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Abstract

Purpose: Sarcoidosis is a diverse condition. The condition currently has a limited body of knowledge surrounding the effect and role of physical activity and exercise on quality of life and disease management. Therefore, this project aimed to preliminarily establish trends and correlations in relationship to quality of life and disease management through environmental and lifestyle factors.

Methods: The project involved a systematic review into physical activity, exercise capacity and muscle strength, two online epidemiological studies looking at environmental and lifestyle factors alongside type and symptoms of the condition. In addition to qualitative questions helping understand the views of patients. While a final study compared an objective (triaxial accelerometry) measure of physical activity against a standardised self-reported measure (IPAQ), in addition to their relationships with physiological and mental measures of sarcoidosis.

Results: Sarcoidosis is typically associated with reduced exercise capacity and muscle strength with reductions more profound in patients reporting fatigue. Although physical activity has been found to be above and below recommended levels. Chapter five found quality of life, number of symptoms and fatigue were predictors ($R^2=.094$) of perceived categories physical activity while accelerometer MVPA found calories burned per day and BMI as predictors ($R^2=.968$). Fatigue was found to be a major issue within the population with number of symptoms and physical activity since diagnosis as predictors within chapter five ($R^2 =.238$) and the SHQ within chapter seven ($R^2=.797$).

Conclusions: This was the first study to look at the role of sarcoidosis effects on work-life balance. A large number of patients (41.5%) reported changing or stopping work due to sarcoidosis and thus the role and effects of physical activity needs further investigation, although the findings suggest MVPA cannot be used as the only form of physical activity measure and others such as steps per day; and light activity should be considered, physical activity is shown to be diverse within the population. Exercise rehabilitation can improve associated symptoms and deconditioning within sarcoidosis, while taught coping methods may be beneficial.

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1. INTRODUCTION/LITERATURE REVIEW

1.1. Sarcoidosis

Sarcoidosis is a non-caseating granulomatous disease (Morand *et al.*, 2015), it is a condition that involves the inflammation of organs and tissues (NHS, 2015a). Sarcoidosis is pulmonary in up to 90% of cases although the condition can affect numerous other locations, such as, the liver and heart, with 25% of cases affecting the skin (Saidha *et al.*, 2012). The granulomas form due to the clustering of lymphocytes cells (Loke *et al.*, 2013; National Heart, Lung and Blood Institute, 2013a), specifically T-cells due to an impaired immunosuppressive function (Broos *et al.*, 2013). The mechanism(s) behind this is not clear, however, regulatory T Cells (Treg) have been shown to have increased apoptosis, which is thought to contribute to the impairment (Broos *et al.*, 2015). The granulomas cause pulmonary fibrosis in 25% of cases (Iannuzzi *et al.*, 2007). Pulmonary fibrosis is the most common mechanism for pulmonary hypertension within sarcoidosis (Handa *et al.*, 2006), pulmonary hypertension involves high blood pressure within the pulmonary arteries (NHS, 2017) and is defined by mean pulmonary artery pressure of ≥ 25 mm Hg at rest during right heart catheterisation (Hoepfer *et al.*, 2013). Other major symptoms include fatigue, muscle weakness and dyspnoea (Wirnsberger *et al.*, 1998; Baughman, 2013). Commonly, patients with pulmonary sarcoidosis present with reduction in maximal breathing capacity, lung volume and diffusing capacity of the lung (D_L) as well as increased airway resistance and hypnocalpnea (Ting and Williams, 1965). Lung capacity has been shown to differ by 16% between those with the condition versus a healthy population (Baydur *et al.*, 2001). Baughman *et al.* (2001) found 46.9% of sarcoidosis patients had a forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio of $> 80\%$ of predictive and a further 13.2% scored $>50-69\%$ of predictive. The mechanisms behind the lung function reductions are multiple; they

include fibrotic scarring to the bronchial walls caused by the formation of granulomas and bronchial hyperactivity (Martinez & Flaherty, 2006; Martusewicz-Boros *et al.*, 2012), suggested as being related to granulomatous inflammation of the bronchial mucosa (Drent & Costabell, 2005), increased body composition as a result of fat mass and a decline in muscle strength (Ostrowski & Barud, 2006) linked to deconditioning.

The 'definitive' aetiology of sarcoidosis remains unknown (Dubrey *et al.*, 2014), however there has been numerous proposed mechanisms, the current research supports the hypothesis that the immune response within sarcoidosis is caused by a putative antigen in an individual with genetic susceptibility (Loke *et al.*, 2013). Sarcoidosis is diagnosed following the exclusion of other probable causes (Judson, 2008), as such, several tests are utilised to diagnose sarcoidosis, which are dependent on assessing the affected organs (NHS, 2015a). Tests include chest X-ray's, computerised tomography (CT), lung function tests, tissue biopsy, blood tests and electrocardiogram (ECG) (National Heart, Lung and Blood Institute, 2013a). This task is a histopathologic and clinical dilemma due to a lack of distinction between sarcoidosis and sarcoid-type tissue reactions (Tchernev *et al.*, 2015) such as lymph node metastases (Nag, 2011). Muller-Quernheim *et al.* (2006) states in up to 40% of cases of chronic beryllium disease has been misdiagnosed as sarcoidosis. Potential triggers of the disease include environmental and occupational factors (Dubrey *et al.*, 2014; Iannuzzi *et al.*, 2007; Newman & Newman, 2012). Kucera *et al.* (2003) found metal work, education, transportation industry and high humidity occupations were associated with sarcoidosis, whilst Newman *et al.* (2004) found those exposed within agricultural employment were at higher risk of sarcoidosis. Specific-work related exposures associated with sarcoidosis included vegetable dust, insecticides, mold and titanium

(Kucera *et al.*, 2003; Newman *et al.*, 2004). Kucera *et al.* (2003) also highlighted the limitations of using job titles as substitutes for exposure to specific agents. This point is further backed by Barnard *et al.* (2005), stating employees of building, gardening and hardware materials having a positive association to sarcoidosis whilst occupations involving exposure to metal fumes and dust being negatively associated with sarcoidosis. Newman & Newman (2012) stated there is a growing body of research supporting multiple causes including inorganic triggers and foreign antigens. Rybicki *et al.* (2004) suggested the risk of sarcoidosis increases with exposure to a photocopier, more specifically to toner dust i.e. an inorganic particle. On top of this Liu *et al.* (2016) found a significant difference for sarcoidosis morality due to occupational exposure based on gender and ethnicity with females and Afro-Caribbean's at higher risk, which conforms to other research in the area (Baughman & Lower, 2011) however the reasoning for this remains unclear. This research highlights the multifactorial nature of sarcoidosis and why such a diverse approach to the disease is needed. Alongside this, an infectious communicable agent has been suggested as an initiating factor within the disease (Du Bois *et al.*, 2003), although literature still lacks a definitive answer, *Mycobacterium spp* has been implicated the most, to date (Saidha *et al.*, 2012). Edmondstone (1988) found UK nurses had a greater number with sarcoidosis, standing at 7.5 times more than expected. Although it is not clear if this is down to greater proximity to those with Sarcoidosis and therefore the communicable agent or if it relates to occupational and environmental factors associated with the health care profession and hospitals such as mold, mildew and high internal humidity (Newman *et al.*, 2004). Another common variable associated to this is seasonal variations, showing peak clustering within spring months (Bardinas *et al.*, 1989; Panayreas *et al.*, 1991), furthermore this seasonal clustering has been recorded in both northern and

southern hemispheres (Wilsher, 1998). Additionally, DNA and RNA of *mycobacterial* and *Propionibacterium acnes* has been found within sarcoid tissues (Iannuzzi *et al.*, 2007). Eishi *et al.* (2002) states *P. acnes* had an increased chance of being involved with the aetiology of sarcoidosis than *mycobacterium* in both European and Japanese sufferers, whilst the only microorganism found within lesions caused by sarcoidosis is *P. acnes* (Eishi, 2013). Saidha *et al.* (2012) suggests the combination of infection followed by an environmental agent such as *Mycobacterium spp* in a genetically predisposed individual as the causation of the disease.

Although anyone can be affected by sarcoidosis, the highest incident rates have been recorded in Scandinavia and Japanese ethnicities (Iannuzzi *et al.*, 2007). The reason for this is unknown, however northern Japan which typically has cold winters and mild summers; much like Scandinavia, has a higher incidence rate than the mild winters and warm summers of southern Japan (Yamaguchi *et al.*, 1989). It is also noteworthy that those of Afro-Caribbean descent also have a higher incident rate than their Caucasian counterparts (Gerke, 2015). Rybicki *et al.* (1997) reported the incident rate of African-Americans as being three times that of Caucasian-Americans, along with higher chronic rates (Baughman *et al.*, 2001) and a mortality rate 12-times higher than Caucasians when adjusted for age (Mirsaeidi *et al.*, 2015). Although the NHS (2015a) suggests sarcoidosis is not inherited, this is primarily down to a lack of consensus and understanding of the genetic makeup of patients, as well as the current understanding among researchers that an external trigger is required in tandem with a predisposition to the disease (Iannuzzi & Rybicki, 2007; Loke *et al.*, 2013). Therefore, it cannot be conclusively stated that there is no familial link. In contrast to this, Rybicki *et al.* (2001) found significantly heightened risk of the disease among first and second-

degree relatives of sarcoidosis relatives. Monozygotic twins have also been noted as having a higher incidence rate in comparison to other siblings (Sverrild *et al.*, 2008). On the other hand, Leil *et al.* (2013) suggests familial clustering may be due to shared environmental exposures and should not be overlooked due to shared genes. Current research supports the notion that human leukocyte antigen (HLA) class I and II are associated with sarcoidosis (Grunewald *et al.*, 2004; Iannuzzi & Rybicki, 2007) and can affect sarcoidosis disease risk as well as severity and phenotype (Grunewald, 2008). An example of this is, the HLA-DRB1*03 & DQB1*0201 alleles being associated with acute onset and resolving sarcoidosis, while HLA-DRB1*15 & DQB1*0601 have been associated with chronic sarcoidosis (Berlin *et al.*, 1997; Sato *et al.*, 2002. Grunewald *et al.*, 2004). However, Grunewald (2008) also states sarcoidosis is affected by multiple genes, unfortunately there is a lack of consensus of these other genes due to discrepancies among research to date (Iannuzzi & Rybicki, 2007). Nevertheless, Spagnolo & Grunewald (2013) states genetics not only determines overall disease susceptibility but also plays a key role in influencing phenotypic expression. However, it is worth noting the suggestion from Rybicki and Iannuzzi (2007) that genes influencing phenotypes may be separate from the genes affecting susceptibility, thus highlighting once again the range and complexity of this disease.

The NHS (2015a) state “most people” with the condition suffer from acute sarcoidosis, where they develop symptoms abruptly and unexpectedly that then clear within a few months-years, the National Heart, Lung and Blood Institute (2013a) state more than half will enter remission within three years of diagnosis, which increases to two-thirds at 10 years of diagnosis with relapse occurring in less than 5% of patients. Unfortunately, there is still a significant number of patients who suffer chronically

from the disease (n=33% at 10 years+), which may be due to the persistence of granulomas leading to fibrotic scarring, which in turn leads to/worsens several debilitating symptoms of the disease (Broos *et al.*, 2013).

1.2. Treatment

Currently, steroids are the predominant form of treatment for all forms of sarcoidosis (Judson, 2012; NHS, 2015a) usually taken in bouts varying from 6-24 months (Jennifer & Rashcovsky, 2004). Of the steroids used, corticosteroids are the predominant drug class (Grutters and Van der Bosch, 2006) with prednisone as the chief prescribed drug (National Heart, Lung and Blood Institute, 2013b). Despite steroids being used as a treatment to improve the condition, they have also been associated with a poorer quality of life (QOL; Judson *et al.*, 2015) as well as lower exercise tolerance; demonstrated through a reduced six-minute walk distance (6MWD) following a six-minute walk test (6MWT) (Alhamad *et al.*, 2010). The exact reasons for this, much like the aetiology of sarcoidosis itself are unknown; however, it has been suggested as another possible side effect of steroid use (Grutters & Van der Bosch, 2006). Other side effects include weight gain, increased blood pressure, cataracts, osteoporosis, increased risk of infection and suppressed hormone production from the adrenal gland (Poetker & Reh, 2010; Liu *et al.*, 2013). These side effects lead to a further prescription of drugs which in-turn lead to a wider range of negative side effects, for example osteoporosis increasing the risk of fractures (Kanis *et al.*, 2000). Typically, vitamin D supplementation is used to aid the elevation of this risk and help maintain healthy bones (Stovall, 2013) however Baughman & Lower (2014) found hypercalcuria and hypercalcemia can result due to this within sarcoidosis patients. Other side effects associated with prednisolone use include increased blood pressure that can lead to hypertension which if left untreated can lead to a stroke or heart attack

among other serious health conditions (NHS, 2016) as well as increased appetite, thinned skin and greater susceptible to bruising (Judson, 2012). Due to the damaging side effects and the current limitations in treating sarcoidosis, novel therapies varying in their approach are required. One example of this is exercise rehabilitation (Naz *et al.*, 2018). Outside of specific novel treatments, improvements of current systems such as better integration between a patient's different specialist doctors and GP is another possible avenue for improving some primary and secondary symptoms. Bird *et al.* (2010) found chronic obstructive pulmonary disease (COPD) patients' quality of life and symptoms improved following a patient focused integrated care facilitation model which involved identifying unmet health care needs and then providing the relevant information and advice. However, as mentioned above, lack of information regarding the cause, flare-up and mechanisms as well as the perceptions of those with the condition is a major limitation to the treatment area. Due to this, greater knowledge is required to aid the formation of better, sarcoidosis tailored treatments. Current research into Sarcoidosis is often narrowly focussed on one aspect and a wider perspective is needed due to the multi-dimensional nature of the condition. Multiple factors compiled together may lead to a trend being discovered that can be utilised to advance research, diagnosis and treatment of the condition. Patients often have their own views regarding triggers of flare ups and how to best minimise the symptoms however research thus far has overlooked their insight opting for a more clinical focus with lung function often the main measure; although lung function has been shown to not correlate with quality of life (Wirnsberger *et al.*, 1998; De Boer & Wilsher, 2012) as well as not predicting an individual's functional limitations (Kallianos *et al.*, 2015).

1.3. The role of non-pharmacological rehabilitation

Reis *et al.* (2007) argues that exercise capacity, breathlessness and quality of life can be improved significantly with appropriate rehabilitation such as upper and lower extremity exercise training in numerous pulmonary diseases, such as COPD, cystic fibrosis, thoracic cage abnormalities and bronchiectasis (Foster & Thomas, 1990; Reis *et al.*, 2007), however little has been noted in sarcoidosis (Marcelis *et al.*, 2015; Strookappe *et al.*, 2015; Naz *et al.*, 2018). Drent *et al.* (2015) argues due to wide ranging effects of sarcoidosis a multidisciplinary approach to its management is required. Generally, “high-frequency, low-impact” exercise can be recommended (Strookappe *et al.*, 2016a), however further studies to fine tune the training parameters are required. As with any chronic condition, modifications of the duration, frequency and intensity of exercise programs are vital to achieve physical benefits (Spruit *et al.*, 2005a; Swigris *et al.*, 2011; Boots *et al.*, 2011; Strookappe *et al.*, 2015).

Deconditioning often occurs within sarcoidosis patients (Mitchell *et al.*, 2012; Fleischer *et al.*, 2014). The typical symptoms of sarcoidosis; fatigue, muscle weakness and dyspnea (Wirnsberger *et al.*, 1998; Baughman, 2013), have been suggested as being pivotal in the deconditioning process (Spruit *et al.*, 2005b; Fleischer *et al.*, 2014). Fatigue has been reported in up to 70% of cases of sarcoidosis (Drent *et al.*, 2014) and cited as decreasing quality of life (Drent *et al.*, 2014; De Boer *et al.*, 2014). The symptoms lead to a decrease in an individual’s daily activities (Mitchell *et al.*, 2012) and increased perception of dyspnoea (O’Donnell 2006) that further limits patients’ participation to activities or structured exercise programmes. Dyspnoea is also associated with a lower quality of life (De Boer *et al.*, 2014), however, the ACSM (2014) argues that a correct training regime can help decrease severity and inflammation of the disease. Each symptom of sarcoidosis typically impacts on

another, where muscle weakness causes increased dyspnoea and this combination has a significant effect on exercise tolerance (Spruit, 2005b). Due to these reasons exercise is not always a possible initial treatment method, or it requires a longer time to take effect than the 6-12 weeks suggested (Reis *et al.*, 2007). These factors and the current limited research in this population, suggest that further studies into improving sarcoidosis patients' exercise tolerance and thusly quality of life are required.

1.4. Exercise Rehabilitation

Exercise is essential for the maintenance and improvement of respiratory function (Cheng *et al.*, 2003; ACSM, 2014). However, reduced physical activity is common among those with sarcoidosis (Spruit *et al.*, 2005a; Marcellis *et al.*, 2013a). The respiratory system's ability to function effects everything an individual does from walking up a flight of stairs to jogging (Battaglia *et al.*, 2015). A reduction in lung function can be the result of numerous reasons, such as; aging, chronic disease, smoking, obesity and muscular disorders such as muscular dystrophy (Ostrowski & Barud, 2006; Sharma & Goodwin, 2006). Reduced lung function has been linked to a decrease in physical activity (Serres *et al.*, 1998), which may be due to a diminished supply of oxygen delivery, and as such results in greater exertion for the same level of work and causes increased fatigue (Boutellier & Piwko, 1992). Additionally, reduced lung function results in an increase in cardiovascular mortality (Sin *et al.*, 2005); although the mechanisms are not fully known, reduced forced expiratory volume (FEV₁) has been associated with atherosclerosis and chronic low-grade systemic inflammation (Sin *et al.*, 2005).

Exercise has also been shown to improve dyspnoea, exercise tolerance, perceived fatigue and quality of life (Taylor *et al.*, 2014). Dyspnoea is the feeling of breathlessness (Antoniou, 2010); it consists of a number of sensations including tightness of the chest, increased effort to breath and air hunger (Nishino, 2011). Exercise tolerance relates to an individual's ability to exercise (Casaburi, 2006; Belfer & Reardon, 2009) and intolerance to exercise has been shown to be a strong predictor of poor quality of life (Belfer & Reardon, 2009; Drent *et al.*, 2014). The quality of life of an individual has been linked to an individuals' exercise tolerance (Drent *et al.*, 2014) however intolerance to exercise is a major symptom of pulmonary sarcoidosis (Hildebrand *et al.*, 2012), with it being the first physiological parameter impaired (Akkoca *et al.*, 2005), with a number of studies have shown sarcoidosis patients to have a decreased perceived quality of life (Hinz *et al.*, 2012; Heer *et al.*, 2013; Drent *et al.*, 2014). Vries and Wirnsberger (2005) suggest that the age range may be a factor, older populations are better at coping with chronic diseases (Loddenkemper *et al.* 1998) but as sarcoidosis peaks between 20-40 years of age (Lenner *et al.*, 2002), there is a greater struggle associated with a decline in quality of life. A limitation of quality of life testing is that it reflects someone's perception of their limitations and therefore changes between individuals (De Vries & Wirnsberger, 2005). In addition, fatigue has been recognised as a disabling symptom within sarcoidosis and listed as a reason for decreased quality of life (Drent *et al.*, 2014); it has also been found to be strongly associated to depression and therefore linked to a decreased quality of life (Leone, 2010). The NHS (2015a) argues that because fatigue cannot be physically identified, it can lead to loneliness. quality of life is made up of a number of categories and therefore any decrease/increase is multidisciplinary, an example is corticosteroid therapy used to treat sarcoidosis often increases fatigue and thus decreases quality of

life (Drent *et al.*, 2014). The NHS (2015a) state fatigue, joint pains, weight loss and night sweats are all symptoms associated with a decrease in quality of life. Therefore, therapies are required to help the condition but also prevent further reductions in quality of life.

Despite sarcoidosis affecting a significant amount of people globally and being second only to asthma in young adults for respiratory diseases (Morgenthau & Iannuzzi, 2011), there is a short supply of research into the condition as well as novel treatments such as with exercise to alleviate the primary and secondary symptoms.

2. AIMS AND OBJECTIVES

2.1. Aims

The aim of this thesis was to establish the impact of physical activity on sarcoidosis and establish trends between environment, physical activity, forms and symptoms of sarcoidosis and medical history. The project aimed to better understand sarcoidosis in relation to multiple internal & external factors such as types and symptoms of sarcoidosis (self-reported), physical activity, length of condition, quality of life, exercise performance and muscle strength.

Firstly, a systematic review (chapter four) aimed to group and better understand the outcome effects of sarcoidosis on exercise capacity, muscle strength and physical activity.

Chapters five and six aimed to establish trends in relation to environment, physical activity and personal views of day-to-day experiences. Patient involvement helped to develop priorities in clinical care and the work aimed to identify patient-reported outcome measures to establish further understanding of the phenotype and exercise capacity of patients.

The primary aim of chapter seven was to ascertain the physical activity patterns in those with pulmonary sarcoidosis with regards to perceived physical activity and actual physical activity. While the secondary aim of the study was to understand the effect of pulmonary sarcoidosis in relation to muscle strength and exercise capacity against physical activity, lung function quality of life as well as how this differs to normative values.

2.2. Objectives

- To establish multifactorial patterns within pulmonary sarcoidosis considering environment, physical activity and medical history as well as patient perceptions.
- To determine the influence and relation of real-world physical activity versus

self-reported physical activity as well as too exercise performance (aerobic) and muscle strength on symptoms and physiological outcomes.

3. GENERAL METHODOLOGIES

This chapter outlines the justification of the quantitative and qualitative research design and methods employed with consideration of research rigor and ethics.

3.1. Participants

Participants with medically diagnosed pulmonary sarcoidosis were selected, all pulmonary radiographic stages (0-IV) and length of time since diagnosis were accepted. All radiographic stages were accepted for several reasons, firstly within chapter five and six all forms of sarcoidosis were accepted and as such participants may not have had pulmonary involvement (stage 0), Siltzbach *et al.*, (1974) states 5-10% have stage 0. Furthermore, pulmonary function abnormalities have been shown not to correlate with the radiographic stage (Criado *et al.*, 2010) while radiographic stage effect on symptom severity is also unknown. A diagnosis of sarcoidosis was accepted provided the participant had been clinically diagnosed ascertained by self-reporting, self-reported sarcoidosis was accepted due to the online approach of chapter five and six as well as the population size and not wanting to discourage any potential participants. However, individuals with diagnosis of other significant respiratory disorders (asthma, COPD, lung cancer, cystic fibrosis) were excluded. For all experimental studies, participants were recruited initially through support groups and online forums from the known sarcoid population.

Exclusion Criterion was altered appropriately between the different studies', within chapter seven the inability to perform physical and/or exercise tests such as

cardiovascular disease or an injury in the past six months that inhibits their ability to perform the tests determined through completion of a sub-maximal fitness test (Appendix 1). Other exclusion factors for chapter seven included pregnancy and an inability to obtain informed consent and cognitive failure making them unable to give consent or understand questionnaires or instruction.

3.2. Equipment and Procedures

3.2.1. Physical Activity

Physical activity was assessed in several different ways across the experimental three studies' (chapters five, six and seven). Within Chapter five physical activity was based purely on self-perception and whether they considered themselves to be physically active based on the question "What are your current physical activity levels?" (adapted from current NHS guidelines of 30 minutes moderate physical activity being considered physical activity for the related day) with a follow-up question to understand whether patients considered themselves to have increased/decreased or remained the same since diagnosis of sarcoidosis (Appendix 2). For chapter six and seven the validated questionnaire of International Physical Activity Questionnaire (IPAQ; Craig et al., 2003) was utilised (Appendix 3). The IPAQ comprises of 27 items across five activity domains asked independently, the domains include job-related physical activity, transportation physical activity, housework/maintenance, recreation/leisure-time physical activity and sitting time. Benefits and thus reasons for the use of the IPAQ were multiple, firstly it has been validated across a range of diverse countries including the U.K and USA (Craig et al., 2003) where the majority of online participants had selected as their nationality and current country of residence within chapter five. Additionally, Craig *et al.* (2003) found strong correlations of test-retest reliability (mean .80) across the populations too. Further research into the IPAQ

also found similar findings of acceptable validity and test-retest ability in both healthy populations (Hagstromer *et al.*, 2006; Oyeyemi *et al.*, 2014) and lung diseases including asthma (Varlaet *et al.*, 2013) and COPD (Liao *et al.*, 2014). For chapter seven real world physical activity was also reported on top of self-reported physical activity (IPAQ) via a tri-axial accelerometer (GT3X+ accelerometer, Actigraph). The device was worn on the right hip for five days the following morning from participants first lab visit, sample rate was set to 100Hz and all participant information (gender, stature, mass, age, ethnicity) was entered including whether the right was their dominant side or not and the data was uploaded and analysed using the Freedson 1998 adult bouts algorithm within the ActiLife programme (Actigraph). Currently there is no consensus of minimum wear time required for accelerometer data (Trost *et al.*, 2005). Due to the population size and length of time with the device (five), a minimum of seven hours wear time per day was required when analysing the data, as too not discourage participation within the study and still allow for an accurate representation of a participant's day, these factors were set within the ActiLife programme before analysis to allow for the removal of any of did not meet the set criterion. The accelerometer was selected due to its accuracy of measuring real world physical activity (Sallis, 2010; Lee & Shrioma, 2014), ease of use for participants (Murphy, 2009; Sallis, 2010) and advantages over self-reporting methods such as the IPAQ (O'Neill *et al.*, 2017). Advantages included no need for participant recall and thus no over/underestimation of activity (Sylvia *et al.*, 2014). Accelerometers have also been used in previous studies within sarcoidosis (Korenromp *et al.*, 2011; Saligan, 2014) and compared/correlated against the IPAQ (Hagstromer *et al.*, 2010; Wanner *et al.*, 2016).

3.2.2. *Quality of life, Depression and Fatigue*

Quality of life, depression and fatigue were measured via three methods across the three experimental studies' (chapters five, six and seven). The sarcoidosis health questionnaire (SHQ; Cox *et al.*, 2003; Appendix 4) for quality of life, the center for epidemiologic studies depression scale for depression (CES-D; Eaton *et al.*, 2004; Appendix 5) and the fatigue assessment scale for fatigue (FAS; Michielsen *et al.*, 2003; Appendix 7) Firstly, the SHQ was selected as it has been shown to be a reliable indicator of quality of life as well as having been created and developed specifically for the condition (sarcoidosis) that the studies' focussed on (Cox *et al.*, 2003). The questionnaire comprised of 29 questions separated into three categories daily functioning, physical functioning and emotional functioning and is based on a 7-point likert scale (Cox *et al.*, 2003). Furthermore, the SHQ has been utilised across the literature too (Cox *et al.*, 2004; De Vries & Drent, 2008; De Boer & Wilsher, 2012) and as such allowed for comparison of the new findings against published literature. While the CES-D was selected due to its validity within the general population (Radloff, 1977) and prior use within sarcoidosis for indicating depressive symptoms (Chang *et al.*, 2001; Cox *et al.*, 2003; Elfferich *et al.*, 2011). The CES-D questionnaire involved 20 questions on a 4-point likert scale. Fatigue has been noted as being significant within sarcoidosis (Baughman, 2013) in terms of its affect and incidence (Drent *et al.*, 2014) and therefore was included within this study. The fatigue assessment scale was chosen due to its use within previous sarcoidosis research (Marcellis *et al.*, 2013a; Drent *et al.*, 2014; Saligan, 2014; Strookappe *et al.*, 2015) and validity within the required population (De Vries *et al.*, 2004). The FAS is a 10-item, 5-point likert scale questionnaire split equally into physical and mental fatigue questions.

3.2.3. *Muscle Strength and exercise performance (aerobic)*

Muscle strength was measured in two ways within chapter seven. The first was handgrip strength (HGS) and the second isokinetic dynamometer. Handgrip strength is a widely used method for measuring muscle strength in a range of populations, healthy and ill (Burtin *et al.*, 2015; Leong *et al.*, 2016). The reason for its regular use is its strong associations with numerous variables including mortality (Oksuzyan *et al.*, 2017), functional ability (Taekema *et al.*, 2010) and quality of life (Jakobsen *et al.*, 2010). In addition to its test-rest reliability (Haward & Griffin, 2002), as well as previously being used within sarcoidosis populations (Korenromp *et al.*, 2011; Strookappe *et al.*, 2015; Strookappe *et al.*, 2016b). Within chapter seven participants were required to hold the hand grip device with a straight arm above their head as the start position and then squeeze the device as hard as they could when bringing the device down towards their body in a side motion while maintaining a straight arm. This was conducted three times per arm (swapping sides for each test) with the mean of the three being recorded. The other method of isokinetic dynamometry was selected due to its ability to isolate specific muscle(s) (Osternig, 1986) such as quadriceps and hamstrings along with its ability to pre-set a desired speed of motion (Nimbarte *et al.*, 2009). The measurements utilised within chapter seven were based on the systematic review (Chapter four, Morton-Holtham *et al.*, ndA) with elbow flexor muscle strength (EFMS), quadricep peak torque (QPT) and hamstring peak torque (HPT) all commonly measured within the sarcoidosis literature (Korenromp *et al.*, 2011; Marcellis *et al.*, 2013b; Drent *et al.*, 2014; Marcellis *et al.*, 2015; Strookappe *et al.*, 2015; Strookappe *et al.*, 2016b). For EFMS the isokinetic dynamometry was set up as per the biodex manual (Biodex System 4, Biodex Corporation, NY, USA), this involved the attachment of the elbow adapter, aligning the shaft red dot with the relevant R or L (based on participants dominant side) and seating the participant.

Following this, the participant was aligned and moved into position before the device range of motion was recorded (maximal flexion and extension of the elbow), the device was set to 120 degrees per second due to the unknown muscle strength of participants taking part. QPT and HPT were set up in a similar fashion with their relevant adapters, again following the biodex manual. For QPT and HGS the device was set to 180 degrees per second. Across the three measurements participants were required to complete five repetitions as fast and as hard as they could, three times with a rest period between. Participants highest score were recorded. The six-minute walk distance (6MWD) is often utilised in clinical populations (Kowalska *et al.* 2012; Marcellis *et al.*, 2013a; Drent *et al.*, 2014; Zieleznik *et al.*, 2015), and is recorded via a six-minute walk test (6MWT) (Butland *et al.*, 1982; American Thoracic Society, 2002). The 6MWT was performed along a straight flat 30 metre course indoors, participants walked as fast as they felt able to for 6 minutes (Butland *et al.*, 1982). No warm-up is required, however participants were seated and rested for a minimum of 20 minutes following their muscle strength tests based on exercise-based pulmonary rehabilitation research (Vainshelboim *et al.*, 2014), additional heart rate (bpm) was checked after the 20 minutes and then at two-minute intervals until heart rate returned to baseline (ACSM, 2014). The 6MWT has been used in a wide range of studies (Alhamad *et al.*, 2010; Baughman *et al.*, 2007; Kallianos *et al.*, 2015), this is due to the increased safety in comparison to an aerobic capacity test ($\dot{V}O_{2max}$) as well as its ease of use and incorporation of low-cost equipment (American Thoracic Society, 2002).

3.2.4. Chapter five and six questionnaire development

Both chapter five (appendix 2) and six involved (appendix 6) online based questionnaires conducted via Qualtrics. An online approach was utilised due to the incidence of sarcoidosis in the U.K. (1 in 10,000; NHS, 2015a) as this allowed us to reach a wider portion of the population via a low-cost method within the U.K. and across the globe. Additionally, the majority of recruitment was via online platforms and therefore continuing the research online removed another barrier of difficulty as participants could start and complete the questionnaires direct from whatever device (smartphone, tablet, PC etc.) they saw our information on. Development of both surveys took a wide and complex approach; validated questionnaires such as the IPAQ, SHQ and FAS (Appendix 3, 4 & 8) were utilised where possible due to their validity and the ability to directly compare previous and current findings. Standardised closed ended questions such as participants smoking status, age, gender and ethnicity (appendix 2) were also utilised alongside the validated questionnaires. Participants had the ability to skip any question barring validated questionnaires once they had been started but were offered the opportunity to skip before starting them, with the questionnaire explained prior to their commitment.

Within chapter five, open-ended qualitative questions (appendix 2) were also included allowing for a further reaching and more comprehensive understanding of patients views on both barriers since sarcoidosis diagnosis as well as factors they feel are beneficial and detrimental to their health.

4. CHAPTER FOUR SYSTEMATIC REVIEW

4.1. A Systematic Review of Physical Activity and Physical Fitness in Sarcoidosis.

4.1.1. Chapter four Abstract

Background: Individuals with sarcoidosis are at risk of deconditioning and heightened non-communicable diseases through decreased muscle strength and physical activity levels. The purpose of this systematic review was to analyse published data to provide an overview of the effects of sarcoidosis on physical activity and physical fitness.

Methods: A systematic search of PubMed and Science Direct, was conducted in February 2018 following PRISMA guidelines, to determine the effects of sarcoidosis on physical activity and fitness. Experimental studies of patients with sarcoidosis in which exercise capacity, physical activity and/or strength were measured were selected.

Results: A total of twenty-two trials with 1488 participants met the inclusion criteria. These studies (published between 1986-2018) found a reduced exercise capacity, physical activity level and muscle strength within sarcoidosis patients, with those with fatigue affected more than non-fatigued sarcoidosis patients.

Conclusions: Physical activity is reduced in sarcoidosis compared to normative values, including sedentary healthy individuals. In addition, muscle strength and exercise capacity are reduced, with a large portion of individuals affected by fatigue. However, three exercise intervention trials demonstrated improved muscle strength and six-minute walk distance alongside decreased fatigue scores. Further well-designed trials with exercise prescription are needed to establish standardised exercise recommendations specific to sarcoidosis.

4.2. Introduction

Physical activity and, by extension, exercise should be a key component of everyone's life for numerous health reasons, including improved quality of life and reduced risk of non-communicable diseases (NHS, 2015b). The need for physical activity and/or exercise within chronic disease(s) is amplified due to its ability to reduce symptoms and therefore improve the health of individuals (Gleeson *et al.*, 2011). However, within chronic disease, specifically interstitial lung diseases (ILD) such as asthma, Chronic Obstructive Pulmonary Disease (COPD) and sarcoidosis (Korenromp *et al.*, 2011; Watz *et al.*, 2011; Saligan, 2014), physical activity has been recorded as lower than healthy counterparts, despite the known public health benefits for both healthy and chronically ill populations (Durstine *et al.*, 2000; Warbuton *et al.*, 2006). For example; regular physical activity within COPD has been shown to reduce not just admissions to hospital, but also all-cause mortality, as well as specifically, respiratory mortality (Garcia-Aymerich *et al.*, 2006), while physical inactivity is the fourth biggest killer across the world's population (Kohl *et al.*, 2012).

Sarcoidosis is a non-caseating granulomatous disease (Morand *et al.*, 2015), a condition that involves the inflammation of organs and tissues (Kobak, 2015). The granulomas form as a result of lymphocyte cells clustering together (Loke *et al.*, 2013). Up to 90% of sarcoidosis cases are pulmonary; however, the condition can affect numerous other locations, such as the liver, heart and skin (Saidha *et al.*, 2012). Despite sarcoidosis affecting a significant number of people globally (sarcoidosis affects 1 in 10,000 in the UK; NHS, 2015a) and being second only to asthma in young adults for respiratory diseases (Morgenthau & Iannuzzi, 2011), there is a short supply of research into the condition, as well as non-pharmacological treatments to alleviate the primary and secondary symptoms. Unfortunately, the typical sarcoidosis symptoms including fatigue, dyspnoea and chronic cough (Wirnsberger *et al.*, 1998;

Baughman, 2013), often lead to decreased levels of physical activity and the negative side effects associated with this, such as muscular atrophy like sarcopenia or cachexia (Cremers *et al.*, 2013), and as such the symptoms have been suggested as being pivotal within the deconditioning process (Fleicher *et al.*, 2014). The loss of muscle mass and strength is a major problem in sarcoidosis (Baughman, 2013) 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 (Martuseeqicz-Boros *et al.*, 2012; Baughman, 2013; Drent *et al.*, 2014) cause greater exertion during physical tasks such as stair climbing or walking (Kallianos *et al.*, 2015), which aids in the faster progression of the deconditioning process and thus compounds the above (Durstine *et al.*, 2013). Although, it is worth noting that within healthy adolescent males, only vigorous physical activity was positively associated with lower body muscle strength (Moliner-Urdiales *et al.*, 2010). Despite these findings (Moliner-Urdiales *et al.*, 2010), it is unclear whether this trend is consistent across all demographics such as age, fitness level and disease severity as those with greater muscular strength/endurance would need to elicit greater effort to improve on current levels such as progressive overloading within bodybuilders seeking increased muscle mass (Helms *et al.*, 2014). 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 (Strookappe *et al.*, 2016a), still much remains unknown, including the effect of sarcoidosis on muscle in terms of strength and mass and the mechanism behind any decrease in terms of how much can be directly associated with sarcoidosis rather than other compounding factors such as reduced physical activity.

Therefore, better understanding of exercise, physical activity and muscle strength within sarcoidosis and the other factors such as lung function and heightened inflammation that may induce changes, may help to improve the treatment and guidance available to patients and thus lead to improved health status and quality of life. A better understanding through compiling all currently available research on exercise, physical activity and muscle strength within 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 the effects of sarcoidosis on physical activity and physical fitness.

4.3. Methodology

4.3.1. Data Sources and Searches

Standardised systematic review methodology based on PRISMA (Moher *et al.*, 2009; Shamseer *et al.*, 2015) was utilised throughout this review. A search of PubMed and Science Direct was conducted in February 2018 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; Shamseer *et al.*, 2015). 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”.

4.3.2. 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.

4.3.3. 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.

4.4. Results

4.4.1. Summary of Studies

In total, 1088 studies were identified following the literature search (Figure 1). Of these studies, 22 articles were included within the review following record screening and having met the inclusion criteria. A total of 1488 sarcoidosis participants were included with studies ranging from 14 – 160 participants (Table 1; Table 2). Of the 22 studies considered, 18 measured lung function, 18 conducted a form of cardiopulmonary exercise testing (CPET; six-minute walk test (6MWT), symptom linked bicycle test etc.), nine assessed muscle strength, eight evaluated fatigue and, two considered physical activity levels within pulmonary sarcoidosis through direct measurement, utilising an accelerometer (Korenromp *et al.*, 2011; Saligan, 2014). Four studies also looked at depression/depressive symptoms (Spruit *et al.*, 2005; Korenromp *et al.*, 2011; Saligan, 2014; Naz *et al.*, 2018), and four studies used healthy matched controls alongside sarcoidosis participants (Spruit *et al.*, 2005a; Korenromp *et al.*, 2011; Kowalska *et al.*, 2012; Braam *et al.*, 2013), while three evaluated the effects of rehabilitation treatment programmes (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015; Naz *et al.*, 2018; Table 2).

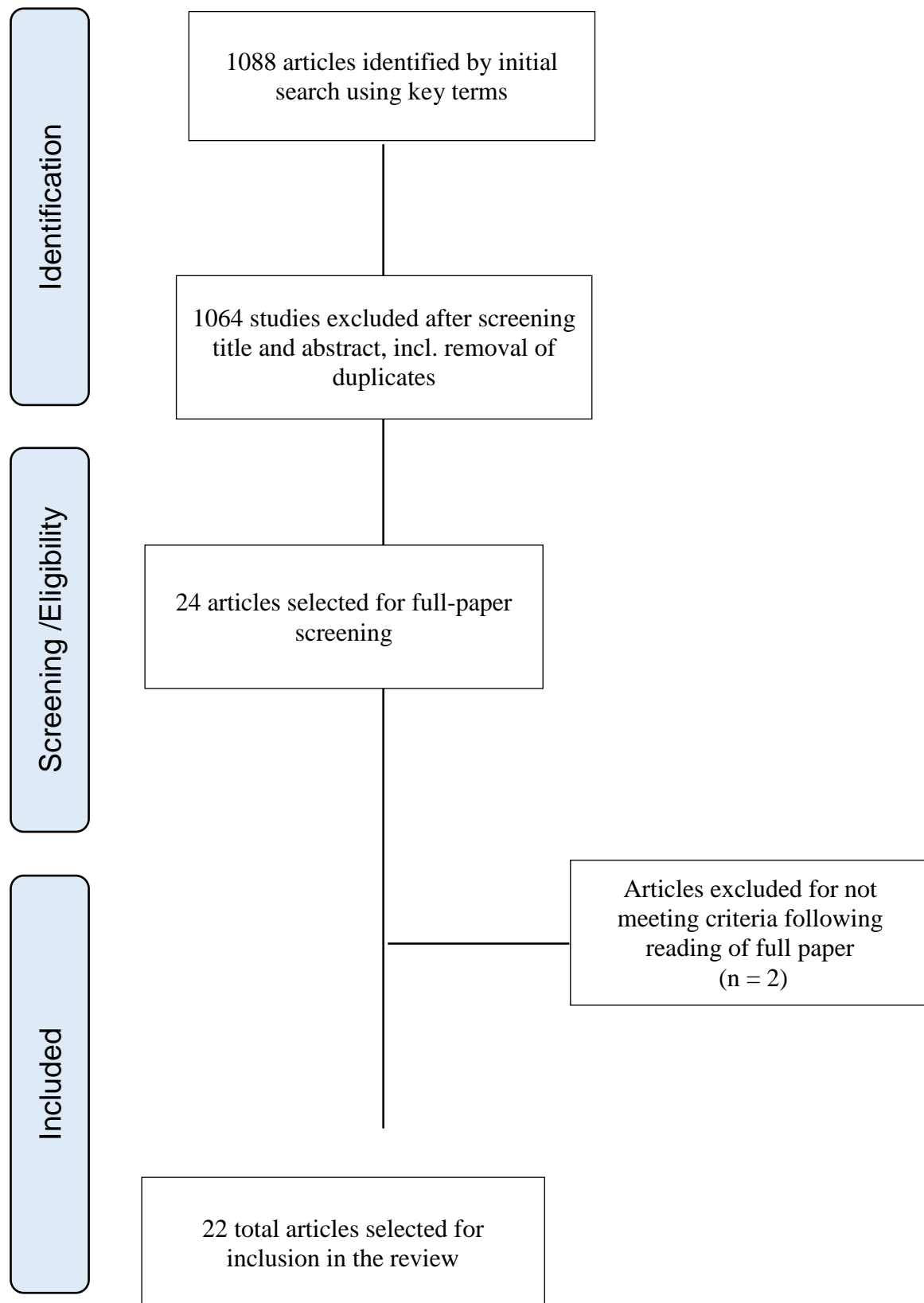


Figure 1. Flow diagram of systematic review search process of study selection.

4.4.2. *Exercise Testing*

Some form of exercise testing was conducted in 18 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 such as warm-up protocol, nutrition intake prior to testing and verbal encouragement frequency and volume were not adjusted for. However, this latter aspect should be noted as a general limitation within sarcoidosis research, due to the lack of specific knowledge regarding confounding factors. 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. The quality of evidence was moderate, though the differing tests and measurements used make it hard to draw clear meaningful conclusions from the exercise testing beyond pulmonary sarcoidosis having a detrimental effect on exercise/functional performance.

