul style="list-style-type: none"> <li>• No significant association between radiographic stage and FEV<sub>1</sub>/FVC%, <math>\dot{V}O_2</math></li> </ul>	<ul style="list-style-type: none"> <li>• Gas exchange changes with exercise may be the most sensitive physiologic measurements to assess the extent of disease in stages (0-2).</li> </ul>

			progressive bicycle exercise ( $\dot{V}O_2 \text{ max}$ )	<p>max, AT, HRR, BR, or <math>VEe/\dot{V}CO_2</math> AT.</p> <ul style="list-style-type: none"> <li>11 participants exercise blood gas measurement was not recorded due to technical issues regarding arterial access.</li> </ul>	<ul style="list-style-type: none"> <li>Remains a lack of a true non-invasive “gold standard” for measuring the extent of disease.</li> </ul>
Akkoca <i>et al.</i> [38]	29  Groups defined by radiographic stage.	<p>Stage 1 mean: 42</p> <p>Stage 2 mean: 42</p> <p>Stage 3 mean: 44</p>	<ul style="list-style-type: none"> <li>Lung function,</li> <li>Exercise Capacity (CPET)</li> </ul>	<ul style="list-style-type: none"> <li>Moderate decrease reported between stages 2 &amp; 3, with significant difference between 1 &amp; 3.</li> <li>Limitation of exercise capacity correlated with radiographic stage.</li> <li>Radiographic stage increases were significantly observed with decreases to <math>\dot{V}O_2</math> /kg (<math>p &lt; 0.05</math>).</li> </ul>	<ul style="list-style-type: none"> <li>Exercise capacity is the earliest impaired physiological parameter.</li> <li>Intolerance to exercise is correlated with radiological stage and worsened by HRR to exercise and circulatory impairment, an effect more prominent in the advanced radiological stages.</li> </ul>
Alhamad <i>et al.</i> [39]	59  Male = 17 Female = 42	Mean: 48	<ul style="list-style-type: none"> <li>Lung function (FVC, FEV<sub>1</sub>, TLC)</li> <li>Exercise Capacity (6MWT)</li> </ul>	<ul style="list-style-type: none"> <li>Mean lung function parameters for FVC, FEV<sub>1</sub> and TLC results, as percentages of predicted values, were <math>77.6 \pm 22.2</math>, <math>77.1 \pm 22.8</math> and <math>78.7 \pm 16.1</math>, respectively.</li> <li>Female 6MWD = 324.1m.</li> <li>Male 6MWD = 409.4m.</li> </ul>	<ul style="list-style-type: none"> <li>DSP is correlated with more factors linked to reduced 6MWD than 6MWD alone, therefore DSP appears to be a useful indicator for functional status within the sarcoidosis population.</li> <li>Pulmonary hypertension and fibrosis associated with reductions to 6MWD.</li> </ul>
Korenromp <i>et al.</i> [4]	75 patients in clinical remission	Non-fatigued mean: 48	<ul style="list-style-type: none"> <li>Lung Function</li> <li>Muscle Strength (HGS &amp; QPT)</li> </ul>	<ul style="list-style-type: none"> <li>Lung function within normal range for all participants.</li> </ul>	<ul style="list-style-type: none"> <li>Fatigue is a frequent severe and chronic issue within clinical remission patients.</li> </ul>

	Male = 33 Female = 42	Fatigued mean: 46	<ul style="list-style-type: none"> <li>• Physical Activity (Accelerometer)</li> <li>• Fatigue (CIS)</li> <li>• QOL (sf-36)</li> <li>• Depression(BDI)</li> <li>• Anxiety (SCL-90)</li> </ul>	<ul style="list-style-type: none"> <li>• HGS mean score lower among fatigued group.</li> <li>• Weekday = 75.14 (fatigued) vs. 82.06 (non-fatigued) accelerations / day.</li> <li>• Weekend = 66.93 (fatigued) vs. 79.81 (non-fatigued) accelerations / day. Norm score = 91 (healthy).</li> <li>• Fatigue = 30.5, with 15.5 on the subscale fatigue severity.</li> <li>• Significantly worse depression and QOL scores among fatigued participants.</li> </ul>	<ul style="list-style-type: none"> <li>• Psychologic distress and reduced QOL are associated with fatigue in addition to, reduced physical activity and muscle weakness in fatigued patients.</li> <li>• On all tests, the mean score of the fatigued group was significantly lower than the mean of the non-fatigued group.</li> </ul>
