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.

Discussion

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

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

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

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

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

Fatigue

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

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

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

Physical Activity

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

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

Muscle Strength

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

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

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

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

Exercise Rehabilitation

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

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

Future Directions

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

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

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

References

1. National Health Service (NHS). Benefits of Exercise. http://www.nhs.uk/Livewell/fitness/Pages/whybeactive.aspx . Date last updated July 13 2015. Date last accessed: December 13 2017.
2. Gleeson, M., Bishop, N. C., Stensel, D. J., Lindley, M. R., Mastana, S. S., Nimmo, M. A. The Anti-inflammatory Effects of Exercise: Mechanisms and Implications for the Prevention and Treatment of Disease. Nature Reviews Immunology 2011; 11: 607-615.
3. Watz, H., Waschi, B., Meyer, T., Magnussen, H. Physical Activity in Patients with COPD. European Respiratory Journal 2011; 33: 262-272.
4. Korenromp, I., Heijnen, C. J., Vogels, O. J., Van den Bosch, J. M., Grutters, J. C. Characterization of Chronic Fatigue in Patients with Sarcoidosis in Clinical Remission. Chest 2011; 140(2): 441-447.
5. Saligan, L. N. The Relationship between Physical Activity, Functional Performance and Fatigue in Sarcoidosis. Journal of Clinical Nursing 2014; 15: 2376-2378.
6. Durstine, J. L., Painterm P., Franklin, B. A., Morgan, D., Pitetti, K. H., Roberts, S. O. Physical Activity for Chronically Ill and Disabled. Sports Medicine 2000; 30(3): 207-219.
7. Warburton, D. E. R., Nicol, C. W., Bredin, S. D. Health Benefits of Physical Activity: The Evidence. Canadian Medical Association Journal 2006; 174(6): 801-809.
8. Garcia-Aymerich, J., Lange, P., Benet, M., Schnohr, P., Anto, J. M. Regular Physical Activity Reduces Hospital Admission and Mortality in Chronic Obstructive Pulmonary Disease: a Population based Cohort Study. Thorax 2006; 61(9): 772-778.
9. Kohl, H., Craig, C. L., Lambert, E., Inoue, S., Alkandari, J. R., Leetongin, G., Kahlmeier, S. The Pandemic of Physical Inactivity: Global Action for Public Health. The Lancet 2012; 380(9838): 294-305.
10. Morand, M., Beauregard, S., Mathieu, S. Systematic Sarcoidosis Revealed by Axillary Electrolysis. Journal of Cutaneous Medicine and Surgery 2015; 19(4): 4-4-406.
11. Kobak, S. Sarcoidosis: A Rheumatologist's Perspective. Therapeutic Advances in Musculoskeletal Disease 2015; 7(5): 196-205.
12. Loke, W. S., Herbert, C., Thomas, P. S. Sarcoidosis: Immunopathogenesis and Immunological Markers. International Journal of Chronic Diseases 2013; 1-13.
13. Saidha, S., Sotirchos, E. S., Eckstein, C. Etiology of Sarcoidosis: Does Infection Play a Role? Yale Journal of Biology and Medicine 2012; 85(1): 133-141.
14. National Health Service (NHS). Sarcoidosis. http://www.nhs.uk/conditions/sarcoidosis/Pages/Introduction.aspx Date last updated: October 12 2015. Date last accessed: December 13 2017.
15. Morgenthau, A. S., Iannuzzi, M. C. Recent Advances in Sarcoidosis. Chest 2011; 139: 174-182.
16. Wirnsberger, R. M., Drent, M., Hekelaar, N., Breteler, M. H., Drent, S., Wouters, E. F., Dekhuijzen, P. N. Relationship Between Respiratory Muscle Function and Quality of Life in Sarcoidosis. European Respiratory Journal 1998; 10(7): 1450-1455.
17. Baughman, R. P. Treatment of Sarcoidosis. Panminerva Medica 2013; 55(2): 175-189.

