EXERCISE FOR PEOPLE WITH SYSTEMIC LUPUS ERYTHEMATOSUS OR SYSTEMIC SCLEROSIS

A thesis submitted by

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B. Ex Sp Sc, M. Clin Ex Phys

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ABSTRACT

Aims: The aim of this research was to identify the effectiveness and experience of exercise in adults with systemic lupus erythematosus (SLE) and systemic sclerosis (SSc). **Methods:** Study 1 is a systematic review on the effectiveness of exercise as adjunct therapy in SLE. Study 2 is a systematic review protocol on exercise and physical therapy in SSc and is ongoing. Study 3 is a qualitative interview study exploring rheumatology practitioners' perspectives of exercise in SLE and SSc. Study 4 is a qualitative focus group study exploring the perspectives of exercise in SSc. Study 5 is a mixed method non-randomised controlled pilot trial exploring the effectiveness of telehealth-supervised exercise in SLE. **Results.** Exercise is undoubtedly a highly valued intervention by rheumatologists, rheumatology nurses, and people living with SLE and SSc, with several measured and perceived benefits and barriers to exercise. Overall, exercise is 'safe', with no reported adverse effects, and is effective in reducing levels of fatigue and depression and improving physical fitness and physical functioning in people with SLE, and has the potential to improve aerobic capacity, exercise tolerance, muscular endurance, fatigue, pain, and life satisfaction in people with SSc. Rheumatology practitioners describe exercise to be beneficial for people with SLE and SSc with few concerns about its safety, admittedly lack time and confidence to prescribe specific exercise for their patients, and importantly, recommend long-term and supervised exercise for this population. People with SSc also describe several benefits to exercise, address disease-related barriers to engaging in exercise, and raise the importance of modified supervised exercise. Key findings from our mixed-method investigation suggest that telehealth-supervised exercise was feasible for, and well-accepted by, adults with SLE, and resulted in some modest health improvements. Importantly, participants described telehealth-supervised exercise as efficient, despite some challenges of exercising from home (such as limited equipment and space), were satisfied by the experience, and would engage in telehealth-supervised again. **Conclusion:** This thesis provides researchers, exercise professionals, rheumatology practitioners, and people with SLE and SSc, with a more comprehensive understanding about the beneficial effects of exercise and highlights some opportunities for further research.

CERTIFICATION OF THESIS

I, Stephanie Frade, declare that the PhD thesis entitled *exercise for people with systemic lupus erythematosus or systemic sclerosis* is not more than 100,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references, and footnotes.

This thesis is the work of Stephanie Frade except where otherwise acknowledged, with the majority of the contribution to the papers presented as a thesis by publication undertaken by the student. The work is original and has not previously been submitted for any other award, except where acknowledged.

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STATEMENT OF CONTRIBUTION

The following detail is the agreed share of contribution for candidate and co-authors in the presented publications in this thesis.

- **Study 1:** Frade S, O'Neill S, Nutter E, Greene D, Cameron M. (2022). Exercise as adjunctive therapy in systemic lupus erythematosus, *Cochrane Database of Systematic Reviews.*

  Stephanie Frade contributed 70% to this study. Sean O'Neill, Elise Nutter (Honours student), David Greene, and Melainie Cameron contributed to the remainder 30% of this study.

- **Study 2**: Frade S, Cameron M, Espinosa-Cuervo, G, Suarez-Almazor ME, Lopez-Olivo MA. Exercise and physical therapy for systemic sclerosis (Protocol). *Cochrane Database of Systematic Reviews* 2022, Issue 3. Art. No.: CD014902. DOI: 10.1002/14651858.CD014902.

  Stephanie Frade contributed 60% to this study. Melainie Cameron, and another authorship team from the MD Anderson Centre in the United States (Gisela Espinosa-Cuervo, Maria Suarez-Almazor, Angeles Lopez-Olivio) contributed to the remainder 40% of this study.

- **Study 3:** Frade S, Cameron M, O'Neill S, Greene D. (2021). Rheumatology Practitioners' View of Exercise in Adults with Systemic Sclerosis or Systemic Lupus Erythematosus, *Journal of Clinical Exercise Physiology*, Vol. 10, No. 4, 134-141. DOI: https://doi.org/10.31189/2165-6193-10.4.134

  Stephanie Frade contributed 80% to this study. Melainie Cameron, Sean O'Neill, and David Greene contributed to the remainder 20% of this study.

- **Study 4:** Frade S, Campbell C, Bird SP, Cameron M. (2022). Barriers and facilitators to exercise for people with Systemic Sclerosis: A qualitative study.

  This study was submitted to the Journal of Clinical Exercise Physiology on the 22nd of September 2022, accepted for publication on the 1st of December 2022, and will be published in September 2023. Stephanie Frade contributed 80% to this paper. Chloe Campbell (Honours student), Stephen. P Bird, and Melainie Cameron contributed to the remainder 20% of this study.

- **Study 5:** Frade S, O'Neill S, Walsh S, Campbell C, Greene D, Bird SP, Cameron M. (2023). Telehealth-supervised exercise in systemic lupus erythematosus: A pilot study.

  This study was submitted to the Lupus journal on the 17th of June 2022, revised following feedback from reviewers, re-submitted on the 17th of January 2023, and accepted for publication on the 25th of January 2023. Stephanie Frade contributed 70% to this paper. Sean O'Neill, Samantha Walsh (Research assistant), Chloe Campbell (Honours student), David Greene, Stephen. P Bird, and Melainie Cameron contributed to the remainder 30% of this study.

OTHER PUBLICATIONS/PRESENTATIONS/CREATIVE WORKS ARISING FROM THIS THESIS

- Frade S, O'Neill S, Greene D, Cameron M. Exercise for systemic sclerosis or systemic lupus erythematosus: A systematic review. *Internal Medicine Journal*, Volume 50, Issue S2, Supplement: 2020 Australian Rheumatology Association 60th Annual Scientific Meeting, 16-19 May 2020 [poster presentation]

- Frade S, Cameron M, O'Neill S, Greene D. Rheumatologists' and rheumatology nurses' perspectives and use of exercise interventions for people with systemic sclerosis and systemic lupus erythematous. *Internal Medicine Journal*, Volume 51, Issue S2, Supplement: 2021 Australian Rheumatology Association 61st Annual Scientific Meeting 21-23 May 2021 [poster presentation]

- Frade S, Cameron M, Greene D, O'Neill S. (2021) Exercise for Systemic Sclerosis or Systemic Lupus Erythematosus: A systematic review. Research to Practice - 9th Exercise Science and Sports Australia Conference: Online, Australia [poster presentation].

- Frade S, O'Neill S, Greene D, Cameron M. Exercise as adjunctive therapy for systemic lupus erythematosus. Cochrane Database of Systematic Reviews 2021, Issue 10. Art. No.: CD014816.

- Frade, S. (2022). Exercise as Medicine in Autoimmune Disease. [Invited speaker: Research to Practice]. Exercise and Sports Science Australia Conference: Online, 19-21 May.

- Frade, S (2022). Lupus: Diagnosis and Management [Invited speaker: Lupus lifestyle event]. BJC Connect: Online, 17 August.

- Frade, S (2021). Autoimmune Diseases: Exercise Right [Fact sheet]. Exercise is Medicine.

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- My supportive and loving husband Andrew Di Lizio for his endless support, encouragement, data assistance, and patience. And for always believing in me.
- My mum, Lita, for giving me the passion, drive, and resilience to keep going.

DEDICATION

This thesis is dedicated to my beautiful mother, Maria (Lita) Frade.

My mum lived with systemic sclerosis (scleroderma) for 14 years. When Mum first told us the news about her diagnosis, my family and I were devastated. It was the first time we had heard about scleroderma, and the unknown and uncertainty about mum's future was frightening. We sadly lost my mum on the 15th of February 2018, a day that I will never forget. My mum and I had a special bond, she was my best friend, my biggest cheerleader in life, and most of all, she was my rock. It was her strength and passion for life that inspired me to do this thesis, to do something that I know she would be proud of, and that could touch the lives of others living with an autoimmune disease. Mum mentioned to me a few times that she wanted to contribute to science, so that others could learn about scleroderma, and so this is my way of doing that for her. It was one of the many conversations that mum, and I had during her final days, and I made a promise to myself that I would take on this journey, to make her proud.

Mum and I always understood and supported each other, which is one of the most special bonds that any mother and daughter can have. Mum and I both share similar autoimmune chronic diseases. I was diagnosed with systemic lupus erythematosus (lupus) in 2008, and in 2015 I was diagnosed with lupus nephritis (kidney failure), which almost took my life. The silver lining was that it sparked an interest in me to learn more about lupus and scleroderma, and take extra care of myself, and my mum.

This PhD is dedicated to my beautiful mum, who I miss so very dearly, and to others living with rare and complex autoimmune diseases, who may share a similar story. Mum and I truly understand what it feels like to live with a disease that can make you feel alone, scared, and uncertain about the future. I hope that this thesis makes a meaningful contribution to research and practice, and most of all, the lives of others living with systemic lupus erythematosus (lupus) or systemic sclerosis (scleroderma).

Yours sincerely, Stephanie Frade

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ABBREVIATIONS

Systemic Sclerosis (SSc)

Systemic Lupus Erythematosus (SLE)

Physical activity (PA)

World health organisation (WHO)

Patient reported outcome measure (PROM)

Health related quality of life (HRQOL)

Quality of life (QOL)

Antiphospholipid antibodies (aPL)

Hydroxychloroquine (HCQ)

Glucocorticoids (GC)

Prednisone (PO)

Intramuscular (IM)

Intravenous (IV)

Methotrexate (MXT)

Azathioprine (AZA)

Belimumab (BEL)

Calcineurin inhibitors (CNIs)

Mycophenolate mofetil (MMF)

Cyclophosphamide (CYC)

Rituximab (RTX)

Systemic Lupus Erythematous disease index (SLEDAI)

British Isles Lupus assessment Group Disease activity index (BILAG)

CHAPTER 1: INTRODUCTION

1.1. Overview of the thesis

This thesis is presented in the format of a thesis by publication. This thesis includes publications that were completed during a Master of Advanced Research, which was then upgraded to a Doctor of Philosophy (PhD). Chapter 1 introduces the rationale for the project and reviews the literature relevant to the research approach. Chapters 2 through 5 are presented as research articles that were published during the period of candidature (Master of Advanced Research and Doctor of Philosophy). Each publication is linked by Statements of Contribution to the advancement of the research area. Chapter 6 contains a general discussion that interprets the significance of findings considering the wider literature and includes key recommendations for research and practice. And the last chapter, Chapter 7, provides an insider perspective about the research topic and PhD journey.

1.2. Overview of the chapter

The objective of this chapter is to provide a background on 1) physical activity and exercise, including current recommendations for chronic conditions, 2) systemic lupus erythematosus (SLE) and systemic sclerosis (SSc), two chronic autoimmune connective tissue diseases that share similar clinical features, often resulting in physical inactivity and reduced health-related quality of life (HRQOL), and 3) current recommendations and evidence on the safety and effectiveness of exercise in SLE and SSc.

1.3. Physical activity and exercise

Physical activity (PA) and exercise are two terms which are often used interchangeably in the literature, however, are different concepts (Caspersen, Powell, & Christenson, 1985). PA is defined as any bodily movement produced by skeletal muscles that require energy expenditure and can include activities of daily living (ADL) such as household, occupational, or sporting activities, or walking and/or strolling for entertainment (Caspersen et al., 1985). Exercise is a subset of PA that is *planned, structured, and repetitive*, and includes a *dosage* (type, intensity,

frequency, and time) and an objective to improve and/or maintain one or more components of physical fitness (Caspersen et al., 1985).

The three main *types* of exercise include aerobic, resistance, and range of movement, as depicted in table 1.1 (Pescatello, 2014)

Table 1.1 Type of exercise (Pescatello, 2014)

Type of exercise	Definition	Examples
Aerobic/ cardiovascular	Exercise that uses large muscle groups, can be maintained continuously, and is rhythmic in nature, and aimed at improving the efficiency of the cardiovascular system.	• Walking • Jogging/running • Cycling • Swimming
Resistance/ strength	Exercise that uses resistance or load to induce muscular contraction, which builds the strength, anaerobic endurance, and size of skeletal muscles.	• Sitting to standing • Walking upstairs • Lifting external weights or resistance bands • Pilates or Yoga
Range of movement/ flexibility	Exercise aimed at improving the mobility of a specific joint.	• Stretching • Yoga • tai chi

The *intensity* of exercise is usually determined by the effort required by the person performing the exercise and can be measured by heart rate (HR) response, or a subjective rating of perceived exertion (RPE) by the person performing the exercise. Intensity is described as high/intense (70% to < 90% of HRmax); or RPE value of 5/10 to 7/10); moderate (55% to < 70% HRmax, or an RPE value of 3/10 to 4/10); or light/low (40% to < 55% HRmax, or an RPE value of 1/10 to 2/10) (Pescatello, 2014). The *frequency* of exercise refers to the number of days per week the exercise session is performed (i.e., 2 days/week), and the *time* of exercise refers to the duration of the single exercise session (i.e., 30 minutes). Exercise may be *supervised* one-on-one or as a group by allied health practitioners such as physiotherapists or exercise physiologists, personal trainers or fitness instructors, or medical health practitioners. It can also be performed independently under no supervision. The

exercise environment may be water-based (indoors or outdoors), or land-based (indoors or outdoors); in a gym or clinic, outdoors at a park, along a walking/bike track, or in one's home. In the literature, exercise can sometimes be classified as a subset of rehabilitation, and further categorised into global (whole body e.g., aerobic and/or resistance exercise) or localised (hand, face, or mouth) exercise and/or rehabilitation (Mugii, Hamaguchi, & Maddali-Bongi, 2018).

The World Health Organisation (WHO) recommends that adults (aged 18-64 years old) with chronic conditions should perform at least 150 to 300 minutes of moderate intense aerobic PA; or at least 75–150 minutes of vigorous-intensity aerobic PA; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week (WHO, 2020). Also, adults with chronic conditions should include muscle-strengthening activities at moderate or greater intensity that involve all major muscle groups on 2 or more days per week, as these provide additional health benefits (WHO, 2020). The WHO also recommends limiting sedentary time and replacing this with PA of any intensity (including light intensity) (WHO, 2020). Although there are PA guidelines for people with chronic conditions, there are currently no specific exercise prescription guidelines or recommendations tailored to people with SLE and SSc.

For the objectives of this thesis, we refer to the safety and effectiveness of aerobic, resistance, and/or range of movement type of *exercise*, at any intensity, frequency, and time, in SSc and SLE.

1.4. Systemic lupus erythematosus

1.1.1 What is systemic lupus erythematosus?

Systemic lupus erythematosus (SLE) is a heterogenous multisystem autoimmune disease characterised by an immune response to self-antigens, resulting in inflammation and damage to joints, tissues, and/or internal organs (Fanouriakis et al., 2019). Manifestations of SLE vary markedly and can be intermittent; specific manifestations include skin disease, neuropsychiatric disease, haematological disease, and renal disease. Common constitutional symptoms include general malaise and fatigue, affecting up to 80% of people with SLE (Sharif et al., 2018), skin rashes (also referred to as a “malar rash” or “butterfly rash” on the face), muscle

and joint pain (Fanouriakis et al., 2019). People with SLE commonly experience peaks and troughs of disease activity and/or symptoms, usually referred to as "disease flares" (Jakez-Ocampo, Rodriguez-Armida, Lima, Llorente, & Atisha-Fregoso, 2020), however, rates of complete remission in SLE are infrequent (Medina-Quiñones, Ramos-Merino, Ruiz-Sada, & Isenberg, 2016; Steiman, Urowitz, Ibañez, Papneja, & Gladman, 2014). Despite a universally accepted definition, experts define a disease flare as "a measurable increase in disease activity usually leading to change of treatment" (Ruperto et al., 2011), and contributes significantly to organ damage accrual. Disease activity simply represents the presence of clinical symptoms and/or organ involvement and is typically measured through validated disease activity indices such as Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) or Systemic Lupus Activity Measure (SLAM), with a "disease flare" corresponding to an increase in score over a period (Ruperto et al., 2011) (refer to section 1.4.4.1 for more information on the measurements of disease activity).

1.1.2 Treatment and management of systemic lupus erythematosus

To improve long-term outcomes and quality of life in people with SLE, treatment should aim for remission of disease signs and symptoms, prevention of damage accrual, and minimisation of drug-side effects (Van Vollenhoven et al., 2017; Van Vollenhoven et al., 2014). Furthermore, prevention of "disease flares" is another goal of the treatment in SLE and can be best managed through assessment of medication adherence, close monitoring (regular blood tests and check-ups), and optimisation of disease control (Fanouriakis et al., 2019). Management or "usual care" in SLE may include, but not limited to, the following pharmacological treatments; conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as hydroxychloroquine (HCQ), prednisolone (Pre) or glucocorticoids (GC), mycophenolate mofetil (MMF), methotrexate (MTX), azathiroprine (AZA), and/or cyclophosphamide (CYC); biological disease-modifying antirheumatic drugs (bDMARDs) such as rituximab (RTX) or belimumab (BEL); nonsteroidal anti-inflammatory drugs (NSAIDS) such as naproxen or Celebrex (Fanouriakis et al., 2019). It may also include non-pharmacological measures such as sun avoidance, supplementation (i.e., vitamin D), education about

the disease and/or comorbidities (i.e., hypertension), and PA or exercise (Fanouriakis et al., 2019). See figure 1.1 for a schematic of the treatment of SLE (Fanouriakis et al., 2019), with the inclusion of adjunct treatment (including exercise), with the goals of either remission or low disease activity.

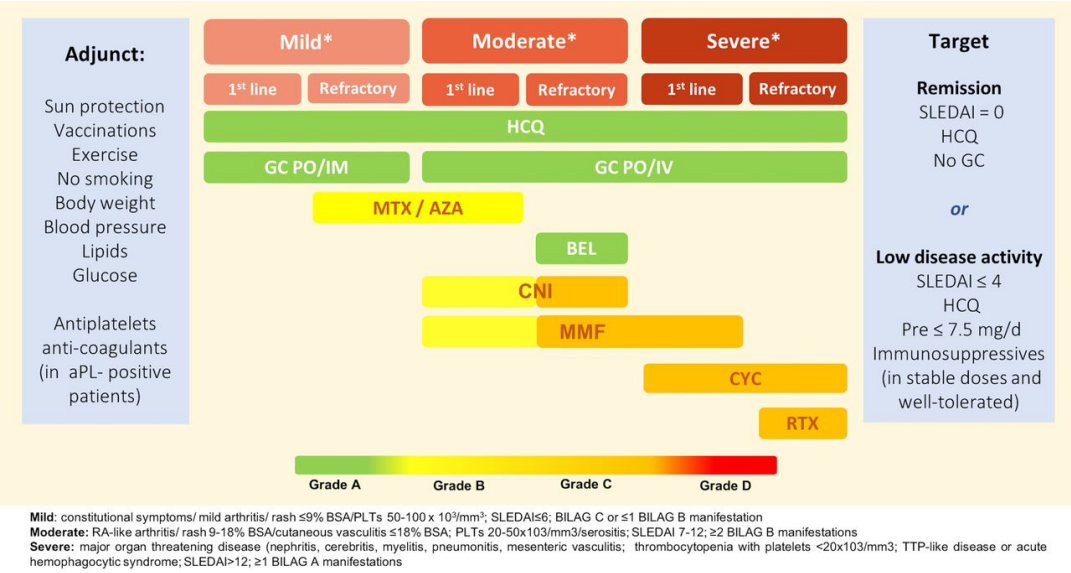

Figure 1.1 Treatment of SLE (Fanouriakis et al., 2019)

Note: PO= Per os (by mouth); IM=intramuscular; IV=intravenous; CNIs=calcineurin inhibitors

1.1.3 Prevalence of systemic lupus erythematosus

SLE is a rare disease with an estimated worldwide prevalence of 20 to 150 cases per 100,000 persons, with higher prevalence in women, particularly those of childbearing ages and certain ethnicities such as Hispanic and Asian populations (Askanase, Shum, & Mitnick, 2012; Maidhof & Hilas, 2012; Nikpour, Bridge, & Richter, 2014). By age, the female: male ratio is 3:1 before puberty, 10–15:1 during childbearing years, with a slight decrease again after menopause, 8:1 (Askanase et al., 2012). The peak age of SLE diagnosis is between 15 to 44 years (Askanase et al., 2012). Prevalence in Australia varies between 19.3-39 persons in 100,000 for non-Aboriginal Australians and 52.0-92.8 persons in 100,000 Aboriginal Australians, with no evidence of Mendelian inheritance of SLE among Aboriginal Australians (Bossingham, 2003; Segasothy & Phillips, 2001).

1.1.4 Comorbidities specific to systemic lupus erythematosus

Common comorbidities of SLE include 1) infections and 2) cardiovascular disease (CVD). The risk of infections is associated with both disease-related and treatment-

related factors including high disease activity, severe leucopoenia, and the presence of renal involvement (Chen et al., 2016), and the use of high dose therapies including glucocorticoids (GC), cyclophosphamide (CYC), mycophenolate mofetil (MMF), and rituximab (RTX) (Singh, Hossain, Kotb, & Wells, 2016). SLE is an independent risk factor for CVD due to both lifestyle and disease-related factors such as persistent disease activity, nephritis, presence of antiphospholipid antibodies (aPL), and the use of GC (Ballocca et al., 2015; Magder & Petri, 2012). It is important to note that the comorbidities described above are not an inclusive list of comorbidities, they are those specifically concerning SLE in the literature (Fanouriakis et al., 2019).

1.1.5 Exercise and physical activity in systemic lupus erythematosus

People with SLE are less physically active than people without SLE, with sixty percent of people with SLE not meeting the WHO recommendations for PA (Margiotta et al., 2018). Additionally, physical inactivity increases the risk of developing comorbidities such as osteoporosis (Gu et al., 2019) and CVD, which are common in people with SLE due to long-term medication use and inherent risk of SLE (Manzi et al., 1997; Schoenfeld, Kasturi, & Costenbader, 2013). Furthermore, a significant inverse relationship between physical activity and fatigue has been identified in people with SLE (Yuen & Cunningham, 2014), thus, it is proposed that exercise is a potential strategy for the management of fatigue in this population, reduce the risk of CVD, and improve overall HRQOL. Importantly, *exercise* is listed as one of the adjunctive therapies in the most updated treatment recommendations for SLE (figure 1.1) (Fanouriakis et al., 2019).

1.1.6 Perspectives and experiences of living with systemic lupus erythematosus

A systematic review of 46 qualitative studies, with a total of 1385 participants, described the overarching experiences and perspectives of adults living with SLE (Sutanto et al., 2013), and identified that adults with SLE need education, psychosocial, and self-care interventions to promote resilience, positive coping strategies, and self-advocacy. As depicted in figure 1.2 (Sutanto et al., 2013), participants with SLE reported the disease to cause a restricted lifestyle because of debilitating fatigue, mental deterioration, pervasive pain, and disruptive episodic symptoms, and subsequently, limiting their ability to engage in exercise, work, and accomplish simple tasks such as getting dressed (Seawell & Danoff-Burg, 2004;

Sutanto et al., 2013). They also described SLE to cause a sense of disrupted identity from prognostic uncertainty, feelings of hopelessness, guilt and punishment, self-consciousness, and feeling socially ostracised. Adults with SLE also felt burdened by the costs of ongoing treatments and found that effective communication between the patient and the health care team promoted a sense of trust and respect. In contrast, participants with SLE described increased resilience, a heightened feeling of empowerment and optimism, and the ability to focus on adopting a healthy lifestyle including engaging in regular exercise and avoiding any stressors that could trigger or exacerbate their symptoms.

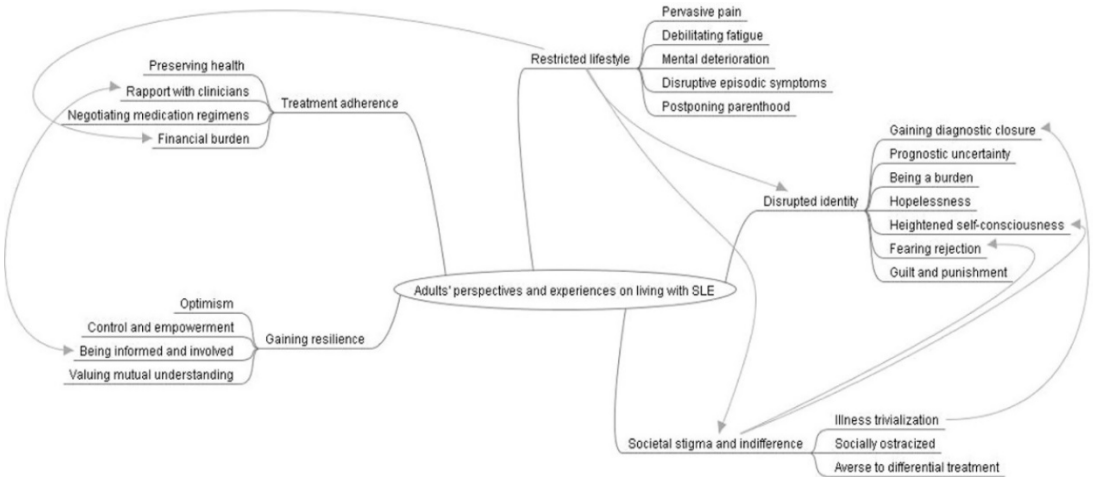

Figure 1.2 Thematic schema of the perspectives of living with SLE (Sutanto et al., 2013)

1.1.6.1 Perspectives of exercise in adults with systemic lupus erythematosus

Few qualitative studies (Keith-Jopp, Coxon, Nikoletou, Morrissey, & Pyne, 2020; Middleton et al., 2018) have been conducted that specifically explore the perspectives of exercise, or the experiences following an exercise intervention, in people with SLE. One explorative qualitative study was recently conducted on the perspectives of physical activity (PA) in adults with SLE, aiming to inform PA promotion efforts for this population (Keith-Jopp et al., 2020). In this study, ten adults with SLE participated in semi-structured interviews at a tertiary Lupus Centre, and an independent lupus group discussed the findings to provide respondent validation and further context to the findings. As shown in figure 1.3, eight overall themes emerged from the interview data, four of which related to their experience of

living with SLE, and four that related specifically to their experiences of exercise which was ultimately underpinned by their experience of the disease. PA activity was described as beneficial for people with SLE, resulting in improved confidence, fatigue, and mental wellbeing, reduced pain, weight loss, and increased strength (Keith-Jopp et al., 2020), similar to other qualitative findings (Middleton et al., 2018), which found yoga to improve flexibility, reduce fatigue and pain. There were barriers to PA engagement for those with SLE, including feeling self-consciousness, fatigue, pain, lack of time, variability in the weather, and accessibility. These barriers were consistent with other qualitative findings (Keith-Jopp et al., 2020; Middleton et al., 2018), such as lack of motivation, pain, and time. People with SLE provided suggestions on ways to facilitate their participation in PA, some of which included improving access to PA, good weather, and having a better routine that incorporates PA, and are more likely to engage in exercise that is low impact, adaptable, and individually tailored (Keith-Jopp et al., 2020).

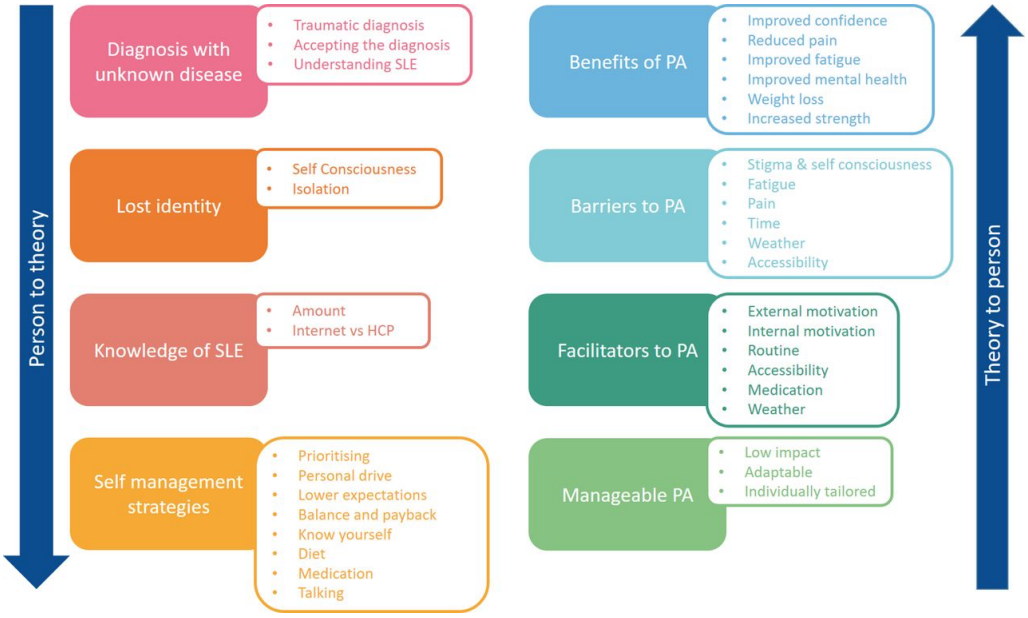

Figure 1.3. Thematic schema of PA perspectives in people with SLE (Keith-Jopp et al., 2020)

1.1.7 Evidence on exercise in systemic lupus erythematosus

Regular exercise training may lead to anti-inflammatory benefits in chronic diseases with systemic low-grade inflammation (e.g., type 2 diabetes) by reducing inflammatory markers, (Perandini et al., 2012), and is regarded as a valuable self-care intervention for this population. Given the potential role of inflammation in the aetiology and clinical symptoms of SLE, including pain and fatigue, it is postulated

that exercise training, if able to alleviate the inflammatory process, could also be helpful in managing the symptoms related to inflammation in this population, which may improve health related quality of life (HRQOL).

To date, exercise intervention studies of people with SLE (Abrahão, Gomiero, Peccin, Grande, & Trevisani, 2016; Avaux et al., 2016; Benatti et al., 2015; Bogdanovic, Djokovic, & Stanisavljevic, 2015; Boström et al., 2016; Carvalho et al., 2005; dos Reis-Neto, da Silva, Monteiro, de Camargo, & Sato, 2013; Miossi et al., 2012; Ramsey-Goldman et al., 2000; Robb-Nicholson et al., 1989; Tench, McCarthy, McCurdie, White, & D'Cruz, 2003) used primarily aerobic exercise as the type of exercise intervention, and varied between being performed either at a specific site (i.e., supervised) or at home (i.e., unsupervised). Typically, exercise was performed two to three times per week for 30 to 50 minutes, achieving an intensity of 60% to 80% of the participant's maximum heart rate (moderate intensity), and the duration of the exercise interventions ranged from 8 to 12 weeks, with one of the aforementioned studies (Boström et al., 2016) monitoring the long-term effect of sustained exercise (12 months) on various outcomes, including adherence. A complete breakdown of the exercise interventions in the most up to date RCTs are included in chapter two of this thesis.

There are currently three systematic reviews on exercise interventions in SLE (Lu & Koo, 2021; O'Dwyer, Durcan, & Wilson, 2017; Wu, Yu, & Tsai, 2017). O'Dwyer et al (2017) included eleven randomised controlled trials of exercise (Abrahão et al., 2016; Avaux et al., 2016; Benatti et al., 2015; Bogdanovic et al., 2015; Boström et al., 2016; Carvalho et al., 2005; dos Reis-Neto et al., 2013; Miossi et al., 2012; Ramsey-Goldman et al., 2000; Robb-Nicholson et al., 1989; Tench et al., 2003). This systematic review revealed that exercise programs appear to be safe and well tolerated by people with SLE, does not adversely affect disease activity, and improves fatigue, depression, and physical fitness. Despite these benefits, no specific exercise recommendations were able to be drawn from the review, and an optimal exercise protocol remains unclear. Furthermore, Wu et al (2017) included two randomised controlled trials and one quasi-experimental study (Carvalho et al., 2005; Ramsey-Goldman et al., 2000; Tench et al., 2003) specifically assessing the effectiveness of exercise on fatigue and confirmed that exercise decreases fatigue

severity. However, the quality of evidence in the included studies was graded as either fair or poor, and further, there were only three studies included in this review, reducing confidence in the findings. No specific exercise recommendations were derived from this review. Lu et al (2021) included five RCTs and four non-RCTs (Abrahão et al., 2016; Bogdanovic et al., 2015; Boström et al., 2016; Carvalho et al., 2005; Gavilán-Carrera et al., 2022; Keramiotou et al., 2020; Lopes-Souza et al., 2021; Ramsey-Goldman et al., 2000; Tench et al., 2003), specifically assessing the effectiveness of exercise on HRQOL and revealed that exercise interventions compared to usual care might be able to improve physical functioning HRQOL (see section 1.4.9.1 for further details about this outcome) in people with SLE. Given the limited number of RCTs on this topic, there is limited evidence on the positive effects of exercise interventions in other aspects of HRQOL. Again, no specific exercise recommendations were drawn from the review. Overall, the available evidence suggests that exercise (broadly speaking), is safe, with no reported adverse effects, and is effective in reducing levels of fatigue and depression and improving physical fitness and physical functioning in people with SLE.

The following sections (1.4.8 to 1.4.11) will describe the commonly used measurement tools and the effect of exercise on key outcomes in SLE. The key outcomes described below have been selected because they are 1) suggested to be of high importance to a person with SLE according to the literature (Fanouriakis et al., 2019) and 2) common outcomes assessed in existing exercise intervention studies in SLE (Lu & Koo, 2021; O'Dwyer et al., 2017; Wu et al., 2017). The outcomes that will be discussed include 1) disease activity, 2) health related quality of life (HRQOL), 3) fatigue, and 4) physiological function. The most utilised measurement tools in existing exercise intervention studies in SLE (Lu & Koo, 2021; O'Dwyer et al., 2017; Wu et al., 2017) for these outcomes will also be discussed in detail. It is important to note that the outcomes and measurement tools described in this thesis are not an exhaustive list.

1.1.8 Disease activity in systemic lupus erythematosus

1.1.8.1 Measurement tools for disease activity in systemic lupus erythematosus

The two measurement tools that assess disease activity in SLE and have been used in existing exercise intervention studies include the Systemic Lupus Erythematosus

Disease Activity Index (SLEDAI*)* (Abrahão et al., 2016; Avaux et al., 2016; Bogdanovic et al., 2015; Boström et al., 2016; dos Reis-Neto et al., 2013; Keramiotou et al., 2020; Miossi et al., 2012) and the Systemic Lupus Activity Measure (SLAM) (Ramsey-Goldman et al., 2000; Tench et al., 2003), with the SLEDAI evidently more commonly used.

The SLEDAI was originally developed to determine disease activity in patients with SLE (Bombardier, Gladman, Urowitz, Caron, & Chang, 1992), and consists of 24 items; 16 clinical items based on current symptoms and disease manifestations, and 8 items based on the most recent laboratory test results, as depicted in appendix I-1. The SLEDAI instrument includes a list of organ manifestations, and the medical practitioner decides whether each manifestation is "present" or "absent" in the last 10 days. It is a weighted instrument, in which descriptors are multiplied by that organ's "weight". These weighted organ manifestations are then totalled into the final score, giving a global score from 0 to 105, with a higher score meaning higher disease activity. SLEDAI-2000 (SLEDAI-2 K) was introduced in 2002 as a measure of global disease activity (D.D. Gladman, D. Ibañez, & M.B. Urowitz, 2002). SLEDAI-2 K is a modification of the original SLEDAI to allow the documentation of persistent disease activity in the descriptors: rash, alopecia, mucosal ulcers, and proteinuria. SLEDAI-2 K has been validated against the classic SLEDAI ($r = 0.97$), predicts mortality ($p = 0.0001$) and proven to be sensitive to change over time (D.D. Gladman et al., 2002). An appropriate SLEDAI-2K score to define active SLE disease is 3 or 4 out of 105, with an increase in score of 3 or more to be considered a "disease flare" (Ruperto et al., 2011). SLEDAI-2K is often used in exercise intervention studies of SLE to identify change in disease activity, and to quantify the safety of exercise (e.g., an increase in SLEDAI score represents worsening of disease). Similarly, disease-related adverse events such as "disease flares" or worsening of symptoms, and non-disease related adverse events such as muscular injuries, are other ways of determining the safety of an exercise intervention.

The Systemic Lupus Activity Measure (SLAM) index was published in 1988 and revised in 1991 to become the Systemic Lupus Activity Measure-Revised (SLAM-R). SLAM is a standardised weighted index for the clinical assessment of SLE disease activity and severity and measures global disease activity within the previous

month (Bae et al., 2001). SLAM-R includes 23 clinical manifestations in nine organs/systems and seven laboratory features and has a possible range of 0 to 81 (higher score representing worse disease activity), as depicted in appendix I-2. The reliability of SLAM was demonstrated with an inter-rater reliability and an inter-visit reliability of 0.86 and 0.73, respectively, and findings for the SLAM-R were similar (0.78 and 0.85, respectively). (Mikdashi & Nived, 2015).

1.1.8.2 Effect of exercise on disease activity in systemic lupus erythematosus

A systematic review performed by O'Dwyer et al (2017) pooled results from three randomised controlled trials of exercise using SLEDAI to assess disease activity before and after an exercise intervention (Abrahão et al., 2016; dos Reis-Neto et al., 2013; Miossi et al., 2012). Results showed that disease activity was not significantly changed following exercise [MD = 0.01; 95% CI: -0.54 to 0.56, p=0.97] (O'Dwyer et al., 2017), which demonstrates that exercise does not worsen, nor does it improve disease activity, speculating that exercise is safe. Another RCT also reported no significant difference in disease activity between the exercise and control group over a 12-month period (p=0.56) (Boström et al., 2016).

Some exercise intervention studies do not explicitly present disease activity data at baseline and post-intervention yet discuss change in disease activity. For example, one study reported 'the analysis of the data from each individual patient showed no aggravation in disease activity as measured by SLEDAI' (Clarke-Jenssen, Fredriksen, Lilleby, & Mengshoel, 2005). Most studies seem to use the outcome disease activity as a way of quantifying the 'safety' of exercise, with no significant change or worsening of disease activity as an indication of an intervention being 'safe'. For example, a pilot study (Ramsey-Goldman et al., 2000) comparing aerobic (n=5) and resistance (n=5) exercise, without a control group, over an 8-month period, reported that both types of exercise were 'safe' and were not associated with significantly increased SLAM scores [MD = 2.80, 95% CI 0.90 to 4.70; MD = 0.40, 95% CI -2.70 to 3.07], respectively, indicating that disease activity did not worsen. However, it is important to understand that changes in disease activity, regardless of the measurement tool used, can be multifactorial. For example, during an exercise intervention the participant may have experienced changes in medication, been exposed to the sun, or had experienced stressful life events. These factors could

influence disease activity, and it is therefore difficult to truly know the effect of exercise alone. Overall, exercise (broadly speaking), is considered 'safe' for people with SLE, with no reported worsening of disease activity or adverse effects during or following an exercise intervention.

1.1.9 Health-related quality of life in systemic lupus erythematosus

1.1.9.1 Measurement tools for HRQOL in systemic lupus erythematosus

Health-related quality of life (HRQOL) is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning and in the context of research, is usually assessed through a patient-reported outcome measure (PROM). HRQOL also includes distinct outcomes such as pain and fatigue, which are both common symptoms reported by people with SLE (Sutanto et al., 2013), and therefore important outcomes to assess following exercise interventions to determine its effectiveness.