4.4.3. *Physical Activity*

Only two studies measured physical activity both via accelerometer’s (Korenromp *et al.*, 2011; Saligan, 2014), where one (Saligan, 2014) compared sarcoidosis patients to age, gender and race-matched, sedentary healthy controls and found sarcoidosis patients to be less physical active and more fatigued in addition to lower functional performing outcomes. The second study (Korenromp *et al.*, 2011) found physical

activity to be reduced in fatigued sarcoidosis patients against non-fatigued sarcoidosis patient values 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 (Korenromp *et al.*, 2011) and participants grouped as fatigued following a self-reported questionnaire recorded lower physical activity than their non-fatigued peers. Additionally, confounding factors were eluded to, but never fully explained, likely due to shortcomings in the body of knowledge, as previously discussed in relation to exercise testing.

4.4.4. *Muscle Strength*

Of the nine studies associated with measurement of muscle strength, elbow flexor muscle strength and quadricep peak torque (Spruit *et al.*, 2005a; Korenromp *et al.*, 2011; Marcellis *et al.*, 2013b; Marcellis *et al.*, 2015; Strookappe *et al.*, 2015; Strookappe *et al.*, 2016b) received the most attention, although hamstring peak torque and handgrip strength were also measured and reported within one (Marcellis *et al.*, 2013b) and three studies (Spruit *et al.*, 2005; Korenromp *et al.*, 2011; Strookappe *et al.*, 2015), 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 reported variables than observed in the exercise testing. Muscle strength was shown to be reduced in comparison to normative values for those with sarcoidosis across all of the nine studies. Marcellis *et al.* (2013b) 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 (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015; Naz *et al.*,

2018) 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, for example (Korenromp *et al.*, 2011) found fatigued participants scored significantly lower than their non-fatigued counter-parts although other confounding factors have not been effectively determined. All rehabilitation studies (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015; Naz *et al.*, 2018) 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, quadriceps (Marcellis *et al.*, 2015), leg strength (Naz *et al.*, 2018) and elbow flexion percentage (Strookappe *et al.*, 2015), despite differing approaches to rehabilitation.

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

References	Participants (N=)	Age Mean age or Range (yrs)	Factors studied	Main Findings	Summary of Findings
Athos et al. (1986)	39 Male = 12 Female = 27	Mean: 39 Range: 21-75	<ul style="list-style-type: none"> • Lung Function (FVC, FEV₁, MVV, DLCO). • Exercise Capacity (Incremental symptom limited exercise test ($\dot{V}O_2$)) • Dyspnoea (MRC) 	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • 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. (1992)	20 Male = 6 Female = 14	Mean: 43 Range: 24-58	<ul style="list-style-type: none"> • Lung function (FVC) • Exercise capacity (Symptom limited maximal exercise testing (peak $\dot{V}O_2$)) • Heart rate 	<ul style="list-style-type: none"> • Forced vital capacity averaged $88 \pm 12\%$ 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. 	<ul style="list-style-type: none"> • 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. (2001)	48	Mean: 41	<ul style="list-style-type: none"> • Lung function (FEV₁, FVC), • Exercise Capacity (6min 	<ul style="list-style-type: none"> • No significant association between radiographic stage and FEV₁/FVC%, $\dot{V}O_2$ 	<ul style="list-style-type: none"> • 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))	<p>max, AT, HRR, BR, or $VE_e/\dot{V}CO_2$ AT.</p> <ul style="list-style-type: none"> • 11 participants exercise blood gas measurement was not recorded due to technical issues regarding arterial access. 	<ul style="list-style-type: none"> • Remains a lack of a true non-invasive “gold standard” for measuring the extent of disease.
Akkoca et al. (2005)	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"> • Lung function, • Exercise Capacity (CPET) 	<ul style="list-style-type: none"> • 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). 	<ul style="list-style-type: none"> • 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.
Spruit et al. (2005)	25 fatigued sarcoidosis Male = 15 Female = 10 21 healthy control Male = 13 Female 8	Mean: 42	<ul style="list-style-type: none"> • Lung function (FVC, FEV₁, TLC) • Muscle Strength (HGS, QPT) • Exercise Capacity (6MWT, maximal incremental exercise test) 	<ul style="list-style-type: none"> • The controls scored significantly (P<0.05) better for all measurements than the sarcoidosis group. • Sarcoidosis: • HGF%pred = 87 • QPT%pred = 67 • 6MWD =605 	<ul style="list-style-type: none"> • Muscle weakness occurs within sarcoidosis (mechanism(s) currently unknown) but associated with fatigue. • Fatigue is also associated with diminished QOL and exercise capacity.

			<ul style="list-style-type: none"> • QOL (SF-36, EQ-5D) • Depression (HADS) 		
Alhamad et al. (2010)	59 Male = 17 Female = 42	Mean: 48	<ul style="list-style-type: none"> • Lung function (FVC, FEV₁, TLC) • Exercise Capacity (6MWT) 	<ul style="list-style-type: none"> • Mean lung function parameters for FVC, FEV₁ 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. 	<ul style="list-style-type: none"> • 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. • Pulmonary hypertension and fibrosis associated with reductions to 6MWD.
Korenromp et al. (2011)	75 patients in clinical remission Male = 33 Female = 42	Non-fatigued mean: 48 Fatigued mean: 46	<ul style="list-style-type: none"> • Lung Function • Muscle Strength (HGS & QPT) • Physical Activity (Accelerometer) • Fatigue (CIS) • QOL (sf-36) • Depression(BDI) • Anxiety (SCL-90) 	<ul style="list-style-type: none"> • Lung function within normal range for all participants. • 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. 	<ul style="list-style-type: none"> • Fatigue is a frequent severe and chronic issue within clinical remission patients. • 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.

				<ul style="list-style-type: none"> Significantly worse depression and QOL scores among fatigued participants. 	
Kowalska et al. (2012)	<p>47 (22 with cardiac involvement)</p> <p>Males = 19 Females = 28</p> <p>As well as 18 healthy volunteers for control</p>	Mean: 48	<ul style="list-style-type: none"> Exercise Capacity (6MWT oxygen saturation, heart rate) 	<ul style="list-style-type: none"> Cardiac sarcoidosis with treatment: 6MWD = 514.81 ± 91.22m. Maximum desaturation = $3.5 \pm 3.7\%$. Cardiac sarcoidosis (no treatment): 6MWD = 567.09 ± 119.06. Maximum desaturation = $1.9 \pm 1.7\%$. No cardiac involvement (no treatment): 6MWD = 20.8 ± 96.22. Maximum desaturation = 2.36 ± 2.87. 	<ul style="list-style-type: none"> 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.
Marcellis et al. (2013b)	<p>92</p> <p>Male = 62 Female = 28</p>	Mean: 46	<ul style="list-style-type: none"> Exercise Capacity (6MWT) Muscle strength (EFMS, HPT, QPT) Fatigue (FAS). 	<ul style="list-style-type: none"> 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 %) <p>Fatigue reported in 86 and 77% of participants.</p>	<ul style="list-style-type: none"> 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.
Marcellis et al. (2013c)	160 Male = 97 Female = 63	Mean: 41	<ul style="list-style-type: none"> • Lung Function (DLCO) • Exercise Capacity (CPET blood gas analysis) 	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • 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.
Braam et al. (2013)	20 sarcoidosis and 10 healthy volunteers for control Male = 16 Female = 14	Healthy Control: 35 Sarc Mod fatigue: 41 Sarc severe fatigue: 37	<ul style="list-style-type: none"> • Exercise Capacity (CPET, Symptom limited incremental exercise test ($\dot{V}O_2$, RER)) • Blood pressure, HR, pulse oximetry, cytokines, stress hormones, ACE and CK (before, after and 3 days after). 	<ul style="list-style-type: none"> • Sarcoidosis w/Mod fatigue: $\dot{V}O_2$ max = 270 ± 67.4 • Sarcoidosis w/Severe fatigue: $\dot{V}O_2$ max = 187 ± 54.2 	<ul style="list-style-type: none"> • Severe fatigue is not correlated with biomarkers nor a reduction of exercise capacity and is only consistently measured via self-reported patient feedback/outcomes.

de Boer et al. (2014)	33 Male = 17 Female = 16	Mean: 48	<ul style="list-style-type: none"> • Lung Function (FEV₁, FVC, DLCO) • Exercise Capacity (MSWT, CPET) 	<ul style="list-style-type: none"> • Mean FEV₁ = 75.7% predicted • Mean FVC = 88.7% predicted • Mean DLCO = 71.4% predicted • MSWT correlated with peak oxygen uptake during CPET 	<ul style="list-style-type: none"> • 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. (2014)	88 Sarcoidosis Male = 61 Female = 28 62 healthy controls	Mean: 46	<ul style="list-style-type: none"> • Lung Function (FEV₁, FVC, DLCO) • Exercise capacity (6MWT) • Muscle strength (EFMS, HPT, QPT) • Fatigue (FAS) • QOL (WHOQOL-BREF) 	<ul style="list-style-type: none"> • Sarcoidosis: FEV₁ (%pred) = 84 • FVC (%pred) = 98. • DLCO (%pred) = 76. • 6MWD Female = 551. • 6MWD Male = 606. • EFMS (%pred) Female = 97.7. • EFMS (%pred) Male = 89.9. • QPT180 (%pred) Female = 84.9. • QPT180 (%pred) Male = 81.4. • HPT180 (%pred) Female = 86.4. • HPT180 (%pred) Male = 81.9. • FAS = 28.6. 	<ul style="list-style-type: none"> • 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.

				<ul style="list-style-type: none"> • QOL reduced in comparison to healthy controls. 	
Saligan (2014)	14 pulmonary sarcoidosis participants as well as 13 age, sex and race matched.	Not stated	<ul style="list-style-type: none"> • Exercise Capacity (6MWT) • Muscle Strength (MVC/kg) • Physical activity (Accelerometer) • Fatigue (FAS) • Depression (HAM-D) 	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • There were significant differences in physical activity, exercise capacity, muscle strength, depression and fatigue scores between sarcoidosis patients and healthy control.
Zieleznik et al. (2015)	74 Sarcoidosis Male = 53 Female = 21 30 Healthy controls	Mean: 45 Range: 29-71	<ul style="list-style-type: none"> • Lung function (FEV₁, FVC) • Exercise Capacity (6MWT) • Fatigue (FAS) 	<ul style="list-style-type: none"> • FEV₁ = 3.18±0.82. • FEV₁ (%) = 90.4±13.1. • FVC = 4.16±1.1. • FVC (%) = 98.9±13.9. • 6MWD (m) = 555.9±91.5. • FAS = 22.9±7.3. 	<ul style="list-style-type: none"> • Fatigue did not correlate with lung function scores or 6MWD. • 43.06% sarcoidosis participants reported no fatigue compared to 76.67% for the control group.

Kallianos et al. (2015)	<p>83</p> <p>Male = 31 Female = 52</p> <p>Patients were grouped according to their radiological stages: Stage I (n=43), Stages II–III (n=31), and Stage IV (n=9).</p>	<p>Mean: 58</p> <p>Range: 36-84</p>	<ul style="list-style-type: none"> • Lung function (FEV₁, FVC, TLC DLCO) • Exercise Capacity (CPET Standard protocol). 	<ul style="list-style-type: none"> • FEV₁, 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. 	<ul style="list-style-type: none"> • 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. (2016b)	<p>146</p> <p>Male = 89 Female = 57</p>	<p>Mean: 47</p>	<ul style="list-style-type: none"> • Lung Function (FEV₁, FVC, DLCO) • Exercise Capacity (6MWT, SRT) • Muscle strength (EFMS, HGS) • Fatigue (FAS) 	<ul style="list-style-type: none"> • FEV₁ (%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. • EFMS (pred%) 100.5±20.4. • FAS 30.2±9.0. 	<ul style="list-style-type: none"> • Exercise capacity partly predicts fatigue. • Fatigue is a substantial problem among sarcoidosis patients, which is affected by many variables.

Chenivesse et al. (2016)	130 Male = 78 Female = 52	Mean: 49 Range: 26-78	<ul style="list-style-type: none"> • Lung Function (FEV₁, FVC, TLC, DLCO) • Exercise Capacity (6MWT) 	<ul style="list-style-type: none"> • FEV₁(% pred) – 80. • FVC (% pred) – 92. • TLC (% pred) – 90. • DLCO (% pred) – 71. • 6MWD – 450. 	<ul style="list-style-type: none"> • Normal DLCO is a good predictor of the absence of severe gas exchange impairment. • The stage 4 group had lower FEV₁, FVC, DLCO scores, in addition to a reduced $\dot{V}O_2$ Peak compared to the other stages.
Mirsaeidi et al. (2016)	108 Male = 21 Female = 87	Mean: 54	<ul style="list-style-type: none"> • Lung function (FEV₁, FVC, DLCO, VC, TLC, FRC) • Exercise Capacity (6MWT) 	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • 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; FEV₁ – 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 – quadriceps 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.

Table 2. Exercise intervention Studies.

References	Study Design	Sample Size (age / gender)	Factors studied	Exercise programme	Main Findings
Marcellis <i>et al.</i> (2015)	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"> • Lung function (FVC, FEV₁, DLCO) • Exercise Capacity (6MWT, Submaximal bicycle test) • Muscle Strength (X-RM leg extension, elbow flexor microFET) • Fatigue (FAS) • QOL (WHOWOL-BREF), • Dyspnoea (MRC, Borg RPE) 	<p>13-week programme (1h x 3 / week)</p> <p>Aerobic endurance: 60% maximal walking speed of 6MWT or cycling at 50% Wmax for 20-30 minutes, increased 3%/ week.</p> <p>Strength Training: 3 sets of 8-10 reps, at 40% multiple-repetition maximum increased 3% /week.</p>	<ul style="list-style-type: none"> • Lung function not reported post-treatment. • ↑ 6MWD. • ↑HR (submaximal). • ↑ Quadricep strength. • ↓ FAS score. • ↑MRC and WHOQOL-BREF.
Strookappe <i>et al.</i> (2015)	Intervention: pre/post measurement design.	90 participants (49 completing treatment, 41 opted not partake in treatment).	<ul style="list-style-type: none"> • Lung function (FVC, FEV₁, DLCO) • Exercise Capacity (SRT, 6MWT) • Muscle strength (HGS, EFMS via microFET) • Fatigue (FAS) • Borg RPE, Dyspnoea (modified Borg) 	<p>12-week programme (1h x 2 / week)</p> <p>Aerobic endurance: Treadmill or stationary cycling at 50-60% peak work.</p> <p>Strength Training: 3 sets of 15-20 reps on 6-8 different exercises at 13-15 Borg RPE.</p>	<ul style="list-style-type: none"> • Lung function unchanged. • ↑ 6MWD. • ↑SRT. • ↑ Elbow flexion. • ↑ HGS. • ↓ FAS Score. • RPE & Dyspnoea scores stable.
Naz <i>et al.</i> (2018)	Intervention: pre/post measurement design.	18 participants (9 undergoing intervention, 9 controls with usual care).	<ul style="list-style-type: none"> • Lung function (FVC & FEV₁) • Exercise Capacity (6MWT) • Muscle Strength (back and leg dynamometer) • Fatigue (FSS) 	<p>12-week programme (2 x week)</p> <p>Aerobic endurance: Treadmill and stationary cycling at 80% & 70% peak speed of 6MWT, increased within symptom tolerance</p>	<ul style="list-style-type: none"> • Lung function unchanged. • ↑ 6MWD. • ↑ Leg Strength. • ↓ FSS Score. • ↑ SGRQ.

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| <ul style="list-style-type: none"> • QOL (SF-36, SGRQ) • Borg Dyspnoea (modified Borg) • Depression and Anxiety (HADS) | <p>when continuous 15min exercise achieved</p> <p>Strength Training:</p> <p>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"> • 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; FEV₁ – 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.

4.5. Discussion

This systematic review identified 22 studies that investigated the influence or levels of physical fitness, physical activity and muscle strength of people with sarcoidosis. The key findings of the review are decreased levels of exercise capacity, physical activity and muscle strength within the sarcoidosis population compared to a healthy population or predicted normative data, with those recorded as fatigued showing greater impairment than non-fatigued sarcoidosis patients (table 1). Unfortunately, there is yet to be an extensive range of controlled and standardised research focussing on exercise within pulmonary sarcoidosis from which clear outcomes can be utilised for treatment policy and to optimise 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 22 studies recorded some sign of impairment as recorded by the variables tested in terms of exercise capacity and physical activity (table 1 & 2). Most prevalent were the reduction in lung function (Alhamad *et al.*, 2010), and by extension $\dot{V}O_2$ peak (Chenivesse *et al.*, 2016), and reduced distance within the six-minute walk test (Marcellis *et al.*, 2013b) or other exercise test performance outcome such as modified shuttle walk test (de Boer *et al.*, 2014) and $\dot{V}O_2$ max (Medinger *et al.*, 2001). 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 pros and cons, an example, the use of cycling which leads to fatigue of the quadriceps (Fletcher *et al.*, 2001) a known muscle group reduced within sarcoidosis (de Boer *et al.*, 2014), with cycling inexperienced participants recording $\dot{V}O_2$ max 10-15% lower than treadmill testing (Fletcher *et al.*, 2001). Whereas, ramp protocols on a treadmill rely on estimating functional capacity

via an activity scale and can lead to under- and over-estimating of functional capacity and lead to premature termination of the exercise test (Fletcher *et al.*, 2001). One issue across the current literature is the lack of understanding of the mechanisms associated with the decreased findings in comparison to predicted and normative values, where the research reported thus far, lacks sufficient depth in the analysis of the findings. For example, Kallianos *et al.* (2015) found exercise capacity to be limited and the first physiological parameter impaired, yet the mechanism(s) responsible for this impairment were not investigated despite the researchers noting both ventilatory and cardiocirculatory factors may 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.* (1992) 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 (Sietsema *et al.*, 1992). 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 (Chenivesse *et al.*, 1995) despite Marcellis *et al.* (2013c) 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 differences observed 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 exercise 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 (Sietsema *et al.*, 1992; Medinger *et al.*, 2001).

4.5.1. *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 (Baughman, 2013) and has been reported to occur in up to 70% of cases (Korenromp *et al.*, 2011). Fatigue is compounded by the secondary effects it has, such as decreased quality of life (Korenromp *et al.*, 2011; Marcellis *et al.*, 2013c) and psychological distress (Korenromp *et al.*, 2011). 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.* (2011) 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. While Zieleznik *et al.* (2015) found fatigue not to correlate with lung function or distance covered within the six-minute walk test. In addition to this, Saligan (2014) found sedentary healthy controls scored statistically significantly lower ($P < 0.01$) 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 (Lassek *et al.*, 2009). Much like the mechanisms behind the reduction in exercise performance, the understanding of the mechanisms behind fatigue remain unknown. Strookappe *et al.* (2016b) 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 (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015; Naz *et al.*, 2018) found that the exercise programmes significantly improved fatigue, by scores of 2.7 and 4.2 respectively, via the fatigue assessment scale (FAS) (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015) and 7, via the fatigue severity scale (FSS) (Naz *et al.*, 2018).

4.5.2. *Physical Activity*

Physical inactivity even within healthy populations has been shown to be a complex and a serious issue (Sparling *et al.*, 2000). Research into physical activity is severely limited within pulmonary sarcoidosis at present, despite the known benefits for the general population including decreased levels of non-communicable diseases as well as lower risk of depression (NHS, 2015b), although physical activity within sarcoidosis has been associated with fatigue (Korenromp *et al.*, 2011) as a confounding factor. Garcia-Aymerich *et al.* (2006) 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 (Garcia-Aymerich *et al.*, 2006). Many physical inactivity factors are known or suggested and thus implementing changes to improve physical activity over a sustained period of time remains difficult (Kohl *et al.*, 2012). Interestingly, Egan *et al.* (2012) found despite pulmonary rehabilitation in COPD 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 behaviour. Korenromp *et al.* (2011) 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 is very a useful insight into sarcoidosis patients' lives and suggests having to work might increase physical activity although job status, hours, or industry occupation were not recorded within the study. A limitation of Saligan's (2014) 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.* (2011) study.

4.5.3. Muscle Strength

Muscle strength is associated with functional limitations (Hairi *et al.*, 2010). Handgrip strength is a useful indicator of quality of life in the elderly (Musalek *et al.*, 2017) as well as young adults (Jakobosen *et al.*, 2010), it is also correlated with mobility (Jakobosen *et al.*, 2010) with poor handgrip strength correlated with lower functional scores Taekema *et al.* (2010). A number of studies demonstrated a reduction in muscle strength within pulmonary sarcoidosis (Spruit *et al.*, 2005a; Korenromp *et al.*, 2011; Marcellis *et al.*, 2013b; Saligan, 2014). Marcellis *et al.* (2013c) 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.* (2016b) found elbow flexor muscle strength to be $100.5 \pm 20.4\%$ of the predicted value using normative data for a healthy population. Handgrip strength also showed mixed results ranging from 87% to 96.8% predicted (Spruit *et al.*, 2005a; Strookappe *et al.*, 2016b) 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 also be beneficial to have comparable data through use of a standardised method for testing muscle strength in sarcoidosis. This review found both isokinetic dynamometry (Marcellis *et al.*, 2013b), back and leg dynamometer (Naz *et al.*, 2018) and microFET (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015) were utilised within the current literature. Muff *et al.* (2016) 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 into why muscle strength was and was not negatively affected by pulmonary sarcoidosis, nevertheless, Marcellis *et al.* (2015), Strookappe *et al.* (2015) and Naz *et al.* (2018) did show significant improvements in muscle strength following completion of their intervention programmes. Participants within Marcellis *et al.*'s (2015) study demonstrated quadricep strength lift ability increased by 10.7kg compared to baseline, Naz *et al.*, (2018) showed a median improvement of 10kg for leg strength while Strookappe *et al.* (2015) recorded a 7.2% increase in elbow flexor muscle strength. Based on this, it can be suggested deconditioning plays a key role in the reduction of muscle strength.

4.5.4. Exercise Rehabilitation

Although exercise-based rehabilitation also referred to as pulmonary rehabilitation (Evans *et al.*, 2010) is known to be beneficial within COPD and asthma, there is a shortage of research into its effect on sarcoidosis. McCarthy *et al.* (2015) 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 (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015; Naz *et al.*, 2018). 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.* (2015) 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.* (2015) check immediately following completion of the structured programme. However, Forkan *et al.* (2006) 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 (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015; Naz *et al.*, 2018) had differing methodologies for the exercise programme; Marcellis *et al.* (2015)

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.* (2015) 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. While Naz *et al.* (2018) 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 an optimal exercise programme for improvements is yet to be known and should be a future research aim. However, Strookappe *et al.* (2015) participants 6MWD improved greater (70m) than Naz *et al.* (2018) and Marcellis *et al.* (2015) participants (40m and 34.6m). Strookappe *et al.* (2015) study also recorded a decrease of 3.8 for their FAS score compared with 2.7 by participants of Marcellis *et al.* (2015) while Naz *et al.* (2018) use of the FSS is not directly comparable, the FAS is more widely used (Marcellis *et al.*, 2013c; de Boer *et al.*, 2014; Saligan, 2014; Zielesnik *et al.*, 2015; Strookappe *et al.*, 2016b). Additionally, Marcellis *et al.* (2015) study found a statistically nonsignificant ($P>0.05$) improvement in elbow flexor muscle strength, which cannot be attributed to the programme due to the limited improvement, whereas Strookappe *et al.* (2015) participants did significantly improve ($P<0.05$) with an

increase of 7.8 of percentage of predicted value (Strookappe *et al.*, 2015). The reasons are unclear, however may be partly explained by working at a higher peak work load aerobically throughout the programme as well as during strength training with Borg RPE used as the measure than 40% multiple-repetition maximum. A limitation of Naz *et al.* (2018) study was the exclusion of upper limb muscle strength testing although their respective measure (leg strength) did improve statistically significantly by 10kg ($P<0.05$), much like Marcellis *et al.* (2015), which reported a quadricep strength increase of 10.7kg.

4.5.5. *Future Directions*

The results of the present systematic review can help to direct future research. Due to the current lack of knowledge and evidence regarding sarcoidosis and exercise, there are a number of desirable areas to be explored. One key factor to explore is exercise and physical activity as a potential rehabilitation option outside of the current pharmacological routes, based on the promising outcomes reported thus far (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015; Naz *et al.*, 2018). Additionally, a future aim should be to identify and create optimised non-pharmacological treatment plan, 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 (NICE, 2017). To achieve these aims, future research will need to be conducted to explore the mechanisms behind the reduction of muscle strength, lung function and exercise performance, as well as any other associated confounding variables such as fatigue (De Kleijn *et al.*, 2009 and impaired heart rate response to exercise (Delobbe *et al.*, 2002). There is a need to determine and understand trends in fatigue and lifestyle factors with the aim to utilise this information to improve quality of life, by understanding the mechanisms, and strategies to address resulting factors

such as impaired gas exchange and heart rate, can be developed. Another useful future direction would be the research supported 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 across the current research.

4.6. Conclusion

In conclusion, the current review has identified that sarcoidosis has been shown to have a detrimental effect on various factors related to exercise such as lung function, quality of life, exercise capacity and physical activity, to name a few. The mechanisms behind these negative effects are complex and remain unknown at present. There is a need for further in-depth studies looking at these variables and their mechanisms as well as greater focus on exercise rehabilitation for improved patient care.

5. CHAPTER FIVE

5.1. Investigation of Factors Related to Quality of Life, Depression and Physical Activity within Sarcoidosis.

5.1.1. Chapter five Abstract

Background: Individuals with sarcoidosis are at risk of numerous mental and physical detriments compared to their healthy counterparts, due to multifactorial reasons. An online cross-sectional observational survey was undertaken to investigate factors influencing these detriments such as fatigue, dyspnoea & deconditioning aiming to provide participant-specific characteristics. These included opinions on current and future treatment options, alongside their fatigue and physical activity levels, including reference to changes in their physical activity due to sarcoidosis. Analysis aimed to inform future direction for sarcoidosis research.

Methods: A online survey using Qualtrics, comprising of validated questionnaires measuring quality of life and depression, in addition to closed quantitative and open-ended qualitative questions surrounding physical activity, employment, smoking and other related daily life questions.

Results: Multiple regression revealed the CES-D and number of symptoms as predictors of quality of life ($R^2 = .509$). The mean number of symptoms reported was 3.79, females reported lower levels of quality of life and higher depressive scores via the CES-D. The majority of both genders reported being either inactive (no activity) or less than two bouts of physical activity a week, in addition 73.79% of the study participants reported decreased levels of physical activity since diagnosis, 41.55% also changed jobs or stopped working due to the disease. While only 38.36% and 25% of the population had been suggested physical activity or diet as a potential treatment method, themes identified as potential improvement

to current care and quality of life were more knowledgeable doctors regarding the condition and better understanding of lifestyle factors such as diet, physical activity and smoking status.

Conclusions: Quality of life appears to be affected by depression and number of symptoms a patient has, physical activity is also detrimentally affected following diagnosis of sarcoidosis and affects both personal and professional life, patient's themes identified included poor lifestyle and heightened levels of stress and anxiety as areas that worsened symptoms and quality of life. More research is required looking at the role and effect of lifestyle on the condition including the number of and severity of the disease as well as depression and quality of life. Taught coping methods for stress and anxiety may also be beneficial for patients and thus needs investigation within the population.

5.2. Introduction

Sarcoidosis involves granulomatous inflammation of organs and tissues (Saidha *et al.*, 2012), which is pulmonary in the majority of cases (90%) but can affect any part of the body (Saidha *et al.*, 2012). Sarcoidosis involves the formation of granulomas via the clustering of lymphocyte cells (National institute of Health, 2013a). The symptoms of sarcoidosis are wide-ranging and can be severe and disabling (Drent *et al.*, 2014), with typical symptoms including fatigue, dyspnoea, chronic cough and muscle weakness (Baughman, 2013). Unfortunately, sarcoidosis suffers from a chronic shortage of research, when compared to other interstitial lung diseases such as asthma or COPD, especially with regards to alternative treatment strategies such as exercise and physical activity. This lack of research is coupled with current researchers' focus solely on results of tests such as lung function, at the expense of patient feedback on the condition, despite lung function being shown to be a poor indicator of overall

health including primary and secondary symptoms within sarcoidosis (Karetzky & McDonough, 1996). Therefore, the objective of the current study and its outcomes are driven by informed patient experiences from a wide range of patients from numerous geographical locations and backgrounds, thus allowing for an improved perspective and understanding of the issues experienced by those with sarcoidosis, including issues related to quality of life and the negative affect of symptoms. Exercise is frequently suggested as a method to improve sarcoidosis symptoms and boost overall health (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015), however both these suggestions currently suffer the same pitfall of limited to no research, both within pulmonary sarcoidosis and the other forms of sarcoidosis (Morton-Holtham *et al.*, ndA). The ACSM (2014) argues that a correct training regime can help decrease severity and inflammation of the disease, with preliminary studies supporting this statement (Holland *et al.*, 20013; Marcellis *et al.*, 2015). However, these specialised training regimes currently have numerous limitations including the lack of an optimised regime/different regimes for the vast range of population with sarcoidosis, the need for further empirical proof across a larger range of the population, the need for qualified practitioners for substantial amounts of the regimes and the current lab-based approach for participants. For exercise to be seriously considered as a “Miracle Cure” as stated by the NHS (2015b) further research must be conducted across a wider range of the population with varying type, time and intensity. The individual must also be considered with regards to their preferences for a truly effective long-term treatment due to the difficulties of people adhering to exercise regimes despite knowing the benefits and consequences. Seefeldt *et al.* (2002) notes successful interventions individualised, accounting for a participant’s personal views of fitness, their needs and outcomes as well as allowing for their control of an activity.

Physical inactivity is common among those with sarcoidosis (Spruit *et al.*, 2005a; Korenromp *et al.*, 2011). Saligan (2014) found sarcoidosis participants had statistically significant lower levels ($P < 0.05$) of physical activity than their healthy age, gender and race matched controls despite the recognised benefits for chronically ill populations (Durstine *et al.*, 2000; Warburton *et al.*, 2006), although one limitation of Saligan's research is the exclusion of physical activity being recorded on weekends and thus leaves an area for future research. However, it is too simplistic to single out sarcoidosis alone as the reason for this as physical activity has been shown to be a complex issue across all populations including healthy and ill, alike (Sparling *et al.*, 2000). Currently sarcoidosis patients' views on physical activity, exercise, diet and their potential benefits are unknown, with exercise and diet often marginalized within this disease to off the cuff remarks therefore collecting participant views alongside current and prior-to-diagnosis levels of physical activity and diet across this period is key to building a platform for future research based on empirical data over the current hearsay. Alongside physical inactivity those with sarcoidosis have been shown to have a higher incidence rate of depression than the general population (Hinz *et al.*, 2012), Saligan (2014) found higher depression scores for sarcoidosis participants than healthy age, gender and race matched controls. Much like physical inactivity, depression is a complex and multifaceted issue, which is likely to be contributed to by both sarcoidosis and non-sarcoidosis factors. One possible contributing factor is frequent hospital visits (Kersnik *et al.*, 2001) such as those associated with steroid treatment due to the required monitoring of a patient. Another factor is the reduced skeletal muscle strength within sarcoidosis (Marcellis *et al.*, 2013a; Saligan, 2014; Marcellis *et al.*, 2015; Strookape *et al.*, 2015) which has been linked to depression and decreased

quality of life (Spruit *et al.*, 2005b). A further sarcoidosis factor is fatigue; a major issue within sarcoidosis (Baughman, 2013). Fatigue has been associated with depression (Leone, 2010) and decreased quality of life (Drent *et al.*, 2014). Korenromp *et al.* (2011) found sarcoidosis patients with fatigue scored worse for depression and quality of life than their non-fatigued counterparts despite both groups being in clinical remission and thus highlights the importance of patient feedback, as fatigue is a self-reported variable (Gawron, 2017). Chang *et al.* (2001) found following adjustments of steroid treatment and non-sarcoidosis factors such as race and income, increased dyspnoea scores predicted depression as a sarcoidosis factor. Whereas the external factors predicting depression were the female gender and limited access to medical care. Currently, there is a lack of knowledge regarding the effect physical activity and/or exercise would have on depression and whether depression scores would improve primarily due to increased physical activity/exercise or whether the improvements of other symptoms associated with depression, such as fatigue, muscle strength and dyspnoea due to higher levels of physical activity/exercise, would then lead to improved depression as a secondary factor. This research will allow for the gathering of the views and thoughts of physical activity and exercise within the population and thus aid in the understanding of the complex role of physical activity and exercise and therefore inform on future research which potentially improve the implementation and maintenance of physical activity and exercise.

Treatment is currently predominantly focused on the use of steroids (Jennifer & Rashcovsky, 2004) and corticosteroid use within sarcoidosis has been linked with diminished quality of life (Cox *et al.* 2004; Drent *et al.*, 2014), with prednisone the most used drug (National institute of Health, 2013). Alongside a decreased quality of

life there are numerous other side effects including osteoporosis, weight gain and increased risk of infection (Poetker & Reh, 2010; Liu *et al.*, 2013). In addition to this, Alhamad *et al.* (2010) found sarcoidosis patients receiving corticosteroids had a decreased exercise performance via the six-minute walk test than their peers not on medication. The reasons for this are unclear, i.e. are they on a treatment of steroids due to needing them and thus already have a decreased exercise performance than the study's counter parts or has the use of the steroids decreased their exercise performance further, nonetheless Grutters and Van der Bosch (2006) suggest the decreased performance is another side effect of the corticosteroid use. There are numerous issues and limitations associated with current treatment practices with uncertainty surrounding the best treatment plan for the different symptoms/issues within the populations, further worsened by the complex nature of the condition. Therefore, research is needed focusing on limiting the side effects of steroid use as the current treatment method while there needs to be a drive towards better treatment methods through the creation of new and novel methods as well as optimizing other treatments currently available. Greater understanding of the symptoms and side effects caused by both sarcoidosis and treatment via patient feedback combined with quantitative scores will allow for a more informed approach to future research.

Therefore, this study aims to establish trends within the quality of life of sarcoidosis in relation to environment, diet, PA and personal views of day-to-day experiences. This is the first study to seek future direction and areas of research via qualitative feedback, patient involvement will help prioritise clinical care and we aim to identify patient-reported outcome measures to establish improved understanding of the condition including, nutritional status and exercise capacity of patients.

5.3. Methodology

5.3.1. Participants

An online survey of 149 participants with self-reported sarcoidosis were voluntarily recruited via online sarcoidosis forums and support groups. Exclusion criteria extended to anyone with an additional interstitial lung disease such as asthma and chronic obstructive pulmonary disease (COPD) as well as those unable to give consent. The study consisted of 189 participants, 40 participants were removed due to incomplete surveys (<50% survey completion removed), 149 participants answers were analysed (n = 44 male, n = 103 female, n = 2 unanswered), ethnicity was also recorded (n = 143 Caucasian, n = 3 Afro-Caribbean, n = 3 mixed Caucasian and Afro-Caribbean).

5.3.2. Design, Equipment and Procedures

The study design was a cross-sectional online observation study investigating quality of life in sarcoidosis and the relationship to the different factors affecting it such as symptoms, types of sarcoidosis, physical activity level and anthropometric data. Questions were formed of likert scales, multiple selection and open-ended questions (Appendix 2). The participants firstly had to read and accept the informed consent for the study, this then lead them onto self-reported anthropometric questions for them to answer including age (Years) mass (kg), stature (cm), gender and ethnicity. Following this they answered independent questions on their symptoms, length & types of sarcoidosis, mould status of their homes, smoking status, medication, physical activity as well as whether physical activity or diet had been suggested as a potential treatment method, two example questions are “Considering your condition, on average, what are the main symptoms you experience. Please select all that apply.” and “Has physical activity been mentioned to you as an option for improving your symptoms by a

physician / GP?” quality of life was measured via the sarcoidosis health questionnaire (SHQ; Cox *et al.*, 2003; Appendix 4) and the presence of depressive symptoms via center for epidemiologic studies depression scale (CES-D; Eaton *et al.*, 2004; Appendix 5). In the section following the two validated questionnaires participants answered close-ended questions on their geographical location, property and employment status & history. The concluding section of the survey comprised of open-ended qualitative questions (Appendix 2) involving the effect of sarcoidosis on their life, what they believe improves as well as negatively affects their symptoms and their ideas regarding which areas of sarcoidosis would most benefit from further support, one example question is “What factors do you believe improve your sarcoidosis symptoms?”.

5.3.3. Data Analysis

The data were analysed via SPSS 24.0 (IBM Corp, Armonk, New York). An exploratory data analysis was first completed; the data were normally distributed and therefore met parametric assumptions, following this a multiple regression was conducted between the different variables. Content analysis was conducted viva NVivo Pro 11 (QRS International, Doncaster, Australia) for the qualitative elements of this study. The content analysis involved the compiling and reviewing of all statements, firstly all questions and their answers were uploaded into Nvivo, the answers to individual questions were then all analysed separately, and their answers highlighted and labelled as nodes (sub-categories) following this the different nodes were grouped based on their overall theme.

5.4. Results

5.4.1. Participant's Characteristics

Of the 189 participants who started the study, 40 were removed due to incomplete surveys. Table 3 displays the characteristics of the participants who partook in the study. Only two participants were aged 30 or younger while the most populous age range was 51-60 (35%). The vast majority of participants self-identified as Caucasians (95%) and female participants outnumbered males by more than double the male quota (69% versus 30%).

Table 3. Characteristics of Participants.

Age (Yrs)	No.	Percentage (%)
21-30	2	1.34
31-40	28	18.79
41-50	45	30.20
51-60	52	34.90
61+	22	14.77
Total	149	100.00
Gender		
Male	44	29.53
Female	103	69.12
Not reported	2	1.34
Total	149	100.00
Ethnicity		
Caucasian	143	96.00
Afro-Caribbean	3	2.00
Mixed Caucasian & Afro-Caribbean	3	2.00
Total	149	100.00

Table 4 highlights the lifestyle and employment of the population overall as well as by gender. Inactive was the most selected level of physical activity for both genders (39%), with the percentage of selected category decreasing as the level of physical activity increased. The majority of participants reported decreased levels of physical activity since diagnosis (73.79%) however males reported a higher percentage of stable physical activity levels than females (32.56 and 12%, respectively) although no significant difference was found ($P>0.05$). Physical activity and diet were not

suggested as a treatment to the majority of participants (61.64 & 75%, respectively). Smoker was the least populous selection (5.59%) in the smoking status category, however there was only a 1% difference between ex-smokers and non-smokers (46 & 47%, respectively), while ‘15-19 cigarettes per day’ was the most selected for males (31.25%) and ‘10-14 per day’ for females (22.64%). People’s homes never having mould (61.38%) was close to double its nearest group of ‘sometimes’ (33.79%).

Table 4. Physical activity and lifestyle factor data.

Physical Activity	All*	Male		Female		
	No.	Percentage (%)	No.	Percentage (%)	No.	Percentage (%)
Inactive	56	38.62	17	39.53	38	38.38
< twice week	39	26.90	12	27.91	26	26.26
3-5 week	38	26.21	10	23.26	28	28.28
5+ Week	12	8.28	4	9.30	7	7.07
Total	144	100	43	100	99	100
Change in PA since diagnosis						
Increased	12	8.28	3	6.98	9	9.00
Decreased	107	73.79	26	60.47	79	79.00
Same	26	17.93	14	32.56	12	12.00
Total	145	100.00	43	100	100	100
PA suggested as treatment						
Yes	56	38.36	18	41.86	38	37.62
No	90	61.64	25	58.14	63	62.38
Total	146	100.00	43	100	101	100.00
Diet suggested as treatment						
Yes	36	25.00	8	18.60	28	27.72

No	110	75.00	35	81.40	73	72.78
Total	146	100.00	43	100	101	100
Smoke Status						
Smoker	8	5.59	1	2.33	7	7.00
Ex-Smoker	63	44.06	17	39.53	46	46.00
Non-smoker	72	50.35	25	58.14	47	47.00
Total	143	100.00	43	100	100	100.00
Amount per day						
1 to 4	11	15.49	1	6.25	9	16.98
5 to 9	13	18.31	2	12.50	10	18.86
10 to 14	16	22.54	4	25.00	12	22.64
15-19	15	21.13	5	31.25	10	18.87
20-24	11	15.49	2	12.50	9	16.98
25+	5	7.04	2	12.50	3	5.66
Total	71	100.00	16	100.00	53	100.00
Mould Status						
Always	7	4.83	3	7.14	4	3.96
Sometimes	49	33.79	13	30.95	36	35.64
Never	87	61.38	26	61.90	61	60.40
Total	145	100.00	42	100	101	100

Asterisk (*) two participants included within all did not report their gender. PA = Physical Activity.

Table 5 highlights the employment status and change since diagnosis. Full-time employment was confirmed for less than half of the population (47.92%) despite being the most selected answer, although over a fifth (23.24%) had indicated that they had stopped working due to the sarcoidosis.

Table 5. Showing employment status and change since diagnosis.

Current employment						
Employed full time	69	47.92	22	52.38	47	47.00
Employed part time	16	11.11	0	0.00	16	16.00
Unemployed looking for work	4	2.78	1	2.38	3	3.00
Unemployed not looking for work	8	5.56	3	7.14	5	5.00
Unemployed receiving disability living allowance or equivalent	26	18.06	9	21.43	16	16.00
Student	1	0.69	0	0.00	1	1.00
Retired	20	13.89	7	16.67	12	12.00
Total	144	100	42	100.00	100	100.00
Employment change since diagnosis						
Stayed the same	69	48.59	19	46.34	50	50.51
Changed due to Sarcoidosis	26	18.31	9	21.95	17	17.17
Changed non-related to Sarcoidosis	14	9.86	3	7.32	10	10.10
Stopped working due to Sarcoidosis	33	23.24	10	24.39	22	22.22
Total	142	100	41	100.00	99	100.00

As seen in Table 6, the types and symptoms of the population are presented overall and by gender. Pulmonary was the most common form of sarcoidosis (97.97%) with lymph nodes and skin, second and third (49.32% & 33.11%, respectively). Fatigue, dyspnoea and joint/bone pain were the most selected symptoms (92.62%, 77.18% & 70.47%, respectively).

Table 6. Showing the type and symptoms of Sarcoidosis.

Type of Sarcoidosis	All*		Male		Female	
	No.	Percentage (%)	No.	Percentage (%)	No.	Percentage (%)
Pulmonary	145	97.97	42	95.45	101	99.02
Skin	49	33.11	10	27.73	37	36.27
Heart	14	9.46	1	2.27	13	12.75
Eye	29	19.54	9	20.45	19	18.63
Endocrine	5	3.38	3	6.82	2	1.96
Nervous	18	12.16	3	6.82	14	13.73
Bone/Joint	43	29.05	11	25.00	30	29.41
Lymph	73	49.32	1	2.27	49	48.04
Organ	23	15.54	4	9.09	19	18.63
Other	17	11.49	2	4.56	15	14.71
Total	148	100.00	44	100.00	102	100.00
Symptoms						
Fatigue	138	92.62	40	90.91	96	93.20
Chronic Cough	71	47.65	25	56.81	45	43.69
Dyspnoea	115	77.18	35	79.55	79	76.70
Joint/bone pain	105	70.47	27	61.36	77	74.76
Rashes	54	36.24	11	25.00	41	39.8`
Sore eyes	52	34.90	12	27.27	39	37.86
Other	30	20.13	9	20.45	21	20.39
Total	149	100	44	100.00	103	100.00

Asterisk (*) two participants included within all did not report their gender.