Kowalska <i>et al.</i> [29]	47 (22 with cardiac involvement)  Males = 19 Females = 28  As well as 18 healthy volunteers for control	Mean: 48	<ul style="list-style-type: none"> <li>• Exercise Capacity (6MWT oxygen saturation, heart rate)</li> </ul>	<ul style="list-style-type: none"> <li>• Cardiac sarcoidosis with treatment: 6MWD = 514.81 ± 91.22m.</li> <li>• Maximum desaturation = 3.5±3.7%.</li> <li>• Cardiac sarcoidosis (no treatment): 6MWD = 567.09 ± 119.06.</li> <li>• Maximum desaturation = 1.9±1.7%.</li> <li>• No cardiac involvement (no treatment): 6MWD = 20.8± 96.22.</li> </ul>	<ul style="list-style-type: none"> <li>• Participants with cardiac involvement and treatment had a lower heart rate during the first minute of the 6MWT as well as desaturating more than the no cardiac involvement group.</li> <li>• Treatment with prednisone decreased both 6MWD and oxygen saturation in comparison to no treatment.</li> <li>• The healthy control group recorded better 6MWD than sarcoidosis groups.</li> </ul>

				<ul style="list-style-type: none"> <li>• Maximum desaturation = <math>2.36 \pm 2.87</math>.</li> </ul>	
Marcellis <i>et al.</i> [40]	160 Male = 97 Female = 63	Mean: 41	<ul style="list-style-type: none"> <li>• Lung Function (DLCO)</li> <li>• Exercise Capacity (CPET blood gas analysis)</li> </ul>	<ul style="list-style-type: none"> <li>• DLCO (mean = <math>83.2 \pm 18.0</math> %)</li> <li>• &lt; 80 % of predicted DLCO in 38 % of participants.</li> <li>• DLCO &lt; 60% indicates significant impairment of gas exchange.</li> <li>• 59% failed to reach 83% of predicted <math>\dot{V}O_2</math> max.</li> </ul>	<ul style="list-style-type: none"> <li>• Symptomatic patients with normal DLCO appeared to have pulmonary gas exchange impairment at maximal exercise</li> <li>• Results suggest that normal DLCO at rest is an inappropriate predictor of abnormal pulmonary gas exchange during exercise.</li> <li>• CPET appeared to offer added value in detecting impaired gas exchange during exercise in patients with unexplained disabling symptoms.</li> </ul>
Marcellis <i>et al.</i> [33]	92 Male = 62 Female = 28	Mean: 46	<ul style="list-style-type: none"> <li>• Exercise Capacity (6MWT)</li> <li>• Muscle strength (EFMS, HPT, QPT)</li> <li>• Fatigue (FAS).</li> </ul>	<ul style="list-style-type: none"> <li>• Reduced 6MWT (41.6 vs. 34.8 %) at baseline and follow-up,</li> <li>• EFMS (6.7 vs. 14.6 %),</li> <li>• QPT (21.3 vs. 18 %),</li> <li>• HPT (13.5 vs. 12.4 %)</li> <li>• Fatigue reported in 86 and 77% of participants.</li> </ul>	<ul style="list-style-type: none"> <li>• Decreased measurements at baseline and follow-up for participants compared to control.</li> <li>• The physical impairments remained stable across baseline and follow-up.</li> <li>• Exercise intolerance, muscle weakness, and fatigue are frequent problems in sarcoidosis patients. Suggests a rehabilitation program should be considered as adjunct therapy in the multidisciplinary management of sarcoidosis.</li> </ul>
Braam <i>et al.</i> [30]	20 sarcoidosis and 10 healthy	Healthy Control: 35	<ul style="list-style-type: none"> <li>• Exercise Capacity (CPET, Symptom limited incremental</li> </ul>	<ul style="list-style-type: none"> <li>• Sarcoidosis w/Mod fatigue: <math>\dot{V}O_2</math> max = <math>270 \pm 67.4</math></li> </ul>	<ul style="list-style-type: none"> <li>• Severe fatigue is not correlated with biomarkers nor a reduction of exercise capacity and is only</li> </ul>

	volunteers for control  Male = 16 Female = 14	Sarc Mod fatigue: 41  Sarc severe fatigue: 37	exercise test ( $\dot{V}O_2$ , RER)) <ul style="list-style-type: none"><li>Blood pressure, HR, pulse oximetry, cytokines, stress hormones, ACE and CK (before, after and 3 days after).</li></ul>	<ul style="list-style-type: none"><li>Sarcoidosis w/Severe fatigue: <math>\dot{V}O_2</math> max = 187±54.2</li></ul>	consistently measured via self-reported patient feedback/outcomes.