For the objective of this thesis, we report pain within HRQOL because pain is commonly assessed and reported within generic HRQOL measurement tools, for example, the Medical Outcomes Survey Short Form 36 (SF36), in existing exercise intervention RCTs (Abrahão et al., 2016; Boström et al., 2016; Lopes-Souza et al., 2021), with only one RCT (Keramiotou et al., 2020) using the visual analogue scale (VAS) for pain, independently. However, we include fatigue as a separate outcome in this thesis because it is usually measured independently with an additional fatigue outcome tool (e.g., fatigue severity scale described in section 1.4.10). Fatigue is also included in HRQOL questionnaires, such as SF36, however this outcome is termed 'vitality' (refer to section 1.4.10.1)

The SF36 is the most widely used HRQOL measurement tool in exercise and SLE studies, with good reliability ($\alpha > 0.85$) and construct validity with respect to the distribution of scores (Brazier et al., 1992; Hays, Sherbourne, & Mazel, 1993). The SF-36 is a patient report outcome measure (PROM) which includes a set of generic, coherent, and easily administered quality-of-life measures that explore eight health domains; physical functioning (10 items), bodily pain (2 items), role limitations due to physical health problems (4 items), role limitations due to personal or emotional problems (4 items), emotional well-being (5 items), social functioning: (2 items),

energy/fatigue (4 items), and general health perceptions (5 items) (Hays et al., 1993). Scores for each domain range from 0 to 100, with a higher score defining a more favourable health state (Ware, 2000). The 36 questions are summarized into physical component summary (PCS) and mental component summary (MCS) scores, though this these summary scores are rarely reported in studies of exercise in SLE, and instead, the individual domains are reported. The SF36 minimal clinically important difference (MCID) cut-offs for the individual domains, set by Strand and Crawford, were defined as follows: >=+5 = improved, -2.5 to +5 = unchanged, and <= -2.5 = worse (Strand & Crawford, 2005).

Another outcome tool to measure HRQOL, specific to SLE, is the LupusQOL, with good validity and reliability in SLE (McElhone et al., 2007). The LupusQOL is a 34-item PROM which includes a set of easily administered quality-of-life measures that are explore with domains that are more specific to lupus than the generic SF36; physical health (8 items), emotional health (6 items), body image (5 items), pain (3 items), planning (3 items), fatigue (4 items), intimate relationships (2 items), and burden to others (3 items). Scores for each domain range from 0 to 100 with a higher score defining a more favourable health state.

A comparison between LupusQOL and SF36 (Touma, Gladman, Ibanez, & Urowitz, 2011) showed a strong correlation between comparable domains (physical health and physical functioning, r=0.75; emotional health and role emotional, r=0.62; pain and bodily pain, r=0.76; fatigue and vitality, r=0.75, all p values < 0.0001, respectively). There was a correlation between the noncomparable domains of the LupusQOL and one of the component scores of SF36 (body image and SF36 MCS, r=0.61; planning and SF36 MCS, r=0.68; intimate relationships and SF36 PCS, r=0.73; burden to others and SF36 MCS, r=0.70, respectively) (Touma et al., 2011). Furthermore, LupusQOL and SF36 are both sensitive to change and reflect improvement and worsening, and equally recommended as a HRQOL instrument in SLE (Nantes, Strand, Su, & Touma, 2018). With this understanding and coupled with the consistency of SF36 use in existing exercise intervention studies in SLE, SF36 was chosen for my intervention study (chapter five) to assess the change in HRQOL following an 8-week telehealth exercise intervention, compared to a control group receiving usual care.

1.1.9.2 Effect of exercise on HRQOL in systemic lupus erythematosus

In a systematic review by O'Dwyer et al. (2017) four studies (Abrahão et al., 2016; Boström et al., 2016; Carvalho et al., 2005; Tench et al., 2003) used the SF36 to evaluate HRQOL in adults with SLE following an exercise intervention. The physical fitness ($p = 0.02$) and vitality domains ($p=0.04$) were significantly improved following a 12-week aerobic exercise program (walking, 60min sessions, 3 times per week), compared to a control group receiving their usual care (Carvalho et al., 2005).

Additionally, physical role functioning, and vitality were significantly improved ($p <0.05$) following a 12-week aerobic exercise program (walking or bicycle, 50min sessions, 3 times/week) compared to a control group receiving usual care and compared to a resistance exercise program (free weights and resistance bands, 50mins, 3 times/week) (Abrahão et al., 2016). There was also a significant difference in emotional role functioning ($p < 0.05$) for the aerobic exercise group (walking or bicycle, 50min sessions, 3 times/week) compared to the control group from baseline to after the intervention (Abrahão et al., 2016). No significant differences were found in the SF36 scores on the other domains (physical functional, social functioning, mental health, bodily pain, and general health) from baseline to after the exercise intervention (Abrahão et al., 2016). Note that this study did not report p values for these domains.

Furthermore, another two studies (Boström et al., 2016; Tench et al., 2003) found no significant differences in any SF36 domains ($p >0.05$), except for mental health ($p=0.002$) which was significantly improved at 6-months, following a 12-week supervised high intensity aerobic and resistance exercise program (60mins, 2 times/week) with less supervision in the subsequent months, when compared to a control group who received usual care (Boström et al., 2016).

In a more recent systematic review by Lu et al. (2021), pooled results of five RCTs (Abrahão et al., 2016; Boström et al., 2016; Keramiotou et al., 2020; Lopes-Souza et al., 2021; Tench et al., 2003) showed that exercise has a significant positive effect on physical function ($p=0.043$), measured by SF36, when compared to a control group. The results of the remaining seven domains of the SF36 (role physical ($p=0.211$); pain ($p=0.759$); general health ($p=0.995$); vitality ($p=0.274$); social functioning ($p=0.526$); role emotional ($p=0.180$); mental health ($p=0.998$)) showed

that exercise did not have a significant effect on all the domains listed above, when compared to a control group. Overall, exercise (broadly speaking) is effective in improving some aspects of HRQOL including self-reported physical fitness, vitality, and emotional wellbeing.

1.1.10 Fatigue in systemic lupus erythematosus

1.1.10.1 Measurement tools for fatigue in systemic lupus erythematosus

Fatigue is a subset of HRQOL, and for this thesis we include it as its own independent outcome because 1) it is one of the most common symptoms reported by people with SLE and within the literature (as described in section 1.4.1 and 1.4.6), and 2) it is usually measured independently, and in addition to HRQOL, in exercise intervention studies in SLE. It is also important to understand that 'fatigue' is termed as 'vitality' in SF-36, and consists of four specific items designed to assess 'vitality' (Ware & Sherbourne, 1992). Vitality is essentially the inverse of fatigue, and the questions pertaining to vitality in SF36 are scored in a way where higher scores represent less fatigue, e.g. "How much of the time during the past 4 weeks did you feel tired?" (All of the time = 1 to none of the time = 6). Furthermore, independent fatigue measurement tools such as FSS or FACIT-F, described in further detail below, have been developed to assess 'fatigue' and 'fatigue severity' in people with chronic disease (Cella, 1997) and the most frequently used instruments in SLE (Barbacki, Petri, Aviña-Zubieta, Alarcón, & Bernatsky, 2019). Other fatigue measurement tools to assess and describe 'fatigue' in existing exercise interventions studies of SLE include the Chalder fatigue scale (CFS) and visual analogue scale (VAS) for fatigue (Tench et al., 2003), the profile of moods state (POMS) and mental adjustment to cancer (MAC), which won't be further described in this thesis because they are less commonly used (Daltroy, Robb-Nicholson, Iversen, Wright, & Liang, 1995). Unlike SF36, FSS is scored in the opposite direction, where higher scores indicate more fatigue/less vitality, e.g., "my motivation is lower when I am fatigued" (strongly disagree = 1 to strongly agree = 7). Whereas unlike SF36, FACIT-F is scored in a way where higher scores represent less fatigue/more vitality. As depicted, the variations in the way fatigue measurements are scored, coupled with the heterogeneity of fatigue measurement tools used in existing exercise intervention studies, makes it difficult to meta-analyse the results using mean difference and

having confidence in the findings, albeit the high risk of bias in exercise intervention studies of SLE.

The FSS (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) is the most widely used and recommended tool to measure fatigue in SLE (Fatigue, 2007), with good reliability ($\alpha = 0.92$) and validity (ICC = 0.94) (Feng et al., 2019), and significant correlation to the vitality domain in SF36 ($r=-0.55$, $p<0.01$) (Feng et al., 2019). The FSS is a PROM that includes 9-items designed to assess fatigue as a symptom of a variety of different chronic conditions. The scale addresses the effects of fatigue on daily functioning, querying its relationship to motivation, PA, work, family, and social life, and asking respondents to rate the ease with which they are fatigued and the degree to which the symptom poses a problem for them. Respondents use a scale ranging from 1 (completely disagree) to 7 (completely agree) to indicate their agreement with nine statements about fatigue. Higher scores on the scale are indicative of more severe fatigue (Krupp et al., 1989), with experts suggesting that a 9.7% to 15% reduction in the final FSS score representing an important improvement (Fatigue, 2007; Goligher et al., 2008)

The Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-Fatigue) is reliable ($\alpha > 0.95$) and has been validated as a fatigue measurement tool in SLE ($\rho = 0.81$) (Lai, Beaumont, Ogale, Brunetta, & Cella, 2011). FACIT-Fatigue (version 4) is a 13-item questionnaire that uses a 5-point Likert-type response scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; and 4 = very much), with scores ranging from 0 to 52 (higher scores indicating less fatigue), as depicted in figure 1.5. Goligher, et al derived 5.9 points as the minimal clinically important difference (MCID) for the FACIT-Fatigue scale in people with SLE, or a chance in score of 11.5% (Goligher et al., 2008).

		Not at all	*A little*	*Somewhat*	*Quite a bit*	*Very much*
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Figure 1.4 FACIT-Fatigue questionnaire (Kosinski, Gajria, Fernandes, & Cella, 2013)

Despite FSS being the most widely used and recommended tool to measure fatigue in SLE (Fatigue, 2007), the FACIT-F has also recently become increasingly popular and widely used (Barbacki et al., 2019), and from a content perspective, the FACIT-F instrument is valid and appropriate for the assessment of fatigue in SLE. Furthermore, as identified above, FACIT-F is a valid and reliable instrument to assess fatigue in SLE. As such, this instrument was chosen for my intervention study (chapter five) to assess the change in fatigue following an 8-week telehealth exercise intervention study, compared to a control group receiving usual care.

1.1.10.2 Effect of exercise on fatigue in systemic lupus erythematosus

A systematic review performed by O'Dwyer et al (2017) pooled results from two studies (Carvalho et al., 2005; Tench et al., 2003) and showed that fatigue, measured by the fatigue severity scale (FSS), significantly improved in the exercise intervention group compared to the control group [MD = -0.61; 95% CI: –1.19 to –0.02]. Tench et al. (2003) also observed a significant difference in fatigue measured on the Chalder fatigue scale post-intervention [MD = -6.0 (95% CI: -10.3 to -1.7], but there was no significant difference measured on the visual analogue scale (p = 0.11). Interestingly, an exercise intervention study (Avaux et al., 2016) comparing supervised exercise to unsupervised home exercise, and to a control group receiving usual care, assessed fatigue using the FSS, and reported a significant reduction in fatigue in both intervention groups (p=0.007 and p=0.003, respectively), which was sustained at their 9-month follow up (p=0.003 and p=0.035, respectively).

In the systematic review performed by Wu et al (2017) pooled results of three studies (Carvalho et al., 2005; Ramsey-Goldman et al., 2000; Tench et al., 2003) showed

that aerobic exercise significantly decreased fatigue severity [MD = -0.52; 95% CI: –0.91 to –0.13, p=0.009], but relaxation exercise did not [MD =.00, 95% CI -0.63 to 0.63, p=1.00], measured by the FSS. Furthermore, the long-term (12-weeks) exercise training effect [MD = 0.68, 95% CI: -1.2 to -0.17, p=0.009] was greater than the short-term (8-weeks) training effect on fatigue [MD = -0.31, 95% CI: -0.91 to 0.29, p=0.31]. Further subgroup analysis findings showed that supervised exercise reduced fatigue to a significantly greater extent than home-based exercise [MD= 0.53, 95% CI -1.00 to -0.06, p=0.03; MD=-0.50, 95% CI -1.21 to 0.21, p=0.16, respectively]. Furthermore, pooled results of vitality in the SF36 (higher scores indicating less fatigue), showed that aerobic exercise had a positive effect on vitality [MD = 14.98; 95% CI: 7.45, 22.52, p< 0.001]. Overall, supervised aerobic exercise that is performed over a longer period (12 weeks), is effective in reducing levels of fatigue in people with SLE.

1.1.11 Physiological function in systemic lupus erythematosus

1.1.11.1 Aerobic capacity

Aerobic capacity or cardiovascular fitness is defined as the maximum amount of oxygen that a person can use per unit of time and body weight (Pescatello, 2014), and is often referred to as Vo2 max or Vo2 peak in the literature. An increase in a person's Vo2 max or Vo2 peak is indicative of an improvement in aerobic capacity or cardiovascular fitness, and following an exercise intervention, is considered a positive outcome. Aerobic capacity can be measured by asking participants to perform a maximal or sub-maximal intensity, symptom-limited, bicycle ergometer or treadmill exercise test, for example. Aerobic capacity is the most common physiological outcome measured in SLE exercise intervention studies, and therefore, for this thesis, we will be focusing on the effect of exercise in aerobic capacity following exercise.

Pooled results from five studies (Boström et al., 2016; Carvalho et al., 2005; dos Reis-Neto et al., 2013; Robb-Nicholson et al., 1989; Tench et al., 2003) demonstrated a significant difference in aerobic capacity favouring exercise compared to controls [MD= 1.85ml/kg/min, 95% CI=1.12 to 2.58, p < 0.00001] (O'Dwyer et al., 2017). Another study (Abrahão et al., 2016) reported significantly higher functional performance/aerobic capacity [MD=205.7metres, 95% CI= 94.7 to

316.8], measured by a 12-minute walk test (T12). T12 involves calculating the distance walked in 12-minutes (the more distance covered in 12-minutes, the better the functional performance/aerobic capacity), which despite being predominately a measure of functional walking capacity, is used to represent aerobic capacity in the literature. Unsurprisingly, participants in the aerobic exercise group had a significant increase in aerobic capacity, measured by T12, compared with those in the resistance exercise group (p=0.001; p=0.000, respectively) (Abrahão et al., 2016). An RCT comparing exercise to no exercise reported an increase in aerobic capacity following a 1-year exercise program, including supervised exercise for 12-weeks followed by less supervision and continuous coaching for the subsequent months, with result showing an increase in VO2 max (l/min) independent of the groups ($p<0.0001$) (Boström et al., 2016). Overall, aerobic exercise is effective in improving aerobic capacity in people with SLE.

1.1.11.2 Muscular strength and function

Other physiological tests such as muscular strength or muscular endurance are rarely assessed in trials of exercise in SLE. An RCT (Abrahão et al., 2016) comparing cardiovascular exercise to resistance exercise, and to a control group, did not measure muscle strength or muscle endurance despite the inclusion of a strength exercise program. The only exercise-related outcome that was measured in the study was aerobic capacity, inherently biased toward the aerobic exercise program. To my knowledge, there is only one exercise intervention study in SLE (Ramsey-Goldman et al., 2000) that assessed muscle strength following an exercise intervention. This study (Ramsey-Goldman et al., 2000) was a two-group comparison of aerobic exercise (n=5) and muscle strength/range of motion exercise (n=5) that assessed isometric strength of two lower extremity muscle groups (quadriceps and hamstrings) using an isokinetic machine. Isokinetic muscle strength testing is performed using a specialised machine that is set at a constant speed of angular motion, where the person is asked to push against the resistance with as much force as they can, giving you a force output in newtons-metres (N.m) This type of device is not readily available, and therefore, to assess muscular strength and function, other forms of strength testing can be used. For example, a five-time sit-to-stand test to measure lower body strength, or a hand grip test to measure hand and upper body

strength, both of which are reliable, valid, and commonly used as acceptable measures of strength (Marlow, Hastings, & Hansson, 2014)

In the aforementioned study (Ramsey-Goldman et al., 2000), quadricep muscle strength improved in both the aerobic and resistance exercise group, though not significantly [MD=12.21, 95% CI -3.04 to 27.46 N.m; MD=22.64, 95% CI 13.44 to 31.84 N.m, respectively], as well as the hamstring muscle group [MD=11.28, 95% CI 3.31 to 19.24 N.m; MD=19.25, 95% CI 8.63 to 29.87 N.m, respectively]. Since the confidence intervals overlapped, there was no clinically significant differences between the two groups. Overall, measurements of strength and function are lacking in exercise intervention studies in people with SLE, and it is therefore difficult to draw conclusions on the effect of exercise in improving strength and function in people with SLE.

1.5. Systemic sclerosis

1.1.12 What is systemic sclerosis?

Systemic sclerosis (SSc), also called scleroderma, is a heterogeneous multisystem autoimmune disease characterised by excessive collagen production and infiltration causing organ and skin fibrosis, and vascular injury (Denton & Khanna, 2017; Van den Hoogen et al., 2013). The hallmark features of SSc are thickening or hardening of the skin and internal organs which can lead to complications such as pulmonary fibrosis, pulmonary arterial hypertension, renal failure, or gastrointestinal complications (Denton & Khanna, 2017; Van den Hoogen et al., 2013). The disease can be classified into two categories: limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc). Limited SSc is confined to the face, forearms, and lower legs up to the knee, while diffuse SSc presents in the proximal limbs and/or the trunk and may progress to the visceral organs, including the kidneys, heart, lungs, and gastrointestinal tract, posing a higher risk of mortality (Lixian Zhong, Melinda Pope, Ye Shen, Jose J. Hernandez, & Lin Wu, 2019). The key features of limited SSc include distal skin sclerosis, long history of Raynaud's phenomenon, frequent late-stage complications such as pulmonary arterial hypertension and severe gut disease. The main features of diffuse SSc include widespread skin sclerosis, short history of Raynaud's phenomenon (RP), increased risk of renal crisis and cardiac involvement,

and high frequency of severe lung fibrosis. (Denton & Khanna, 2017; Van den Hoogen et al., 2013).

1.1.13 Treatment and management of systemic sclerosis

There are currently no treatments available to cure SSc, however, many of the different symptoms of SSc can be alleviated by pharmacological treatments, including, but not limited to immunosuppressives, glucocorticoids, blood vessel modulating, and biologics (Denton & Khanna, 2017). Considering the systemic nature of the disease, pharmacological management of SSc is recommended according to the organ/s involved, as depicted in table 1.2 (Otylia Kowal-Bielecka et al., 2017). It is recommended that SSc is managed with a combination of pharmacologic and non-pharmacologic therapies (such as exercise) and should also include early diagnosis of the disease and internal organ involvement (Otylia Kowal-Bielecka et al., 2017). Due to the multifaceted clinical manifestations of SSc, its management requires the combined expertise of different medical specialists and allied health professionals, in addition to rheumatologic care, to maximise adequate disease control and prevent complications (Farina et al., 2022). Furthermore, it is suggested that open communication and a multidisciplinary person-centred care approach, including listening to the experiences and perspectives of those living with the disease, can help improve treatment efficiency and overall HRQOL (Nakayama et al., 2016).

Table 1.2. Pharmacological management of SSc (Otylia Kowal-Bielecka et al., 2017)

Organ involvement	Pharmacological management
SSc- Raynaud's Phenomenon (RP)	• Dihydropyridine-type calcium antagonists (e.g., nifedipine) • Intravenous iloprost
Digital ulcers in SSc	• Intravenous iloprost • Phosphodiesterase-5 (PDE-5) inhibitors • Endothelin receptor antagonists (Bosentan)
SSc- Pulmonary arterial hypertension (PAH)	• Endothelin receptor antagonists (ambrisentan, bosentan and macitentan) • PDE-5 inhibitors (sildenafil, tadalafil) • Riociguat

	• Intravenous epoprostenol • Prostacyclin analogues (iloprost, treprostinil) • Selexipag

Skin and lung disease	• Conventional synthetic disease-modifying antirheumatic drugs (csDMARDS)
	  o Methotrexate
	  o Mycophenolate
	  o Cyclophosphamide
	• Biologic synthetic disease-modifying antirheumatic drugs (bDMARDS)
	  o Tocilizumab
	• Nintetanib (Ofev)

Scleroderma renal crisis (SRC)	• ACE inhibitors
SSc-related gastrointestinal disease	• Proton pump inhibitors (PPI) • Prokinetic drugs • Antibiotics • Cyclophosphamide • Mycophenolate

1.1.14 Prevalence and incidence of systemic sclerosis

SSc is a rare disease with an estimated overall prevalence of 17.6 to 23 cases per 100 000 persons, and an overall incident rate of 1.4 cases per 100 000 persons per year (Bairkdar et al., 2021; Lixian Zhong et al., 2019). In Australia, data between 1993 and 2002 estimate a mean prevalence of 21.4 cases per 100 000 persons, and a mean cumulative incidence of 1.5 cases per 100 000 persons per year (Roberts-Thomson et al., 2006). SSc predominates in females, with prevalence and incidence rates being 5 times higher in women than men (Bairkdar et al., 2021; L. Zhong, M. Pope, Y. Shen, J. J. Hernandez, & L. Wu, 2019). The typical onset of the disease is between the ages of 40 and 50 years, and it appears that both the prevalence and incidence are higher in European ancestry and native American populations (Lixian Zhong et al., 2019). The aetiology and pathogenesis of SSc is not clear, however, genetic predisposition and environmental factors, including infectious agents, chemical exposure, and vitamin D deficiency are associated with the disease (Lixian Zhong et al., 2019).

1.1.15 Exercise and physical activity in systemic sclerosis

Although physical activity is considered important for health benefits in all people (Reiner, Niermann, Jekauc, & Woll, 2013), and those with an autoimmune disease (Perandini et al., 2012), data from a large SSc national cohort (Azar et al., 2018) demonstrated that approximately 50% of people with SSc are physically inactive. Further, among those who reported to be exercising, walking was most reported (Azar et al., 2018). Another study comparing physical activities (including sport, commuting, work or school, household, and leisure) in people with SSc to their healthy counterparts, demonstrated a significant difference in time spent in all activities (1704 minutes/week vs 2614 minutes/week, respectively, $p>0.001$) (Liem et al., 2018). People with SSc experience a wide array of barriers that may impede their engagement in exercise (further discussed in section 1.5.5.1). Joint stiffness and contractures, shortness of breath, fatigue, and pain are some examples of barriers that have been identified for people with SSc to engage in exercise (Harb et al., 2020). Furthermore, the aerobic capacity, measured by Vo2 peak, was demonstrated to be significantly lower ($p=0.04$) in those with SSc (without pulmonary or cardiac involvement), compared to healthy controls (Oliveira et al., 2007). Reasons for reduced aerobic capacity is due to joint pain and limited range of motion, fatigue, and dyspnoea resulting from lung involvement (Cuomo et al., 2010; Pettersson et al., 2017). Importantly, the use of rehabilitation interventions, including exercise, is advocated in the management of people with SSc (Kowal-Bielecka et al., 2009), aiming to improve the overall functioning of the individual and to support people in managing activities of daily living. Evidence on the effectiveness of exercise will be discussed in section 1.5.6.

1.1.16 Perspectives of living with systemic sclerosis

A systematic review (Nakayama et al., 2016) including 26 qualitative studies (12 journal articles, 7 abstracts, and 7 dissertations) (Brown, Somerset, McCabe, & McHugh, 2004; Cinar et al., 2012; Ennis, Herrick, Cassidy, Griffiths, & Richards, 2013; Joachim & Acorn, 2003; Kocher, Adler, & Spichiger, 2013; Mendelson & Poole, 2007; Mendelson, Poole, & Allaire, 2013; Oksel & Gündüzoğlu, 2014; Sandqvist, Hesselstrand, Scheja, & Håkansson, 2012; Tanja Alexandra Stamm et al., 2014; T. A. Stamm et al., 2011; Suarez-Almazor, Kallen, Roundtree, & Mayes,

2007), with a total of 463 participants, described the overarching experiences and perspectives of adults living SSc (Figure 1.6). Nakayama et al., recommend a multidisciplinary approach with person-centred care that encompasses strategies to promote self-esteem and self-efficacy. It is also suggested that open communication between the health care team and patients may help to improve treatment satisfaction and overall HRQOL in people with SSc. This review revealed six major themes that summarized the experiences of those living with SSc, including; distressing appearance transformation because of radical facial changes and subsequent identity loss; palpable physical limitations due to skin hardening, painful skin ulcerations, and lack of energy; social impairment from not being to fulfill social, family, and work duties, and losing independence; navigating uncertainty with ambiguity about their illness and prognosis; and feeling alone and misunderstood while experiencing invisible suffering. In contrast, some people with SSc describe a gradual acceptance about their disease and feeling relatively optimistic by "taking a positive spin".

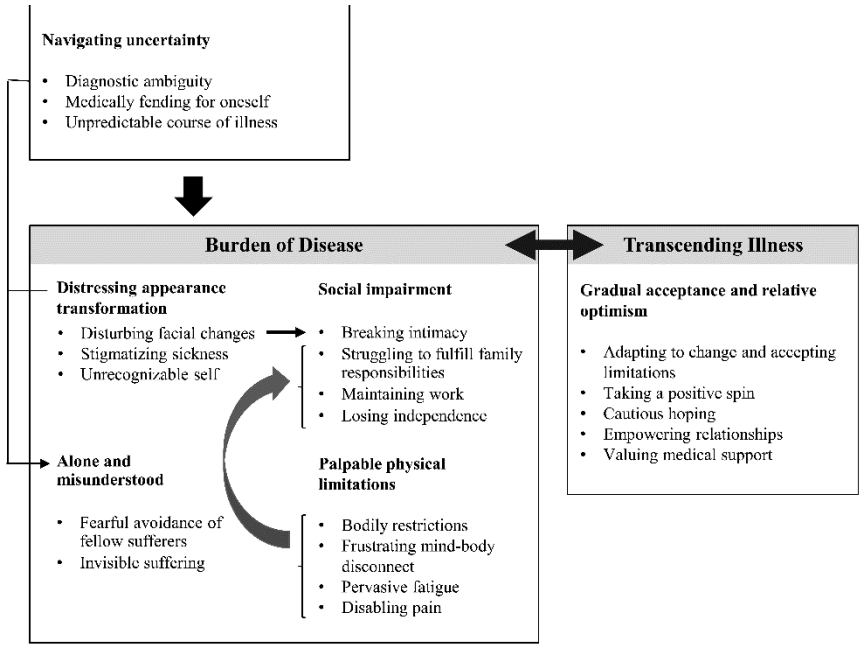

Figure 1.5 Thematic schema representing experiences and perspectives of adults living with scleroderma (Nakayama et al., 2016)

A qualitative study explored the perspectives and experiences of 30 adults living with SSc (Sumpton et al., 2017) and described similar themes to those expressed in the review. The experiences of living with SSc were described to cause restrictive pain, debilitating physical changes, and pervasive exhaustion. Having SSc was also expressed to cause a deprivation of social function, with a loss of work and career opportunity, social isolation, and a loss of intimacy with partners. There was also a sense of disintegration of identity due to the stigmatising physical changes to their appearance, invisibility of the illness, and feeling alone and powerless. People with SSc also report insecurity in their care, with ambiguity around their diagnosis and cause, and a fear of progression of their disease. On the contrary, having SSc was described to make people feel a sense of control of their own health and optimism about their treatment and monitoring, and wanting to "avoid the sick role" (Sumpton et al., 2017). To my knowledge, this is the most recent qualitative study that has explored the overall experiences of what it is like for those living with SSc.

Quantitative results derived from two questionnaires (n=260 patients, and n=47 caregivers) (Galetti, Nunzio, Brogelli, Mirisola, & Garbagnati, 2021) express similar views to those captured in qualitative interviews (Sumpton et al., 2017), highlighting that pulmonary fibrosis and hand/feet/joint involvement in those with SSc are extremely burdensome, resulting in decreased work productivity, limiting relationship and social life, and impacting psychological status and activities of daily living.

1.1.16.1 Perspectives and experiences of exercise in systemic sclerosis

A qualitative study of individual interviews (Pettersson, Nordin, Svenungsson, Alexanderson, & Boström, 2020) explored the experiences of exercise/PA in 16 Swedish adults with SSc. Exercise/PA were experienced as essential for life and health and as an effective treatment. Exercising reduced fear of deterioration and made the participants feel healthy and satisfied with themselves. However, participants also experienced disease-related barriers to exercise such as shortness of breath and pain, and they expressed a concern about their disease or symptoms worsening from exercise. Participants felt generally confident in PA/exercise and expressed that further education and support from healthcare could facilitate them in being more engaged.

Furthermore, a quantitative study (Harb et al., 2020) addressed barriers and facilitators to PA in people with SSc, and participants expressed similar disease-related barriers to the qualitative findings (Pettersson et al., 2020), such as fatigue, Raynaud's phenomenon, joint stiffness and contractures, shortness of breath, gastrointestinal problems, and difficulty gripping exercise equipment. Social and personal barriers included a lack of motivation and difficult committing to exercise, feeling embarrassed or discouraged due to physical ability, appearance, or judgement from others, fear of injury or extended recovery time, and anxiety during exercise. Other barriers included finding time available to schedule exercise into their routine, and the high costs related to exercise.

More recently, a quantitative study (Liem et al., 2021) assessed the use and satisfaction of physical therapy (PT), including exercise, over a 2-year period, and their needs and preferences regarding PT, in the form of a 37-item survey, on 204 people (median age 63 years, 81% females, 68% with limited SSc) with SSc. Survey results showed that 63% of people had used or were using PT. The most frequently reported active treatment were muscle strengthening (n=92, 72%), range of motion (n=77, 60%), and aerobic exercise (n=72, 56%). Other forms of PT included specific SSc hand (n=20, 15%) and mouth opening (n=7, 6%) exercises, and manual therapy that included massage or passive mobilisation (n=83, 65%). Regarding the needs and preferences of PT, 85% (n=161) stated that specific knowledge about SSc is necessary for physical therapist to treat patients with SSc. Furthermore, 47% (n=96) of those with SSc preferred to receive more information about PT, whereas 63% (n=128) expressed the need to continue, start, or restart PT in the future (n=128, 63%). Of these 128 participants, 44% (n=56) preferred individual continuous therapy, and 57% of the 128 participants (n=73) preferred a physical therapist close to home.

1.1.17 Evidence of non-pharmacological interventions in systemic sclerosis

Considering there are currently no curative pharmacological treatments available for people with SSc, exercise along with other non-pharmaceutical interventions is a possible way to ease the disease burden and improve physical function and HRQOL (Maddali-Bongi & Del Rosso, 2016; Maddali Bongi et al., 2009). However, there is limited information and specific guidelines about non-pharmacological care in SSc,

including exercise. This is largely due to heterogeneity in interventions, and outcomes, and because the studied samples are in many cases small and/or lacking control groups (Maddali-Bongi & Del Rosso, 2016; Willems et al., 2015).

Although small and unpowered, what we do know about the effects of 'exercise' more broadly in studies of adults *with* or *without* SSc pulmonary involvement is that those who participate in aerobic exercise and aerobic combined with resistance exercise improves exercise tolerance, cardiorespiratory fitness, walking distance, muscle strength and function, and HRQOL (Alexanderson, Bergegård, Björnådal, & Nordin, 2014; Antonioli et al., 2009; Chernev, Gustafson, & Medina-Bravo, 2009; Oliveira, Portes, Pettersson, Alexanderson, & Boström, 2017; Maddali Bongi et al., 2009; Mugii et al., 2018; Pinto et al., 2011; Rannou et al., 2017; Schouffoer et al., 2011; Shoemaker, Wilt, Dasgupta, & Oudiz, 2009). Specifically, exercise has shown positive effects in physical capacity and HRQOL in those with SSc that have no or mild lung disease, and could be considered 'safe', with no reported adverse events associated with exercise (Oliveira et al., 2017). However, it is important to understand that there are few studies specifically measuring the effect of exercise in those with moderate to severe lung disease, and thus results of exercise should be considered with caution.

A systematic review (Liem, Vliet Vlieland, Schoones, & Vries-Bouwstra, 2019) evaluating the safety and effectiveness of exercise in SSc highlights the scarcity and diversity of existing literature of exercise in SSc. However, Liem et al., describe exercise to be considered 'safe' according to the available literature, and indicate a possible positive effect, with no affirmative conclusions. This systematic review included a total of five intervention studies that specifically address global (whole-body) exercise (Alexanderson, Bergegård, et al., 2014; Mitropoulos, Gumber, Akil, & Klonizakis, 2019; Mitropoulos, Gumber, Crank, Akil, & Klonizakis, 2018; Oliveira, Dos Santos Sabbag, De Sa Pinto, Borges, & Lima, 2009; Pinto et al., 2011), and a further four studies that focused on localised (hand and mouth) exercise. Although hand and mouth exercises are important and relevant to people with SSc, these finding won't be discussed in this thesis because 1) hand and mouth exercise are *typically* more aligned with other health professionals such as hand therapists,

occupational therapists, or dentists, and 2) the focus of this thesis is on whole-body exercise.

The existing whole-body exercise intervention studies in SSc all include aerobic exercise (Alexanderson, Bergegård, et al., 2014; Mitropoulos et al., 2019; Mitropoulos et al., 2018; Oliveira et al., 2009; Pinto et al., 2011), specifically including treadmill walking, or upper/lower body cycle ergometry. Resistance exercise is also included in three of these studies (Alexanderson, Bergegard, Bjornadal, & Nordin, 2014; Mitropoulos et al., 2019; Pinto et al., 2011), specifically consisting of a combination of upper and lower body resistance-based exercises focusing on major muscle groups, with a volume of 2 to 4 sets and 8 to 12 repetitions. The intensity of the exercise programs was predominately light to moderate intensity, generally from 20 to 60 mins per session and 2 to 3 times per week, with two of these studies consisting of 30-minutes of high intensity interval training (HIIT) 2 times per week (Mitropoulos et al., 2019; Mitropoulos et al., 2018). All the exercise programs included in the existing intervention studies were supervised. Each of the existing exercise intervention studies will be described in further detail in section 1.5.7.

1.1.17.1 Outcomes measured in systemic sclerosis

The outcomes and measurement tools utilised in exercise intervention studies of SSc are exceptionally heterogenous and tend to focus on HRQOL and physiological function more broadly, using various measurement tools, as depicted in table 1.3. As such, we will outline all the outcomes included in the existing exercise intervention studies in SSc more generally, rather than discussing each outcome in detail.

Table 1.3
Common outcomes and measurement tools used in existing studies of aerobic and/or resistance exercise in SSc

Outcome	Outcome tool
Functional ability/physical capacity	• 6-minute walking test (Alexanderson, Bergegård, et al., 2014; Mitropoulos et al., 2018)
Aerobic capacity	• Submaximal arm/leg cycle ergometer test (Mitropoulos et al., 2019; Mitropoulos et al., 2018)

	• Maximal Vo2 treadmill test: Bruce protocol (Oliveira et al., 2009; Pinto et al., 2011) • Submaximal Vo2 treadmill test (Alexanderson, Bergegård, et al., 2014)
Muscle strength/function	Dynamic strength • 1 repetition maximum load bench press • 1 repetition maximum load leg press Isometric strength • Handgrip strength using a handheld dynamometer • Back pull (no further information provided) Muscle function • 30-second sit-to-stand test Balance and mobility • Timed up and go test (Pinto et al., 2011)
Muscle endurance	• Shoulder flexion: Functional index 2 (maximum number of repetitions in 60 seconds) • Hip flexion: Functional index 2 (maximum number of repetitions in 60 seconds) • (Alexanderson, Bergegård, et al., 2014)
Quality of life	• EQ-5D-5L: a generic measure of health state by considering five key dimensions of daily living: mobility, self-care, ability to undertake usual activities, pain, anxiety/depression (Mitropoulos et al., 2019; Mitropoulos et al., 2018) • WHOQOL-bref Health questionnaire (Oliveira et al., 2009) • SF36 Health questionnaire (Alexanderson, Bergegård, et al., 2014)
Persons' perception of their: • Fatigue • Raynaud's phenomenon • Global disease impact on wellbeing … during the past week	• Visual analogue scale (VAS) (0 to 100) (Alexanderson, Bergegård, et al., 2014)
Activity limitation	• Stanford Health Assessment Questionnaire (HAQ) (Alexanderson, Bergegård, et al., 2014)

1.1.18 Evidence of existing exercise intervention studies in systemic sclerosis

A prospective study of seven female adults with SSc without pulmonary involvement, and seven healthy controls took part in an 8-week, twice weekly, moderate-intensity aerobic exercise program (30 minutes of treadmill walking) and this resulted in improvements in exercise tolerance and aerobic capacity (Oliveira et al., 2009), with no reported dropouts or adverse events. Further, a single subject experimental design (Alexanderson, Bergegård, et al., 2014) included four adults with SSc (3 female and one male, two with lung fibrosis) who participated in an 8-week, three times per week, moderate to high aerobic (stationary bike) and muscular endurance exercise (hip and shoulder flexion) program. This study demonstrated varying improvements in Vo2 peak, muscular endurance, and fatigue. However, for one of the participants with pulmonary involvement, the intensive aerobic exercise was not tolerated well. Severe dyspnoea and coughing occurred at all attempts to increase loads from moderate to high intensity. Exercise was therefore ceased, and a lung screening test revealed increased bronchial obstruction and fluid in the lungs. A potential consideration that authors discuss is that mycophenolate mofetil treatment was stopped four months before entering the study, which could have contributed to this outcome (Alexanderson, Bergegård, et al., 2014).

Another intervention study (Pinto et al., 2011) involving 11 adults with SSc (8 with no evidence of pulmonary involvement) completed a 12-week combined aerobic and resistance exercise program, two times per week. Each session included 30 minutes of resistance exercises (4 sets of 8–12 maximal repetitions for the main muscle groups, 5 exercises for upper and lower extremities) followed by 20 minutes of treadmill aerobic exercise, at the corresponding heart rate of approximately 70% of VO2 peak. This combined exercise program significantly improved muscle strength, measured by a 1 repetition maximum leg press (p=0.0006), isometric hand grip strength (p=0.02), and isometric low back strength (p=0.001), though not significantly for bench press (p=0.08). This exercise program also improved muscle function, measured by timed up and go (p=0.12) and 30-second sit-to-stand test (p=0.04), though not significantly. There were no changes in Vo2 peak (pre:21.6 +-1.2; post 22.1 +-1.6 ml/kg/min), however, heart rate at rest was significantly reduced (p=0.02) after the exercise program, and in addition, the workload (speed and

gradient on the treadmill) and the time to complete the test increased, which is a positive outcome of the test. Throughout the study there were no reports of pain, muscle injury, cramps, muscle soreness, bruise, excessive exhaustion, or any apparent exercise-related adverse events. It is important to note that these studies (Alexanderson, Bergegård, et al., 2014; Oliveira et al., 2009; Pinto et al., 2011) include small sample sizes and an inherent contribution to bias (e.g., participants in these studies could have a pre-existing view in favour of exercise), and therefore, the results cannot be generalisable to all people with SSc and include a small effect size.

An RCT (Mitropoulos et al., 2018) comparing two different high intensity interval training (HIIT) exercise programs was conducted on 34 adults (65.3 ± 11.6 years old) with limited cutaneous SSc (lcSSc), who were randomly allocated into a cycling group (n=11), arm cranking (n=11), or control group (n=12). The exercise groups underwent a 12-week supervised exercise program, two time per week. Each session included a 5-minute warm up and cool down, and their allocated HIIT session which included cycling (arm or legs) for 30 seconds at 100% of their peak power output (PPO) interspersed by 30 seconds of passive recovery, for a total of 30 minutes. Compliance to the 12-weeks program was 92% and 88%, for the arm cycling and leg cycling group, respectively, with one drop out in each group. No exercise-related complications were reported. Vo2 peak significantly increased in both exercise groups ($p<0.01$, $d=1.36$); life satisfaction, measured on a 0 to 10 scale, improved significantly ($p<0.01$) in both exercise groups; Raynaud's phenomenon pain, measured on a 5-point Likert scale, reduced significantly in both exercise groups ($p< 0.05$); endothelial-dependant vasodilatation improvement was greater ($p<0.05$, $d=1.07$) in the arm cycling group compared to leg cycling and controls, and arm cycling seems to be the preferred mode of exercise for study participants compared to leg cycling ($p<0.05$). Also notably, the recommended training dose (e.g., a 12-week HIIT program, twice per week), appeared to be sufficient and tolerable for this population.

A subsequent RCT (Mitropoulos et al., 2019) using the former HIIT arm cycling protocol (Mitropoulos et al., 2018) and resistance exercise comprising five upper-body exercises (chest press, arms lateral raise, biceps curl, triceps extension and handgrip dynamometer) further explored the effectiveness microvascular function in

people with lcSSc. This study included 32 participants with limited SSc who were randomly into 2 groups (exercise and control group). The exercise program was performed two times per week for 12 weeks. The exercise group had significant improvements in the time to peak endothelial-dependent reactivity (91 ± 42s, d = 1.06, p = 0.007), and endothelial-independent function (3.16 ± 2, d = 1.17, p = 0.005) compared to the control group (Note: ability of the upper body extremity blood vessels (hands) to dilate). This study suggests the effectiveness of a combined upper body aerobic and resistance exercise program in improving vasodilation in people with lcSSc, an important finding in SSc due to the diseases' pathogenesis resulting in vascular damage. Overall, the available evidence on the effectiveness of exercise in SSc suggests that exercise has the potential to improve aerobic capacity, exercise tolerance, muscular endurance, fatigue, pain, and life satisfaction in people with SSc.