18. Cremers, J. P., Drent, M., Elfferich, M. D., Nelemans, P. J., Wijnen, P. A., Witteman, B. J., Schols, A. M. Body Composition Profiling in a Dutch Sarcoidosis Population. Sarcoidosis Vasculitis Diffuse Lung Disease 2013; 30(4): 289-299.
19. Fleischer, M., Hinz, A., Brahler, E., Wirtz, H., Bosse-Henck, A. Factors Associated with Fatigue in Sarcoidosis. Respiratory Care 2014; 59(7): 1086-1094.
20. Drent, M., Marcellis, R., Lenssen, A., De Vries, J. Association Between Pulmonary Functions and Quality of Life in Sarcoidosis. Sarcoidosis Vasculitis and Diffuse Lung Diseases 2014; 31(2): 117-128.
21. Martusewicz-Boros, M. M., Boros, W. P., Wiatr, E., Wesolowski, S., Roszkiwski-Slitz K. Bronchial Hyperactivity in Sarcoidosis Patients: Correlation with Airflow Limitation Indices. Sarcoidosis Vasculitis and Diffuse Lung Diseases 2012; 29(2): 99-106.
22. Kallianos, A., Zarogoulidis, P., Ampatzoglou, F., Trakada, G., Gialafos, E., Pitsiou, G., Pataka, A., Veletza, L., Zarogoulidis, K., hohenforst-Schmidt, W., Petridis, D., Kioumis, I., Rapti, A. Reduction of Exercise Capacity in Sarcoidosis in Relation to Disease Severity. Patient Preference and Adherence 2015; 18(9): 1179-1188.
23. Durstine, J. L., Gordon, B., Wang, Z., Luo, X. Chronic Disease and the Link to Physical Activity. Journal of Sport and Health Science 2013; 2(1): 3-11.
24. Moliner-Urdiales, D., Ortega, F. B., Vicente-Rodriquez, G., Rey-Lopez, J. P., Garcia-Marco, L., Widhalm, K., Sjostrom, M., Moreno, L. A., Castillo, M. J., Ruiz, J. R. Association of Physical Activity with Muscular Strength and Fat-Free Mass in Adolescents: The Helena Study. European Journal of Applied Physiology 2010; 109(6): 1119-1127.
25. Helms, E., Fitschen, P. J., Aragon, A., Cronin, J., Schoenfeld, B. J. Recommendations for Natural Bodybuilding Contest Preparation: Resistance and Cardiovascular Training. The Journal of Sports Medicine and Physical Fitness 2014; 55(3): 164-178.
26. Strookappe, B., De Vries, J., Elfferich, M., Kuijpers, P., Knevel, T., Drent, M. Predictors of Fatigue in Sarcoidosis: The Value of Exercise Testing. Respiratory Medicine 2016; 116: 49-54.
27. Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine 2009; 6(7): e1000097.
28. Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L. A. Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) 2015 – Elaboration and Explanation. The British Medical Journal 2015; 349.
29. Kowalska, A., Puscinska, E., Golian-Geremek, A., Czemiawska, J., Stoklosa, A., Kram, M., Tomkowski, W. Z., Gorecka, D. Six-minute Walk Test in Sarcoidosis Patients with Cardiac Involvement. Pneumonlogia L Alergologia Polska 2012; 80(5): 430-438.
30. Braam, A. W., de Haan, S. N., Vorselaars, A. D., Rijkers, G. T., Grutters, J. C., van den Elshout, F. J., Korenromp, I. H. Influence of Repeated Maximal Exercise Testing on Biomarkers and Fatigue in Sarcoidosis 2013; 33: 57-64.
31. Marcellis, R., Van der Veeke, M., Mesters, I., Drent, M., De Bie, R., De Vries, G., Lenssen, A. Does Physical Training Reduce Fatigue in Sarcoidosis? Sarcoidosis, Vasculitis and Diffuse Lung Diseases: The Official Journal of WASOG 2015; 32(1): 53-62.

32. Strookappe, B., Swigris, J., De Vries, J., Elfferich, M., Knevel, T., Drent, M. Benefits of Physical Training in Sarcoidosis. Lung 2015; 193(5): 701-708.
33. Marcellis, R. G., Lenssen, A. F.,, Kleynen, S., De Vries, J., Drent, M. Exercise Capacity, Muscle Strength and Fatigue in Sarcoidosis: A Follow-up Study. Lung 2013; 191(3): 247-256.
34. Naz, L., Ozalevil, S., Ozkan, S., Sahin, H. Efficacy of a Structured Exercise Program for Improving Functional Capacity and Quality of Life in Patients with Stage 3 and 4 Sarcoidosis: A Randomized Controlled Trial. Journal of Cardiopulmonary Rehabilitation and Prevention 2018; 38(2), 124-130.
35. Athos, L., Mohler, J. G., Sharma, O. P. Exercise Testing in the Physiologic Assessment of Sarcoidosis. Annals of the New York Academy of Sciences 1986; 465: 491-501.
36. Sietsema, K. E., Kraft, M., Ginzton, L., Sharma, O. E. Abnormal Oxygen Uptake Responses to Exercise in Patients with Mild Pulmonary Sarcoidosis. Chest 1992; 102(3): 838-845.
37. Medinger, A., E., Samir, K., Preshant, R. K. Sarcoidosis: The Value of Exercise Testing. Chest 2001; 120(1): 93-101.
38. Akkoca, O., Celik, G., Ulger, F., Arbak, P., Saryal, S., Karabiyikoglu, G., Alper, D. Exercise Capacity in Sarcoidosis. Study of 29 Patients. Medicina Clinica 2005; 124(18): 686-689.
39. Alhamad, E. H., Shaik, S. A., Idrees, M. M., Alanezi, M. O., Isnani, A. C. Outcome Measures of the 6 Minute Walk Test: Relationships with Physiologic and Computed Tomography Findings in Patients with Sarcoidosis. BMC Pulmonary Medicine 2010; 10(42): 10-42.
40. Marcellis, R. G., Lenssen, A. F., de Vries, G. J., Baughman, R. P., van der Grinten, C. P., Verschakelen, J. A., De Vries, J., Drent, M. Is There an Added Value of Cardiopulmonary Exercise Testing in Sarcoidosis Patient? Lung 2013; 191(1): 43-52.
41. De Boer, D. S., Kolbe, J., Wilsher, M. L. The Relationships among Dyspnoea, Health-related Quality of Life and Psychological Factors in Sarcoidosis. Respirology 2014; 19(7): 1019-1024.
42. Zieleznik, K., Jastrzebski, D., Ziora, D. Fatigue in Patients with Inactive Sarcoidosis does not Correlate with Lung Ventilation Ability or Walking Distance. Pilot Study. Advances in Respiratory Medicine 2015; 83(1): 14-22.
43. Chenivesse, C., Boulanger, S., Langlois, C., Wemeau-Stervinou, L., Perez, T., Wallaert, B. Oxygen Desaturation During a 6-minute Walk Test as a Predictor of Maximal Exercise-induced Gas Exchange Abnormalities in Sarcoidosis. Journal of Thoracic Disease 2016; 8(8): 1995-2003.
44. Mirsaeidi, M., Omar, H. R., Baughman, R., Machado, R., Sweiss, N. The Association Between BNP, 6MWD test, DLCO% and Pulmonary Hypertension in Sarcoidosis. Sarcoidosis Vasculitis and Diffuse Lung Diseases: The Official Journal of WASOG 2016; 33(4): 317-320.
45. Fletcher, G. F., Balady, G. J., Amsterdam, E. A., Chaitman, B., Eckel, R., Fleg, J., Froelicher, V. F., Leon, A. S., Pina, I. L., Rodney, R., Simons-Morton, D. A., Williams, M. A., Bazzarre, T. (2001). Exercise Standard for Testing and Training. *Circulation*, 104, 1694-1740.