de Boer <i>et al.</i> [41]	33  Male = 17 Female = 16	Mean: 48	<ul style="list-style-type: none"><li>Lung Function (FEV<sub>1</sub>, FVC, DLCO)</li><li>Exercise Capacity (MSWT, CPET)</li></ul>	<ul style="list-style-type: none"><li>Mean FEV<sub>1</sub> = 75.7% predicted</li><li>Mean FVC = 88.7% predicted</li><li>Mean DLCO = 71.4% predicted</li><li>MSWT correlated with peak oxygen uptake during CPET</li></ul>	<ul style="list-style-type: none"><li>Both FVC and DLCO correlated with the two exercise measures.</li><li>MSWT is a symptom-limited maximal exercise test comparable with full CPET in assessing functional capacity in sarcoidosis.</li><li>Peak <math>\dot{V}O_2</math> during CPET correlated with MSWT distance.</li></ul>
Drent <i>et al.</i> [20]	88 Sarcoidosis  Male = 61 Female = 28  62 healthy controls	Mean: 46	<ul style="list-style-type: none"><li>Lung Function (FEV<sub>1</sub>, FVC, DLCO)</li><li>Exercise capacity (6MWT)</li><li>Muscle strength (EFMS, HPT, QPT)</li><li>Fatigue (FAS)</li></ul>	<ul style="list-style-type: none"><li>Sarcoidosis: FEV<sub>1</sub> (%pred) = 84 FVC (%pred) = 98. DLCO (%pred) = 76.</li><li>6MWD Female = 551.</li><li>6MWD Male = 606.</li><li>EFMS (%pred) Female = 97.7.</li><li>EFMS (%pred) Male = 89.9.</li></ul>	<ul style="list-style-type: none"><li>Males scored lower than female across all muscle strength tests however performed better during the 6MWT.</li><li>QOL is diminished and associated with both exercise capacity and fatigue especially within the physical health domain.</li></ul>

			<ul style="list-style-type: none"> <li>• QOL (WHOQOL-BREF)</li> </ul>	<ul style="list-style-type: none"> <li>• QPT180 (%pred) Female = 84.9.</li> <li>• QPT180 (%pred) Male = 81.4.</li> <li>• HPT180 (%pred) Female = 86.4.</li> <li>• HPT180 (%pred) Male = 81.9.</li> <li>• FAS = 28.6.</li> <li>• QOL reduced in comparison to healthy controls.</li> </ul>	