1.6. Justification and aims of this thesis

Perhaps by virtue of their rarity, SSc and SLE are underexplored diseases. There is a reasonable case for exercise as a sensible intervention to assist in the management of these chronic diseases, particularly through the anti-inflammatory response, beneficial effects, and the prevention of sequelae due to physical deconditioning. However, additional academically rigorous intervention studies, with more participants, are required to improve our certainty in the safety and effectiveness of exercise in people with SLE and SSc. Furthermore, quantitative outcomes alone can be influenced by the episodic nature and unpredictability of the diseases, thus, the inclusion of qualitative methods within exercise intervention studies will complement our understanding of the participants multifaceted response to exercise.

The original rationale for this thesis was to determine an appropriate dosage of exercise (frequency, intensity, timing and type) best suited to achieve sustainable and positive effects on key outcomes in people with SS or SLE, and concurrently identify any risks or adverse events associated with the use of exercise. However, due to barriers encountered during the period of candidature, including the COVID-19 pandemic and subsequent lockdowns, amendments to the aims and planned studies were made accordingly. As such, the overarching aim of this thesis has been adapted to update and increase the existing knowledge of exercise safety and effectiveness in SLE and SSc (study 1 and 2), explore and describe the perspectives

and experiences of exercise in this population that can inform future exercise intervention studies (study 3 and 4), and introduce a novel exercise intervention suited to the episodic nature of the disease and unpredictable environment at the time of study implementation (study 5). The originally planned exercise intervention protocol is included as an appendix (appendix D) in this thesis to demonstrate the high-level and rigorous exercise intervention study that was originally considered.

The aims of the five included studies are:

1. To evaluate the safety and effectiveness of structured exercise as adjunctive therapy for adults with systemic lupus erythematosus.
2. To evaluate the efficacy and safety of exercise and physical therapies in people with systemic sclerosis.
3. To explore rheumatologists' and rheumatology nurses' perspectives and use of exercise interventions for adults with systemic lupus erythematosus or systemic sclerosis.
4. To explore and describe the experiences of exercise in adults with systemic sclerosis.
5. To explore the feasibility and effectiveness of telehealth-supervised exercise for people with systemic lupus erythematous.

CHAPTER 2: STUDY 1 AND 2 - SYSTEMATIC REVIEWS

2.1. Overview of the chapter

In lieu of a literature review, this chapter comprises two manuscripts published in the Cochrane Database of Systemic Reviews. The first publication (study 1) is a systematic review of exercise as an adjunctive therapy in systemic lupus erythematosus. The second publication (study 2) is a protocol for a systematic review of exercise and physical therapy in systemic sclerosis. Study 2 involves collaboration with international authors from the MD Anderson Centre and includes a broader aspect of the thesis topic, with the addition of physical therapies. The full review is currently in progress, with completion expected following the period of candidature.

2.2. Study 1: Exercise as adjunctive therapy in systemic lupus erythematosus

The review was submitted for peer review to the *Cochrane Database of Systematic Reviews* on the 31st of July 2022 and is currently undergoing final editorial proofs prior to publication. This manuscript is presented as prepared for publication.

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Exercise as adjunctive therapy for systemic lupus erythematosus

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Abstract

Background

Systemic lupus erythematosus (SLE) is a rare, chronic autoimmune inflammatory disease with a prevalence varying from 4.3 to 150 people in 100,000, or approximately five million people worldwide. Systemic manifestations frequently include internal organ involvement, a characteristic malar rash on the face, pain in joints and muscles and profound fatigue. Exercise is purported to be beneficial for people with SLE. For this review, we focused on studies that examined all types of structured exercise as an adjunctive therapy in the management of SLE.

Objectives

To evaluate the benefits and harms of structured exercise as adjunctive therapy for adults with SLE compared with usual pharmacological care, usual pharmacological care plus placebo and usual pharmacological care plus non-pharmacological care.

Search methods

We used standard, extensive Cochrane search methods. The latest search date was 30 March 2022.

Selection criteria

We included randomised controlled trials (RCTs) of exercise as an adjunct to usual pharmacological treatment in SLE compared with placebo, usual pharmacological care alone and another non-pharmacological treatment. Major outcomes were fatigue, functional capacity, disease activity, quality of life, pain, serious adverse events, and withdrawals due to any reason, including any adverse events.

Data collection and analysis

We used standard Cochrane methods. Our major outcomes were 1. fatigue, 2. functional capacity, 3. disease activity, 4. quality of life, 5. pain, 6. serious adverse events, and 7. withdrawals due to any reason. Our minor outcomes were 8. responder rate, 9. aerobic fitness, 10. depression, and 11. anxiety. We used GRADE to assess certainty of evidence. The primary comparison was exercise compared with placebo.

Main results

We included 13 studies (540 participants) in this review. Studies compared exercise as an adjunct to usual pharmacological care (antimalarials, immunosuppressants, and oral glucocorticoids) with usual pharmacological care plus placebo (one study); usual

pharmacological care (six studies); and another non-pharmacological treatment such as relaxation therapy (seven studies). Most studies had selection bias, and all studies had performance and detection bias. We downgraded the evidence for all comparisons because of a high risk of bias and imprecision.

Exercise plus usual pharmacological care versus placebo plus usual pharmacological care

Evidence from a single small study (17 participants) that compared whole body vibration exercise to whole body placebo vibration exercise (vibrations switched off) indicated that exercise may have little to no effect on fatigue, functional capacity, and pain (low-certainty evidence). We are uncertain whether exercise results in fewer or more withdrawals (very low-certainty evidence). The study did not report disease activity, quality of life, and serious adverse events.

The study measured fatigue using the self-reported Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue), scale 0 to 52; lower score means less fatigue. People who did not exercise rated their fatigue at 38 points and those who did exercise rated their fatigue at 33 points (mean difference (MD) 5 points lower, 95% confidence interval (CI) 13.29 lower to 3.29 higher).

The study measured functional capacity using the self-reported 36-item Short Form health questionnaire (SF-36) Physical Function domain, scale 0 to 100; higher score means better function. People who did not exercise rated their functional capacity at 70 points and those who did exercise rated their functional capacity at 67.5 points (MD 2.5 points lower, 95% CI 23.78 lower to 18.78 higher).

The study measured pain using the SF-36 Pain domain, scale 0 to 100; lower scores mean less pain. People who did not exercise rated their pain at 43 points and those who did exercise rated their pain at 34 points (MD 9 points lower, 95% CI 28.88 lower to 10.88 higher).

More participants from the exercise group (3/11, 27%) withdrew from the study than the placebo group (1/10, 10%) (risk ratio (RR) 2.73, 95% CI 0.34 to 22.16).

Exercise plus usual pharmacological care versus usual pharmacological care alone

The addition of exercise to usual pharmacological care may have little to no effect on fatigue, functional capacity, and disease activity (low-certainty evidence). We are uncertain whether the addition of exercise improves pain (very low-certainty evidence), or results in fewer or more withdrawals (very low-certainty evidence). Serious adverse events and quality of life were not reported.

Exercise plus usual care versus another non-pharmacological intervention such as receiving information about the disease or relaxation therapy

Compared with education or relaxation therapy, exercise may reduce fatigue slightly (low-certainty evidence), may improve functional capacity (low-certainty evidence), probably results in little to no difference in disease activity (moderate-certainty evidence), and may result in little to no difference in pain (low-certainty evidence). We are uncertain whether exercise results in fewer or more withdrawals (very low-certainty evidence). Quality of life and serious adverse events were not reported.

Authors' conclusions

Due to low- to very low-certainty evidence, we are not confident on the benefits of exercise on fatigue, functional capacity, disease activity, and pain, compared with placebo, usual care, or advice and relaxation therapy. Harms data were not well reported.

Plain language summary

What are the benefits and risks of exercise for people with systemic lupus erythematosus?

Key messages

Exercise in addition to usual care may have little benefit on fatigue, functional capacity, and pain in people with systemic lupus erythematosus (SLE).

No studies reported side effects during exercise. However, we have low confidence in the overall evidence.

What is systemic lupus erythematosus?

SLE (or 'lupus') is a disease in which the body's immune (defence) system mistakenly attacks healthy tissue in many parts of the body. It is a long-term disease (one that lasts longer than six weeks and is usually life-long). Often, SLE causes pain in joints and muscles, and extreme tiredness. Symptoms can improve temporarily, or worsen suddenly (flares).

How is systemic lupus erythematosus treated?

Management or 'usual care' in SLE may include, but not limited to, treatment with medicines such as disease modifying antirheumatic drugs (DMARDs) or non-steroidal anti-inflammatory drugs (NSAIDs). It may also include treatments that do not medicines such as sun avoidance, supplementation (i.e. vitamin D), education about the disease and other illnesses (i.e. hypertension), and physical activity or exercise. Regular exercise training could serve as an adjunct treatment for people with SLE.

What did we want to find out?

We wanted to find out if exercise in addition to usual medicines improved fatigue, functional capacity (ability to perform normal everyday tasks), quality of life, pain, and disease activity, and caused no harm.

What did we do?

We searched for studies that investigated structured exercise programmes such as aerobic exercise, resistance, stretching or combinations of these (including a specific dosage of exercise, e.g. frequency, intensity, time, type) in addition to usual care compared with placebo (pretend medicine), usual care alone, or another non-medicine intervention (e.g. relaxation therapy) in people with SLE.

We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 13 studies that involved 540 participants with SLE that included a structured exercise programme that lasted up to 12 weeks in duration. Usual care included DMARDs and glucocorticoids.

The main results of the review are:

1. Whole body vibration exercise plus usual care may result in little to no effect on fatigue, functional capacity, and pain when compared to whole body placebo vibration exercise (vibration switched off) plus usual care (1 study, 17 participants).

The study measured fatigue using the Functional Assessment of Chronic Illness Therapy – Fatigue domain (FACIT-Fatigue) (0 to 52 scale, where 0 means no fatigue) and at 12 weeks fatigue improved by 5 points in the exercise group compared to the group that did not exercise:

– People who exercised rated their fatigue at 33 points.

– People who did not exercise rated their fatigue at 38 points.

The study measured functional capacity using the Functional Capacity domain in the 36-item Short Form health questionnaire (SF-36) (0 to 100 scale, where 100 means best function) and at 12 weeks function worsened by 2.5 points in the exercise group compared to the group that did not exercise:

– People who exercised rated their functional capacity at 67.5 points.

– People who did not exercise rated their functional capacity at 70 points.

The study measured pain on the Pain domain of the SF-36 (0 to 100 scale, where 0 means no pain) and at 12 weeks pain improved by 9 points in the exercise group compared to the group that did not exercise:

– People who exercised rated their pain at 34 points.

– People who did not exercise rated their pain at 43 points.

More people from the exercise group (27%) withdrew from the study compared those in the placebo group (10%).

The study did not measure disease activity or quality of life.

2. Exercise plus usual care may result in little to no effect on fatigue, functional capacity, and disease activity when compared to usual care alone. And we are uncertain whether exercise improves pain when compared to usual care alone.

3. Exercise plus usual care may reduce fatigue, improve functional capacity, and probably results in little to no difference in disease activity, and may result in little to no difference in pain when compared to another non-medicine intervention plus usual care.

No studies reported any serious side effects that were related to the exercise programme during or following the intervention.

What are the limitations of the evidence?

We have little confidence in the evidence because the number of studies was very small, and it is possible that people in the studies were aware of which treatment they were getting.

Most studies assessed the effectiveness of exercise for a short duration (12 weeks or less) and it is unclear if people would adhere to exercise over time. More rigorous studies of structured exercise over a period of time longer than 12 weeks are needed to improve our confidence in the benefits and safety of exercise in people with SLE.

How up to date is this evidence?

The evidence is up-to-date to 30 March 2022.

Summary of findings

Summary of findings 1

Summary of findings table - Exercise plus usual pharmacological care compared to placebo plus usual pharmacological care for systemic lupus erythematosus

Exercise plus usual pharmacological care compared to placebo plus usual pharmacological care for systemic lupus erythematosus

Patient or population: systemic lupus erythematosus
Setting: community
Intervention: exercise plus usual pharmacological care
Comparison: placebo plus usual pharmacological care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo plus usual pharmacological care	Risk with exercise plus usual pharmacological care				
Fatigue (FACIT-Fatigue, score 0-52, lower scores indicate less fatigue) follow-up: 12 weeks	The mean fatigue (FACIT-Fatigue, score 0-52, lower scores indicate less fatigue) was **38** points	MD **5 points lower** (13.29 lower to 3.29 higher)	-	17 (1 RCT)	⨁⨁⨀⨀ Low[b,c]	Exercise may have little to no effect on fatigue.
Functional capacity (SF-36 Function Capacity domain, score 0-100, higher scores indicate better functional capacity) follow-up: 12 weeks	The mean functional capacity (SF-36 Function Capacity domain, score 0-100, higher scores indicate better functional capacity) was **70** points	MD **2.5 points lower** (23.78 lower to 18.78 higher)	-	17 (1 RCT)	⨁⨁⨀⨀ Low[b,c]	Exercise may have little to no effect on functional capacity.
Pain (SF-36 Pain domain, score 0-100, lower scores indicate less pain) follow-up: 12 weeks	The mean pain (SF-36 Pain domain, score 0-100, lower scores indicate less pain) was **43** points	MD **9 points lower** (28.88 lower to 10.88 higher)	-	17 (1 RCT)	⨁⨁⨀⨀ Low[b,c]	Exercise may have little to no effect on pain.
Disease activity - not measured	-	-	-	-	-	This outcome was measured at baseline, but it was not reported at end of intervention.
Quality of life - not measured	-	-	-	-	-	This outcome was measured, but the Mental Component Summary score was not reported.
Serious adverse events - not reported	-	-	-	-	-	No serious adverse events were reported.
Withdrawals due to any reason follow-up: 12 weeks	100 per 1000	**273 per 1000** (34 to 1000)	**RR 2.73** (0.34 to 22.16)	21 (1 RCT)	⨁⨀⨀⨀ Very low[b,c]	We are uncertain whether exercise results in fewer or more withdrawals.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_432987629440706015.

[a] Usual pharmacological care consisted of immunosuppressants and glucocorticoids.
[b] Downgraded one level due to risk of detection and potentially selection bias.
[c] Downgraded one level due to small number of participants from a single trial.

Summary of findings 2

Summary of findings table - Exercise plus usual pharmacological care compared to usual pharmacological care alone for systemic lupus erythematosus

Exercise plus usual pharmacological care compared to usual pharmacological care alone for systemic lupus erythematosus

Patient or population: systemic lupus erythematosus
Setting: community
Intervention: exercise plus usual pharmacological care
Comparison: usual pharmacological care alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual pharmacological care alone	Risk with exercise plus usual pharmacological care				
Fatigue (Fatigue Severity Scale, score 1-7, lower score indicates less fatigue) follow-up: 12 weeks	The mean fatigue (Fatigue Severity Scale, score 1-7, lower score indicates less fatigue) was **5.4** points	MD **0.6 points lower** (1.4 lower to 0.2 higher)	-	104 (2 RCTs)	⨁⨁⊖⊖ Low[a,b]	Exercise plus usual pharmacological care may have little to no effect on fatigue.[c]
Functional capacity (SF-36 Physical Function domain, score 0-100, higher scores indicate better functional capacity) follow-up: 12 weeks	The mean functional capacity (SF-36 Physical Function domain, score 0-100, higher scores indicate better functional capacity) was **60** points	MD **5.4 points higher** (5.97 lower to 16.75 higher)	-	96 (2 RCTs)	⨁⨁⊖⊖ Low[a,b]	Exercise plus usual pharmacological care may have little to no effect on functional capacity.
Disease activity (SLEDAI scale, scores 0-105, lower scores indicate less disease activity) follow-up: 12 weeks	The mean disease activity (SLEDAI scale, scores 0-105, lower scores indicate less disease activity) was **0.5** points	MD **0.26 points lower** (3.69 lower to 3.17 higher)	-	100 (2 RCTs)	⨁⨁⊖⊖ Low[a,b]	Exercise plus usual pharmacological care may have little to no effect on disease activity.
Quality of life - not reported	-	-	-	-	-	This outcome was measured, but the Mental Component Summary score was not reported.
Pain (SF-36 Bodily Pain domain, score 0-100, lower scores indicate less pain) follow-up: 12 weeks	The mean pain (SF-36 Bodily Pain domain, score 0-100, lower scores indicate less pain) was **38** points	MD **16 points higher** (0.18 lower to 32.18 higher)	-	31 (1 RCT)	⨁⊖⊖⊖ Very low[a,b]	We are uncertain whether exercise improves pain.
Serious adverse events - not reported	-	-	-	-	-	No serious adverse events were reported.
Withdrawals for any reason follow-up: 12 weeks	175 per 1000	**161 per 1000** (93 to 280)	**RR 0.92** (0.53 to 1.60)	235 (6 RCTs)	⨁⊖⊖⊖ Very low[a,b]	We are uncertain whether exercise results in fewer or more withdrawals.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_433149155812397472.

[a] Downgraded one level for risk of detection bias in unblinded trials with self-reported outcomes.
[b] Downgraded one level due to low participant numbers and the confidence intervals included a large effect and no effect.
[c] Usual pharmacological care consists of immunosuppressants, steroids and antimalarials

Summary of findings 3

Summary of findings table - Exercise plus usual pharmacological care compared to another intervention (education, joint aids, or relaxation) plus usual pharmacological care for systemic lupus erythematosus

Exercise plus usual pharmacological care compared to another intervention (education, joint aids, or relaxation) plus usual pharmacological care for systemic lupus erythematosus

Patient or population: systemic lupus erythematosus
Setting: community
Intervention: Exercise plus usual pharmacological care
Comparison: another intervention (education, joint aids, or relaxation) plus usual pharmacological care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with another intervention (education, joint aids, or relaxation) plus usual pharmacological care	Risk with Exercise plus usual pharmacological care				
Fatigue (Fatigue Severity Scale, scores 0-7, lower scores indicate less fatigue) follow-up: 12 weeks	The mean fatigue (Fatigue Severity Scale, scores 0-7, lower scores indicate less fatigue) was **5.3** points	MD **0.51 points lower** (0.88 lower to 0.14 lower)	-	119 (2 RCTs)	⊕⊕⊖⊖ Low[a,b]	Exercise plus usual pharmacological care may reduce fatigue slightly.
Functional capacity (SF-36 Physical Function domain, score 0-100, higher scores indicate better functional capacity) follow-up: 12 weeks	The mean functional capacity (SF-36 Physical Function domain, score 0-100, higher scores indicate better functional capacity) was **41.4** points	MD **13.2 points higher** (6.17 higher to 20.22 higher)	-	182 (3 RCTs)	⊕⊕⊖⊖ Low[a,c]	Exercise plus usual pharmacological care may increase functional capacity.
Disease activity (SLEDAI scale, score 0-105, lower scores indicate less disease activity) follow-up: 12 weeks	The mean disease activity (SLEDAI scale, score 0-105, lower scores indicate less disease activity) was **1.2** points	MD **0.034 points higher** (0.476 lower to 0.544 higher)	-	184 (4 RCTs)	⊕⊕⊕⊖ Moderate[a]	Exercise plus usual pharmacological care probably results in little to no difference in disease activity.SMD is 0.02 [-0.28 , 0.32] . Baseline control group SD for converting SMD to MD was 1.7 and taken from Abrahao 2016.
Pain (VAS Pain scale, score 0-10, lower scores indicates less pain) follow-up: 12 weeks	The mean pain (VAS Pain scale, score 0-10, lower scores indicates less pain) was **4.97** points	MD **1.59 points lower** (2.46 lower to 0.71 lower)	-	121 (2 RCTs)	⊕⊕⊖⊖ Low[a,c]	Exercise plus usual pharmacological care may result in little to no difference in pain.
Withdrawals for any reason follow-up: 12 weeks	49 per 1000	**43 per 1000** (6 to 289)	**RR 0.89** (0.13 to 5.94)	317 (7 RCTs)	⊕⊖⊖⊖ Very low[a,d]	We are uncertain whether exercise results in fewer or more withdrawals.
Serious adverse events - not reported	-	-	-	-	-	No serious adverse events were reported.
Quality of life - not reported	-	-	-	-	-	This outcome was measured, but the Mental Component Summary score was not reported.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_433149459092821699.

[a] Downgraded one level due to risk of detection bias in unblinded trials with self-reported outcomes.
[b] Downgraded one level due to low participant numbers and the confidence intervals included a large effect and no effect.

[c] Downgraded one level due to possible imprecision. The confidence intervals included a small effect and a large effect.
[d] Downgraded two levels due to very few events.

Background

Description of the condition

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease with a wide spectrum of clinical and serological manifestations caused by autoantibody production, complement activation, and immune complex deposition. The pathogenesis of SLE is characterised by the formation of autoantibodies and a breakdown in the immune milieu of the body leading to an unregulated inflammatory response and consequent internal organ and tissue damage (Fanouriakis 2019). Systemic manifestations frequently include internal organ involvement, a characteristic malar rash on the face, sicca symptoms, and profound fatigue. People with SLE experience multiple, varied symptoms and laboratory abnormalities that occur in different combinations, at different time points. SLE is heterogeneous, meaning that symptoms vary widely from one person to the next, for example, one person may develop a rash, while another may have high blood pressure, joint pain, and anaemia. Although SLE constitutes the most common form of lupus, which is the broad term to describe the disease, there are other forms of lupus which include discoid lupus erythematosus (DLE) or cutaneous lupus erythematosus (CLE), characterised by mostly cutaneous involvement (Fanouriakis 2019).

SLE is a rare disease with an incidence of approximately 1 to 10 per 100,000 person-years and a prevalence varying from 4.3 to 150 people in 100,000 (Nikpour 2014), or approximately five million people worldwide. The prevalence in Australia varies between 19.3 and 39 people in 100,000 for non-Aboriginal Australians and 52.0 to 92.8 people in 100,000 for Aboriginal Australians (Bossingham 2003; Segasothy 2001). There is a higher SLE incidence in Asian (especially Chinese), African, and Hispanic populations. These last two populations are especially associated with high disease activity and damage. SLE can affect both men and women of any age, with 90% being female. It predominantly affects young women and middle-aged women, between the ages of 15 and 45 years. By age, the female:male ratio is 3:1 before puberty, 10 to 15:1 during childbearing years, with a slight decrease again after menopause at 8:1 (Askanase 2012).

SLE has a severe and pervasive effect on people living with the disease, with people reporting the disease to cause debilitating fatigue; mental deterioration; pervasive pain; disrupted identity from feeling of hopelessness, guilt and punishment, or feeling as though they are a burden (Sutanto 2013). In contrast, some people have also reported the disease to have increased their resilience, empowerment, and optimism. Debilitating pain, musculoskeletal manifestations, fatigue, and renal and cutaneous problems were reported to limit people's ability to work and participate in family and social activities (Sutanto 2013).

People with SLE are at higher risk of developing comorbidities such as osteoporosis (Gu 2020) and atherosclerotic cardiovascular disease (CVD) (Manzi 1997; Schoenfeld 2013). CVD risk amongst people with SLE compared to the general population is at least doubled. While older people with SLE appear to have the highest absolute risks of CVD, young women have alarmingly high relative risks, given the rarity of CVD in the comparable general population (Schoenfeld 2013). People with SLE are also less physically active than people without SLE (Margiotta 2018), with 60% of people not meeting sufficient physical activity

guidelines according to the World Health Organization (WHO) recommendations. Subsequent inactivity may add to the heightened risk of secondary complications, as well as lead to physical deconditioning and poor health-related quality of life.

Management or 'usual care' in SLE may include, but is not limited to, the following pharmacological treatments; conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as hydroxychloroquine, prednisolone or glucocorticoids, mycophenolate mofetil, methotrexate, azathioprine, cyclophosphamide, or a combination of these; biological disease-modifying antirheumatic drugs (bDMARDs) such as rituximab or belimumab; non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen or celecoxib(Fanouriakis 2019). It may also include non-pharmacological measures such as sun avoidance; supplementation (i.e. vitamin D); education about the disease or comorbidities (i.e. hypertension), or both; and physical activity or exercise (Fanouriakis 2019). Regular exercise training could serve as an adjunct treatment for people with SLE to reduce the risk of developing secondary complications, help manage symptoms related to the disease, and improve key clinical outcomes such as quality of life and fatigue.

Description of the intervention

The treatment for SLE depends on the organs and systems involved as well as disease severity. It can include topical applications for skin problems, NSAIDs for musculoskeletal diseases, and immunosuppression. Common medications to treat the inflammatory response associated with subsequent widespread organ involvement include corticosteroids, immune suppressants, hydroxychloroquine, and biological agents (Ali 2018).

Exercise is generally used as an adjunct to pharmacological management of SLE (Yorganci 2020). For this review, we focused on studies that examined all types of structured exercise as an adjunctive therapy in the management of SLE. Evidence suggests that exercise interventions are safe, with no change in disease activity or adverse events, and effective in managing key clinical outcomes such as fatigue (Del Pino-Sedeno 2016; O'Dwyer 2017; Wu 2017; Yuen 2014). According to the American College of Sports Medicine (ACSM), exercise is defined as a type of physical activity consisting of planned, structured, and repetitive bodily movement done to improve or maintain (or both) one or more components of physical fitness (Pescatello 2014).

The three main types of exercise include aerobic, resistance, and range of movement. Aerobic exercise relies primarily on the cardiovascular system and represents a broad range of physical activities such as walking, jogging, cycling, and dancing (Pescatello 2014). Resistance exercise can be provided via specifically designed equipment such as resistance bands, hand weights, and machines, or achieved via functional means such as stair climbing, rising from a chair, and lifting groceries to induce muscular contraction, which builds the strength, anaerobic endurance, and size of skeletal muscles (Pescatello 2014). Range of motion exercise refers to activity aimed to improve movement of a specific joint, for example, yoga, tai chi, or stretching (Pescatello 2014). Exercise intensity may be high (70% to less than 90% of heart rate maximum (HR_{max}) or a rating of perceived exertion (RPE) value of 5/10 to 7/10), moderate (55% to less than 70% HR_{max} or an RPE value of 3/10 to 4/10), or light (40% to less than 55% HR_{max} OR an RPE value of 1/10 to 2/10).

The exercise intervention may be supervised by allied health practitioners, medical health practitioners, or other exercise professionals, and can be individually supervised or supervised in a group setting, or it can be completely unsupervised and performed independently. Unsupervised exercise is usually reported as home-based exercise, but can also include exercising in a park or in a gym without supervision. While people with SLE are advised to avoid sun exposure, which may limit their interest or raise concern about

exercise, it is important to know that not all exercise is performed outdoors. The exercise environment may be water-based (indoors or outdoors), land-based (indoors or outdoors), in a gym or clinic, outdoors at a park or along a walking or bike track, or in ones' home (Pescatello 2014).

How the intervention might work

Regular exercise training may lead to anti-inflammatory benefits in chronic diseases with systemic low-grade inflammation (i.e. type 2 diabetes) by reducing inflammatory markers (Perandini 2012), and is regarded as a valuable self-care intervention for this population. Given the potential role of inflammation in the aetiology and clinical symptoms of SLE, including pain, redness, and swelling, if exercise training is able to alleviate the inflammatory process, it could be a helpful intervention in treating the symptoms related to inflammation in SLE (Perandini 2012). Exercise is beneficial in reducing fatigue (Del Pino-Sedeno 2016; Neill 2006; Wu 2017; Yuen 2014), improving symptoms of depression (Da Hora 2019; Kelley 2015), and improving quality of life (Da Hora 2019; Sieczkowskaa 2020). The benefits of exercise are similar in other rheumatic, inflammatory conditions with improvements in quality of life (Sieczkowskaa 2020), reduced inflammation (Metsios 2020; Perandini 2012), and reduced joint damage and symptoms (Sveaas 2017). Importantly, it is suggested that exercise does not deleteriously affect disease activity (O'Dwyer 2017), and positively influences fatigue (O'Dwyer 2017; Wu 2017; Yuen 2014), which is a significant concern for most people with SLE. As such, exercise could serve as an adjunct non-pharmaceutical therapy for people with SLE to assist in the management of disease-related symptoms such as fatigue and pain, as well as preventing comorbidities such as osteoporosis and CVD.

Why it is important to do this review

To date, there are currently three systematic reviews that assess the safety and effectiveness of exercise in adults with SLE, two of which were published in 2017 and one in 2021 (O'Dwyer 2017; Wu 2017; Lu 2021).

One review found exercise improved depression and fatigue and not alter disease activity in adults with SLE compared to control groups (O'Dwyer 2017). Meta-analyses of seven studies found that disease activity was unchanged following exercise interventions (mean difference (MD) 0.01, 95% confidence interval (CI) −0.54 to 0.56), fatigue decreased in the exercise intervention group compared to controls (MD −0.52, 95% CI −0.91 to −0.13), and depression scores decreased in the exercise groups compared to the controls (standardised mean difference (SMD) −0.40 standard deviations (SD), 95% CI −0.71 to −0.09) (Abrahão 2016; Boström 2016; Carvalho 2005; Dos Reis-Neto 2013; Miossi 2012; Robb-Nicholson 1989; Tench 2003). Most of these studies were at risk of selection and reporting bias.

The review by Wu 2017 found that a 12-week supervised aerobic exercise programme reduced fatigue for people with SLE with mild disease activity. Meta-analysis of three trials showed that aerobic exercise training decreased fatigue severity compared to controls (MD −0.52, 95% CI −0.91 to −0.13), and had a positive effect on the 36-item Short Form (SF-36) Vitality subscale (MD 14.98, 95% CI 7.45 to 22.52) (Carvalho 2005; Ramsey-Goldman 2000; Tench 2003). However, the quality of evidence assessed using PEDro was downgraded to fair (Tench 2003) or poor (Ramsey-Goldman 2000).

The review by Lu 2021 found that exercise improved some aspects of quality of life in people with SLE. Meta-analysis of five RCTs (Abrahão 2016; Bostrom 2016; Keramiotou 2020; Lopes-Souza 2021; Tench 2003) showed a positive effect of exercise on the physical health

and function aspect (SF-36 Physical Function and LupusQOL Physical Health) of health-related quality of life amongst participants with SLE (Hedges' g: 0.468, 95% CI 0.206 to 0.730; P < 0.001). Heterogeneity between studies was low (I^2 = 19.2%; P = 0.292).

These three reviews found that exercise is effective in managing concerning symptoms of SLE including fatigue, depression, and some aspects of qualify of life. However, more studies, with more participants are needed to strengthen these results, and the optimal exercise protocol is yet to be determined. Therefore, it is important to perform this systematic review to capture any additional trials, update the existing evidence, and identify the safety and effectiveness of exercise in adults with SLE. We conducted the review according to the guidelines recommended by the Cochrane Musculoskeletal Editorial Board (Ghogomu 2014).

Objectives

To evaluate the benefits and harms of structured exercise as adjunctive therapy for adults with SLE compared with usual pharmacological care, usual pharmacological care plus placebo and usual pharmacological care plus non-pharmacological care.

Methods

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-RCTs. We included parallel and cross-over trials, and cluster-RCTs, using either non-intervention or active controls. There were no language restrictions. We included abstracts and studies with unpublished data.

Types of participants

We included trials of adults (aged 18 years or greater), diagnosed with SLE according to the study author's report; American College of Rheumatology (ACR) criteria or European League Against Rheumatism (EULAR) criteria (or both), with systemic disease involving at least two body sites or organ systems. We excluded trials of participants with SLE and another diagnosed condition in different groups (i.e. group one = people with SLE, group 2 = people with rheumatoid arthritis) if the effect of the intervention could not be determined on the participants with SLE alone. We included intervention trials without regard to race, sex, or disease duration of participants.

Types of interventions

Structured exercise

Adjunct to usual care, an intervention consisting of structured exercise performed at any duration, frequency, intensity, and of any type was included. The type of exercise intervention included either an individual type of exercise or a combination of various types (e.g. resistance training alone or resistance training combined with aerobic training). Exercise interventions were structured, recurring, and prescriptions included specific dosage information (i.e. frequency, intensity, timing, type). Aerobic exercise could include, but was

not limited to, walking (treadmill or free), cycling (stationary or free), swimming, or aerobics classes. Range of movement exercise could include Pilates; yoga; tai chi; or active, ballistic, and static stretching. Other forms of exercise such as sports, games, and recreational activities such as dancing, lawn bowls, and Wii fit could be included. Exercise environments could include water- or, land-based exercise, indoor or outdoor settings, home-based or community led, supervised or unsupervised, face-to-face or telehealth.

Usual pharmacological care

Usual pharmacological care could include, but not limited to, the following standard pharmacological drug treatments; antimalarials such as hydroxychloroquine, NSAIDs, glucocorticoids such as prednisone, immunosuppressives such as mycophenolate, and biologicals such as belimumab or rituximab. Other non-pharmacological measures may also have included sun avoidance, commonly prescribed supplementation (i.e. vitamin D), and education about the disease or managing comorbidities such as hypertension, for example (Fanouriakis 2019).

Comparisons

We included any RCT that evaluated the effect of exercise as an adjunct therapy to usual care, compared to:

1. usual pharmacological care plus placebo;
2. usual pharmacological care alone;
3. usual pharmacological care plus another intervention that was non-pharmacological (e.g. relaxation, counselling, education, support group).

We excluded studies if the exercise intervention was not structured (i.e. the exercise intervention did not have a dosage for frequency, intensity, or duration of exercise) or if the exercise intervention was an acute or single bout of exercise (i.e. one individual session of exercise or one exercise test).

Types of outcome measures

Studies were not excluded on the basis of outcome reporting.

Major outcomes

1. **Fatigue**: Mean or mean change in fatigue assessed by Fatigue Severity Scale (FSS), Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) (FACIT group; Lai 2011), or other relevant fatigue scales such as Profile Of Moods State (POMS).
2. **Functional capacity:** Mean or mean change in functional capacity measured by the Physical Component Score (PCS) of the 36-item Short-Form (SF-36), or Physical Function subscale of the SF-36, or other physical function or disability scales.
3. **Disease activity:** Mean or mean change in SLE scores on validated disease activity indices such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Systemic Lupus Erythematosus Disease Activity Index SELENA Modification (SELENA-SLEDAI), modified SELENA-SLEDAI Flare Index (SFI) (Petri 1999; Petri 2005); British Isles Lupus Assessment Group index (BILAG) (Hay 1993; Isenberg 2000); or other similar validated indices.
4. **Quality of life:** Mean or mean change in quality of life assessed by the Mental Component Score (MCS) of the SF-36, or similar assessments such as Lupus Quality Of Life (LupusQOL) (Doward 2009; McElhone 2007).

5. **Pain:** Mean or mean change in pain measured by the Visual Analogue Scale (VAS) for pain, the numerical rating scale (NRS) for pain, or the Bodily Pain subscale of the SF-36.
6. **Serious adverse events** (SAEs): including number of SAEs, or number of people with one or more SAE.
7. **Withdrawals due to any reason**

Minor outcomes

1. **Composite responder rate**, as defined with the Systemic lupus erythematosus Responder Index (SRI), where a responder is defined as a person with
    a. a 4-point or greater reduction in SELENA-SLEDAI score;
    b. no new BILAG A or no more than one new BILAG B domain score; and
    c. no deterioration from baseline in the physician's global assessment by 0.3 points or greater (Furie 2009).
2. **Aerobic capacity:** Mean or mean change in aerobic capacity assessed by predicted or absolute value of maximum rate of oxygen consumption (VO_{2max}).
3. **Depression**: Mean or mean change in depression assessed by Beck-Depression Index (BDI) or other relevant depression scales such as Hospital Anxiety and Depression Scale (HADS).
4. **Anxiety**: Mean or mean change in anxiety assessed using HADS or other relevant anxiety scales.

We analysed all exercise interventions in the pooled primary analysis. For efficacy outcomes, we extracted data from the end of intervention time point. We defined the end of intervention as the time when the structured exercise intervention had completed. We extracted adverse event outcomes at the last time point (i.e. proportion who had an event by the end of the trial).

Search methods for identification of studies

Electronic searches

We searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL, SPORTDiscus, and Web of Science. We also conducted a search of ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO trials portal (www.who.int/ictrp/en/). We searched all databases from their inception to 30 March 2022, and we imposed no restriction on language of publication.

See Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6 for the search strategies.

Searching other resources

We did not contact organisations to obtain additional references.

Data collection and analysis

Selection of studies

Two review authors (SF, EN) independently screened titles and abstracts for inclusion of all the potentially relevant studies we identified as a result of the search, and coded them as 'retrieved' (eligible or potentially eligible/unclear) or 'did not retrieve'. We retrieved the full-text study reports/publications and two review authors (SF, EN) independently screened the full texts and identified studies for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreements through discussion with a third review author (MC). We identified and excluded duplicates. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1; PRISMA Group 2009; prisma-statement.org/PRISMAStatement/Default.aspx).

Data extraction and management

Two review authors (SF, EN) extracted the following study characteristics from included studies.

1. Methods: study design, total duration of study, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: number, mean age, age range, sex, disease duration, severity of condition, diagnostic criteria, important SLE baseline data, medication, inclusion criteria, and exclusion criteria.
3. Interventions: intervention; comparison; concomitant medications; and specific components of the intervention including type, frequency, intensity, and duration of the exercise intervention, and whether the exercise intervention was supervised. This was assessed using the Consensus on Exercise Reporting Template (CERT): Explanation and Elaboration Statement (bjsm.bmj.com/content/50/23/1428Slade 2016).
4. Outcomes: major and minor outcomes specified and collected, and time points reported.
5. Characteristics of the design of the trial as outlined in the Assessment of risk of bias in included studies section.
6. Notes: funding for trial, and notable declarations of interest of trial authors.

Two review authors (SF, MC) independently extracted outcome data from included studies. We extracted the number of events and number of participants per treatment group for dichotomous outcomes, and means, SDs, and number of participants per treatment group for continuous outcomes. We noted in the Characteristics of included studies table if outcome data were not reported in a usable way and when data were transformed or estimated from a graph. We resolved disagreements by consensus or by involving a third review author (SO). One review author (SF) transferred data into RevMan Web. We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports.

If more than one measure for an outcome was reported, we extracted only the one reported by most of the included trials (i.e. FSS for fatigue). In the event of multiple outcome reporting, if both final values and change from baseline values were reported for the same outcome, we extracted the final values, as reported in the publication. Similarly, if data were analysed based on an intention-to-treat (ITT) sample and another sample (e.g. per-protocol, as-treated), we extracted the ITT sample for both outcomes assessing benefits and outcomes assessing harms. If data for more than one time point were provided, we used the 'end of structured exercise intervention' time point for the meta-analysis.

Assessment of risk of bias in included studies

Two review authors (SF, MC) independently assessed risk of bias using the RoB 1 tool for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions, chapter 8 (*Higgins 2017). We resolved any disagreements by discussion or by involving other review authors (SO, DG). We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias (potential threats to validity such as unit of analysis issues, inappropriate or unequal application of co-intervention across treatment groups).

We graded each potential source of bias as high, low, or unclear risk, and provided a quote from the study report together with a justification for our judgement in the risk of bias table. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for objective outcome measures which may be different from a participant-reported scale). In addition, we considered the impact of missing data by key outcomes.

Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the risk of bias table.

When considering treatment effects, we considered the risk of bias for the studies that contributed to that outcome.

We presented the figures generated by the RoB 1 tool to provide summary assessments of the risk of bias.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol (Frade 2021), and reported any deviations from it in the Differences between protocol and review section.

Measures of treatment effect

We analysed dichotomous data as RRs when the outcome was a rare event (approximately less than 10%), with 95% CIs. We analysed continuous data as MD (if studies use the same scale) or SMD (if studies use different scales) with 95% CIs. We entered data presented as a scale with a consistent direction of effect across studies.

When studies used different scales to measure the same conceptual outcome (e.g. disability), we calculated SMDs instead, with corresponding 95% CIs. We back-translated SMDs to a typical scale (e.g. 0 to 10 for pain) by multiplying the SMD by a typical among-person SD (e.g. the SD of the control group at baseline from the most representative trial) as recommended in *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020a).