46. Lassek, W. D., Gaulin, S. J. C. (2009). Costs and Benefits of Fat-free Muscle Mass in Men: Relationship to Mating Success, Dietary Requirements, and Native Immunity. *Evolution & Human Behavior*, 30(5), 322-328.
47. Sparling, P. B., Owen, N., Lambert, E. V., Haskell, W. L. Promoting Physical Activity: The New Imperative for Public Health. Health Education Research 2000; 15(3): 367-376.
48. National Health Service (NHS). Benefits of Exercise: http://www.nhs.uk/Livewell/fitness/Pages/whybeactive.aspx Date last updated: July 13th 2015. Date last accessed: December 15 2017.
49. Garcia-Aymerich, J., Lange, P., Benet, M., Schnohr, P., Anto, J. M. (2006). Regular Physical Activity Reduces Hospital Admission and Mortality in Chronic Obstructive Pulmonary Disease: A Population Based Cochort Study. *Thorax*, 61(9), 739-739.
50. Egan, C., Deering, B. M., Blake, C., Fullen, B. M., McCormack, N. M., Spruit, M. A., Costello, R. W. (2012). Short Term and Long Term Effects of Pulmonary Rehabilitation on Physical Activity in COPD. *Respiratory Medicine*, 106(12), 1671-1679.
51. Hairi, N. N., Cumming, R. G., Naganathan, V., Handelsman, D. J., Le Couteur, D. G., Creasey, H., Waite, L. M., Seibel, M. J., Sambrook, P. N. (2010). Loss of Muscle Strength, Mass (Sarcopenia), and Quality (Specific Force) and Its Relationship with Functional Limitation and Physical Disability: The Concord Health and Ageing in Men Project. *Journal of the American Geriatrics Society*, 58(11), 2055-2062.
52. Musalek. C., Krchengast, S. (2017). Grip Strength as an Indictor of Health-Related Quality of Life in Old Age-A Pilot Study. *International Journal of Environmental Research and Public Health*, 14(12).
53. Jakobosen, L. H., Rask, I. K., Kondrup, J. (2010). Validation of Handgrip Strength and Endurance as a Measure of Physical Function and Quality of Life in Healthy Subjects and Patients. *Nutrition*, 26(5), 542-550.
54. Taekema, D. G., Gussekloo, J., Maier, A. B., Westendrop, R. G. J., de Craen, A. J. M. (2010). Handgrip Strength as a Predictor of Functional, Psychological and Social Health. A Prospective Population-based Study Among the Oldest Old. *Age and Ageing*, 39(3), 331-337.
55. Trosclair, D., Bellar, D., Judge, L. W., Smith, J., Mazerat, N., Brignac, A. (2011). Hand-Grip Strength as a Predictor of Muscular Strength and Endurance. *Journal of Strength and Conditioning Research*, 25, s99.
56. Muff, G., Dufour, S., Meyer, A., Severac, F., Favret, F., Geny, B., Lecocq, J., Isner-Horobeti, M. (2016). Comparative Assessment of Knee Extensor and Flexor Muscle Strength Measured using a Hand-Held vs. Isokinetic Dynamometer. *Journal of Physical Therapy Science*, 28(9), 2445-2451.
57. Evans, R. A., Singh, S. J., Collier, R., Loke, I., Steiner, M. C., Morgan, M. D. L. (2010). Generic, Symptom based, Exercise Rehabiliation; Integrating Patients with COPD and Heart Failure. *Respiratory Medicine*, 104(10), 1483-1481.
58. McCarthy, B., Casey, D., Devane, D., Murphy, K., Murphy, E., Lacasse, Y. (2015). Pulmonary Rehabilitation for Chronic Obstructive Pulmonary Disease. *The Cochrane Library*.