Saligan [5]	14 pulmonary sarcoidosis participants as well as 13 age, sex and race matched.	Not stated	<ul style="list-style-type: none"> <li>• Exercise Capacity (6MWT)</li> <li>• Muscle Strength (MVC/kg)</li> <li>• Physical activity (Accelerometer)</li> <li>• Fatigue (FAS)</li> <li>• Depression (HAM-D)</li> </ul>	<ul style="list-style-type: none"> <li>• Sarc: 6MWD - 502±84. MVC/kg – 26.06. Mean Energy Expenditure – 1324. Mean FAS – 27.4±5.7. HAM – D - 8.6±5.0.</li> <li>• Control: 6MWD - 607±77. MVC/kg – 32.71. Mean Energy Expenditure – 1748. Mean FAS – 14.2±3.5. HAM – D - 2.5±2.2.</li> </ul>	<ul style="list-style-type: none"> <li>• There were significant differences in physical activity, exercise capacity, muscle strength, depression and fatigue scores between sarcoidosis patients and healthy control.</li> </ul>
Zieleznik <i>et al.</i> [42]	74 Sarcoidosis  Male = 53 Female = 21	Mean: 45  Range: 29-71	<ul style="list-style-type: none"> <li>• Lung function (FEV<sub>1</sub>, FVC)</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> = 3.18±0.82.</li> <li>• FEV<sub>1</sub> (%) = 90.4±13.1.</li> <li>• FVC = 4.16±1.1.</li> <li>• FVC (%) = 98.9±13.9.</li> </ul>	<ul style="list-style-type: none"> <li>• Fatigue did not correlate with lung function scores or 6MWD.</li> </ul>

	30 Healthy controls		<ul style="list-style-type: none"> <li>• Exercise Capacity (6MWT)</li> <li>• Fatigue (FAS)</li> </ul>	<ul style="list-style-type: none"> <li>• 6MWD (m) = 555.9±91.5.</li> <li>• FAS = 22.9±7.3.</li> </ul>	<ul style="list-style-type: none"> <li>• 43.06% sarcoidosis participants reported no fatigue compared to 76.67% for the control group.</li> </ul>
Kallianos <i>et al.</i> [22]	83 Male = 31 Female = 52  Patients were grouped according to their radiological stages: Stage I (n=43), Stages II–III (n=31), and Stage IV (n=9).	Mean: 58 Range: 36-84	<ul style="list-style-type: none"> <li>• Lung function FEV<sub>1</sub>, FVC, TLC DLCO)</li> <li>• Exercise Capacity (CPET Standard protocol).</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>, FVC, TLC were found to be mildly impaired solely in stage IV (means ± standard deviation: 72.44±28.00, 71.33±26.70, and 59.78±21.72, respectively).