Table 7 highlights the quality of life as measured by the sarcoidosis health questionnaire (SHQ) and the sub-scales of emotional, physical and daily functioning (score range 1-7), as well as depression score, measured via the center for epidemiologic studies depression scale (CES-D). A mean score of 3.41 was recorded for the SHQ while CES-D mean score was 25.75, females however scored lower on the SHQ and CES-D (3.34 & 26.14) than their male counterparts (3.58 & 24.86) and both genders scored lowest on emotional functioning (3.31 & 3.08, respectively) out of the three domains for the SHQ.

Table 7. Showing the quality of life and depression scores as well as standard deviation split by gender (No significant difference between genders; $P>0.05$; $n= 145$ for SHQ & 141 for CES-D).

Gender	EF \pm SD	PF \pm SD	DF \pm SD	SHQ \pm SD	CES-D \pm SD
Male	3.31 \pm 1.11	3.88 \pm 1.01	3.56 \pm 1.07	3.58 \pm 0.94	24.86 \pm 10.64
Female	3.08 \pm 0.88	3.64 \pm 0.80	3.28 \pm 0.93	3.34 \pm 0.75	26.14 \pm 9.46
Combined	3.15 \pm 0.96	3.71 \pm 0.88	3.37 \pm 0.98	3.41 \pm 0.82	25.75 \pm 9.85

EF = Emotional Functioning, SD = standard deviation, PF = Physical Functioning, DF = Daily Functioning, SHQ = Sarcoidosis Health Questionnaire, CES-D = Center for Epidemiologic Studies Depression Scale.

Table 8 highlights the multiple regression findings for the number of symptoms self-reported. Quality of life, fatigue, number of types of sarcoidosis and self-reported physical activity levels were found to be significant predictors of number of symptoms, accounting for 46.1% of the variance.

Table 8. Showing the multiple regression findings with number of symptoms as the dependent variable.

Model	R ²	B	Sig.
1			
Constant		6.89	.001
QOL	.287	-.91	.001
2			
Constant		8.17	.001
QOL		-.76	.001
Fatigue	.380	-1.67	.001
3			
Constant		7.46	.001
QOL		-.70	.001
Fatigue		-1.67	.001
No. Types	.420	.18	.003
4			
Constant		7.10	.001
QOL		-.75	.001
Fatigue		-1.77	.001
No. Type		.19	.001
PA levels	.461	.30	.002

QOL = quality of life, No. Types = number of types of sarcoidosis, PA levels = physical activity levels. Dependent variable = number of symptoms.

Table 9 shows quality of life, number of symptoms and self-reported fatigue were found to be significant predictors of self-reported physical activity levels, accounting for 9.4% of the variance within the data.

Table 9. Multiple regression predictors of self-reported physical activity levels.

Model	R ²	B	Sig.
1			
Constant		1.32	.001
QOL	.031	.20	.037
2			
Constant		.27	.637
QOL		.34	.003
No. Symptoms	.066	.15	.023
3			
Constant		-.61	.386
QOL		.33	.004
No. Symptoms		.21	.004
Fatigue	.094	.67	.040

QOL = quality of life, No. Symptoms = number of symptoms. Dependent variable = physical activity levels.

Table 10 shows the R squared, beta and the significance of the variable within the model. The CES-D was the biggest predictor of quality of life ($R^2 = .397$) while both variables CES-D and number of symptoms had a significant effect on the model ($P = 0.001$).

Table 10. Displaying the predictors of quality life via multiple regression findings.

Model	R ²	B	Sig.
1			
Constant		4.76	.001
CES-D	.397	-.05	.001
2			
Constant		5.29	.001
CES-D	.509	-.04	.001
No. Symptoms		-.21	.001

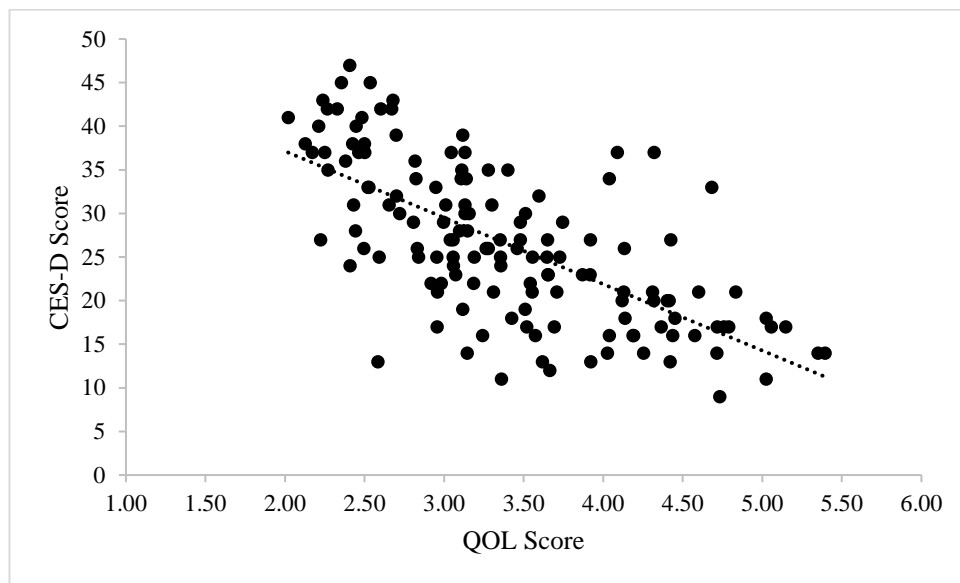
CES-D = Center for Epidemiologic Studies Depression Scale, No. Symptoms = number of symptoms. Dependent variable = quality of life.

Table 11 highlights the findings of the multiple regression into predictors of self-reported fatigue. Number of symptoms and physical activity change since diagnosis were found to be significant predictors, explaining 23.8% of the variance within the data.

Table 11. Multiple regression predictors of self-reported fatigue.

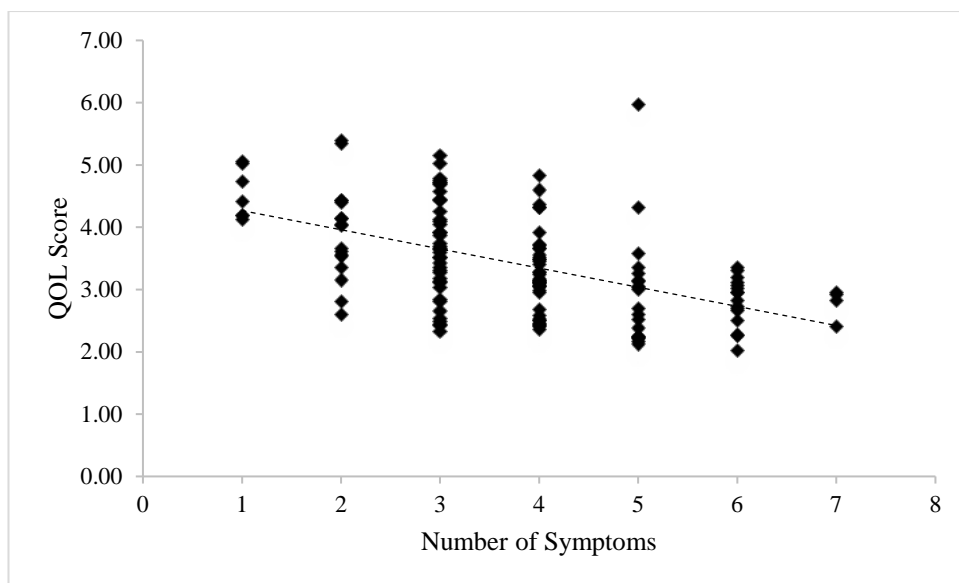
Model	R ²	B	Sig.
1			
Constant		1.40	.001
No. Symptoms	.196	-.08	.001
2			
Constant		1.25	.001
No. Symptoms		-.08	.001
PA change	.238	.09	.006

No, Symptoms = number of symptoms, PA change = physical activity change since diagnosis. Dependent variable = fatigue.



QOL = Quality of Life, CES-D = Centre for Epidemiologic Studies Depression Scale

Figure 2. Correlation between quality of life and CES-D (P = 0.001).



QOL = Quality of Life

Figure 3. Correlation between number of symptoms and quality of life.

5.4.2. Content analysis

Table 12 highlights the key themes identified via the content analysis as well as interesting quotes surrounding these themes.

Table 12. Showing themes identified via content analysis alongside definitions and quotes.

Themes	Quotes
Limiting of activities/tasks	<ul style="list-style-type: none"> - I am unable to do most/all of my hobbies - unable to complete many normal day to day tasks - The slightest effort results in struggling to breathe. - I am less active and I have barely enough energy to accomplish necessary tasks - Physically I am not able to work or do many normal things.
Exercise, Physical activity and Diet	<ul style="list-style-type: none"> - I sought help from the hospital dieticians while receiving treatment and this was successful - Advice on mobilisation exercise programs that would help inflamed joints - Swimming has helped immensely - On good days I get in as much as physically possible - Swimming has helped my breathing, - Light exercise seems to help improve some of my pain
Poor Lifestyle	<ul style="list-style-type: none"> - Poor diet. Physical inactivity - Smoking and I don't know how to quit

	<ul style="list-style-type: none"> - I don't have the money to eat the way I should be eating on a better diet - Irregular eating patterns - Airborne particles such as icing sugar, flour, dust if sweeping
Lack of Understanding	<ul style="list-style-type: none"> - Friends and family have no idea of all the problems related to sarcoidosis - Poor understanding from employer who is an NHS trust - Lack of clear information on the web/from medical professionals - Consultants, I never get to see the same one and I always feel that they are winging it - Family's lack of understanding can be awful as are doctors - The lack of awareness in society - Dr who treats the disease and understands the complexity
Anxiety and Stress	<ul style="list-style-type: none"> - Mindfulness is helping control anxiety and stress responses - Staying away from stress - Absence of stress - Stress has major impact on my Sarcoid symptoms - Stress also exasperates my symptoms
Importance of Sleep	<ul style="list-style-type: none"> - Feel that if I could sleep properly I would feel better able to cope - Lack of sleep due to pain - Minimum of 7 1/2 hours sleep a night - More sleep during the day. - Sleep and the right care
The Role of Medication	<ul style="list-style-type: none"> - Prednisolone has helped reduce problems - If I feel more symptomatic or get an infection, I double my steroids for 48 hours which helps - The higher dose of steroids but would rather not take them cause of the side effects - Put on prednisolone my symptoms have improved massively - Higher dose steroids but don't want them as weight ballooned literally

5.5. Discussion

The primary aim of this study was to determine and better understand trends relating to the quality of life of sarcoidosis patients in terms of their physical activity, diet and environment and their personal views of living with the disease.

5.5.1. Participant characteristics

Only two participants within this study identified as being under 30 years of age, Bresnitz *et al.*, 1983) states 20-40 years old as the age range for the predominant onset period of sarcoidosis, however a later study by Baughman *et al.* (2001) found peak onset of sarcoidosis associated with 35-45 years of age. The data collected better supports Baughman *et al.* (2001) with the age range 41-50 and 51-60 being the most selected (30.20% & 34.90%, respectively). Although, no definitive answers can be made from the data as the analytics of the support groups used for recruitment remains unknown and this elder population selection may simply represent the make-up of the support groups. One limitation of this study is the lack of depth around age and better understanding may have been achieved through participants stating their current age or using smaller age ranges. Additionally, age at diagnosis was not recorded and thus this is a limitation as the recorded time since diagnosis lacks the required depth although age at diagnosis itself does not necessarily associate or correlate with the age of sarcoidosis onset due to various reasons. Reasons include misdiagnosis as well as a lack of symptoms on onset (Belfer & Stevens, 1998), however the data collected (time since diagnosis) still has value and aids in the analysis and understanding of other relevant variables. Of note, a greater proportion of females participated in the research (69.12%). Birnbaum and Rifkin (2014) state females are more likely to develop sarcoidosis and although the reasons for this are unknown, hormones have been suggested to be a compounding factor (Birnbaum & Rifkin, 2014). However, the representation of the genders within this study are likely to have been affected due to the recruitment methods as women may make up a greater proportion of the support groups approached. Deans *et al.* (1998) and Krizek *et al.* (1999) both found that females were more likely to join cancer support groups, outnumbering males 3 to 1

(Dean *et al.*, 1998) and these findings may be applicable to sarcoidosis support groups too. Much like age and gender, ethnicity may also have been influenced by the demographic of the support groups. 96% self-identified as Caucasian despite the incidence rate being suggested as 10 times higher for the black population than their white counterparts (Birnbaum & Rifkin, 2014), although Kamangar *et al.* (2017) state much more conservative figures with 11 per 100,000 for Caucasians, rising to 34 per 100,000 in black populations, specifically African-Americans. The utilised support groups were based within the United Kingdom and the United states of America and this may in part explain the predominant Caucasian selection, as Northern Europeans and African Americans have been suggested as having the highest incident rate globally (Iannuzzi *et al.*, 2007; Sharma, 2008). Within breast cancer, those of higher socio-economic status are more likely to seek health information regarding their condition online (McMullan, 2006) and this trend may transfer across to other conditions including sarcoidosis and warrants further investigation. Following demographic (ethnicity, gender & age) adjustments, lower socio-economic status has been linked to increased severity at presentation despite socio-economic status not affecting sarcoidosis risk (Iannuzzi *et al.*, 2007).

5.5.2. *Types of sarcoidosis and symptoms*

The majority of participants selected pulmonary sarcoidosis (97.97%), with lymph node involvement second (49.32%) and skin third (33.11%), and despite nine categories listing different forms of sarcoidosis, 11.49% still selected “other”. The mean number of types of sarcoidosis recorded was 2.83, highlighting the varied and complex nature of the condition and thus the difficulty in understanding and treating it. This study’s findings are consistent with current literature as Iannuzzi *et al.* (2007) state that more than 90% of sarcoidosis cases have pulmonary, lymph node, skin

involvement or a combination of these different types. The complexity of sarcoidosis is further represented through the recorded symptoms. Fatigue as a symptom was reported at higher than expected levels (92.62%) among the participants, Drent *et al.* (2012) states 50-70% of patients report fatigue, dyspnoea (77.18%) was also found to be higher than previous studies. Yeager *et al.* (2005) reported dyspnoea in 51% of the population while de Boer *et al.* (2014) reported the symptom in 64% of participants, joint involvement has been reported between 14-38% (Wilcox *et al.*, 2000; Awada *et al.*, 2003). However, within this study joint/bone pain was recorded at 70.47% and made up one of the top three selected symptoms, while 20.13% selected “other” in addition to the six other listed symptoms. It is unclear why symptoms have been reported with higher frequency than reported in previous literature, however the increased levels of reported symptoms may be the reason itself as participants with greater severity and number of symptoms may be more inclined to participate than those with milder manifestations of the disease. The mean number of symptoms was 3.79, following a stepwise multiple regression quality of life was shown to be best predictor of number of symptoms ($R^2 = .287$; $R = .536$, $P = .001$). Quality of life, fatigue, number of types of sarcoidosis and self-reported physical activity levels accounted for 46.1% of the variance within the data ($R^2 = .461$) and that the model was a significant predictor of number of symptoms, $F(4, 137) = 29.29$, $P = .001$. All variables contributed significantly to the model ($P < 0.05$). Therefore, a decrease in symptoms or symptom severity is a possible method for improving the quality of life of those with sarcoidosis. Fatigue has been shown to be associated with quality of life, Korenromp (2014) found patients identified as fatigued scored significantly worse for quality of life (short form-36) than non-fatigued patients. Following a stepwise multiple regression patient reported fatigue was found not to be a predictor of quality

of life and via a bivariate correlation between the two variables shown to have only a weak correlation. It is worth noting however that fatigue was not quantified such as by completing the fatigue assessment scale (FAS) and was simply selected from a range of symptoms, therefore the level of fatigue may vary widely between participants. Boer *et al.* (2014) found dyspnoea was also associated with a lower quality of life score, although both symptoms have been shown not to be predicted by lung function (Boer *et al.*, 2014; Strookappe *et al.*, 2016b). However, fatigue has been correlated with dyspnoea and stated as being a valid indicator for dyspnoea level within sarcoidosis (Jastrzebski *et al.*, 2015). Fatigue is known to be a multifactorial issue (Strookappe *et al.*, 2016b), causes include treatment (e.g. corticosteroid use), inflammation and comorbidities (Gerke *et al.*, 2015), and the other symptoms listed are also known to be multifactorial (Jastrzebski *et al.*, 2015), therefore the relationship and interaction between the number of symptoms and quality of life is likely to be multifaceted by both primary and secondary outcomes of the symptoms such as physical activity (Korenromp, 2011) and depression (Chang *et al.*, 2001).

5.5.3. Lifestyle

Despite the known benefits of physical activity and a healthy balanced diet, sarcoidosis patients are not being suggested these as a way to better manage and treat their condition from qualified professionals, with only 38.36% having been suggested utilising physical activity/exercise while suggestion of diet as a method drops to 25% of the study's population. The majority of participants reported being sedentary and physically inactive, participants selected inactive or active twice or less a week for 65.52% of the study's population (Table 4), which is consistent with previously reported findings for the general population, such that 33% of 19-64-year olds in the U.K. in 2016 did not meet current U.K. physical activity guidelines (British Heart

Foundation, 2017). This figure however does not take into account people's health and therefore may overestimate levels of inactivity for healthy individuals. The reasons for this are numerous and complex, involving those associated with sarcoidosis, such as symptoms including fatigue and dyspnoea (Korenromp *et al.*, 2011; Baughman, 2013), and general population issues, including both environment and social factors such as childcare and support from family and friends ((Seefeldt *et al.*, 2002). A limitation of this study was the lack of space for participant views on their physical activity habits. A multiple regression did not reveal physical activity levels or physical activity change since diagnosis as predictors of quality of life. Although, following a bivariate correlation physical activity change since diagnosis did produce a weak correlation (.374, $P = .001$). One possible reason for this could be that the ability to perform physical activity has a greater effect on someone's perceived quality of life than current levels of physical activity. Physical activity is an area where there is a need for greater focus and insight within sarcoidosis and the general population as physical inactivity currently is the fourth biggest cause of mortality globally (Kohl *et al.*, 2012). The need for greater focus on understanding physical inactivity and methods to increase activity levels is further shown when considering 73.79% of this study's sarcoidosis population reported a decrease in physical activity since diagnosis. While the decrease is unlikely to be attributed solely to the onset of sarcoidosis, due to external factors affecting the general population such as age (Milanovic *et al.*, 2013), it does however demonstrate the need for a disease-specific physical activity programme to aid in the maintenance and improvement of physical activity. Additionally, health-related behaviours have been shown to track from childhood into adulthood thus highlighting the need for early intervention in relation to physical activity and attitudes towards it (Kohl & Cook, 2013). Self-efficacy, for example has

been shown to be a predictor of physical activity participation (Park *et al.*, 2014) and as such has been suggested as a focus for improving physical activity over a sustained time period (Green *et al.*, 2006; Park *et al.*, 2014). As such, self-efficacy within sarcoidosis should have a greater focus to aid understanding and development of a disease specific physical activity questionnaire. Seefeldt *et al.* (2002) note that successful interventions are? individualised, accounting for a participant's personal views of fitness, their needs and outcomes as well as allowing for their control of an activity. Sarcoidosis does play an important role as highlighted by Saligan's (2014) study showing lower levels of physical activity than age, gender and race-matched, sedentary healthy controls. The reduction in physical activity levels comparatively against healthy controls and pre-sarcoidosis levels, is likely affected by a combination of primary and secondary symptoms of the condition, such as fatigue (Korenromp *et al.*, 2011) and deconditioning (Fleischer *et al.*, 2014). Within this study, quality of life, number of symptoms and fatigue were found to be predictors of physical activity levels, accounting for 9.4% ($R^2 = .094$, $P < 0.05$) of the variance within the data. All variables contributed significantly to the model (< 0.05). While number of symptoms and physical activity change since diagnosis were found to be predictors of fatigue, accounting for 23.8% ($R^2 = .24$, $P < 0.001$) of the variance. Number of symptoms ($B = -.08$) and physical activity change since diagnosis ($B = .09$) both contributed significantly to the model ($P = 0.001$ and $P = 0.006$, respectively). Although, this may be down to the unvalidated method employed for data collection of perceived activity levels. It is also worth noting that improving exercise capacity appears not to be enough in raising activity levels. Egan *et al.* (2012) found despite improvements to exercise capacity following pulmonary rehabilitation within COPD, physical activity post-treatment remained unchanged from baseline data. Through the content analysis

of the patient's qualitative feedback from open questions regarding barriers, detriments, beneficial factors relating to sarcoidosis and future areas for treatment and care of the condition. Poor lifestyle alongside stress and anxiety were identified as themes for worsening management of symptoms and quality of life. Barriers included a lack of understanding of peers, family and employers, limitation of previous ability to conduct activities such as exercise, housework, work, playing with children, exemplified through the quote "I am unable to do most/all of my hobbies" in addition to poor integration of medical care, a major issue due to the diverse nature of the condition. Themes identified as future areas for improving patients care, symptoms and quality of life were lifestyle improvements including diet, physical activity, smoking status and hours of sleep, more knowledgeable doctors regarding the condition in terms of specialists and initial GP care and a reduction of stress and anxiety. One patient noted "Mindfulness is helping control anxiety and stress responses" and as such is an area that requires attention and could potentially improve treatment in a relatively short period of time in comparison to the development of better suited medication. Merkes (2010) found mindfulness-based stress reduction improved patients' ability to cope with symptoms, quality of life and enhanced health outcomes in chronic diseases including rheumatoid arthritis, chronic fatigue syndrome and type 2 diabetes.

While smoking status falls outside of diet into lifestyle, it is an area with interesting findings within sarcoidosis as the incidence rate of the disease has been stated as being higher among non-smokers (Valeyre *et al.*, 1988), although within this study non-smokers made up 50.35% while ex and current smokers consisted of 49.65% (table 4). It has been suggested that smoking provides some form of protective role against

developing the disease (Peros-Golubicic & Ljubic, 1995), alternatively, smoking may reduce the severity of the disease (Valeyre *et al.*, 1988). The reasons for this remain unknown however the immunosuppressive properties of tobacco have been suggested (Sopori, 2002) as a potential reason, additionally the recognised detrimental effects of smoking may lead to smokers not seeking medical help and therefore leading to their under representation within the sarcoidosis population (Peros-Golubicic & Ljubic, 1995). However, within this study incident rate between non-smokers and ex/current smokers varies by 0.35%, no correlation or significant difference ($P>0.05$) was reported between amount smoked per day and quality of life including the three subscales and thus questions the above research, a larger population sample may lead to a clearer understanding. This lack of consensus highlights the need for further study within the condition with regards to smoking status. Due to the lack of knowledge about the formation and development of the condition as well as its progression, an extensive multi-dimensional outlook is required to build an initial base of information.

Several environmental factors have been identified within sarcoidosis and suggested as increasing the risk of the disease, despite the mechanisms behind this remaining unclear. Such factors include metal work, education, transportation industry and high humidity occupations (Kucera *et al.*, 2003). Kucera *et al.* (2003) stated mould as an occupational factor, although mould is associated with both work buildings and homes. Terceli *et al.* (2011) found fungal exposure in the homes of Slovenian sarcoidosis patients to be significantly higher than their control counter parts, for both newly diagnosed and recurrence groups, (33.6 N-acetylhexosaminidase (NAHA) U/m^3 and 39.9 NAHA U/m^3 , respectively versus 10.0 NAHA U/m^3). The current study reported participants as 'always' or 'sometimes having' mould within their homes

38.62% of the time (Table 4). A limitation however is the lack of testing to confirm amount and type of mould per home as there are numerous different forms of mould, with different forms associated with different reactions such as allergic and disease activity (Chapman, 2005). Additionally, the study only focused on current homes and therefore does not consider mould involvement at earlier stages of their life or whether their place of work has mould, for example Bush *et al.* (2006) states hypersensitivity pneumonitis requires a high-dose or prolonged exposure and as such is linked to occupation. Terceci *et al.* (2011) findings warrant further research into the effects of mould within patient's homes and whether this is a trend reported across geographical locations, a limitation of this research however is the lack of genetic evaluation involved, as the onset of sarcoidosis has been suggested as being from a combination of genetic and environmental factors (Luisetti *et al.*, 2000). Participants employment for full/part time stood at 59.03% with a further 13.89% retired, 18.06% were unemployed and receiving disability living allowance or equivalent. Of note, 41.55% of participants reported changing or stopping jobs due to their sarcoidosis (table 4). While the majority of those with the condition worked, the odds of receiving disability payments was only marginally better than 1 in 5 (18.06%; table 4) and thus suggests a disabling effect of the disease. It is worth noting, however, that it was not reported whether the disability living allowance was being received exclusively for sarcoidosis or not and participants may have had other conditions limiting their ability to work. As such, this area requires further research.

5.5.4. *Quality of life /Depression*

Quality of life and depression was measured via SHQ and CES-D, respectively. The mean SHQ score was 3.41, although males scored higher (3.58) than females (3.34), which agrees with previous research showing that females with sarcoidosis have a lower quality of life than their male counterparts (De Vries *et al.*, 1999). Females also scored slightly lower for depressive symptoms, although there was no significant difference ($P > 0.05$) for both quality of life and CES-D, in addition to the quality of life sub-scales (Table 7). A multiple regression was carried out to investigate whether number of types & symptoms, fatigue, age and depressive score (CES-D) could significantly predict participants quality of life. The results indicated CES-D and number of symptoms account for 50.9% of the variance and that the model was a significant predictor of quality of life, $F(2,142) = 73.66$, $P = 0.001$. Both CES-D ($B = .043$) and number of symptoms ($B = .208$) significantly contributed to the model ($P = 0.001$). There are likely to be numerous reasons for this, depression is associated with a reduced quality of life much like a number of sarcoidosis symptoms such as fatigue, dyspnoea and reduced exercise capacity (Korenromp *et al.*, 2011; Drent *et al.*, 2014; Saligan, 2014). These same reasons for a reduction in quality of life are also likely to contribute to higher depressive scores. Chang *et al.* (2001) found increased dyspnoea was a predictor of depression within sarcoidosis. Nowik *et al.* (2017) reported improvements to depression scores within sarcoidosis following pulmonary rehabilitation including at one year follow up. Nowik *et al.* (2017) findings highlights the potential benefit of pulmonary rehabilitation within sarcoidosis alongside improvements to exercise capacity, dyspnoea, fatigue and quality of life shown within asthma (Trevor *et al.*, 2015), idiopathic pulmonary fibrosis (Swigris *et al.*, 2011) and COPD (Reis *et al.*, 2007; Spencer & McKeough, 2010). As we as highlighting the complexity and interaction of this multifactorial condition (sarcoidosis), additionally

participants within the current study and previous others (Korenromp *et al.*, 2014; Saligan, 2014) reported low levels of physical activity and thus demonstrates scope for improvement.

5.5.5. *Limitations/Future Directions*

The mean number of types of sarcoidosis (2.83) and symptoms (3.79) experienced by patients highlights the diverse complexity of the condition and warrants further research into the interactions between different types of sarcoidosis and their associated symptoms with regards to quality of life and treatment guidelines (De Vries & Drent, 2008). Another limitation and area for future research is the genetic element of the disease. Genetic analysis is key to better understanding this disease and knowing the genetic makeup of the participants would better enable the understanding of the formation and development of sarcoidosis. For example, environmental factors such as exposure to organic dust or airborne agents, have been linked to the increased inflammatory response and resultant progression of pulmonary sarcoidosis (Stopinsek *et al.*, 2016), however this has not been looked at alongside the genetics of sarcoidosis patients and whether certain genes such as HLA are more susceptible to select environment factors (i.e Insecticides) compared to others (Dardiotis *et al.*, 2013).

5.6. **Conclusions**

In conclusion, participant feedback has highlighted the diverse nature of the condition and the barriers they face receiving patient care such as lack of knowledge regarding the condition and poor integration between different areas of medical care despite the multifactorial nature of sarcoidosis. Patient feedback has also highlighted areas for greater focus such as stress and anxiety reduction as well as the role of lifestyle factors on management of the condition and quality of life. This feeds back into the quantitative data reported, with CES-D and number of symptoms indicated as

predictors for quality of life while quality of life, number of symptoms and fatigue predictors of physical activity levels. The onset of sarcoidosis has also been shown to detrimentally affect physical activity levels alongside personal and professional life, and as such lifestyle (diet, physical activity, smoking status, sleep etc.) was identified as an area with potential beneficial improvements to symptoms and quality of life. There is still a wide range of different areas requiring research that could lead to improvements across the population however, overall two areas are prominently identified, the role and effects of lifestyle on sarcoidosis, including the number of types and severity of the disease, in addition to depression and quality of life, particularly considering potential benefits of stress and anxiety reduction through taught coping methods such as mindfulness.

6. CHAPTER SIX

6.1. A Epidemiological Study into Sarcoidosis: Physical Activity Levels in Relation to Symptom Severity.

6.1.1. Chapter six Abstract

Background: There is a large body of research supporting staying physically active and as such is often suggested within pulmonary sarcoidosis. However, individuals with sarcoidosis are at risk of numerous mental and physical detriments compared to their healthy counterparts such as fatigue, dyspnoea and deconditioning. In addition to this, relatively little is known regarding the impact physical activity on the condition, hence this requires further research. An online cross-sectional observation survey investigating physical activity levels and fatigue within sarcoidosis.

Methods: The study involved an online survey using Qualtrics, comprising of validated questionnaires measuring physical activity and fatigue, in addition to closed quantitative questions to obtain anthropometric data and information on types of sarcoidosis and time since diagnosis.

Results: The majority of participants (92.59%) reported fatigue, with 22.22% reporting extreme fatigue via the fatigue assessment scale (FAS). Obese BMI (25+) accounted for the majority of participants 44.64%, despite 49.06% reporting high levels of physical activity via the IPAQ. Fatigue, gender and sitting time explained 37.5% of the variance within the IPAQ physical activity data.

Conclusions: The analysed population was diverse with regards to physical activity and anthropometrics. Nonetheless, fatigue is a major issue within the population and is moderately correlated to dyspnoea, another important symptom.

6.2. Introduction

Physical activity (PA) is recommended across all ages and health conditions. Physical activity descriptions range from “Miracle Cure” (NHS, 2015b) to “the best buy for public health” (MacAuley *et al.*, 2015), highlighting the importance of physical activity. The current U.K. guidelines for adult’s physical activity are 150 minutes of moderate or 75 minutes of high intensity and/or a combination of the two is recommended per week with a minimum of two days involving strengthening exercises of all major muscle groups (Department of Health, 2011). General benefits of regular physical activity include decreased risk of osteoarthritis (Borer, 2005) depression and non-communicable diseases (NHS, 2015b) as well as an important role in the prevention and management of hypertension (Diaz & Shimbo, 2013). While within chronic obstructive pulmonary disease (COPD) regular physical activity has been linked to reduced all-cause mortality (Garcia-Aymerich *et al.*, 2006) and reduced risk of exacerbations within asthma (Garcia-Aymerich *et al.*, 2009). Despite the known wide-ranging benefits to physical activity; much like diet, there is no known average physical activity level among sarcoidosis patients. This is an important area that requires further investigation for a number of reasons including the better understanding of the role their disease plays with physical activity, understanding their risk profile both specific and non-specific to sarcoidosis and also allow for a better integrated health plan and thus care of patients. Within sarcoidosis itself, Saligan (2014)’s research found sarcoidosis patients had lower physical activity levels than age and race matched, sedentary controls, with daily energy expenditure of 1324 kcal (sarcoidosis) and 1748kcal (control), although BMI was significantly different ($P<0.05$) for the two groups, 34 for sarcoidosis and 25 for controls, which may in part explain the differences. A small number of studies have shown improvements to

primary and secondary symptoms including quality of life and fatigue following the completion of an exercise program within sarcoidosis (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015; Naz *et al.*, 2018). However, exercise adherence, especially long term and within disease populations is notoriously difficult for a range of reasons including baseline physical fitness, marital status, fatigue level, exercise self-efficacy and history of PA, as well as mood disturbance due to treatment (Neupert *et al.*, 2009; Shang *et al.*, 2012; Nam *et al.*, 2013). For example, pulmonary rehabilitation within mild COPD has been shown to significantly improve exercise capacity and quality of life (Jacome & Marques, 2014), however despite this, Heerema-Poelman *et al.* (2013) found COPD patients following a home care maintenance exercise program post completion of pulmonary rehabilitation had a dropout rate of 36.7% within the first year, which highlights the difficulties of maintenance for exercise prescription. A better understanding of the populations' typical physical activity and variances to this may allow for the creation of specifically tailored programmes and thus improve adherence and with-it long-term results, for example, older persons (64 ± 4.5 years) have been shown to have increased exercise adherence when receiving a behavioral programme alongside their exercise prescription (Azizan *et al.*, 2013). Physical activity/exercise has been linked to numerous benefits within sarcoidosis including improved quality of life (Drent *et al.*, 2014; Saligan, 2014; Naz *et al.*, 2018) and aerobic capacity/exercise performance (6MWD) (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015; Naz *et al.*, 2018) as well as reductions to fatigue (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015; Naz *et al.*, 2018) and depression (Naz *et al.*, 2018). Additionally, understanding a population's physical activity levels provides a wide range of other benefits such as the ability to calculate their risk of other conditions

associated inactivity and therefore lead to a better understanding of what sarcoidosis directly and indirectly influences.

Therefore, the aim of this study is to identify trends in physical activity levels in a sarcoidosis patient population and investigate relationships between fatigue and physical activity.

6.3. Methodology

6.3.1. Participants

An online survey of 56 participants with self-reported sarcoidosis completed an online survey. Participants were voluntarily recruited via online sarcoidosis forums and support groups. Exclusion criteria extended to anyone with an additional interstitial lung disease such as asthma and chronic obstructive pulmonary disease (COPD) as well as those unable to give consent. The study consisted of 18 males, 38 females and one other(non-specified), ethnicity was also recorded (n = 54 Caucasian, n = 1 Black African, n = 2 Mixed Caucasian and Black-Caribbean). There was a drop-out of 24 participants, participants results were removed from analysis if they had completed less than 50% of part A.

6.3.2. Design, Equipment and Procedures

The study design was a cross-sectional online observation study that consisted of an online survey (Appendix 6). The participants firstly had to read and accept the informed consent for the study, which then lead them onto anthropometric and demographic questions including age (Years) mass (kg), stature (cm), gender(sex), BMI (body mass index) and ethnicity. Following this they answered validated questionnaires relating to physical activity via the International physical activity questionnaire (IPAQ; Craig et al., 2003) a questionnaire comprised of 27 items across five activity domains asked independently. One example question is “Think about only

those physical activities you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do vigorous physical activities like aerobics, running, fast bicycling, or fast swimming in your leisure time?" (Appendix 3). Fatigue was measured via Fatigue assessment scale (FAS; Michielsen et al., 2003), a 10-item questionnaire with a 5-point likert scale, split into 5 physical fatigue and 5 mental fatigue questions with an example question being "I get tired very quickly" (Appendix 7), with answers ranging from "never" to "always". Dyspnoea was measured via the MRC dyspnoea scale (MRC; Fletcher *et al.*, 1959), consisting of five grades ranging from 1 (not troubled by breathes except on strenuous exercise) to 5 (too breathless to leave the house, or breathless when dressing/undressing) (Appendix 8).

6.3.3. *Data Analysis*

The data were analysed via SPSS 24.0 (IBM Corp, Armonk, New York). An exploratory data analysis (EDA) was first completed; the data were normally distributed and therefore met parametric assumptions. Following this, a multiple regression was conducted, P value was set at <0.05.

6.4. **Results**

6.4.1. *Participant characteristics*

Table 13 displays the characteristic data of the participants who partook in the study. No participants were aged under 30 while the most populous age range was 51-60 years. Females accounted for more than twice the male participation within the study and the vast majority of participants self-identified as Caucasian. The two biggest groups for time since diagnosis were less than two years and more than five years, with only a difference of five participants between the two groups.

Table 13. Characteristics of Subjects (n=57, unless otherwise stated).

Age (Yrs)	No.	Percentage (%)
31-40	8	14.04
41-50	17	29.82
51-60	25	43.86
61+	7	12.28
Gender		
Male	18	31.58
Female	38	66.67
Ethnicity		
Caucasian	54	95.00
Black African	1	2.00
Mixed Caucasian & Afro-Caribbean	2	4.00
Time since Diagnosis*		
Less than 2 years	26	46.43
3-5 years	9	16.07
More than 5 years	21	37.50

* = 56 participants

Table 14 highlights the anthropometric characteristics (mass, stature and BMI) of participants including their gender breakdown. Overall 91-100kg was the most selected category however males most selected was 100+kg while females most selected was at the opposite end at 51-60kg and no one reported being under 50kg. The majority of participants selected 161-170cm as their stature and this was the same for both genders (38.89 & 55.26%, respectively). No participants calculated their BMI to be under 18.5, with a BMI of 30+ being the most selected (44.64%).

Table 14. Mass, Stature, Body mass index and participant selected types of sarcoidosis.

	All*		Male		Female	
	No.	Percentage (%)	No.	Percentage (%)	No.	Percentage (%)
Mass (kg)						
51-60	8	14.04	0	0.00	8	21.05
61-70	7	12.28	1	5.56	5	13.16
71-80	8	14.04	2	11.11	6	15.79

81-90	11	19.30	4	22.22	7	18.42
91-100	12	21.05	5	27.78	7	18.42
100+	11	19.30	6	33.33	5	13.16
Total	57	100.00	18	100.00	38	100.00
Stature (cm)						
Under 150	2	3.51	0	0.00	2	5.26
151-160	7	12.28	1	5.56	6	15.79
161-170	28	49.12	7	38.89	21	55.26
171-180	12	21.05	3	16.67	9	23.68
181-190	7	12.28	6	33.33	0	0.00
191-200	0	0.00	0	0.00	0	0.00
200+	1	1.75	1	5.56	0	0.00
Total	57	100.00	18	100.00	38	100.00
BMI						
18.5-25	15	26.79	1	5.88	13	34.21
25-30	16	28.57	4	23.53	12	31.58
30+	25	44.64	12	70.59	13	34.21
Total	56	100.00	17	100.00	38	100.00

BMI = Body Mass Index.

Table 15 shows all participants who partook within this study selected pulmonary sarcoidosis (100%) with Lymph nodes being the second most common (34.55%), the mean number of types of sarcoidosis a participant selected as having was above two, standing at 2.41.

Table 15. Sarcoidosis types with the mean, median and mode for the number of types.

Types of Sarcoidosis						
Pulmonary	55	100.00	18	100.00	37	100.00
Skin	11	20.00	4	22.22	7	18.92
Lymph nodes	19	34.55	6	33.33	13	35.14
Bone/joint	12	21.82	4	22.22	8	21.62
Eye	16	29.09	5	27.78	11	29.73
Nervous system	5	9.09	3	16.67	2	5.41
Endocrine	3	5.45	3	16.67	0	0.00
Organ	7	12.73	2	11.11	5	13.51
Total	55	100.00	18	100.00	37	100.00
Number of types of Sarcoidosis						
Mean	2.41		2.56		2.34	
Median	2.00		2.00		2.00	
Mode	1.00		1.00		1.00	

Table 16 displays the validated questionnaires and scale results of the participants. Only four participants (7.41%) were classified as non-fatigued via the fatigue assessment scale (FAS) and, grade 2 was the most populous answer for the MRC dyspnoea scale, followed by grades 3 and 4. Physical activity levels, as determined by the IPAQ showed the “high” classification being the most common (49.06%) however results varied by gender, where females self-reported physical activity classified as high (63.89%), while males self-reported physical activity classified as moderate for the majority (58.82%). As well as lower levels of physical activity, males recorded higher levels of sitting per day than their female counterparts (375mins.p/d &

352mins.p/d, respectively) however females reporting low levels of physical activity recorded the highest amount of sitting (515mins.p/d).

Table 16. Fatigue status, MRC dyspnoea, physical activity level and mean minutes sitting per day.

	All*		Male		Female	
	No.	Percentage (%)	No.	Percentage (%)	No.	Percentage (%)
Fatigue Status						
No Fatigue (Scored 21 or under)	4	7.41	2	11.76	2	5.41
Fatigued (Scored 22-34)	38	70.37	10	58.82	28	75.68
Extreme Fatigued (Scored 35 or above)	12	22.22	5	29.41	7	18.92
Total	54	100.00	17	100.00	37	100.00
MRC Dyspnoea Scale						
Grade 1	5	9.09	3	16.67	2	5.41
Grade 2	21	38.18	6	33.33	15	40.54
Grade 3	13	23.64	3	16.67	10	27.03
Grade 4	13	23.64	4	22.22	9	24.32
Grade 5	3	5.45	2	11.11	1	2.70
Total	55	100.00	18	100.00	37	100.00
Physical Activity Level						
Low	9	16.98	4	23.53	5	13.89
Moderate	18	33.96	10	58.82	8	22.22
High	26	49.06	3	17.65	23	63.89
Total	53	100.00	17	100.00	36	100.00
Mean minutes sitting/per day						
Low	456±172		375±158		555±157	

Moderate	414±163	414±182	415±136
High	289±126	303±89	287±130
All	360±164	375±158	352±166

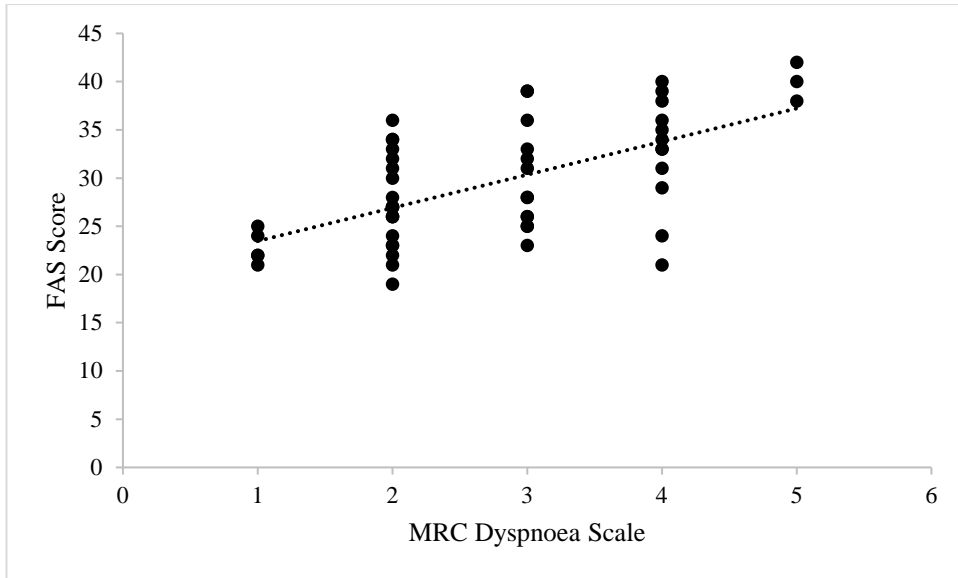
Low = Failure to meet other categories; Moderate = Moderate 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 600 MET-min/week; High = 7 days of any combination of walking, moderate- or vigorous- intensity activities accumulating at least 3000 MET-minutes/week; Grade 1 = Not troubled by breathless except on strenuous exercise; Grade 2 = Short of breath when hurrying on a level or when walking up a slight hill; Grade 3 = Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace; Grade 4 = Stops for breath after walking 100 yards, or after a few minutes on level ground; Grade 5 = Too breathless to leave the house, or breathless when dressing/undressing. * = 56 Participants.