We assumed a minimal clinically important difference (MCID) of 1.5 points in a 10-point Likert scale for pain; and 10 points on a 100-point Likert scale for function or disability into the calculator. Using a cross-sectional approach (Goligher 2008) derived 5.9 points as the MCID for the FACIT-Fatigue scale in people with SLE. The MCID for the FSS has been reported as a decrease of 1 point on the 7-point scale (Nordin 2016). The MCID for LupusQOL is estimated using an anchor-based approach as mean changes in LupusQOL domains when minimal change (deterioration = −3 or −2 points; improvement = 2 or 3 points) (McElhone 2016). SF-36 score can be expressed in two subscores according to the domains they explore: a PCS and an MCS. We considered 3.74 for PCS and 1.7 for MCS as minimal important differences (Leung 2011). For measures with no previously reported clinically important threshold, we used the SMD interpretation where values greater than 0.8 were considered clinically significant (large effect). A change of 4 points on the SLEDAI scale is considered the MCID; however, this has not yet been well established (Brunner 2010).

For dichotomous outcomes, we calculated the absolute percent change from the difference in the risks between the intervention and control groups using GRADEpro GDT and expressed as a percentage (GRADEpro GDT).

For continuous outcomes, we calculated the absolute percent change by dividing the MD by the scale of the measure.

Unit of analysis issues

Where a single trial reported multiple trial arms, we included only the relevant arms. If two comparisons (e.g. exercise programme 1 and exercise programme 2 versus placebo) were combined in the same meta-analysis, we combined the two exercise groups into one intervention to avoid double-counting. We listed all treatment arms in the Characteristics of included studies table, even if they were not used in the review.

We analysed non-standard designs (i.e. cluster-RCTs and crossover RCTs) using methods appropriate to the design as suggested in Sections 23.1.4, 23.1.5, and 23.2.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020b).

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when data were not available for all participants). Where this was not possible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results using a sensitivity analysis. We described any assumptions and imputations to handle missing data and explored the effect of imputation using sensitivity analyses.

For dichotomous outcomes (e.g. number of withdrawals due to adverse events), we calculated the withdrawal rate using the number of participants randomised in the group as the denominator.

For continuous outcomes (e.g. mean change in pain score), we calculated the MD or SMD based on the number of participants analysed at that time point. If the number of participants analysed was not presented for each time point, we used the number of randomised participants in each group at baseline.

Where possible, we computed missing SDs from other statistics such as standard errors, CIs, or P values, according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 10; Deeks 2020). If SDs could not be calculated, we imputed them (e.g. from other studies in the meta-analysis) (Deeks 2020).

Assessment of heterogeneity

We assessed clinical and methodological diversity in terms of participants, interventions, outcomes, and study characteristics for the included studies to determine whether a meta-analysis was appropriate. This was conducted by observing these data from the data extraction tables. We assessed statistical heterogeneity by visual inspection of the forest plot to assess obvious differences in results between the studies, and using the I^2 and Chi^2 statistical tests.

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 10; Deeks 2020), the interpretation of an I^2 value of 0% to 40% might 'not be important'; 30% to 60% may represent 'moderate' heterogeneity; 50% to 90% may represent 'substantial' heterogeneity; and 75% to 100% represents 'considerable' heterogeneity. We kept in mind that the importance of the I^2 statistic depends on: magnitude and direction of effects and strength of evidence for heterogeneity.

The Chi^2 test was interpreted where a $P \leq 0.10$ indicated evidence of statistical heterogeneity.

If we identified substantial heterogeneity, we reported it and investigated possible causes by following the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 10; Deeks 2020).

Assessment of reporting biases

We created and examined a funnel plot to explore possible small-study biases. In interpreting funnel plots, we examined the different possible reasons for funnel plot asymmetry as outlined in Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* and related this to the results of the review (Page 2020). If we were able to pool more than 10 trials, we undertook formal statistical tests to investigate funnel plot asymmetry, and followed the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 13; Page 2020).

To assess outcome reporting bias, we checked trial protocols against published reports. For studies published after 1 July 2005, we screened the Clinical Trial Register at the International Clinical Trials Registry Platform of the WHO (apps.who.int/trialssearch) for the a priori trial protocol. We evaluated whether selective reporting of outcomes was present.

Data synthesis

We undertook meta-analyses only where this was meaningful (i.e. if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense). We anticipated that the following comparisons would be used.

1. Exercise plus usual pharmacological care versus placebo
2. Exercise plus usual pharmacological care versus usual pharmacological care
3. Exercise plus usual pharmacological care versus another intervention (e.g. education about exercise, counselling about exercise, relaxation exercises).

We used a random-effects model. We analysed all types of exercise interventions in the pooled primary analysis.

Subgroup analysis and investigation of heterogeneity

If there were sufficient data, we would have conducted subgroup analyses for fatigue according to components of exercise. We had restricted subgroup analyses to the primary time point. We anticipate that the following exercise components may be useful.

1. Types of exercise (aerobic, resistance, relaxing/range of motion)
2. Exercise setting (supervised or unsupervised/home-based exercise)

The reason for including components of an exercise programme in the subgroup analyses is to be able to identify an optimal exercise for improving fatigue in people with SLE, which has been implicated for future research in previous reviews (O'Dwyer 2017; Wu 2017). This information will be critical for informing both practitioners and patients regarding the most appropriate exercise prescription. Pooled evidence from three studies showed that aerobic exercise training significantly decreased fatigue severity compared to relaxing exercise (Carvalho 2005; Ramsey-Goldman 2000; Tench 2003), and supervised exercise reduced fatigue symptoms to a significantly greater extent than home-based exercise (Wu 2017).

We would have used the formal test for subgroup interactions in Review Manager Web (RevMan Web 2022), and use caution in the interpretation of subgroup analyses as advised in Section 9.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2021). We would compare the magnitude of the effects between the subgroups by assessing the overlap of the CIs of the summary estimate. Non-overlap of the CIs indicates statistical significance.

Sensitivity analysis

We planned to carry out the following sensitivity analyses to investigate the robustness of the treatment effect on fatigue.

1. Impact of including studies with high or unclear risk of selection, detection, and attrition biases
2. Impact of including studies with imputed data

Summary of findings and assessment of the certainty of the evidence

At least two review authors (SF, MC) assessed the certainty of the supporting evidence behind each estimate of treatment effect using the GRADE approach, for the major outcomes: Fatigue, functional capacity, disease activity, quality of life, pain, serious adverse events, and withdrawals. We used methods and recommendations described in *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 14; Schünemann 2020a). We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence as it relates to the studies that contributed data to the meta-analyses for the prespecified outcomes, and reported the certainty of evidence as high, moderate, low, or very low.

We used GRADEpro GDT software to prepare and display the summary of findings tables (GRADEpro GDT). We justified all decisions to downgrade the certainty of evidence for each outcome using footnotes, and we made comments to aid the reader's understanding of the review where necessary. We provided the number needed to treat for an additional beneficial outcome (NNTB) or harmful outcome (NNTH) and absolute percent change in the 'Comments' column of the summary of findings table.

We preselected the following important outcomes for inclusion in the summary of findings tables.

1. Mean or mean change in fatigue assessed by FSS, FACIT-F, or other relevant fatigue scales such as POMS.
2. Mean or mean change in functional capacity measured by the PCS of the SF-36, or physical function subscale of the SF-36, or other physical function or disability scales.
3. Mean or mean change in SLE scores on validated disease activity indices such as the SLEDAI, SELENA-SLEDAI, modified SELENA-SLEDAI SFI; BILAG; or other similar validated indices.
4. Mean or mean change in quality of life assessed by the MCS of the SF-36, or similar assessments such as LupusQOL.
5. Mean or mean change in pain measured by VAS for pain, NRS for pain, or the bodily pain subscale of the SF-36.
6. SAEs, number of SAEs, or number of participants with one or more SAE.
7. Withdrawals due to any reason

We produced three summary of findings tables for the following comparisons.

1. Exercise plus usual pharmacological care versus placebo plus usual pharmacological care.
2. Exercise plus usual pharmacological care versus usual pharmacological care.
3. Exercise plus usual pharmacological care versus another intervention (e.g. education about exercise, counselling about exercise, relaxation exercises) plus usual pharmacological care.

For efficacy outcomes, we extracted data at the end of intervention time point. We extracted adverse event outcomes at the last time point (i.e. proportion who had an event by the end of the trial).

Interpreting results and reaching conclusions

We followed the guidelines in *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 15; Schünemann 2022b), for interpreting results, and were aware of distinguishing a lack of evidence of effect from a lack of effect. We based our conclusions only on findings from the quantitative or narrative synthesis, according to Synthesis Without Meta-analysis (SWiM) reporting guideline of included studies for this review (Campbell 2020). Our implications for research suggested priorities for future research and outlined what the remaining uncertainties are in the area.

Results

Description of studies

Details of the included studies are listed in Table 1 and the Characteristics of included studies table.

Results of the search

The search was conducted up to 30 March 2022. It yielded 1613 records across six databases (CENTRAL, MEDLINE, Embase, CINAHL, SPORTDiscus, and Web of Science). After removal of duplicates, 1089 records remained. Of these, we retrieved 41 for full-text screening on the basis of title and abstract. We deemed 13 RCTs eligible for inclusion (Abrahão 2016; Avaux 2016; Benatti 2015; Benatti 2018; Bostrom 2016; Daltroy 1995; Dos Reis-Neto 2013; Hashemi 2022; Kao 2021; Keramiotou 2020; Lopes-Souza 2021; Miossi 2012; Tench 2003). We excluded 27 articles, one trial is awaiting classification (Boedecker 2020), and there are no ongoing studies. See Figure 1 for the PRISMA flow diagram of search results (Page 2021).

Included studies

Study design and setting

Studies were conducted in Brazil (7/13, 53%), Europe (3/13, 23%), the US (1/13, 8%), the UK (1/13, 8%), and Iran (1/13, 8%), Six studies were two-arm parallel RCTs (Benatti 2018; Bostrom 2016; Daltroy 1995; Hashemi 2022; Keramiotou 2020; Lopes-Souza 2021), two studies were two-arm parallel quasi-RCTS (Dos Reis-Neto 2013; Kao 2021), four studies were three-arm parallel RCTs (Abrahão 2016; Benatti 2015; Miossi 2012; Tench 2003), and one study was a three-arm parallel quasi-RCT (Avaux 2016).

Participants

There were a total of 540 participants with SLE who commenced the intervention, and 463 participants who completed the intervention (86%). There were 77 participants who dropped out of the studies (reasons reported in the Characteristics of included studies table). Across included trials the mean age of participants ranged from 21.5 to 53 years, and mean duration of disease from 2.5 to 21 years. Most studies diagnosed SLE using the ACR criteria for SLE. It is unclear whether included participants had comorbidities as this was not clearly reported in the included studies. Participants were on various pharmacological treatments including csDMARDs such as hydroxychloroquine, prednisolone or glucocorticoids, mycophenolate mofetil, methotrexate, azathioprine, and cyclophosphamide; bDMARDs such as rituximab or belimumab; and NSAIDs such as naproxen or celecoxib. See Table 1.

Interventions and comparators

Control group interventions

All 13 studies compared a type of exercise, or a combination of types of exercise, plus usual care, to a control group that received either one of the following.

1. Placebo plus usual care[a] (Lopes-Souza 2021).
    a. In this study, the exercise intervention included whole body vibration exercise where participants were asked to stand on a vibrating platform, and the placebo intervention also stood on a vibration platform, except the vibration was turned off.
2. Usual care alone[a] (Avaux 2016; Benatti 2015; Benatti 2018; Bostrom 2016; Hashemi 2022; Tench 2003).
3. Another non-pharmacological intervention plus usual care[a] (Abrahão 2016; Daltroy 1995; Dos Reis-Neto 2013; Kao 2021; Keramiotou 2020; Miossi 2012; Tench 2003). Other non-pharmacological interventions included:

a. participants received information about the disease, and were informed that they would receive the intervention after the study was finished, and they would be invited to participate in the intervention that proved the most effective (Abrahão 2016);

b. participants were contacted by the research team once per week. They were also asked to fill out questionnaires, and were encouraged to maintain their current level of activity (Daltroy 1995);

c. participants received information about the disease. They received clear instruction not to start any exercise for the next 16 weeks (Dos Reis-Neto 2013);

d. participants received information about the disease. They were asked to maintain their usual lifestyle (Kao 2021);

e. participants had four sessions of training in alternative methods of performing daily activities, use of aids, joint protection, and energy conservation (Keramiotou 2020);

f. participants received information about their disease. They were advised to remain physically inactive (Miossi 2012);

g. participants listened to a relaxation audio tape in a quiet, warm, and darkened room for 30 minutes, three times per week. Participants were seen by an exercise professional every two weeks for a supervised relaxation session (Tench 2003).

[a]Usual care included pharmacological treatments: csDMARDs such as hydroxychloroquine, prednisolone or glucocorticoids, mycophenolate mofetil, methotrexate, azathioprine, and cyclophosphamide; bDMARDs such as rituximab or belimumab; and NSAIDs such as naproxen or celecoxib.

Exercise interventions

All 13 studies included a structured exercise programme as part of their intervention. The summary of interventions can be found in Table 2, and summarised below.

1. **Type of exercise:** four studies included aerobic exercise (Benatti 2018; Daltroy 1995; Dos Reis-Neto 2013; Tench 2003), seven studies included a combination of aerobic and resistance exercise (Abrahão 2016; Avaux 2016; Benatti 2015; Bostrom 2016; Hashemi 2022; Kao 2021; Miossi 2012), one study included a combination of resistance exercise and stretching (Keramiotou 2020), and one study included whole body vibration exercise, which is a subgroup of resistance training, better classified as muscle activation/neuromuscular training complementary to resistance training (Lopes-Souza 2021).
2. **Intensity of exercise:** one study was low intensity (Lopes-Souza 2021), seven studies were moderate intensity (Abrahão 2016; Avaux 2016; Daltroy 1995; Hashemi 2022; Kao 2021; Keramiotou 2020), one study was high intensity (Bostrom 2016), and four studies did not clearly report the intensity (Benatti 2015; Benatti 2018; Dos Reis-Neto 2013; Miossi 2012).
3. **Frequency of exercise:** participants undertook two exercise sessions per week in five studies (Benatti 2015; Benatti 2018; Bostrom 2016; Lopes-Souza 2021; Miossi 2012), three sessions per week in five studies (Abrahão 2016; Daltroy 1995; Dos Reis-Neto 2013; Hashemi 2022; Tench 2003), five sessions per week in one study

(Kao 2021), daily in one study (Keramiotou 2020), and a total of three hours over the entire week, with no clarity on the number of sessions per week in one study (Avaux 2016).

4. **Duration of the exercise intervention:** the exercise intervention had a duration of 12 weeks in 11 studies (Abrahão 2016; Avaux 2016; Benatti 2015; Benatti 2018; Bostrom 2016; Daltroy 1995; Kao 2021; Keramiotou 2020; Lopes-Souza 2021; Miossi 2012; Tench 2003), with a 24-week follow-up in three studies (Daltroy 1995; Keramiotou 2020; Lopes-Souza 2021), and a 24-week plus 52-week follow-up in one study (Bostrom 2016). The exercise intervention had a duration of 16 weeks in one study (Dos Reis-Neto 2013), and eight weeks in one study (Hashemi 2022).

Outcomes

See Table 3 and Table 4 for further details on the major and minor outcomes in the included studies.

Exercise plus usual pharmacological care versus placebo plus usual pharmacological care

Major outcomes

One trial compared a structured exercise intervention to a placebo control (Lopes-Souza 2021). The certainty of evidence was low for fatigue, functional capacity, and pain, and very low for withdrawals due to any reason. We extracted data from the end of the intervention (i.e. 12 weeks). The major outcomes are reported in summary of findings Table 1.

Fatigue

Lopes-Souza 2021 measured overall fatigue (mean or mean change) using the FACIT-F, which we used in our analyses. It had a scale with 13 items scored from 0 to 4. Overall scores ranged from 0 to 52, with a lower final score indicating greater fatigue. However, for consistency with other analyses of fatigue, we reversed the scale so that a lower score indicates less fatigue.

Functional capacity

Lopes-Souza 2021 measured overall functional capacity (mean or mean change) using the SF-36 Functional Capacity/Physical Function domain, which we used in our analyses. Scores ranged from 0 to 100, with higher scores indicating better functional capacity.

Disease activity

Lopes-Souza 2021 did not report disease activity.

Quality of life

Lopes-Souza 2021 partially reported quality of life using the SF-36 Quality of Life questionnaire; however, authors did not report the MCS and PCS scores, and, therefore, this was not used in our analyses.

Pain

Lopes-Souza 2021 measured pain using the SF-36 Quality of Life questionnaire, Pain domain, which we used in our analyses. Scores ranged from 0 to 100, with higher scores indicating less pain. However, for consistency with other pain scales (i.e. VAS), we reversed the scale so that a lower score indicated less pain.

Serious adverse events

Lopes-Souza 2021 reported no SAEs.

Withdrawals due to any reason

Lopes-Souza 2021 reported three participant dropouts from the exercise group (one participant withdrew before the six-week analysis due to low back pain, and two withdrew before the 12-week analysis due to personal reasons) and one participant withdrew from the control group before the six-week analysis due to personal reasons.

Minor outcomes

Composite responder rate

Lopes-Souza 2021 did not report composite responder rate.

Aerobic fitness

Lopes-Souza 2021 did not report aerobic fitness.

Depression

Lopes-Souza 2021 did not report depression.

Anxiety

Lopes-Souza 2021 did not report anxiety.

Exercise plus usual pharmacological care versus usual pharmacological care alone

Six trials compared exercise plus usual pharmacological care versus usual pharmacological care alone (Avaux 2016; Benatti 2015; Benatti 2018; Bostrom 2016; Hashemi 2022; Tench 2003).

Major outcomes

Fatigue

Two trials measured and reported overall fatigue (mean or mean change) using the Krupp FSS, with scores ranging from 1 to 7, lower scores indicating less fatigue, which we used in our analyses (Avaux 2016; Tench 2003). Tench 2003 also measured overall fatigue using the Chalder Fatigue Scale (CFS) and VAS for fatigue; however we extracted data from the FSS only. Four trials did not measure or report (or both) fatigue (Benatti 2015; Benatti 2018; Bostrom 2016; Hashemi 2022).

Functional capacity

Two trials measured overall functional capacity (mean or mean change) using the SF-36 Physical Function domain, which we used in our analyses (Bostrom 2016; Tench 2003). Scores ranged from 0 to 100, with higher scores indicating better functional capacity. Four trials did not measure or report (or both) functional capacity (Avaux 2016; Benatti 2015; Benatti 2018; Hashemi 2022).

Disease activity

One trial measured disease activity using the SLEDAI, which we used in our analyses (Bostrom 2016). Scores ranged from 0 to 105, with lower scores indicating less disease activity. Tench 2003 measured disease activity using the SLAM measuring system, which we used in our analyses. Scores ranged from 0 to 83, with lower scores indicating less disease activity. Four trials did not measure or report (or both) change in disease activity before and after the intervention (Avaux 2016; Benatti 2015; Benatti 2018; Hashemi 2022).

Quality of life

Two trials partially reported quality of life using the SF-36 Quality of Life questionnaire; however, authors did not report the MCS and PCS scores, and, therefore, could not be used in our analyses (Bostrom 2016Tench 2003). Four trials did not measure or report (or both) quality of life (Avaux 2016; Benatti 2015; Benatti 2018; Hashemi 2022).

Pain

Bostrom 2016 measured and recorded pain using the SF-36 Quality of Life questionnaire, Pain domain, which we used in our analyses. Scores ranged from 0 to 100, with higher scores indicating less pain. For consistency with other pain scales (i.e. VAS), we reversed the score so that a lower score indicated less pain. Tench 2003 measured pain using the SF-36 Quality of Life questionnaire; however, authors did not report the Pain domain, and, therefore, this was not used in our analyses. Four trials did not measure or report (or both) pain (Avaux 2016; Benatti 2015; Benatti 2018; Hashemi 2022).

Withdrawals due to any reason

Avaux 2016 had three participants withdraw from the intervention; two due to personal reasons, and one due to a disease flare; however, it is unclear which group they were part of, and they were not included in our analyses. Benatti 2018 had eight participants withdraw from the intervention for the following reasons: four participants withdrew from the control group (one was pregnant, three for personal reasons) and four participants withdrew from the exercise group (one fractured a limb outside of training sessions, three for person reasons). Another two participants withdrew due to a disease flare (one from each group). Bostrom 2016 had three participants withdraw from the control group (one had depression/cognitive impairment, one had untreated dementia, one had suspected relapse of breast cancer). Tench 2003 had 14 participants withdraw due to any reason: four participants withdrew from the exercise group, five participants withdrew from the active control group (relaxation) and five participants withdrew from the usual care control group. Note that six participants dropped out of treatment and eight participants completed the study but did not wish to repeat the walking test to exhaustion at the end of the intervention. Two trials had no withdrawals from the intervention due to any reason that were reported (Benatti 2015; Hashemi 2022).

Serious adverse events

None of the six trials reported any SAEs (Avaux 2016; Benatti 2015; Benatti 2018; Bostrom 2016; Hashemi 2022; Tench 2003).

Minor outcomes

Composite responder rate

None of the six studies reported composite responder rate (Avaux 2016; Benatti 2015; Benatti 2018; Bostrom 2016; Hashemi 2022; Tench 2003).

Aerobic fitness

Bostrom 2016 recorded aerobic capacity using the maximum oxygen consumption (VO_{2max} in litres/minute), with higher scores indicating better aerobic capacity. Tench 2003 recorded aerobic capacity using peak oxygen consumption (VO_{2peak} in millilitres/kilogram/minute), with higher scores indicating better aerobic capacity. Four trials did not measure or report (or both) aerobic capacity (Avaux 2016; Benatti 2015; Benatti 2018; Hashemi 2022).

Depression

Tench 2003 recorded depression using the HADS – Depression subscale. Scores ranged from 0 to 21, with lower scores indicating a better outcome. Five trials did not measure or report (or both) depression (Avaux 2016; Benatti 2015; Benatti 2018; Bostrom 2016; Hashemi 2022).

Anxiety

Tench 2003 recorded anxiety using the HADS – Anxiety subscale. Scores ranged from 0 to 21, with lower scores indicating a better outcome. Five trials did not measure or report (or both anxiety (Avaux 2016; Benatti 2015; Benatti 2018; Bostrom 2016; Hashemi 2022).

Exercise plus usual pharmacological care versus another non-pharmacological intervention plus usual pharmacological care

Seven studies compared exercise plus usual pharmacological care versus another non-pharmacological intervention plus usual pharmacological care (Abrahão 2016; Daltroy 1995; Dos Reis-Neto 2013; Kao 2021; Keramiotou 2020; Miossi 2012; Tench 2003).

Major outcomes

Fatigue

Daltroy 1995 measured fatigue using the MAC questionnaire and POMS Fatigue questionnaires; however, these were not included in our analyses because the results for the participants with SLE were not available separately from those of the participants with rheumatoid arthritis. Keramiotou 2020 measured overall fatigue using the LupusQOL – Fatigue questionnaire, which we used in our analyses. Scores ranged from 0 to 100, with higher scores indicating less fatigue. For consistency with other fatigue scales (i.e. FSS), we reversed the scale so that a lower score indicated less fatigue. Tench 2003 measured fatigue using the Krupp FSS, which we used in our analyses. Scores ranged from 1 to 7, with lower scores indicating less fatigue. Tench 2003 used the CFS, VAS Fatigue, and the SF-36 Quality of Life questionnaire, Vitality domain; however, these were not used in our analyses. Four trials did not measure or report (or both) overall fatigue (Abrahão 2016; Dos Reis-Neto 2013; Kao 2021; Miossi 2012).

Functional capacity

Two trials measured functional capacity using the SF-36 Quality of Life questionnaire, Physical Function domain, which we used in our analyses (Abrahão 2016; Tench 2003). Scores ranged from 0 to100, with higher scores indicating better functional capacity. Keramiotou 2020 measured functional capacity using the LupusQOL questionnaire Physical Health domain, which we used in our analyses. Scores ranged from 0 to100, with higher scores indicating better functional capacity. Keramiotou 2020 also assessed functional capacity using the Health Assessment Questionnaire (HAQ); however, this was not used in our analyses. Four trials did not measure or report (or both) functional capacity (Daltroy 1995; Dos Reis-Neto 2013; Kao 2021; Miossi 2012).

Disease activity

Three trials measured disease activity using the SLEDAI, which we used in our analyses (Abrahão 2016; Dos Reis-Neto 2013; Miossi 2012). Scores ranged from 0 to 105, with lower scores indicating less disease activity. Tench 2003 measured disease activity using the SLAM measuring system, which we used in our analyses. Scores ranged from 0 to 83, with lower scores indicating less disease activity. Two trials measured fatigue using the SLEDAI; however, authors do not report the mean and SD, and, therefore, we were unable to use these in our analyses (Kao 2021; Keramiotou 2020). Two trials did not measure or report (or both) change in disease activity before and after the intervention (Daltroy 1995; Miossi 2012).

Quality of life

Two trials partially reported quality of life using the SF-36 Quality of Life questionnaire; however, authors did not report the MCS and PCS scores, and, therefore, these were not used in our analyses (Abrahão 2016; Tench 2003). Keramiotou 2020 partially reported quality of life using the LupusQOL questionnaire; however, they reported only Physical Health and Fatigue domains, and, therefore, were not used in our analyses. Four trials did not measure or report (or both) quality of life (Daltroy 1995; Dos Reis-Neto 2013; Kao 2021; Miossi 2012).

Pain

Abrahão 2016 measured pain using the SF-36 Quality of Life Pain questionnaire, which we used in our analyses. Scores ranged from 0 to100, with higher scores indicating less pain. For consistency with other scales (i.e. VAS), we reversed the scale so that lower scores indicated less pain. Tench 2003 also used the SF-36 Quality of Life questionnaire to measure quality of life; however, authors did not report the Pain domain, and, therefore, this was not used in our analyses. Keramiotou 2020 measured pain using the VAS Pain, which we used in our analyses. Scores ranged from 0 to 10, with lower scores indicating less pain. Four trials did not report quality of life (Daltroy 1995; Dos Reis-Neto 2013; Kao 2021; Miossi 2012).

Withdrawals due to any reason

Abrahão 2016 had two participants withdraw from the control group for an unknown reason. Keramiotou 2020 had two participants from the exercise group withdraw; however, the reasons were not reported. Tench 2003 had 14 participants withdraw from the study: four participants withdrew from the exercise group, five participants withdrew from the active control group (relaxation), and five participants withdrew from the usual care control group. Note that six participants dropped out of treatment and eight participants completed the study but did not wish to repeat the walking test to exhaustion at the end of the intervention. Four trials did not clearly report withdrawals due to any reason (Daltroy 1995; Dos Reis-Neto 2013; Kao 2021; Miossi 2012).

Serious adverse events

Seven trials reported no SAEs (Abrahão 2016; Daltroy 1995; Dos Reis-Neto 2013; Kao 2021; Keramiotou 2020; Miossi 2012; Tench 2003).

Minor outcomes

Composite responder rate

None of the seven trials measured or reported (or both) composite responder rate (Abrahão 2016; Daltroy 1995; Dos Reis-Neto 2013; Kao 2021; Keramiotou 2020; Miossi 2012; Tench 2003).

Aerobic fitness

Daltroy 1995 measured aerobic capacity using a 12-minute walking test; however, this was not used in our analyses. Two trials measured aerobic capacity using VO_{2peak} (in millilitres/kilogram/minute), which we used in our analyses (Dos Reis-Neto 2013; Tench 2003). Higher scores indicated better aerobic capacity. Four trials did not measure or report (or both) aerobic capacity (Abrahão 2016; Kao 2021; Keramiotou 2020; Miossi 2012).

Depression

Abrahão 2016 measured depression using the BDI, which we used in our analyses. Scores ranged from 0 to 63, with lower scores indicating a better outcome. Daltroy 1995 measured depression using the Center for Epidemiologic Studies Depression Scale (CES-D) and was not used in our analyses because we were unable to differentiate the participants with SLEW from those with rheumatoid arthritis. Scores ranged from 0 to 60, with lower scores indicating

a better outcome. Tench 2003 measured depression using the HADS – Depression subscale and was not used in our analyses. Scores ranged from 0 to 21, with lower scores indicating a better outcome. Four trials did not measure or report (or both) depression (Dos Reis-Neto 2013; Kao 2021; Keramiotou 2020; Miossi 2012).

Anxiety

Tench 2003 measured anxiety using the HADS – Anxiety subscale. Scores ranged from 0 to 21, with lower scores indicating a better outcome. Six trials did not measure anxiety (Abrahão 2016; Daltroy 1995; Dos Reis-Neto 2013; Kao 2021; Keramiotou 2020; Miossi 2012).

Excluded studies

We excluded 27 studies for the following reasons.

1. **Ineligible intervention:** exercise was either acute (one single bout of exercise) or did not meet our inclusion criteria of an exercise intervention being structured, recurring, and including specific dosage information (i.e. frequency, intensity, timing, type).
2. **Ineligible participant population:** intervention group included participants with SLE, however, control group participants were healthy controls.
3. **Ineligible study design:** studies were not randomised, or did not include a control group, and did not meet the inclusion criterion of an RCT.
4. **Duplicate study:** this was the abstract to one of our included studies (Abrahão 2016).

The list of all 27 excluded studies, with reason, can be found in the Characteristics of excluded studies table.

Risk of bias in included studies

The overall risk of bias assessment of the included studies is presented in Figure 2 and Figure 3.

Allocation

Random sequence

We judged five studies at low risk of bias because they used and reported an appropriate method of randomisation (Abrahão 2016; Benatti 2015; Bostrom 2016; Keramiotou 2020; Tench 2003).

We assessed five studies at unclear risk of bias because the methods used to generate allocation sequence were not described, or were unclear (Benatti 2018; Daltroy 1995; Hashemi 2022; Lopes-Souza 2021; Miossi 2012).

We judged three studies at high risk of bias because their methods of randomisation were not truly random (i.e. quasi-randomised), despite authors reporting the study to be randomised (Avaux 2016; Dos Reis-Neto 2013; Kao 2021).

Allocation concealment

We judged two studies at low risk of bias, since they provided adequate information on the method of allocation concealment (Abrahão 2016; Keramiotou 2020).

For 10 studies, the method used to conceal allocation sequence was unclear, or not described (Benatti 2015; Benatti 2018; Bostrom 2016; Daltroy 1995; Dos Reis-Neto 2013; Hashemi 2022; Kao 2021; Lopes-Souza 2021; Miossi 2012; Tench 2003).

We judged one study at high risk of bias because the selection of participants based on their geographical location was deemed as selection bias (Avaux 2016).

Blinding

Participant blinding

We judged all studies at high risk of bias. Blinding participants and care providers is difficult because of the nature of the intervention. Most of the included studies did not report information on blinding, or a masking procedure for treatment allocation or delivery. No studies reported using a blinding procedure (sham or attentional comparator, or blinding of study hypothesis).

Outcome assessor

We judged all studies at high (Avaux 2016; Bostrom 2016; Dos Reis-Neto 2013) or unclear risk of bias (Abrahão 2016; Benatti 2015; Benatti 2018; Daltroy 1995; Hashemi 2022; Kao 2021; Keramiotou 2020; Lopes-Souza 2021; Miossi 2012; Tench 2003). Most included studies used subjective outcomes (self-reporting). Because participants were not blind to the treatment allocation (i.e. inability to bind an exercise trial), we considered the outcomes assessors to be unblinded.

Incomplete outcome data

We judged seven studies at low risk of attrition bias (Abrahão 2016; Daltroy 1995; Hashemi 2022; Kao 2021; Lopes-Souza 2021; Miossi 2012; Tench 2003).

We judged six studies at high risk of attrition bias because of withdrawals throughout the intervention with no clear reporting of ITT analyses (Avaux 2016; Benatti 2015; Benatti 2018; Bostrom 2016; Dos Reis-Neto 2013; Keramiotou 2020).

Selective reporting

We judged five studies at low risk of reporting bias, because all outcomes reported were prespecified in their methods (Daltroy 1995; Dos Reis-Neto 2013; Hashemi 2022; Kao 2021; Miossi 2012).

We judged seven studies at a high risk of bias because we found outcomes listed in their methods and not reported in the results (e.g. the MCS of the SF-36) (Abrahão 2016; Avaux 2016; Benatti 2015; Benatti 2018; Bostrom 2016; Keramiotou 2020; Lopes-Souza 2021; Tench 2003).

Other potential sources of bias

We judged all studies at a low risk of other bias because we identified no other potential sources of bias.

Effects of interventions

Exercise plus usual pharmacological care versus placebo plus usual pharmacological care

One study compared exercise plus usual care versus placebo plus usual care (Lopes-Souza 2021).

Major outcomes

See: Summary of findings table 1.

Fatigue (FACIT-Fatigue, 0 to 52 scale, lower score indicates less fatigue severity, MCID 5.9 points)

One study (17 participants) found that exercise may result in little to no effect on fatigue. The mean fatigue score for the placebo plus usual care group was 38 points, and the mean fatigue score for the exercise plus usual care group was 33 points (MD −5 points, 95% CI −3.29 lower to 13.29; Analysis 1.1). There was no clinically meaningful benefit. Because of study limitations, we downgraded the evidence two levels for high risk of bias and imprecision; we rated the certainty of evidence as low.

Functional capacity (SF-36 Physical Function, 0 to 100 scale, higher scores indicate better function, MCID 10 points)

One study (17 participants) found that exercise may have little to no effect on functional capacity. The mean functional capacity score for the placebo plus usual care group was 70 points, and the mean functional capacity score for the exercise plus usual care group 67.5 points (MD −2.5 points, 95% CI −23.78 to 18.78; Analysis 1.2). There was no important clinically meaningful benefit. Because of study limitations, we downgraded the evidence two levels for high risk of bias and imprecision; we rated the certainty of evidence as low.

Disease activity

The study did not report disease activity.

Quality of life

The study did not report quality of life.

Pain (SF-36 Pain, 0 to 100 scale, lower scores indicate less pain, MCID 10 points)

One study (17 participants) found that exercise may have little to no effect on pain. The mean pain score was 43 points for the placebo plus usual care group, and the mean pain score was 34 points for the exercise plus usual care group (MD −9 points, 95% CI −28.88 to 10.88; Analysis 2.4). There was no important clinically meaningful benefit. Because of study limitations, we downgraded the evidence by two levels for high risk of bias and imprecision; we rated the certainty of evidence as low.

Serious adverse events

No SAEs reported.

Withdrawals due to any reason

We are uncertain whether exercise results in fewer or more withdrawals (RR 2.73, 95% CI 0.34 to 22.16; 1 study). The study reported three dropouts from the exercise group; one participant withdrew before the six-week analysis due to low back pain ("not related directly with the intervention"), and two withdrew before the 12-week analysis for personal reasons, and one participant withdrew from the control group before the six-week analysis for personal reasons.

Minor outcomes

Composite responder rate

The study did not measure or report composite responder rate.

Aerobic fitness

The study did not measure or report aerobic fitness.

Depression

The study did not measure or report depression.

Anxiety

The study did not measure or report anxiety.

Exercise plus usual pharmacological care versus usual pharmacological care alone

Six studies compared exercise plus usual care versus usual care alone (Avaux 2016; Benatti 2015; Benatti 2018; Bostrom 2016; Hashemi 2022; Tench 2003).

Major outcomes

See: Summary of findings table 2.

Fatigue (FSS, scale 1 to 7, lower score indicates less fatigue, MCID 1 point)

Two studies (104 participants) found that exercise plus usual care may have little to no effect on mean fatigue. The mean fatigue score in the usual care alone group was 5.4 points, and the mean fatigue score for the exercise plus usual care group was 4.8 points (MD −0.6 points, 95% CI −1.4 to 0.2; Analysis 2.1; Avaux 2016; Tench 2003). Statistical heterogeneity was not important (I^2 = 0%). There was no clinically meaningful benefit. Because of study limitations, we downgraded the evidence two levels for high risk of bias and imprecision; we rated the certainty of evidence as low.

Functional capacity (SF-36 Physical Function, scale 0 to 100, higher score indicates better function, MCID 10 points)

Two studies (96 participants) found that exercise plus usual care may have little to no effect on functional capacity. The mean physical function score in the usual care alone group was 60 points, and the mean physical function score for the exercise plus usual care group was 65.4 points (MD 5.4 points, 95% CI −5.97 to 16.75; Analysis 2.2; Bostrom 2016; Tench 2003). Statistical heterogeneity was not important (I^2 = 0%). There was no clinically meaningful benefit. Because of study limitations, we downgraded the evidence two levels for high risk of bias and imprecision; we rated the certainty of evidence as low.

Disease activity (SLEDAI, scale 0 to 105, lower score indicates less disease activity, MCID 4 points)

Two studies (100 participants) found that exercise plus usual care may have little to no effect on disease activity. The mean disease activity score in the usual care alone group was 0.5 points, and the mean disease activity score for the exercise plus usual care group was 0.43 points (MD −0.07 points, 95% CI −2.8 to 2.66; Analysis 2.3; Bostrom 2016; Tench 2003). Statistical heterogeneity was significant (I^2 = 88%). There was no clinically meaningful benefit. Because of study limitations, we downgraded the evidence two levels for high risk of bias and imprecision. We rated the certainty of evidence as low.

We back-translated the SMD by multiplying the SMD by the SD of the control group at baseline from the most representative trial (Tench 2003).

Quality of life

No studies reported quality of life.

Pain (SF-36 Bodily Pain, scale 0 to 100, lower scores indicate less pain, MCID 10 points)

One study (31 participants) reported pain. We are uncertain whether exercise improves pain. The mean pain score in the usual care alone group was 38 points, and the mean pain score for the exercise plus usual care group was 52 points (MD 16 points, 95% −CI 0.18 to 32.18; Analysis 2.4; Bostrom 2016). There was no important clinically meaningful benefit. Because of study limitations, we downgraded the evidence three levels for high risk of bias and imprecision (low participant numbers and the CIs included a large effect and no effect). We rated the certainty of evidence as very low.

Serious adverse events

No SAEs were reported.

Withdrawals due to any reason

We are uncertain whether exercise results in fewer or more withdrawals (RR 0.92, 95% CI 0.53 to 1.60). Avaux 2016 reported three withdrawals from the study; two for personal reasons, and one due to a disease flare; however, it is unclear which group they were part of, and, therefore, they were not included in our analyses. Benatti 2018 had eight participants withdraw from the intervention; four participants withdrew from the control group (one was pregnant, three for personal reasons) and four participants withdrew from the exercise group (one fractured limb outside of training sessions, three for person reasons). Another two participants withdrew due to a disease flare (one from each group). Bostrom 2016 had three participants withdraw from the control group (one had depression/cognitive impairment, one had untreated dementia, one had suspected relapse of breast cancer). Tench 2003 had 14 participants withdraw due to any reason. Four participants withdrew from the exercise group, five participants withdrew from the active control group (relaxation), and five participants withdrew from the usual care control group. Note that six participants dropped out of treatment and eight participants completed the study but did not wish to repeat the walking test to exhaustion at the end of the intervention. Two trials had no withdrawals from the intervention due to any reason that were reported (Benatti 2015; Hashemi 2022).

Minor outcomes

Composite responder rate

No studies measured or reported (or both) composite responder rate.

Aerobic capacity (peak VO_2, higher scores indicate better aerobic capacity)

Three studies (109 participants) found that exercise plus usual pharmacological care may improve aerobic capacity score when compared to usual pharmacological care alone, however the improvement was not clinically important (MD 1.27 points, 95% CI −0.59 to 3.12; Analysis 2.5; Benatti 2018; Bostrom 2016; Tench 2003).

Depression (BDI, scale 0 to 63, lower scores indicate less depression)

One study (65 participants) found that exercise plus usual pharmacological care may improve depression score when compared to usual pharmacological care alone, however the improvement was not clinically important (MD −0.29 points, 95% CI −0.78 to 0.20; Analysis 2.6; Tench 2003).

Anxiety (HADS, scale 0 to 21, lower scores indicate less anxiety)

One study (65 participants) found that exercise plus usual pharmacological care may improve anxiety score when compared to usual pharmacological care alone, however the improvement was not clinically important (MD −0.80 points, 95% CI −3.02 to 1.42; Analysis 2.7; Tench 2003).