</li> <li>• DLCO was reduced in stages 2-4.</li> <li>• Peak oxygen consumption during exercise was decreased and varied by stage; Stage 1: 48%, Stages 2–3: 52%, Stage 4: 78%.</li> <li>• Only stage 1 and 4 reported as having a significant difference.</li> </ul>	<ul style="list-style-type: none"> <li>• Exercise capacity is the first impaired physiological parameter in sarcoidosis, with it being found to be limited from stage I.</li> <li>• The mechanisms responsible for exercise limitation are multifactorial and correlated with the radiological extent of the disease.</li> <li>• Exercise limitation may be attributed to both ventilatory and cardiocirculatory impairment.</li> </ul>
Strookappe <i>et al.</i> [26]	146 Male = 89 Female = 57	Mean: 47	<ul style="list-style-type: none"> <li>• Lung Function (FEV<sub>1</sub>, FVC, DLCO)</li> <li>• Exercise Capacity (6MWT, SRT)</li> <li>• Muscle strength (EFMS, HGS)</li> <li>• Fatigue (FAS)</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> (%pred) - 87.6 ± 19.7.</li> <li>• FVC (%pred) - 94.7 ± 18.7.</li> <li>• DLCO (%pred) - 79.3 ± 18.0.</li> <li>• 6MWD 536±104.</li> <li>• SRT 26.8±6.3.</li> <li>• HGS (pred%) 91.1±22.7.</li> </ul>	<ul style="list-style-type: none"> <li>• Exercise capacity partly predicts fatigue.</li> <li>• Fatigue is a substantial problem among sarcoidosis patients, which is affected by many variables.</li> </ul>

				<ul style="list-style-type: none"> <li>• EFMS (pred%) 100.5±20.4.</li> <li>• FAS 30.2±9.0.</li> </ul>	
Chenivesse <i>et al.</i> [43]	130 Male = 78 Female = 52	Mean: 49 Range: 26-78	<ul style="list-style-type: none"> <li>• Lung Function (FEV<sub>1</sub>, FVC, TLC, DLCO)</li> <li>• Exercise Capacity (6MWT)</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>(% pred) – 80.</li> <li>• FVC (% pred) – 92.</li> <li>• TLC (% pred) – 90.</li> <li>• DLCO (% pred) – 71.</li> <li>• 6MWD – 450.</li> </ul>	<ul style="list-style-type: none"> <li>• Normal DLCO is a good predictor of the absence of severe gas exchange impairment.</li> <li>• The stage 4 group had lower FEV<sub>1</sub>, FVC, DLCO scores, in addition to a reduced <math>\dot{V}O_2</math> Peak compared to the other stages.</li> </ul>