Table 17 highlights the results of a multiple regression into predictors of IPAQ physical activity categories. Fatigue measured via FAS, gender and average time spent sitting per day (mins) were found to be significant predictors, explaining 37.5% of the variance within the data.

Table 17. Multiple regression predictors of IPAQ physical activity categories.

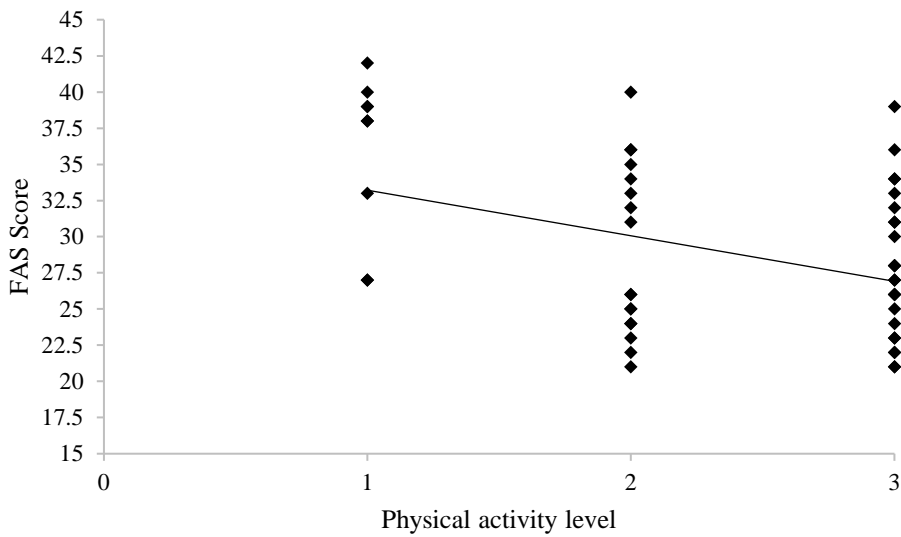
Model	R ²	B	Sig.
1			
Constant		3.95	.001
FAS	.192	-.06	.001
2			
Constant		3.03	.001
FAS		-.05	.001
Gender	.293	.52	.012
3			
Constant		3.19	.001
FAS		-.04	.008
Gender		.51	.009
Sitting Time	.375	-.01	.017

FAS = fatigue assessment scale, sitting time = time spent sitting per day. Dependent variable = IPAQ derived physical activity categories.



FAS = Fatigue assessment scale.

Figure 4. Correlation between MRC dyspnoea scale and the fatigue assessment scale.



1 = low physical activity, 2 = moderate physical activity, 3 = high physical activity.

Figure 5. Correlation between physical activity level and fatigue assessment scale.

6.5. Discussion

6.5.1. *Participant characteristics*

All participants within this study self-reported pulmonary sarcoidosis, but many reported multiple types of the disease, with the mean number of forms/types of sarcoidosis being above 2 (Table 15). This highlights the diverse and complex nature

of the condition and the need for consideration of treatment guidelines for the affected population as there are numerous different combinations and interactions between the different forms, in addition to varying levels of severity. A limitation of this study, however, was not collecting data on the severity of all symptoms. The majority of participants reported having been diagnosed less than two years ago (46.43%), which fits with the current views of sarcoidosis being acute in the majority of cases (NHS, 2015a), Judson *et al.* (2003) states 80% are likely to improve over the first two years of the condition's diagnosis, similarly, Mana *et al.* (1994) found only 22% with sarcoidosis over 2 years. However, this still leaves a large proportion of the population with chronic sarcoidosis, where the disease is unlikely to resolve (Judson *et al.*, 2003). Hunninghake *et al.* (1999) states 10-30% with the condition have chronic sarcoidosis and within this study 37.5% selected being diagnosed more than five years ago. The reason for this is unclear, one possible reason to explain the levels of chronic sarcoidosis reported may be increased incentive on behalf of those with chronic sarcoidosis to help improve the understanding of the condition and aid the current body of knowledge due to frustration with the daily issues that accompany the condition for many. For example, current treatment does not improve progression chances of the condition (Rissmiller & James, 2017). Treatment currently focuses on symptomatic management and is associated with numerous side-effects such as weight gain (Liu *et al.*, 2013). The top two selected age groups within the study were 41-50 and 51-60 years, which may partly explain the high chronic levels of sarcoidosis reported as the onset of sarcoidosis has been associated with those aged 20-40 years old (Brenitz & Storm, 1983) although Baughman *et al.* (2001) found 35-45 years old to be the peak age for sarcoidosis onset. A limitation of this study is the lack of depth on the specific ages of participants, with greater depth, the peak onset reported by

Baughman *et al.* (2001) may have also been obtainable within this study however it is not possible to say based on the structure of the data recorded. Ungprasert *et al.* (2017) found the age women were diagnosed was significantly higher than their male counterparts, 48.3 versus 42.8 years old respectively, and therefore the age ranges observed within this study may be influenced by the increased female participation compared to male (n=38 versus n= 18 participants). The body mass index (BMI) (please see Table 14) was split relatively evenly (1 participant difference) between 18.5-25 (normal), 25-30 (overweight) and 30+ (obese) for female participants, while males were predominantly obese (70.59%). The reasons for this are likely to be many and consist of sarcoidosis and non-sarcoidosis factors, one possible attribute may be related to the suggested later onset of sarcoidosis in females (Ungprasert *et al.* 2017), as sarcoidosis is associated with decreased levels of physical activity (Korenromp *et al.*, 2011; Saligan, 2014) and weight gain is associated with the primary medication prescribed (prednisolone; Liu *et al.*, 2013). Therefore, the weight gain difference may be linked to time with the condition. The condition is associated with deconditioning related to major symptoms including fatigue, dyspnoea and chronic cough (Baughman, 2013) and as such has been suggested to lead to decreased physical activity levels. A multiple regression was carried out to investigate whether gender, sitting time, fatigue (FAS), dyspnoea, number of types or BMI could significantly predict participants IPAQ physical activity. The results of the regression indicated that FAS, gender and sitting time explained 37.5% of the variance and that the model was a significant predictor of IPAQ physical activity, $F(3,47) = 9.39$, $P = 0.001$. While all three variables contributed significantly to the model ($B = -.04, .51, -.001$, $P < 0.05$, respectively). Korenromp (2011) found self-reported fatigued sarcoidosis patients had reduced levels of physical activity against non-fatigued participants with the condition

and both groups were reduced compared to a healthy control. Gosse (2014) found BMI when self-reported tend to be underestimated with misclassification increasing with BMI score, additionally, sarcoidosis is associated with muscular atrophy (Cremers *et al.*, 2013) and thus can lead to lower BMI scores.

6.5.2. *Physical activity/sitting hours p/d*

There is severely limited physical activity research within sarcoidosis at present, however some preliminary research is starting to form a baseline understanding. Korenromp *et al.* (2011) found higher levels of inactivity for those with the condition compared to healthy controls, with those reporting as fatigued reporting lower levels of activity than non-fatigued patients. Our findings remain unclear as non-fatigued participants reported higher levels than those reported as extremely fatigued for Mets-mins/week (3112.5 ± 442.71 & 1847.83 ± 2905.85) however fatigued participants reported the highest Mets-mins/week of all groups (6325.33 ± 6205.82), although this group showed a very large standard deviation, suggesting some fatigued individuals have high levels of physical activity and bring up the mean for the group overall, there is also a limitation of different group size (Table 16) and therefore may be not a fair representation of their group as a population. In addition to Korenromp *et al.* (2011) findings, Saligan (2014) found sarcoidosis participants had lower functional performance outcomes, more fatigue and were less physically active than age, gender and ethnically-matched sedentary healthy controls. Although Saligan's (2014) research highlights key information regarding physical activity, for example greater

levels of physical activity than already sedentary controls, it fails to offer depth due to the exclusion of activity levels of physically active healthy controls and normative values for age and gender matched data. Additionally, Saligan (2014) only recorded during weekdays whilst Korenromp researched both weekdays and weekends and found a sharp drop in activity over the weekend, with fatigued participants reducing activity the most despite being the most inactive. Garcia-Aymerich *et al.*'s (2006) research highlights the potential benefits of physical activity and found COPD patients even with "low" self-reported physical activity had fewer hospital admissions and lower mortality rate than those reporting "very low". 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. This study utilised the IPAQ and found 83% reported moderate-high levels of physical activity, with 49% recording high levels of physical activity based on the IPAQ's guidelines (Table 14). It is worth noting that there were clear differences between genders, where males recorded 17.65% as being highly active while 63.89% of females recorded as high. A limitation is the self-reported aspect, where disadvantages include external factors such as social desirability and the need to rely on memory recall, in addition to being less robust in measuring light and moderate physical activity (Sylvia *et al.*, 2015). Validity could be increased through the use of accelerometers to record real world physical activity data (Prince *et al.*, 2008). Although, the IPAQ has shown moderate validity in comparison to accelerometer data (Wanner *et al.*, 2016), it is worth noting that the IPAQ has been shown to produce repeatable data and been stated as being as good as other established self-reported physical activity questionnaires (Cora *et al.*, 2003).

Mean minutes sitting per day decreased as the physical activity level increased, with the exception being moderate activity males who sat 39 minutes more than low activity males, however, all groups have sizeable standard deviations (Table 14) and thus highlights the volatility despite being within the same physical activity threshold. This is an area wide issue as based on current UK guidelines (Department of Health, 2010) it is possible to meet both the sedentary and physically active thresholds. There are numerous implications for being sedentary for too long, despite being active outside of this, and this is a growing area of research. Owen *et al.* (2010) states prolonged bouts of sitting compromises metabolic health irrespective of an individual's physical activity levels. Prolonged bouts of sedentary behaviour including sitting has been associated with a range of detrimental health risks including type 2 diabetes and premature mortality (Dunstan *et al.*, 2012). Korenromp *et al.* (2011) previously found fatigue was associated with reduced activity levels however physical activity is a complex issue, and will consist of numerous reasons, such as environmental factors including lack of affordability and childcare as well as social factors including peer and family support (Seefeldt *et al.*, 2002) although based on the current findings, improving fatigue may be beneficial for improving physical activity levels (Korenromp *et al.*, 2011; Saligan, 2014). Additionally, improving participants dyspnoea score may also improve activity levels in addition to other variables such as quality of life. Dyspnoea is a major symptom of sarcoidosis (Baughman, 2013), and has been suggested as being important within the deconditioning process and thus reduced activity levels as well as increased dyspnoea predicted depression as a sarcoidosis factor (Chang *et al.*, 2001).

6.5.3. *Fatigue/MRC dyspnoea scale*

Only four participants (7.41%) were identified as non-fatigued via the FAS within this study, while only five (9.09%) selected grade 1 on the MRC dyspnoea scale (i.e. only felt breathless during strenuous exercise; Table 14). This data highlights the significant effect of fatigue and dyspnoea on sarcoidosis patients and its importance for understanding the condition and development of future treatment options. Extreme fatigue, signified by a score above 35 on the FAS, was reported in 22.22% of participants, while 37 participants (85.46%) selected grade 2-4, with 5.45% selecting grade 5 (reported as being too breathless to leave the house, or breathless when dressing/undressing). This highlights the impact the disease can have on someone's life and once again the complexity of physical activity as patients may wish to have higher levels of physical activity however their MRC dyspnoea score may be a limiting factor to this as well as their everyday life. A multiple regression was undertaken to check if any were predictors of the MRC dyspnoea scale, nothing was found to be a predictor. The reason for this remains unclear but may be due to how the scale is reported and the differences with how the other variables are measured. Improved understanding of the interaction between fatigue and dyspnoea is required, as well as their role in affecting physical activity, deconditioning and quality of life in sarcoidosis as well as greater understanding with regards to the potential benefits of better targeted treatment of these symptoms and the wider effect this would have on a sarcoidosis patient.

6.6. Conclusions and Future Directions

One future direction would be isolating the different combinations of the condition and severity scores, such as pulmonary and skin sarcoidosis and pulmonary and bone/joint sarcoidosis and looking into greater depth at their effects on BMI, physical activity, fatigue and other key variables. Gaining greater depth and understanding of

the different correlated variables such as physical activity, FAS and dyspnoea and the interactions between them is vital, a large cohort of diverse (geographical and demographically) sarcoidosis patients looking at this longitudinally is required.

Based on the current study's findings, sarcoidosis patients are a diverse population not dissimilar to the general population. The key symptoms of dyspnoea and fatigue do moderately correlate with each other while higher levels of self-reported physical activity have been linked with reduced FAS scores.

7. CHAPTER SEVEN

7.1. The Relationship Between a Direct Measure of Physical Activity Against Self-Reported Physical Activity, Muscle Strength, Quality of life and Exercise Capacity.

7.1.1. Chapter seven Abstract

Background: Physical activity is frequently suggested as beneficial within sarcoidosis however little is currently known about physical activity patterns within the condition as well as its role and effect on other key physiological and mental variables. Additionally, self-reported measures such as the IPAQ are regularly utilised within research due to their ease of use and low cost however their validity and accuracy within sarcoidosis in comparison to an objective measure (tri-axial accelerometer) is currently unknown.

Methods: A lab-based approach was utilised with participants visiting twice to validate their variable measurements. Participants undertook exercise capacity (6MWT), lung function (FEV₁, FVC, PEF), muscle strength (HGS, QPT, HPT, EFMS), quality of life (SHQ) and fatigue (FAS) tests in addition to wearing a tri-axial accelerometer for five days between visits.

Results: Participants recorded above recommended levels of physical activity via the accelerometer (109mins MVPA per day) and reported a large difference via the IPAQ (43 minutes), neither were predictors of each other, however Calories burned per day and BMI were found to be predictors of accelerometer MVPA ($R^2 = .968$). Handgrip strength reported strong bivariate correlations with gender (.809), body fat percentage (.794), elbow flexor muscle strength (.961) and forced vital capacity (.865) although only elbow flexor muscle strength was found to be a predictor ($R^2 = .913$).

Conclusions: Physical activity patterns are diverse within sarcoidosis much like the general public, while physical activity's relation to other variables appears limited although the variables are multi-faceted. Handgrip strength and six-minute walk distance may be a good indicator of a range of other key variables within the condition.

7.2. Introduction

Physical activity (PA) is recommended across all ages and health conditions, albeit at different intensities and durations. For adults (19-64 years) in the U.K. 150 minutes of moderate exercise, 75 minutes of high intensity exercise or a combination of the two is recommended per week (Department of Health, 2011). Descriptions of Physical activity range from “Miracle Cure” (NHS, 2015b) to “the best buy for public health” (MacAuley *et al.*, 2015), which highlights the perceived importance of physical activity, further backed up by reports that physical inactivity is the fourth biggest killer across the world's population (Kohl *et al.*, 2012). Unfortunately, the physical activity guidelines are not met by everyone. In the UK 2015/16 26% of adults (16+ years) were classified as inactive i.e. less than 30 minutes of physical activity a week (NHS Digital, 2017) with physical inactivity being worse in those with interstitial lung diseases (ILD) such as asthma, chronic obstructive pulmonary disease (COPD) and Sarcoidosis (Watz *et al.*, 2009; Korenromp *et al.*, 2011; Drent *et al.*, 2014; Saligan, 2014), despite the known public health benefits for both healthy and chronically ill populations. For example, regular physical activity within COPD has been shown to reduce not just admission to hospital but also all-cause mortality as well as specifically respiratory mortality (Garcia-Aymerich *et al.*, 2006). Physical activity has frequently been suggested as beneficial for sarcoidosis patients (NHS, 2015a). This is due to a host of specific and non-specific benefits to those with the condition, such as the overall improvement to health including decreased levels of non-communicable diseases as

well as lower risk of depression (NHS, 2015b). Although anyone can suffer from depression, sarcoidosis patients have been shown to have increased levels (Hinz *et al.*, 2012). Physical activity also helps not only to slow and stop deconditioning, a major issue within sarcoidosis (Fleischer *et al.*, 2014), but also aids the reversal of this process (Strookappe *et al.*, 2015). Despite the known wide-ranging benefits of physical activity, there is no reported average physical activity level among sarcoidosis patients, with the few studies that have been undertaken showing decreased levels of normative values compared to healthy-aged match controls through both self-reported real world (accelerometer) methods (Korenromp *et al.*, 2011; Vasudevan *et al.*, 2013; Saligan, 2014). Self-reported measures of physical activity such as the International physical activity questionnaire (IPAQ) are important tools in better understanding the physical activity levels across large population sizes due to their ease of use and low costs (Biddle *et al.*, 2011). Although they are useful in gaining knowledge within a population, especially one that has limited data such as sarcoidosis, the evidence obtained can only be utilised to the benefit of research and the population if the data is valid for that population. As such, the IPAQ and other self-reported measures need to be validated against the tri-axial accelerometer to understand their validity and justify their use in further studies. Craig *et al.* (2003) found the IPAQ to be a valid tool to measure adults' (18 -65 years) physical activity, with similar correlation strength (.43 for UK population) to other self-reported measures. The weak-moderate correlation found between IPAQ and accelerometer within a healthy population further highlights the need to quantify both self-reported and objective measure of physical activity. To the IPAQ's benefit Carlos *et al.* (2012) found the IPAQ did reveal some metabolic and cardiovascular disease risk factors thus underlying self-reported measures do have a place within research, however it did not

reveal them all in comparison to accelerometer derived physical activity and as such implementation of only the IPAQ could therefore lead to the underestimation and missing of some disease risk factor relationships. Furthermore, Dyrstad *et al.* (2014) found participants reported increased vigorous activity and less sedentary time via the short form-IPAQ than their accelerometer measurements. The inhibiting factors for the reported decreased levels of physical activity remain unclear too, although it is likely attributed to the symptoms of the condition and other lifestyle factors that the U.K's whole population faces as well as regular comorbidities for sarcoidosis such as hypertension, thyroid disorders and obesity (Martuseqicz-Borors *et al.*, 2015). The distribution of these factors on the effect of physical activity levels remains unknown and is an area for future research, as knowing this, is vital for the development of a disease-specific treatment plan. Sarcoidosis currently lacks specific guidelines, unlike similar conditions such as COPD and asthma (ACSM, 2014; National Institute of Health and Care Excellence (NICE), 2016). Due to this, sarcoidosis patients are often given advice on exercise and other forms of physical activity such as walking or dancing that are not underpinned by specific research of their condition and as such are potentially less effective or irrelevant for the condition. Holland *et al.* (2015) states the unique presentation of ILD, including sarcoidosis, requires modifications of exercise prescription for individuals and this was also noted as a key issue by Strookappe *et al.* (2016) in a systematic review of physical activity and training in Sarcoidosis.

The effect of pulmonary sarcoidosis on exercise capacity and strength in comparison to a healthy population is limited and needs further research. Reductions to both exercise capacity and muscle strength indicated by lower results than normative values, are known primary symptoms of Sarcoidosis (Spruit, 2005a; Hildebrand *et al.*,

2012; Baughman, 2013), which continue to get progressively worse with the onset of secondary symptoms such as deconditioning (Mitchell *et al.*, 2012; Fleischer *et al.*, 2014). The symptoms of sarcoidosis in tandem with the varied manifestations (Skin, liver, heart etc. (Saidha *et al.*, 2012)) of the disease alongside pulmonary, make it incredibly hard for accurate, appropriate suggestions for physical activity, especially when considering the current lack of evidence. This is highlighted by the role of fatigue within sarcoidosis, which is recognised as a major factor within the disease (Baughman, 2013) and therefore needs considering when creating an exercise prescription plan. In addition to this, pulmonary impairment has been reported via exercise testing despite normal pulmonary function results (Miller *et al.*, 1995), while Delobbe *et al* (2002) also found limited maximal exercise capacity within sarcoidosis patients despite no signs of pulmonary or cardiac impairment at rest. Additionally, vital components of any exercise programme seeking to achieve physical benefits include duration, frequency and intensity (Spruit *et al.*, 2005a; Swigris *et al.*, 2011; Boots *et al.*, 2011; Strookappe *et al.*, 2015).

Hence, increased understanding of the effects of pulmonary sarcoidosis in relation to physical activity and fitness is required as well as comparison to a healthy age matched normative values to allow for the data to be considered alongside other ILD's. This is vital as Kohl *et al.* (2012) states instead of an individualised behavioral science approach, focus is needed on populations as well as the complex interactions with physical inactivity factors. Further research into this area is required as exercise training has been shown to be in some cases just as, or more, effective than medical treatment across a wide range of chronic conditions (Pedersen & Saltin, 2015). Within Sarcoidosis, Marcellis *et al.* (2013a) argues rehabilitation should be utilised alongside any pharmacological treatment despite the need for future research on potential

benefits while Strookappe *et al.* (2016) also state that, although further randomised controlled trials are needed, the effects of physical training seem promising from the current limited research.

Therefore, the primary aim of this study was to ascertain physical activity patterns in those with pulmonary sarcoidosis with regards to perceived physical activity and actual physical activity. The secondary aim of the study was to understand the effect of pulmonary sarcoidosis in relation to muscle strength and exercise capacity against physical activity and lung function as well as how these differ from normative values.

7.3. Methodology

7.3.1. Participants

Participants with medically diagnosed pulmonary sarcoidosis were selected. They were recruited through support groups and online forums. A diagnosis of sarcoidosis was accepted provided the participant had been clinically diagnosed with pulmonary sarcoidosis, ascertained by self-reporting. The study consisted of 8 participants (n = 3 male, n = 5 female) of whom seven were Caucasian and one was mixed Caucasian and Afro-Caribbean. Participants mean age (\pm standard deviation) was 50 ± 8 years with mass and stature $81\pm 17.94\text{kg}$ & $172\pm 10.33\text{cm}$, respectively.

7.3.2. Exclusion Criterion

Exclusion criterion included contraindications to (not able to perform) physical tests or exercise testing - e.g. unstable cardiovascular disease, oncological, cardiac, neurological or orthopaedic history making them unable to participate, , or an injury in the past 6 months that inhibits ability to perform exercise testing, both determined via a sub-maximal fitness screening form (appendix 1). Additionally, patients with a concurrent and predominant diagnosis of another significant respiratory disorder (for example: asthma, COPD, cystic fibrosis, or lung cancer) were excluded. Other reasons

for exclusion included pregnancy, physical disability (non-ambulatory patient e.g. wheelchair or bed-bound), inability to obtain informed consent and cognitive failure making them unable to give consent or understand questionnaires or instruction.

7.3.3. Design, Equipment and Procedures

The study used a prospective cross-sectional observational design with no intervention. Observational exercise testing included both endurance exercise and muscle strength. Patients participating in this study were treated according to current guidelines (Costabel & Hunninghake, 1999). As such, diagnostic procedures or current treatment was not postponed or impacted on by participation in this study. Participants were invited to attend the laboratory for testing on two occasions separated by a minimum of 6 days and maximum of 14 days to measure physical activity, fatigue, aerobic fitness and muscular strength with exercise testing at the Human Performance laboratory, Kingston University, London to establish the influence on symptoms, physiological and psychological outcomes. Exercise testing followed standardised guidelines (ACSM, 2016). Appropriate health and risk stratification screening was performed via a sub-maximal exercise screening form based on a PAR-Q (appendix 1). During visit one, participants signed an informed consent form (appendix 9) and had any questions answered before continuing. They were then put through a screening process beginning with physical examination: characteristics such as anthropometric data (stature, mass, heart rate (HR), blood pressure, age, BMI, fat% (Bodpod, Cosmed/ Bioelectric Impedance Analysis (BIA), Tanita) were collected. Following this, participants conducted a lung function test via computer spirometry (Oxycon Pro, VIASYS GmbH, Eric Jaeger, Hoechberg, Germany). Their predicted results were corrected for ethnicity (Bellamy, 2005), where Afro-Caribbean predicted results were decreased by 13% (Bellamy, 2005).

Participants then conducted muscle strength testing using an isokinetic dynamometer (Biodex System 4, Biodex Corporation, NY, USA); tests included: elbow flexor muscle strength (EFMS), quadriceps peak torque (QPT) and hamstring peak torque (HPT), in addition to this handgrip strength (HGS) was also assessed via handgrip digital dynamometer (Accord Medical Products). A minimum rest period of 20 minutes followed (Vainshelboim *et al.*, 2014) based on exercise-based pulmonary rehabilitation research. Heart rate (bpm) was checked at the end of this period and in two-minute intervals until HR returned to baseline as per ACSM (2014) guidelines, physical testing did not take place until this return to baseline. Following the rest period, participants conducted a six-minute walk test (6MWT). During the test, participants were measured for Borg rate of perceived exertion and Borg Dyspnoea at 2-minute intervals and at completion of the test. Oxygen saturation levels of participants were recorded during the 6MWT via a portable pulse oximeter at the same intervals as the perceived exertion and dyspnoea. Once the 6MWT had been completed, participants completed three questionnaires, the fatigue assessment scale (FAS; De Vries *et al.*, 2004), international physical activity questionnaire (IPAQ; Ekelund *et al.*, 2003) and Sarcoidosis Health Questionnaire (SHQ; Cox *et al.*, 2003). Before leaving, participants were given tri-axial accelerometers (GT3X+ accelerometer, ActiGraph, Pensacola, Florida), which were used to measure the participants physical activity for five days, to establish habitual physical activity levels and compare against the results of the IPAQ.

During the second lab visit, participants returned their accelerometers and followed the same pattern of testing from the first visit, excluding the questionnaires (SHQ, FAS & IPAQ) and anthropometric information. The order of testing followed ACSM (2016) guidelines.

Six Minute Walk Test: Performed along a straight flat 30 metre course indoors, participants walk at their own pace for 6 minutes (Butland *et al.*, 1982). No warm-up is required however participants rest in the seated position 10 minutes before the test in accordance with American Thoracic Society (2002) guidelines.

Sarcoidosis Health Questionnaire (SHQ): The questionnaire comprised of 29 questions separated into three categories daily functioning, physical functioning and emotional functioning and is based on a 7-point Likert scale (Cox *et al.*, 2003).

International Physical Activity Questionnaire (IPAQ): IPAQ comprises of 27 items across five activity domains asked independently.

Fatigue Assessment Scale (FAS): - FAS is a 10-item questionnaire with a 5-point likert scale, it is split into 5 physical fatigue and 5 mental fatigue questions.

Borg rate of perceived exertion and Borg Dyspnoea: The Borg rate of perceived exertion scale (Borg RPE) allows participants to express how exerted they feel via a numbered scale (Borg, 1982), modified Borg Dyspnoea scale (Borg DS) allows participants to express their shortness of breath (Borg, 1982).

Oxygen saturation levels (SpO₂): Oxygen saturation levels of participants was recorded during the 6MWT via a portable pulse oximeter, the device was fitted to the participants finger and checked every 30 seconds throughout.

Isokinetic Dynamometer: A Biodex system was utilized to look at dominant upper and lower limb strength via elbow flexor muscle strength (EFMS), quadriceps peak torque (QPT) and hamstring peak torque (HPT) tests, with rest periods of 60 seconds between repeated tests as per Parcell *et al.* (2002) research findings.

Hand Dynamometer: Utilised to measure hand grip strength following ACSM (2014) guidelines.

Accelerometer: Participants kept this on their persons (right hip) for five days, starting the morning following their lab visit to measure real world physical activity. Set up included initializing the device and setting the sample rate to 100Hz, inputting start and end time as well as participant information (gender, stature, mass, age, ethnicity) in addition to location of the device (right hip) and whether this was their dominant side. Participants were required to wear the device for a minimum of seven hours per day, for a minimum of four days over the five-day wear period.

7.3.4. *Data analysis*

The data were analysed via SPSS 24.0 (IBM Corp, Armonk, New York). An exploratory data analysis was first completed; the data was normally distributed and therefore met parametric assumptions, a paired samples t-test was utilized in addition to a bivariate correlation between the different variables. Bivariate correlation strength was based on Evans (1996) guide (weak = .2 - .39, moderate = .4 - .59, strong = .60+). Data are presented as mean and standard deviation (SD). In addition to this, multiple regression was carried out to look for predictors of the different variables such as accelerometer MVPA. Analysis of the raw accelerometer data was conducted through Actigraph (ActiGraph, Pensacola, Florida), Freedson VM3 (2011) (Sasaki *et al.*, 2011) was used for energy and cut-point calculations before being exported to excel and transferred for analysis within SPSS.

7.4. **Results**

Of the eight participants who undertook the study, there were no drop-outs. Table 18 displays the characteristics of the participants who partook in the study. The age range of participants was 36-61 years, with body fat range 10.30-60.00%, males fell within lean (6-17%) and normal (18-22%) while three females fell within overweight (32-39%) and two within obese (40%+). This is in contrast to participants BMI score, three

participants were reported as obese (30+) via the BMI scale (National institute for health and care excellence, 2014), one as overweight (25-29.9) and four were a healthy weight (18.5-24.9).

Table 18. Characteristics of Subjects.

Characteristics	All (n=8)	Male (n=3)	Female (n=5)
Age (yrs)	50±8	46±10	53±6
Stature (cm)	172.01±10.33	182.53±7.49	165.70±5.56
Mass (kg)	81.32±17.94	72.63±3.19	86.53±20.89
Body fat (%)	32.63±15.17	15.91±4.05	42.66±9.50

Table 19 highlights the recorded measurements for both first and second visit, in addition to any statistically significant differences between them. Both hamstring peak torque and percentage of predicted FVC were found to be significantly different between visits ($P < 0.05$). 6MWD mean changed by 34.25m however no significant statistical difference was observed ($P > 0.05$), while EFMS & QPT results showed a small but non-significant increase non-significant ($P > 0.05$).

Table 19. Mean, standard deviation and statistical significance of lung function, six-minute walk test, borg exertion & dyspnoea as well as muscle strength, including significance between visits.

Measurement	First Visit	Second Visit	Sig.
FEV ₁ (L)	2.60±0.80	2.68±0.87	.107
% FEV ₁ (%)	84.10±14.28	86.52±13.73	.114
FVC (L)	3.00±0.93	3.36±1.25	.057
%FVC (%)	80.87±14.82	88.92±12.70	.037*
PEF (L/m)	6.74±1.84	6.45±1.19	.510
6MWD (m)	565.63±88.55	599.88±69.34	.069

Borg RPE	11±1	10.5±2	.313
Borg Dys	2.5±1	2.5±1	.856
EFMS (N·m)	22.63±6.46	26.26±7.87	.065
QPT (N·m)	56.81±23.84	74.81±16.47	.075
HPT (N·m)	25.50±11.05	36.69±11.35	.015*
HGS (kg)	34.75±14.39	32.75±12.98	.082

Asterisk (*) = Significant difference (P<0.05); Borg RPE = Borg rating of perceived exertion; Borg Dys = Borg scale of dyspnoea;

HGS = handgrip strength; HPT = hamstring peak torque; QPT = quadricep peak torque; EFMS = elbow flexor muscle strength;

6MWD = six minute walk distance; PEF = peak expiratory flow; %FVC = percentage of forced vital capacity; = FVC = forced vital capacity; %FEV1 = percentage of forced expiratory volume in one second; FEV1 = forced expiratory volume in one second.

Table 20 shows the reported quality of life for both genders. The overall mean for SHQ was 4.26, with males scoring higher in total and every sub-scale (EF, PF & DF) than their female counterparts. Mean score for fatigue was 27.88, with females self-reporting higher levels of fatigue (28.60), with one extreme fatigued and four fatigued in comparison to males (26.67), with one extreme fatigued and two non-fatigued. There was no significance difference between the genders for any of the variables reported in the table (P>0.05).

Table 20. Showing mean and standard deviation of quality of life, fatigue (no statistical difference between the genders P > 0.05).

Variables	All	Male	Female
SHQ	4.26±0.90	4.77±0.95	3.96±0.70
EF	4.08±0.81	4.57±1.00	3.78±0.74
PF	4.31±1.04	5.06±1.00	3.87±0.78
DF	4.40±1.04	4.67±1.19	4.24±0.90
FAS			
Fatigue Score	27.88±9.32	26.67±13.89	28.60±4.67

No Fatigue	2	2	0
Fatigued	4	0	4
Extreme Fatigue	2	1	1

SHQ = Sarcoidosis Health Questionnaire; EF = Emotional functioning; PF = Physical Functioning; DF = Daily Functioning; FAS

= Fatigue Assessment Scale.

Table 21 shows self-reported physical activity via IPAQ and measured physical activity via accelerometer. Four self-identified as high physical activity status, with two each in low and moderate categories. Moderate and vigorous physical activity (MVPA) per day was 152mins for self-reported (IPAQ). The male participants reported higher amounts of MVPA than their female counterparts (309 & 57 mins, respectively; $P = 0.768$). In addition, sitting time per day was reported as 448mins per day, participants sat for just under three times their reported MVPA. However, the table included two male outliers (reported excessive MVPA, up to 23 hours per day) without their inclusion the mean met-minutes/week were 2078 ± 1798 while MVPA per day was 55 ± 64 , a substantial difference. The outliers would have been excluded completely if the sample size was bigger as their reported MVPA was not representative of achievable within daily hours. The accelerometer data recorded MVPA as 109mins per day over a five-day period, where males recorded higher levels of MVPA than females (118 & 104, respectively) albeit with a smaller difference than IPAQ MVPA (14min difference, $P = 0.946$). Accelerometry also reported smaller standard deviations than the IPAQ for example IPAQ MVPA per day SD was 182 compared to 44 for the accelerometer. No statistical difference was reported between the genders for accelerometer MVPA or IPAQ MVPA ($P > 0.05$), or any of the other variables (Met-minutes/week, Kcals per day, sitting per day and steps per day).

Table 21. Highlighting the differences between self-reported physical activity and real world physical activity.

Physical activity status	All	Male	Female
IPAQ			
Low	2	0	2
Moderate	2	1	1
High	4	2	2
Mets-Minutes/week [#]	6755±8467	14171±9861	2305±1886
7 Day MVPA (mins) [#]	1061±1274	2163±1410	400±487
MVPA per day (mins) [#]	152±182	309±201	57±70
Sitting per day (mins)	448±117	397±123	478±102
Accelerometer			
5 Day MVPA (mins)	503±239	568±237	463±231
MVPA per day (mins)	109±44	118±42	104±45
Moderate Activity per day (mins)	82±32	86±21	79±33
Vigorous Activity per day (mins)	27±13	32±12	24±13
Average Kcals per day	824±399	789±271	844±458
Steps per day	7258±2199	7734±2666	6973±1804

IPAQ = International physical activity questionnaire; MVPA = moderate to vigorous physical activity; # = including two male outliers.

Table 22 highlights the results of a multiple regression into predictors of accelerometer MVPA. Calories burned per day and BMI were found to be significant predictors, explaining 96.8% of the variance within the data.

Table 22. Multiple regression predictors of accelerometer MVPA.

Model	R ²	B	Sig.
1			
Constant		34.24	.183
Kcals per day	.783	.09	.019
2			
Constant		83.209	.011
Kcals per day		.12	.003
BMI	.968	-2.53	.025

Kcals per day = calories burned per day. BMI = body mass index. Dependent variable = accelerometer MVPA.

Table 23 highlights the results of a multiple regression into predictors of fatigue. Only quality of life findings via the SHQ was found to be a significant predictor, explaining 79.7% of the variance within the data.

Table 23. Multiple regression predictors of the fatigue assessment scale

Model	R ²	B	Sig.
1			
Constant		49.93	.001
SHQ	.797	-5.38	.017

SHQ = Sarcoidosis health questionnaire. Dependent variable = Fatigue (Fatigue assessment scale).

Table 24 highlights the results of a multiple regression into predictors of the distance walked in the six-minute walk test (6MWD). Gender and BMI were found to be significant predictors, explaining 99.1% of the variance within the data.

Table 24. Multiple regression predictors of the six-minute walk distance

Model	R²	B	Sig.
1			
Constant		980.10	.001
Gender	.880	-220.10	.006
2			
Constant		1014.295	.001
Gender		-177.02	.001
BMI	.991	-3.809	.009

BMI = body mass index. Dependent variable = Six-minute walk distance

Table 25 highlights the results of a multiple regression into predictors of fatigue. Only elbow flexor muscle strength was found to be a significant predictor, explaining 91.3% of the variance within the data.

Table 25. Multiple regression predictors of the Handgrip strength

Model	R²	B	Sig.
1			
Constant		-7.04	.283
EFMS	.913	1.62	.003

EFMS = elbow flexor muscle strength. Dependent variable = Handgrip strength.

Table 26 highlights the results of a multiple regression into predictors of fatigue. Only hamstring peak torque found to be a significant predictor, explaining 87.3% of the variance within the data.

Table 26. Multiple regression predictors of the quadriceps peak torque

Model	R²	B	Sig.
1			
Constant		17.60	.135
HPT	.873	1.53	.006

HPT = Hamstring peak torque Dependent variable = Quadriceps peak torque.

7.5. Discussion

The primary aim of this study was to ascertain physical activity patterns and understand differences between perceived physical activity and actual physical activity in pulmonary sarcoidosis patients. Furthermore, in order to gain greater insight and understanding into the effect of pulmonary sarcoidosis on physical activity, muscle strength, quality of life, exercise capacity, lung function and oxygen saturation were also measured.

7.5.1. *Physical activity self-reported and real world*

The main findings of this study highlight the differences between perceived and actual physical activity levels as well as issues surrounding self-reported physical activity in addition to growing the body of knowledge within the clinical population of pulmonary sarcoidosis. Four participants self-reported high levels of physical activity with two each in moderate and low. Males self-reported higher Met-minutes/week (14171) than females (2305), a difference of 11866 met-minutes/week. However, those data include the two male outliers and without their inclusion the one other male reported 918 compared to the female mean of 2305. The two outliers were included as participants, both reported up to a possible 23 hours day of physical activity, much of it moderate or vigorous, excluding sleep or sitting time). This highlights issues associated with self-reported questionnaires, for example within the IPAQ the questions are open-ended for activity levels across a range of situations (work, commuting, leisure) and as such the hours are unlimited for each scenario. Although it is worth noting due to the format of the questionnaire, it is impossible to say which day of the week involved which activity. This is a key limitation of the IPAQ and should be addressed by changing the question from asking how many days per week to having separate and defined boxes for each day of the week and their relevant

physical activity for each category. This way researchers would be able to break down and rank their physical activity to each day of the week. In addition to between genders within genders there was also a large variation in reported Met-minutes/week with standard deviation being 9861(males) and 1886 (females), the male's standard deviation is inflated by the outliers however the female's standard deviation is still high. These large differences highlight the limitations associated with self-reported physical activity such as being less robust at measuring light-moderate activity, over- and under-estimation of activity levels and requiring participant recall of past events (Sylvia *et al.*, 2014) and as such is highlighted by the outliers met-minute/week totals of 17037 and 24558. The two outliers are extreme examples of limitations associated with the IPAQ as well as the effect of a small sample size (n=8). In addition to the lack of clear days of the week being reported within the IPAQ, the number of working hours and how many days per week worked being specified by a participant was also a shortcoming too. For example, the first outlier reported four hours of walking five days per week, six hours of moderate activity four days per week and six hours of vigorous activity one day per week for just their work physical activity. They also reported high levels of activities at home (5 hours of house chores twice per week). While the other four hours of walking five days per week, six hours of moderate activity five days per week and eight hours of vigorous activity twice per week, Hastromer *et al.* (2005) also found similar outliers with extremely high levels of physical activity such as five hours cycling to and from work daily and a minimum of 60-120 minutes of vigorous activity at work daily. The outliers may arise through a misunderstanding of the questions asked, these overestimations may have been avoided if participants were required to state how many days they worked in the last seven weeks and their number of hours worked before progressing to levels of activity.

Further, improvements could be made by highlighting the guidance that the IPAQ only wants activities that lasted a minimum of ten minutes at a time, much like it's current highlighting of only involving the last seven days. Another adjustment to improve the accuracy of the IPAQ would be to include an example completed IPAQ beforehand involving their answers and a description of their day/week such as moderate/vigorous activity being less than the requested minimum length and as such not being included within their answers. It is worth noting dyspnoea is a major issue within sarcoidosis (Baughman, 2013) and may in-part explain the overestimation of MVPA within the IPAQ, as vigorous activity is described as making you breathe much harder than normal while moderate activity should make you breath somewhat harder than normal. Therefore, the IPAQ may need to be modified specially for sarcoidosis to ensure accurate results.