59. Forkan, R., Pumper, B., Smyth, N., Wirkkala, H., Ciol, M. A., Shumway-Cook, A. Exercise Adherence Following Physical Therapy Intervention in Older Adults with Impaired Balance. Physical Therapy 2006; 86(3): 401-410.
60. National Institute for Health and Care Excellence. Patient Experience in Adult NHS Services: Improving the Experience of Care for People using Adult NHS Services. https://www.nice.org.uk/guidance/cg138/chapter/1-guidance Last updated: February 2012. Last accessed: December 13 2017.
61. De Kleijn, W., De Vries, J., Lower, E. E., Elfferich, M., D., Baughman, R. P., Drent, M. Fatigue in Sarcoidosis: A Systematic Review. Current Opinion in Pulmonary Medicine 2009; 15(5): 499-506.
62. Delobbe, A., Perrault, H., Maitre, J., Robin, S., Hossein-Foucher, C., Wallaert, B., Aguilaniu, B. Impaired Exercise Response in Sarcoid Patients with Normal Pulmonary Function. Sarcoidosis, Vasculitis and Diffuse Lung Diseases: Official Journal of WASOG 2002; 19(2): 148-153.

217

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 *et al*. [35]	39 Male = 12 Female = 27	Mean: 39 Range: 21-75	• Lung Function (FVC, FEV_1, MVV, DLCO). • Exercise Capacity (Incremental symptom limited exercise test ($\dot{V}O_2$)) • Dyspnoea (MRC)	• Pulmonary limitation to exercise occurred in 29% (stage 0 & 1) and 95% (stage 2 & 3). • $\dot{V}O_2$ was not reported. • 89% reported dyspnoea.	• Severe abnormalities of gas exchange occurred more frequently from submaximal exercise studies. • No single test or combination of lung function, arterial blood gas, or pulmonary symptom tests could precisely predict pulmonary limitation to exercise.
Sietsema *et al*. [36]	20 Male = 6 Female = 14	Mean: 43 Range: 24-58	• Lung function (FVC) • Exercise capacity (Symptom limited maximal exercise testing (peak $\dot{V}O_2$)) • Heart rate	• Forced vital capacity averaged 88±12% of predicted value. • 11 of 20 patients failed to reach > 80% of predicted maximum $\dot{V}O_2$, although all but 3 of them met criteria for maximal or near-maximal effort. • 7 of the 11 had one or more abnormal $\dot{V}O_2$ response to exercise.	• Impairment in the rate of delivery and utilisation of oxygen during exercise, despite normal lung functions. • Reduced maximal exercise capacity, abnormal efficiency of pulmonary gas exchange. • Exertional symptoms and their absence predicted neither normal or abnormal results of exercise testing.
Medinger *et al*. [37]	48	Mean: 41	• Lung function (FEV_1, FVC), • Exercise Capacity (6min	• No significant association between radiographic stage and FEV_1/FVC%, $\dot{V}O_2$	• Gas exchange changes with exercise may be the most sensitive physiologic measurements to assess the extent of disease in stages (0-2).

			progressive bicycle exercise ($\dot{V}O_2$ max))	max, AT, HRR, BR, or VEe/$\dot{V}CO_2$ AT. • 11 participants exercise blood gas measurement was not recorded due to technical issues regarding arterial access.	• Remains a lack of a true non-invasive "gold standard" for measuring the extent of disease. .
Akkoca *et al*. [38]	29 Groups defined by radiographic stage.	Stage 1 mean: 42 Stage 2 mean: 42 Stage 3 mean: 44	• Lung function, • Exercise Capacity (CPET)	• Moderate decrease reported between stages 2 & 3, with significant difference between 1 & 3. • Limitation of exercise capacity correlated with radiographic stage. • Radiographic stage increases were significantly observed with decreases to $\dot{V}O_2$ /kg ($p<0.05$).	• Exercise capacity is the earliest impaired physiological parameter. • 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.
Alhamad *et al*. [39]	59 Male = 17 Female = 42	Mean: 48	• Lung function (FVC, FEV_1, TLC) • Exercise Capacity (6MWT)	• Mean lung function parameters for FVC, FEV_1 and TLC results, as percentages of predicted values, were 77.6 ± 22.2, 77.1 ± 22.8 and 78.7 ± 16.1, respectively. • Female 6MWD = 324.1m. • Male 6MWD = 409.4m.	• DSP is correlated with more factors linked to reduced 6MWD than 6MWD alone, therefore DSP appears to be a useful indictor for functional status within the sarcoidosis population. • Pulmonary hypertension and fibrosis associated with reductions to 6MWD.
Korenromp *et al*. [4]	75 patients in clinical remission	Non-fatigued mean: 48	• Lung Function • Muscle Strength (HGS & QPT)	• Lung function within normal range for all participants.	• Fatigue is a frequent severe and chronic issue within clinical remission patients.