Mirsaeidi <i>et al.</i> [44]	108 Male = 21 Female = 87	Mean: 54	<ul style="list-style-type: none"> <li>• Lung function (FEV<sub>1</sub>, FVC, DLCO, VC, TLC, FRC)</li> <li>• Exercise Capacity (6MWT)</li> </ul>	<ul style="list-style-type: none"> <li>• FEV1% 74.3±28.5.</li> <li>• FVC% 83.5±25.3.</li> <li>• DLCO% 61±18.6.</li> <li>• VC% 88±23.9.</li> <li>• TLC% 84.3±17.1.</li> <li>• FRC% 101.6±20.6.</li> <li>• 6MWD – 364.4±77.3.</li> </ul>	<ul style="list-style-type: none"> <li>• These tests are useful for tracking the progression of pulmonary hypertension associated with sarcoidosis.</li> </ul>

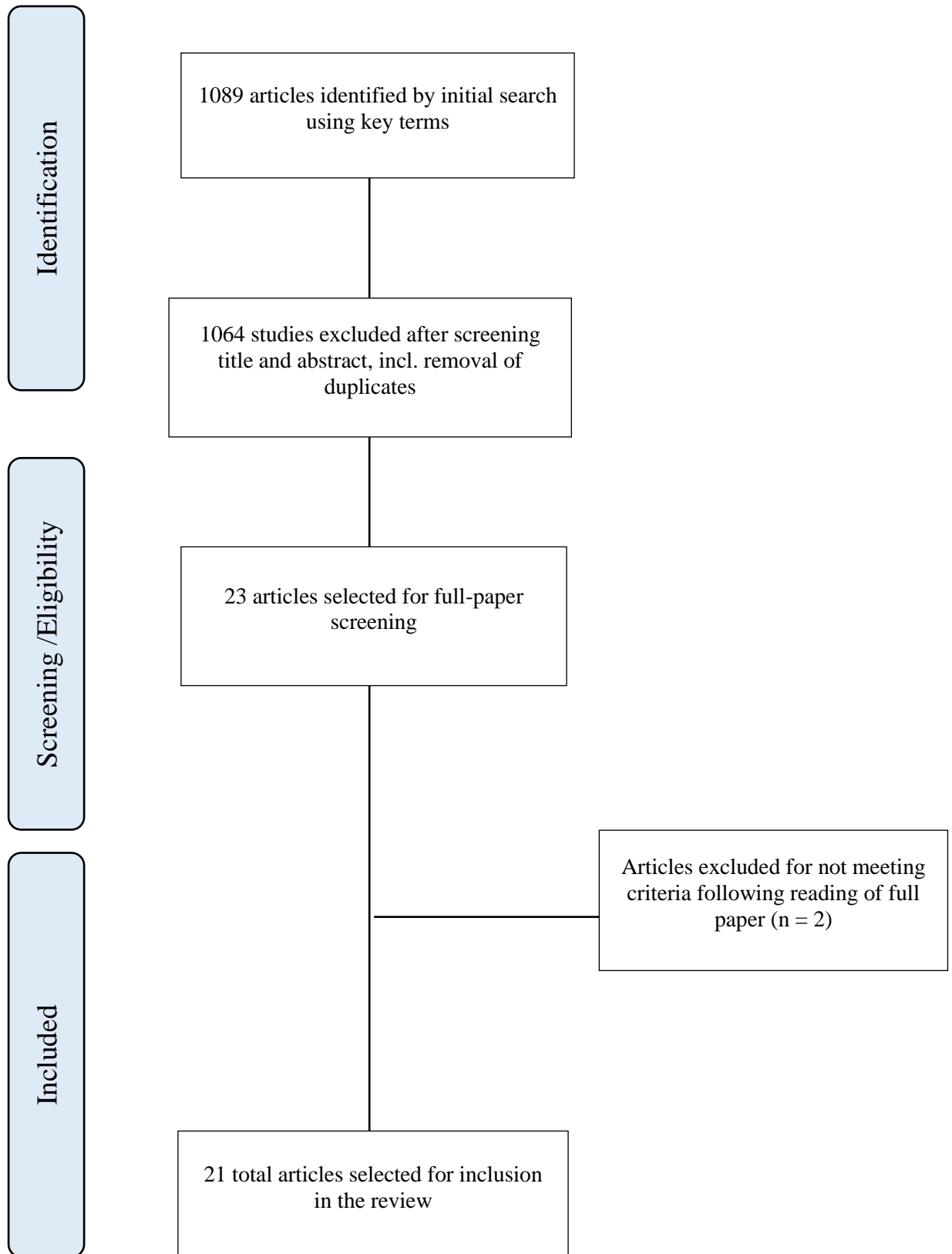
219 Definition of abbreviations: 6MWT- 6 minute walk test; 6MWD – 6 minute walk distance; QOL - quality of life, DLCO- diffusing capacity of the lungs for carbon monoxide;  
220 CPET – Cardiopulmonary exercise testing; FAS – fatigue assessment scale; FVC – Forced vital capacity; TLC – total lung capacity; FEV<sub>1</sub> – forced expiratory volume in one  
221 second; VC – vital capacity; FRC – functional residual capacity; MVV – Maximal voluntary ventilation; Ve/Vco<sub>2</sub> AT - ventilatory equivalent for carbon dioxide at anaerobic  
222 threshold; HRR – heart rate reserve; BR – breathing reserve; DSP – distance saturation product; CIS – checklist individual strength; SCL-90 – symptom checklist 90 ; BDI –  
223 beck depression inventory for primary care ; SF-36 – Medical outcomes study 36-item health survey; QPT – quadricep peak torque; HPT – hamstring peak torque; EFMS –  
224 elbow flexor muscle strength; ACE - angiotensin converting enzyme; CK – creatine kinase; RER – respiratory exchange ratio; HR – heart rate; MSWT - Modified shuttle walk  
225 test; HGS – handgrip strength; SRT – steep ramp test; MRC – Medical Research Council Dyspnoea Scale; HAM – D – Hamilton Depression Rating Scale; MVC – Maximum  
226 voluntary contraction; %pred – Percent of Predicted.