The current guidelines recommendation of 600 met-minutes/week (Kyu *et al.*, 2016) have been argued as being set too low. Disease risk including diabetes, breast & colon cancer and stroke events have recorded major reductions with physical activity up to 3000-4000 met-minutes/week (Kyu *et al.*, 2016) with further reductions noted at higher amounts too, albeit at a lower percentage rate (Kyu *et al.*, 2016). Through the IPAQ, both genders reported above minimum met-minutes/week (14171 & 2305, respectively), although females (n =5) are missing potential health benefits compared to their male counterparts (n=3). Kyu *et al.* (2016) meta-analysis found those reported as highly active (>8000 met-minutes/week) had risk reductions of 21% for colon cancer, 28% for diabetes and 26% for stroke events compared to inactive individuals (< 600 met-minutes/week). However, it is worth noting the limitations of self-reported data, for example moderate-vigorous physical activity (MVPA) per day within the IPAQ was recorded as 152mins with a higher standard deviation (182) and thus

highlights the issue, further demonstrated by the accelerometer MVPA per day (109 ± 44) being 39% less than self-reported with a much smaller deviation, although which does include the outliers. Males (including the two outliers) reported 252 more MVPA minutes per day than females (57 minutes) via the IPAQ, despite only recording a mean difference of 32 minutes (12%) more via the accelerometer, which implies males over-report their physical activity and shows the accelerometer to have increased validity against the self-reported IPAQ. The males (including two outliers) reported a 62% reduction on their IPAQ accelerometer MVPA compared to their self-reported data while females under-reported their MVPA via the IPAQ by 28%. The two outliers mean difference between accelerometer MVPA and IPAQ is a 74% overestimation while interestingly when excluding the outlier's participants under-reported their IPAQ MVPA with a 91% difference between MVPA IPAQ and accelerometer. This again highlights the serious limitations and issues with self-reported measures and specifically the IPAQ as the adjusted participants real world physical activity nearly doubles (91%) their reported levels. Interestingly, the outlier participants were closer to their real physical activity levels than the adjusted remaining participants. In addition to the issues stated above regarding the outlier's discrepancies, greater details with regards to the types of activities that are included within moderate and vigorous activity may help reduce levels of under-reporting. Additionally, discrepancies such as the 91% under-reporting may arise due to the different methods applied between the IPAQ and accelerometer. For example, the IPAQ only wants moderate/vigorous activity reported that lasted at least 10 minutes while an accelerometer records all activity while worn and therefore MVPA bouts of five minutes for example would not be reported if following the IPAQ correctly which in turn may build up across a day/week if a participant conducts numerous short bouts

of MVPA. Dyrstad *et al.* (2014) reported a 47% difference between males and females via self-reported IPAQ results compared with difference between the genders from the accelerometer data. Hagstromer *et al.* (2010) suggests participants field of work may affect the efficiency of the accelerometer such as manual activities which is generally a male occupation and thus is partly behind the discrepancies in addition to differential bias between education groups. Unfortunately, the lack of data on job & educational level within our study does not allow us to understand or adjust for these confounding factors. Numerous collected variables within chapter seven such as MVPA IPAQ, age, gender, HGS, EFMS, QPT, HPT, FAS, SHQ, calories burned per day, BMI, steps per day and body fat percentage were utilised within a multiple regression to investigate whether any were significant predictors of accelerometer MVPA. The results showed only calories burned per day and BMI were predictors, explaining 94.7% of the variance within the data. Both variables were significant contributors to the model calories burned per day ($B = .118$, $P = 0.001$) and BMI ($B = 2.528$, $P = 0.025$). Accelerometer MVPA and IPAQ MVPA were found not to be predictors of each other within the study's findings, there was a difference of 39% between accelerometer MVPA and IPAQ MVPA, which highlights a difference between people's perception and/or memory recall with real world activity. However, it is worth noting the sample size for this analysis was very small ($n=6$) which was made smaller by the removal of outliers. The issue of people's perception of physical activity is exemplified by the two outliers due to their 74% overestimation and the other participants under-reporting (91%). Calories burned per day was found only to be a predictor of accelerometer MVPA ($R^2 = .783$) and not IPAQ MVPA, BMI was however found to be a predictor of calories burned per day. Therefore, further research should be contacted regarding the usefulness/accuracy & validity of using the IPAQ within Sarcoidosis. Raask *et al.*

(2017) found a correlation of .31 between short form IPAQ and accelerometer in adolescent boys, vastly different to this study's findings. Interestingly the boys underreported their MVPA similar to this study's finding however the boys underreported by 13 minutes compared to 43 minutes within the current study, a marked difference. Raask *et al.* (2017) states that to use self-reported questionnaires as a measure of meeting guidelines than greater accuracy is required in addition to correlational agreement such as the large difference of 43 MVPA minutes per day within the current study. Adults have been shown to typically overreport their activity levels via the IPAQ in comparison to accelerometer data (Boon *et al.*, 2008; Ottevaere *et al.*, 2011; Benefitez-Porress *et al.*, 2013; O'Neill *et al.*, 2017). Boon *et al.* (2008) found a seven-day overestimate of 583 minutes for the IPAQ against the accelerometer data, one strength of Boon *et al.* (2008) research was the immediate IPAQ testing following the completion of the seven-day accelerometer wear time. A limitation of the current study methods was that participants self-reported physical activity was recorded on their first visit, following which they then wore the accelerometer and due to this the results may vary slightly as activity does week to week and is not a direct measure covering the IPAQ's timeframe. Furthermore, the population in use may affect the accuracy and validity of the IPAQ. For example, O'Neill *et al.* (2017) found IPAQ under-reported sedentary but over-reported MVPA for Bronchiectasis patients against an accelerometer. While Sievi *et al.* (2017) reported an intraclass correlation of .40 for time spent in moderate physical activity (>MET) between accelerometer and self-reported physical activity with a 44.5% difference within COPD patients. Although, Sievi *et al.* (2017) utilised the German Physical Activity Questionnaire (G-PAQ-50+), which may in part explain the differences between this study and their findings, however it does highlight the lack of accuracy between self-reported physical

activity and accelerometer data within a respiratory condition. O'Neil *et al.* (2017) suggested that the IPAQ is not an accurate measure within the bronchiectasis population and therefore this may be the case for the Sarcoidosis population too, however more research within this area is required for a greater understanding, including the validation of the IPAQ within sarcoidosis. A systematic review by Lee *et al.* (2011) found no studies met minimal acceptable standard of correlation (.50) with the studies ranging from .09-.39 for total physical activity level. Whilst a systematic review into direct versus self-reported physical activity (Prince *et al.*, 2008) found correlations were typically low-moderate and highlighted there is no clear pattern for mean differences. The current study's findings following a multiple regression show IPAQ MVPA do not predict real world physical activity levels, however further research is required with a much larger sample size. Self-reported methods resulted in higher physical activity levels measurements (Boon *et al.*, 2008; Ottevaere *et al.*, 2011; Benefitez-Porress *et al.*, 2013; O'Neill *et al.*, 2017), similar to the current chapter's findings. Da Silva *et al.* (2017) suggests both accelerometry and self-reported physical activity are complementary of one another and should be utilised in combination. It is worth noting participants' physical activity within this study are well above current guidelines for physical activity (150mins moderate or 75mins of vigorous/combination of both; Department of Health, 2011) with the equivalent of 137 minutes of physical activity per day when vigorous activity is adjusted (one-minute vigorous activity equals two minutes of moderate activity according to current guidelines (Department of Health, 2011). This implies that they surpass the weekly guidelines by 809 adjusted minutes but somehow fall below the 10,000 steps per day (Tudor-Locke & Bassett, 2004). This data subverts the current understanding of physical activity within the sarcoidosis population, with Korenromp

et al. (2011) and Saligan (2014) both finding physical activity reduced to normative figures as well as age, gender and ethnicity-matched healthy sedentary controls (Saligan, 2014). The reason behind this is unclear however a sample size ($n=8$) can be considered one potential reason for these findings and highlights the need for further research into physical activity as there are no clear patterns for the sarcoidosis population as a whole. Another possible reason may be due to the combination of the complexity of physical activity and its associated factors (Kohl *et al.*, 2012). In addition to the diverse nature of sarcoidosis (Baughman, 2013) and therefore creates a wide range of potential interactions between the two. Such as, high levels of drive and self-efficacy for physical activity/exercise within an individual coupled with severe fatigue and dyspnoea, or sarcoidosis limiting the patient's ability to work and thus effects their socio-economic status and ability to partake in their preferred activities. These diverse possible interactions may be leading to extremely varied physical activity patterns across the disease. Currently, the effect of sarcoidosis on physical activity is not known and may be less influential than other factors associated to physical activity such as lifestyle. Fatigue has previously been associated with reduced activity levels (Korenromp *et al.*, 2011; Saligan, 2014) while the current chapter following a multiple regression found only the SHQ was a predictor of FAS from the study's variables ($R^2 = .797$). Interestingly, Bahmer *et al.* (2018) found there to be a weak correlation (.254) between physical activity (classified as steps per day) and fatigue (MFI-20). While none of the other variables were found to be predictors of steps per day within this current study. The variances between the research are not clear but the two different measures of fatigue may play a role as well as the complexity and diverse nature of physical activity and the condition mentioned above. Interestingly, both accelerometer and IPAQ MVPA were not predictors of QOL and

thus highlights the multifaceted nature of quality of life and people's perception of what is beneficial to their QOL. Moreover, 6MWD, hand grip strength, elbow flexor muscle strength, quadricep peak torque and hamstring peak torque were also not found to be predictors of accelerometer MVPA. One potential reason for this may be because MVPA does not stipulate what activity is being conducted i.e. strength training/running/cycling etc. and therefore it is certain activities conducted and not simply physical activity itself that influences these variables. Additionally, MVPA only takes up a small amount of time within an individual 24-hour day cycle (Rosenberger *et al.*, 2016), the current study finding of 109 minutes per day only represent 8% of their 24-hour cycle and therefore light intensity physical activity may also play an influential role. Furthermore, despite females meeting and surpassing current physical activity guidelines they recorded above recognised acceptable levels of body fat (42.66%; Jeukendrup & Gleeson, 2010). Much like the rest of this disease the reasons behind this are unclear and there are likely multiple reasons playing a part. One factor may be steps per day, females recorded a daily mean of 6973 steps, 30.27% lower than the recommendation of 10,000 (Tudor-Locke & Bassett, 2004). This suggests despite participants undertaking higher than suggested MVPA, their movement levels outside of this are reduced and/or limited, this may be due to many factors such as type of work or other lifestyle factors of participants. Furthermore, although participants within this study were found to be surpassing physical activity guidelines, outside of physical activity and MVPA of an individual prolonged sitting has been noted as having detrimental cardiovascular and metabolic effects (Hamilton *et al.*, 2008). This study found participants sat for more than 7 hours per day (448mins). Owen *et al.* (2010) states prolonged bouts of sitting compromises metabolic health despite reaching recommended physical activity levels across the

duration of the day/week. Dunstan *et al.* (2012) states prolonged sedentary behaviour such as sitting is associated with numerous health outcomes including type 2 diabetes and premature mortality rates. It is worth noting however breaks in sedentary time has been associated positively with reduced metabolic risk independent of total sedentary time and MVPA (Healy *et al.*, 2008). The area is continuing to build a body of knowledge, however research focusing on children aged between 8-11 years has shown frequent breaks in sedentary time and sedentary bouts lasting 1-4 minutes have been associated with reduced metabolic risk and BMI scores in comparison to longer bouts of sedentary behavior (Saunders *et al.*, 2013). Future findings from this area will be able to address issues with both sarcoidosis and public health.

7.5.2. *Exercise Capacity*

Participants recorded a 6MWD of 565.63m (visit 1) and 599.88m (visit 2) with no significant difference between the two visits ($P>0.69$). Their mean across the two visits was 582.75 ± 81.35 m, which is 11.75m further than Casanova *et al.* (2011) mean of healthy subjects. Although it is worth noting Casanova *et al.* (2011) had a much larger sample size ($n=444$) and conducted the research with people ranging from 40-80 years of age with a distance covered range of 380-782m and therefore may help explain the mean score as age has been shown to be linked with 6MWD (Chetta *et al.*, 2006) with the effect of age more prominent in those >60 years of age (Casanova *et al.*, 2011). Additionally, Casanova *et al.* (2011) found 69% of participants walked further in their second test and this may part explain the increased distance between visits one and two, potentially due to familiarisation with the procedure or a desire to better their previous distance. However, the current study's finding may not be representative of the population as a whole due to the limited number of participants and their physical activity levels within the study compared to previous research (Korenromp *et al.*,

2011; Saligan, 2014). Sarcoidosis has been associated with decreased 6MWD when compared against a healthy population previously (Baughman *et al.*, 2007). Baughman *et al.* (2007) found 51% walked < 400 metres whilst 22% walked <200 metres compared to a healthy population with a mean of 571 metres (Casanova *et al.*, 2011). A combination of reasons has been suggested for this. Kallianos *et al.* (2015) associated ventilatory and cardiocirculatory issues such as arrhythmias and advanced heart block (Doughan & Williams, 2006). Whilst, Bourbonnais and Samvati (2008) found those with sarcoidosis- associated pulmonary hypertension had lower 6MWD than sarcoidosis patients without, supporting ventilatory and cardiocirculatory problems as delimitating factors (Kallianos *et al.*, 2015). Wallaert *et al.* (2011) reported impaired heart rate and circulatory impairment as mechanisms for limiting exercise capacity following cardiopulmonary exercise testing at lower radiographic stages of sarcoidosis (I & II) however the research also suggests the latter stage (IV) limitations are influenced greater by ventilatory and gas exchange impairments. Thus, there appears to be a greater dynamic nature to the mechanisms behind this reduction to exercise capacity than currently understood, therefore ventilatory and cardiocirculatory cannot be thought of as the only explanation. Within the current study however radiographic stage was not recorded and as such it is unclear the role radiographic stage played on the results. For example, it is unknown whether recruitment and participation involved more motivated individuals who in turn are more active and take more care due to the condition and thus were able to walk further compared to others with progressed levels of sarcoidosis with other underlying health issues. Exercise intolerance is the impaired ability to perform physical exercise in comparison to normative values (Kitzman & Groban, 2011). Exercise intolerance is multi-factorial (Kitzman & Groban, 2008) and includes factors such as muscle

weakness and poor lung function, both of which are often compounded by the effects of deconditioning (Strookappe *et al.*, 2015). Garin *et al.* (2009) states regarding interstitial lung disease (ILD), 6MWD analysis should consider vascular, pulmonary and musculoskeletal exercise limitations. Additionally, Quesada-Rodriguez *et al.* (2014) states pulmonary rehabilitation is underutilised within ILD including sarcoidosis despite participants benefiting as much as other groups such as COPD (Pitta *et al.*, 2008; Puhan *et al.*, 2011) which have a much higher rate of pulmonary rehabilitation. Benefits include improvements to dyspnoea, QOL and functional exercise capacity (6MWD) (Holland *et al.*, 2008) although long term effects need further research (Holland *et al.*, 2008), Ryerson *et al.* (2014) found improvements to physical activity, depression score and QOL were significantly better at 6 months follow-up than pre-pulmonary rehabilitation, although Egan *et al.*, (2012) found despite pulmonary rehabilitation in COPD improving exercise capacity, physical activity remained unchanged from baseline and thus highlights the complex nature of physical activity. It is worth noting that $\dot{V}O_2\text{max}$ has been shown to improve following resistance training in non-clinical subjects with low scores ($\leq 25\text{ml/kg/min}$ and $\leq 40\text{ml/kg/min}$) in older (60 years+) and young (20-40 years), respectively; (Ozaki *et al.*, 2013). The effect of resistance training for improving $\dot{V}O_2\text{max}$ in clinical populations such as ILD is currently unknown. Delobbe *et al.* (2002) states $\dot{V}O_2\text{max}$ is typically impaired 25-30% in sarcoidosis although the studies did not differ between those with normal and impaired pulmonary or muscle function. Delobbe *et al.* (2002) suggested impaired heart rate response to exercise, alongside the ventilatory issues within pulmonary sarcoidosis. Additionally, there are also musculoskeletal issues, such as, decreased muscle strength (Strookappe *et al.*, 2015) affecting patients in a wide range of ways; exercise capacity & tolerance, QOL and deconditioning to name

a few (Mitchell *et al.*, 2012; Fleischer *et al.*, 2014; Marcellis *et al.*, 2013a; Strookappe *et al.*, 2015).

The 6MWD following a multiple regression of this study's variables was found only to be predicted by gender and BMI ($R^2 = .985$). The findings indicated that the model explained 98.5% of the variance and that the model was a significant predictor of 6MWD, $F(2,3) = 166.47$, $P = .001$. Gender ($B = -177.02$, $P = 0.001$) and BMI ($B = -3.809$, $P = 0.009$) contributed significantly to the model. Marcellis *et al.* (2013b) findings of a low correlation (.39) between QOL (World Health Organization quality of life – Brief; WHO-B) and 6MWD% predicted although it is worth noting a different QOL questionnaire was used (WHO-B & SHQ) as well as the slightly different variable. Although maximal testing such as the $\dot{V}O_{2max}$, which is utilised to measure the amount of oxygen the body can consume and use aerobically when performing maximal intensity exercise therefore defining the upper limits of the cardiorespiratory system (Hawkins *et al.*, 2007), is considered safe within healthy populations, those with underlying disease (i.e. Sarcoidosis) have an increased risk of complications and adverse effects (Roca *et al.*, 1992) such as exacerbating symptoms including chronic cough and dyspnoea. Therefore, another method of testing is required; this leads us to VO_{2peak} prediction models, however there are numerous known limitations to these including limited gender and age representation as well as lack of adjustment for varying fitness levels (Tsiaras *et al.*, 2010; Kendall *et al.*, 2012; Lamberts & Davidowitz, 2014). Prediction models are only useful within a very limited range of participants similar to those used when creating the model (Malek *et al.*, 2005). Previously, fat free mass and BMI has been associated with 6MWD within obese individuals (de Souza *et al.*, 2009; Correia de Faria Santarem *et al.*, 2015), while

Olufunke *et al.* (2014) only found a weak correlation (.356) within healthy participants. Interestingly however Rastogi *et al.* (2012) found that in asthmatic adolescents, a condition sarcoidosis is often mistaken for (Kalkanis & Judson, 2013), BMI was a significant predictor of 6MWD for obese participants whilst percent predicted FEV₁ predicted 6MWD in normal weight participants. Neither were found to be predictors within the current study's findings although this may be due to a small sample size (n=8). Zielesnik *et al.* (2015) found fatigue not to be correlated to 6MWD (.01), a similar finding to this study's results, therefore despite fatigue being perceived as highly disabling, its effect may be separate to exercise performance. One possibility is although fatigue is self-reported as highly disabling it not the key factor for exercise performance due to the range of other issues such as cardiovascular, pulmonary and musculoskeletal and because of this performance is inhibited before fatigue can play a role (Zielesnik *et al.*, 2015). There is still a great amount of research required to fully understand the different variables and how they interact with each other as well as the extent of their interactions.

Based on Alangari and Al-Hazzaa's (2004) research of isokinetic peak torque in young male adults as normative values (QPT = 67.4 N·m; HPT 41.9 N·m) participants recorded 97.64% and 74.22% of their predicted QPT and HPT. A limitation of using these values is the population as they were young adult males and therefore do not accurately represent the participants within our study, another limitation of our study was the lack of an age, gender matched healthy control group to use for normative values. Cremers *et al.* (2013) found 25% of sarcoidosis participants within their study suffered from muscle atrophy, Spruit *et al.* (2005a) found participants scored 87% & 67% of their predicted hand grip strength (HGS) and quadricep peak torque (QPT) respectively, while Marcellis *et al.* (2011) found scores of 96% for handgrip and

79.3% for QPT against an age and gender matched control. Participants mean score from two visits was 62.85 N·m for QPT and 48.35 N·m for HPT, in comparison to this study's findings of 65.81 N·m for QPT and 31.10 for HPT. The difference in HPT observed may partly explain the reduced 6MWD (mean = 582m) of participants in this study against Marcellis *et al.* (2011) sarcoidosis participants (618m). Strookappe *et al.* (2015) used Marthiowetz *et al.* (1986) handgrip scores to calculate percentage of HGS within their study, based on this method this current study's results show participants scored 93.77% in comparison to Strookappe *et al.* (2015) findings of 89.6% pre-intervention, it is worth noting however that HGS normative scores were based on 19 years of age participants and therefore may not accurately represent the clinical population's true predicted HGS, nonetheless these findings once again highlight the differences across sarcoidosis patients and as such reinforce the complexity of the issue. Marcellis *et al.* (2011) also reported percent of population with muscle strength reductions recording HGS (15%), EFMS (12%), QPT (27%) and HPT (18%). This highlights the prominence of reduced muscle strength across the population although it is too simplistic to state sarcoidosis as the only cause for the reported reductions, due to this we need greater research to understand the role of the disease with regards to muscle strength. Physical inactivity (disuse) is one confounding factor for muscle strength with both sarcoidosis and non-disease aspects, while others factor non-specific to the disease include age and gender. This is a very important area within sarcoidosis as muscle weakness is associated with increased all-cause mortality in all populations, specifically the elderly (Rantanen, 2003; Clark & Manini, 2010). Ruiz *et al.* (2008) found the association between muscle strength and all-cause mortality continues following adjustment for cardiorespiratory fitness. Therefore, one future direction is for major muscle groups across the body to be looked at in both isolation

and together to further understand the reasons behind the increased mortality rates. Swallow *et al.* (2006) found quadricep strength in COPD predicts mortality, whilst Bohannon (2008) argues hand-grip strength measured via a dynamometer should be considered a vital measure, Norman *et al.* (2011) states hand grip strength can predict short and long-term mortality, thus further research is required to gain a greater understanding of the role and effect of muscle strength within sarcoidosis. Additionally, further research is needed between exercise performance and the effects of delimitating factors on exercise capacity and whether it is relevant to adjust the results of these tests such as $\dot{V}O_2\text{max}$. Strookappe *et al.* (2016) found lower limb strength correlated closer to 6MWD than upper limb, likely due to the physiological demands of walking as the findings are as expected within sarcoidosis and healthy populations too. Strookappe *et al.* (2016) muscle strength test of chair rise time (CRT) measuring quadricep strength was less correlated (.48) than the current study's QPT (.843, $P = 0.009$). The discrepancy may arise from the differences of testing, isokinetic QPT isolates the quadriceps strength while CRT relies upon a number of other muscles such as glutes and hamstrings. And thus, weaknesses elsewhere or issues with balance may affect the outcome, leading to an untrue representation of muscle strength. Currently it is not clear in sarcoidosis patients the degree to which muscle weakness, cardiocirculatory and ventilatory issues affect exercise capacity. For example, the current body of knowledge does not identify whether improving muscle strength to normative levels improves patients $\dot{V}O_2\text{max}$ or whether the ventilatory issues limit the capacity before muscle strength becomes a delimiting factor. Although, it is worth noting Delobbe *et al.* (2002) found reduced maximal exercise capacity within sarcoidosis patients without impaired pulmonary function. Despite these current shortcomings, there is a growing area of literature of exercise rehabilitation within

sarcoidosis including both cardiovascular activities as well as weight bearing exercises (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015; Naz *et al.*, 2018). At present only three studies have researched exercise rehabilitation as a treatment and management method to improve symptoms and QOL (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015; Naz *et al.*, 2018) although results thus far have been promising with statistically significant ($P < 0.05$) improvements recorded for muscle strength, exercise performance, fatigue scores and QOL. Each study had a different rehabilitation program however, of the three, Strookappe *et al.* (2015) had the largest improvement for 6MWD (70m) and FAS (decrease of 3.8). Strookappe *et al.* (2015) also recorded a significant ($P < 0.05$) improvement to EFMS of 7.8% predicted value, whereas Marcellis *et al.* (2015) reported only a non-significant improvement ($P > 0.05$) although Marcellis *et al.* (2015) did report a significant ($P < 0.05$) improvement of 10.7kg in weight lifting strength of the quadriceps. The difference of results is likely attributed to the difference in training methods, Marcellis *et al.*'s (2015) weight lifting exercises started at 40% maximum multiple repetition and increased progressively by 3%, while Strookappe *et al.* (2015) utilized patient feedback and aimed for an intensity of 13-15 on the Borg scale, reassessing and adjusting after every session, Naz *et al.* (2018) also utilized patient feedback however they used the Borg modified dyspnea scale aiming for 4-6. Therefore, future research must focus on optimising exercise as a rehabilitation method, likely personalised to each undergoing patient due to the complexity of the condition.

Handgrip strength is already utilised across different populations and conditions due to its correlations with mortality (Oksuzyan *et al.*, 2017) and test-retest ability (Haward & Griffin, 2002). Following a multiple regression involving this study's

variables, only EFMS was found to be a significant predictor of HGS ($R^2 = .913$, $F(1,4)$, $P = .003$). While HGS reported significant ($P < 0.05$) strong bivariate correlations with gender (.809, $P = 0.015$), FEV₁ (.885, $P = 0.003$), FVC (.865, $P = 0.006$), PEF (.921, $P = 0.001$) and body fat percentage (.794, $P = 0.019$) The findings warrant further investigation into the predictor values of HGS within pulmonary sarcoidosis, Jeong *et al.* (2017) found COPD patients QOL was associated with their HGS although this study's data reported a weak bivariate correlation of .193 ($P > 0.05$) for HGS and SHQ. Holmes *et al.* (2017) found elder people (>70 years of age) with a strong HGS were associated with a better PEF, while the current study's findings found a strong positive bivariate correlation between HGS and PEF (.921, $P = 0.001$) although following a multiple regression PEF was not found to be a predictor of HGS. QPT and HPT were the only predictors of each other ($R^2 = .873$, $F(1,4)$, $P = 0.006$). While HGS and EFMS were the only predictors of each other too ($R^2 = .913$, $F(1,4)$, $P = .003$), the reasons for this are not known but may be likely due to being utilised within the same activation phases/tasks. The findings suggest muscle strength is relatively stable across the body for sarcoidosis patients and that the condition does not prevalently isolate one specific muscle group.

7.6. Conclusions and Future Directions

Accelerometer MVPA was found to be predicted by calories burned per day and BMI, there was a large difference (43 minutes) between accelerometer and IPAQ MVPA. Only met minutes per week was a predictor for IPAQ MVPA. Participants scored below their predicted for muscle strength tests, HGS (93.77%), QPT (97.64%) and HPT (74.22%). Overall, the complexities and diverse nature of sarcoidosis was highlighted across the wide-ranging variables and there remains numerous questions to be answered. An increase in sample size is required, future focus on 6MWD and

HGS may be appropriate due to their bivariate correlations, potentially allowing the greater management and treatment of the disease. Exercise rehabilitation involving both cardiovascular and strengthening exercises shows promise within Sarcoidosis and further research must be conducted to understand not only the optimal exercise programme but also the long-term effects of rehabilitation and adherence once home-based. COPD and other ILD's rehabilitation research may work as a base for the expansion of this area. Physical activity patterns remain uncertain but represent an area which requires greater focus due to the known issues with inactivity. One future direction would be a larger sample sized study to allow for the distinguishing of separate and distinctive physical activity groups (low/moderate/high) and how their other variables (muscle strength, fatigue, lung function etc.) match up as well as greater information gathering on the forms of physical activity performed.

8. GENERAL DISCUSSION

8.1. Physical Activity

Physical activity was investigated across chapters four, five, six and seven. Methods for understanding physical activity ranged from a simple non-validated multiple choice closed-ended question focusing on how often they thought they were throughout a typical week, the international physical activity questionnaire and a tri-axial accelerometer. Interestingly, when asked through the multiple choice (chapter five) the majority of participants (65.52) reported no physical activity or less than two bouts per week of physical activity however when questioned on physical activity through the IPAQ within chapter six, only 16.98% fell within the low category. Although exact numbers are unknown it is likely many participants completed both chapter five and six due to the same recruitment methods being employed. The reason(s) for this stark change remain unclear but may be attributed to firstly a misunderstanding of the question within chapter five such as an oversight of what physical activity is and/or an overestimation of activity levels within the IPAQ when asked separately. Allender *et al.* (2006) states activities such as gardening and housework are not traditionally thought of as physical activity and as such participants may have ignored these activities when answering chapter five's question. Listing common traditional and non-traditional forms of physical activity may help combat any potential issue. On the other hand, physical activity levels within sarcoidosis has been shown to be diverse and the change in participants involved may explain the difference (Korenromp *et al.*, 2011; Saligan, 2014, Morton-Holtham *et al.*, ndB). For example, within chapter six participants reported 360 minutes of sitting per day compared to 448 minutes per day within chapter seven despite exceeding current physical activity guidelines derived from a tri-axial accelerometer (MVPA = 109mins

per day), the IPAQ derived MVPA was not found to be a predictor of accelerometer MVPA although a strong bivariate correlation was found (.875, $P = 0.022$) despite a large difference (43 minutes overreported per day via IPAQ) between the two instrument findings, which raises questions of accuracy and validity further coupled by the two outliers that reported a possible 23 hour day made up of walking plus moderate and vigorous activity excluding sleep and sedentary time. With regards to chapter six it is worth noting chapter six did not use an accelerometer and thus participants may have had higher real world MVPA than chapter seven participants. Additionally, reduced sitting time may relate to light physical activities and as such not be represented by MVPA. The current projects findings of above guideline MVPA was opposite to previous accelerometer research within sarcoidosis (Korenromp *et al.*, 2011; Saligan, 2014) and thus highlights the diverse patterns across the population although the lack of consistency with weekend testing within the current study (Morton-Holtham *et al.*, ndA) may help explain part of the difference as Korenromp *et al.* (2011) found a drop in physical activity at weekends, additionally Korenromp *et al.* (2011) study focussed on those with sarcoidosis in clinical remission. As physical activity patterns are diverse, an area that requires further focus is activity change following diagnosis/onset of symptoms. Chapter five reported 73.79% of participants decreased physical activity following diagnosis with a further 41.55% of the study's participants changing or stopping work due to issues related to the condition. These findings are novel and of interest as currently change from no sarcoidosis to onset of the condition has not been looked at. The findings imply sarcoidosis has a major direct effect on the daily functioning of patients and future research should look at minimising these detrimental effects as well as how employers can best support their employee's.

8.2. Muscle Strength

Due to the online approach of chapter five and six, only chapter seven directly measured muscle strength (QPT, HPT, EFMS and HGS) while chapter four findings into muscle strength were used as baseline measures for the condition. In line with previous research participants reported lower than predicted levels of strength, HGS (93.77%), QPT (97.64%) and HPT (74.22%). The reasons for the reduced score remain unclear although the deconditioning process has previously been stated (Mitchell *et al.*, 2012; Fleischer *et al.*, 2014). Based on chapter seven's findings it is likely other factors also play an important role as participants met and exceeded current physical activity guidelines (table 21), a potential important factor regarding the guidelines could be type of activity carried out. For example, the physiological effects of brisk walking/running vary from the effects of weight training. Therefore, the type of activity being conducting during MVPA may be vital in maintain muscle strength and limiting deconditioning. Hand grip strength was found to have strong bivariate correlations with numerous variables such as lung function (FEV₁, FVC, PEF), gender, body fat percentage, muscle strength (EFMS, QPT, HPT) and 6MWD however only EFMS was found to be a predictor. HGS is a useful indicator of functional ability in numerous populations (Burtin *et al.*, 2015; Leong *et al.*, 2016) and thus needs further research within sarcoidosis.

8.3. Quality of life and Fatigue

Quality of life and fatigue were key variables throughout the project. Fatigue was the most selected symptom within chapter five (92.62%) however a limitation was the lack of measuring the severity such as via the FAS and therefore it remains unknown the level of fatigue per participant, as some may have been found to be non-fatigued

against the FAS's validated scale (Michielsen et al., 2003; De Vries *et al.*, 2004). However, chapter six and seven found 92.59% and 75% of participants were fatigued or extremely fatigued via the FAS. This thesis therefore highlights the significance of fatigue within sarcoidosis and the importance of improving and managing the symptoms of fatigue in this population. Exercise rehabilitation within sarcoidosis has been shown to improve fatigue scores (Marcellis *et al.*, 2015; Strookappe *et al.*, 2015; Naz *et al.*, 2018) and therefore is an area that must be taken forward with further research. Quesada-Rodriguez *et al.* (2014) highlights lack of awareness as the reason for lower levels of pulmonary rehabilitation within ILD, Holland *et al.* (2013) states this non-pharmacological treatment needs to become more prominent among chest physicians to increase the referral rates and care of patients with ILD's. An issue that could be improved with greater emphasis and evidence from future research into other ILD's, this problem highlights the multifaceted nature of long-term care offered to those with chronic conditions such as pulmonary sarcoidosis.

Quality of life was measured via the SHQ within chapter five and seven. Participants scored a mean 3.41 and 4.26 within chapter five and seven, respectively. Within both studies' females scored worse 3.34 (chapter five) and 3.96 (seven) than compared to their male counterparts 3.58 (five) and 4.77 (seven) although there was no significant difference ($P>0.05$) for either study. Quality of life has been shown to be multifactorial, being affected by numerous factors including depression score (CES-D), number of symptoms, 6MWD, HPT and exercise rehabilitation. Therefore, the reason behind the difference reported between chapter five and seven is likely to be made up of multiple factors too, although both accelerometer and IPAQ MVPA were found not to be predictors of quality of life, the types of activities undertaken during

MVPA such as weight lifting and aerobic activities; much like those conducted within exercise rehabilitation programs may explain the difference in quality of life in part. Another possible factor is the number of symptoms per participant, chapter five found a CES-D and number of symptoms were predictors of quality of life, chapter five participants reported a mean of over 3 (3.79) symptoms while chapter seven did not record number of symptoms and therefore the participants may have had less than their chapter five counterparts. Additionally, as previously mentioned chapter seven had a lower number of fatigued participants (75%) than those reporting the symptom within chapter five (92.62%).

8.4. Patient Views

The inclusion of open-ended qualitative questions within chapter five was a novel and extremely important aspect of the project and sarcoidosis research overall. Participants revealed often feeling overlooked and ignored by the very people that treated them highlighted by the quote “Consultants, I never get to see the same one and I always feel that they are winging it”. The key themes highlighted via the content analysis were sarcoidosis causing the ‘limiting of activities’ (“The slightest effort results in struggling to breathe”), the ‘benefits of exercise, physical activity and diet’ (“light exercise seems to help improve some of my pain”), the ‘detrimental effect of poor lifestyle choices’ (“smoking and I don’t know how to quit”), ‘lack of understanding by friends, family and employers’ (“family’s lack of understanding can be awful as are doctors”), ‘the role of medicine’ (“the higher dose of steroids but would rather not take them cause of the side effects”), ‘importance of sleep’ (“feel that if I could sleep properly I would feel better able to cope”) and ‘anxiety and stress’ (“stress has major impact on my Sarcoid symptoms”). This feedback can be beneficial in formulating new areas of research such as the role of mindfulness-based training (Merkes, 2010)

and also justify current and future research areas by providing real-life views on a situation, such as the effect of fatigue on their daily life. For example, fatigue is a self-reported measure and has not been linked to clear physiological mechanisms within sarcoidosis yet chapter seven found fatigue strongly correlated to the SHQ (.812, $P = 0.014$) but not 6MWD (.385, $P > 0.05$). Therefore, the role of fatigue requires further investigation.

8.5. Limitations and Strengths

Although the current thesis has identified important findings, there are several limitations that cannot be dismissed. One limitation to the current work is the vast nature of sarcoidosis and its ability to affect almost any part of the body (Saidha *et al.*, 2012). This may make comparisons between participants difficult as their conditions can vary (NHS, 2015a) and currently the effects of different forms of sarcoidosis (pulmonary, skin, organ) has not been isolated. Additionally, severity of the disease can vary despite sharing the same radiographic stage exemplified by the lack of correlation between stages and lung function (Criado *et al.*, 2010). Another limitation is due to the low incidence rate of sarcoidosis (1 in 10,000; NHS, 2015a) where participants are sparsely spread throughout the country therefore increasing the difficulty of recruitment, exemplified through the small sample size of chapter seven ($n=8$). In addition to this, many aspects of chapters five, six and seven comprise of self-reported measures including SHQ, IPAQ, CES-D, FAS, MRC etc. therefore participants may intentionally and unintentionally alter their answers causing an under or over statement of their symptoms/physical activity levels etc (Swann *et al.*, 2005; Sylvia *et al.*, 2014). With regards to the physical tests, prior practice and familiarisation was also a concern as it can lead into an increase in performance and

alter the results (Casanova *et al.*, 2011) although Dias *et al.* (2005) argues familiarisation allows for more accurate results. Outside of the population size and tests utilised across the project, a lack of depth in some key areas has limited the analysis and understanding of results. On reflection, one key example would be the lack of the actual age of participants on diagnosis and participants own estimates on when they noticed the onset of symptoms. This would have been useful as the data could have been checked against previously suggested age groups for onset of the condition, as well as a better understanding the progression of the disease over-time. While wrongly diagnosed participants is also a concern, up to 40% of chronic beryllium disease cases has been misdiagnosed as sarcoidosis (Muller-Quernheim *et al.*, 2006). In addition to the limitations of the three experimental studies there were also delimitations, these included the extensive use of closed-ended Likert scale questionnaires although likert scales have been shown to be valid indicators of levels of agreement and are quantifiable (Joshi *et al.*, 2015), the use of a limited amount of possible options limits the participants to ticking the most appreciate box as opposed to expressing how they truly feel (Hartley, 2014), however open-ended qualitative questions were included in chapter five to combat this delimitation (Kelley *et al.*, 2003). Another delimitation was the self-reported home-based approach to chapter five and six, as participants could have altered their responses from the reality of their lives although the home-based approach also has benefits such as no time pressure or constraints on participants, allowing for greater detail with regards to the qualitative questions and honesty throughout due to the confidential nature of completing at home on their personal computer and reduced social desirability factors. Despite the limitations and delimitation above, there was also numerous strengths and new insights gained by conducting this thesis. One key strength was being the first known

research allowing patient feedback on highly regarded patient areas of care such as barriers faced and what improves/worsens the condition. Patients reported feeling isolated and overlooked by doctors and other medical professionals despite a lack of faith in their ability to treat the condition. The inclusion of their thoughts and ideas can help improve both short-term and long-term care and quality of life of patients through making adjustments such as further training for relevant doctors or improved integration between the services as well as allowing for better planning for future research via evidence-led co-creation as a pathway to impact. Greenhalgh *et al.* (2016) states co-creation is a growing trend and it has the potential to reduce beneficial research not being implemented or utilised within the real world. For example, lifestyle choices and the management of stress and anxiety were important themes emphasised by patients and thus highlights the potential of future research into these areas. Another strength was the inclusion of physical activity patterns within the condition, as there is currently little known but is a developing area of interest. For example, chapter seven helped to show the reliability and validity of the IPAQ in relation to pulmonary sarcoidosis against the gold standard of a tri-axial accelerometer as well as the correlation of real-world physical activity against key variables such as quality of life, fatigue and muscle strength.

8.6. Future Directions

Due to the vast and varied nature of the condition coupled with a shortage of research, there remains numerous avenues for future research. This project was always designed to establish trends and gain baseline information on a range of key aspects of sarcoidosis and due to this would not provide definitive answers but aid future research into key areas such as the improvement to quality of life and functional ability.

Therefore, three future areas for research would be to expand on the three experimental studies conducted within this project with regards to sample size and depth, as per the mentioned limitations (e.g. age at onset of sarcoidosis). An increase in sample size would aid in the establishment of trends and patterns (e.g. physical activity/sedentary behaviour) within sarcoidosis (Hajian-Tilaki, 2011), similar research in asthma utilised 5000 participants (Subbarao *et al.*, 2010) while another utilised the combination of 27 different datasets obtained via national health surveys and routine health and social care datasets. This highlights the differing approaches to sample size and methods for gathering data within epidemiological research. In addition, findings from this project have also highlighted new/under-researched areas for improving the treatment and management of sarcoidosis. One future direction based on the findings of chapter four would be to further establish the benefits of an exercise rehabilitation program including its effect on long-term measures as this has not currently been looked at. As well as the effectiveness and ease of implementation of a home-based method, as at present all research into exercise rehabilitation has been conducted under-supervision and thus could limit the benefit to a proportion of the population if only recommended as a class/event which required attendance (Dalal *et al.*, 2010). Another interesting future direction would be the effect of mindfulness-based training in sarcoidosis in relation to stress, anxiety and quality of life etc. Quality of life is known to be reduced within those with sarcoidosis (Hinz *et al.*, 2012; Heer *et al.*, 2013; Drent *et al.*, 2014). While mindfulness-based training has been shown to be a relatively fast method (eight-week program) of providing a clinically significant improvement to quality of life within asthma even at a 12 month follow up (Pbert *et al.*, 2012). Other chronic conditions including chronic fatigue syndrome, rheumatoid arthritis and type 2 diabetes have shown benefits from the training (Merkes, 2010) and was noted as

beneficial for a participant via the content analysis of chapter five 's open-ended qualitative questions. Based on the findings of chapter seven, future research is required to understand physical activity patterns within sarcoidosis and any sub-sets of the population, this should be extended beyond simple sedentary, light, moderate and vigorous activity times and include the types of activity conducted such as strength training, running, vacuuming etc. and the effect of type of activity against key variables including quality of life, fatigue, muscle strength, depression, exercise performance etc. This is of importance as greater understanding of the effects of different types of exercise and/or physical activity would aid in the development and establishment of guidelines specific to sarcoidosis and therefore lead to improvements of patient care. An alternative area with limited but promising research within sarcoidosis and other ILD's is inspiratory muscle training (IMT). IMT is a method of breathing exercises for pulmonary rehabilitation (Hill, 2006; Shaji *et al.*, 2013), it has been shown to have several beneficial outcomes (Karadalli *et al.*, 2016) in a range of conditions including asthma (Silva *et al.*, 2013), COPD (Gosselink *et al.*, 2011) and cystic fibrosis (Houston *et al.*, 2013) as well as sarcoidosis (Karadalli *et al.*, 2016). These benefits include decreases in dyspnoea as well as increasing exercise capacity in COPD and sarcoidosis (Gosselink *et al.*, 2011; Karadalli *et al.*, 2016), while another key benefit shown within healthy populations is the improvement of rate of perceived recovery (McConnel, 2011). When considering exercise as a treatment for sarcoidosis, improving perceived recovery could potentially increase the benefits of the treatment through not only greater effort on the part of the participant but lower dropout rates as the perceived difficulty of training would decrease too, however this would need to be researched further.

Although techniques for IMT do differ, threshold loading is the most commonly used and involves breathing through a spring-loaded device, with individualised intensity (Gloeckl *et al.*, 2013). Based on current literature threshold loading for 15-20 minutes daily is recommended (Langer *et al.*, 2009), Enright and Unnaithan (2011) state training at 80% of maximum inspiratory pressure led to increases in lung volume, work capacity and perceived exertion in healthy population, with high intensity workloads being labelled as optimal for maximizing effectiveness (Brilla, 2012).

8.7. Impact and application

The impact of this project was to influence the development of specific recommendations for exercise and physical activity aimed to improve clinical care pathways for pulmonary sarcoidosis as an adjunct to pharmacological treatment. The findings will help characterise patients with pulmonary sarcoidosis to help establish modifiable lifestyle habits with tailored exercise, physical activity. This project will aid in the development of current guidelines to inform future service planning, treatment provision and support for patients with the condition.

8.8. Conclusions

The novel and key findings from the current thesis are firstly, exercise rehabilitation appears to improve the effects of deconditioning and symptoms within sarcoidosis. Quality of life has been shown to be affected by the number of symptoms reported and depression score as well as discontent with quality of care on the patient's behalf due to a perceived lack of knowledge by doctors (both GP and specialists) and a lack of integration between the different services. Sarcoidosis physical activity patterns being diverse across the population much like the condition itself. Although muscle strength does appear to be reduced across the population based on this project and previous research findings. Handgrip strength had numerous moderate and strong bivariate

correlations but only elbow flexor muscle strength was found to be a predictor, further research is required into the possibility of handgrip strength being a useful indicator for a range of key. The content analysis shows an appetite for information regarding beneficial lifestyle changes relevant to the condition such as diet, smoking cessation and exercise programs. Overall it can be stated that physical activity is diverse and not always reduced within the population, fatigue is a major issue and the effect sarcoidosis has on work needs further investigation.