	Male = 33 Female = 42	Fatigued mean: 46	• Physical Activity (Accelerometer) • Fatigue (CIS) • QOL (sf-36) • Depression(BDI) • Anxiety (SCL-90)	• HGS mean score lower among fatigued group. • Weekday = 75.14 (fatigued) vs. 82.06 (non-fatigued) accelerations / day. • Weekend = 66.93 (fatigued) vs. 79.81 (non-fatigued) accelerations / day. Norm score = 91 (healthy). • Fatigue = 30.5, with 15.5 on the subscale fatigue severity. • Significantly worse depression and QOL scores among fatigued participants.	• Psychologic distress and reduced QOL are associated with fatigue in addition to, reduced physical activity and muscle weakness in fatigued patients. • On all tests, the mean score of the fatigued group was significantly lower than the mean of the non-fatigued group.
Kowalska *et al*. [29]	47 (22 with cardiac involvement) Males = 19 Females = 28 As well as 18 healthy volunteers for control	Mean: 48	• Exercise Capacity (6MWT oxygen saturation, heart rate)	• Cardiac sarcoidosis with treatment: 6MWD = 514.81 ± 91.22m. • Maximum desaturation = 3.5±3.7%. • Cardiac sarcoidosis (no treatment): 6MWD = 567.09 ± 119.06. • Maximum desaturation = 1.9±1.7%. • No cardiac involvement (no treatment): 6MWD = 20.8± 96.22.	• 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. • Treatment with prednisone decreased both 6MWD and oxygen saturation in comparison to no treatment. • The healthy control group recorded better 6MWD than sarcoidosis groups.

				• Maximum desaturation = 2.36 ± 2.87.	
Marcellis *et al*. [40]	160 Male = 97 Female = 63	Mean: 41	• Lung Function (DLCO) • Exercise Capacity (CPET blood gas analysis)	• DLCO (mean = 83.2 ± 18.0 %) • < 80 % of predicted DLCO in 38 % of participants. • DLCO < 60% indicates significant impairment of gas exchange. • 59% failed to reach 83% of predicted $\dot{V}O_2$ max.	• Symptomatic patients with normal DLCO appeared to have pulmonary gas exchange impairment at maximal exercise • Results suggest that normal DLCO at rest is an inappropriate predictor of abnormal pulmonary gas exchange during exercise. • CPET appeared to offer added value in detecting impaired gas exchange during exercise in patients with unexplained disabling symptoms.
Marcellis *et al*. [33]	92 Male = 62 Female = 28	Mean: 46	• Exercise Capacity (6MWT) • Muscle strength (EFMS, HPT, QPT) • Fatigue (FAS).	• Reduced 6MWT (41.6 vs. 34.8 %) at baseline and follow-up, • EFMS (6.7 vs. 14.6 %), • QPT (21.3 vs. 18 %), • HPT (13.5 vs. 12.4 %) • Fatigue reported in 86 and 77% of participants.	• Decreased measurements at baseline and follow-up for participants compared to control. • The physical impairments remained stable across baseline and follow-up. • 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.
Braam *et al*. [30]	20 sarcoidosis and 10 healthy	Healthy Control: 35	• Exercise Capacity (CPET, Symptom limited incremental	• Sarcoidosis w/Mod fatigue: $\dot{V}O_2$ max = 270±67.4	• Severe fatigue is not correlated with biomarkers nor a reduction of exercise capacity and is only

	volunteers for control Male = 16 Female = 14	Sarc Mod fatigue: 41 Sarc severe fatigue: 37	exercise test ($\dot{V}O_2$, RER)) • Blood pressure, HR, pulse oximetry, cytokines, stress hormones, ACE and CK (before, after and 3 days after).	• Sarcoidosis w/Severe fatigue: $\dot{V}O_2$ max = 187±54.2	consistently measured via self-reported patient feedback/outcomes.
de Boer *et al.* [41]	33 Male = 17 Female = 16	Mean: 48	• Lung Function (FEV_1, FVC, DLCO) • Exercise Capacity (MSWT, CPET)	• Mean FEV_1 = 75.7% predicted • Mean FVC = 88.7% predicted • Mean DLCO = 71.4% predicted • MSWT correlated with peak oxygen update during CPET	• Both FVC and DLCO correlated with the two exercise measures. • MSWT is a symptom-limited maximal exercise test comparable with full CPET in assessing functional capacity in sarcoidosis. • Peak $\dot{V}O_2$ during CPET correlated with MSWT distance.
Drent *et al.* [20]	88 Sarcoidosis Male = 61 Female = 28 62 healthy controls	Mean: 46	• Lung Function (FEV_1, FVC, DLCO) • Exercise capacity (6MWT) • Muscle strength (EFMS, HPT, QPT) • Fatigue (FAS)	• Sarcoidosis: FEV_1 (%pred) = 84 FVC (%pred) = 98. DLCO (%pred) = 76. • 6MWD Female = 551. • 6MWD Male = 606. • EFMS (%pred) Female = 97.7. • EFMS (%pred) Male = 89.9.	• Males scored lower than female across all muscle strength tests however performed better during the 6MWT. • QOL is diminished and associated with both exercise capacity and fatigue especially within the physical health domain.