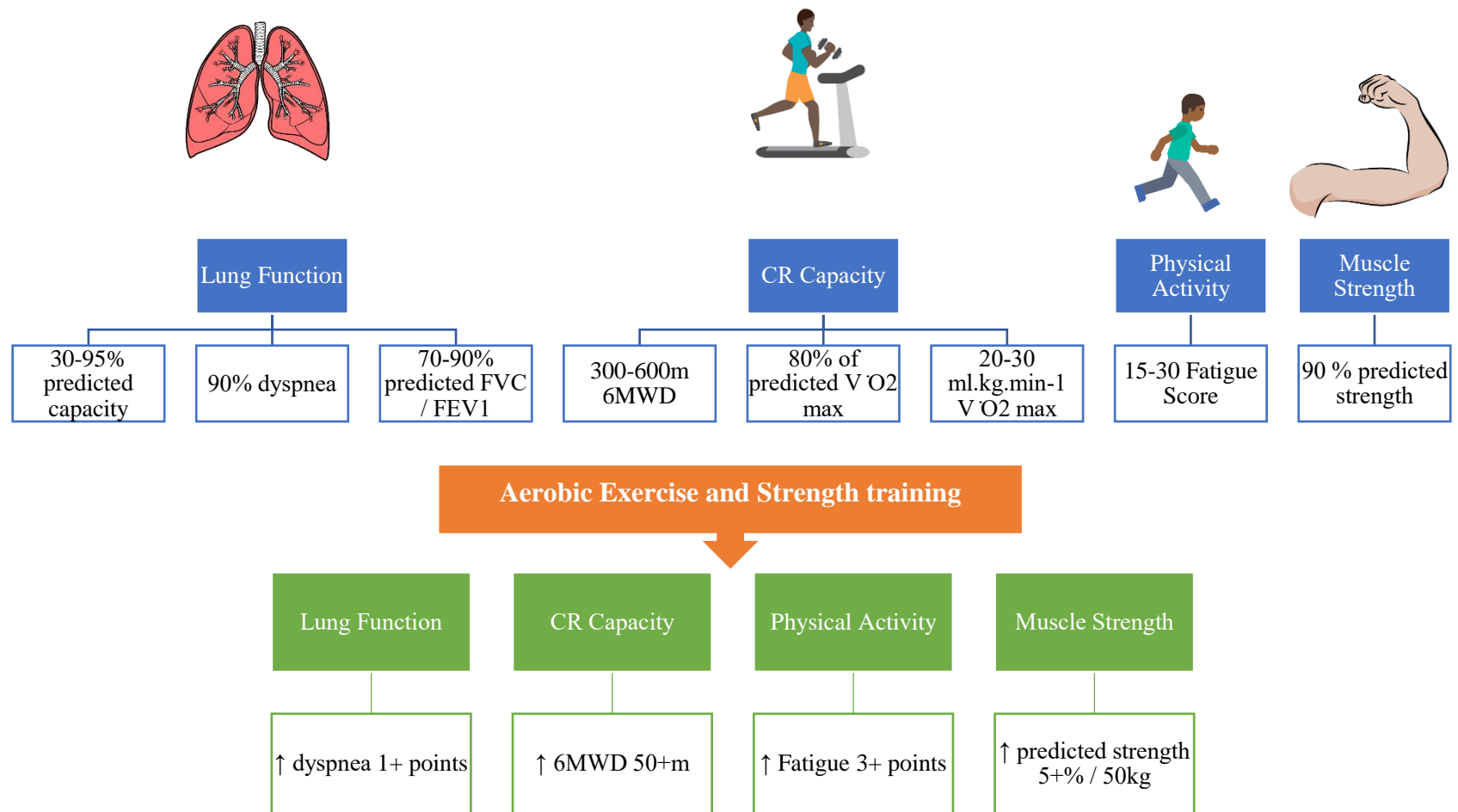
References	Study Design	Sample Size (age / gender)	Factors studied	Exercise programme	Main Findings
Marcellis <i>et al.</i> [31]	Intervention: pre/post measurement design.	24 patients with fatigue complaints and/or exercise intolerance.  18 patients completed (50.3±10.4years / 4 females & 14 males).	<ul style="list-style-type: none"> <li>• Lung function (FVC, FEV<sub>1</sub>, DLCO)</li> <li>• Muscle Strength (X-RM leg extension, elbow flexor microFET)</li> <li>• Fatigue (FAS)</li> <li>• QOL (WHOWOL-BREF),</li> <li>• Dyspnoea (MRC, Borg RPE)</li> </ul>	13-week programme (1h x 3 / week) Aerobic endurance: 60% maximal walking speed of 6MWT or cycling at 50% Wmax for 20-30 minutes, increased 3%/ week. Strength Training: 3 sets of 8-10 reps, at 40% multiple-repetition maximum increased 3% /week.	<ul style="list-style-type: none"> <li>• Lung function not reported post-treatment.</li> <li>• ↑ 6MWD.</li> <li>• ↑HR (submaximal).</li> <li>• ↑ Quadricep strength.</li> <li>• ↓ FAS score .</li> <li>• ↑MRC and WHOQOL-BREF.</li> </ul>
Strookappe <i>et al.</i> [32]	Intervention: pre/post measurement design.	90 participants (49 completing treatment, 41 opted not partake in treatment).	<ul style="list-style-type: none"> <li>• Lung function (FVC, FEV<sub>1</sub>, DLCO)</li> <li>• Exercise Capacity (SRT, 6MWT)</li> <li>• Muscle strength (HGS, EFMS via microFET)</li> <li>• Fatigue (FAS)</li> <li>• Borg RPE, Dyspnoea (modified Borg)</li> </ul>	12-week programme (1h x 2 / week) Aerobic endurance: Treadmill or stationary cycling at 50-60% peak work. Strength Training: 3 sets of 15-20 reps on 6-8 different exercises at 13-15 Borg RPE.	<ul style="list-style-type: none"> <li>• Lung function unchanged.</li> <li>• ↑ 6MWD.</li> <li>• ↑SRT.</li> <li>• ↑ Elbow flexion.</li> <li>• ↑ HGS.</li> <li>• ↓ FAS Score.</li> <li>• RPE &amp; Dyspnoea scores stable.</li> </ul>