Exercise plus usual pharmacological care versus another non-pharmacological intervention plus usual pharmacological care

Seven studies compared exercise plus usual care versus another non-pharmacological intervention plus usual care (Abrahão 2016; Daltroy 1995; Dos Reis-Neto 2013; Kao 2021; Keramiotou 2020; Miossi 2012; Tench 2003).

Major outcomes

See: Summary of findings table 3.

Fatigue (FSS, scale 1 to 7, lower scores indicate less fatigue severity, MCID 1 point)

Two studies (119 participants) found that exercise plus usual care may reduce fatigue. The mean fatigue score in the non-pharmacological interventions (joint aids and information about their disease, education, and relaxation therapy) plus usual care was 5.3 points, and the mean fatigue score for the exercise plus usual care group was 4.79 points (MD −0.51 points, 95% CI −0.88 to −0.14; Analysis 3.1; Keramiotou 2020; Tench 2003). Statistical heterogeneity was not important (I^2 = 0%). There was no clinically meaningful benefit. Because of study limitations, we downgraded the evidence two levels for high risk of bias and imprecision; we rated the certainty of evidence as low.

We back-translated the SMD by multiplying the SMD by the SD of the control group at baseline from the most representative trial (Tench 2003).

Functional capacity (SF-36 Physical Function, scale 0 to 100, higher scores indicate better functional capacity, MCID 10 points)

Three studies (182 participants) found that exercise plus usual care may increase functional capacity. The mean functional capacity score in the other non-pharmacological interventions (joint aids and information about their disease, education, and relaxation therapy) plus usual care was 41.4 points, and the mean functional capacity score for the exercise plus usual care group was 54.6 points (MD 13.2 points, 95% CI 6.17 to 20.22; Analysis 3.2; Abrahão 2016; Keramiotou 2020; Tench 2003). There was a clinically meaningful benefit. Because of study limitations, we downgraded the evidence two levels for high risk of bias and imprecision. We rated the certainty of evidence as low.

Note that one study (Keramiotou 2020) used Lupus QOL to assess functional capacity; scale 0 to 100, higher scores indicate better functional capacity.

We back-translated the SMD by multiplying the SMD by the SD of the control group at baseline from the most representative trial (Abrahão 2016).

Disease activity (SLEDAI, scale 0 to 52, lower scores indicate lower disease activity, MCID 4 points)

Four studies (184 participants) founds that exercise plus usual care probably results in little to no difference in disease activity. The mean disease activity score in the other non-pharmacological interventions (joint aids and information about their disease, education, and relaxation therapy) plus usual care was 1.2 points, and the mean disease activity score for the exercise plus usual care group was 1.22 points this is SMD but you have written MD, so thats wrong. report as SMD then back-translate to MD to back-tranlsate you need to multiply the SMD by the SD of the control group at baseline from the most representative trial, as you have written in the methods Measures of treatment effect section (MD 0.02 points, 95% CI −0.28 to 0.32; Analysis 3.3; Abrahão 2016; Dos Reis-Neto 2013; Miossi 2012; Tench 2003). Statistical heterogeneity was not significant (I^2 = 1%). There was no clinically meaningful benefit. Because of study limitations, we downgraded the evidence one level for high risk of bias We rated the certainty of evidence as moderate.

Note that one study (Tench 2003) used SLAM to measure disease activity; scale 0 to 83, lower scores indicate less disease activity.

We back-translated the SMD by multiplying the SMD by the SD of the control group at baseline from the most representative trial (Abrahão 2016).

Quality of life

This outcome was measured; however, the MCS score of the SF-36 Quality of Life questionnaire was not reported and, therefore was unable to be included in the analysis.

Pain (VAS, scale 0 to 10, lower scores indicate less pain, MCID 1.5 points)

Two studies (121 participants) found that exercise plus usual care may result in little to no difference in pain. The mean pain score in the other non-pharmacological interventions (joint aids and information about their disease, education, and relaxation therapy) plus usual care was 4.97 points, and the mean pain score for the exercise plus usual care group was -0.29 points (MD −1.59 points, 95% CI −2.46 to -0.71 ; Analysis 3.4; Abrahão 2016; Keramiotou 2020). Statistical heterogeneity was significant (I^2 = 74%). Because of study limitations, we downgraded the evidence two levels for high risk of bias and imprecision. We rated the certainty of evidence as low.

Note that one study (Abrahão 2016) used the SF-36 Bodily Pain domain to measure pain; scale 0 to 100, lower scores indicates less pain.

We back-translated the SMD by multiplying the SMD by the SD of the control group at baseline from the most representative trial (Abrahão 2016).

Serious adverse events

No SAEs were reported.

Withdrawals due to any reason

We are uncertain whether exercise results in fewer or more withdrawals (RR 0.89, 95% CI 0.13 to 5.94). Abrahão 2016 reported two participant withdrawals from the control group for an unknown reason. Keramiotou 2020 reported two participant withdrawals from the exercise group; however, the reasons were not reported. Tench 2003 reported 14 participant withdrawals from the intervention; four participants withdrew from the exercise group, five participants withdrew from the active control group (relaxation), and five participants withdrew from the usual care group. Note that six participants dropped out of treatment and eight participants completed the study but did not wish to repeat the walking test to exhaustion at the end of the intervention. Four trials did not clearly report withdrawals due to any reason (Daltroy 1995; Dos Reis-Neto 2013; Kao 2021; Miossi 2012).

Minor outcomes

Composite responder rate

No studies measured or reported (or both) composite responder rate.

Aerobic fitness (peak VO_2, higher scores indicate better aerobic capacity)

Two studies (99 participants) found an improvement in aerobic capacity score with exercise plus usual care compared to another non-pharmacological intervention (joint aids and information about their disease, education, and relaxation therapy) (MD 1.19 points, 95% CI −1.64 to 4.02; Analysis 3.5; Dos Reis-Neto 2013; Tench 2003). There was no clinically meaningful benefit.

Depression (BDI, scale 0 to 63, lower scores indicate less depression)

One study (61 participants) found that exercise plus usual pharmacological care may improve depression score when compared to another non-pharmacological intervention (joint aids and information about their disease, education, or relaxation therapy) however the improvement was not clinically important (MD −1.40 points, 95% CI −4.61 to 1.81; Analysis 3.6; Abrahão 2016).

Anxiety (HADS, scale 0 to 21, lower scores indicate less anxiety)

One study (61 participants) found that exercise plus usual pharmacological care may improve anxiety score when compared to another non-pharmacological intervention (joint aids and information about their disease, education, or relaxation therapy) however the improvement was not clinically important (MD −1.10 points, 95% CI −3.61 to 1.41; Analysis 3.7; Tench 2003).

Subgroup and sensitivity analyses

Given the small number of studies, we did not conduct subgroup analysis to explore the possible effect of type of exercise (resistance versus cardiorespiratory) on estimated effect size. Neither did we conduct a sensitivity analysis, because we judged all studies at unclear or high risk of bias for most items.

Assessment of publication bias

We had planned to assess publication bias by visual inspection of funnel plots, but we did not generate funnel plots because of the limited number of studies (fewer than 10), and the risk of an underpowered test. We were unable to determine the existence of publication bias.

Discussion

Summary of main results

The main purpose of this review was to evaluate the effectiveness of structured exercise as an adjunctive therapy to usual pharmacological care for people with SLE. Overall, 13 RCTs (540 participants) met the inclusion criteria. The structured exercise programmes amongst the 13 included studies varied; see Table 2, therefore the results of this review are not specific to one type or dosage of exercise. All studies compared a type of exercise, or a combination of types of exercise, plus usual pharmacological care, to a control group that received one of the following; placebo plus usual pharmacological care (Lopes-Souza 2021); usual pharmacological care alone (Avaux 2016; Benatti 2015; Benatti 2018; Bostrom 2016; Hashemi 2022; Tench 2003); or another non-pharmacological intervention (education about the disease/exercise, relaxation therapy, etc.) plus usual pharmacological care (Abrahão 2016; Daltroy 1995; Dos Reis-Neto 2013; Kao 2021; Keramiotou 2020; Miossi 2012; Tench 2003).

We found low-certainty evidence indicating that structured exercise plus usual pharmacological care compared to placebo plus usual pharmacological care may result in little to no effect on fatigue, functional capacity, and pain, measured after the completion of the intervention. And we are uncertain whether exercise results in fewer or more withdrawals (very low-certainty evidence).

We found low-certainty evidence that structured exercise plus usual pharmacological care compared with usual pharmacological care alone may result in little to no effect on fatigue, functional capacity, and disease activity, measured after the completion of the intervention. And we are uncertain whether exercise improves pain (very low-certainty evidence) or results in fewer or more withdrawals (very low-certainty evidence).

We found low- to moderate-certainty evidence that structured exercise plus usual pharmacological care compared to another non-pharmacological intervention (relaxation, education, support aids) plus usual pharmacological care may reduce fatigue (low-certainty evidence), may improve functional capacity (low-certainty evidence), probably results in little to no difference in disease activity (moderate-certainty evidence), and may result in little to no difference in pain (low-certainty evidence), measured after the completion of the intervention. We are uncertain whether exercise results in fewer or more withdrawals (very low-certainty evidence).

We have no clear evidence that structured exercise can induce more adverse events. No studies clearly reported an adverse event as an outcome, or elaborated further on the reasons for a withdrawal and whether this led to further complications, hospitalisation, or

death. We were unable to draw any conclusions.

Overall completeness and applicability of evidence

The evidence provided by this review is limited to the 13 included RCTs that assessed the effectiveness of exercise plus usual pharmacological care versus a control group (placebo plus usual pharmacological care, usual pharmacological care alone, another non-pharmacological intervention plus usual pharmacological care). One RCT that is potentially eligible for this review is awaiting classification because their results have not yet been reported in full (Boedecker 2020).

All studies compared exercise in addition to their usual pharmacological care to no additional exercise; however, there was heterogeneity between exercise interventions with no dose control between the studies. The included studies investigated several different types and combinations of exercise components. Aerobic exercise, in particular walking, was the most frequent exercise type. However, the components were incompletely described in most trials. For example, the material used, who provided the intervention, how it was supervised, and where the exercise was delivered were often missing. The exercise dosage, and level of supervision, could not be explored with indirect statistical techniques, such as meta-regression. Thus, we did not investigate heterogeneity by the type of exercise, or supervision because we were unable to isolate these components from the included studies.

Twelve studies assessed outcome measures at the end of the intervention only (i.e. 12 weeks), which may not have accounted for the long-term effect of exercise, and its feasibility (Abrahão 2016; Avaux 2016; Benatti 2015; Benatti 2018; Daltroy 1995; Dos Reis-Neto 2013; Hashemi 2022; Kao 2021; Keramiotou 2020; Lopes-Souza 2021; Miossi 2012; Tench 2003). Importantly, because SLE may progress or vary over time, it is necessary to assess outcome measurements at more time points, and over a longer period of time (greater than 12 months) to verify the relationship between treatment effect and outcomes (i.e. fatigue).

Most exercise programmes were delivered in conjunction with drug therapy (standard NSAIDs, DMARDs, or biological agents). The benefits of exercise interventions, depending on the type of drug therapy received, could not be determined. Therefore, we do not know if some drugs in addition to exercise have better or worse outcomes for people with SLE. Also, no study specifically evaluated the efficacy of exercise with biological medication versus standard NSAID or DMARD therapy.

An important consideration is that most participants in the studies had minimal disease activity (SLEDAI score less than 4) at baseline, and, therefore, the overall results could not be applicable to all people with SLE. Also, considering that people with SLE can experience varying symptoms and degree of symptoms over time, the change in outcomes from baseline to the end of intervention need to be read with caution (i.e. the change in outcome reporting might be more a reflection of how they were feeling on that day of testing, rather than a change in feelings before and after the intervention).

Other outcomes needed to understand more about the risk/benefit ratio of exercise, which have been included in this review, is participant-reported fatigue, quality of life, pain, depression, and anxiety. Importantly, these outcomes should be evaluated using standardised outcome tools that are validated in SLE (e.g. FACIT) (Lai 2011), as well as dynamic muscle strength and aerobic fitness, which could be observed to link the relationship between disease-related outcomes and exercise. With respect to the instruments used to measure health-related quality of life, the SF-36 was the most frequently used tool in the included studies. Although the use of the SF-36 allows for comparison of

quality of life in various diseases, it lacks characteristic details that are specific in SLE, such as body image and intimate relationships (McElhone 2010). SLE-specific instruments, such as the 34-item LupusQOL developed by McElhone and colleagues in 2007 (McElhone 2007) and the 40-item SLEQOL developed by Leong and colleagues in 2005 (Leong 2005), might be able to offer enhanced responsiveness to changes in health-related quality of life than the SF-36. Future studies may want to use these instruments either alone or in combination with a generic measure to ensure that both disease-specific and wider aspects of quality of life are assessed.

Inherent with exercise trials, it is difficult to blind participants to the intervention. Therefore, bias introduced by a placebo effect can potentially overestimate the efficacy of an intervention, particularly in the evaluation of subjective outcomes. As such, future trial designs could instead be double blinded and compare different modes (aerobic, resistance, range of motion), intensities (low, moderate, and high according to RPE or percentage of maximum heart rate), time of exercise (i.e. 10-minute or 60-minutes bouts), or a combination of these to increase our understanding of exercise guidelines in SLE. In addition, to minimise detection bias, consistent blinding of outcomes assessors is recommended, since participants cannot be blinded to the intervention.

There was heterogeneity between outcome measures amongst studies and outcomes that were included in dose-matched studies. There was also methodological limitations, risk of bias, and an overall limited number of participants in the studies. The evidence derived from the included studies does not allow strong conclusions to be drawn about which specific components of exercise are best in terms of dose of exercise, and level of supervision. There needs to be 1. more studies completed assessing the effects of exercise in people with varying levels of disease activity; 2. more participants in the trials; 3. homogeneous outcomes that are more sensitive to change in SLE (i.e. FACIT-Fatigue, LupusQOL, SLEDAI, etc.; 4. trials that compare various doses of exercise (i.e. aerobic versus resistance training on fatigue, disease activity etc.); and 5. longitudinal study designs that focus on change in disease-related outcomes as well as exercise adherence, physical activity levels, and sustainability of outcomes over a longer period of time.

Quality of the evidence

We had concerns about the risk of bias for all studies included: eight (62%) studies had either high or unclear allocation concealment; all failed to blind participants or outcome assessors; six (46%) had incomplete outcome data; and seven (54%) had a high risk of selective reporting. Given the number of studies included in the review, we cannot rule out the existence of a small-study effect, explaining the magnitude of the positive results we found.

We considered statistically significant group differences between exercise plus usual pharmacological care versus a control group (placebo plus usual pharmacological care, usual pharmacological care alone, or another non-pharmacological intervention such as relaxation therapy, support aids, or education about the disease plus usual pharmacological care). For each comparison, the number of studies (fewer than 10), and small samples (many studies were small, with fewer than 100 participants) might have contributed to a low-power analysis. Low power is associated with bias (Button 2013). Most studies we included were at high or unclear risk of bias, which suggests that the estimated effects might be overestimated, and reduces the likelihood that they reflect a true effect. We cannot provide conclusions with a high level of confidence. The magnitude of the estimated effects may change with larger studies.

We only presented the findings of trials that reported the major outcomes of interest in Summary of findings table 1; Summary of findings table 2; Summary of findings table 3; and used the GRADE approach to assess the certainty of the evidence examined for each outcome (Schünemann 2020a). Most of the evidence was downgraded to low or very low certainty, based on two factors: risk of bias and imprecision with small trials and large CIs.

Potential biases in the review process

We made all attempts to reduce the bias involved in the review process by including the best available evidence. All studies included were RCTs or quasi-RCTs. However, by restricting the inclusion criteria to RCTs only, we may have limited the number of included trials and potentially missed useful additional evidence. We conducted an extensive search of the literature in all relevant databases and identified all relevant trials meeting the reviews' eligibility criteria. None of the review authors have been involved in the conduct of the included trials. A minimum of two review authors independently selected studies, extracted data, assessed the risk of bias, and graded the certainty of evidence in all studies. Even though we searched as extensively as possible, we may have missed eligible studies, such as studies reported only in dissertations or conference proceedings. For missing data, we systematically sought information from study authors. However, most of our attempts to contact study authors were unsuccessful, and most data came from published sources.

This review has some limitations. We could not determine whether participants who received usual pharmacological care also completed their own exercise independent of the trials exercise intervention, because the included studies poorly described the content of usual pharmacological care interventions. In some studies, we could not determine what constituted usual care. Participants in the usual pharmacological care groups could have practised exercises, or could have been on more drugs than outlined in the study, which could explain why there was a smaller effect size or no effect when comparing exercise to a control group. A possible explanation could also be the result of performance bias, due to lack of blinding, inherent in exercise interventions and when using subjective participant-reported outcome measures (PROMs). Another limitation was the heterogeneous use of outcome measures amongst the included studies, making it difficult to meta-analyse the data.

We found wide variations amongst the trials, likely related to different exercise components. Despite the prespecification stated in our protocol, we could not perform subgroup analyses to explore heterogeneity for factors such as exercise supervision or modalities of exercises. We had to decide what type of 'exercise' should be included; we excluded single bouts of exercise (i.e. one exercise session or exercise test), or unstructured exercise (i.e. no clear dosage prescription). The cutoff might be contentious, particularly with unstructured exercise, and discussion regarding whether to include structured and unstructured exercise into another review should be considered. Last, the number of included studies and participants in this review was too small.

Agreements and disagreements with other studies or reviews

Three different systematic reviews have examined the effects of exercise in people with SLE (Lu 2021; O'Dwyer 2017; Wu 2017). None included all the RCTs we identified, all of which compared the effects of exercise to placebo, usual care alone, or another non-pharmacological intervention.

O'Dwyer 2017 performed a systematic review and included 11 studies (Abrahão 2016; Avaux 2016; Benatti 2015; Bogdanovic 2015; Bostrom 2016; Carvalho 2005; Dos Reis-Neto 2013; Miossi 2012; Ramsey-Goldman 2000; Robb-Nicholson 1989; Tench 2003), consisting of six RCTs and five quasi-RCTs. Five studies compared an exercise intervention to a control group (usual care, or unchanged physical activity status) (Bostrom 2016; Carvalho 2005; Dos Reis-Neto 2013; Miossi 2012; Robb-Nicholson 1989), and two studies compared an aerobic exercise programme to a range of movement/muscle strength programme (Bogdanovic 2015; Ramsey-Goldman 2000). The systematic review included seven studies in the meta-analyses (Abrahão 2016; Boström 2016; Carvalho 2005; Dos Reis-Neto 2013; Miossi 2012; Robb-Nicholson 1989; Tench 2003). Meta-analyses were deemed appropriate for four outcomes: disease activity, fatigue, aerobic capacity, and depression. Results showed that disease activity was not changed following exercise interventions (MD 0.01, 95% CI −0.54 to 0.56), fatigue decreased in the exercise intervention group compared to controls (MD −0.52, 95% CI −0.91 to −0.13), and depression scores lowered in the exercise groups compared to the controls (SMD −0.40 SD, 95% CI −0.71 to −0.09). Most of these studies were at risk of selection and reporting bias.

Wu 2017 performed a systematic review and included three studies (Carvalho 2005; Ramsey-Goldman 2000; Tench 2003), consisting of two RCTs and one quasi-experimental study. Aerobic exercise, three times a week and of moderate intensity, was a common component of the three studies. Two studies were conducted in a supervised setting and one study was based at home. One study had a duration of eight weeks and two studies had a duration of 12 weeks. All three studies were included in the meta-analyses and showed that compared to controls aerobic exercise training decreased fatigue severity (MD −0.52, 95% CI −0.91 to −0.13), and showed a positive effect on the SF-36 Vitality subscale (MD 14.98, 95% CI 7.45 to 22.52). However, the quality of evidence assessed using PEDro was downgraded to fair (Tench 2003) or poor (Ramsey-Goldman 2000).

Lu 2021 performed a systematic review on the effects of exercise on health-related quality of life and included nine studies, consisting of five RCTs (Abrahão 2016; Bostrom 2016; Keramiotou 2020; Lopes-Souza 2021; Tench 2003), and four non-RCTs (random allocation or control group were not available). Not all studies used the SF-36 Health-related Quality of Life measure or all of its subscales, therefore, nine separate meta-analyses were conducted, including: one analysis on all five studies regardless of the health-related quality of life measure; another analysis on four studies that used the SF-36 Physical Function domain; and seven analyses on studies that used the remaining seven domains of the SF-36. The results of the meta-analysis of the five RCTs showed a positive effect of exercise on the physical health and function aspect (SF-36 Physical Function and LupusQOL Physical Health) of health-related quality of life amongst participants with SLE (Hedges' g: 0.468, 95% CI 0.206 to 0.730; P < 0.001). Heterogeneity between studies was low (I^2 = 19.2%; P = 0.292).

Our findings are largely consistent with the findings of the above systematic reviews in terms of exercise effectiveness. The differences with our review are that we have included an updated trial (Hashemi 2022), and we have only included RCTS, whereas the other reviews also included other study designs. Also, we included three separates analyses to evaluate the effectiveness of exercise as 'adjunctive therapy' in SLE (exercise plus usual pharmacological care versus 1. Placebo plus usual pharmacological care, 2. Usual pharmacological care alone, and 3. Another non-pharmacological intervention plus usual pharmacological care). This review adds to the existing knowledge of exercise in SLE by emphasising that exercise can be used as an adjunctive therapy to the usual pharmacological care for SLE. The reason this is important is that most people with SLE will be taking or practising one or more pharmaceutical or non-pharmaceutical interventions (or both), thus exercise should be considered as adjunctive to this; it would be difficult to know

the true effect of exercise alone on people with SLE. Furthermore, this review revealed the lack of homogeneous study designs, outcome tools used, and lack of detail in exercise prescription amongst trials, and has shown the need for more rigorous studies in SLE and exercise to be considered.

Authors' conclusions

Implications for practice

We found low-certainty evidence indicating that structured exercise plus usual care compared to placebo plus usual care may result in little to no effect on fatigue, functional capacity, and pain, measured after the completion of the intervention. We are uncertain whether exercise results in fewer or more withdrawals (very low-certainty evidence).

We found low-certainty evidence that structured exercise plus usual care compared with usual care alone may result in little to no effect on fatigue, functional capacity, and disease activity, measured after the completion of the intervention. We are uncertain whether exercise improves pain (very low-certainty evidence) or results in fewer or more withdrawals (very low-certainty evidence).

We found moderate- to low-certainty evidence that structured exercise plus usual care compared to another non-pharmacological intervention (relaxation, education, support aids) plus usual care may reduce fatigue (low-certainty evidence), may improve functional capacity (low-certainty evidence), probably results in little to no difference in disease activity (moderate-certainty evidence), and may result in little to no difference in pain (low-certainty evidence), measured after the completion of the intervention. We are uncertain whether exercise results in fewer or more withdrawals (very low-certainty evidence).

We are uncertain of the potential for harm from structured exercise, because of the limited number of studies reporting adverse events. We are unable to distinguish the best dosage of exercise, including frequency, intensity, type, or its mode of delivery.

Considering there is low-certainty evidence on the benefits and harms of exercise, clinicians should ensure that exercise is tailored to the individual, prescribed according to the individuals' physical abilities and limitations, and monitored by an exercise professional (e.g. exercise physiologist, physical therapist, physiotherapist). People with systemic lupus erythematosus (SLE) should seek advice from their healthcare team when starting any new exercise programme, choose exercise that they enjoy, that is individually appropriate to their physical ability, and avoid exercising in the sun when the ultraviolet index is high (greater than 3).

Implications for research

The evidence for the major outcomes was moderate, low, or very low certainty, so new studies could change the estimate effects. This review has raised new questions to answer and implications for further research.

The long-term effects of structured exercise for people with SLE, and whether they are clinically relevant are unclear. Longitudinal studies of exercise in SLE that report harms data (adverse events and withdrawals, with reason) on more people with SLE, followed for a longer duration (i.e. exercise performed for more than three months) are needed to improve our understanding of the benefit/risk ratio of exercise. Furthermore, well-designed

trials are needed to elucidate the benefits/harms of exercise in SLE, focusing on important outcomes such as disease activity using standardise outcome tools such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)-2K, damage indices such as Systemic Lupus International Collaborating Clinics Damage Indices (SLICC-DI), and specifically looking at changes in serological markers including anti-double stranded DNA (anti-dsDNA), complement levels C3 and C4, as well as inflammatory markers erythrocyte sedimentation rate, C-reactive protein, and interleukin-6. Adverse events were rarely measured or reported (or both) in the included trials. Whether structured exercise as an adjunct therapy to usual care produces harmful effects is difficult to determine. Studies should systematically investigate and report adverse events.

Future trials of exercise in SLE should provide an accurate description of the content, dose, application, and adherence to the exercise interventions. The Consensus on Exercise Reporting Template, or the CONSORT Template for Intervention Description and Replication should be used in future trials of exercise to improve the description of exercise programmes and facilitate its application and findings in clinical practical. Furthermore, new trials of exercise in SLE could be well-designed and double blinded to effectively compare different modes (aerobic, resistance, range of motion), intensities (low, moderate, and high according to rating of perceived exertion or percentage of maximum heart rate), time of exercise (i.e. 10-minute or 60-minutes bouts), or a combination of these. We also recommend that future trials include more diverse participants (disease activity, age, sex, race/ethnicity, functional capacity), and results be further analysed by subgroups. In particular, we recommend that participants with higher disease activity (SLEDAI greater than 4) be included in future exercise trials. Further research should aim to determine the efficacy of exercise interventions in people with SLE receiving different therapies (non-steroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, biological agents, and no treatment).

Last, standardised efficacy outcomes in exercise trials for people with SLE are needed. For example, all studies using the 36-item Short Form questionnaire to assess quality of life should report the Mental Component Summary and Physical Component Summary scores. All trials should report disease activity using a standardised and validated tool such as SLEDAI to report changes in disease activity before and following an intervention, to add further information regarding the potential harms or benefits of exercise. Furthermore, all trials should measure and report fatigue, functional capacity, and other exercise capacity measures such as aerobic capacity and strength to determine the effectiveness of the exercise intervention.

Acknowledgements

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Data and analyses

Comparison 1

Exercise plus usual pharmacological care versus placebo plus usual pharmacological care (exercises versus placebo)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Fatigue (FACIT fatigue, score 0–52, lower scores indicate less fatigue)	1	17	Mean Difference (IV, Random, 95% CI)	-5.00 [-13.29, 3.29]
1.2 Functional capacity (SF-36 Function Capacity domain, score 0–100, higher scores indicate better functional capacity)	1	17	Mean Difference (IV, Random, 95% CI)	-2.50 [-23.78, 18.78]
1.3 Pain (SF-36 Pain domain, score 0–100, lower scores indicate less pain)	1	17	Mean Difference (IV, Random, 95% CI)	-9.00 [-28.88, 10.88]
1.4 Withdrawals for any reason	1	21	Risk Ratio (M-H, Random, 95% CI)	2.73 [0.34, 22.16]

Comparison 2

Exercise plus usual pharmacological care versus usual pharmacological care alone (exercise versus usual care alone)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Fatigue (Fatigue Severity Scale, score 1–7, lower score indicates less fatigue)	2	104	Mean Difference (IV, Random, 95% CI)	-0.59 [-1.40, 0.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Functional capacity (SF-36 Physical Function domain, score 0–100, higher scores indicate better functional capacity)	2	96	Mean Difference (IV, Random, 95% CI)	5.39 [-5.97, 16.75]
2.3 Disease activity (various scales, lower scores indicate less disease activity)	2	100	Mean Difference (IV, Random, 95% CI)	-0.26 [-3.69, 3.17]
2.4 Pain (SF-36 Pain domain, score 0–100, lower scores indicate less pain)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.5 Aerobic capacity (peak oxygen uptake, higher scores indicate better aerobic capacity)	3	109	Mean Difference (IV, Random, 95% CI)	1.27 [-0.59, 3.12]
2.6 Depression (various scales, lower score indicates less depression)	1	65	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.78, 0.20]
2.7 Anxiety (HADS Anxiety, score 0–21, lower score indicates less anxiety)	1	65	Mean Difference (IV, Random, 95% CI)	-0.80 [-3.02, 1.42]
2.8 Withdrawals for any reason	6	235	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.53, 1.60]

Comparison 3

Exercise plus usual pharmacological care versus another non-pharmacological intervention plus usual pharmacological care (exercise versus active control)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Fatigue (various scales, lower score indicate less fatigue)	2	119	Std. Mean Difference (IV, Random, 95% CI)	-0.51 [-0.88, -0.14]
3.2 Functional capacity (various scales, higher scores indicate better functional capacity)	3	182	Mean Difference (IV, Random, 95% CI)	13.20 [6.17, 20.22]
3.3 Disease activity (various scales, lower scores indicate less disease activity)	4	184	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.28, 0.32]
3.4 Pain (various scales, lower score indicates less pain)	2	121	Mean Difference (IV, Random, 95% CI)	-1.59 [-2.46, -0.71]
3.5 Aerobic capacity (peak oxygen uptake, higher scores indicate better aerobic capacity)	2	99	Mean Difference (IV, Random, 95% CI)	1.19 [-1.64, 4.02]
3.6 Depression (BDI, score 0–63, lower scores indicate less depression)	1	61	Mean Difference (IV, Random, 95% CI)	-1.40 [-4.61, 1.81]
3.7 Anxiety (HADS Anxiety, score 0–21, lower score indicates less anxiety)	1	61	Mean Difference (IV, Random, 95% CI)	-1.10 [-3.61, 1.41]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size	
3.8 Withdrawals for any reason	7	317	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.13, 5.94]	

History

Protocol first published: Issue 10, 2021

Contributions of authors

All review authors contributed to each stage of the review including screening of articles, extraction of study characteristics, extraction of outcomes, review of risk of bias, GRADE assessment, writing, and proofreading the review.

SF: screening included and excluded studies, extraction of study characteristics, extraction of outcomes, risk of bias, GRADE, summary of findings table, writing the review, proofreading the review.

SO: review of risk of bias, summary of findings, review of the results and discussion.

EN: screening included and excluded studies and extraction of characteristics of studies, and review of the additional tables.

DG: reviewed and corroborated risk of bias.

MC: review of risk of bias, summary of findings table, review of the results and discussion.

Declarations of interest

SF: none.

SO: none.

EN: none.

DG: none.

MC: none.

Sources of support

Internal sources

- University of Southern Queensland, Australia

  The University of Southern Queensland provided in-kind support in the form of time release, library support, and computer and print access for SF and MC to complete this review.

External sources

- New Source of support, Other

Differences between protocol and review

We made the following changes from the protocol (Frade 2021).

We clarified the definition of usual care: "Usual pharmacological care could include, but not limited to, the following standard pharmacological drug treatments; antimalarials such as hydroxychloroquine, NSAIDs, glucocorticoids such as prednisone, immunosuppressives such as mycophenolate, biologicals such as belimumab or rituximab, and/or c. Other non-pharmacological measures may also have included sun avoidance, commonly prescribed supplementation (i.e. vitamin D), and education about the disease or managing comorbidities such as hypertension, for example (Fanouriakis 2019)."

We changed the preferred order of the data synthesis to reflect the hierarchy of the control group:

1. Exercise plus usual care versus placebo plus usual care
2. Exercise plus usual care versus usual care alone
3. Exercise plus usual care versus another non-pharmacological intervention (e.g. education about exercise, counselling about exercise, relaxation exercises) plus usual care.

We changed the major outcome: 'withdrawals due to adverse events' to 'withdrawals for any reason,' inclusive of any adverse events. We removed withdrawals from the minor outcomes.

The review authors who screened the titles and abstracts, and full-text, has been changed to SF and EN. The third review author has been changed to MC.

Extraction of study characteristics has been changed from one author (SF) to two authors (SF, EN) who will both spot-check for accuracy.

We clarified the definition of end time point of data extraction to be when the structured exercise intervention had completed (i.e. the exercise intervention went for 12 weeks; however, participants were advised to continue to exercise and were followed up).

We did not do the following: in the 'Effects of interventions' results section and the 'What happens' column of the summary of findings table, we provided the absolute percent change and the NNTB or NNTH (the NNTB or NNTH was provided only when the outcome shows a clinically significant difference).

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Abrahão 2016

Study characteristics

Methods	**Study design:** single-centre, parallel-group, 3-arm RCT **Setting:** Rheumatology Services at the Interlagos Specialty Outpatient Clinic, Santo Amaro University (UNISA), São Paulo, Brazil **Time trial period:** study process occurred between March 2011 and March 2012 **Interventions:** cardiovascular exercise plus usual care vs resistance exercise plus usual care vs control group plus usual care **Sample size calculation:** sample size calculated based on primary outcome considering a clinically significant difference with moderate treatment effect of 40%. Considering a significance level of 5% and power of 90%, they estimated 20 participants in each group. **Analysis:** data presented take into consideration that 2 participants dropped out of study, thus ITT analyses performed to adjust the analysis of the intervention effects.

Participants

Number of participants

1. Screened: 92 (29 were not eligible and did not meet inclusion criteria)
2. Randomised: 63 (21 in cardiovascular exercise group, 21 in resistance exercise group, 21 in the control group)
3. Included in analyses: 61 participants included in the 3-month analysis (2 participants from the control group abandoned the study without reason)

Inclusion criteria

1. Aged ≥ 18 years
2. Diagnosis of SLE according to ACR criteria

Exclusion criteria

1. Absolute or relative contraindications to physical exercise according to ACSM guidelines
2. Not being available for 2 consecutive weeks during 12-week study period
3. Participation in regular physical activity in past 6 months

Baseline characteristics

Total participants (n = 63) comprised 61 women and 2 men, mean age 42.9 (SD 14.4) years, with mean BMI 28.7 (SD 10.6) kg/m^2, and mean disease duration 3.8 (SD 3.3) years

Cardiovascular exercise group (n = 21)

1. Mean age: 43.8 (SD 14.6) years
2. Mean BMI: 27.5 (SD 10.4) kg/m^2
3. Mean disease duration: 4.9 (SD 4.3) years
4. Mean SLEDAI disease activity: 1.8 (SD 0.6) points
5. Mean BDI: 20.6 (SD 5.3) points
6. Mean 12-min walk test: 1019.7 (SD 224.9) m
7. Mean SF-36
    a. Physical Role Functioning: 33.3 (SD 34.5)
    b. Physical Functioning: 38.7 (SD 27.9)
    c. Vitality: 30.3 (SD 18.8)
    d. Emotional Role Functioning: 27.1 (SD 28.1)
    e. Social Role Functioning: 34.2 (SD 23.9)
    f. Mental Health: 25.6 (SD 21.2)
    g. Bodily Pain: 24.2 (SD 23.9)
    h. General Health Perception: 37.5 (SD 26.3)
    i. Change in Health Status: 3.3 (SD 0.8)

Resistance training exercise group (n = 21)

1. Mean age: 39.1 (SD 14.4) years
2. Mean BMI: 27.8 (SD 11.6) kg/m^2
3. Mean disease duration: 3.5 (SD 3.3) years
4. Mean SLEDAI disease activity: 1.4 (SD 0.6) points
5. Mean BDI: 19.4 (SD 5.0) points
6. Mean 12-min walk test: 911.2 (SD 171.8) m
7. Mean SF-36
    a. Physical Role Functioning: 17.3 (SD 16.5)
    b. Physical Functioning: 33.3 (SD 14.4)
    c. Vitality: 28.3 (SD 17.1)
    d. Emotional Role Functioning: 18.8 (SD 20.7)
    e. Social Role Functioning: 21.8 (SD 16.4)
    f. Mental Health: 29.0 (SD 15.7)
    g. Bodily Pain: 24.2 (SD 15.3)
    h. General Health Perception: 22.4 (SD 12.5)
    i. Change in Health Status: 3.2 (SD 0.8)

Control group (n = 21)

1. Mean age: 46.1 (SD 14.1) years
2. Mean BMI: 30.9 (SD 10.1) kg/m^2
3. Mean disease duration: 3.08 (SD 1.7) years
4. Mean SLEDAI disease activity: 2.3 (SD 1.7) points
5. Mean BDI: 19.1 (SD 5.6) points
6. Mean 12-min walk test: 936.5 (SD 169.1) m
7. Mean SF-36

	a. Physical Role Functioning: 24.9 (SD 27.2) b. Physical Functioning: 41.9 (SD 21.7) c. Vitality: 29.4 (SD 16.3) d. Emotional Role Functioning: 24.7 (SD 17.9) e. Social Role Functioning: 28.9 (SD 23.9) f. Mental Health: 23.6 (SD 13.7) g. Bodily Pain: 22.0 (SD 15.5) h. General Health Perception: 32.4 (SD 26.3) i. Change in Health Status: 3.4 (SD 0.7) **Pretreatment group differences:** the 3 groups were homogeneous for age, disease duration, weight, and height at baseline.
Interventions	**Exercise: cardiovascular training group plus usual care** 1. **Frequency of exercise sessions:** 3 times/week 2. **Intensity of exercise:** moderate intensity (65–75% of maximum HR according to the ACSM guidelines). Exercise intensity determined by HR reserve (HRR), which was calculated by HRR = MHR – RHR. MHR determined using: MHR = 205 − (0.42 × age). 3. **Time of exercise session:** 50 min per session 4. **Type of exercise:** cardiovascular exercise walking and bicycle ergometry interventions (Model CLB 10 Classic, Caloi, Sao Paulo, Brazil). Each training session consisted of a 10-min warm-up followed by 30 min of exercise at target HR and a 10-min cool-down. 5. **Duration of intervention:** 12 weeks 6. **Supervision/setting:** trained professional in Rheumatology Services at Interlagos Specialty Outpatient Clinic **Exercise: resistance training group plus usual care** 1. **Frequency of exercise sessions:** 3 times/week 2. **Intensity of exercise:** moderate intensity (65–75% of 1 repetition maximum (1 RM) according to the ACSM guidelines). To establish the training intensity for each participant, their 1 RM for each exercise was determined. Training intensity changed over time as the participants progressed. 3. **Time of exercise session:** 50 min per session 4. **Type of exercise:** resistance training exercise. Each session consisted of 8 exercises, including holds (crucifix) with free weights, extension-machine exercises, rowing exercise with an elastic band, knee flexion with ankle weights, 2-arm biceps curls, adduction exercises with an elastic band, French curls, and abdominal exercises. Training involved small and large muscle group exercises. Participants performed 3 sets of 15 repetitions with rest intervals of 1 min between sets. 5. **Duration of intervention:** 12 weeks 6. **Supervision/setting:** trained professional in the Rheumatology Services at Interlagos Specialty Outpatient Clinic **Control group (another non-pharmacological intervention plus usual care)** Participants in control group received usual care and information about the disease, but no exercise intervention. These participants were informed that they would receive the intervention after the study was finished, and they would be invited to participate in the intervention that proved the most effective.
Outcomes	All outcomes measured at baseline and at 3 months. 1. **Health-related quality of life:** measured using the SF-36. Measure is grouped into 8 domains: Physical Functioning, Physical Role Functioning, Bodily Pain, General Health Perceptions, Vitality, Social Role Functioning, Emotional Role Functioning, and Mental Health. Scores on each subscale ranged from 0 to 100, with 0 = worst health status and 100 = best health status. Change in health status after intervention from baseline was also assessed. 2. **Severity of depression:** measured using BDI. This is a 21-item, multiple-choice inventory. Individual scale items are scored on a 4-point continuum (0 = least, 3 = most), with a total summed score range of 0–63. Lower scores indicate a better outcome. 3. **Disease activity:** measured using SLEDAI. This gives a score range of 0–101, higher score = higher overall disease activity. 4. **Aerobic capacity:** measured using the 12-min walk test. The more distance covered in 12 min = the better the outcome.
Notes	**Country:** Brazil **Funding:** no funding source reported **Trial registration:** ClinicalTrials.gov as NCT01016665. **Serious adverse events:** none reported **Other adverse events:** none reported **Total adverse events:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported as an RCT and clearly reported randomisation process. Quote: "Allocation sequence was generated using a computer-generated randomisation chart".
Allocation concealment (selection bias)	Low risk	Allocation sequence clearly reported. Quote: "…was concealed in opaque sealed envelopes that were opened just before the intervention was started".