			• QOL (WHOQOL-BREF)	• QPT180 (%pred) Female = 84.9. • QPT180 (%pred) Male = 81.4. • HPT180 (%pred) Female = 86.4. • HPT180 (%pred) Male = 81.9. • FAS = 28.6. • QOL reduced in comparison to healthy controls.	
Saligan [5]	14 pulmonary sarcoidosis participants as well as 13 age, sex and race matched.	Not stated	• Exercise Capacity (6MWT) • Muscle Strength (MVC/kg) • Physical activity (Accelerometer) • Fatigue (FAS) • Depression (HAM-D)	• Sarc: 6MWD - 502±84. MVC/kg – 26.06. Mean Energy Expenditure – 1324. Mean FAS – 27.4±5.7. HAM – D - 8.6+5.0. • Control: 6MWD - 607±77. MVC/kg – 32.71. Mean Energy Expenditure – 1748. Mean FAS – 14.2±3.5. HAM – D - 2.5+2.2.	• There were significant differences in physical activity, exercise capacity, muscle strength, depression and fatigue scores between sarcoidosis patients and healthy control.
Zieleznik *et al*. [42]	74 Sarcoidosis Male = 53 Female = 21	Mean: 45 Range: 29-71	• Lung function (FEV_1, FVC)	• FEV1 = 3.18±0.82. • FEV1 (%) = 90.4±13.1. • FVC = 4.16±1.1. • FVC (%) = 98.9±13.9.	• Fatigue did not correlate with lung function scores or 6MWD.

	30 Healthy controls		• Exercise Capacity (6MWT) • Fatigue (FAS)	• 6MWD (m) = 555.9±91.5. • FAS = 22.9±7.3.	• 43.06% sarcoidosis participants reported no fatigue compared to 76.67% for the control group.
Kallianos *et al*. [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	• Lung function $FEV_{1,}$ FVC, TLC DLCO) • Exercise Capacity (CPET Standard protocol).	• $FEV_{1,}$ 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). • DLCO was reduced in stages 2-4. • Peak oxygen consumption during exercise was decreased and varied by stage; Stage 1: 48%, Stages 2–3: 52%, Stage 4: 78%. • Only stage 1 and 4 reported as having a significant difference.	• Exercise capacity is the first impaired physiological parameter in sarcoidosis, with it being found to be limited from stage I. • The mechanisms responsible for exercise limitation are multifactorial and correlated with the radiological extent of the disease. • Exercise limitation may be attributed to both ventilatory and cardiocirculatory impairment.
Strookappe *et al*. [26]	146 Male = 89 Female = 57	Mean: 47	• Lung Function (FEV_1, FVC, DLCO) • Exercise Capacity (6MWT, SRT) • Muscle strength (EFMS, HGS) • Fatigue (FAS)	• FEV_1 (%pred) - 87.6 ± 19.7. • FVC (%pred) - 94.7 ± 18.7. • DLCO (%pred) - 79.3 ± 18.0. • 6MWD 536±104. • SRT 26.8±6.3. • HGS (pred%) 91.1±22.7.	• Exercise capacity partly predicts fatigue. • Fatigue is a substantial problem among sarcoidosis patients, which is affected by many variables.

				• EFMS (pred%) 100.5±20.4. • FAS 30.2±9.0.	
Chenivesse *et al*. [43]	130 Male = 78 Female = 52	Mean: 49 Range: 26-78	• Lung Function (FEV_1, FVC, TLC, DLCO) • Exercise Capacity (6MWT)	• FEV_1(% pred) – 80. • FVC (% pred) – 92. • TLC (% pred) – 90. • DLCO (% pred) – 71. • 6MWD – 450.	• Normal DLCO is a good predictor of the absence of severe gas exchange impairment. • The stage 4 group had lower FEV_1, FVC, DLCO scores, in addition to a reduced $\dot{V}O_2$ Peak compared to the other stages.
Mirsaeidi *et al*. [44]	108 Male = 21 Female = 87	Mean: 54	• Lung function (FEV_1, FVC, DLCO, VC, TLC, FRC) • Exercise Capacity (6MWT)	• FEV1% 74.3±28.5. • FVC% 83.5±25.3. • DLCO% 61±18.6. • VC% 88±23.9. • TLC% 84.3±17.1. • FRC% 101.6±20.6. • 6MWD – 364.4±77.3.	• These tests are useful for tracking the progression of pulmonary hypertension associated with sarcoidosis.

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; CPET – Cardiopulmonary exercise testing; FAS – fatigue assessment scale; FVC – Forced vital capacity; TLC – total lung capacity; FEV_1 – forced expiratory volume in one second; VC – vital capacity; FRC – functional residual capacity; MVV – Maximal voluntary ventilation; Ve/Vco2 AT - ventilatory equivalent for carbon dioxide at anaerobic threshold; HRR – heart rate reserve; BR – breathing reserve; DSP – distance saturation product; CIS – checklist individual strength; SCL-90 – symptom checklist 90 ; BDI – beck depression inventory for primary care ; SF-36 – Medical outcomes study 36-item health survey; QPT – quadricep peak torque; HPT – hamstring peak torque; EFMS – elbow flexor muscle strength; ACE - angiotensin converting enzyme; CK – creatine kinase; RER – respiratory exchange ratio; HR – heart rate; MSWT - Modified shuttle walk test; HGS – handgrip strength; SRT – steep ramp test; MRC – Medical Research Council Dyspnoea Scale; HAM – D – Hamilton Depression Rating Scale; MVC – Maximum voluntary contraction; %pred – Percent of Predicted.

227 **Table 2.** Exercise intervention Studies.