Naz <i>et al.</i> [34]	Intervention: pre/post measurement design.	18 participants (9 undergoing intervention, 9 control with usual care).	<ul style="list-style-type: none"> <li>• Lung function (FVC &amp; FEV<sub>1</sub>)</li> <li>• Exercise Capacity (6MWT)</li> <li>• Muscle Strength (back and leg dynamometer)</li> <li>• Fatigue (FSS)</li> </ul>	12-week programme (2 x week) Aerobic endurance: Treadmill and stationary cycling at 80% & 70% peak speed of 6MWT, increased	<ul style="list-style-type: none"> <li>• Lung function unchanged.</li> <li>• ↑ 6MWD.</li> <li>• ↑ Leg Strength.</li> <li>• ↓ FSS Score.</li> <li>• ↑ SGRQ.</li> </ul>

	<ul style="list-style-type: none"> <li>• QOL (SF-36, SGRQ)</li> <li>• Borg Dyspnoea (modified Borg)</li> <li>• Depression and Anxiety (HADS)</li> </ul>	<p>within symptom tolerance when continuous 15min exercise achieved</p> <p>Strength Training: Amount of sets not stated, 8-10 reps on 8 exercises at 4-6 modified Borg, increased 2-10% following ability of 1-2 extra reps.</p> <ul style="list-style-type: none"> <li>• SF-36 unchanged.</li> <li>• ↓Dyspnoea.</li> <li>• ↓HADS.</li> </ul>
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228 Definition of abbreviations: QOL - quality of life, SRT – steep ramp test; Borg RPE – Borg rating of perceived exertion; FAS – fatigue assessment scale; FSS – fatigue severity  
229 scale; HGS – handgrip strength; EFMS – elbow flexor muscle strength; 6MWT – six minute walk test; DLCO – diffusing capacity of the lungs for carbon monoxide; FVC –  
230 Forced vital capacity; FEV<sub>1</sub> – forced expiratory volume in one second; MRC – medical research council dyspnoea scale; WHOWOL-BREF - World Health Organization  
231 Quality of Life Instruments; SF-36 – 36-item Short Form survey ; SGRQ - St. Georges respiratory questionnaire; HADS – Hospital depression and anxiety scale



**Figure 1.** Flow diagram of systematic review search process of study selection.



**Figure 2.** A schematic diagram to demonstrate the association between Sarcoidosis and Exercise Training