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients in the control group received usual care and information about the disease, but no exercise intervention. These patients were informed that they would receive the intervention after the study was finished". Comment: it is evident that participants were not blinded to the study groups; judged at high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor reported: unclear The personnel conducting the assessor reported outcome for aerobic capacity was not clearly identified, and, therefore, it is unclear whether assessors were blinded to the study design and groups. Authors did report that the same rheumatologist clinically evaluated participants during the course of the intervention, who was blinded to the hypothesis; however, it is unclear if they were blinded to the groups. Participant reported: high Assessors (i.e. participants) were not blinded to the self-reported outcome measures (i.e. fatigue); judged at high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants dropped out of study for unknown reasons, and ITT was performed to analyse intervention effects.
Selective reporting (reporting bias)	High risk	Authors assessed QoL using the SF-36 questionnaire; however, did not report the Mental Component Summary score or the Physical Component Summary score, or both.
Other bias	Low risk	No other biases.

Avaux 2016

Study characteristics	
Methods	**Study design:** quasi-randomised 3-arm parallel RCT **Setting:** supervised training group trained in the hospital-based revalidation centre under the supervision of a multidisciplinary team, while the home training group exercised at home on their own. **Time trial period:** process occurred between June 2012 and January 2013 **Interventions:** home training group plus usual care vs supervised training group plus usual care vs plus usual care (control group) **Sample size calculation:** pilot and exploratory study, therefore, study author did not perform statistical power analyses. **Analysis:** results were compared by paired t-tests or Wilcoxon signed rank tests, as appropriate.

Participants	**Number of participants** 1. Screened: 45 2. Randomised: 42 (18 in home training group, 15 in supervised training group, and 9 in control group). 3 did not meet the inclusion criteria at baseline (screening failures: FSS too low in 1, and major physical disability in 2). 3. Included in 3-month analyses: 39 (17 in home training group, 14 in supervised training group, 8 in control group). 3 participants left the protocol during the first 3 months due to disease flare (n = 1), or personal reasons (n = 2). However, it is unclear which reason was associated to which group. 4. Included in 9-month analyses: 29 (13 in home training group, 10 in supervised training group, and 6 in control group). 10 participants declined evaluation at 9 months. **Inclusion criteria** 1. Diagnosis of SLE according to ACR criteria. 2. Presence of fatigue, as defined by a Krupp's FSS ≥ 3.7 3. Followed at their lupus clinic **Exclusion criteria** 1. If fatigue was due to anaemia, iron deficiency, hypothyroidism, or any other organic cause, as assessed by the same senior clinician 2. If they had extreme physical disability compromising exercise **Baseline characteristics** Total participants comprised 40 women and 2 men ***Home training group (n = 18)*** 1. Gender (F/M): 16/2 2. Mean age: 37 (SD 7) years 3. Mean disease duration: 12 (SD 7) years 4. Mean SLEDAI disease activity: 2.33 (SD 3.78) points 5. Mean SLICC/ACR-DI: 0.6 (SD 0.9) points 6. Mean FSS: 5.8 (SD 0.7) points 7. Mean PWC $_{75\%}$/kg: 1.1 (SD 0.4) 8. Mean Borg scale: 4.6 (SD 3.5) ***Supervised training group (n = 15)*** 1. Gender (F/M): 15/0 2. Mean age: 43 (SD 7) years 3. Mean disease duration: 16 (SD 10) years 4. Mean SLEDAI disease activity: 3.60 (SD 3.87) points 5. Mean SLICC/ACR-DI: 0.5 (SD 0.7) points 6. Mean FSS: 5.8 (SD 0.7) points 7. Mean PWC $_{75\%}$/kg: 1.0 (SD 0.3) 8. Mean Borg scale: 5.7 (SD 5.1) ***Control group (n = 9)*** 1. Gender (F/M): 9/0 2. Mean age: 46 (SD 11) years 3. Mean disease duration: 16 (SD 10) years 4. Mean SLEDAI disease activity: 1.78 (SD 2.72) points 5. Mean SLICC/ACR-DI: 0.4 (SD 0.7) points 6. Mean FSS: 5.3 (SD 1.2) points 7. Mean PWC $_{75\%}$/kg: 1.0 (SD 0.3) 8. Mean Borg scale: 5.7 (SD 5.1) **Pretreatment group differences:** baseline characteristics of the 3 groups did not differ.

Interventions	**Exercise: home training group plus usual care** 1. **Frequency of exercise sessions:** not specified. Participants were asked to perform 3 hours of exercise per week. 2. **Intensity of exercise:** moderate intensity (60–80% of theoretical MHR). The modified Borg scale was used to determine participant's perception of exertion at $PWC_{75\%}$. 3. **Time of exercise session:** not specified. Participants were asked to perform 3 hours of exercise per week. 4. **Type of exercise:** endurance exercise (walking or bicycle) and strengthening exercises (elastic band or weights for upper and lower limbs), performed at home on their own. 5. **Duration of intervention:** 12 weeks 6. **Setting:** unsupervised and performed at home. **Exercise: supervised training group plus usual care** 1. **Frequency of exercise sessions:** not specified. Participants were asked to perform 3 hours of exercise per week. 2. **Intensity of exercise:** moderate intensity (60–80% of theoretical MHR). The modified Borg scale was used to determine participant's perception of exertion at $PWC_{75\%}$. 3. **Time of exercise session:** not specified. Participants were asked to perform 3 hours of exercise per week. 4. **Type of exercise:** endurance exercise (walking or bicycle) and strengthening exercises (elastic band or weights for upper and lower limbs), performed in hospital-based revalidation centre under supervision of multidisciplinary team. 5. **Duration of intervention:** 12 weeks 6. **Supervision/setting:** supervised by multidisciplinary team in hospital-based revalidation centre. At the start of programme, the home and supervised groups participated in a multidisciplinary information session about the benefits of exercise in SLE, during which practical information was also delivered. Participants in the home and supervised groups were asked to record their number of training hours. **Control group (usual care alone)** Participants in the control group did not participate in the information session and were asked not to change their level of physical activity.
Outcomes	All outcomes measured at baseline, 3 months, and 9 months. 1. **Change in fatigue:** measured using Krupp's FSS. FSS is a 9-item questionnaire, scored on a 7-point Likert scale with 1 = strongly disagree, and 7 = strongly agree. Minimum raw score is 9 and maximum score is 63. However, the mean of all scores can also be taken with a minimum score of 1 and a maximum score of 7. Higher score = greater fatigue severity. A change score of 1.9 points is considered a clinically important change. 2. **Cardiorespiratory endurance:** assessed as physical working capacity (expressed in Watts/kilogram bodyweight) measured at 75% of the predicted MHR ($PWC_{75\%}$/kg). This index was calculated during a multistage submaximal bicycle test, starting at 30 W and increased by 30 W every 2 min, until participant's HR reached ≥ 75% of predicted value. The modified BORG scale was used to determined participant's perception of exertion at $PWC_{75\%}$*(data not shown in this study)*. 3. **Compliance:** measured by training hours recorded by participants. They subdivided participants into 2 groups, those who performed > 50% of prescribed exercises (compliant group n = 15) and those who performed less (non-compliant group n = 15), irrespective of their initial assignment to the home or supervised group.
Notes	**Country:** Belgium **Funding:** grant from Association Lupus Erythémateux, via the Fonds pour la Recherche Scientifique en Rhumatologie/Fondation Roi Baudouin. **Trial registration:** not reported **Serious adverse events:** none reported **Other adverse events:** 1 participant withdrew following the 3-month analysis due to a disease flare. However, it is unclear which arm the participant was part of, or the extent of the disease flare. **Total adverse events:** none reported **Data analysis:** contacted authors to request missing data for FSS scores; however, no response received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Although the authors reported randomisation in the methods, we considered this study to be quasi-randomised. Method of randomisation was not truly random; judged at high risk of bias. Quote: "Patients living less than 30 min away from the hospital were included in the supervised training group (STG), the others in the home training group (HTG). Those patients who declined to train (n = 4) or refused their allocation (n = 7) constituted the control group (CG)."
Allocation concealment (selection bias)	High risk	No allocation concealment was reported in the article. However, based on the randomisation process described above, there was a selection bias based on the geographical location of the participants; judged at high risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Being an active exercise intervention, it is not possible to blind the participants and supervisors of the intervention; judged at high risk of bias.

Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessor reported: unclear risk It is unclear whether the outcome assessor assessing the outcome physical working capacity was also the exercise programme supervisor, and, therefore, the blinding of outcome assessment was unclear. Participant reported: high risk Outcomes such as fatigue is a participant-reported outcome, and the participants knew which group they were in; judged at high risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	Authors did not clearly report any data for participants who withdrew from the study after baseline. We assumed that analysis was conducted per protocol, and not ITT; judged at high risk of bias.
Selective reporting (reporting bias)	High risk	Authors clearly reported that they did not show data for cardiorespiratory endurance at 3 months and 9 months, despite it being measured. Quote: "By contrast, the $PWC_{75\%}$/kg and the Borg scale did not improve over time in none of the 3 groups, nor at month 3, neither at month 9 (data not shown)".
Other bias	Low risk	No other biases.

Benatti 2015

Study characteristics	
Methods	**Study design:** single-centre, parallel-group, 3-arm RCT. Study is part of a larger clinical trial that aims to comprehensively investigate the effects of exercise training on autonomic function and cardiorespiratory parameters (data previously published), inflammatory markers, and cardio-metabolic risk factors in people with SLE (registered at ClinicalTrials.gov as NCT01515163) (Miossi 2012). **Setting:** Laboratory of Physical Conditioning for Rheumatologic Patients of the School of Medicine, University of Sao Paulo, Brazil **Time trial period:** not reported **Interventions:** supervised exercise training group SLE plus usual care vs non-trained SLE control group (usual care alone) vs healthy controls who performed a supervised exercise training group **Sample size calculation:** not reported **Analysis:** Kolmogorov–Smirnov's test with Lilliefor's correction revealed that only the glucose levels and total cholesterol levels showed a normal distribution. Therefore, all other dependent variables were tested by non-parametric tests. Independent samples were compared using the Mann–Whitney U test, whereas dependent samples were compared using the Wilcoxon test. Glucose and total cholesterol levels were tested by an unpaired T test for independent samples and the paired T test for dependent samples. Furthermore, Fisher's exact tests were used to compare the use of drugs at baseline between SLE trained (SLE-TR) and non-trained (SLE-NT) groups. Finally, effect sizes were calculated. The significance level was set at $P < 0.05$. All analyses were performed using Statistical Package for Social Sciences (SPSS), version 19.0 for Windows.

Participants	**Number of participants with SLE** 1. Screened and met inclusion criteria: 45 2. Randomised: 40 (20 allocated to exercise training group, and 20 allocated to the non-trained group). 5 did not agree to participate. 3. Included in 3-month analyses: 33 (17 in exercise training group and 16 in the non-trained group). 3 participants withdrew from exercise training group, and 4 participants withdrew from the non-trained group. All for personal reasons. **Number of participants (healthy controls)** 1. Screened and met inclusion criteria: 20 (2 did not agree to participate) 2. Allocated to training group: 18 (7 withdrew due to personal reasons) 3. Included in 3-month analyses: 11 **Inclusion criteria** 1. Diagnosed with SLE according to the ACR criteria 2. Aged 20–40 years 3. Physically inactive for ≥ 6 months before entering study 4. SLEDAI ≤ 4 **Exclusion criteria** 1. Cardiovascular and musculoskeletal disorders 2. Kidney and pulmonary involvements 3. Peripheral neuropathy 4. Use of tobacco 5. Treatment with statins or fibrate 6. Secondary rheumatic disease (e.g. Sjögren's syndrome, fibromyalgia, and antiphospholipid syndrome) 7. Use of antihypertensive drugs **Baseline characteristics** All 33 participants were women. ***Supervised training group (n = 17)*** 1. Mean age: 31.3 (SD 5.9) years 2. Mean BMI: 25.9 (SD 5.7) kg/m^2 3. Mean disease duration: 6.1 (SD 3.0) years 4. Mean SLEDAI disease activity: 0 . 9 (SD 1.4) points 5. Mean cumulative prednisone dose: 31.2 (SD 33.7) g 6. Mean prednisone dose: 11.5 (SD 12.8) mg 7. Number (%) drugs: a. Prednisone: 12 (70.6%) b. Azathioprine: 9 (52.9%) c. Chloroquine: 11 (64.7%) d. Methotrexate: 1 (5.9%) e. Mycophenolate mofetil: 5 (29.4%) f. Cyclophosphamide: 2 (11.8%) ***Non-trained SLE controls (n = 16)*** 1. Mean age: 29.7 (SD 5.3) years 2. Mean BMI: 26.3 (SD 8.3) kg/m^2 3. Mean disease duration: 6.1 (4.8) years 4. Mean SLEDAI disease activity: 1.2 (SD 1.4) points 5. Mean cumulative prednisone dose: 21.8 (SD 15.6) g 6. Mean prednisone dose: 7.2 (SD 8.6) mg 7. Number (%) drugs: a. Prednisone: 10 (62.5%) b. Azathioprine: 7 (43.7%) c. Chloroquine: 10 (62.5%) d. Methotrexate: 4 (25.0%) e. Mycophenolate mofetil: 2 (12.5%) f. Cyclophosphamide: 0 (0%) ***Healthy control group (n = 11)*** 1. Mean age: 30.9 (SD 7.2) years 2. Mean BMI: 23.9 (SD 3.1) kg/m^2 **Pretreatment group differences:** groups were similar regarding age, weight, height, and BMI. Supervised training and non-trained groups had similar drug regimens (P > 0.05).

Interventions	**Exercise: supervised training group SLE plus usual care** 1. **Frequency of exercise sessions:** 2 times/week 2. **Intensity of exercise:** HR corresponding to the interval between ventilatory anaerobic threshold and 10% below respiratory compensation point. 3. **Time of exercise session:** cardiovascular endurance exercise = 30 min and strength exercise = time not specified, per session. 4. **Type of exercise:** cardiovascular endurance exercise (treadmill walking) and strength exercises (7 exercises for major muscle groups: 4 sets of 8–12 repetitions maximum for each exercise) 5. **Duration of intervention:** 12 weeks **Non-trained SLE control group (usual care alone)** Participants remained physically inactive. **Exercise: healthy control group** 1. **Frequency of exercise sessions:** 2 times/week 2. **Intensity of exercise:** HR corresponding to the interval between ventilatory anaerobic threshold and 10% below respiratory compensation point. 3. **Time of exercise session:** cardiovascular endurance exercise = 30 min and strength exercise = time not specified, per session. 4. **Type of exercise:** cardiovascular endurance exercise (treadmill walking) and strength exercises (7 exercises for major muscle groups: 4 sets of 8–12 repetitions maximum for each exercise) 5. **Duration of intervention:** 12 weeks
Outcomes	All outcomes measured at baseline and 3 months. Specifically, blood samples were collected following a 12-hour overnight fast and 48–72 hours after the last exercise session. **Outcomes** 1. **Blood measurements and HDL composition:** total cholesterol, HDL, LDL, VLDL, triglycerides, apolipoprotein A-I, apolipoprotein A-II, apolipoprotein B, apolipoprotein E, insulin, glucose.
Notes	**Country:** Brazil **Funding:** no funding source reported **Trial registration:** NCT01515163 **Serious adverse events:** none reported **Other adverse events:** none reported **Total adverse events:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported as an RCT. Quote: "Randomly assigned (1:1) using a computer-generated randomization code to either participate in a supervised exercise training program (SLETR; n = 17) or to remain physically inactive (SLE-NT; n = 16). Gender-, BMI-, and age-matched healthy subjects (C-TR; n = 11) also performed a supervised exercise training program as a control group".
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not clearly reported, and, therefore, it was unclear whether it was included.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Being an active exercise intervention, it is not possible to blind the participants and supervisors of the intervention; judged at high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor reported: unclear risk It is unclear whether the outcome assessor was also the exercise supervisor, and, therefore, the blinding of outcome assessment was unclear.
Incomplete outcome data (attrition bias) All outcomes	High risk	3/17 from the trained group withdrew (18% withdrawals), 4/16 from the non-trained group withdrew (25% withdrawals). No evidence of ITT analyses.
Selective reporting (reporting bias)	High risk	Missing data from subanalysis. Quote: "In a further sub-analysis, it was showed that the SLE patients with and without Hydroxychloroquine (HCQ) had a comparable response to exercise training in terms of changes in lipid profile (data not shown)".
Other bias	Low risk	No other biases.

Benatti 2018

Study characteristics	
Methods	**Study design:** single-centre, parallel-group, 2-arm RCT **Setting:** intrahospital gymnasium, Laboratory of Physical Conditioning for Rheumatologic Patients of the School of Medicine (LACRE), University of São Paulo, Brazil **Time trial period:** not reported **Interventions:** supervised exercise training plus usual care vs usual care alone **Sample size calculation:** not reported. **Analysis:** to minimise the impact of interindividual variability, all values were converted into delta scores (i.e. post−pre values) and thereafter tested by a mixed model, considering pre values from all dependent variables as covariates. Tukey post hoc was used for multiple comparisons. Baseline data were compared using Fisher's exact tests and unpaired Student's t-tests. Cohen's d was used to determine between-group effect sizes for dependent variables. The significance level was previously set at $P \leq 0.05$, with a trend towards significance being accepted at $P \leq 0.1$. All analyses were performed using SAS 9.2, SAS Institute Inc., Cary, NC, USA. Data were presented as means ± SDs. Post hoc power analyses were performed with the assistance of the G-Power software (Version 3.1.2) and demonstrated a power of 70% and 60% at an alpha level of 5% to detect significant differences in insulin sensitivity (assessed by the HOMA IR and AUCinsulin in response to the MT) between trained and non-trained participants, with effect sizes of −1.0 and −0.8.

Participants

Number of participants

1. Screened: 900 (708 did not meet inclusion criteria)
2. Invited to participate: 192 (129 did not agree to participate, and 34 withdrew before baseline assessments)
3. Randomised: 29 (14 allocated to the trained group, and 15 allocated to the non-trained group.
4. Included in 3-month analyses: 19 (9 in trained group and 10 in non-trained group). 5 withdrew from the trained group (1 limb fracture, 1 disease flare, 3 personal reasons), and 5 withdrew from the non-trained group (1 pregnant, 1 disease flare, 3 personal reasons).

Inclusion criteria

1. Diagnosed with SLE according to the ACR criteria
2. Aged < 45 years
3. SLEDAI ≤ 4

Exclusion criteria

1. Aged > 45 years
2. BMI ≥ 35 kg/m^2
3. SLEDAI > 4
4. Prednisone dose > 10 mg/day
5. Menopause; diagnosed type 2 diabetes, cardiovascular dysfunction, rhythm and conduction disorders, musculoskeletal disturbances, current kidney and pulmonary involvements, peripheral neuropathy; tobacco use; use of statins, fibrate, insulin or insulin sensitisers; and other systemic autoimmune diseases.

Baseline characteristics

All 29 participants were women.

Supervised training group (n = 14)

1. Mean age: 34.8 (SD 4.1) years
2. Mean BMI: 26.3 (SD 3.4) kg/m^2
3. Mean disease duration: 9.8 (SD 4.1) years
4. Mean SLEDAI disease activity: 0.22 (SD 0.67) points
5. Mean cumulative glucocorticoid dose: 42.1 (SD 31.8) g/kg bodyweight
6. Mean current glucocorticoid dose: 1.7 (SD 3.5) mg
7. Number (%) drugs:
    a. Glucocorticoid: 2 (22%)
    b. Hydroxychloroquine: 5 (56%)
    c. Methotrexate: 2 (SD%)
    d. Azathioprine: 5 (56%)
    e. Mycophenolate: 1 (11%)
    f. Cyclophosphamide: 0 (0%)
    g. Oral contraceptive: 6 (67%)
8. Physical inactivity level
    a. Sedentary time (% of day): 56.2 (9.6%)
    b. Total MVPA: 29.1 (SD 13.7) min/day
    c. MVPA in > 10-minute bouts): 8.6 (SD 7.7) min/day

Non-trained SLE controls (n = 15)

1. Mean age: 32.4 (SD 6.5) years
2. Mean BMI: 26.2 (SD 3.8) kg/m^2
3. Mean disease duration: 8.5 (SD 5.9) years
4. Mean SLEDAI disease activity: 0.40 (SD 1.26) points
5. Mean cumulative glucocorticoid dose: 32.4 (SD 19.1) g/kg
6. Mean current glucocorticoid dose: 2.0 (SD 4.2) mg
7. Number (%) drugs:
    a. Glucocorticoid: 2 (20%)
    b. Hydroxychloroquine: 7 (70%)
    c. Methotrexate: 2 (20%)
    d. Azathioprine: 4 (40%)
    e. Mycophenolate: 2 (20%)
    f. Cyclophosphamide: 0 (0%)
    g. Oral contraceptive: 6 (60%)
8. Physical inactivity level
    a. Sedentary time (% of day): 59.4 (8.4%)
    b. Total MVPA: 25.4 (SD 17.4) min/day
    c. MVPA in > 10-minute bouts): 6.8 (SD 8.5) min/day

	Pretreatment group differences: groups were similar regarding age, BMI, body composition, physical activity levels, current clinical treatment, disease activity status, and disease duration (all P > 0.05).
Interventions	**Exercise: supervised training group plus usual care** 1. **Frequency of exercise sessions:** 2 times/week 2. **Intensity of exercise:** HR corresponding to the interval between ventilatory anaerobic threshold and 10% below respiratory compensation point 3. **Time of exercise session:** 40–60 min (5-min warm-up, followed by 30–50 min, and a 5-min cool-down). Walking duration increased every 4 weeks, from 30 to 50 min. 4. **Type of exercise:** aerobic exercise (treadmill walking) 5. **Duration of intervention:** 12 weeks **Non-trained control group (usual care alone)** Participants were strongly instructed to maintain their usual living activities throughout the study.
Outcomes	All outcomes measured at baseline and 3 months. 1. **Body composition** (bodyweight, fat mass, lean mass, and trunk fat): measured by DEXA using Hologic densitometry equipment. 2. **Skeletal muscle protein expression and GLUT4 translocation** in response to the meal test 3. **Aerobic capacity:** ventilatory anaerobic threshold, time at respiratory compensation point, time to exhaustion, VO_{2peak}), HR_{peak}: measured by a graded maximal treadmill test. 4. **Blood parameters** C3, C4, ESR, creatine phosphokinase, creatinine, urea, C-reactive protein, platelets, leukocytes, erythrocytes, haematocrit: measured by blood samples. 5. **Insulin sensitivity and beta cell function estimates:** measured by blood samples. 6. **Dietary intake:** total energy, protein, carbohydrate, fat.
Notes	**Country:** Brazil **Funding:** no funding source reported **Trial registration:** NCT01515163 **Serious adverse events:** none reported **Other adverse events:** 1 withdrew from the intervention group due to a disease flare (unclear whether this was associated with the exercise intervention) and 1 withdrew from the control group due to a disease flare. **Total adverse events:** 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as RCT; however, the randomisation process was unclear. Quote: "Nineteen adult women with SLE were randomly assigned …"
Allocation concealment (selection bias)	Unclear risk	No allocation concealment was reported; judged at unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Being an active exercise intervention, it is not possible to blind the participants and supervisors of the intervention; judged at high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor reported: unclear risk It is unclear whether the outcome assessor was also the exercise supervisor, and, therefore, the blinding of outcome assessment is not clear.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Due to technical issues, four patients (one from SLE-TR [training group] and three from SLE-NT [no training group]) were not assessed for glucagon and two patients from SLE-NT were not assessed for proinsulin levels". Therefore, judged at high risk of bias.
Selective reporting (reporting bias)	High risk	Soma data not shown. Quote: "Importantly, baseline comparisons using Fisher's exact tests and unpaired T tests analyses of those who were lost to follow-up and those who retained in each group did not show any drop-out bias (data not shown)".
Other bias	Low risk	No other biases.

Bostrom 2016

Study characteristics	
Methods	**Study design:** single-centre, parallel-group, 2-arm RCT **Setting:** Department of Rheumatology at Karolinska University Hospital, Solna, Stockholm, Sweden **Time trial period:** not reported **Interventions:** exercise plus usual care vs usual care alone **Sample size calculation:** not reported **Analysis:** software used to analyse data: SAD System 9.1, SAS Institute Inc., Cary, USA for Mixes- and Genmode procedures and Statistica 7.1, StaSoft, Inc. Tulsa, USA

Participants

Number of participants

1. Assessed for eligibility: 128 (88 declined to participate, 5 did not meet inclusion criteria)
2. Randomised: 35 (18 to intervention, 17 to control group)
3. Included at 3 months: 32 (18 in intervention group, and 14 in control group). 3 participants were excluded from control group after 2 weeks due to depression/cognitive impairment, untreated dementia, suspected relapse breast cancer.
4. Included at 6 months: 29 (16 in intervention group, and 13 in control group). 2 dropouts in intervention group; 1 was ill with concomitant systemic alveolitis, and 1 was not motivated. 1 dropout in control group due to being ill.
5. Included at 12 months: 27 (15 in intervention group, and 12 in control group). 1 dropout in intervention group due to being too ill, and 1 dropout in control group for unknown reason.
6. Included in 3-month, 6-month, and 12-month analysis: 25 (12 in intervention group, and 13 in control group).

Inclusion criteria

1. Fulfilled ≥ 4 ACR criteria for SLE.
2. Women with SLE who were followed regularly at the Department of Rheumatology, Karolinska University Hospital, Solna, Sweden.
3. Aged 18–70 years.
4. Stable and low-to-moderate disease activity and organ damage according to a rheumatologist's evaluation.

Exclusion criteria

1. Symptoms or signs during the preceding 6 months indicating cardiovascular disease, pulmonary embolus, pulmonary fibrosis, cerebrovascular disease, uncontrolled diabetes, dyspnoea at rest, pulmonary hypertension, angina pectoris, and myocardial infarction during the year before study entry.
2. American Heart Association absolute contraindications for exercise testing were applied.
3. Performed regular aerobic fitness training sessions at fixed times as this would interfere with the randomised study of the physical activity programme

Baseline characteristics

Exercise intervention group (n = 18)

1. Mean age: 52 (SD 10) years
2. Mean BMI: 26.5 (SD 5.8) kg/m^2
3. Mean disease duration: 15 (SD 9) years
4. Median SLEDAI disease activity: 1 (quartiles Q1–Q3 0–8) points
5. Median SLICC: 0 (quartiles Q1–Q3 0–1) points
6. Median prednisolone: 3.1 (quartiles Q1–Q3 0–5) mg
7. Number of participants who were/on:
    a. Beta-blockers: 3
    b. Smokers: 3
    c. Employed: 10
    d. Sick listed (full or part-time)/other (studying/unemployed): 5/1
    e. Sickness (full or part-time)/retirement pension: 9/1

Exercise intervention group baseline outcomes (n = 17)

1. Median SF-36
    a. Physical Role Functioning: 75 (quartiles Q1–Q3 25–100)
    b. Physical Functioning: 75 (quartiles Q1–Q3 55–85)
    c. Vitality: 35 (quartiles Q1–Q3 25–45)
    d. Emotional Role Functioning: 66.7 (quartiles Q1–Q3 33.3–100)
    e. Social Role Functioning: 75 (quartiles Q1–Q3 62.5–75)
    f. Mental Health: 68 (quartiles Q1–Q3 60–84)
    g. Bodily Pain: 51 (quartiles Q1–Q3 41–62)
    h. General Health Perception: 35 (quartiles Q1–Q3 25–45)

Exercise intervention group baseline outcomes (n = 12)

1. Mean VO_{2max}: 20.5 (SEM 1.3) mL/kg/min
2. Mean maximum workload: 114.9 (SEM 5.4) watts
3. Mean maximum exercise time: 9.6 (SEM 0.5) min

Control group (n = 17)

1. Mean age: 53 (SD 9) years
2. Mean BMI: 25.8 (SD 3.9) kg/m^2
3. Mean disease duration: 21 (SD 14) years
4. Median SLEDAI disease activity: 2 (quartiles Q1–Q3 0–3) points
5. Median SLICC: 0 (quartiles Q1–Q3 0–2) points
6. Median prednisolone: 1.3 (quartiles Q1–Q3 0–5) mg
7. Number of participants who were/on:

a. Beta-blockers: 1

b. Smokers: 4

c. Employed: 7

d. Sick listed (full or part-time)/other (studying/unemployed: 1/2

e. Sickness (full or part-time)/retirement pension: 9/1

Control group baseline outcomes (n = 14)

1. Median SF-36

a. Physical Role Functioning: 50 (quartiles Q1–Q3 0–100)

b. Physical Functioning: 67.5 (quartiles Q1–Q3 55–75)

c. Vitality: 55 (quartiles Q1–Q3 30–65)

d. Emotional Role Functioning: 66.7 (quartiles Q1–Q3 0–100)

e. Social Role Functioning: 62.5 (quartiles Q1–Q3 50–87.5)

f. Mental Health: 66 (quartiles Q1–Q3 52–88)

g. Bodily Pain: 63 (quartiles Q1–Q3 41–74)

h. General Health Perception: 51 (quartiles Q1–Q3 30–65)

Control group baseline outcomes (n = 13)

1. Mean VO_{2max}: 20.5 (SEM 1.3) mL/kg/min
2. Mean maximum workload: 119.9 (SEM 5.7) watts
3. Mean maximum exercise time: 10.1 (SEM 0.6) min

Pretreatment group differences: no differences at baseline between participants who participated in whole study period (n = 27) and dropouts (n = 8) concerning age, disease duration and VO_{2max} (mL/kg/min). There were no significant main effects of time, main effects of group, or interactions group × time concerning bodyweight and BMI.

Interventions

Exercise intervention group plus usual care

Phase 1 (0–3 months)

1. **Frequency of exercise sessions:** 2 times/week
2. **Intensity of exercise:** high (65–80% of maximum HR or a rating of 13–16 out of 20 on the Borg Rating of Perceived Exertion scale)
3. **Time of exercise session:** 60 min per session
4. **Type of exercise:** mainly aerobic exercise (about 20 min) and muscle strength and endurance exercise (about 15 min). Note: participants could alternatively choose any preferred self-managed high-intensity physical activity, as some participants lived far from the hospital.
5. **Duration of intervention:** 12 weeks (supervised as described above).

Note: physical activity at low-to-moderate intensity was self-managed and consisted of any type of preferred physical activity.

Phase included: 1-hour education session held by a rheumatologist and another by a physiotherapist to educate them on: their disease, the risk for cardiovascular disease, the treatment of the disease, and the importance of, and how to perform, physical activity and exercise. It also included education on how to use a HR monitor, how to assess intensity according to Borg Rating of Perceived Exertion scale, and how to document physical activity with modes, frequency, durations, and intensities. This phase also included supervised exercise training, 30 min of individual coaching of physical activity at 6- and 12 weeks, loan and use of HR monitor, and use of a physical activity diary.

Phase 2 (4–9 months)

During this period, the physical activity was self-managed with the help of videotapes or sound cassettes (or both) from the high-intensity aerobic group exercise programme performed during the first 3 months. As an alternative, any physical activity at high intensity could be chosen.

This phase included: 30 min of individual coaching of physical activity at 6 and 9 months, use of HR monitor, and use of the physical activity diary. Participants also received 10 min of telephone support which reduced towards the end of 12 months.

Phase 3 (9–12 months)

This phase included use of the HR monitor and physical activity diary.

Control group (usual care alone)

Participants were asked not to change their physical activity lifestyle during the study period and they were not given any specific information related to the study.

Outcomes

All outcomes measured at baseline; at month 0 (2–3 weeks after baseline when the intervention started); and after 3, 6, and 12 months.

1. **Aerobic capacity:** VO_{2max} in mL/kg/min), maximum watts, and maximum exercise time duration was recorded. In addition to VO_{2max}, 60% and 80% of VO_{2max} were measured. This outcome was measured using a maximal symptom-limited, bicycle ergometer exercise test (test was terminated when participant had indicated exhaustion). The higher the result, the better the outcome.
2. **Frequency of physical activity:** physical activity defined as all types of housework, gardening, walking, dancing, or regular physical activity that increase HR and exertion levels. This was measured by 2 self-reported questionnaires concerning frequency of physical activity for high intensity physical activity and low-to-moderate physical activity performed during the week (i.e. how often have you been physically active at high intensity, at least 30 minutes? "Never or irregularly, once a week, 2–3 times per week, 4–5 times per week, or 6–7 times per week").
3. **Health-related quality of life:** measured using the SF-36. Each of the 8 domains were reported. Possible score for each of the 8 subscales is 0–100; the higher the score, the better the function.
4. **Disease activity:** measured using the modified version of SLEDAI. This gave a score range 0–101, and the higher the score, the higher the overall disease activity.
5. **Organ damage:** measured using the SLICC. Score range 0–46, where 0 indicates no damage and 46 worst damage.

Notes	**Country:** Sweden. **Funding:** supported by grants from The Swedish Rheumatism Association, the Vardal Foundation, the Board of Research and Postgraduate Education and the Centre for Health Care Science, Karolinska Institutet, Sweden. **Trial registration:** not reported. **Serious adverse events:** none reported. **Other adverse events:** none reported. **Total adverse events:** none reported. **Data analysis:** we contacted study authors to request missing data for SLEDAI scores; however, we received no response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported as an RCT. Quote: "The remaining 35 patients were block randomized, by a statistician not involved in the study otherwise, into an intervention group (I-group, n=18) or a control group (C-group, n=17)."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was reported. However, the method of concealment was not reported. Quote: "The result of the randomization was concealed until interventions were assigned."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Being an active exercise intervention, it is not possible to blind the participants and supervisors of the intervention; judged at high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessor reported: low risk Blinding of outcome assessments were reported. Quote: "The assessments throughout the study were performed by professionals who were blinded to which group the patient had been randomized to." Participant reported: high risk Assessors (i.e. participants) were not blinded to self-reported outcomes measures (i.e. fatigue); judged at high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	All participants and all participant outcomes were accounted for in the statistical analysis. Quote: "All patients who had data from at least one sampling time point measurement were included in the statistical analyses. Problems caused by missing data for one or more time points do not arise when fitting models in Mixed- and Genmode procedures, provided that the missing data can be assumed missing at random."
Selective reporting (reporting bias)	High risk	Study authors assessed QoL using the SF-36; however, the Mental Component Summary score and Physical Component Summary scores were not reported. Study authors did not report mean and SD for outcomes.
Other bias	Low risk	No other biases.

Daltroy 1995

Study characteristics

Methods	**Study design:** single-centre, parallel-group, 2-arm RCT **Setting:** home-based exercise intervention **Time trial period:** not reported **Interventions:** exercise plus usual care vs another non-pharmacological intervention plus usual care **Sample size calculation:** sample size calculations were based on the desire to detect a 15% improvement in exercise tolerance test time, using a 2-tailed t-test, with alpha set at 0.01. Based on results from their pilot study, 24 participants per group provided 80% power to detect this difference. They determined 50 participants per disease group, to maintain power within diagnosis. **Analysis:** differences between the 4 diseases-by-treatment groups at baseline were tested with F or Chi^2 tests, as appropriate. For each outcome (exercise tolerance test, endurance, fatigue, depression, helplessness), a set of relevant variables were selected, by stepwise linear regression, for use as covariates and selected for significance easting to reduce the likelihood of false positives due to multiple testing. Overall tests of the intervention effect were performed with multivariate analysis of variance. All analyses were performed with SAS on an IBM PS2 computer.

Participants	**Number of total participants (SLE and RA)** 1. Who received recruitment letters: 196 participants with RA (84 required further information) and 158 participants with SLE (77 required further information) 2. Screened: 40 participates with RA and 35 participants with SLE (2 were ineligible, and to dropped out before testing. It is unclear who had SLE or RA). 3. Randomised: 71 total participants (RA and SLE). 35 to treatment (n = 16 with SLE, n = 19 with RA), and 36 to control (n = 18 with SLE, n = 18 with RA). 4. Number included in 3-month analysis: 34 participants with SLE (16 in treatment group, 18 in control group). **Inclusion criteria (SLE and RA)** 1. Met the ACR criteria for SLE or RA 2. Aged 18–50 years 3. Had permission from their primary physician 4. Currently, exercising < 3 times/week 5. Signed informed consent **Exclusion criteria (SLE and RA)** 1. Safety considerations such as serum creatinine > 3.0 mg/dL, haematocrit < 30%, previous myocardial infarction, previous cerebral vascular accidents, severe cognitive impairment, diastolic blood pressure > 100 mmHg at rest, or severe arthritis of ≥ 3 weight-bearing joints. **Baseline characteristics of participants with SLE** All 34 participants with SLE were women. **Treatment group (n = 16)** 1. Mean age: 38.8 (SEM 1.2) years 2. Mean SLAM disease activity: 6.3 (SEM 1.1) points 3. Mean ESR: 19.7 (SEM 4.6) mm/h 4. Mean creatinine: 1.0 (SEM 0.07) mg/dL 5. Mean haematocrit 40.5 (SEM 0.8) mg% 6. % exercise at least occasionally: 81% 7. % high school or more: 72% 8. % smoker: 19% 9. % taking steroids: 38% 10. % taking NSAIDs: 31% 11. Mean exercise tolerance: 9.0 (SEM 0.5) min 12. Mean endurance: 14.2 (SEM 2.0) min 13. Mean MAC fatigue: 22.3 (SEM 2.6) points 14. Mean POMS Fatigue: 9.4 (SEM 1.6) points 15. Mean CES-D: 11.4 (SEM 2.5) points 16. Mean Arthritis Helplessness Index: 31.4 (SEM 1.6) points **Control group (n = 18)** 1. Mean age: 31.3 (SEM 1.5) years 2. Mean SLAM disease activity: 6.7 (SEM 0.8) points 3. Mean ESR: 35.5 (SEM 6.0) mm/h 4. Mean creatinine: 0.8 (SEM 0.04) mg/dL 5. Mean haematocrit 37.9 (SEM 1.4) mg% 6. % exercise at least occasionally: 72% 7. % high school or more: 72% 8. % smoker: 22% 9. % taking steroids: 61% 10. % taking NSAIDs: 67% 11. Mean exercise tolerance: 8.0 (SEM 0.4) min 12. Mean endurance: 14.0 (SEM 2.0) min 13. Mean MAC Fatigue: 20.3 (SEM 1.8) points 14. Mean POMS Fatigue: 9.9 (SEM 1.2) points 15. Mean CES-D: 16.3 (SEM 2.4) points 16. Mean Arthritis Helplessness Index: 330.1 (1.3) points **Pretreatment group differences:** no differences amongst the 4 treatment-by-diagnosis groups.

Interventions	**Exercise: treatment group plus usual care** 1. **Frequency of exercise sessions:** 3 times/week 2. **Time of exercise session:** 30 min per session 3. **Intensity of exercise:** moderate-to-high (60–80% of maximum HR achieved on the exercise tolerance test) 4. **Type of exercise:** aerobic exercise performed on a stationary bike that was set up in their home. 5. **Duration of intervention:** 12 weeks A physiotherapist contacted the participant once a week to update logs of exercise, report of symptoms, and perceived fatigue. Pulse oximeters were provided to help participants monitor their HRs and as a compliance-enhancing strategy. The physiotherapist instructed the participant at home when setting up the bike, and made a second visit 2–3 weeks later at an exercise session to check the participants' ability to follow the regimen correctly. **Control group (another non-pharmacological intervention plus usual care)** Participants were encouraged to maintain their current level of activity during the 12-week programme. They also filled out questionnaires and were contacted once per week as an attention control.
Outcomes	All outcomes measured at baseline and 3 months. 1. **Fatigue** a. Measured using the MAC questionnaire, which assesses energy for daily activities. The MAC scale is the sum of 4 VAS, and ranges from 0 (no fatigue/lots of energy) to 40 (extreme fatigue/no energy). Higher scores indicate worse fatigue. b. Measured using the POMS Fatigue questionnaire, which assesses mood. The POMS scale sums responses to 6 adjectives (bushed, tired, etc.) on a 5-point Likert scale, covering the last week, and has response ranging from 0 (not at all fatigued) to 30 (extremely fatigued). Higher scores indicate worse fatigue. 2. **Depression:** measured using the CES-D, a 20-item measure of the frequency of various somatic and psychological symptoms over the last month. Scores range from 0 (no depression) to 60 (extremely depressed). A score of > 16 indicates clinical depression. 3. **Helplessness:** helplessness, or the perceived lack of ability to control and cope with one's arthritis, measured by the 15-item Arthritis Helplessness Index, with scores ranging from 15 (low helplessness) to 60 (great helplessness). 4. **Exercise tolerance:** measured using a graded exercise tolerance test using a cycle ergometer, starting at 30 W and increasing by 30 W every 3 min until the participant asked to stop the test. Electrocardiogram, blood pressure, and symptoms were carefully monitored for signs of exercise intolerance. Exercise test was stopped if the participant exhibited angina, fall in blood pressure, severe shortness of breath, ≥ 3 premature ventricular contractions in sequence. The time taken to complete the test was recorded (higher the time = the better the outcome).
Notes	**Country:** US. **Funding:** not reported. **Trial registration:** not reported. **Serious adverse events:** none reported. **Other adverse events:** none reported. **Total adverse events:** none reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was reported but unclear how this process was completed; judged at unclear risk of bias.
Allocation concealment (selection bias)	Unclear risk	No allocation concealment reported; judged at unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Being an active exercise intervention, it is not possible to blind the participants and supervisors of the intervention; judged at high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor reported: unclear risk It is unclear whether the assessors were blinded from the intent of the study or knew which participants were in which group. Quote: "The testing was administered by a cardiologist and nurse in an exercise physiology laboratory." Participant reported: high risk Assessors (i.e. participants) were not blinded to study groups, and performed self-reported outcome measures (i.e. depression); judged at high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.
Selective reporting (reporting bias)	Low risk	All outcome measures were reported for all participants.
Other bias	Low risk	No other bias identified.