References	Study Design	Sample Size (age / gender)	Factors studied	Exercise programme	Main Findings
Marcellis *et al*. [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).	• Lung function (FVC, FEV_1, DLCO) • • Muscle Strength (X-RM leg extension, elbow flexor microFET) • Fatigue (FAS) • QOL (WHOWOL-BREF), • Dyspnoea (MRC, Borg RPE)	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.	• Lung function not reported post-treatment. • ↑ 6MWD. • ↑HR (submaximal). • ↑ Quadricep strength. • ↓ FAS score . • ↑MRC and WHOQOL-BREF.
Strookappe *et al*. [32]	Intervention: pre/post measurement design.	90 participants (49 completing treatment, 41 opted not partake in treatment).	• Lung function (FVC, FEV_1, DLCO) • Exercise Capacity (SRT, 6MWT) • Muscle strength (HGS, EFMS via microFET) • Fatigue (FAS) • Borg RPE, Dyspnoea (modified Borg)	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.	• Lung function unchanged. • ↑ 6MWD. • ↑SRT. • ↑ Elbow flexion. • ↑ HGS. • ↓ FAS Score. • RPE & Dyspnoea scores stable.
Naz *et al*. [34]	Intervention: pre/post measurement design.	18 participants (9 undergoing intervention, 9 control with usual care).	• Lung function (FVC & FEV_1) • Exercise Capacity (6MWT) • Muscle Strength (back and leg dynamometer) • Fatigue (FSS)	12-week programme (2 x week) Aerobic endurance: Treadmill and stationary cycling at 80% & 70% peak speed of 6MWT, increased	• Lung function unchanged. • ↑ 6MWD. • ↑ Leg Strength. • ↓ FSS Score. • ↑ SGRQ.

	• QOL (SF-36, SGRQ) • Borg Dyspnoea (modified Borg) • Depression and Anxiety (HADS)	within symptom tolerance when continuous 15min exercise achieved 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.	• SF-36 unchanged. • ↓Dyspnoea. • ↓HADS.

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 scale; HGS – handgrip strength; EFMS – elbow flexor muscle strength; 6MWT – six minute walk test; DLCO – diffusing capacity of the lungs for carbon monoxide; FVC – Forced vital capacity; FEV_1 – forced expiratory volume in one second; MRC – medical research council dyspnoea scale; WHOWOL-BREF - World Health Organization Quality of Life Instruments; SF-36 – 36-item Short Form survey ; SGRQ - St. Georges respiratory questionnaire; HADS – Hospital depression and anxiety scale