9. References

- ACSM. (2014). *Guidelines for Exercise Testing and Prescription* (9th ed.). Philadelphia: Lippincott Williams & Wilkins.
- ACSM. (2016). *Exercise Management for Persons with Chronic Diseases and Disabilities* (4th ed.). Philadelphia: Lippincott Williams & Wilkins.
- Aeberli, I., Gerber, P. A., Hochuli, M., Kohler, S., Haile, S. R., Gouni-Berthold, I., Berthold, H. K., Spinass, G. A., Berneis, K. (2011). Low to Moderate Sugar-Sweetened Beverage Consumption Impairs Glucose and Lipid Metabolism and Promotes Inflammation in Healthy Young Men: A Randomized Controlled Trial. *The American Journal of Clinical Nutrition*, 94(2), 479-485.
- Akkoca, O., Celik, G., Ulger, F., Arbak, P., Saryal, S., Karabiyikoglu, G., Alper, D. (2005). Exercise Capacity in Sarcoidosis. Study of 29 Patients. *Medicina Clinica*, 124(18), 686-689.
- Alangari A. S., Al-Hazzaa, H. M. (2004). Normal Isometric and Isokinetic Peak Torques of Hamstring and Quadriceps Muscle in Young Adult Saudi Male. *Neurosciences*, 9(3), 165-170.
- Alhamad, E., H., Shaik, S. A., Idrees, M. M., Alanezi, M. O., Isnani, A. C. (2010). Outcome Measures of the 6 Minute Walk Test: Relationships with Physiologic and Computed Tomography Findings in Patients with Sarcoidosis. *BMC Pulmonary Medicine*, 10, 10-42.
- Allam, M. F., Lucane, R. A. (2004). Selenium Supplementation for Asthma. *Cochrane Database Systematic Reviews*, 2.
- Allender, S., Cowburn, G., Foster, C. (2006). Understanding Participation in Sport and Physical Activity Among Children and Adults: A Review of Qualitative Studies. *Health Education Research*, 21(6), 826-835.
- American Thoracic Society. (2002). ATS Statement: Guidelines for the Six-Minute Walk Test. *American Journal of Respiratory Critical Care Medicine*, 166, 111-117.
- 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.
- Azizan, A., Justine, M., Kuan, C. S. (2013). Effects of a Behavioral Program on Exercise Adherence and Exercise Self-Efficacy in Community-Dwelling Older Persons. *Current Gerontology and Geriatrics Research*, 21-30.
- Bahmer, T., Watz, H., Develaska, M., Waschki, B., Rabe, K. F., Maqnuessen, H., Kirsten, D., Kirsten, A. M. (2018). Physical Activity and Fatigue in Patients with Sarcoidosis. *Respiration*, 95(1), 18-26.
- Bardinas, F., Morera, J., Fite, E., Plasencia, A. (1989). Seasonal Clustering of Sarcoidosis. *Lancet*, 2(8660), 455-466.
- Barnard, J., Rose, C., Newman, L., Canner, M., Martyny, J., McCammon, C., Bresnitz, E., Rossman, M., Thompson, B., Rybicki, B., Weinberger, S. E., Moller, D. R.,

- McLennan, G., Hunninghake, G., De Palo, L., Baaughman, R. P., Iannuzzi, M. C. M., Judson, M. A., Knatterud, G. L., Teirstein, A. S., Yeager, H., Johns, C. J., Rabin, D. L., Cherniack, R. (2005). Job and Industry Classifications Associated with Sarcoidosis in a case-control etiologic study of Sarcoidosis. *Journal of Occupational and Environmental Medicine*, 47(3), 226-234.
- Barouki, R., Gluckman, P. D., Grandjean, P., Hanson, M., Heindel, J. J. (2012). Developmental Origins of Non- Communicable Disease: Implications for Research and Public Health. *Environmental Health*, 11-42.
- Barr, S. I. (1999). Effects of Dehydration on Exercise Performance. *Canadian Journal of Physiology*, 24(2), 164-172.
- Bast, A., Weseler, A., Haenen, G., Den Hartlog, G. (2010). Oxidative Stress and Antioxidants in Interstitial Lung Disease. *Current Opinion in Pulmonary Medicine*, 16(5), 516-520.
- Baughman, R. P., Teirstein, A. S., Judson, M. A., Ross,am, M. D., Yeager, H., Bresnitz, E. A., De Palo, L., Hunninhhake, G., Iannuzzi, M. C., Johns, C. J., McLennan, G., Moller, D. R., Newman, L. S., Rabin, D. L., Rose, C., Rybicki B., Weinberger, S. E., Terrin, M. L., Knatterud, G. L., Cherniak, R. (2001). Clinical Characteristics of Patients in a Case Control Study of Sarcoidosis. *American Journal of Respiratory and Critical Care Medicine*, 164(10), 1885-1889.
- Baughman, R. P. (2013). Treatment of Sarcoidosis. *Panminerva Medica*, 55(2), 175-189.
- Baughman, R. P., Lower, E. E. (2011). Who Dies from Sarcoidosis and Why? *American Journal of Respiratory and Critical Care Medicine*, 183(11).
- Baughman, R. P., Lower, E. E. (2014). Goldilocks, Vitamin D and Sarcoidosis. *Arthritis Research & Therapy*, 16(3), 111.
- Baydur, A., Alsalek, M., Louie, S. G., Sharma, O. P. (2001). Respiratory Muscle Strength, Lung Function and Dyspnea in Patients with Sarcoidosis. *Chest*, 120(1), 120-128.
- Bellamy, D. (2005). *Spirometry in Practice* (2nd E.d.). London: The British Thoracic Society.
- Benitez-Porres, J., Delgado, M., Ruiz, J. R. (2013). Comparison of Physical Activity Estimates using International Physical Activity Questionnaire (IPAQ) and Accelerometry in Fibromyalgia Patients: The Al-Andalus Study. *Journal of Sports Sciences*, 31(16), 1741-1752.
- Berlin, M., Fogdell-Helm. A., Olerup, O., Eklund, A., Grunewald, J. (1997). HLA-DR Predicts the Prognosis in Scandinavian Patients with Pulmonary Sarcoidosis. *American Journal of Respiratory Critical Care Medicine*, 156(5).
- Biddle, S. J., Gorely, T., Pearson, N., Bull, F. C. (2011). An Assessment of Self-reported Physical Activity Instruments in Young People for Population surveillance: Project ALPHA. *International Journal of Behavioral Nutrition and Physical Activity*, 8(1).
- Bilsborough, S. A., Crowe, T. C. (2003). Low-Carbohydrate Diets: What are the Potential Short- and Long-term Health Implications. *Asia Pacific Journal of Clinical Nutrition*, 12(4), 396-404.

- Bird, S., Noronha, M., Sinnott, H. (2010). An Integrated Care Facilitation Model Improves Quality of Life and Reduces Use of Hospital Resources by Patients with Chronic Obstructive Pulmonary Disease and Chronic Heart Failure. *Australian Journal of Primary Health*, 16(4), 326-333.
- Blomhoff, R., Blomhoff, H. K. (2006). Overview of Retinoid Metabolism and Function. *Journal of Neurobiology*, 66(7), 606-630.
- Bohannon, R. (2008). HandGrip Dynamometry Predict Future Outcome in Aging Adults. *Journal of Geriatric Physical Therapy*, 31(1), 3-10.
- Boon, R. M., Hamlin, M. J., Steel, G. D., Ross, J. J. (2010). Validation of the New Zealand Physical Activity Questionnaire (NZPAQ-LF) and the International Physical Activity Questionnaire (IPAQ-LF) with Accelerometry. *British Journal of Sports Medicine*, 44(10), 741-746.
- Boots, A. W., Haenen G. R. M., Bast, A. (2008). Health Effects of Quercetin: From Antioxidant to Nutraceutical. *European Journal of Pharmacology*, 585 (2-3), 325-337.
- Boots, A. W., Drent, M., Swenen, E. L. R., Moonen, H. J., Bast, A., Haenen, G. R. M. (2009). Antioxidant Status Associated with Inflammation in Sarcoidosis: A Potential Role for Antioxidant. *Respiratory Medicine*, 103 (3), 364-372.
- Boots, A. W., Drent, M., De Boer, V. C. J., Bast, A., Haenen, G. R. M. (2011). Quercetin Reduces Markers of Oxidative Stress and Inflammation in Sarcoidosis. *Clinical Nutrition*, 30(4), 506-512.
- Borer, K. T. (2005). Physical Activity in the Prevention and Amelioration of Osteoporosis in Women: Interaction of mechanical, Hormonal and Dietary Factors. *Sports Medicine*, 25(9), 779-830.
- Borg, G. A. (1982). Psychological Bases of Perceived Exertion. *Medicine and Science in Sport and Exercise*, 14(5), 377-381.
- Bourbonnais, J. M., Samvati, L. (2008). Clinical Predictors of Pulmonary Hypertension in Sarcoidosis. *European Respiratory Journal*, 32, 296-302.
- Boyer, J., Liu, R. H. (2004). Apple Phytochemicals and their Health Benefits. *Nutrition Journal*, 3 (5).
- Braam, A. W., de Haan, S. N., Vorselaars, A. D., Rijkers, G. T., Grutters, J. C., van den Elshout, F. J., Korenromp, I. H. (2013). Influence of Repeated Maximal Exercise Testing on Biomarkers and Fatigue in Sarcoidosis. *Brain, Behavior and Immunity*, 33: 57-64.
- Bresnitz, E. A., Strom, B. L. (1983). Epidemiology of Sarcoidosis. *Epidemiologic Reviews*, 5(1), 124-156.
- Brilla, L. R. (2012). Perspectives on Breathing in Sports and Health. *Journal of Sports Medicine & Doping Studies*, 2(5), 1-3.
- British Heart Foundation. (2017). Physical Inactivity and Sedentary Behaviour Report. Retrieved 28th December 2017 from

- Broos, C. E., Van Nimwegen, M., Hoogsteden, H. C., Hendriks, R. W., Kool, M., Van Den Blink, B. (2013). Granuloma Formation in Pulmonary Sarcoidosis. *Frontiers in Immunology*, 4.
- Broos, C. E., Van Nimwegen, M., Kleinjan, A., Berge, B. T., Muskens, F., Veen, J., Annema, J. T., Lambrecht, B. N., Hoogsteden, H. C., Hendricks, R. W., Kool, M., Van den Blink, B. (2015). Impaired Survival of Regulatory T Cells in Pulmonary Sarcoidosis. *Respiratory Research*, 16.
- Burtin, C., Ter Riet, C., Puhan, M. A., Waschki, B., Garcia-Aymerich, J., Pinto-Plata, V., Celli, B., Watz, H., Spruit, M. A. (2016). Handgrip Weakness and Mortality Risk in COPD: A Multicenter Analysis. *Thorax*, 71(1), 86-87.
- Butland, R. J., Pang, J., Gross, E. R., Woodcock, A. A., Geddes, D.M. (1982). Two, six, and 12 minute walking tests in respiratory disease. *British Medical Journal*, 284:1607–1608.
- Casanova, C., Celil, B. R., Barria, P., Casas, A., Cote, C., De Torres, J. P., Jardim, J., Lopez, M. V., Marin, J. M., Montes, M., Pinto-plata, V., Aguirre-Jamie, A. (2011). The 6-min Walk Distance in Healthy Subjects: Reference Standards from Seven Countries. *European Respiratory Journal*, 37, 150-156.
- Celis-Morales, C. A., Perez-Bravo, F., Ibanez, L., Salas, C., Bailey, M. E., Gill, J. M. (2012). Objective vs Self-reported Physical Activity and Sedentary Time: Effects of Measurement Method on Relationships with Risk Biomarkers. *Plos One*,
- Chandra, R. K. (1983). Mucosal Immune Responses in Malnutrition. *The New York Academy of Sciences*.
- Chang, B., Steimel, J., Moller, D. R., Baughman, R. P., Judson, M. A., Yeager, H., Teirstein, A. S., Rossman, M. D., Rand, C. S. (2001). Depression in Sarcoidosis. *American Journal of Respiratory and Critical Care Medicine*, 163(2).
- Cheng, H., Kong, J., Underwood, C., Petocz, P. (2018). Systematic Review and Meta-analysis of the Effect of Protein and Amino Acid Supplements in Older Adults with Acute or Chronic Conditions. *British Journal of Nutrition*, 119(5), 527-542.
- 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.
- Chetta, A., Zanini, A., Pisi, G., Aiello, M., Tzani, P., Neri, M., Olivieri, D. (2006). Reference Values for the 6-min Walk Test in Healthy Subjects 20-50 Years Old. *Respiratory Medicine*, 100(9), 1573-1578.
- Cheung, C. L., Nguyen, U., Au, E., Tan, K., Kung, A. (2013). Association of Handgrip Strength with Chronic Diseases and Multimorbidity. *Age*, 35(3), 929-941.

- Clark, B. C., Manini, T. M. (2010). Functional Consequences of Sarcopenia and Dynapenia in the Elderly. *Current Opinion in Clinical Nutrition and Metabolic Care*, 13(3), 271-276.
- Correia de Faria Santarem, G., de Cleve, R., Santo, M. A., Bernhard, A. B., Gadducci, A. V., Maria, J., Greve, D., Silvia, P. R. (2015). Correlation between Body Composition and Walking Capacity in Severe Obesity. *Plos One*, 10(6).
- Costabel, U., Hunninghake, G. W. (1999). ATS/ERS/WASOG Statement on Sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. *The European Respiratory Journal*, 14(4), 735-737.
- Cox, C. E., Donohue, J. F., Brown, C. D., Kataria, Y. P., Judson, M. A. (2003). The Sarcoidosis Health Questionnaire: A New Measure of Health-Related Quality of Life. *American Journal of Respiratory and Critical Care Medicine*, 169(3), 323-329.
- Cox, C. E., Donohue, J. F., Brown, C. D., Kataria, Y. P., Judson, M. A. (2004). Health-related Quality of Life of Persons with Sarcoidosis. *Chest*, 125(3), 997-1004.
- Craig, C. L., Marshall, A. L., Siostrum, M., Bauman, A. E., Booth, M. L., Ainsworth, B. E., Pratt, M., Ekelund, U., Yngve, A., Sallis, J. F., Oja, P. (2003). International Physical Activity Questionnaire: 12-Country Reliability and Validity. *Medicine and Science in Sports Exercise*, 35(8), 1381-1395.
- Cremers, J. P., Drent, M., Elffeirch, M. D., Nelemans, P. J., Wijnen, P. A., Witteman, B. J., Schols, A. M. (2013). Body Composition Profiling in a Dutch Sarcoidosis Population. *Sarcoidosis Vasculitis and Diffuse Lung Diseases*, 30(4).
- Criado, E., Sanchez, M., Ramirez, J., Arguis, P., de Caralt, T. M., Perea, R. J., Xaubet, A. (2010). Pulmonary Sarcoidosis: Typical and Atypical Manifestations at High-Resolution CT with Pathologic Correlation. *Radiographics*, 30(6), 1567-1586.
- Culver, D. A., Baughman, R. P., Cordova, F. C., Barney, J. B., Shlobin, O. A., Engel, P., Denblink, B., Nathan, S. D. (2015). Six Minute Walk Testing in Patients with Sarcoidosis Associated Pulmonary Hypertension. *American Journal of Respiratory and Critical Care Medicine*, 151.
- Da Silva, R. P., Sperandio, E. F., Matheus, A. C., Lauria, V. T., de Alemeida, F. R., de Almeida, V. R., Gagliardi, A. R., Arantes, R. L., Romiti, M., Dourado, V. Z. (2017). Use of Combined Method, Accelerometer and International Physical Activity Questionnaire, to Determinate Occurrence of Physical Inactivity in Adults. *Mortiz*, 23(2), Epub.
- De Goma, E. M., Leeper, N. J., Heidenreich, P. A. (2008). Clinical Significance of High-Density Lipoprotein Cholesterol in Patients with Low Low-density Lipoprotein Cholesterol. *Journal of the American College of Cardiology*, 51(1), 49-55.
- De Boer, S., Wilsher, M. L. (2012). Validation of the Sarcoidosis Health Questionnaire in a non-US Population. *Respirology*, 17(3), 519-524.

- De Boer, D. S., Kolbe, J., Wilsher, M. L. (2014). The Relationships among Dyspnoea, Health-related Quality of Life and Psychological Factors in Sarcoidosis. *Respirology*, 19(7), 1019-1024.
- De Kleijn, W., De Vries, J., Lower, E. E., Elfferich, M., D., Baughman, R. P., Drent, M. (2009). Fatigue in Sarcoidosis: A Systematic Review. *Current Opinion in Pulmonary Medicine*, 15(5): 499- 506.
- De Kleijn, W., Drent, M., Vermunt, J. K., Shigemitsu, H., De Vries, J. (2011). Types of Fatigue in Sarcoidosis Patients. *Journal of Psychosomatic Research*, 71(6), 416-422.
- Delobbe, A., Perrault, H., Maitre, J., Robin, S., Hossein-Foucher, C., Wallaert, B., Anguilaniu, B. (2002). Impaired Exercise Response in Sarcoid Patients with Normal Pulmonary Function. *Sarcoidosis, Vasculitis and Diffuse Lung Diseases: Official Journal of WASOG*, 19(2), 148-153.
- Department of Health (2010). Sedentary Behaviour and Obesity: Review of the Current Scientific Evidence. Retrieved 15 February 2018 from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213745/dh_12_8225.pdf
- Department of Health (2011). Physical Activity Guidelines for Adults (19-64 Years). Retrieved 31st January 2018 from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/213740/dh_128145.pdf
- De Souza, S. A., Faintuch, J., Fabris, S. M., Nampo, F. K., Luz, C., Fabio, T. L., Sitta, I. S., de Batista Fonseca, I. C. (2009). Six-minute Walk Test: Functional Capacity of Severely Obese Before and After Bariatric Surgery. *Official Journal of American Society for Bariatric Surgery*, 5(5), 540-543.
- De Vries, J., Michielsen, H., Van Heck, G. L., Drent, M. (2004). Measuring Fatigue in Sarcoidosis: The Fatigue Assessment Scale (FAS). *British Journal of Health Psychology*, 9(3), 279-291.
- De Vries, J., Drent, M. (2008). Quality of Life and Health Status in Sarcoidosis: A Review of the Literature. *Clinics in Chest Medicine*, 29(3), 525-532.
- Dhooria, S., Gupta, D. (2014). Oxidative Stress in Sarcoidosis. *Studies on Respiratory Disorders*, 191-201.
- Dias, R. M. R., Cyrino, E. S., Salvador, E. P., Caldeira, L. F. S., Nakamura, F. Y., Papst, R. R., Bruna, N., Gurjao, A. L. D. (2005). Influence of Familiarization Process on Muscular Strength Assessment in 1-RM Tests. *The Revista Brasileira de Medicina do Esporte*, 11(1).
- Diaz, K. M., Shimbo, B. (2013). Physical Activity and the Prevention of Hypertension. *Current Hypertension Report*, 15(6), 659-668.
- Doughan, A. R., Williams, B. R. (2006). Cardiac Sarcoidosis. *Heart*, 9(2), 282-288.

- Drent, M., Costabel, U. (2005). *Sarcoidosis*. Wakefield, UK: The Charlesworth Group.
- Drent, M., Marcellis, R., Lenssen, A., De Vries, J. (2014). Association Between Pulmonary Functions and Quality of Life in Sarcoidosis. *Sarcoidosis Vasculitis and Diffuse Lung Diseases*, 31(2), 117-128.
- Drent, M., Strookappe, B., Hoitsma, E., De Vries, J. (2015). Consequences of Sarcoidosis. *Clinics in Chest Medicine*, 36(4), 727-737.
- Du Bois, R. M., Goh, N., McGrath, D., Cullinan, P. (2003). Is there a Role for Microorganisms in the Pathogenesis of Sarcoidosis? *Journal of Internal Medicine*, 252(1), 4-17.
- Dubrey, S., Shah, S., Hardman, T., Sharma, R. (2014). Sarcoidosis: The Links Between Epidemiology and Aetiology. *Postgraduate Medical Journal*, 90, 582-589.
- Dunstan D. W., Howard, B., Healy, G. N., Owen, N. (2012). Too Much Sitting – A Health Hazard. *Diabetes Research and Clinical Practice*, 97(3), 368-376.
- Durstine, J. L., Painter P., Franklin, B. A., Morgan, D., Pitetti, K. H., Roberts, S. O. (2000). Physical Activity for Chronically Ill and Disabled. *Sports Medicine*, 30(3): 207-219.
- Durstine, J. L., Gordon, B., Wang, Z., Luo, X. (2013) Chronic Disease and the Link to Physical Activity. *Journal of Sport and Health Science*, 2(1): 3-11.
- Dyrstad, S. M., Hansen, B. H., Holme, I. M., Anderssen, S. A. (2014). Comparison of Self-Reported Versus Accelerometer-measured Physical Activity. *Medicine and Science in Sports and Exercise*, 46(1), 99-106.
- Edmondstone, W. M. (1998). Sarcoidosis in Nurses: Is there an Association? *Thorax*, 43(4), 342-343.
- 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.
- Eishi, Y., Suga, M., Ishige, I., Kobayashi, D., Yamada, T., Takemura, T., Takizawa, T., Koike, M., Kudoh, S., Costabel, U., Guzman, J., Rizzato, G., Gambacorta, M., Du Bois, R., Nicholson, A. G., Sharma, O. P., Ando, M. (2002). Quantitative Analysis of Mycobacterial and Propionibacterial DNA in Lymph Nodes of Japanese and European Patients with Sarcoidosis. *Journal of Clinical Microbiology*, 40(1), 198-204.
- Eishi, Y. (2013). Etiologic Aspect of Sarcoidosis as a Allergic Endogenous Infection Caused by Propionibacterium Acnes. *BioMed Research International*, 1-18.
- Ekelund, U., Yngve, A., Sallis, J. F., Oja, P. (2003). International Physical Activity Questionnaire: 12-Country Reliability and Validity. *Medicine and Science in Sports Exercise*, 35(8), 1381-1395
- Elfferich, M., De Vries, J., Drent, M. (2011). Type D or “Distressed” Personality in Sarcoidosis and Idiopathic Pulmonary Fibrosis. *Sarcoidosis Vasculitis and Diffuse Lung Diseases*, 28(1), 65-71.

- Enright, P. L., Unnithan, V. B. (2011). Effect of Inspiratory Muscle Training Intensities on Pulmonary Function and Work Capacity in People Who are Healthy: A Randomized Controlled Trial. *Journal of American Physical Therapy Association*, 91(6), 894-905.
- Evans, J. D. (1996). *Straightforward statistics for the behavioral sciences*. Pacific Grove, CA: Brooks/Cole Publishing.
- Evans, R. A., Singh, S. J., Collier, R., Loke, I., Steiner, M. C., Morgan, M. D. L. (2010). Generic, Symptom based, Exercise Rehabilitation; Integrating Patients with COPD and Heart Failure. *Respiratory Medicine*, 104(10), 1483-1481.
- Esmarck, B., Andersen, J. L., Olsen, S., Richter, E. A., Mizuno, M., Kjaer, M. (2004). Timing of Post-Exercise Protein Intake is Important for Muscle Hypertrophy with Resistance Training in Elderly Humans. *The Journal of Physiology*.
- Ferrazza, A. M., Martolini, D., Valli, G., Palange, P. (2009). Cardiopulmonary Exercise Testing in the Functional and Prognostic Evaluation of Patients with Pulmonary Diseases. *Respiration*, 77, 3-17.
- Field, A. (2013). *Discovering Statistics using IBM SPSS STATISTICS*, London, Sage.
- Fletcher, C. M., Elmes, P. C., Fairbairn, A. S., Wood, C. H. (1959). Significance of Respiratory Symptoms and the Diagnosis of Chronic Bronchitis in a Working Population. *The British Medical Journal*, 2, 257-266.
- Fleischer, M., Hinz, A., Brahler, E., Wirtz, H., Bosse-Henck, A. (2014). Factors Associated with Fatigue in Sarcoidosis. *Respiratory Care*, 59(7), 1086-1094.
- 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.
- Fortunato, R. L., de Freitas Alves, C., Teixeira, M. M., Rogerio, P. (2012). Quercetin: A Flavonoid with the Potential to treat Asthma. *Brazilian Journal of Pharmaceutical Sciences*, 48(4).
- 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.
- Foster, S., Thomas, H. M. (1990). Pulmonary Rehabilitation in Lung Disease other than Chronic Obstructive Pulmonary Disease. *American Review of Respiratory Disease*, 141, 601-604.
- Galgani, J., Ravussin, E. (2008). Energy Metabolism, Fuel Selection and Body Weight Regulation. *International Journal of Obesity*, 32, 109-119.
- 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 Cohort Study. *Thorax*, 61(9), 739-739.

- Garcia-Aymerich, J., Varraso, R., Anto, J. M., Camargo, C. A. (2009). Prospective Study of Physical Activity and Risk of Asthma Exacerbation in Older Women. *American Journal of Respiratory and Critical Care Medicine*, 179(11), 999-1003.
- Garin, M. C., Highland, K. B., Silver, R. M., Strange, C. (2009). Limitations to the 6-minutes Walk Test in Interstitial Lung Disease and pulmonary Hypertension in Scleroderma. *The Journal of Rheumatology*, 36(2), 330-336.
- Gerke, A. K. (2014). Morbidity and Mortality in Sarcoidosis. *Current Opinion in Pulmonary Medicine*, 20(5), 472-478.
- Gleeson, M., Bishop, N. C., Stensel, D. J., Lindley, M. R., Mastana, S. S., Nimmo, M. A. (2011). The Anti-inflammatory Effects of Exercise: Mechanisms and Implications for the Prevention and Treatment of Disease. *Nature Reviews Immunology*, 11: 607-615.
- Gloeckl, R., Marinov, B., Pitta, F. (2013). Practical Recommendations for Exercise Training in Patients with COPD. *European Respiratory Review*, 22(128), 178-186.
- Gosse, M. A. (2014). How Accurate is Self-reported BMI?. *Nutrition Bulletin*, 39(1), 105-114.
- Gosselink, R., De Vos, J., Van den Heuvel, S. P., Segers, J., Decramer, M., Kwakkel, G. (2011). Impact of Inspiratory Muscle Training in Patients with COPD: What is the Evidence?. *European Respiratory Journal*, 37(2), 416-425.
- Greenhalgh, T., Jackson, C., Shaw, S., Janamian, T. (2016). Achieving Research Impact Through Co-creation in Community-Based Health Services: Literature Review and Case Study. *The Milbank Quarterly*, 94(2), 392-429.
- Grunewald, J., Eklund, A., Olerup, O. (2004). Human Leukocyte Antigen Class I Alleles and the Disease Course in Sarcoidosis Patients. *American Journal of Respiratory and Critical Care Medicine*, 169(6), 696-702.
- Grunewald, J. (2008). Genetics of Sarcoidosis. *Current Opinion Pulmonary Medicine*, 14(5), 434-439.
- Grutters, J. C., Van Den Bosch, J. M. M. (2006). Corticosteroid Treatment in Sarcoidosis. *European Respiratory Journal*, 28(3), 627-636.
- Hagstromer, M., Ainsworth, B. E., Oja, P., Sjostrom, M. (2010). Comparison of a Subjective and an Objective Measure of Physical Activity in a Population Sample. *Journal of Physical Activity and Health*, 7(4), 541-550.
- Hagstromer, M., Oja, P., Sjostrom, M. (2006). The International Physical Activity Questionnaire (IPAQ): A Study of Concurrent and Construct Validity. *Public Health Nutrition*, 9(6), 755-762.
- Hajian-Tilaki, K. (2011). Sample Size Estimation in Epidemiologic Studies. *Caspian Journal of Internal Medicine*, 2(4), 289-298.
- Hartley, J. (2014). Some Thoughts on Likert-type Scales. *International Journal of Clinical and Health Psychology*, 14(1), 83-86.

- 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.
- Hamilton, M. T., Healy, G. N., Dunstan, D. W., Zderic, T. W., Owen, N. (2008). Too Little Exercise and Too Much Sitting: Inactivity Physiology and the Need for New Recommendations on Sedentary Behavior. *Current Cardiovascular Risk Reports*, 2, 292.
- Handa, T., Nagai, S., Miki, S., Fushimi, Y., Ohta, K., Mishima, M., Izumi, T. (2006). Incidence of Pulmonary Hypertension and its Clinical Relevance in Patients with Sarcoidosis. *Chest*, 129(5), 1246-1252.
- Harbo, T., Brincks, J., Andersen, H. (2012). Maximal Isokinetic and Isometric Muscle Strength of Major Muscle Groups Related to Age, Body mass, Height, and Sex in 178 Healthy Subjects. *European Journal of Applied Physiology*, 112(1).
- Hawkins, M. N., Raven, P. B., Snell, P. G., Stray-Gundersen, J., Levine, B. D. (2007). Maximal Oxygen Uptake as a Parametric Measure of Cardiorespiratory Capacity. *Medicine and Science in Sports and Exercise*, 39(1), 103-107.
- Heerema-Poelman, A., Stuive, I., Wemple, J. B. (2013). Adherence to a Maintenance Exercise Program 1 Year after Pulmonary Rehabilitation: What are the Predictors of Dropout?. *Journal of Cardiopulmonary Rehabilitation and Prevention*, 33(6), 419-426.
- Helms, E., Fitschen, P. J., Aragon, A., Cronin, J., Schoenfeld, B. J. (2014). Recommendations for Natural Bodybuilding Contest Preparation: Resistance and Cardiovascular Training. *The Journal of Sports Medicine and Physical Fitness*, 55(3): 164-178.
- Healy, G. N., Dustan, D. W., Salmon, J., Cerin, E., Shaw, J. E., Zimmet, P. Z., Owen, N. (2008). Breaks in Sedentary Time: Beneficial Associations with Metabolic Risk. *Diabetes Care*, 31(4), 661-666.
- Hawkins, M. N., Raven, P. B., Snell, P. G., Stray-Gundersen, J., Levine, B. D. (2007). Maximal Oxygen Uptake as a Parametric Measure of Cardiorespiratory Capacity. *Medicine and Science in Sport and Exercise*, 39(1), 103-107.
- Hilderbrand, K., Przybyłowski, T., Maskey-Warzechowska, M., Wiwala, J., Chazan, R. (2012). Response to Physical Exercise in Sarcoidosis. *European Respiratory Journal*, 40.
- Hill, N. S. (2006). Pulmonary Rehabilitation. *Proceedings of the American Thoracic Society*, 3(1), 66-74.
- Hinz, A., Brahler, E., Mode, R., Wirtz, H., Bosse-Henck, A. (2012). Anxiety and Depression in Sarcoidosis: The Influence of Age, Gender, Affected Organs, Concomitant Diseases and Dyspnea. *Sarcoidosis Vasculitis and Diffuse Lung Diseases*. 29(2), 139-146.

- Hoeper, M. M., Bogaard, H. J., Condliffe, R., Frantz, R., Khanna, D., Kurzyna, M., Langleben, D., Manes, A., Satoh, T., Torres, F., Wilkins, M. R., Badesch, D. B. (2013). Definitions and Diagnosis of Pulmonary Hypertension. *Journal of the American College of Cardiology*, 62(25), 42-50.
- Holick, M. F. (2004). Vitamin D: Importance in the Prevention of Cancers, Type 1 Diabetes, Heart Disease, and Osteoporosis. *The American Journal of Clinical Nutrition*, 79(3), 363-371.
- Holick, M. F. (2008). Vitamin D Deficiency: A Worldwide Problem with Health Consequences. *The American Journal of Clinical Nutrition*, 97(1), 1080-1086.
- Holland, A. E., Hill, C. J., Conron, M., Munro, P., McDonald, C. F. (2008). Short Term Improvement in Exercise Capacity and Symptoms Following Exercise Training in Interstitial Lung Disease. *Thorax*, 63, 549-554.
- Holland, A. E., Wadell, K., Spruit, M. A. (2013). How to Adapt the Pulmonary Rehabilitation Programme to Patients with Chronic Respiratory Disease Other than COPD. *European Respiratory Review*, 22, 577-586.
- Holland, A. E., Downman, L. M., Hill, C. J. (2015). Principles of Rehabilitation and Reactivation: Interstitial Lung Disease, Sarcoidosis and Rheumatoid Disease with Respiratory involvement. *Respiration*, 89(2), 89-99.
- Holmes, S. J., Allen, S. C., Roberts, H. C. (2017). Relationship between Lung Function and Grip Strength in Older Hospitalized Patients: A Pilot Study. *International Journal of Chronic Obstructive Pulmonary Disease*, 12, 1207-1212.
- Houston, B.W., Mills, N., Solis-Moya, A. (2013). Inspiratory muscle training for cystic fibrosis. *Cochrane Database System Rev*, 11.
- Hunninghake, G. Q., Costabel, U., Ando, M., Baughman, R., Cordier, J. F., du Bois, R., Eklund, A., Kitaichi, M., Lynch, J., Rizzato, G., Rose, C., Selroos, O., Semenzato, G., Sharma, O. P. (1999). ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. *Sarcoidosis, Vasculitis and Diffuse Lung Diseases*, 16(2), 149-173.
- Huppmann, P., Sczepanski, B., Boensch, M., Winterkamp, S., Schoneheit-Kenn, U., Neurohr, C., Behr, J., Kenn, K. (2013). Effects of Inpatient Pulmonary Rehabilitation in Patients with Interstitial Lung Diseases. *European Respiratory Journal*, 42, 444-453.
- Iannuzzi, M. C., Benjamin, A., Rybicki, B., Teirstein, A. (2007). Sarcoidosis. *The New England Journal of Medicine*, 357, 2153-2165.
- Iannuzzi, M. C., Rybicki, B. A. (2007). Genetics of Sarcoidosis. *American Thoracic Society*, 4(1), 108-116.
- Ivanisevic, J., Kotur, J., Stefanovic, A., Ilic, J. (2012). Dyslipidemia and Oxidative Stress in Sarcoidosis Patients. *Clinical Biochemistry*, 45(9), 677-682.

- Jacome, C., Marques, A. (2014). Pulmonary Rehabilitation for Mild COPD: A Systematic Review. *Respiratory Care*, 59(4), 588-594.
- 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.
- Janssen, I., LeBlanc, A. G. (2010). Systematic Review of the Health Benefits of Physical Activity and Fitness in School-aged Children and Youth. *International Journal of Behavioral Nutrition and Physical Activity*, 7.
- Jennifer, J., Rashcovsky, K. (2004). Sarcoidosis. *American Family Physician*, 70(2), 312-322.
- Jeong, M., Kang, H. K., Song, P., Park, H. K., Jung, H., Lee, S. S., Koo, H. K. (2017). Hand Grip Strength in Patients with Chronic Obstructive Pulmonary Disease. *International Journal of Chronic Obstructive Pulmonary Disease*, 9(12), 2385-2390.
- Jeukendrup, A., Gleeson, M. (2010). *Sports Nutrition 2nd ed.* Leeds, Yorkshire: Human Kinetics.
- Joshi, A., Kale, S., Chandel, S., Pal, D. K. (2015). Likert Scale: Explored and Explained. *British Journal of Applied Science and Technology*, 7(4), 396-403.
- Judson, M. A., Baughman, R. P., Thompson, B. W., Cherniak, R. (2003). Two Year Prognosis of Sarcoidosis: The ACCESS Experience. *Sarcoidosis, Vasculitis and diffuse lung diseases*, 20(3), 204-211.
- Judson, M. A. (2008). The Diagnosis of Sarcoidosis. *Clinics in Chest Medicine*, 29(3), 415-427.
- Judson, M. A. (2012). The Treatment of Pulmonary Sarcoidosis. *Respiratory Medicine*, 106(10), 1351- 1361.
- Judson, M. A., Chaudhry, H., Louis, A., Lee, K., Yucel, R. (2015). The Effect of Corticosteroids on Quality of Life in a Sarcoidosis Clinic: The Results of a Propensity Analysis. *Respiratory Medicine*, 109(4), 526-531.
- Kalkanis, A., Judson, M. A. (2013). Distinguishing Asthma from Sarcoidosis: An Approach to a Problem that is not Always Solvable. *The Journal of Asthma*, 50(1), 1-6.
- 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. (2015). Reduction of Exercise Capacity in Sarcoidosis in Relation to Disease Severity.
- Kanis, J. O., Johnell, A., Odeon, Sernbo, I., Redlund-Johnell, I., De Laet, C., Jonsson, B. (2000). Long-Term Risk of Osteoporotic Fracture in Malmo. *Osteoporosis International*, 11(8), 669-674.
- Karadalli, M. N., Bosnak-Guclu, M., Camcioglu, B., Kokturk, N., Turktas, H. (2016). Effects of Inspiratory Muscle Training in Subjects with Sarcoidosis: A Randomized Controlled Clinical Trail. *Respiratory Care*, 61(4), 483-494.

- Karetzky, M., McDonough, M. (1996). Exercise and Resting Pulmonary Function in Sarcoidosis. *Official Journal of WASOG*, 13(1), 43-49.
- Kelley, K., Clark, B., Brown, V., Sitzia, J. (2003). Good Practice in the Conduct and Reporting of Survey Research. *International Journal for Quality in Health Care*, 15(3), 261-266.
- Kendall, K. L., Fukuda, D. H., Smith, A. E., Cramer, J. T., Stout, J. R. (2012). Predicting Maximal Aerobic Capacity (VO₂max) from the Critical Velocity Test in Female collegiate Rowers. *Journal of Strength and Conditioning*, 26, 733-738.
- Kersnik, J., Scvab, I., Vegnuti, M. (2001). Frequent Attenders in General Practice: Quality of Life, Patient Satisfaction, Use of Medical Services and GP Characteristics. *Scandinavian Journal of Primary Health Care*, 19(3), 174-177.
- Kirk, J. K., Graves, D. E., Lipkin, E. W., Austin, M., Margolis, K. L. (2008). Restricted-Carbohydrate Diets in Patients with Type 2 Diabetes: A Meta-analysis. *Journal of American Diet Association*, 108(1), 91-100.
- Kitzman, D. W., Groban, L. (2008). Exercise Intolerance. *Heart Failure Clinics*, 4(1), 99-115
- Kitzman, D. W., Groban, L. (2011). Exercise Intolerance. *Cardiology Clinics*, 29(3), 461-477.
- Knekt, P., Kumpulainen, J., Jarvinen, R., Rissanen, H., Heliovaara, M., Reunanen, A., Hakulinen, T., Aromaa, A. (2002). Flavonoid Intake and Risk of Chronic Diseases. *The American Journal of Clinical Nutrition*, 76(3), 560-568.
- Kobak, S. Sarcoidosis: A Rheumatologist's Perspective. *Therapeutic Advances in Musculoskeletal Disease* 2015; 7(5): 196-205.
- 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.
- 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.
- Kosmas, C. E., Martinez, I., Sourlas, A., Boyza, K. V., Campos, F. N., Torres, V., Montan, P. D., Guzman, E. (2018). High-Density Lipoprotein (HDL) Functionality and its Relevance to Atherosclerotic Cardiovascular Disease. *Drugs in Context*, 7.
- Kouba, J. (2005). Impact of Environment, Ethnicity, and Culture on Nutrition and Health. *Nutrition and Oral Medicine*, 45-60.
- Koutsokera, A., Papaioannou, A. L., Malli, F., Kiropoulos, T. S., Katsabeki, A., Kerenidi, T., Gourgoulisanis, K. L., Daniil, Z. D. (2009). Systemic Oxidative Stress in Patients with Pulmonary Sarcoidosis. *Pulmonary Pharmacology and Therapeutics*, 22(6), 603-607.
- Kowalska, A., Puscinska, E., Golian-Geremek, A., Czemiawska, J., Stoklosa, A., Kram, M., Tomkowski, W. Z., Gorecka, D. (2012). Six-minute Walk Test in Sarcoidosis Patients with Cardiac Involvement. *Pneumonologia i Alergologia Polska*, 80(5): 430-438.

- Kucera, G. P., Rybicki, B. A., Kirkey, K. L., Coon, S. W., Major, M. L., Maliarik, M. J., Iannuzzi, M. C. (2003). Occupational Risk Factors for Sarcoidosis in African-American Siblings. *Chest*, 123(5), 1527-1535.
- Kyu, H. H., Bachman, V. F., Alexander, L. T., Mumford, J. E., Afsin, A., Estep, K., Veerman, J. L., Delwice, K., Lannarone, M. L., Moyer, M. L., Cercy, K., Vos, T., Murray, C. K., Forouzanfar, M. H. (2013). Physical Activity and Risk of Breast Cancer, Colon Cancer, Diabetes, Ischemic Heart Disease, and Ischemic Stroke Events: Systematic Review and Dose-response Meta-analysis for the Global Burden of Disease Study 2013. 354.
- Labunskyy, V. M., Lee, B. C., Handy, D. E., Loscalzo, J., Hatfield, D. L., Gladyshev, V. N. (2011). Both Maximal Expression of Selenoproteins and Selenoprotein Deficiency Can Promote Development of Type 2 Diabetes-Like Phenotype in Mice. *Antioxidants and Redox Signaling*, 14(12), 2327-2336.
- Langer, D., Hendriks, E. J. M., Burtin, C., Probst, V., Van der Schans, C. P., Paterson, W. J., Verhoef-de Wijk, M. C. E., Straver, R. V. M., Klaassen, M., Troosters, T., Decramer, M., Ninane, V., Delguste, P., Muris, J., Gosselink, R. (2009). A Clinical Practice Guideline for Physiotherapists Treating Patients with Chronic Obstructive Pulmonary Disease based on a Systemic Review of Available Evidence. *Clinical Rehabilitation*, 23(5), 445-462.
- Lamberts, R. P., Davidowitz, K. J. (2014). Allometric Scaling and Predicting Cycling Performance in (well-) Trained Female Cyclists. *International Journal of Sports Medicine*, 35, 217-222.
- 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.
- Lee, I. M., Shiroma, E. J. (2014). Using Accelerometers to Measure Physical Activity in Large-Scale Epidemiologic Studies: Issues and Challenges. *British Journal of Sports Medicine*, 48(3), 197-201.
- Leidy, N. K., Wilcox, T. K., Jones, P. W., Murray, L., Winnette, R., Howard, K., Petriollo, J., Powers, J., Sethi, S. (2010). Development of the EXacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT): A Patient-Reported Outcome (PRO) Measure. *Value in Health*, 13(8), 965-975.
- Leil, I., Salimbene, I., Varone, F., Fuso, L., Valente, S. (2013). Husband and Wife with Sarcoidosis: Possible Environmental Factors Involved. *Multidisciplinary Respiratory Medicine*, 8(1).
- Leong, D. P., Teo, K. K., Rangarajan, S., Kutty, V. R., Lanus, F., Hui, C., Quanyong, X., Zhenzhen, Q., Jiinhua, T., Noorhassim, I., Al Habib, K., Moss, S. J., Rosengren, A., Akalin, A. A., Rahman, O., Chifamba, J., Orlandini, A., Kumar, R., Yeates, K., Gupta, R., Yusufali, A., Dans, A., Avezum, A., Lopez-Jaramillo, P., Poirier, P., Heidari, H., Zatonska, K., Iqbal, R., Khatib, R., Yusuf, S. (2016). Reference Ranges of Handgrip Strength from 125,462 Healthy Adults in 21 Countries: A Prospective Urban Rural Epidemiologic (PURE) Study. *Journal of Cachexia, Sarcopenia and Muscle*, 7(5), 535-546.