Dos Reis-Neto 2013

Study characteristics	
Methods	**Study design:** quasi-randomised 2-arm parallel controlled trial **Setting:** Rheumatology Division and Cardiology Division, Universidade Federal de São Paulo/Escola Paulista de Medicina (UNIFESP/EPM), São Paulo, Brazil **Time trial period:** unknown **Interventions:** exercise training plus usual care vs another non-pharmacological intervention plus usual care **Sample size calculation:** unknown **Analysis:** statistical analysis performed through normality tests, Student's t-test and non-parametric tests for data with non-normal distribution. P < 0.05 considered significant.

Participants

Number of participants

1. Screened: 224 (99 participants not eligible and did not meet inclusion criteria, and 76 participants quit for personal reasons)
2. Allocated into 2 groups according to convenience: 44 (23 in exercise group, and 21 in control group)
3. Included in 3-month analyses: 38 (5 participants in exercise group left for personal reasons, and 1 participant from control group left for personal reasons)

Inclusion criteria

1. Aged 18–45 years
2. Diagnosis of SLE according to ACR criteria

Exclusion criteria

1. Haemoglobin < 10 mg/dl
2. Neuropsychiatric, pulmonary, articular, or vascular damage that would not allow the practice of exercise
3. Coronary disease
4. Heart failure (functional class > II)
5. Pulmonary hypertension
6. Uncontrolled hypertension
7. Creatinine ≥ 1.4 mg/dL
8. BMI ≥ 35 kg/m²
9. Diabetes mellitus
10. Uncontrolled hypothyroidism
11. Smoking in last 12 months
12. Pregnancy
13. Menopause
14. Use of statins or regular practice of exercise in past 3 months and overlap with other autoimmune rheumatic diseases, except antiphospholipid syndrome

Baseline characteristics

All 38 participants were women, mean age 35.3 (SD 6.8) years, mean BMI 26.0 (SD 4.7) kg/m^2, and mean disease duration 78.9 (SD 65.0) months

Exercise group (n = 18)

1. Mean age: 35.3 (SD 6.8) years
2. Mean BMI: 26.9 (SD 4.7) kg/m^2
3. Mean disease duration: 79.8 (SD 65.0) months
4. White ethnicity, n: 7 (38.9%)
5. Mean SLEDAI disease activity: 2.0 (SD 2.1) points
6. Median SLICC/ACR-DIL 0 (minimum–maximum 0–1)
7. Prednisone use, n: 10 (55.6%)
8. Mean current prednisone dose: 2 (minimum and maximum value = 0 to 40) mg
9. Antimalarial use, n: 13 (72.2%)
10. Immunosuppressive drug use, n: 8 (44.4%)
11. Antihypertensive use, n: 3 (16.7%)
12. Aspirin use, n: 2 (11.1%)
13. Contraceptive use, n: 3 (16.7%)
14. Mean systolic blood pressure: 122.1 (SD 14.4) mmHg
15. Mean diastolic blood pressure: 80.3 (SD 7.4) mmHg
16. Mean abdominal circumference: 87.2 (SD 9.9) cm
17. Mean waist:hip ratio: 0.81 (SD 0.06)
18. Mean fasting glucose: 84.6 (SD 4.9) mg/dL
19. Mean total cholesterol: 161.4 (SD 32.9) mg/dL
20. Mean HDL: 50.8 (SD 16.0) mg/dL
21. Mean LDL: 88.3 (SD 22.9) mg/dL
22. Mean triglycerides: 109.9 (SD 48.3) mg/dL
23. Coronary artery disease family history, n: 4 (22.2%)
24. Hypertension, n: 4 (22.2%)
25. Dyslipidaemia, n: 4 (22.2%)

Control group (n = 20)

1. Mean age: 30.8 (SD 7.2) years
2. Mean BMI: 25.7 (SD 4.0) kg/m^2
3. Mean disease duration: 107.9 (SD 91.3) months
4. White ethnicity, n: 9 (45.0%)
5. Mean SLEDAI disease activity: 2.4 (SD 2.3) points

	6. Median SLICC/ACR-DI: 0 (minimum–maximum 0–2) 7. Prednisone use, n: 13 (65.0%) 8. Mean current prednisone dose: 5 (minimum and maximum value = 0 to 30) mg 9. Antimalarial use, n: 16 (80.0%) 10. Immunosuppressive drug use, n: 14 (70.0%) 11. Antihypertensive use, n: 7 (35.0%) 12. Aspirin use, n: 3 (15.0%) 13. Contraceptive use, n: 8 (40.0%) 14. Mean systolic blood pressure: 115.8 (SD 13.0) mmHg 15. Mean diastolic blood pressure: 74.0 (SD 9.3) mmHg 16. Mean abdominal circumference: 86.1 (SD 10.0) cm 17. Mean waist:hip ratio: 0.79 (SD 0.06) 18. Mean fasting glucose: 81.3 (SD 6.1) mg/dL 19. Mean total cholesterol: 164.1 (SD 38.0) mg/dL 20. Mean HDL: 49.4 (SD 12.3) mg/dL 21. Mean LDL: 95.1 (SD 31.9) mg/dL 22. Mean triglycerides: 97.2 (SD 35.8) mg/dL 23. Coronary artery disease family history, n: 3 (15.0%) 24. Hypertension, n: 1 (5.0%) 25. Dyslipidaemia, n: 5 (25.0%) **Pretreatment group differences:** groups were homogeneous for age, ethnicity, BMI, abdominal circumference, waist:hip ratio, fasting glucose, total cholesterol, HDL, coronary artery disease family history, and dyslipidaemia at baseline.
Interventions	**Exercise training group plus usual care** 1. **Frequency of exercise sessions:** 3 times/week 2. **Intensity of exercise:** HR corresponding to the ventilatory 1 threshold obtained from ergospirometry and monitored by frequency meter (Poland Electro, Kempele, Finland). Intensity of walking was unclear. 3. **Time of exercise session:** 60 min sessions (10-min warm-up, 40 min of walking and 10-min cool-down) 4. **Type of exercise:** walking, outdoors in the morning 5. **Duration of intervention:** 16 weeks 6. **Supervision/setting:** in the morning at a public park, supervised by a physical educator or physician. **Control group (another non-pharmacological intervention plus usual care)** Participants received usual care and information about the disease, but no exercise intervention. Received clear instruction not to start any exercise programme for the next 16 weeks.
Outcomes	Outcomes measures at baseline and postintervention (16 weeks) 1. **Endothelial function:** measured using resting diameter, hyperaemia diameter and flow-mediated dilation, ergospirometry. Non-invasive methods of measuring endothelial function include ultrasound flow-mediated dilation, salbutamol-mediated endothelial function measured by pulse wave analysis or pulse contour analysis, flow-mediated magnetic resonance imaging, laser Doppler flowmetry, and flow-mediated pulse amplitude tonometry. 2. **Ergospirometric assessment:** ergospirometry was performed at the laboratory of the Center for Studies in Psychobiology and Exercise using a Quark PFT ergospirometric testing device. (pulmonary function test) (Cosmed, Italy). Measured through the continuous analysis of carbon monoxide and methane (tracer) fractions with fast analysers. Normal value is 95% confidence interval. Test measures the amount of air the lungs can hold. Test also measures how forcefully one can empty air from the lungs. 3. **Disease Activity:** measured using the SLEDAI. This gives a score range 0–101, and the higher the score, the higher the overall disease activity.
Notes	**Country:** Brazil **Funding:** no funding source reported **Trial registration:** NCT01712529 **Serious adverse events:** unclear **Other adverse events:** unclear **Total adverse events:** unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Study was quasi-RCT and the method of randomisation was not truly random; judged at high risk of bias. Quote: "Prospective study where the patients were divided into two groups according to their convenience, those who were willing to train where placed into the exercise group (EG) and those who were not available were allocated into the control group (CG)".
Allocation concealment (selection bias)	Unclear risk	No allocation concealment was reported; judged at unclear risk of bias.

Blinding of participants and personnel (performance bias) All outcomes	High risk	Being an active exercise intervention, it is not possible to blind the participants and supervisors of the intervention; judged at high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessor reported: low risk Quote: "All assessments were performed at baseline (0 weeks) and end of intervention (16 weeks), in both the EG [exercise] and CG [control] by blinded evaluators". In the exercise group, assessments were performed 72 hours after the last training session to reduce the possible effects of acute exercise. Participant reported: high risk Because the assessor (i.e. participants) were not blinded to the self-reported outcomes measures (i.e. fatigue); judged at high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	5/23 in exercise group withdrew (22% withdrawals). No evidence of ITT analyses.
Selective reporting (reporting bias)	Low risk	All outcome measures were clearly reported.
Other bias	Low risk	No other biases.

Hashemi 2022

Study characteristics	
Methods	**Study design:** single-centre, parallel-group, 2-arm RCT **Setting:** Hafez hospital, Shiraz University of Medical Sciences, Shiraz, Southern Iran **Trial time period:** September 2015 to March 2016 **Interventions:** combined aerobic running and anaerobic Pilates exercise training programme plus usual care vs usual care alone **Sample size calculations:** authors did not describe how the sample size was estimated. **Analysis:** continuous variables were first checked for normality, followed by assessment using parametric tests to compare the means since the data were normal. Data were compared by parametric and non-parametric a multiple comparison t-test. Data are presented as mean ± SDs of the mean of ≥ 3 independent experiments. $P \leq 0.05$ were considered to be statistically significant.

Participants

Number of participants

1. Screened: 30 (6 participants were excluded from the study for not participating in post-test measurements: 1 from exercise group and 5 from control group)
2. Randomised: 24 (14 in exercise group and 10 in control group)
3. Included in 2-month analyses: 19 (10 in exercise group and 9 in control group). 4 from the exercise group were not included in analyses, and 1 from control group was not included in analyses.

Inclusion criteria

1. Aged 20–29 years
2. Diagnosis of SLE according to ACR
3. SLEDAI < 4

Exclusion criteria

1. Showing severe illness with SLEDAI scores > 5
2. Exhibiting any other systemic or rheumatic disorders capable of limiting physical function or its assessment
3. Undertaking regular exercise training ≥ 3 times/week
4. Having significant mental problems such as severe depression
5. Severe cardiovascular disease or very poor cardiovascular fitness

Baseline characteristics

All 24 participants were women. Mean age 29.00 (SD 3.19) years in exercise group and 21.50 (SD 5.52) years in control group

Exercise group (n = 10)

1. Mean age: 29.00 (SD 3.19) years
2. Number of participants, gender male: 0
3. Number of participants, gender female: 14
4. Number of participants, marital status, single: 3
5. Number of participants, marital status, married: 12
6. Number of participants, education, diploma: 5
7. Number of participants, education, bachelor: 2
8. Number of participants, education, unemployed: 6
9. Number of participants, employment, employed: 5
10. Number of participants, employment, student: 4
11. Number of participants with pain and inflammation, yes: 7
12. Number of participants with pain and inflammation, no: 3
13. Number of participants with cutaneous findings, yes: 4
14. Number of participants with cutaneous findings, no: 3
15. Number of participants with family history, yes: 1
16. Number of participants with family history, no: 5
17. Height: 1.63 (SD 0.03) m
18. Weight: 67.70 (SD 14.82) kg
19. BMI: 25.51 (SD 5.95) kg/m^2
20. Mean disease duration: 8.30 (SD 4.62) years

Control group (n = 9)

1. Mean age: 21.50 (SD 5.52) years
2. Number of participants, gender male: 0
3. Number of participants, gender female: 10
4. Number of participants, marital status, single: 4
5. Number of participants, marital status, married: 6
6. Number of participants, education, diploma: 2
7. Number of participants, education, bachelor: 5
8. Number of participants, education, unemployed: 6
9. Number of participants, employment, employed: 4
10. Number of participants, employment, student: 0
11. Number of participants with pain and inflammation, yes: 7
12. Number of participants with pain and inflammation, no: 1
13. Number of participants with cutaneous findings, yes: 2
14. Number of participants with cutaneous findings, no: 6
15. Number of participants with family history, yes: 1
16. Number of participants with family history, no: 5
17. Height: 1.59 (SD 0.63) m
18. Weight: 60.33 (SD 9.06) kg

	19. BMI: 23.71 (SD 3.31) kg/m^2 20. Mean disease duration: 7.73 (SD 3.73) years **Pretreatment group differences:** groups were homogeneous for age, sex, and disease duration.
Interventions	**Exercise group** 1. **Frequency of exercise sessions:** 3 times/week 2. **Intensity of exercise:** stage 2 of session (aerobic exercise programme, including 10 min of cycling and 10 min of running, both at intensity 50–60% maximum, as predetermined in the VO_{2peak} measurements. 3. **Time of exercise session:** 60 min per session (40 min for the first week, to allow for acclimatisation, but increased thereafter). 4. **Type of exercise:** Pilates exercise, which is classified as low-intensity resistance exercise. Each exercise session consisted of 4 stages, including 1. 10-min warm-up, 2. aerobic exercise programme (10-min cycling and 10 min running), 3. 60-min Pilates training using bodyweight as the resistive load, and 4. 10-min cool-down. Borg scale used to assess participant's perception of physical exertion during aerobic exercises that were used in stage 2. 5. **Duration of intervention:** 8 weeks 6. **Supervision/setting:** unknown **Control group** Participants received usual care and information about the disease, but no exercise intervention.
Outcomes	Serum levels of IFN-γ, TNF-α, IL-6, IL-2, IL-4, IL-5, IL-9, IL-10, IL-13, IL-17A, IL-17F, IL-21, and IL-22, and cytokines were measured in all 24 participants by cytokine assay. Although some levels of IFN-γ decreased after 8 weeks, no differences found in the participants' levels between the intervention or control groups. The levels of TNF-α, while increasing in control group, decreased in intervention group. Although participants with SLE presented higher levels of IL-2 at baseline, the levels of IL-2 decreased after 8 weeks in both the intervention and control groups. Levels of IL-4 and IL-5 decreased in intervention group compared with control group. Levels of IL-10, IL-13, and IL-22 increased after 8 weeks. Control group showed increased levels of IL-10, IL-13, and IL-22 compared with intervention group.
Notes	**Country:** Iran **Funding:** supported by Shiraz University of Medical Sciences **Trial registration:** unknown **Serious adverse events:** none reported **Other adverse events:** none reported **Total adverse events:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors reported that participants were randomised into groups; however they did not report randomisation methods; judged at unclear risk of bias. Quote: "The patients were randomly divided into two groups, including exercise (n = 15) and control (n = 15) groups."
Allocation concealment (selection bias)	Unclear risk	Insufficient description of the method of concealment; judged at unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Being an active exercise intervention, it is not possible to blind the participants and supervisors of the intervention; judged at high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor reported: unclear risk Blinding of participants and investigators was not clearly reported; judged at unclear risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other biases.

Kao 2021

Study characteristics

Methods	**Study design:** quasi-randomised 2-arm parallel controlled trial **Setting:** Division of Allergy, Immunology & Rheumatology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan 2 School of Medicine, Tzu Chi University, Hualien, Taiwan 3 Center of Physical Education, Tzu Chi University, Hualien, Taiwan 4 Sports Medicine Center, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan. **Time trial period:** unknown **Interventions:** aerobic exercise combined with resistance training plus usual care vs another non-pharmacological intervention plus usual care **Sample size calculation:** unknown **Analysis:** normally distributed parameters are presented as mean (SD) and were analysed using an unpaired t-test to compare the baseline differences between the control and combined exercise groups. Non-normally distributed values were presented as medians (IQR) and were analysed using the Mann-Whitney U test.
Participants	**Number of participants** 1. Screened: 26 (3 participants dropped out for personal reasons) 2. Randomised: 23 (12 in exercise group and 11 in control group) 3. Included in 12-week analyses: 23 participants **Inclusion criteria** 1. Aged 20–65 years 2. Diagnosis of SLE according to ACR, or SLICC criteria for the classification of SLE **Exclusion criteria** 1. Pregnant 2. Uncontrolled hypertension 3. Severe anaemia 4. Conditions that were unsuitable for exercise (e.g. chronic lung disease and active arthritis) **Baseline characteristics** All 23 participants were women. ***Exercise group (n = 12)*** 1. Mean age: 38.75 (SD 12.78) years 2. Median BMI: 22.32 (IQR 19.85–23.86) kg/m^2 3. Median WBC: 4.81 (IQR 3.31–6.65) $10^3/\mu L$ 4. Mean haemoglobin: 11.82 (SD 1.54) g/dL 5. Median number of platelet: 294 (IQR 206–334) $10^3/\mu L$ 6. Median ESR: 28.5 (IQR 8.3–37.8) mm/hour 7. Mean creatinine: 0.67 (SD 0.11) mg/dL 8. Median anti-dsDNA: 19.05 (IQR 1.03–42.55) IU/mL 9. Median SLEDAI-2K: 2 (IQR 0–5.5) points 10. Mean complement 3: 95.00 (SD 26.42) mg/dL 11. Mean complement 4: 16.99 (SD 7.24) mg/dL 12. Mean fat body mass: 34.15% (SD 6.12%) ***Control group (n = 11)*** 1. Mean age: 40.27 (SD 9.97) years 2. Median BMI: 23.5 (IQR 21.2–26.5) kg/m^2 3. Median WBC: 6.44 (IQR 3.43–7.47) $10^3/\mu L$ 4. Mean haemoglobin: 11.75 (SD 1.56) g/dL 5. Median number of platelet: 259 (IQR 237–303) $10^3/\mu L$ 6. Median ESR: 23.5 (IQR 10.5–58.8) mm/hour 7. Mean creatinine: 0.57 (SD 0.12) mg/dL 8. Median anti-dsDNA: 19.90 (IQR 0.60–35.00) IU/mL 9. Median SLEDAI-2K: 4 (IQR 2–10) 10. Mean complement 3: 95.24 (SD 15.68) mg/dL 11. Mean complement 4: 18.80 (SD 8.18) mg/dL 12. Mean fat body mass: 37.49% (SD 6.66%) **Pretreatment group differences:** groups were homogeneous at baseline for body composition, disease activity, 2-km walking test, and executive function test.

Interventions	**Exercise plus usual care** 1. **Frequency of exercise sessions:** 5 days/week 2. **Intensity of exercise:** moderate intensity determined by HRR 50–50%, according to the ACSM guidelines. HRR = MHR − RHR. MHR determined using formula: MHR = 205 − (0.42 × age). 3. **Time of exercise session:** 30 min per session (3- to 5-min warm-up, 4 sets of combined exercise session for approximately 30 min in total, and final set of 3- to 5-min of relaxation and stretching). Each set of combined exercise lasting for 7 min 15 s, with a brief break between sets. 4. **Type of exercise:** aerobic exercise combined with bodyweight or 500–620 mL of dumbbell water weights for resistance training. Combined exercise sessions consisted of various styles of basic exercises, alternating workouts of legs with trunk movement, and arm exercises. 5. **Duration of intervention:** 12 weeks 6. **Supervision/setting:** home-based exercise. The research team member contacted participants periodically by telephone or text messages to ensure their compliance. Each week the participants reported their maximal HR after each exercise session by written logs. Instructed by an exercise physiologist/professional exercise instructor on the performance of aerobic exercise combined with resistance training and the skills of HR measurement at rest and after exercise. **Control group (another non-pharmacological intervention plus usual care)** Participants received usual care and information about the disease, but no exercise intervention. They were to maintain their usual lifestyle.
Outcomes	All outcomes measured at baseline and postintervention (12 weeks). 1. **Disease activity:** measured using SLEDAI-2K at baseline and after 12-week intervention. This gives a score range 0–101, higher score = higher the overall disease activity. 2. **Executive performance (reaction time and the performance index):** measured using the go/no-go test and Stroop Task. a. **G o/no go:** upon receiving an indicative stimulus for action (i.e. go signal), which was displayed on a computer screen, the participant pressed the assigned keyboard button as quickly as possible. Alternatively, upon receiving a distractor stimulus (i.e. no-go signal), the participant held their action. The participants performed a set of go (160 trials) and no-go (40 trials) stimuli. Reaction time measured as mean time required for pressing the button after the stimuli. Accuracy defined as the percentage of correct responses to both the indicative and distractor stimuli. b. **Stroop Task:** comprised a series of colour words presented on a screen. In the incongruent trial (100 trials in total), a mismatch existed between the name of the colour and the colour shown on the screen. In the congruent trials (100 trials in total), colour words were presented as a matching colour. All the words were written in the official national language and were displayed on the screen 1 at a time. The participants were asked to respond as quickly as possible by pressing the corresponding keyboard button that represented the actual colour and make as few errors as possible during this task. Reaction time measured as time required for pressing the button after the word appeared on the screen. Accuracy for each of the congruent and incongruent trials was calculated as the percentage of correctly pressed keyboard buttons. 3. **Physical fitness:** measured using a 2-km walking test. The faster the test was completed (lower time recorded), the better the result of the physical fitness test was. Recorded in minutes and seconds.
Notes	**Country:** Taiwan **Funding:** Tzu Chi Medical Mission Project 105–03–02 (TCMMP105–03–02), Buddhist Tzu Chi Medical Foundation, Taiwan **Trial registration:** unknown **Serious adverse events:** none reported **Other adverse events:** none reported **Total adverse events:** none reported **Data analysis:** contacted study authors to request missing data for SLEDAI; however, no response received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Study was quasi-randomised; judged at high risk of bias. Quote: "The participants were allocated based on their willingness to either the exercise or control group."
Allocation concealment (selection bias)	Unclear risk	No allocation concealment reported; judged at unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Being an active exercise intervention, it is not possible to blind the participants and supervisors of the intervention; judged at high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor reported: unclear risk Exercise group were instructed by an exercise physiologist/professional exercise instructor. The participants were taught to measure their own HR range. Research team member contacted the home-based exercise participants privately to ensure compliance. Participants reported their own HR range each week. Unclear whether the outcome assessor was also the exercise instructor/exercise physiologist.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of selective reporting.

Selective reporting (reporting bias)	Low risk	All outcome measures were reported.
Other bias	Low risk	No other biases.

Keramiotou 2020

Study characteristics	
Methods	**Study design:** quasi-randomised 2-arm parallel controlled trial **Setting:** Greece **Time trial period:** unknown. **Interventions:** exercise group (combined resistance and stretching) plus usual care vs another non-pharmacological intervention plus usual care **Sample size calculation:** a sample size of 32 participants per group was required for an 80% probability of demonstrating a difference of 15% between comparison groups (exercise: −25% (SD 20%) vs control: −10% (SD 20%)) in percentage change of DASH score from baseline to 12 weeks with a significance of < 5% (2-tailed test). Participants of pilot study were included in the final sample. The estimation of sample size was performed using G*Power V.3.1.9.2 programme. **Analysis:** data were expressed as mean ± SD or median (in case of violation of normality) for continuous variables and as percentages for categorical data. The Kolmogorov Smirnov test utilised for normality analysis of the parameters. The comparison of variables at each time point between interventions was performed using the independent samples t-test or non-parametric Mann-Whitney test. All tests were 2-sided, and statistical significance was set at P < 0.05. All analyses were carried out using the statistical package SPSS V.21.00 (IBM Corporation).

Participants

Number of participants

1. Screened: 293 (52 declined eligibility checks, 240 were assessed, 156 did not meet inclusion criteria, 9 declined to participate)
2. Randomised: 75 (39 in exercise group: 7 did not start, and not included in analysis, and 36 in control group: 6 did not start, and not included in analysis)
3. Included in 3-month analyses: start of intervention 62 participants. End of intervention 60 participants (2 participants from the exercise group abandoned study without reason).

Inclusion criteria

1. Aged ≥ 18 years
2. Diagnosis of SLE according to the 2012 SLICC classification criteria for SLE
3. Upper limb arthralgias
4. Difficulty in performing activities of daily living (DASH score > 10)
5. Stable drug regimen for ≥ 12 weeks

Exclusion criteria

1. Upper limb fracture or surgery in previous 6 months
2. Physiotherapy programme in previous 6 months
3. Pregnancy

Baseline characteristics

All 62 participants were women.

Exercise group (combined resistance and stretching) (n = 32)

1. Mean age: 43.34 (SD 8.90) years
2. Female, n: 31 (96.9%)
3. Marital status, n: 10 (31.3%) single, 19 (59.4%) married
4. Education status, n: 30 (93.8%) secondary, 2 (6.3%) university
5. In employment, n: 25 (78.12%)
6. Dominant right hand, n: 32 (100%)
7. Median disease duration: 6 (IQR 10) years
8. Mean SLEDAI-2K: 4.25 (SD 3.24) points
9. Lupus low disease activity state: 18 (56.3%)
10. Mean SLICC: 0.34 (SD 0.60) points
11. Median symptomatic joint culture: 10 (IQR 11)
12. Mean swollen joint count: 1.39 (SD 3.05)
13. Arthritis, n: 5 (15.62%)
14. Fibromyalgia, n: 4 (12.5%)
15. Mean VAS: 5.81 (SD 1.67)
16. Corticosteroid use n: 20 (54.1%)
17. Mean prednisolone dosage: 4.63 (SD 5.55) mg
18. Hydroxychloroquine use n: 26 (81.3%)
19. Immunosuppressive agents use n: 15 (46.9%)
20. Biologic agents use n: 1 (3.1%)
21. Mean DASH: 39.02 (SD 16.10)
22. Mean HAQ score: 0.81 (SD 0.45) points
23. Mean grip strength, DH: 22.86 (SD 8.77)
24. Mean pinch strength jaws DH: 4.27 (SD 2.01)
25. Mean Purdue DH: 13.25 (SD 2.05)
26. Mean LupusQOL: 56.44 (SD 22.62)
27. Mean LupusQOL Fatigue: 56.63 (SD 23.74)

Control group (n = 30)

1. Mean age: 48.77 (SD 12.38) years
2. Female, n: 27 (90%)
3. Marital status, n: 6 (20%) single, 20 (66.7%) married
4. Education status, n: 28 (93.3%) secondary, 2 (6.7%) university
5. In employment, n: 19 (63.33%)
6. Dominant right hand, n: 27 (90%)
7. Median disease duration: 11 (IQR 15)
8. Mean SLEDAI-2K: 4.20 (SD 3.58)
9. Lupus low disease activity state: 13 (43.3%)
10. Mean SLICC: 0.63 (SD 0.93)
11. Median symptomatic joint culture: 11 (IQR 7)

	12. Mean swollen joint count: 1.43 (SD 2.53) 13. Arthritis, n: 6 (20%) 14. Fibromyalgia, n: 3 (10%) 15. Mean VAS: 6.03 (SD 1.77) 16. Corticosteroid use n: 17 (46.0%) 17. Mean prednisolone dosage: 4.97 (SD 5.80) mg 18. Hydroxychloroquine use n: 25 (83.3%) 19. Immunosuppressive agents use n: 15 (50.0%) 20. Biological agents use n: 3 (10%) 21. Mean DASH: 43.08 (SD 16.39) 22. Mean HAQ score: 1.10 (SD 0.55) 23. Mean grip strength, DH: 21.42 (SD 9.75) 24. Mean pinch strength jaws DH: 3.91 (SD 2.19) 25. Mean Purdue DH: 12.27 (SD 2.36) 26. Mean lupus QoL: 51.25 (SD 20.62) 27. Mean lupus QoL fatigue: 49.44 (SD 21.03) **Pretreatment group differences:** difference between groups in percentage changes of DASH, HAQ, grip strength, pinch strength, LupusQOL Physical Health and Fatigue, and VAS scores from baseline to 6, 12, and 24 weeks, and from baseline to 12 weeks for dexterity test (P < 0.001).
Interventions	**Exercise group (combined resistance and stretching) plus usual care** 1. **Frequency of exercise sessions:** 7 days/week 2. **Intensity of exercise:** moderate intensity. Initial intensity of exercise set at a moderate level and programme was reassessed, using a modified Borg Scale (a tool to measure a persons' perception of their effort and exertion, breathlessness, and fatigue during physical work) to maintain the same intensity, in every face-to-face session with the hand therapist at 0, 3, 6, and 9 weeks. 3. **Time of exercise session:** 30 min per session 4. **Type of exercise:** upper-limb exercises (9 strengthening and stretching exercises for the upper extremities with a stick, 10 strengthening and stretching exercises for the fingers, and 11 strengthening exercises against resistance with therapeutic putty). 5. **Duration of intervention:** 12 weeks (and 24 weeks' follow-up, we did not report these measurements) 6. **Supervision/setting:** none reported **Control group (another non-pharmacological intervention plus usual care)** Participants had 4 sessions of training in alternative methods of performing daily activities, use of aids, joint protection and energy conservation, additionally to assessment at baseline, 6, 12, and 24 weeks, in order to keep them also committed and motivated. All participants received the same training in alternative methods of performing daily activities, use of aids, joint protection, and energy conservation.
Outcomes	1. **Performance of daily activities:** measured using DASH at baseline, 6, 12, and 24 weeks. It was 30 items regarding symptoms and function. Items were scored on a scale from 1 (no difficulty) to 5 (extreme difficulty/unable to do). A high score indicates a decreased ability in performances of daily activities. 2. **Functional ability:** measured using the HAQ. Total score 0–3, in 0.125 increments. Lower scores indicate better function, and higher scores indicate worse function and greater disability. Measured at baseline, 6, 12, and 24 weeks. 3. **Grip and pinch strength:** measured using the Jamar dynamometer and pinch gauge tool using the DH at baseline, 6, 12, and 24 weeks. 3 trials were recorded, and the mean score was recorded after attempts complete by participants. 4. **Dexterity:** measured using the Purdue pegboard test at baseline, 6, 12, and 24 weeks. DH was required to be used. Participants were asked to take as many pins as possible in 30 s, out of a cup and place each 1 into a hole in a board. The greater the number of pins the better the result. 5. **QoL:** measured using the LupusQOL Questionnaire at baseline, 6, 12, and 24 weeks. Evaluating 8 domains, each domain is scored separately, score range 0–100, with greater values indicating better QoL. 6. **Pain:** measured using VAS Pain, scored on 0–10 scale, with a lower score indicating less pain. Measured at baseline, 6, 12, and 24 weeks. 7. **Fatigue:** measured using the LupusQOL Fatigue domain at baseline, 6, 12, and 24 weeks. Score range 0–100, higher the score indicates less fatigue.
Notes	**Country:** Greece **Funding:** study authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors. **Trial registration:** NCT03802578 **Serious adverse events:** none reported **Other adverse events:** none reported **Total adverse events:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	RCT. Quote: "Block size 4 randomisation was used to allocate 75 patients."

Allocation concealment (selection bias)	Low risk	Allocation was unmasked to participants and therapists delivering the exercise programme. Rheumatologists working in the 2 hospitals evaluated all participants and were masked to group allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Being an active exercise intervention, it is not possible to blind the participants and supervisors of the intervention; judged at high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor reported: unclear risk Quote: "A hand therapist (KK) assessed all patients at baseline, 6, 12 and 24 weeks. Rheumatologists working in the two hospitals evaluated all participants and were masked to group allocation. Clinical evaluation included tender and swollen joint count." It is unclear from this statement whether the hand therapist was also masked to group allocation; judged at unclear risk. Participant reported: high risk Participants were not blinded to the study, and outcomes were self-reported; judged at high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	In the summary table of results, it was unclear how many participants were included in the postintervention outcome data, considering 2 participants withdrew from the exercise programme at 6 weeks, with no clear reason for dropout. Quote: "One patient in the exercise group was diagnosed with influenza and treated with oseltamivir." However, it was unclear whether this was the participant that dropped out, and they did not report anything regarding the second participant who dropped out.
Selective reporting (reporting bias)	High risk	The LupusQOL is used to assess QoL; however, authors did not report all domains. Only Physical Health and Fatigue domains were reported.
Other bias	Low risk	No other biases.

Lopes-Souza 2021

Study characteristics	
Methods	**Study design:** randomised controlled 2-arm parallel trial **Setting:** Laboratorio de Vibracoes Mecanicas e Practicas Integrativas, Departamento de Biofisica, Instituto de Biologia Roberto Alcantara Gomes, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil **Time trial period:** recruited between May 2017 and November 2018 **Interventions:** WBWV plus usual care vs placebo (isometry) plus usual care **Sample size calculation:** performed by a previous study using the HAQ based on minimal clinically important difference of 0.22 in HAQ score (SD 0.19) between 2 groups. **Analysis:** descriptive analysis performed by mean ± SD for continuous variables, and absolute and relative frequency for categorical variables. To compare the variables between the intervention groups, the t test was used for the continuous variables and the Chi^2 test for the categorical variables. To evaluate the effect of the intra group intervention according to the moment of the evaluation (time) the paired t test was used, as well as 95% confidence intervals were calculated. The difference between the initial and final means of each group and the comparison of this difference between groups was performed using the paired t test. To minimise the effect of possible confounding variables on outcomes, the different variables between the groups at randomisation were considered as adjustment variables when comparing the intervention between the groups. The adjusted model was performed by multiple linear regression. For all analyses performed, the value of $P < 0.05$ was considered statistically significant.

Participants

Number of participants

1. Screened: 77 (56 excluded for unknown reasons, 24 excluded for not meeting inclusion criteria, and 32 declined to participate)
2. Randomised: 21 (11 in exercise group and 10 in isometry group)
3. Included in 6-week analyses: 19 participants (10 in exercise group and 9 in isometry group; 1 participant from WBVE group discontinued due to low back pain, and 1 participant discontinued from the isometry group for personal reasons)
4. Included in 12-week analyses: 17 participants (2 from exercise group discontinued for personal reasons)

Inclusion criteria

1. Women aged 30–60 years
2. Diagnosis of SLE for ≥ 6 months
3. Chronic glucocorticoids use for ≥ 3 years
4. On stable drug therapy for ≥ 2 months
5. Had chronic diseases control
6. No activity or period of exacerbation and attended Department of Rheumatology

Exclusion criteria

1. Current or prior smoking habits
2. History of alcohol abuse
3. Low impact fractures
4. Aseptic hip necrosis
5. Using assistive devises
6. Hip or knee replacement surgery
7. Pregnant
8. Comorbidities that could be affected by WBVE
9. Neurological or psychiatric disease

Baseline characteristics

All 21 participants were women

WBVE group (n = 11)

1. Mean age: 48.5 (SD 4.7) years
2. Mean BMI: 26.9 (SD 5.3) kg/m^2
3. Caucasian (believed to be white people) n: 8 (73%)
4. Not Caucasian n: 3 (27%)
5. Diabetes n: 2 (18%)
6. Hypertension n: 7 (63%)
7. Dyslipidaemia n: 3 (27%)
8. Mean lupus diagnosis time: 13.5 (SD 5.2) years
9. Mean lupus treatment prednisone (change in daily dose): 5.3 (SD 5.3) mg
10. Mean lupus treatment prednisone (change in cumulative dose 6 months): 896 (SD 337) months
11. Mean lupus treatment time of prednisone use: 13.3 (SD 5.4) years
12. Lupus treatment hydroxychloroquine n: 8 (73%)
13. Lupus treatment immunosuppressants n: 10 (90%)
14. Mean skeletal mass index: 6.5 (SD 0.7) kg/m^2
15. Mean handgrip: 33.2 (SD 8.3) kg
16. Mean Timed Up and Go: 10.2 (SD 2.5) s

Isometry group (n = 10)

1. Mean age: 47.0 (SD 7.9) years
2. Mean BMI: 4.8 (SD 3.3) kg/m^2
3. Caucasian (believed to be white people) n: 6 (60%)
4. No Caucasian: 4 (40%)
5. Diabetes n: 2 (10%)
6. Hypertension n: 7 (70%)
7. Dyslipidaemia n: 2 (20%)
8. Mean lupus diagnosis time: 14.8 (SD 7.1) years
9. Mean lupus treatment prednisone (change in daily dose): 5.0 (SD 1.9) mg
10. Mean lupus treatment prednisone (change in cumulative dose 6 months): 963 (SD 950) months
11. Mean lupus treatment time of prednisone use: 14.8 (SD 7.1) years
12. Lupus treatment hydroxychloroquine n: 7 (70%)
13. Lupus treatment immunosuppressants n: 7 (70%)
14. Mean skeletal mass index: 5.9 (SD 0.6) kg/m^2
15. Mean handgrip: 33.2 (SD 6.2) kg

	16. Mean Timed Up and Go: 9.1 (SD 1.5) s **Pretreatment group differences:** groups were homogeneous for age, BMI, lupus diagnosis time, and indices related to sarcopenia at baseline.
Interventions	**Exercise group: WBVE plus usual care** Participants stood on a vibrating platform. 1. **Frequency of exercise sessions:** 2 times/week (24 hours between sessions) 2. **Intensity of exercise:** a. Week 1–4: 10 bouts of 30 s, frequency of 30 Hz, D 1.23 mm, and a peak of 2.22 g. b. Week 5–8: 10 bouts of 60 s, frequency of 40 Hz,D 0.95 mm, and a peak of 3.06 g. c. Week 9–12: 10 bouts of 60 s, frequency of 50 Hz, D 0.88 mm, and a peak of 4.40 g. 3. **Time of exercise session:** a. Week 1–4: 2-min warm-up, 5 min. b. Week 5–12: 2-min warm-up, 10 min WBVE. 4. **Type of exercise:** WBVE is a subgroup of resistance training, better classified as muscle activation or neuromuscular training complementary to resistance training. The participants were positioned on the vibrating platform with 130° of knee flexion. 5. **Duration of intervention:** 12 weeks 6. **Supervision/setting:** unclear if there was supervision present during intervention. **Control group: placebo (isometry) plus usual care** Participants stood on a vibrating platform (switched off). 1. **Frequency of exercise sessions:** 2 times/week (24 hours between sessions) 2. **Intensity of exercise:** light-to-moderate intensity, warm-up was performed in the same way as in the WBVE group. 3. **Time of exercise session:** a. Week 1–4: 2-min warm-up, 5 min stood on a vibrating platform . b. Week 5–12: 2-min warm-up, 10 min stood on a vibrating platform . 4. **Type of exercise:** participants were requested to maintain stance with 130° of knee flexion on the same vibrating platform (turned off). The deck panel remained covered. The cycles, working, and rest times corresponded to the weeks, consistent with the WBVE group, but without vibration. 5. **Duration of intervention:** 12 weeks 6. **Supervision/setting:** unclear if there was supervision present during intervention.
Outcomes	1. **Fatigue:** measured using the FACIT-Fatigue (version 4) is a 13-item questionnaire that uses a 5-point Likert-type response scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; and 4 = very much), with scores ranging from 0 to 52 (higher scores indicating less fatigue). FACIT-Fatigue scale was completed before the intervention at weeks 0, 6, and 12. 2. **Functional capacity:** measured using the HAQ and the Timed Up and Go test. a. The HAQ consists of 20 questions, which represent common daily activities, and evaluates 8 categories: dress and physical presence, wake up, feed, walk, hygiene, reach, footprint, and other day-to-day activities. The answer alternatives for each question are 'no difficulty' (score = 0), with 'some difficulty' (score = 1), "very difficult" or 'using an auxiliary device' (score = 2) and 'unable to do' (score = 3). The highest score obtained for any question in a given subcategory determines the score for it. A final score is calculated based on the sum of the highest scores in each subcategory divided by the number of subcategories that were answered. Total score range from 0 (no disability) to 3 (severe disability). The HAQ questionnaire was completed by the women just before the intervention at 0, 6, and 12 weeks. b. The Timed Up and Go consisted of measuring the time use for participants to stand up from a chair, walking 3 m, turning, returning to the chair and sitting down. Instructed to walk in a comfortable and safe pace. The final score was the duration of time in which it took for the participant to complete this test, safely and correctly. 3. **QoL:** measured using the SF-36, which is a common tool for assessing QoL in chronic diseases, and it can be used in any disease, including SLE. It consists of 36 items, grouped into 8 domains covering physical and mental health. The 8 domains include: Functional Capacity, Physical Role Functioning, Pain, General Health, Vitality, Social Role Functioning, Emotional Role Limitations, and Emotional Wellbeing. The score of these domains ranges from 0 to 100, higher scores indicate better health. The SF-36 survey was completed by the women at 0, 6, and 12 weeks. 4. **Hand grip strength**: evaluated by a hand-held dynamometer performed through 3 evaluations, where the participant held the dynamometer (EMG830RF, EMG System, Sao Jose dos Campos/SP) with the DH 3 times in a row for 5 'seconds.' The best value of the 3 measurements was used to classify sarcopenia. Quote: "The higher the score, the better the strength."
Notes	**Country:** Brazil **Funding:** study authors received no financial support for the research, authorship, or publication of the article. **Trial registration:** Brazilian Registry of Clinical Trials under number RBR-2b4bzq. **Serious adverse events:** none reported **Other adverse events:** none reported **Total adverse events:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Study reported to be randomised in the manuscript, and was registered as an RCT; however, randomisation process was not reported.
Allocation concealment (selection bias)	Unclear risk	No allocation concealment was reported, and therefore it is unclear whether it was included.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Considering participants in both groups were on a vibrating platform, either turned on for those in the exercise group or turned off in the placebo group, we did not think that people in the placebo group could be truly blinded; judged at high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor reported: unclear The personnel conducting the outcomes or intervention (or both) were not clearly identified, and, therefore, it was unclear whether assessors were blinded to the intervention. Participant reported: high Assessors (i.e. participants) were not blinded to the self-reported outcome measures (i.e. fatigue); judged at high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up reported.
Selective reporting (reporting bias)	High risk	Authors assessed QoL with the SF-36; however, the Mental Component Summary score and Physical Component Summary scores were not reported.
Other bias	Low risk	No other biases.