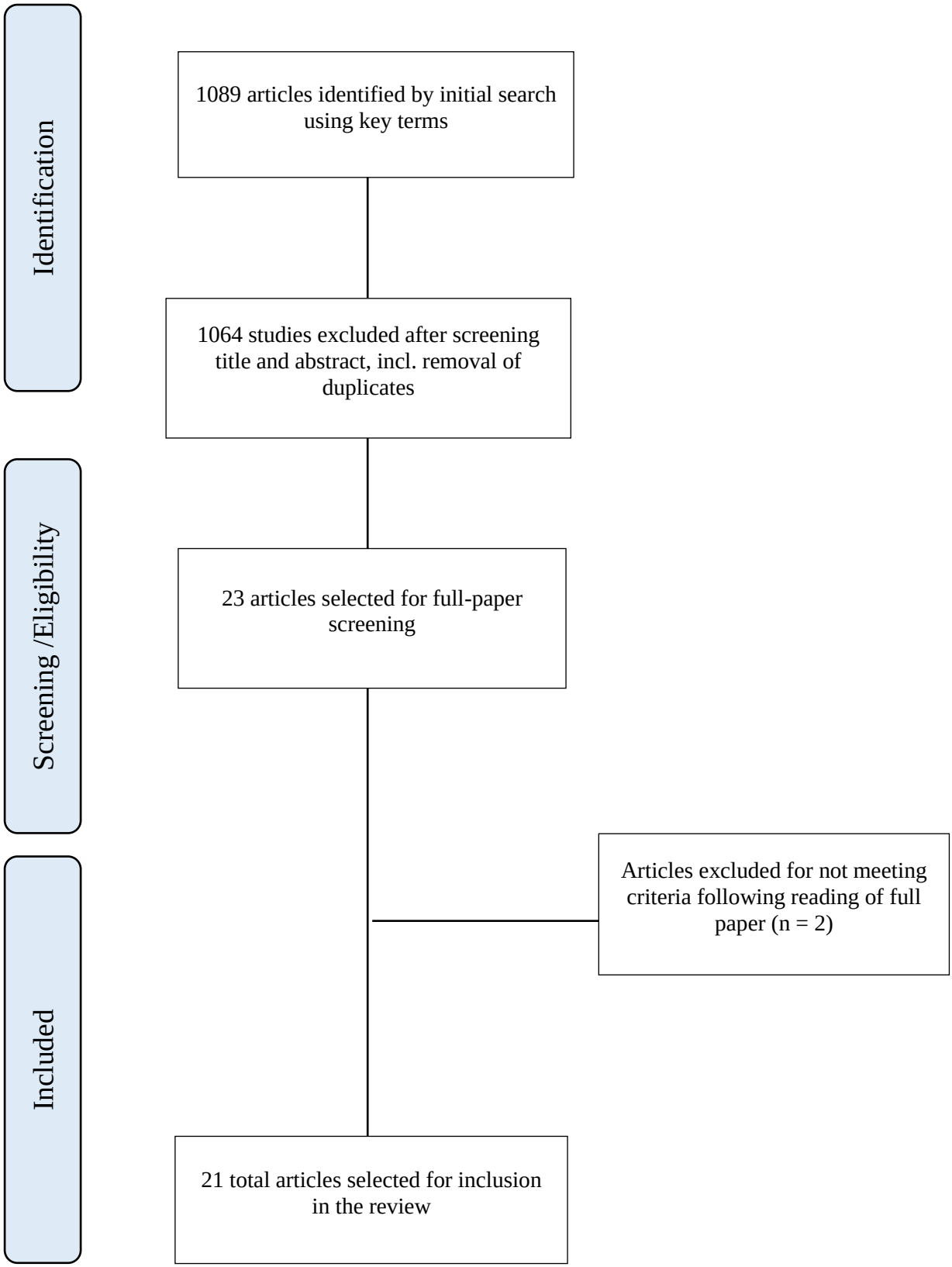

Figure 1. Flow diagram of systematic review search process of study selection.

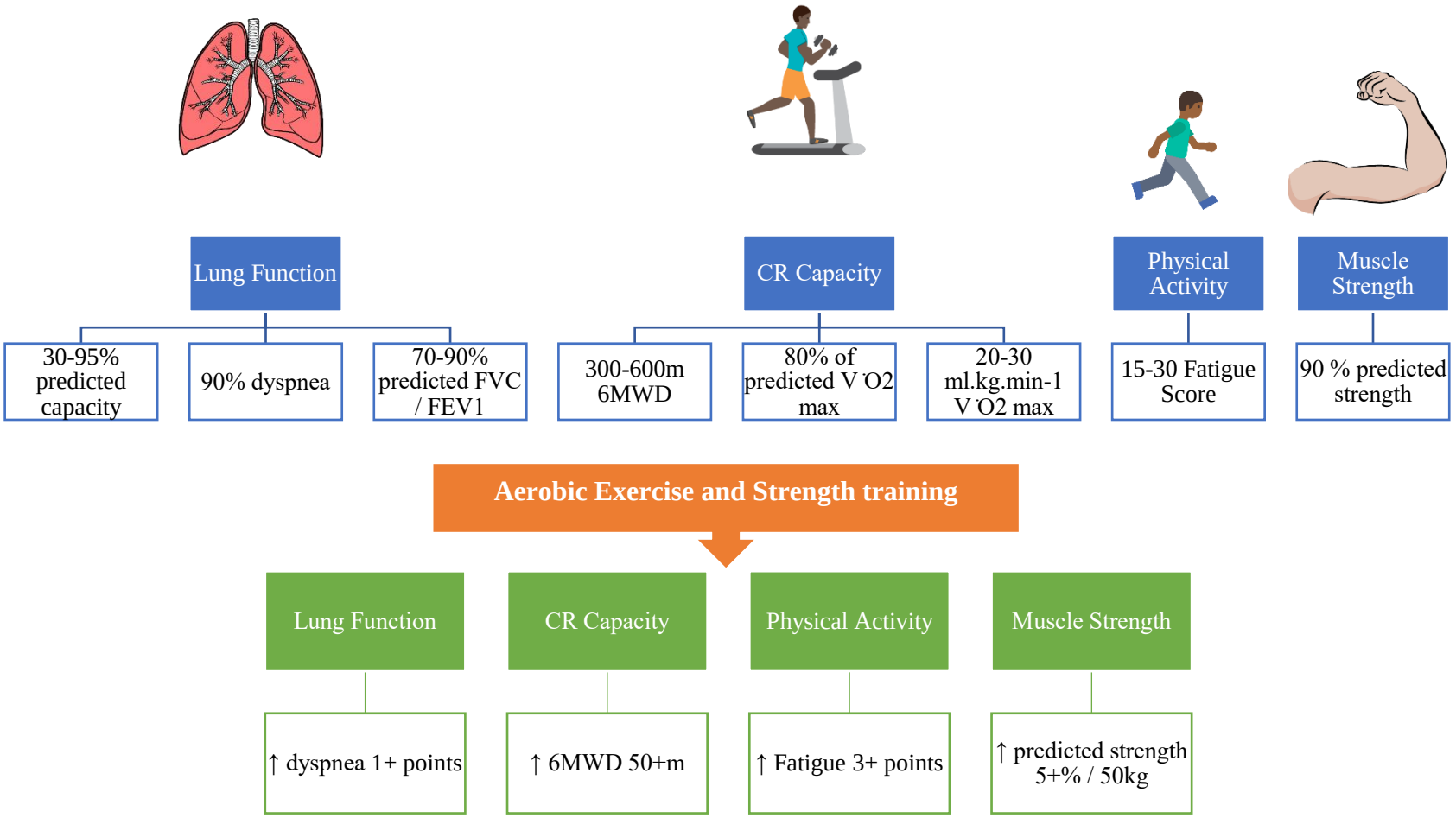

Figure 2. A schematic diagram to demonstrate the association between Sarcoidosis and Exercise Training