- Li, C., Li, L., Luo, J., Huang, N. (1998). Effect of Turmeric Volatile Oil on the Respiratory Tract. *Zhongguo Zhong*, 23(10), 624-625.
- Liu, D., Ahmet, A., Ward, L., Krishnamoorthy, P., Mandelcorn, E., Leigh, R., Brown, J. P., Cohen, A., Kim, H. (2013). A Practical Guide to the Monitoring and Management of the Complications of Systemic Corticosteroid Therapy. *Allergy, Asthma & Clinical Immunology*, 9(30).
- Liao, S., Benzo, R., Ries, A. L., Soler, X. (2014). Physical Activity Monitoring in Patients with Chronic Obstructive Pulmonary Disease. *Chronic Obstructive Pulmonary Diseases*, 1(2), 155-165.
- Liu, H., Patel, D., Welch, A. M., Wilson, C., Mroz, M. M., Rose, C. S., Van Dyke, M., Swigris, J. J., Hamzeh, N., Maier, L. (2016). Association Between Occupational Exposures and Sarcoidosis: An Analysis from Death Certificates in the United States, 1988-1999. *Chest*, 150(2), 289-298.
- Loke, W. S., Herbert, C., Thomas, P. S. (2013). Sarcoidosis: Immunopathogenesis and Immunological Markers. *International Journal of Chronic Diseases*, 2013, 1-13.
- MacAuley, D., Bauman, A., Fremont, P. (2015). Exercise: Not a Miracle Cure, Just Good Medicine. *The British Medical Journal*, 350.
- Malek, M. H., Housh, T. J., Derger, D. E., Coburn, J. W., Beck, T. W. (2005). A New Non-exercise-based Vo₂max Prediction Equation for Aerobically Trained Men. *Journal of Strength and Conditioning*, 19, 559-565.
- Mana, J., Salazar, A., Manresa, F. (1994). Clinical Factors Predicting Persistence of Activity in Sarcoidosis: A Multivariate Analysis of 193 Cases. *Respiration*, 61, 219-225.
- Marcellis, R. G., Lanssen, A. F., Kleynen, S., De Vries, J., Drent, M. (2011). Exercise Capacity, Muscle Strength, and Fatigue in Sarcoidosis: A Follow-up Study. *European Respiratory Journal*, 38, 628-634.
- Marcellis, R. G., Lenssen, A. F., De Vries, J., Drent, M. (2013a). Reduced Muscle Strength, Exercise Intolerance and Disabling Symptoms in Sarcoidosis. *Current Opinion in Pulmonary Medicine*, 19(5), 524-530.
- Marcellis, R. G., Lanssen, A. F., Kleynen, S., De Vries, J., Drent, M. (2013b). Exercise Capacity, Muscle Strength, and Fatigue in Sarcoidosis: A Follow-up Study. *Lung*, 191(3), 247-256.
- Marcellis, R. G., Lenssen, A. F., De Vries, J., De Vries, G., Baughman, R. P., Van der Grinten, C. P., Verschakelen, J. A., Drent, M. (2013c). Is There an Added Value of Cardiopulmonary Exercise Testing in Sarcoidosis Patients?. *Lung*, 191(1), 43-52.
- Marcellis, R., Van der Veeke, M., Mesters, I., Drent, M., De Bie, R., De Vries, G., Lenssen, A. (2015). Does Physical Training Reduce Fatigue in Sarcoidosis? *Sarcoidosis, Vasculitis and Diffuse Lung Diseases: Official Journal of WASOG*, 32(1), 53-62.
- Mathiowetz, V., Wiemer, D. M., Federman, S. M. (1986). Grip and Pinch Strength: Norms for 6- to 19-year-olds. *The American Journal of Occupational Therapy*, 40(10), 705-711.

- Martinez, F. J., Flaherty, K. (2006). Pulmonary Function Testing in Idiopathic Interstitial Pneumonias. *American Thoracic Society*, 3(4), 315-321.
- Martusewicz-Boros, M. M., Boros, W. P., Wiatr, E., Wesolowski, S., Roszkiwski-Slitz K. (2012). Bronchial Hyperactivity in Sarcoidosis Patients: Correlation with Airflow Limitation Indices. *Sarcoidosis Vasculitis and Diffuse Lung Diseases*, 29(2), 99-106.7
- Maryland Medical Center (2014). Sarcoidosis. Retrieved 5th April 2017 from <http://umm.edu/health/medical/altmed/condition/sarcoidosis>
- McCarthy, B., Casey, D., Devane, D., Murphy, K., Murphy, E., Lacasse, Y. (2015). Pulmonary Rehabilitation for Chronic Obstructive Pulmonary Disease. *The Cochrane Library*.
- McConnel, A. (2011). *Breathe Strong, Perform Better*. UK: Human Kinetics.
- Medinger, A., E., Samir, K., Preshant, R. K. Sarcoidosis: The Value of Exercise Testing. *Chest* 2001; 120(1): 93-101.
- Michielsen, H. J., De Vries, J., Van Heck, G. L. (2003). Psychometric Qualities of a Brief Self-reported Measure: The Fatigue Assessment Scale. *Journal of Psychosomatic Research*, 54(4), 345-352.
- Miller, A., Brown, L. K., Sloanne, M. F., Bhuptani, A., Teirstein, A. S. (1995). Cardiorespiratory Responses to Incremental Exercise in Sarcoidosis Patients with Normal Spirometry. *Chest*, 107(2), 323-329.
- Mitchell, D. N., Wells, A., Spiro, S. G., Moller, D. R. (2012). *Sarcoidosis*. Florida: CRC Press.
- Mensink, R. P., Katan, M. B. (1989). Effect of a Diet Enriched with Monounsaturated or Polyunsaturated Fatty Acids on Levels of Low-Density and High-Density Lipoprotein Cholesterol in Healthy Women and Men. *The New England Journal of Medicine*, 321, 436-441.
- Mirsaeidi, M., Machado, R. F., Schraufnagel, D., Sweiss, N. J., Baughman, R. P. (2015). Racial Difference in Sarcoidosis Mortality in the United States. *Chest*, 147(2), 438-449.
- Mitchell, D. N., Wells, A., Spiro, S. G., Moller, D. R. (2012). *Sarcoidosis*. Florida: CRC Press.
- Mohanty, B., Mahanty, A., Ganguly, S., Sankar, T. V., Chakraborty, K., Rangasamy, A., Paul, B., Sarma, D., Mathew, S., Asha, K. K., Behera, B., Aftabuddin, M., Akhtar, M. S., Sahi, N., Mitra, T., Banerjee, S., Paria, P., Das, D., Das, P., Vijayan, K. K., Laxmanan, P. T., Sharma, A. P. (2014). Amino Acid Compositions of 27 Food Fishes and Their Importance in Clinical Nutrition. *Journal of Amino Acids*, Epub.
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G. (2009). The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLOS Medicine*, 6(7): e1000097.

- Moliner-Urdiales, D., Ortega, F. B., Vicente-Rodriguez, G., Rey-Lopez, J. P., Garcia-Marco, L., Widhalm, K., Sjostrom, M., Moreno, L. A., Castillo, M. J., Ruiz, J. R. (2010). Association of Physical Activity with Muscular Strength and Fat-Free Mass in Adolescents: The Helena Study. *European Journal of Applied Physiology*, 109(6): 1119-1127.
- Moore, D. R., Robinson, M. J., Fry, J. L., Tang, J. E., Glover, E. I., Wilkinson, S. B., Prior, T., Tarnopolsky, M. A., Phillips, S. M. (2009). Ingested Protein Dose Response of Muscle and Albumin Protein Synthesis after Resistance Exercise in Young Men. *The American Journal of Clinical Nutrition*, 89(1), 161-168.
- Morand, M., Beauregard, S., Mathieu, S. (2015). Systematic Sarcoidosis Revealed by Axillary Electrolysis. *Journal of Cutaneous Medicine and Surgery*, 19(4).
- Moreno-Macias, H., Romieu, I. (2014). Effects of Antioxidant Supplements and Nutrients on Patients with Asthma and Allergies. *The Journal of Allergy and Clinical Immunology*, 133 (5), 1237-1244.
- Morgenthau, A. S., Iannuzzi, M. C. (2011). Recent Advances in Sarcoidosis. *Chest*, 139, 174-182.
- Morton-Holtham, L., Moir, H. J., Swann, N. (ndA). A Systematic Review of Physical Activity and Physical Fitness in Sarcoidosis. Unpublished: *Thesis Chapter 4*.
- Morton-Holtham, L., Moir, H. J., Swann, N. (ndB). The Relationship Between a Direct Measure of Physical Activity Against Self-Reported Physical Activity, Muscle Strength, Quality of life and Exercise Capacity. *Unpublished: Thesis Chapter 7*.
- Morris, C. G. (1992). *Academic Press Dictionary of Science and Technology*. London: Academic Press.
- 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.
- Mukherjee, M., Stoddart, A., Gupta, R. P., Nwaru, B. I., Farr, A., Heaven, M., Fitzsimmons, D., Bandyopadhyay, A., Aftab, C., Simpson, C. R., Lyons, R. A., Fischbacher, C., Dibben, C., Sheilds, M. D., Phillips, C. J., Strachan, D. P., Davies, G. A., Mckinstry, B., Sheikh, A. (2016). The Epidemiology, Healthcare and Societal Burden and Costs of Asthma in the UK and its Member Nations: Analyses of Standalone and Linked National Databases. *BMC Medicine*, 14(1), 113.
- Muller-Quernheim, J., Gaede, K. I., Fireman, E., Zissel, G. (2006). Diagnosis of Chronic Beryllium Disease within Cohorts of Sarcoidosis Patients. *European Respiratory Journal*, 27, 1190-1195.
- Murphy, S. L. (2009). Review of Physical Activity measurement using Accelerometers in Older Adults: Considerations for Research Design and Conduct. *Preventive Medicine*, 48(2), 108-114.

- Musalek, C., Krchengast, S. (2017). Grip Strength as an Indicator of Health-Related Quality of Life in Old Age-A Pilot Study. *International Journal of Environmental Research and Public Health*, 14(12).
- Nag, S. (2011). Sarcoidosis-Like Reactions. *Intech Open*.
- Nam, S., Dabrosielski, D., Stewart, K. J. (2013). Predictors of Exercise Intervention Dropout in Sedentary Individuals with Type 2 Diabetes. *Journal of Cardiopulmonary Rehabilitation and Prevention*, 32(6), 370-378.
- National Heart, Lung and Blood Institute. (2013a). What are the Signs and Symptoms of Sarcoidosis? Retrieved 17th March 2017 from <http://www.nhlbi.nih.gov/health/health-topics/topics/sarc>
- National Heart, Lung and Blood Institute. (2013b). How is Sarcoidosis Diagnosed? Retrieved 17th March 2017 from <http://www.nhlbi.nih.gov/health/health-topics/topics/sarc/diagnosis>
- National institute for health and care excellence (NICE). (2014). Obesity: Identification, Assessment and Management. Retrieved 25th April 2018 from <https://www.nice.org.uk/guidance/cg189/ifp/chapter/obesity-and-being-overweight>
- National Institute for Health and Care Excellence (NICE). (2016). Chronic Obstructive Pulmonary Disease in Adults. Retrieved 22nd May 2017 from <https://www.nice.org.uk/guidance/qs10>
- National Institute for Health and Care Excellence (NICE). (2017) Patient Experience in Adult NHS Services: Improving the Experience of Care for People using Adult NHS Services. Retrieved December 13th 2017 from <https://www.nice.org.uk/guidance/cg138/chapter/1-guidance>
- Naz, L., Ozalevil, S., Ozkan, S., Sahin, H. (2018). 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*, 38(2), 124-130.
- Neupert, S. D., Lachman, M. E., Whitbourne, S. B. (2013). Exercise Self-Efficacy and Control Beliefs Predict Exercise Behavior After an Exercise Intervention for Older Adults. *Journal of Aging and Physical Activity*, 17(1), 1-16.
- Newman, K. L., Newman, L. S. (2012). Occupational Causes of Sarcoidosis. *Current Opinion in Allergy and Clinical Immunology*, 12(2), 145-150.
- Newman, L. S., Rose, C. S., Bresnitz, E. A., Rossman, M. D., Barnard, J., Frederick, M., Terrin, M.L., Weinberger, S. E., Moller, D. R., McLennan, G., Hunninghake, G., De Palo, L., Baughman, R. P., Iannuzzi, M. C., Judson, M. A., Knatterud, G., Thompson, B. W., Teirstein, A. S., Rabin, D. L., Rybicki, B. A., Cherniack, R. (2004). A Case Control Etiologic Study of Sarcoidosis. Environmental and Occupational Risk Factors. *American Journal of Respiratory and Critical Care Medicine*, 170(12).
- NHS. (2015a). Sarcoidosis. Reviewed 14th March 2017 from <http://www.nhs.uk/conditions/sarcoidosis/Pages/Introduction.aspx>

- NHS. (2015b). Benefits of Exercise. Reviewed 24th April 2017 from <http://www.nhs.uk/Livewell/fitness/Pages/whybeactive.aspx>
- NHS. (2016). High Blood Pressure (Hypertension). Reviewed 8th March 2017 from [http://www.nhs.uk/Conditions/Blood-pressure-\(high\)/Pages/Introduction.aspx#risks](http://www.nhs.uk/Conditions/Blood-pressure-(high)/Pages/Introduction.aspx#risks)
- NHS. (2017), Pulmonary Hypertension. Retrieved 5th June 2017 from <http://www.nhs.uk/conditions/pulmonary-hypertension/Pages/introduction.aspx>
- Nicholls, S. J., Lundman, P., Harmer, J. A., Cutri, B., Griffiths, K. a., Rye, K., Barter, P. J., Celemajer, D. S. (2006). Consumption of Saturated Fat Impairs the Anti-Inflammatory Properties of High Density Lipoproteins and Endothelial Function. *Journal of the American College of Cardiology*, 48(4), 715-720.
- Nielsen, F. H. (2014). Effects of Magnesium Depletion on Inflammation in Chronic Disease. *Current Opinion in Clinical Nutrition and Metabolic Care*, 17(6), 525-530.
- Nimbarte, A. D., Aghazadeh, F., Bogolu, S. C. R., Rajulu, S. L. Understanding the Effect of Speed of Exertion on Isokinetic Strength Using a Multiaxial Dynamometer. *International Journal of Occupational Safety and Ergonomics*, 15(3), 255-263.
- Norman, K., Stobaus, N., Gonzalez, M. C., Schulzke, J-D., Pirlich, M. (2011). Hand Grip Strength: Outcome Predictor and Marker of Nutritional Status. *Clinical Nutrition*, 30(2), 135-142.
- Norton, R. L., Hoffman, P. R. (2013). Selenium and Asthma. *Molecular Aspects of Medicine*, 33(1), 98-106.
- O'Donnel, D. E. (2006). Impacting Pateint-Centred Outcomes in COPD: Breathlessness and Exercise Tolerance. *European Respiratory Review*, 15(99), 37-41.
- Olufunke, A. A., Chikodi, N. A., Ajuluchukwu, J. N., Jaja, S. I. (2014). Prediction Equations for 6-minute Walk Distance in apparently Healthy Nigerians. *Hong Kong Physiotherapy Journal*, 32(2), 65-72.
- Oksuzyan, A., Demakakos, P., Shkolnikova, M., Thinggaard, M., Vaupel, J. W., Christensen, K., Shkolnikov, V. M. (2017). Handgrip Strength, and its prognostic value for Mortality in Moscow, Denmark, and England. *Plos One*.
- O'Neil, B., McDonough, S. M., Wilson, J. J., Bradbury, I., Hayes, K., Kirk, A., Kent, L., Cosgrove, D., Bradley, J. M., Tully, M. A. (2017). Comparing Accelerometer, Pedometer and a Questionnaire for Measuring Physical Activity in Bronchiectasis: A Validity and Feasibility Study. *Respiratory Research*, 18(16).
- Osterniq, L. R. (1986). Isokinetic Dynamometry: Implications for Muscle Testing and Rehabilitation. *Exercise and Sport Science Reviews*, 14, 45-80.
- Ostrowski, S., Barud, W. (2006). Factors Influencing Lung Function: Are the Predicted Values for Spirometry Reliable Enough? *Journal of Physiology and Pharmacology*, 57(4), 263-271.
- Ottevaere, C., Huybrechts, I., De Bourdeaudhuji, I., Sjostrom, M., Ruiz, J. R., Ortega, F. B., Hagstromer, M., Widhalm, K., Molnar, D., Moreno, L. A., Beghin, L., Kafatos, A.,

- Polito, A., Manios, Y., Martinez-Gomez, D., De Henauw, S. (2011). Comparison of the IPAQ-A and Actigraph in Relation to Vo2Max Among European Adolescents: The Helena Study. *Journal of Science and Medicine in Sport*, 14(4), 317-324.
- Owen, N., Healy, G. N., Matthews, C. E. (2010). Too Much Sitting: The Population-Health Science of Sedentary Behavior. *Exercise and Sport Sciences Reviews*. 38(3), 105-113.
- Oyeyemi, A. L., Bello, U. M., Philemon, S. T., Aliyu, B. N., Majidadi, R. W., Oyeyemi, A. Y. (2014). *BMI Open*, 4(12), e005820.
- Ozaki, H., Loenneke, J. P., Thiebaud, R. S., Abe, T. (2013). Resistance Training Induced Increase in VO₂max in Young and Older Subjects. *European Review of Aging and Physical Activity*, 10(2), 107-116.
- Panayias, S., Theodorakopoulos, P., Bouras, A., Constantopoulos, S. (1991). Seasonal Occurrence of Sarcoidosis in Greece. *Lancet*, 338(8765), 510-511.
- Panedo, F., Dahn, J. (2005). Exercise and Well-being: A Review of Mental and Physical Health Benefits Associated with Physical Activity. *Current Opinion in Psychiatry*, 18(2), 189-193.
- Parcell, A. C., Sawyer, R. D., Tricoli, V. A., Chinevere, T. D. (2002). Minimum Rest Period for Strength Recovery During a Common Isokinetic Testing Protocol. *Medicine and Science in Sports Exercise*, 34(6), 1018-1022.
- Pbert, L., Madison, J. M., Druker, S., Olendzki, N., Magner, R., Reed, G., Carmody, J. (2012). Effect of Mindfulness Training on Asthma Quality of Life and Lung Function: A Randomized Controlled Trial. *Thorax*, 67(9), 769-776.
- Pedersen, B. K., Saltin, B. (2015). Exercise as Medicine – Evidence for Prescribing Exercise as Therapy in 26 Different Chronic Diseases. *Scandinavian Journal of Medicine and Science in Sports*, 3, 172.
- Pellegrino, R., Viegi, G., Brusasco, V., Crapo, R. O., Burgos, F., Casaburi, R., Coates, A., Van der Grinten, C. P. M., Gustafsson, P., Hankinson, J., Jensen, R., Johnson, D. C., Macintyre, N., McKay, R., Miller, M. R., Navajas, D., Pedersen, O. F., Wagner, J. (2005). Interpretative Strategies for Lung Function Tests. *European Respiratory Journal*, 26(5), 948-968.
- Peros-Golubicic, T., Ljubic, S. (1995). Cigarette Smoking and Sarcoidosis. *Acta Medica Croatica*, 49(4), 187-193.
- Pitta, F., Troosters, T., Probst, V. S., Langer, D., Decramer, M., Gosselink, R. (2008). Are Patients with COPD More Active After Pulmonary Rehabilitation?. *Chest*, 134(2), 273-280.
- Pludowski, P., Holick, M. F., Pilz, S., Wagner, C. L., Hollis, B. W., Grant, W. B., Shoenfeld, Y., Lerchbaum, E., Llewellyn, D. J., Kienreich, K., Soni, M. (2013). Vitamin D Effects on Musculoskeletal Health, Immunity, Autoimmunity, Cardiovascular Disease, Cancer, Fertility, Pregnancy, Dementia and Mortality – A Review of Recent Evidence. *AutoImmunity Reviews*, 12(10), 976-989.

- Poetker, D. M., Reh, D. D. (2010). A Comprehensive Review of the Adverse Effects of Systemic Corticosteroids. *Otolaryngol Clinics of North America*, 43(4), 753-758.
- Powers, S. K., Nelson, W. B., Hudson, M. B. (2011). Exercise-induced Oxidative Stress in Humans: Cause and Consequences. *Free Radical Biology and Medicine*, 51(5), 942-950.
- Prince, S., Adamo, K. B., Hamel, M. E., Hardt, J., Gorber, S. C., Tremblay, M. (2008). A Comparison of Direct Versus Self-report Measures for Assessing Physical Activity in Adults: A Systematic Review. 5(56).
- Puhan, M. A., Gimeno-Santos, E., Scharplatz, M., Troosters, T., Walters, E. H., Steurer, J. (2011). Pulmonary Rehabilitation Following Exacerbations of Chronic Obstructive Pulmonary Disease. *Cochrane Database Systematic Reviews*, 10.
- Quesada-Rodrigues, N., Aldana, N., Alhanoun, E., Sukhal, S., Harris, G., Nafsi, G., Cohen, R. A., Tulaimat, A. (2014). Effect of Pulmonary Rehabilitation on 6-Minute Walk Distance in Sarcoidosis and Other Interstitial Lung Diseases in Comparison with COPD. *American Journal of Respiratory and Critical Care Medicine*, 189.
- Raask, T., Maestu, J., Latt, E., Jurimae, J., Vainik, U., Kinstabel, K. (2017). Comparison of IPAQ-SF and Two Other Physical Activity Questionnaires with Accelerometer in Adolescent Boys. *PLOS*.
- Radloff, L. S. (1977). The CES-D Scale. A Self-report Depression Scale for Research in the General Population. *Applied Psychological Measurement*, 1, 385-401.
- Rantanen, T. (2003). Muscle Strength, Disability and Mortality. *Scandinavian Journal of Medicine & Science in Sports*, 13(1), 3-8.
- Rastogi, D., Khan, U. I., Isasi, C. R., Coupey, S. M. (2012). Associations of Obesity and Asthma with Functional Exercise Capacity in Urban Minority Adolescents. *Pediatric Pulmonary*, 47(11), 1061-1069.
- Reiner, M., Neiermann, C., Jekauc, D., Woll, A. (2013). Long-term Health Benefits of Physical Activity – A Systematic Review of Longitudinal Studies. *BMC Public Health*, 13.
- Reis, A. L., Bauldoff, G. S., Carlin, B. W., Cassaburi, R., Emery, C. F., Mahler, D. A., Make, B., Rochester, C. L., Zuwallack, R., Herrerias, C. (2007). Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest*, 4-42.
- Reverson, C. J., Cayou, C., Topp, F., Hilling, L., Camp, P. G., Wilcox, P. G., Khalil, N., Collard, H. R., Garvey, C. (2014). Pulmonary Rehabilitation Improves Long-term Outcomes in Interstitial Lung Disease: A Prospective Cohort Study. *Respiratory Medicine*, 108(1), 203- 210.
- Rissmiller, R., James, W. E. (2017). Sarcoidosis: The Organs Involved. A Primer for Primary Care Physicians. *International Archives of Internal Medicine*, 1(1).
- Roca, J., Whipp, B. J., Agusti, A., Anderson, S. D., Casaburi, R., Cotes, J. E., Donner, C. F., Estenne, M., Folgering, H., Higenbottam, T. W., Killian, K. J., Palange, P., Pastessio, A., Prefuat, C., Sergyseis, R., Wagner, P. D., Weisman, L. (1997). Clinical Exercise

Testing with Referenceto Lung Diseases: Indications, Standardization and Interpretation Strategies. *European Respiratory Journal*, 10(11).

- Rogério, A. P., Kanashiro, A., Fontanari, C., da Silva, E. V. G., Lucisano-Valim, Y. M., Soares, E. G., Faccioli, L. H. (2007). Anti-inflammatory Activity of Quercetin and Isoquercitrin in Experimental Maurine Allergic Asthma. *Inflammation Research*, 56(10), 402-408.
- Rosenberger, M. E., Buman, M. P., Haskell, W. L., McConnell, M. V., Carstensen, L. L. (2016). 24 Hours of Sleep, Sedentary Behavior and Physical Activity with Nine Wear Devices. (2016). *Medicine and Sciences in Sports and Exercise*, 48(3), 457-465.
- Ruiz, J. R., Sui, X., Lobelo, F., Morrow, J. R., Jackson, A., Siostrom, M., Blair, S. N. (2008). Association Between Muscular Strength and Mortality in Men: Prospective Cohort Study. *British Medical Journal*, 337.
- Rybicki, B. A., Amend, K. L., Maliarik, M. J., Iannuzzi, M. C. (2004). Photocopier Exposure and Risk of Sarcoidosis in African-American Sibs. *Sarcoidosis, Vasculitis and Defuse Lung Diseases: Official Journal of WASOG*, 21(1), 49-55.
- Rybicki, B. A., Iannuzzi, M. C. (2007). Epidemiology of Sarcoidosis: Recent Advances and Future Prospects. *Seminars in Respiratory and Critical Care Medicine*, 28(1), 22-35.
- Rybicki, B. A., Iannuzzi, M. C., Frederick, M. M., Thompson, B. W., Rossman, M. D., Bresnitz, E. A., Terrin, M. L., Moller, D. R., Barnard, J., Baughman, B. P., De Palo, L., Hunninghake, G., Johns, C., Judson, M. A., Knatterud, G. L., McLennan, G., Newman, L. S., Rabin, D. L., Rose, C., Teirstein, A. S., Weinberger, S. E., Teager, H., Cherniack, R. (2001). Familial Aggregation of Sarcoidosis – A Case-Control Etiologic Study of Sarcoidosis. *American Journal of Respiratory and Critical Care Medicine*, 164(11), 2085-2091.
- Rybicki, B. A., Major, M., Popovich, J., Maliarik, M. J., Iannuzzi, M. C. (1997). Racial Differences in Sarcoidosis Incidence: A 5-year Study in Health Maintenance Organization. *American Journal of Epidemiology*, 145(3), 234-241.
- Ryerson, C. J., Cayou, C., Topp, F., Hilling, L., Camp, P. G., Khalil, N., Collard, H. R., Garvey, C. (2014). Pulmonary Rehabilitation Improves Long-term Outcomes in Interstitial Lung Disease: A Prospective Cohort Study. *Respiratory Medicine*, 108(1), 203-210.
- Saidha, S., Sotirchos, E. S., Eckstein, C. (2012). Etiology of Sarcoidosis: Does Infection Play a Role? *Yale Journal of Biology and Medicine*, 85(1), 133-141.
- Saligan, L. (2014). The Relationship between Physical Activity, Functional Performance, and Fatigue in Sarcoidosis. *Journal of Clinical Nursing*, 23, 2376-2379.
- Sallis, J. F. (2010). Measuring Physical Activity: Practical Approaches for Program Evaluation in Native American Communities. *Journal of Public Health Management and Practice*, 16(5), 404-410.
- Sasaki, J. E., John, D., Freedson, P. S. (2011). Validation and Comparison of Actigraph Activity Monitors. *Journal of Science and Medicine in Sport*, 14(5), 411-416.

- Sato, H., Grutters, J. C., Pantelidis, P., Mizzon, A. N., Ahmad, T., Van Houte, A. J., Lammers, J. W., Van Den Bosch, J. M., Welsh, K. L., Du Bois, R. M. (2002). HLA-DQB1*0201: A Marker for Good Prognosis in British and Dutch Patients with Sarcoidosis. *American Journal of Respiratory Cell and Molecular Biology*, 27(4), 406-412.
- Saunders, T. J., Tremblay, M. S., Mathieu, M. E., Henderson, M., O'Loughlin, J., Tremblay, A., Chaput, J. (2013). Associations of Sedentary Behavior, Sedentary Bouts and Breaks in Sedentary Time with Cardiometabolic Risk in Children with a Family History of Obesity. *Plos One*, 8(11).
- Secor, E. R., Shah, S. J., Guernsey, L., Schramm, C., Thrall, R. (2012). Bromelain Lim/its Airway Inflammation in an Ovalbumin-induced Murine Model of Established Asthma. *Alternative Therapies in Health and Medicine*, 18(5), 9-17.
- Seefeldt, V., Malina, R. M., Clark, M. A. (2002). Factors Affecting Levels of Physical Activity in Adults. *Sports Medicine*, 32(3), 143-168.
- Shaheen, S. O., Sterne, J. A. C., Thompson, R. L., Songhurst, C. E., Margetts, B. M., Burney, P. G. J. (2001). Dietary Antioxidant and Asthma in Adults. *American Journal of Respiratory and Critical Care Medicine*, 164(10), 1823-1828.
- Shaheen, S. O., Newson, R. B., Rayman, M. P., Wong, A. P., Tumilty, M. K., Philips, J. M., Potts, J., Kelly, F. J., White, P. T., Burney, P. G. (2007). Randomised, Double Blind, Placebo-controlled Trial of Selenium Supplementation in Adult Asthma. *Thorax*, 62(6).
- Shang, J., Wenzel, J., Krumm, S., Griffith, K., Stewart, K. (2012). Who Will Drop Out & Who Will Drop In, Exercise Adherence in a RCT among Patients Receiving Active Cancer Treatment. *Cancer Nursing*, 35(4), 312-322.
- Shaji, H., Cecily, J., Alotaibi, A. A. (2013). Effectiveness of Breathing Exercises on Pulmonary Function Parameters and Quality of Life with Chronic Obstructive Pulmonary Disease. *International Journal of Health Sciences and Research*, 3(11), 80-85.
- Shamseer, L., Moher, D., Clarke, M., Gherzi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L. A. (2015). Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) 2015 – Elaboration and Explanation. *The British Medical Journal*, 349.
- Sietsema, K. E., Kraft, M., Ginzton, L., Sharma, O. (1992). Abnormal Oxygen Uptake Responses to Exercise in Patients with Mild Pulmonary Sarcoidosis. *Chest*, 102(3), 838-845.
- Sievi, N. A., Brutsche, B. T., Frey, M., Irani, S., Leuppi, J. D., Thurnheer, R., Kohler, M., Calarenbach, C. F. (2017). Accelerometer- Versus Questionnaire-based Assessment of Physical Activity and their Changes over time in Patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease*, 12, 1113-1118.
- Siltzbach, L. E., James, D. G., Neville, E., Turiaf, J., Battesti, J. P., Sharma, O. P., Hosoda, Y., Mikami, R., Odaka, M. (1974). Course and Prognosis of Sarcoidosis Around the World. *The American Journal of Medicine*, 57(6), 847-852.

- Silva, I.S., Fregonezi, G.A., Dias, F.A., Ribeiro, C.T., Guerra, R.O., Ferreira, G.M. (2013). Inspiratory Muscle Training for Asthma. *Cochrane Database System Rev*, 9.
- Sopori, M. (2002). Effects of Cigarette Smoke on the Immune System. *Nature Reviews Immunology*, 2, 372-377.
- Spagnolo, P., Grunewald, J. (2013). Recent Advances in the Genetic of Sarcoidosis. *Journal of Medical Genetics*, 50(5), 290.
- 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.
- Spruit, M. A., Thomeer, M., Gosselink, R., Troosters, T., Kasran, A., Debrock, A., Demedts, M., Decramer, M. (2005a). Skeletal Muscle Weakness in Patients with Sarcoidosis and its Relationship with Exercise Intolerance and Reduced Health Status. *Thorax*, 60(1), 32-38.
- Spruit, M. A., Wouters, E. F. M., Gosselink, R. (2005b). Rehabilitation Programmes in Sarcoidosis: A Multidisciplinary Approach. *European Respiratory Monograph*, 32, 316-326.
- Stenton, C. (2008). The MRC Breathlessness Scale. *Occupational Medicine*, 58(3), 226-227.
- Strookappe, B., Swigris, J., De Vries, J., Elfferich, M., Knevel, T., Drent, M. (2015). Benefits of Physical Training in Sarcoidosis. *Lung*, 193(5), 701-708.
- Strookappe, B., Saketkoo, L. A., Elfferich, M., Holland, A., De Vries, J., Knevel, T., Drent, M. (2016a). Physical Activity and Training in Sarcoidosis: Review and Experience-based Recommendations. *Expert Review of Respiratory Medicine*, 10(10), 1057-1068.
- Strookappe, B., De Vries, J., Elfferich, M., Kujpers, P., Knevel, T., Drent, M. (2016b). Predictors of Fatigue in Sarcoidosis: The Value of Exercise Testing. *Respiratory Medicine*, 116(49-54).
- Stopinsek, S., Ihan, A., Salobir, B., Tercelj, M., Simcic, S. (2016). Fungal Cell Wall Agents and Bacterial Lipopolysaccharide in Organic Dust as Possible Risk Factors for Pulmonary Sarcoidosis. *Journal of Occupational Medicine and Toxicology*, 11(46).
- Stovall, D. W. (2013). *Osteoporosis: Diagnosis and Management*. New York: Springer Publishing Company.
- Subbarao, P., Mandhane, P. J., Sears, M. R. (2009). Asthma: Epidemiology, Etiology and Risk Factors. *Canadian Medical Association Journal*, 181(9), 181-190.
- Sunycz, J. A. (2008). The Use of Calcium and Vitamin D in the Management of Osteoporosis. *Therapeutics and Clinical Risk Management*, 4(4), 827-836.
- Sverrild, A., Backer, V., Kyvik, K. O., Kaprio, J., Milman, N., Svendsen, C. B., Thomsen, S. F. (2008). Heredity in Sarcoidosis: A Registry-based Twin Study. *Thorax*, 63(10), 894-896.

- Swallow, E. B., Reyes, D., Hopkinson, N. S., Man, W., Porcher, R., Cetti, E. J., Moore, A. J., Moxham, J., Polkey, M. I. (2006). Quadriceps Strength Predicts Mortality in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease. *Thorax*, 62(2).
- Swan, G. (2004). Findings from the Latest National Diet and Nutrition Survey. *The Proceedings of the Nutrition Society*, 63(4), 505-512.
- Swann, A. A., Charles, M. E., Cara, E. B., Moore, C. G., Cunningham, J. E., Fulton, J., Hebert, J. R. (2005). The Effect of Social Desirability and Social Approval on Self-Reports of Physical Activity. *American Journal of Epidemiology*, 161(4), 389-398.
- Swigris, J. J., Fairclough, D. L., Morrison, M., Make, B., Kozora, E., Brown, K. K., Wamboldt, F. S. (2011). Benefits of Pulmonary Rehabilitation in Idiopathic Pulmonary Fibrosis. *Respiratory Care*, 56(6), 783-789.
- Sylvia, L. G., Bernstein, E. E., Hubbard, J. L., Keating, L., Anderson, E. J. (2014). Practical Guide to Measuring Physical Activity. *Journal of the Academy of Nutrition and Dietetics*, 114(2), 199-208.
- Tabak, C., Arts, I. C., Smit, H. A., Heederik, D., Kromhout, D. (2001). Chronic Obstructive Pulmonary Disease and Intake of Catchins, Flavonols and Flavones: the MORGEN Study. *American Journal of Respiratory Critical Care Medicine*, 164(1), 61-64.
- Taekema, D. G., Gussekloo, J., Maier, A. B., Westendorp, 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.
- Tam, M., Gomez, S., Gonzalez-Gross, M., Marcos, A. (2003). Possible Roles of Magnesium on the Immune System. *European Journal of Clinical Nutrition*, 57(10), 1193-1197.
- Tang, J. E., Moore, D. R., Kujbida, G. W., Tarnopolsky, M. A., Philips, S. M. (2009). Ingestion of Whey Hydrolysate, Casein, or Soy Protein Isolate: Effects on Mixed Muscle Protein Synthesis at Rest and Following Resistance Exercise in Young Men. *Journal of Applied Physiology*, 107(3), 987-992.
- Taylor, R. S., Sagar, V. A., Davies, E. J., Briscoe, S., Coats, A. J., Dalal, H., Lough, F., Reese, K., Singh, S. (2014). Exercise based Rehabilitation for Heart Failure. *Cochrane Database of Systematic Reviews*, 4.
- Tchernev, G., Chokoeva, A. A., Schiavone, C., Erme, A. M., Tana, C., Darling, M., Kaley, J., Gianfaldoni, S., Wollina, U., Lotti, T., Patterson, J. W. (2015). Sarcoidosis Exclusion Criteria: The Simple Truth for a Complicated Diagnosis. *Journal of Biological Regulators and Homeostatic Agents*, 1, 5-9.
- Tercelj, M., Salobir, B., Harlander, M., Rylander, R. (2011). Fungal Exposure in Homes of Patients with Sarcoidosis – An Environmental Exposure Study. *Environmental Health*, 10(8).
- Thomas, J. R., Nelson, J. K., Silverman, S. J. (2011). *Research Methods in Physical Activity* (6th eds.). Champaign: Human Kinetics.
- Ting, E. R., Williams, M. H. (1965). Mechanics of Breathing in Sarcoidosis of Lung. *The Journal of the American Medical Association*, 192(7), 619-624.

- Tome, D. (2017). Muscle Protein Synthesis and Muscle Mass in Healthy Older Men. *The Journal of Nutrition*, 147(12), 2209-2211.
- Trost, S. G., McIver, K. L., Pate, R. R. (2005). Conducting Accelerometer-based Activity Assessments in Field-based Research. *Medicine and Science in Sports and Exercise*, 37(11), 531-543.
- Tsiaras, V., Zafeiridis, A., Dipla, K., Patras, K., Geogoulis, A., Kellis, S. (2010). Prediction of Peak Oxygen Uptake from a Maximal Treadmill test in 12 to 18 Year-old Active Male Adolescents. *Paediatric Exercise Science*, 22(4), 624-637.
- Tudor-Locke, C., Bassett, D. R. (2004). How Many Steps/Day are Enough? Preliminary Pedometer Indices for Public Health. *Sports Medicine*, 34(1), 1-8.
- Ungprasert, P., Crowson, C. S., Matteson, E. L. (2017). Influence of Gender on Epidemiology and Clinical Manifestations of Sarcoidosis: A Population-based Retrospective Cohort Study 1976-2013. *Lung*, 195(1), 87-91.
- Urso, M. L., Clarkson, P. M. (2003). Oxidative Stress, Exercise and Antioxidant Supplementation. *Toxicology*, 189, (2), 41-54.
- Uzun, H., Yanardag, H., Gelisgen, R., Genc, H., Uygun, S., Vehid, S., Karter, Y., Demirci, S. (2008). Levels of Paraoxonase, An index of antioxidar defense, in patients with active Sarcoidosis. *Current Medical Research and Opinion*, 24(6), 1651-1657.
- Vainshelboim, B., Oliverira, J., Weiss, L., Fox, B. D., Fruchter, O., Kramer, M. R. (2014). Exercise Training-Based Pulmonary Rehabilitation Program is Clinically Beneficial for Idiopathic Pulmonary Fibrosis. *Respiration*, 88, 378-388.
- Valeyre, D., Soler, P., Clerici, C., Pre, J., Battesti, J. P., Georges, R., Hance, A. J. (1988). Smoking and Pulmonary Sarcoidosis: Effect of Cigarette Smoking on Prevalence, Clinical Manifestations, Alveolitis and Evolution of the Disease, *Thorax*, 43, 516-524.
- Vasudevan, S., Maddocks, M., Chamberlain, S., Spinou, A., Wood, C., Jolley, C., Birring, S. S. (2013). P197 Physical Inactivity in Sarcoidosis. *Thorax*, 68(3).
- Verdon, F., Burnand, B., Stubi, C. L., Bonard, C., Graff, M., Michaud, A., Bischoff, T., de Vebey, M., Studer, J. P., Herzig, L., Chapuis, C., Tissot, J., Pecoud, A., Favrat, B. (2003). Iron Supplementation for Unexplained Fatigue in Non-Anaemic Women: Double Blind Randomised Placebo Controlled Trial. *British Medical Journal*, 324.
- Verlaet, A., Morerira, A., Sa-Sousa, A., Barros, R., Santos, R., Morreira, P., Fonseca, J. (2013). Physical Activity in Adults with Controlled and Uncontrolled Asthma as Compared to Healthy Adults: A Cross-sectional Study. *Clinical and Translational Allergy*, 15(3), 1.
- Violeta, V., Filipovic, S., Zugic, V., Videnovic, J., Gvozdenovic, B. (2007). Depression Sarcoidosis: CES-D Scale in Sarcoidosis Patients. *Chest*, 132(4).
- Yamaguchi, M., Hosoda, Y., Sasaki, R., Aoki, K. (1989). Epidemiological Study on Sarcoidosis in Japan. Recent Trends in Incidence and Prevalence Rates and Change in Epidemiological Features. *Sarcoidosis*, 6(2), 138-146.

- Wallaert, B., Talleu, C., Wemeau-Stervinou, L., Duhamel, A., Robin, S., Aguilaniu, B. (2011). Reduction of Maximal Oxygen Uptake in Sarcoidosis: Relationship with Disease Severity. *Respiration*, 82, 501-508.
- Wanner, M., Probst-Hensch, N., Kriemler, S., Meier, F., Autenrieth, C., Martin, B. W. (2016). Validation of the Long International Physical Activity Questionnaire: Influence of Age and Language Region. *Preventive Medicine Reports*, 250-256.
- Warburton, D. E. R., Nicol, C. W., Bredin, S. D. (2006). Health Benefits of Physical Activity: The Evidence. *Canadian Medical Association Journal*, 174(6), 801-809.
- Ware, J. E., Sherbourne, C. D. (1992). The MOS 36-item Short-form Health Survey (SF-36). I. Conceptual Framework and Item Selection. *Medical Care*, 30(6), 473-483.
- Watz, H., Waschi, B., Meyer, T., Magnussen, H. Physical Activity in Patients with COPD. *European Respiratory Journal* 2011; 33: 262-272.
- Whitton, C., Nicholson, S. K., Roberts, C., Prynne, C. J., Pot, G., Olson, A., Fitt, E., Cole, D., Teucher, B., Bates, B., Henderson, H., Pigott, S., Deverill, C., Swan, G., Stephen, A. M. (2011). National Diet and Nutrition Survey: UK Food Consumption and Nutrient Intakes from the First Year of the Rolling Programmes and Comparisons with Previous Surveys. *British Journal of Nutrition*, 106(12), 1899-1914.
- Williams, A. W., Boileau, T., Erdman, J. W. (1998). Factors Influencing the Uptake and Absorption of Carotenoids. *Experimental Biology and Medicine*, 218(2), 106-108.
- Wilsher, M. L. (1998). Seasonal Clustering of Sarcoidosis Presenting with Erythema Nodosum. *European Respiratory Journal*, 12(5), 1197-1199.
- Wirnsberger, R. M., Drent, M., Hekelaar, N., Breteler, M. H., Drent, S., Wouters, E. F., Dekhuijzen, P. N. (1998). Relationship Between Respiratory Muscle Function and Quality of Life in Sarcoidosis. *European Respiratory Journal*, 10(7), 1450-1455.
- World Health Organization. (2017). Benefits of a Balanced Diet. Retrieved 2nd May 2017 from <http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/benefits-of-a-balanced-diet>
- Yin, K., Agrawal, D. (2014). Vitamin D and Inflammatory Diseases. *Journal of Inflammation Research*, 7, 69-87.
- Zieleznik, K., Jastrzebski, D., Ziara, D. (2015). Fatigue in Patients with Inactive Sarcoidosis does not Correlate with Lung Ventilation Ability or Walking Distance. Pilot Study. *Advances in Respiratory Medicine*, 83(1), 14-22.

10. Appendices

10.1. Appendix 1) Physical Activity Questionnaire (PAR-Q)

Physical Activity Readiness
Questionnaire - PAR-Q
(revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO	
<input type="checkbox"/>	<input type="checkbox"/>	1. Has your doctor ever said that you have a heart condition <u>and</u> that you should only do physical activity recommended by a doctor?
<input type="checkbox"/>	<input type="checkbox"/>	2. Do you feel pain in your chest when you do physical activity?
<input type="checkbox"/>	<input type="checkbox"/>	3. In the past month, have you had chest pain when you were not doing physical activity?
<input type="checkbox"/>	<input type="checkbox"/>	4. Do you lose your balance because of dizziness or do you ever lose consciousness?
<input type="checkbox"/>	<input type="checkbox"/>	5. Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?
<input type="checkbox"/>	<input type="checkbox"/>	6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
<input type="checkbox"/>	<input type="checkbox"/>	7. Do you know of <u>any other reason</u> why you should not do physical activity?

If
you
answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active — begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal — this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever — wait until you feel better; or
- if you are or may be pregnant — talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____

DATE _____

SIGNATURE OF PARENT
or GUARDIAN (for participants under the age of majority) _____

WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.



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continued on other side...

Study 1: Establishing the existence of multifactorial patterns within Sarcoidosis.

Start of Block: Information and informed consent

Q1.1 Information Sheet: Establishing the existence of non-pharmacological multifactorial patterns within Pulmonary Sarcoidosis. Ethics Code: 1617/028

Thank you for considering being a participant in this project. Below you will find a short background to our work, and an outline of what you will be required to do as a participant in this study. The aim of this study is to establish the existence of any patterns or traits within pulmonary sarcoidosis specifically looking at the interaction of multiple factors and their combined outcome. Unfortunately Sarcoidosis has a chronic shortage of research. This lack of research is coupled with current researchers' focus solely on results of tests such as lung function, at the expense of patient feedback on the condition, despite lung function being shown to be a poor indicator of overall health including primary and secondary symptoms within sarcoidosis. Therefore, the purpose for the current study and its future findings are driven by informed patient experience from a wide range of patients from numerous geographical locations and backgrounds.

Am I eligible to take part in the study? You are eligible to take part in the study if you have been diagnosed with pulmonary sarcoidosis (this can be in addition to other forms of sarcoidosis and conditions) and over the age of 18 years.

What is expected of me? The study will involve you completing an electronic questionnaire comprised of four validated surveys, with closed ended questions such as gender & age as well as open questions including your experiences and views on what improves/worsens your symptoms. The procedure involves completing an online survey that will take approximately 30 minutes. Your responses will be confidential and we do not collect identifying information such as your name, email address or IP address.

What are the benefits of taking part? The benefits of this study will be to investigate the possible existence of non-pharmacological multifactorial patterns within Pulmonary sarcoidosis. The study will not only add knowledge to the current body of research but also help identify future areas of relevant research that may have been overlooked before or lacked scientific support.

What are the risks of taking part? No identified risks other than those of typical computer use and minor emotional distress. Some questions might cause minor emotional distress, although this risk is very low, as most of the questions are general (e.g. type of sarcoidosis) and not personalised. In cases where participants find some of the questions upsetting, they will have the option to skip them or exit the questionnaire at any time. Risks associated with using display screen equipment e.g. PC, Laptops, include upper limb disorders, back ache, fatigue, stress and temporary

eye strain or headaches. Ensure you are positioned correctly and the questionnaire will only take a maximum of 30 minutes to complete. However, take short pauses and breaks if necessary.

What if I have a question or a query? We are happy to answer any queries that you may have regarding the study. In the event of having any health concerns, we will advise you to contact your GP for further screening and advice.

What if I decide to withdraw? Participants are permitted to withdraw from the study at any time and data from them will not be used.

What about my Confidentiality? Any information given to us by you will remain confidential and all data will be kept anonymous. All data will be coded and saved as encrypted password protected files on a PC. Results of testing and analysis along with age, gender will be recorded. Participants will remain anonymous throughout the research, including the publication of the research which may result in availability of the research at the University Learning Resources Centre, through scientific journals and conference presentation. Any hard copy versions will be kept in locked offices/cabinets of lead applicant. The only personnel authorised to access the data will be the researcher, principal investigator and the project participants (their individual data only).

If you have any questions or problems, please do not hesitate to contact the researchers or project supervisor: Name of Researcher: Luke Morton-Holtham Email: K1214556@kingston.ac.uk Name of Supervisor: Dr Hannah Moir Email: H.Moir@kingston.ac.uk Tel: 020 8417 2876

Thank you for your time & contribution to this study.

ELECTRONIC

INFORMED

CONSENT:

By clicking agree, you are agreeing to participate in this study, acknowledging that you understand that you can withdraw at any time, and understand that all the data collected will be confidential and stored securely in line with the Data Protection Act (2003).

It is important to mention that you will not need to provide your name, as this study is anonymous. However, you will need to provide basic demographic background information which will remain confidential. There are no risks of taking part in the study, but if you have any concerns whilst answering the questions, withdrawal from the study is permitted at any time, and the data collected up to that point will not be used. Please contact the researchers if you have any queries.

Statement by Participant By clicking on the "agree" button below indicates that you consent to the following statements: *I confirm that I have read and understood the information sheet/letter of invitation for this study. I have been informed of the purpose, risks, and benefits of taking part. "Establishing the existence of non--pharmacological multi-factorial patterns within Pulmonary sarcoidosis." I understand what my involvement will entail and any questions have been answered to my satisfaction. I understand that my participation is entirely voluntary, and that I can withdraw at any time without prejudice. I understand that all information obtained will be confidential. I agree that research data gathered for the study may be published provided that I cannot be identified as a subject. Contact information has been provided should I (a) wish to seek further information from the investigator at any time for purposes of clarification (b) wish to make a complaint.*

Statement by investigator *I have explained this project and the implications of participation in it to this participant without bias and I believe that the consent is informed and that he/she understands the implications of participation.* Name of investigator: Luke Morton-Holtham

By clicking on the "agree" button below indicates that you consent to the following statements: *I confirm that I have read and understood the information sheet/letter of invitation for this study. I have been informed of the purpose, risks, and benefits of taking part. "Establishing the existence of non-pharmacological multifactorial patterns within Pulmonary sarcoidosis." I understand what my involvement will entail and any questions have been answered to my satisfaction. I understand that my participation is entirely voluntary, and that I can withdraw at any time without prejudice. I understand that all information obtained will be confidential. I agree that research data gathered for the study may be published provided that I cannot be identified as a subject. Contact information has been provided should I (a) wish to seek further information from the investigator at any time for purposes of clarification (b) wish to make a complaint.*

Statement by investigator *I have explained this project and the implications of participation in it to this participant without bias and I believe that the consent is informed and that he/she understands the implications of participation.*

Name of investigator: Luke Morton-Holtham

Signature of investigator: 23/06/17

Luke Morton Holtham

Signature of investigator: 23/06/17

If you do not wish to participate in the research study, please decline participation by clicking on the "disagree" button _

Agree (1)

Disagree (2)

Skip To: End of Survey If Information Sheet: Establishing the existence of non-pharmacological multifactorial patterns with... = Disagree

Page Break

Q2.1 Please indicate your age range (years):

20 or Under (1)

21-30 (2)

31-40 (3)

41-50 (4)

51-60 (5)

61+ (6)

Q2.2 Please indicate your ethnicity:

- White (English / Welsh / Scottish / Northern Irish / British/Irish/Gypsy Traveller (1)
 - Black Caribbean (2)
 - Black African (3)
 - Black British (4)
 - Mixed White & Black-Caribbean (5)
 - Mixed White & Black African (6)
 - Mixed White & Asian (7)
 - Asian/Asian British (8)
 - Indian (9)
 - Pakistani (10)
 - Bangladeshi (11)
 - Japanese (12)
 - Chinese (13)
 - Arab (14)
 - Other (please describe): (15)
-

Q2.3 Please select your gender:

- Male (1)
 - Female (2)
 - Other (please specify): (3)
-

Q2.4 Please select your nationality / citizenship:

- United Kingdom (1)
 - Poland (2)
 - India (3)
 - Pakistan (4)
 - Republic of Ireland (5)
 - Germany (6)
 - France (7)
 - Romania (8)
 - Portugal (9)
 - United States of America (10)
 - Spain (11)
 - Other (please specify): (12)
-

Q2.5 Thinking about your sarcoidosis, please select how you were first diagnosed:

- GP (1)
 - Consultant (2)
 - Specialist (3)
 - Other (please specify): (4)
-

Q2.6 Please select how long you have been diagnosed with sarcoidosis:

- Less than two years (1)
 - 3-5 years (2)
 - 5 years or more (3)
-

Q2.7 Considering your condition, select the type(s) of sarcoidosis you have. Please select all that apply.

- Pulmonary (1)
 - Skin (2)
 - Heart (3)
 - Eye (4)
 - Endocrine system (5)
 - Nervous system (6)
 - Bone/Joint (7)
 - Lymph nodes (8)
 - Organ (spleen/liver/kidney) (9)
 - Other (please specify): (10)
-

Q2.8 Considering your condition, on average, what are the main symptoms you experience. Please select all that apply.

- Fatigue (1)
 - Persistent Cough (dry cough) (2)
 - Shortness of breath (trouble breathing, wheezing, or pain) (3)
 - Painful Joints or bones (4)
 - Rashes / red bumps on the skin (5)
 - Sore eyes (6)
 - Other (please specify): (7)
-

Q2.9 Please select your current medication.

- Prednisolone (1)
 - Methotrexate (2)
 - Leflunomide (3)
 - Hydroxchloroquine (4)
 - Other (please specify): (5)
-

Page Break

Q2.10

Thank you for your responses.

The next section will feature lifestyle factors associated with sarcoidosis, specifically smoking status, physical activity and diet. Please click next to continue.

If you do not wish to complete this section please select skip.

Skip (1)

Skip To: End of Block If Thank you for your responses. The next section will feature lifestyle factors associated with S... = Skip

Page Break

Q2.11 Please select your current smoking status:

- Smoker (1)
- Ex-smoker (2)
- Non-smoker (3)

Skip To: Q2.13 If Please select your current smoking status: = Non-smoker

Q2.12 Please select the appropriate range for amount of cigarettes smoked per day:

- 1-4 (1)
- 5-9 (2)
- 10-14 (3)
- 15-19 (4)
- 20-24 (5)
- 25+ (6)

Page Break

Q2.13

Thank you for your responses. The following section relates to physical activity and diet.

Please click next to continue.

Page Break

Q2.14 What are your current physical activity levels?

- Inactive (1)
 - Less than twice a week (2)
 - 3-5 times a week (3)
 - 5+ times a week (4)
-

Q2.15 Considering your physical activity levels since being diagnosed with sarcoidosis, please select the most relevant option:

- Increased physical activity levels (1)
 - Decreased physical activity levels (2)
 - Stayed the same (3)
-

Q2.16 Has physical activity been mentioned to you as an option for improving your symptoms by a physician / GP ?

- Yes (1)
 - No (2)
-

Q2.17 Has a change in diet been mentioned to you for improving your symptoms by a physician / GP?

- Yes (1)
 - No (2)
-

Page Break

Q3.1

The following questions relate to the sarcoidosis Health Questionnaire (Cox, 2003)

This questionnaire is designed to allow people with sarcoidosis to describe how sarcoidosis affects their daily lives. Please read each question carefully and select the option that best represents how you feel. Answer each and every item, thinking back about how you have felt over the past 2 weeks. **All questions** within this section must be answered. Please do not skip any questions! There are **29 questions** in total. Thanks for your time.

If you do not wish to complete this section please select skip.

Skip (1)

Skip To: End of Block If The following questions relate to the Sarcoidosis Health Questionnaire (Cox, 2003) This questio... = Skip

Page Break

Q98

Answer each and every item, thinking back about how you have felt over the past 2 weeks.

During the past two weeks:

Q3.2

Been bothered by headaches?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time` (7)
-

Q3.3 Felt that you needed medications to function day to day?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.4 Felt that you were full of energy?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.5 Experienced mood swings?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.6 Been bothered by skin or hair problems related to sarcoidosis?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.7 Felt your breathing was completely comfortable during your normal daily activities?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.8 Worried about the amount of pain or discomfort you might have experienced?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.9 Felt that everything you did took a lot of effort or made you tire easily?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.10 Felt satisfied with the support you get from your family and friends?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.11 Had joint pains?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.12 Felt shortness of breath walking up stairs, the length of a city block, or up a small hill?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.13 Felt that you expect your health to be good in the future?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.14 Had a cough?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.15 Felt that your physical problems interfered in your social activities with family and friends?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.16 Felt that you accomplished all that you wanted?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.17 Been discouraged by recent weight gain?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.18 Felt bodily pain?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.19 Felt that you could concentrate easily?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.20 Felt that your emotional problems affected your relationships with family, friends, or co-workers?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.21 Felt that sarcoidosis controls your life?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.22 Had a good night's sleep?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.23 Felt depressed?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.24 Been bothered by problems with your eyes or eyesight?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.25 Felt satisfied with the appearance of your body?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.26 Experienced wheezing?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.27 Worried that your sarcoidosis might flare up or get worse?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.28 Felt confidence in yourself and your abilities?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.29 Felt that you were as healthy as others your age?

- All of the time (1)
 - Most of the time (2)
 - A good bit of the time (3)
 - Some of the time (4)
 - A little bit of the time (5)
 - Very little of the time (6)
 - None of the time (7)
-

Q3.30 Been discouraged by physical limitations in performing your normal daily activities or your job?

- All of the time (1)
- Most of the time (2)
- A good bit of the time (3)
- Some of the time (4)
- A little bit of the time (5)
- Very little of the time (6)
- None of the time (7)

Page Break

End of Block: Quality of life (Sarcoidosis Health Questionnaire)

Start of Block: Depression - CES-D

Q4.1

Thank you for your responses so far. The next section relates to the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). **All questions** within this section must be answered. There are **20 questions** to complete.

If you do not wish to complete this section please select skip.

Skip (1)

Skip To: End of Block If Thank you for your responses so far. The next section relates to the Center for Epidemiologic Stu... = Skip

Page Break

Q101 Please read each question carefully, then circle one of the numbers to the right to indicate how you have felt or behaved during the past week, including today.

Q4.2 I was bothered by things that don't normally bother me.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.3 I did not feel like eating; my appetite was poor.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.4 I felt that I could not shake off the blues even with help from my family or friends.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.5 I felt that I was just as good as other people.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.6 I had trouble keeping my mind on what I was doing.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.7 I felt depressed.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.8 I felt everything I did was an effort.

- Most or all of the time (5-7 days) (1)
- Occasionally or a moderate amount of time (3-4 days) (2)
- Some or a little of the time (1-2 days) (3)
- Rarely or none (Less than 1 day) (4)

Q4.9 I felt hopeful about the future.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.10 I thought my life has been a failure.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.11 I felt fearful.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.12 My sleep was restless.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.13 I was happy.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.14 I talked less than usual.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.15 I felt lonely.

- Most or all of the time (5-7 days) (1)
- Occasionally or a moderate amount of time (3-4 days) (2)
- Some or a little of the time (1-2 days) (3)
- Rarely or none (Less than 1 day) (4)

Q4.16 People were unfriendly.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.17 I enjoyed life.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.18 I had crying spells.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.19 I felt sad.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.20 I felt people dislike me.

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Q4.21 I could not get "going".

- Most or all of the time (5-7 days) (1)
 - Occasionally or a moderate amount of time (3-4 days) (2)
 - Some or a little of the time (1-2 days) (3)
 - Rarely or none (Less than 1 day) (4)
-

Page Break

End of Block: Depression - CES-D

Start of Block: Study One - Part Two

Q5.1

Thank you for your responses.
The next section relates to environment and employment.

Please click next to continue. If you do not wish to complete this section please select skip.

Skip (1)

Skip To: End of Block If Thank you for your responses. The next section relates to environment and employment. Please cl... = Skip

Page Break

Q5.2 Please select the region you currently live in:

- Wales (1)
 - Scotland (2)
 - Northern Ireland (3)
 - North East England (4)
 - North West England (5)
 - Yorkshire & the Humber (6)
 - East Midlands (7)
 - West Midlands (8)
 - East of England (9)
 - South East England (10)
 - South West England (11)
 - London (12)
 - Other (please specify): (13)
-

Q99 How long have you resided in this region?

- Less than 6 months (1)
- 6 months to 1 year (2)
- 1 to 3 years (3)
- 3 to 5 years (4)
- 5 to 10 years (5)
- Over 10 years (6)

Q5.3 Does your property contain mold?

- Sometimes (1)
 - Never (2)
 - Always (3)
-

Q5.4 What is your current employment status?

- Employed full time (1)
- Employed part time (2)
- Unemployed looking for work (3)
- Unemployed not looking for work (4)
- Unemployed receiving disability living allowance or equivalent (5)
- Student (6)
- Retired (7)

Skip To: Q5.6 If What is your current employment status? != Employed full time

Skip To: Q5.6 If What is your current employment status? != Employed part time

Q5.5 Please select your type of employment:

- Manager, director, senior official (e.g. corporate, proprietors) (1)
 - Professional (e.g. science, research, health, education, business, media) (2)
 - Associate professional and technical (e.g. technicians, health and social care professional, culture, public service) (3)
 - Administrative and secretarial (4)
 - Skilled trades (e.g. agricultural, metal, electrical, construction, textiles) (5)
 - Caring, leisure and other service (e.g. personal service, leisure & travel) (6)
 - Sales and customer service (7)
 - Process, plant and machine operatives (e.g. transport, machine operatives) (8)
 - Elementary (e.g. agricultural, administration, clearing, security, sales, storage, services) (9)
 - Retired (10)
 - Other (please specify): (11)
-

Q5.6 Has your occupation changed since being diagnosed with sarcoidosis?

- Stayed the same (1)
 - Changed due to sarcoidosis (2)
 - Changed non-related to sarcoidosis (3)
 - Stopped working due to sarcoidosis (4)
-

Page Break

Q6.1

Thank you for your responses. This final section involves open ended qualitative questions.

Please click next to continue. If you do not wish to complete this section please select skip.

Skip (1)

Skip To: End of Survey If Thank you for your responses. This final section involves open ended qualitative questions. Plea... = Skip

Page Break

Q6.2 How has sarcoidosis affected your life?



Q6.3

What barriers have you faced since being diagnosed with sarcoidosis?



Q6.4

What factors do you believe improves your sarcoidosis symptoms?



Q6.5 What factors do you believe negatively affects your symptoms?

Q6.6 Please specify any ideas and/or area(s) in which you feel you could most benefit from additional support related to your condition.

Q103 A follow-up interview and/or focus group may be conducted regarding the findings of study one and two. If you are willing to take part please leave your details. Thank you again for taking the time to participate in our project.

Name (1) _____

E-mail (2) _____

Q102 **End of survey.**

Please select the 'submit' button to save and submit your responses.

Please note, once you submit, your responses can not be changed.

Submit (1)

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (October 2002)

LONG LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health-related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is encouraged to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an **International Physical Activity Prevalence Study** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

Yes

No

→

Skip to PART 2: TRANSPORTATION

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

_____ **days per week**

No vigorous job-related physical activity

Skip to question 4

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

_____ **hours per day**

_____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____ **days per week**

No moderate job-related physical activity

Skip to question 6

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

No job-related walking ~~Skip~~ **to PART 2: TRANSPORTATION**

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**
_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ **days per week**

No traveling in a motor vehicle **→** **Skip to question 10**

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**
_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

No bicycling from place to place **→** **Skip to question 12**

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**
_____ **minutes per day**

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

No walking from place to place → **Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY**

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ **hours per day**
_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

No vigorous activity in garden or yard → **Skip to question 16**

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

No moderate activity in garden or yard → **Skip to question 18**

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

No moderate activity inside home → **Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY**

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**
_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

No walking in leisure time → **Skip to question 22**

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**
_____ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

No vigorous activity in leisure time → **Skip to question 24**

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**

_____ minutes per day

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ days per week

No moderate activity in leisure time → **Skip to PART 5: TIME SPENT SITTING**

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

_____ hours per day

_____ minutes per day

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ hours per day

_____ minutes per day

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ hours per day

_____ minutes per day

This is the end of the questionnaire, thank you for participating.

10.4. Appendix 4) Sarcoidosis Health Questionnaire

During the past 2 weeks , how often have you:	All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	Very little of the time	None of the time
Been bothered by headaches?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Felt that you needed medications to function day to day?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Felt that you were full of energy?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Experienced mood swings?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Been bothered by skin or hair problems related to sarcoidosis?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Felt your breathing was completely comfortable during your normal daily activities?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Worried about the amount of pain or discomfort you might have experienced?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Felt that everything you did took a lot of effort or made you tire easily?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Felt satisfied with the support you get from your family and friends?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
During the past 2 weeks , how often have you:	All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	Very little of the time	None of the time
Had joint pains?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Felt shortness of breath walking up stairs, the length of a city block, or up a small hill?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Felt that you expect your health to be good in the future?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Had a cough?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Felt that your physical problems interfered in your social activities with family and friends?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Felt that you accomplished all that you wanted?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Been discouraged by recent weight gain?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Felt bodily pain?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Felt that you could concentrate easily?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Felt that your emotional problems affected your relationships with family, friends, or co-workers?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Felt that sarcoidosis controls your life?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Had a good night's sleep?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Felt depressed?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Been bothered by problems with your eyes or eyesight?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Felt satisfied with the appearance of your body?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Experienced wheezing?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Worried that your sarcoidosis might flare up or get worse?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Felt confidence in yourself and your abilities?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Felt that you were as healthy as others your age?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Been discouraged by physical limitations in performing your normal daily activities or your job?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

10.5. Appendix 5) Center for Epidemiologic Studies Depression Scale
(CES-D Scale)

Center for Epidemiologic Studies Depression Scale (CES-D Scale)

Page 1 of 1

Patient Name: _____ Date: _____

Instructions: Please read each question carefully, then circle one of the numbers to the right to indicate how you have felt or behaved during the past week, including today.

	BARELY OR NONE OF THE TIME (LESS THAN 1 DAY)	SOME OR A LITTLE OF THE TIME (1-2 DAYS)	OCCASIONALLY OR A MODERATE AMOUNT OF TIME (3-4 DAYS)	MOST OR ALL OF THE TIME (5-7 DAYS)
1. I was bothered by things that usually don't bother me.	0	1	2	3
2. I did not feel like eating; my appetite was poor.	0	1	2	3
3. I felt that I could not shake off the blues even with help from my family or friends.	0	1	2	3
4. I felt that I was just as good as other people.	0	1	2	3
5. I had trouble keeping my mind on what I was doing.	0	1	2	3
6. I felt depressed.	0	1	2	3
7. I felt that everything I did was an effort.	0	1	2	3
8. I felt hopeful about the future.	0	1	2	3
9. I thought my life had been a failure.	0	1	2	3
10. I felt fearful.	0	1	2	3
11. My sleep was restless.	0	1	2	3
12. I was happy.	0	1	2	3
13. I talked less than usual.	0	1	2	3
14. I felt lonely.	0	1	2	3
15. People were unfriendly.	0	1	2	3
16. I enjoyed life.	0	1	2	3
17. I had crying spells.	0	1	2	3
18. I felt sad.	0	1	2	3
19. I felt that people dislike me.	0	1	2	3
20. I could not get "going."	0	1	2	3

CO-OCCURRING DISORDERS PROGRAM: SCREENING AND ASSESSMENT

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13

Study 2 - Sarcoidosis 4 day food log incorporating symptom scales and physical activity levels.

Start of Block: Information and informed consent

Q67 Information Sheet: Establishing the existence of non-pharmacological multifactorial patterns within Pulmonary Sarcoidosis Study: Impact of diet and physical activity on symptom of pulmonary sarcoidosis.
Ethics Code: 1617/028 Thank you for considering being a participant in this project. Below you will find a short background to our work, and an outline of what you will be required to do as a participant in this study.

The aim of this study is to establish the effect of pulmonary sarcoidosis on a patient's diet and physical activity levels and the influence on their symptoms to establish any trends.

Various recommendations are given to patients with pulmonary sarcoidosis to help manage the disease, including a healthy lifestyle, such as following a healthy diet or being as physically active as you can. Anecdotally, foods high in antioxidants and anti-inflammatories have been suggested as an approach for managing the symptoms of sarcoidosis. Alongside this, exercise and physical activity are frequently recommended alongside any pharmacological treatment to improve symptoms and the overall health status of an individual. Physical activity has been defined as any body movement that works your muscles and requires more energy than resting, examples include walking, running, dancing, swimming, yoga, and gardening. However current research into diet, exercise and sarcoidosis is limited, therefore the aim of the current study is to establish physical activity and dietary patterns in pulmonary sarcoidosis.

Am I eligible to take part in the study?

You are eligible to take part in the study if you have been diagnosed with pulmonary sarcoidosis (this can be in addition to other forms of sarcoidosis and conditions) and over the age of 18 years.

What is expected of me? The study comprises of two sections:

Section 1: Involves you completing an online electronic questionnaire comprised of validated surveys looking at physical activity, fatigue and symptoms.

The procedure involves completing an online survey that will take approximately 20 minutes. Your responses will be confidential and we do not collect identifying

information such as your name, email address or IP address.

Section 2: Involves you completing a 7 day food and physical activity diary log.

You will be required to maintain your normal habitual lifestyle. You will then be asked to complete a food diary of what you consume on a daily basis for 7 days in a row, including timings, food types and quantity. Alongside this you will be required to log your physical activity (including length of time, type and intensity). This information will be collected via either a computer-based electronic file, or sent to you as a hardcopy, according to your preference. You will be asked to provide your contact details at the end of the electronic questionnaire so that the researchers can send you the 7 day diary log with further instructions, please note, this information will not be saved / linked with your responses to the online survey to maintain anonymity and confidentiality.

What are the benefits of taking part?

The benefits of this study will not only add knowledge to the current body of research but also help identify future areas of relevant research that may have been overlooked before or lacked scientific support.

What are the risks of taking part?

No identified risks other than those of typical computer use. Risks associated with using display screen equipment e.g. PC, Laptops, include upper limb disorders, back ache, fatigue, stress and temporary eye strain or headaches. Ensure you are positioned correctly and the questionnaire will only take a maximum of 30 minutes to complete. However, take short pauses and breaks if necessary.

What if I have a question or a query?

We are happy to answer any queries that you may have regarding the study. In the event of having any health concerns, we will advise you to contact your GP for further screening and advice.

What if I decide to withdraw?

Participants are permitted to withdraw from the study at any time and data from them will not be used.

What about my Confidentiality?

Any information given to us by you will remain confidential and all data will be kept anonymous. All data will be coded and saved as encrypted password protected files on a PC. Results of testing and analysis along with age, gender, stature and mass will be recorded. Participants will remain anonymous throughout the research, including the publication of the research which may result in availability of the research at the University Learning Resources Centre, through scientific journals and conference presentation. Any hard copy versions will be kept in locked offices/cabinets of lead applicant.

The only personnel authorised to access the data will be the researcher, principal investigator and the project participants (their individual data only).

If you have any questions or problems, please do not hesitate to contact the researchers or project supervisor:

Name of Researcher: Luke Morton-Holtham
Email: K1214556@kingston.ac.uk

Name of Supervisor: Dr Hannah Moir
Email: H.Moir@kingston.ac.uk
Tel: 020 8417 2876

Thank you for your time & contribution to this study. **ELECTRONIC INFORMED CONSENT:**

By clicking agree, you are agreeing to participate in this study, acknowledging that you understand that you can withdraw at any time, and understand that all the data collected will be confidential and stored securely in line with the Data Protection Act (2003).

It is important to mention that you will not need to provide your name, as this study is anonymous. However, you will need to provide basic demographic background information which will remain confidential. There are no risks of taking part in the study, but if you have any concerns whilst answering the questions, withdrawal from the study is permitted at any time, and the data collected up to that point will not be used. Please contact the researchers if you have any queries.

Statement by Participant By clicking on the "agree" button below indicates that you consent to the following statements: I confirm that I have read and understood the information sheet/letter of invitation for this study. I have been informed of the purpose, risks, and benefits of taking part. "*Establishing the existence of non-pharmacological multi-factorial patterns within Pulmonary sarcoidosis.*" I understand what my involvement will entail and any questions have been answered to my satisfaction. I understand that my participation is entirely voluntary, and that I can withdraw at any time without prejudice. I understand that all information obtained will be confidential. I agree that research data gathered for the study may be published provided that I cannot be identified as a subject. Contact information has been provided should I (a) wish to seek further information from the investigator at any time for purposes of clarification (b) wish to make a complaint. **Statement by investigator** I have explained this project and the implications of participation in it to this participant without bias and I believe that the consent is informed and that he/she understands the implications of participation. Name of investigator: Luke Morton-Holtham

Luke Morton Holtham *Signature of investigator:* 23/06/17
If you do not wish to participate in the research study, please decline participation by clicking on the "disagree" button

Agree (1)

Disagree (2)

Skip To: End of Survey If Information Sheet: Establishing the existence of non-pharmacological multifactorial patterns with... = Disagree

End of Block: Information and informed consent

Start of Block: Section one:

Q1 Please select your age range (years):

20 or under (1)

21-30 (2)

31-40 (3)

41-50 (4)

51-60 (5)

61+ (6)

Q2 Please indicate your ethnicity

- White (English / Welsh / Scottish / Northern Irish / British/Irish/Gypsy Traveller (1)
 - Black Caribbean (2)
 - Black African (3)
 - Black British (4)
 - Mixed White & Black Caribbean (5)
 - Mixed White & Black African (6)
 - Mixed White & Asian (7)
 - Asian/Asian British (8)
 - Indian (9)
 - Pakistani (10)
 - Bangladeshi (11)
 - Japanese (12)
 - Chinese (13)
 - Arab (14)
 - Other (Please specify) (15)
-

Q4 Please select your gender:

- Male (1)
 - Female (2)
 - Other (Please specify) (3)
-

Q3 Please select your weight range (kg):

- Under 50 (1)
 - 51-60 (2)
 - 61-70 (3)
 - 71-80 (4)
 - 81-90 (5)
 - 91-100 (6)
 - 100+ (7)
-

Q76 Please select your height range (cm):

- Under 150 (1)
 - 151-160 (2)
 - 161-170 (3)
 - 171-180 (4)
 - 181-90 (5)
 - 191-200 (6)
 - 200+ (7)
-

Q77 Please select your BMI Range. (If you do not know your BMI, you can calculate it by dividing your weight in kg by your height in meters and then dividing the answer

by your height (meters) again. For example for a person of 70kg weight and 1.8m height would be $70/1.8 = 38.8 > 38.8/1.8 = 21.6$ Therefore their BMI is 21.6

- Under 18.5 (1)
 - 18.5-25 (2)
 - 25-30 (3)
 - 30+ (4)
-

Q72 Please select how long you have been diagnosed with sarcoidosis:

- Less than two years (1)
 - 3-5 years (2)
 - 5 years or more (3)
-

Q73

Considering your condition, select the type(s) of sarcoidosis you have. Please select all that apply.

- Pulmonary (1)
 - Skin (2)
 - Heart (3)
 - Eye (4)
 - Endocrine system (5)
 - Nervous system (6)
 - Bone/Joint (7)
 - Lymph nodes (8)
 - Organ (spleen/liver/kidney) (9)
 - Other (please specify): (10)
-

End of Block: Section one:

Start of Block: International physical activity questionnaire (IPAQ)

Q5 Thank you for your answers so far. The next section involves the international physical activity questionnaire. The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires, with 5 domains. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health-related physical activity. The questionnaire involves a maximum of 27 questions and each question requires an answer. If you **do not** wish to complete this questionnaire please select 'skip' and you will be taken to the following section.

- Skip (1)

Skip To: End of Block If Thank If Thank you for your answers so far. The next section involves the international physical activity... = Skip

Q69 We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport. Think about all the vigorous and moderate activities that you did in the last 7 days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

Q35

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3. Please select next to continue.

Q6

Do you currently have a job or do any unpaid work outside your home?

Yes (1)

No (2)

Skip To: Q36 If Do you currently have a job or do any unpaid work outside your home? = No

Q7 The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part**

of your work? Think about only those physical activities that you did for at least 10 minutes at a time.

- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- None (8)

Skip To: Q9 If The next questions are about all the physical activity you did in the last 7 days as part of your... = None

Q8 How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

- Hours per day (1)

 - Minutes per day (2)

-

Q9 Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical

activities like carrying light loads **as part of your work**? Please do not include walking.

- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- None (8)

Skip To: Q13 If Again, think about only those physical activities that you did for at least 10 minutes at a time.... = None

Q11 How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

- Hours per day (1)

 - Minutes per day (2)

-

Q12 During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- None (8)

Skip To: Q36 If During the last 7 days, on how many days did you walk for at least 10 minutes at a time as part o... = None

Q13 How much time did you usually spend on one of those days **walking** as part of your work?

- Hours per day (1)

 - Minutes per day (2)

-

Q36 **PART 2: TRANSPORTATION PHYSICAL ACTIVITY** These questions are about how you traveled from place to place, including to places like work, stores, movies, and _____ so _____ on. Please select next to continue.

Q14 During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- None (8)

Skip To: Q17 If During the last 7 days, on how many days did you travel in a motor vehicle like a train, bus, car... = None

Q15 How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

- Hours per day (1)

 - Minutes per day (2)

-

Q17 Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- None (8)

Skip To: Q18 If Now think only about the bicycling and walking you might have done to travel to and from work, to... = None

Q16 How much time did you usually spend on one of those days to **bicycle** from place to place?

- Hours per day (1)

 - Minutes per day (2)

-

Q18 During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- None (8)

Skip To: Q37 If During the last 7 days, on how many days did you walk for at least 10 minutes at a time to go fro... = None

Q19 How much time did you usually spend on one of those days *walking from place to place*?

- Hours per day (1)

 - Minutes per day (2)

-

Q37 PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family. Please select next to continue.

Q20
Think about only those physical activities that you did for at least 10 minutes at a time.

During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- None (8)

*Skip To: Q22 If Think about only those physical activities that you did for at least 10 minutes at a time.
During... = None*

Q21 How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

- Hours per day (1)

 - Minutes per day (2)

-

Q22 Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate**

activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- None (8)

Skip To: Q25 If Again, think about only those physical activities that you did for at least 10 minutes at a time.... = None

Q23 How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

- Hours per day (1)

 - Minutes per day (2)

-

Q25 Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate**

activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home?**

- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- None (8)

Skip To: Q38 If Once again, think about only those physical activities that you did for at least 10 minutes at a... = None

Q24 How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

- Hours per day (1)

 - Minutes per day (2)

-

Q38

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned. Please select next to continue.

Q26

Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- None (8)

Skip To: Q28 If Not counting any walking you have already mentioned, during the last 7 days, on how many days did... = None

Q27

How much time did you usually spend on one of those days **walking** in your leisure time?

- Hours per day (1)

 - Minutes per day (2)

-

Q28 Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical

activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- None (8)

*Skip To: Q30 If Think about only those physical activities that you did for at least 10 minutes at a time.
During... = None*

Q29 How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

- Hours per day (1)

 - Minutes per day (2)

-

Q30 Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate**

physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- None (8)

Skip To: Q39 If Again, think about only those physical activities that you did for at least 10 minutes at a time.... = None

Q31 How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

- Hours per day (1)

 - Minutes per day (2)

-

Q39

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

Please select next to continue.

Q40

During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

Hours per day (1)

Minutes per day (2)

Q33 During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

Hours per day (1)

Minutes per day (2)

Q34

Thank you for taking the time to complete the IPAQ questionnaire please click 'next' to continue.

End of Block: International physical activity questionnaire (IPAQ)

Start of Block: MRC breathlessness scale

Q41

The following survey item is a scale. Please select the most relevant statement for you.

If you do not want to complete this item, please select 'skip'.

Otherwise, please select next to continue.

Skip (1)

Skip To: End of Block If The following survey item is a scale. Please select the most relevant statement for you. If you d... = Skip

Q42 Select the statement most accurate to your current personal situation:

- Not troubled by breathlessness except on strenuous exercise (1)
- Short of breath when hurrying on the level or walking up a slight hill (2)
- Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace. (3)
- Stops of breath after walking about 100 yards or after a few minutes on level ground. (4)
- Too breathless to leave the house, or breathless when undressing. (5)

End of Block: MRC breathlessness scale

Start of Block: Fatigue assessment Scale

Q43

Thank you for your answers so far.

Below are a number of questions about possible complaints. Please select the answer to each question that is applicable to you. Please give an answer to each question, even if you do not have any complaints at the moment. The aim of this questionnaire is to find out how you experience your complaints. There are no correct or incorrect answers. It is important that you are honest.

If you do not wish to complete the fatigue assessment scale then please select Skip, otherwise please select next to continue.

- Skip (1)

Skip To: End of Block If Thank you for your answers so far. Below are a number of questions about possible complaints. P... = Skip

Q70

The following **ten** statements refer to how you usually feel. Per statement you can choose one out of five answer categories, varying from 'Never' to 'Always'.

Please select the answer to each question that is most applicable to you.

Q44 I am Bothered by fatigue

- Never (1)
 - Sometimes (2)
 - Regularly (3)
 - Often (4)
 - Always (5)
-

Q46
I get tired very quickly

- Never (1)
 - Sometimes (2)
 - Regularly (3)
 - Often (4)
 - Always (5)
-

Q48
I don't do much during the day

- Never (1)
 - Sometimes (2)
 - Regularly (3)
 - Often (4)
 - Always (5)
-

Q49 I have enough energy for everyday life

- Never (1)
 - Sometimes (2)
 - Regularly (3)
 - Often (4)
 - Always (5)
-

Q50
Physically, I feel exhausted

- Never (1)
 - Sometimes (2)
 - Regularly (3)
 - Often (4)
 - Always (5)
-

Q51
I have problems to start things

- Never (1)
 - Sometimes (2)
 - Regularly (3)
 - Often (4)
 - Always (5)
-

Q52

I have problems to think clearly

- Never (1)
 - Sometimes (2)
 - Regularly (3)
 - Often (4)
 - Always (5)
-

Q53

I feel no desire to do anything

- Never (1)
 - Sometimes (2)
 - Regularly (3)
 - Often (4)
 - Always (5)
-

Q54

Mentally, I feel exhausted

- Never (1)
 - Sometimes (2)
 - Regularly (3)
 - Often (4)
 - Always (5)
-

Q55

When I am doing something, I can concentrate quite well.

- Never (1)
- Sometimes (2)
- Regularly (3)
- Often (4)
- Always (5)

End of Block: Fatigue assessment Scale

Start of Block: Section two:

Q74

Section

two:

If you are willing to participate in the second part of this study, please provide your name and email address below and the research team will be in touch with further information.

If you would prefer to receive the second part of this study as a hardcopy, please provide your postal address.

Additionally a follow-up interview and/or focus group may be conducted regarding the findings of study one and two. If you are willing to take part please leave your details and indicate in the relevant box.

Thank you again for taking the time to participate in our project.

Name (1) _____

Email Address: (2)

Address (optional): (3)

Address 2 (4) _____

City (5) _____

Postal code (6) _____

Country (7) _____

Telephone number (optional): (8)

Please state (yes/no) if would like to be part of a follow-up interview/focus group. (9) _____

Q71
End of _____ **of** _____ **survey.**

Please select the 'submit' button to save and submit your responses.

Please note, once you submit, your responses can not be changed.

Submit (1)

End of Block: Section two:

10.7. Appendix 7) Fatigue Assessment Scale (FAS)

Fatigue Assessment Scale (FAS)

Below are a number of questions about possible complaints. Please circle the answer to each question that is applicable to you. Please give an answer to each question, *even if you do not have any complaints at the moment*. The aim of this questionnaire is to find out how you experience your complaints. There are no correct or incorrect answers. It is important that you are honest.

General information:

Date: __-__-200__

Name: _____

Date of birth: __-__-19__

Sex: male / female

Using prednisolone: no / yes

Year of diagnosis of sarcoidosis: _____

e-mail address: _____

Information given by the physician:

TTT: normal / disturbed

Disorder: sarcoidosis / diabetes / other: _____

Prednisolone (corticosteroid) use: no / yes

Methotrexate use: no / yes

Other immunoregulatory drug use: no / yes

email: lidinfo@lung.azm.nl

The following ten statements refer to how you usually feel. Per statement you can choose one out of five answer categories, varying from Never to Always. Please circle the answer to each question that is applicable to you. Please give an answer to each question, *even if you do not have any complaints at the moment*.

1 = Never, 2 = Sometimes; 3 = Regularly; 4 = Often and 5 = Always.

	Never	Sometimes	Regularly	Often	Always
1. I am bothered by fatigue	1	2	3	4	5
2. I get tired very quickly	1	2	3	4	5
3. I don't do much during the day	1	2	3	4	5
4. I have enough energy for everyday life	1	2	3	4	5
5. Physically, I feel exhausted	1	2	3	4	5
6. I have problems to start things	1	2	3	4	5
7. I have problems to think clearly	1	2	3	4	5
8. I feel no desire to do anything	1	2	3	4	5
9. Mentally, I feel exhausted	1	2	3	4	5
10. When I am doing something, I can concentrate quite well	1	2	3	4	5

10.8. *Appendix 8) MRC Breathlessness Scale*

The MRC Breathlessness Scale

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking about 100 yds or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

10.9. *Appendix 9) Informed Consent*

I, the undersigned, do hereby acknowledge:

- Consent to perform a health-related fitness appraisal consisting of the evaluation of (tick appropriate boxes):

<input type="checkbox"/> Standing Height	<input type="checkbox"/> Hand Grip Strength (R/L)
<input type="checkbox"/> Weight	<input type="checkbox"/> Push-Ups (max #)
<input type="checkbox"/> Waist Circumference	<input type="checkbox"/> Sit and Reach
<input type="checkbox"/> Body fat percentage	<input type="checkbox"/> Vertical Jump/Leg Power
<input type="checkbox"/> Six-minute walk test	<input type="checkbox"/> Lung Function
<input type="checkbox"/> Quadricep/Hamstring Peak Torque	
- Consent to answer questions concerning my current levels of physical activity participation and my lifestyle;
- Understanding that my heart rate and blood pressure will be measured prior to and at the completion of the appraisal;
- Understanding that the results from my health-related fitness appraisal will assist in determining the type and amount of physical activity most appropriate for my level of fitness;

- Consent to perform a supervised exercise training session (if desired) based on the findings of my fitness appraisal, consisting of a warm-up, cardiovascular training, musculoskeletal training, flexibility exercises and a cool-down;
- Consent to have my blood pressure and heart rate measured periodically during my supervised exercise training session(s);
- Understanding that there are potential risks during exercise (i.e., episodes of transient light headedness, loss of consciousness, abnormal blood pressure, chest discomfort, leg cramps, and nausea), in rare instances heart rhythm disturbances or heart attacks, and that I assume willfully those risks;
- Obligation to immediately inform the Investigator of any pain, discomfort, fatigue, or any other symptoms that I may suffer during and immediately after the appraisal and/or exercise training session;
- Understanding that I may stop or delay any further exercise if I so desire and that the Investigator may terminate the exercise session upon observation of any symptoms of undue distress or abnormal response;
- Understanding that I may ask any questions or request further explanation or information about the procedures at any time before, during, and after exercise;
- That I have read, understood, and completed the Physical Activity Readiness Questionnaire (PAR-Q) and answered NO to all the questions and/or received clearance to participate in unrestricted physical activity/exercise from a physician.

This form must be completed, signed and submitted to Investigator, along with the completed PAR-Q, at the time of the appraisal. The form must also be witnessed at the time of signing.

I AGREE THAT I HAVE READ AND UNDERSTAND THIS DOCUMENT

Printed Name of Client	Signature of Client	Date

Printed Name of Witness (Investigator)	Signature of Witness (Investigator)	Date