Miossi 2012

Study characteristics	
Methods	**Study design:** randomised controlled 3-arm parallel trial **Setting:** Laboratory of Physical Conditioning for Rheumatologic Patients of the School of Medicine, University of Sao Paulo, Sao Paulo, Brazil **Time trial period:** May 2010 and April 2011 **Interventions:** exercise trained participants with SLE plus usual care vs non-trained participants with SLE vs healthy controls group **Sample size calculation:** not reported **Analysis:** effect sizes were estimated for the postintervention assessments using the pooled SDs of the 2 independent samples at postintervention. The significance level was previously set at $P < 0.05$. All analyses were performed using SAS software, version 8.2. Data were presented as mean and SD. As the primary analysis, ITT analysis was used for each comparison irrespective of the compliance with exercise testing. Missing data were imputed using the unconditional mean imputation at 12 weeks and postintervention.

Participants

Number of participants

1. Screened: 45 (2 participants withdrew for personal reasons, and 3 failed follow-up from the SLE non-trained group. 1 participant failed follow-up from the SLE trained group. 3 participants withdrew for personal reasons and 2 failed follow-up from the control group).
2. Randomised: 45 (15 allocated to the SLE trained group, 15 allocated to the SLE non-trained group, and 15 allocated to the control group).
3. Included in final analysis: 32 (14 participants from the SLE trained group, 10 participants from the SLE non-trained group, and 8 participants from the control group.

Inclusion criteria

1. Aged 20–40 years
2. Disease activity < 4 according to SLEDAI
3. Physically inactive for ≥ 6 months before entering study

Exclusion criteria

1. Cardiovascular dysfunction
2. Rhythm and conduction disorders
3. Musculoskeletal disturbances
4. Kidney and pulmonary involvements
5. Peripheral neuropathy
6. Use of tobacco
7. Treatment with lipid-lowering drugs
8. Fibromyalgia
9. Use of chronotropic or antihypertensive drugs

Baseline characteristics

All 32 participants were women.

Trained group (participants with SLE) **(n = 14)**

1. Mean age: 31.4 (SD 5.9) years
2. Mean weight: 65.4 (SD 11.1) kg
3. Mean height: 1.6 (SD 0.05) m
4. Mean BMI: 25.3 (SD 4.7) kg/m^2
5. Mean SLEDAI disease activity: 0.9 (SD 1.5) points
6. Disease duration: 6.1 years
7. Drug prednisone n: 10 (66.7%)
8. Drug prednisone ≥ 20 mg/day n: 2 (13.3%)
9. Drug azathioprine n: 8 (53.3%)
10. Drug chloroquine n: 12 (80%)
11. Drug methotrexate n: 1 (6.7%)
12. Drug mycophenolate mofetil n: 4 (26.7%)
13. Drug cyclophosphamide n: 1 (6.7%)
14. Drug medroxyprogesterone n: 4 (26.7%)
15. Mean resting HR: 96.6 (SD 24.0) beats per min
16. Mean peak HR: 170.7 (SD 13.4) beats per min
17. Mean VO_{2peak}: 24.8 (SD 4.8) mL/kg/min
18. Mean chronotropic reserve: 81.3 (SD 15.0)
19. Mean rest to VAT: 29.8% (SD 18%) relative change for HR
20. Mean respiratory compensation point: 64.6% (SD 26.1%) relative change for HR
21. Mean rest to peak HR: 81.1% (SD 21.8%) relative change for HR
22. Mean HR recovery 1 24.0 (SD 9.8)
23. Mean HR recovery 2: 39.5 (SD 10.3)
24. Mean chronotropic reserve before: 81.3 (SD 15.0)
25. Mean chronotropic reserve after: 95.4 (SD 9.2)
26. Mean rest to VAT before: 29.8% (SD 18.8%) relative change for HR
27. Mean rest to VAT after: 56.0% (22.2%) relative change for HR
28. Mean rest to RCP before: 69.6 (SD 26.1)
29. Mean rest to RCP after: 102.1 (SD 22.1)
30. Mean rest to peak exercise before: 81.1 (SD 21.8)
31. Mean rest to peak exercise after: 129.3 (SD 21.8)
32. Mean change in HR recovery 1 before: 24.1 (SD 9.8)
33. Mean change in HR recovery 1 after: 40.9 (SD 10.3)
34. Mean change in HR recovery 2 before: 39.5 (SD 10.3)
35. Mean change in HR recovery 2 after: 57.2 (SD 11.9)

***Non-trained group (participants with SLE)* (n = 10)**

1. Mean age: 31.0 (SD 4.8) years
2. Mean weight: 58.7 (SD 7.2) kg
3. Mean height: 1.6 (SD 0.07) m
4. Mean BMI: 23.6 (SD 1.9) kg/m^2
5. Mean SLEDAI disease activity: 1.0 (SD 1.3) points
6. Disease duration: 6.4 years
7. Drug prednisone n: 8 (61.5%)
8. Drug prednisone ≥ 20 mg/day, n: 1 (7.1%)
9. Drug azathioprine n: 5 (38.4%)
10. Drug chloroquine n: 12 (92.3%)
11. Drug methotrexate n: 3 (23.0%)
12. Drug mycophenolate mofetil n: 2 (15.3%)
13. Drug cyclophosphamide n: 0 (0%)
14. Drug medroxyprogesterone n: 7 (53.8%)
15. Mean resting HR: 94.7 (SD 14.2) beats per min
16. Mean peak HR: 165.1 (SD 13.7) beats per min
17. Mean VO_{2peak}): 25.5 (SD 3.1) mL/kg/min
18. Mean chronotropic reserve: 76.1% (SD 18.1%)
19. Mean rest to VAT: 38.9% (SD 21.7%) relative change for HR
20. Mean RCP: 54.9% (SD 21.1%) relative change for HR
21. Mean rest to peak HR: 69.8% (SD 19.3%) relative change for HR
22. Mean HR recovery 1: 25.4 (SD 12.8)
23. Mean HR recovery 2: 37.9 (SD 13.1)
24. Mean chronotropic reserve before: 76.1 (SD 18.1)
25. Mean chronotropic reserve after: 75.6 (SD 16.6)
26. Mean rest to VAT before: 38.9% (SD 21.7%) relative change for HR
27. Mean rest to VAT after: 34.9% (SD 15.7%) relative change for HR
28. Mean rest to RCP before: 54.9 (SD 12.0)
29. Mean rest to RCP after: 68.7 (SD 25.3)
30. Mean rest to peak exercise before: 69.8 (SD 19.3)
31. Mean rest to peak exercise after: 90.6 (SD 30.3)
32. Mean change in HR recovery 1 before: 25.4 (SD 12.8)
33. Mean change in HR recovery 1 after: 26.7 (SD 9.3)
34. Mean change in HR recovery 2 before: 37.8 (SD 13.1)
35. Mean change in HR recovery 2 after: 39.5 (SD 13.4)

Healthy control group (n = 8)

1. Mean age: 30.9 (SD 8.3) years
2. Mean weight: 61.3 (SD 7.7) kg
3. Mean height: 1.6 (SD 0.06) m
4. Mean BMI: 23.9 (SD 3.2) kg/m^2
5. Drug prednisone n: 1 (0%)
6. Drug prednisone ≥ 20 mg/day: 1
7. Drug azathioprine n: 0.47 (0%)
8. Drug methotrexate n: 0.3 (0%)
9. Drug mycophenolate mofetil n: 0.65 (0%)
10. Drug cyclophosphamide n: 1 (0%)
11. Drug medroxyprogesterone n: 0.2 (0%)
12. Mean resting HR: 90.4 (SD 9.2) beats per min
13. Mean peak HR: 182.6 (SD 5.5) beats per min
14. Mean VO_{2peak}: 31.0 (SD 4.8) mL/kg/min
15. Mean chronotropic reserve: 93.5% (SD 4.9%)
16. Mean rest to VAT: 49.2% (SD 15.4%) relative change for HR
17. Mean RCP: 85.0% (SD 19.8%) relative change for HR
18. Mean rest to peak HR: 103.6% (SD 18.3%) relative change for HR
19. Mean HR recovery 1: 33.8 (SD 6.6)
20. Mean HR recovery 2: 52.0 (SD 5.7)
21. Mean chronotropic reserve before: 93.5 (SD 4.9)
22. Mean chronotropic reserve after: 95.9 (SD 10.4)

	23. Mean rest to VAT before: 49.2% (SD 15.4%) relative change for HR 24. Mean rest to VAT after: 49.6% (SD 21.5%) relative change for HR 25. Mean rest to RCP before: 85.0 (SD 19.8) 26. Mean rest to RCP after: 98.4 (SD 18.8) 27. Mean rest to peak exercise before: 103.6 (SD 18.3) 28. Mean rest to peak exercise after: 121.6 (SD 23.3) 29. Mean change in HR recovery 1 before: 33.8 (SD 6.6) 30. Mean change in HR recovery 1 after: 38.2 (SD 10.0) 31. Mean change in HR recovery 2 before: 52.0 (SD 5.7) 32. Mean change in HR recovery 2 after: 53.6 (SD 7.6) **Pretreatment group differences:** the 3 groups were homogeneous for age, height, and resting HR at baseline.
Interventions	**Exercise: trained SLE plus usual care** 1. **Frequency of exercise sessions:** 2 times/week 2. **Intensity of exercise:** HR corresponding to the interval between VAT and 10% below RCP 3. **Time of exercise session:** 80 min per session 4. **Type of exercise:** training session composed of 5-min treadmill warm-up followed by 35–40 min of resistance training, 30 min of treadmill aerobic training, and 5 min of stretching. Resistance training included 7 exercises for the main muscle groups (e.g. bench press, leg press, leg extension). Participants were required to perform 4 sets of 8–12 RM, except during the first week, when a reduced volume of 2 sets of 15–20 RM for each exercise was performed (as an adaptation period to resistance training). Cardiorespiratory exercise test was performed on a treadmill (Centurion, Model 200, Micromed) using a maximal-graded exercise protocol. 5. **Duration of intervention:** 12 weeks 6. **Supervision/setting:** all sessions were monitored by 1 fitness professional. **Non-trained SLE group (another non-pharmacological intervention plus usual care)** Physically inactive women were advised to remain physically inactive. Participants received usual care and information about the disease, but no exercise intervention. **Heathy control group** 1. **Frequency of exercise sessions:** 3 times/week 2. **Intensity of exercise:** HR corresponding to the interval between VAT and 10% below RCP. 3. **Time of exercise session:** 80 min per session 4. **Type of exercise:** training session composed of 5-min treadmill warm-up followed by 35–40 min of resistance training, 30 min of treadmill aerobic training, and 5 min of stretching. Resistance training included 7 exercises for the main muscle groups (e.g. bench press, leg press, leg extension). Participants were required to perform 4 sets of 8–12 RM, except during the first week, when a reduced volume of 2 sets of 15–20 RM for each exercise was performed (as an adaptation period to resistance training). Cardiorespiratory exercise test was performed on a treadmill (Centurion, Model 200, Micromed) using a maximal-graded exercise protocol. 5. **Duration of intervention:** 12 weeks 6. **Supervision/setting:** all sessions were monitored by 1 fitness professional. Participants with SLE and healthy controls had not engaged in regular physical activity programme for ≥ 6 months before the commencement of study and were instructed to maintain their usual living activities and not to engage in any other regular exercise programme throughout the study.
Outcomes	1. **Cardiorespiratory fitness (VO_{2peak}):** oxygen consumption and carbon dioxide output were obtained through breath-by-breath sampling and expressed as a 30-s mean using an indirect calorimetry system (Cortex Model Metalyzer III B). This was measured using a maximal-graded exercise test on a treadmill. Measured at baseline and 12 weeks. 2. **Chronotropic reserve:** HR response during exercise was evaluated by the formula chronotropic reserve = [peak HR − resting HR/220 − age − resting HR] × 100. HRR was defined as the difference between HR at peak exercise and at both the first (HR recovery 1) and (HR recovery 2) minutes after exercise. Absolute change was used to calculate the difference between the HR at peak exercise and at the first and second minutes after the exercise test. Relative change for HR was calculated for the intervals between rest to VAT, rest to RCP, and rest to peak exercise. Measured at baseline and 12 weeks.
Notes	**Country:** Brazil **Funding:** the Laboratory of Physical Conditioning for Rheumatologic Patients received an institutional grant from Bank of America Merrill Lynch. Dr Benatti's work was supported by the Fundaco de Amparo a Pesquisa do Estado de Sao Paulo. Dr Borba's work was supported by the Conselho Nacional de Desenvolvimento Cientıfico e Tecnologico and the Federico Foundation. Dr Bonfa's work was supported by the Fundacao de Amparon a Pesquisa do Estado de Sao Paulo and the Federico Foundation. **Trial registration:** unknown **Serious adverse events:** none reported **Other adverse events:** none reported **Total adverse events:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as an RCT but unclear how randomisation was performed; judged at unclear risk of bias. Quote: "Physically inactive women with SLE were randomly assigned to participate in a supervised exercise training program (T group) or to remain physically inactive (NT group)."

Allocation concealment (selection bias)	Unclear risk	No allocation concealment was reported; judged at unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Being an active exercise intervention, it is not possible to blind the participants and supervisors of the intervention; judged at high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor reported: unclear risk No blinding of outcome assessments was reported; judged at unclear risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of selecting reporting.
Selective reporting (reporting bias)	Low risk	All outcome measures were reported.
Other bias	Low risk	No other biases.

Tench 2003

Study characteristics	
Methods	**Study design:** 3-arm RCT **Setting:** Bone and Joint Research Unit, Department of Psychological Medicine, Barts; the London, Queen Mary's School of Medicine and Dentistry; National Sports Medicine Institute; Barts and the London NHS Trust, London, UK **Time trial period:** unknown **Interventions:** aerobic exercise programme plus usual care vs another non-pharmacological intervention (relaxation exercise) plus usual care vs usual care alone **Sample size calculation:** in a previous study of exercise therapy and fibromyalgia, 50% of participants considered themselves moderately improved by the treatment compared with 10% of controls receiving flexibility training. By assuming similar treatment responses with a = 0.05 and a power of 90%, the study authors calculated that 30 participants would be required for each group. **Analysis:** statistical analysis used the SPSS 10.0 for Windows software package (SPSS, Chicago, IL, USA). All participants who underwent random allocation were analysed according to group assignment. The Clinical Global Impression Change score was analysed categorically; a score of 1 or 2 was considered clinically important. We compared the proportions of participants rating themselves clinically improved by ITT analysis by means of ×2 analysis with Fisher's exact test for small numbers. 1-way analysis of variance with Bonferroni correction or the Kruskal–Wallis test was used to compare means and medians of each variable in the 3 groups as appropriate.

Participants

Number of participants

1. Screened: 93
2. Randomised: 93 (33 in exercise group, 28 in relaxation group, and 32 in control group). 11 participants did not commence the intervention; 6 in exercise group, 4 in relaxation group, and 1 in control group dropped out of treatment (did not attend a single supervised exercise sessions or return any dairy sheets).
3. Included in the 12-week analyses: 79 (14 did not attend the 12-week physiological assessment; 4 in exercise group, 5 in relaxation group, and 5 in control group). 6/14 participants had dropped out of study, and 8/14 had completed the study but did not wish to repeat the walking test to exhaustion.

Inclusion criteria

1. Aged 16–55 years
2. Diagnosis of SLE according to ACR criteria

Exclusion criteria

1. Evidence of active severe myositis
2. Evidence of active severe nephritis
3. Neurological involvement
4. Cardiac disease
5. Pulmonary disease
6. Pregnancy

Baseline characteristics

All 93 participants were women. Mean age 39 (SD 0.8) years, median disease duration 30 (IQR 10–14) months, median SLAM score of 5 (IQR 3–8), and median SLICC/ACR damage index score of 0 (IQR 0–0).

Exercise group (n = 33)

1. CFS: mean 22 (SEM 1.3)
2. VAS: mean 33 (SEM 10)
3. FSS: mean 5.4 (SEM 0.2)
4. PSQI: median 8 (IQR 5–12)
5. HAD Anxiety: mean 9.0 (SEM 0.8)
6. HAD Depression: mean 5.0 (SEM 0.7)
7. SF-36 Physical Function: mean 62 (SEM 5)
8. SF-36 Role Physical: median 25 (IQR 0–63)
9. SF-36 Vitality: mean 37 (SEM 3)
10. SLAM: median 5 (IQR 3–8)
11. Test duration: mean 9.8 (SEM 0.6) min
12. Peak oxygen uptake: mean 23.1 (SEM 0.9) mL/kg/min
13. Maximum ventilation: mean 61.5 (SEM 3)
14. Maximum HR: median 173 (IQR 158–181) beats per min
15. Recovery HR: mean 99 (SEM 2.6) beats per min
16. BMI: median 25 (IQR 23–29) kg/m^2

Relaxation group (n = 28)

1. CFS: mean 24 (SEM 1.6)
2. VAS mean 290 (SEM 11)
3. FSS: mean 5.4 (SEM 0.2)
4. PSQI: median 8 (IQR 6–12)
5. HAD Anxiety: mean 9.9 (SEM 0.9)
6. HAD Depression: mean 7.9 (SEM 0.8)
7. SF-36 Physical Function: mean 61 (SEM 5)
8. SF-36 Role Physical: median 12.5 (IQR 0–75)
9. SF-36 Vitality: mean 32 (SEM 4)
10. SLAM: median 6 (IQR 3–8)
11. Test duration: mean 10.8 (SEM 0.8) min
12. Peak oxygen uptake: mean 24.2 (SEM 1.5) mL/kg/min
13. Maximum ventilation: mean 59.6 (SEM 4)
14. Maximum HR: median 168 (IQR 153–185) beats per min
15. Recovery HR: mean 104 (SEM 3.1) beats per min
16. BMI: median 24 (IQR 22–28) kg/m^2

Control group (n = 32)

1. CFS: mean 24 (SEM 1.7)
2. VAS: mean 286 (SEM 12)
3. FSS: mean 5.5 (SEM 0.2)

	4. PSQI: median 7 (IQR 6–12) 5. HAD Anxiety: mean 8.8 (SEM 0.7) 6. HAD D: mean 6.4 (SEM 0.6) 7. SF-36 Physical Function: mean 61 (SEM 4) 8. SF-36 Role Physical: median 12.5 (IQR 0–50) 9. SF-36 Vitality: mean 36 (SEM 4) 10. SLAM: median 5 (IQR 4–8) 11. Test duration: mean 10.6 (SEM 0.7) min 12. Peak oxygen uptake: mean 22.5 (SEM 1.3) mL/kg/min 13. Maximum ventilation: mean 59.1 (SEM 3) 14. Maximum HR: median 166 (IQR 155–186) beats per min 15. Recovery HR: mean 100 (SEM 2.9) beats per min 16. BMI: median 26 (IQR 22–30) kg/m^2 **Pretreatment group differences:** the 3 groups were homogeneous for age, BMI, and disease duration at baseline.
Interventions	**Exercise plus usual care** 1. **Frequency of exercise sessions:** 3 times/week 2. **Intensity of exercise:** moderate intensity; HR corresponding to 60% of peak oxygen consumption 3. **Time of exercise session:** 30–50 min per session 4. **Type of exercise:** walking was encouraged, but participants were encouraged to take other forms of exercise such as cycling and swimming also 5. **Duration of intervention:** 12 weeks 6. **Supervision/setting:** participants were asked to exercise at home at least three times per week for between 30 and 50 minutes and were seen by an exercise professional every 2 weeks for a supervised exercise session. **Another non-pharmacological intervention (relaxation) plus usual care** 1. **Frequency of exercise sessions:** 3 times/week 2. **Intensity of exercise:** unclear 3. **Time of exercise session:** 30 min 4. **Type of exercise:** participants were asked to listen to a relaxation audiotape a minimum of 3 times/week for 30 min, in a darkened room where it was warm and quiet. 5. **Duration of intervention:** 12 weeks 6. **Supervision/setting:** participants were asked to listen to a 30-minute relaxation audio tape a minimum of three times per week in a darkened, warm, and quiet room, and were seen every two weeks for a supervised relaxation session. **Control group (usual care alone)** Participants were asked to continue with their normal daily activity pattern and specifically asked to avoid doing any extra physical activities. They were reviewed at follow-up but not seen at any other times.

Outcomes	1. **Fatigue:** measured using the FSS, CFS, and VAS a. **FSS:** FSS is a 9-item questionnaire, scored on a 7-point Likert scale with 1 = strongly disagree, and 7 = strongly agree. Minimum raw score is 9 and maximum score is 63. However, the mean of all scores can also be taken with a minimum score of 1 and a maximum score of 7. Higher score = greater fatigue severity. A change score of 1.9 points is considered a clinically important change. Measured at baseline and 12 weeks. b. **CFS:** was originally perceived as comprising 2 subscales that evaluate fatigue in the physical and mental domains. Items are rated on a 4-point Likert scale (0 = better than usual, 1 = no more than usual, 2 = worse than usual, 3 = much worse than usual), with higher scores indicating greater fatigue. Measured at baseline and 12 weeks. c. **VAS:** measured using VAS for fatigue. Study authors did not report which scale was used. However, lower scores on VAS usually indicate a better outcome. Measured at baseline and 12 weeks. 2. **Anxiety:** measured using the HADS questionnaire, which consists of 7 questions for anxiety and 7 questions for depression. Questions are compiled, but scored separately. Score range is 0–21. Lower scores indicate a better outcome (a score of 8–10 is mild, 11–14 moderate, and 15–21 severe). 3. **Depression:** measured using the HADS questionnaire, which consists of 7 questions for anxiety and 7 questions for depression. Questions are compiled, but scored separately. Score range is 0–21. Lower scores indicate a better outcome (a score of 8–10 is mild, 11–14 moderate, and 15–21 severe). 4. **Sleep:** measured using the PSQI, which is a self-rated questionnaire that assesses sleep quality and disturbances over a 1-month period. Consisting of 19 individual items, generating 7 'component' scores that include; subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Score range from 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a final global score (ranging from 0 to 21). Higher scores indicate worse sleep quality. 5. **Disease activity:** measured using the SLAM, which includes both dimensions: disease activity and disease severity over the previous 4 weeks. It assesses 9 organ systems (subjective items include, fatigue, myalgia, arthralgia) and 7 laboratory items. There are 32 items. Score range from 0 to 83. Lower score indicates less disease activity. 6. **QoL:** measured using the SF-36, which is a common tool for assessing the QoL in chronic diseases, and it can be used in any disease, including SLE. It consists of 36 items, grouped into 8 domains covering physical and mental health. The 8 domains include: Functional Capacity, Physical Role Functioning, Pain, General Health, Vitality, Social Role Functioning, Emotional Role Limitations, and Emotional Wellbeing. The score of these domains ranges from 0 to 100, higher scores indicate better health. The study reported Physical Function, Physical Role, and Vitality domains. 7. **Self-rated CGI change:** this is a stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication. Comprised of 2 companion 1-item measures evaluating severity of psychopathology from 1 to 7 and change from the initiation of treatment on a scale of 1 to 7. Rated on a 7-point scale, this indicates the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients).
Notes	**Country:** UK **Funding:** study author CMT was funded by the Arthritis Research Campaign (TO519), the Joint Research Board of St Bartholomew's Hospital (XMKY) and the British Medical Association Doris Hillier Award. **Trial registration:** unknown **Serious adverse events:** none reported **Other adverse events:** none reported **Total adverse events:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation has been reported. Quote: "All 93 patients were randomly allocated to the exercise programme, the relaxation programme or to no intervention, using a minimisation protocol."
Allocation concealment (selection bias)	Unclear risk	No allocation concealment clearly reported, and, therefore, it was unclear whether this was concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Being an active exercise intervention, it is not possible to blind the participants and supervisors of the intervention; judged at high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor reported: unclear risk No blinding of outcome assessment (disease activity) was clearly reported. Participant reported: high risk Participants completed self-reported outcomes, and participants knew which group they were in; judged a high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Authors reported an ITT method of analysis.
Selective reporting (reporting bias)	High risk	Authors did not report scores for all 8 domains in the SF-36: Physical Functioning (10 items); Physical Role Limitations (4 items); Bodily Pain (2 items); General Health Perceptions (5 items); Energy/Vitality (4 items); Social Functioning (2 items); Emotional Role Limitations (3 items), and Mental Health (5 items). Authors also did not report the PCS score and the MCS score for this outcome.
Other bias	Low risk	No other biases.

ACR: American College of Rheumatology; ACR-DI: American College of Rheumatology Damage Index; ACSM: American College of Sports Medicine; BDI: Beck-Depression Index; BMI; body mass index; CES-D: Center for Epidemiologic Studies Depression Scale; CFS: Chandler Fatigue Scale; DASH: Disabilities of the Arm, Shoulder, and Hand; DH: dominant hand; dsDNA: double-stranded DNA; DEXA: dual-energy X-ray absorptiometry; ESR: erythrocyte sedimentation rate; FACIT-Fatigue: Fatigue Assessment of Chronic Illness Therapy – Fatigue subscale; FSS: Fatigue Severity Score; HAQ: Health Assessment Questionnaire; HDL: high-density lipoprotein; HRR: heart rate reserve; IFN: interferon; IL: interleukin; IQR: interquartile range; ITT: intention-to-treat; LDL: low-density lipoprotein; LupusQOL: Lupus Quality Of Life; MAC: Mental Adjustment to Cancer; MHR: maximum heart rate; MVPA: moderate to vigorous physical activity; n: number; NSAID: non-steroidal anti-inflammatory drug; PCS: Physical Component Score; POMS: Profile Of Moods State; PSQI: Pittsburgh Sleep Quality Index; PWC75%: 75% of the predicted maximal heart rate; QoL: quality of life; RA: rheumatoid arthritis; RCT: randomised controlled trial; RHR: resting heart rate; RM: repetitions maximum; SD: standard deviation; SEM: standard error of the mean; SF-36: 36-item Short Form; SLAM: Systemic Lupus Activity Measure; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics; TNF: tumour necrosis factor; VAS: Visaula Analogue Scale; VAT: ventilator anaerobic threshold; VLDL: very low-density lipoprotein; VO_{2max}: maximum rate of oxygen consumption; VO_{2peak}: peak oxygen consumption; WBC: white blood cell; WBVE: whole body vibration exercise.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abrahao 2009	Conference abstract of 1 of the included studies (Abrahão 2016).
Ahn 2015	Ineligible study design (not an RCT) and ineligible intervention (not a structured exercise intervention).
Barnes 2010	Ineligible intervention (not a structured exercise intervention).
Bogdanovic 2015	Ineligible study design (not an RCT).
Bostrom 2013	Review of the literature (not a trial).
Cenedeze 2016	Ineligible intervention (single bout of exercise and not a structured exercise intervention).
Chapman 2020	Ineligible study design (not an RCT).
Clarke-Jenssen 2005	Ineligible study design (not an RCT).
Da Silva 2013	Ineligible intervention (study of an acute bout of exercise, and did not include an intervention of exercise over a period of time).
De Carvalho 2005	Ineligible study design (not an RCT).
Gavilan-Carrera 2020	Ineligible study design (study was a non-randomised clinical trial).
Gordon 2017	Ineligible study design (not an RCT).
Haglo 2021	Ineligible patient population: included people with SLE among other rheumatic diseases, and we were unable to distinguish results for the participants with SLE alone.
Hasni 2021	Ineligible study design: not an RCT. Single-group observational study.
Isenberg 1981	Ineligible intervention (study of an acute bout of exercise, and did not include an intervention of exercise over a period of time).
Mak 2020	Review of the literature (not a trial).
Martinez 2021	Inelgibile study design (not an RCT). Abstract of the excluded study (Hasni 2021).
Martinez-Rosales 2020	Ineligible study design (not an RCT). Study part of another inelgibile study (Soriano-Maldonado 2018).
Perandini 2014	Ineligible study design (not an RCT) and ineligible patient population (control group were healthy controls, and there was no control group of people with SLE).
Ramsey-Goldman 2000	Ineligible study design (not an RCT).
Sheikh 2019	Ineligible study design (not an RCT).
Sieczkowska 2022	Ineligible patient population: study of adolescents with juvenile idiopathic arthritis.
Soriano-Maldonado 2018	Ineligible study design (not an RCT).

Study	Reason for exclusion
Tench 2002	Indelible study design (cross-sectional design comparing outcomes in people with SLE and without SLE, and not an RCT of an exercise intervention).
Youssef 2021	Ineligible study design: not an RCT.
Yuen 2011	Ineligible study design (not an RCT).
Zeppieri-Caruana 2018	Review of the literature (not a trial).

RCT: randomised controlled trial.

Characteristics of studies awaiting classification [ordered by study ID]

Boedecker 2020

Methods	**Study design:** 3-arm randomised controlled trial **Setting:** Division of Nephrology, Rheumatology, and Immunology outpatient clinic of the University Medical Center Mainz, Germany **Time trial period:** study registration in May 2019 and enrolment began in May 2019. **Interventions:** aerobic exercise versus anaerobic exercise versus usual care **Sample size calculation:** sample size determined after recruiting and screening multiple participants to determine if they fit the inclusion criteria. **Analysis:** data analysis is ongoing, and results were expected to be submitted for publication in January 2021.
Participants	**Number of participants** 1. Screened: 40 (10 did not meet inclusion criteria) 2. Randomised: 30: 10 in aerobic exercise group, 10 in anaerobic exercise group, and 10 in control group (1 participant withdrew before first performance test and before the programme due to a fracture; unclear which group this participant was randomised to). 3. Included in analyses: 25 participants were included in the 12-week analysis (1 participant has not yet completed the study, and 3 participants withdrew from the study: 1 due to repeated colds so that regular sport was not possible, 1 had a relapse of Crohn's disease during study, and 1 stated that continuing to exercise was not possible due to physical strain). **Inclusion criteria** 1. Aged 18–65 years 2. Diagnosis of SLE by the classification ACR criteria and the 2019 EULAR /ACR Classification Criteria for SLE 3. Positive antinuclear antibody titre (≥ 1:80) or anti-dsDNA c (≥ 200 IU/mL) or positive anti-dsDNA autoantibody (≥ 30 IU/mL) 4. SLE Disease Activity Index ≥ 4 5. For 30 day prior, stable immunosuppressive therapy with steroid (0–20 mg/day) or other immunosuppressive medication such as hydroxychloroquine, chloroquine, azathioprine, methotrexate, mycophenolate mofetil, ciclosporin, belimumab, rituximab. **Exclusion criteria** 1. Pregnancy 2. Active lupus nephritis, myocarditis, or pericarditis 3. Physical activity > 2 times a week **Baseline characteristics** All 30 participants were women. No other baseline characteristics were reported.

Interventions	**Anaerobic exercise programme** 1. **Frequency of exercise sessions:** 3 times/week 2. **Intensity of exercise:** each exercise session was to be adjusted (intensity) by interpreting of the training data and the rating of perceived pain and load every week. The recommendations are based on heart rate in training zones related to individual anaerobic threshold. 3. **Time of exercise session:** 20–50 min for each training session. Including 5-min warm-up and 5-min cool-down. Anaerobic training sessions are performed using an intermittent protocol with heart rate above the individual anaerobic threshold for 2–3 min per interval. The progression stages in the anaerobic exercise group range from 3 intervals (1 interval of 3 min + 2 intervals of 2 min each) up to 8 intervals (8 intervals of 3 min each) with a 2-min walking break between intervals. 4. **Type of exercise:** walking or running should be the main part of endurance training sessions. Performing 1 or 2 strength training session weekly or integrating specified strength training exercises into the endurance training (e.g. at the end of running or walking) was also suggested. 10 strength exercises for major muscle groups that can be trained separately with elastic resistance bands, 3 sets with 15 repetitions per exercise each week was created for compilation. The compilation also includes 10 relaxation exercises, recommended for after strength training sessions. 5. **Duration of intervention:** 12 weeks 6. **Supervision/setting:** every Monday, an individualised training schedule was sent to each participant in both intervention groups. Participants are given a weekly protocol, where all physical activities during the week, including all recommended (endurance and strength) and additional activities, should be recorded. After each week, a sports therapist analyses the training data to adapt the schedule for the following week according to participant self-reported values of pain and training load. **Aerobic exercise programme** 1. **Frequency of exercise sessions:** 3 times/week 2. **Intensity of exercise:** each exercise session was to be adjusted (intensity) by interpreting of the training data and the rating of perceived pain and load every week. The recommendations are based on heart rate in training zones related to individual anaerobic threshold. 3. **Time of exercise session:** 20–50 min for each training session. Including 5-min warm-up and 5-min cool-down. Anaerobic training sessions are performed by using an intermittent protocol with heart rate above the individual anaerobic threshold for 2–3 min per interval. The aerobic exercise group performs aerobic training sessions for the whole programme. 4. **Type of exercise:** walking or running should be the main part of endurance training sessions. Performing 1 or 2 strength training session weekly or integrating specified strength training exercises into the endurance training (e.g. at the end of running or walking) was also suggested. 10 strength exercises for major muscle groups that can be trained separately with elastic resistance bands, 3 sets with 15 repetitions per exercise each week was created for compilation. The compilation also includes 10 relaxation exercises, recommended for after strength training sessions. 5. **Duration of intervention:** 12 weeks 6. **Supervision/setting:** every Monday, an individualised training schedule was sent to each participant in both intervention groups. Participants are given a weekly protocol, where all physical activities during the week, including all recommended (endurance and strength) and additional activities, should be recorded. After each week, a sports therapist analyses the training data to adapt the schedule for the following week according to participant self-reported values of pain and training load. **Usual care** To assess the effect of the intervention programme, the control group (treatment as usual) will participate in voluntary exercise that is assessed using a questionnaire for habitual physical activity. These participants also received a smartwatch.

Outcomes	**Primary outcomes** 1. **VO_{2peak}:** measured using spiroergometry at weeks 0 and 12. **Secondary outcomes** 1. **Fatigue Scale for Motor and Cognitive Functions:** scale consists of 20 items using a 5-point Likert scale, from absolutely agree to absolutely disagree, to assess cognitive fatigue (10 items) and motor fatigue (10 Fatigue Scale for Motor and Cognitive Functions items). The scores for cognitive and motor fatigue are added for the sum score. A cutoff value of 43 indicates mild fatigue, whereas higher values are associated with moderate fatigue (≥ 53) or severe fatigue (≥ 63). Outcome measured at weeks 0, 12, and 24. 2. **Beck-Depression Inventory:** questionnaire consists of 21 sets of statements, which are ranked in terms of severity from 0 to 3. The sum (range 0–63) indicates the severity of depression. The standardised scale is 0–8, no depression; 9–13, minimal depression; 14–19, mild depression: 20–28, moderate depression, 29–63: severe depression. Outcome measured at weeks 0, 12, and 24. 3. **SLE disease activity index:** index consists of 24 items including clinical and laboratory variables to measure disease activity within the previous 10 days. Maximum score 105, scores > 3 indicate a mild or moderate flare, and scores ≥ 12 indicate a severe flare. Outcome measured at weeks 0, 12, and 24. 4. **Disease Activity Score-28:** score indicates rheumatoid arthritis disease activity and treatment response. It is composed of 4 measures including the number of swollen or tender joints, C-reactive protein level, and patient's health assessment. A total score is calculated using the formula. Values range from 2.0 to 10, where a higher value indicates higher disease activity. The score is a valuable tool to assess the severity of joint involvement and activity in SLE. Outcome measured at weeks 0, 12, and 24. 5. **Work Ability Index:** self-assessment questionnaire used to assess the work ability of the patients. The questionnaire covers 6 dimensions including current work ability, as well as past 2-year estimation amongst others: 7–27 points indicates poor, 28–36 points indicates moderate, 37–43 points indicates good, and 44–49 points indicates very good work ability. Outcome measured at weeks 0, 12, and 24. 6. **Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index:** scoring system includes a score to measure the activity of skin lesions and a score to measure the damage to skin lesions in people with discoid lupus erythematosus and cutaneous lupus erythematosus. The score is used as a follow-up parameter. It has been shown that scores correlate well with the physician's and patient's global assessment of disease activity. Outcome measured at weeks 0, 12, and 24. 7. **Autoantibody titres:** DNA b (standard value ≤ 20 IU). Outcome measured at weeks 0, 12, and 24. 8. **Complement level:** C3c and C4 levels (standard values: C3c: 0.9–1.8 g/L; C4: 0.1–0.4 g/L). Outcome measured at weeks 0, 12, and 24. 9. **Circulating, cell-free DNA levels:** concentration of circulating, cell-free DNA (ng/mL) measured before, during, and after laboratory standardised stepwise exercise test from capillary and venous blood samples. After centrifugation of the samples, the circulating cell-free DNA is determined by a direct quantitative real-time polymerase chain reaction method from plasma without previous DNA extraction. Compared to healthy participants, participants with SLE show higher circulating cell-free DNA plasma levels. Outcome measured at weeks 0 and 12. 10. **Extracellular vesicles:** relative amount of extracellular vesicle subpopulations analysed using bead isolation and size exclusion chromatography followed by protein marker characterisation. Outcome measured at weeks 0 and 12. 11. **Lactate levels:** to estimate the lactate threshold, capillary blood samples were taken from the fingertips using end-to-end capillary with a defined volume of 20 µL (sodium heparin (EKF-Diagnostics GmbH) before analysis using the Biosen S-Line (EKF-Diagnostics GmbH). In this study, capillary blood samples were taken at the beginning of the test, after each step of treadmill walking, and 3 min after exhaustion. All samples were quantified directly after the test. To define the anaerobic lactate acid threshold or individual anaerobic threshold the Dickhuth model (baseline) +1.5 mmol/L model was used. Outcome measured at weeks 0 and 12. 12. **Ventilatory threshold:** change in ventilatory threshold after 12 weeks compared to baseline. Outcome measured at weeks 0 and 12. 13. **Muscle mass:** muscle mass measured in absolute mass (kilograms) including internal organs using bioelectrical impedance analysis. Outcome measured at weeks 0 and 12. 14. **Borg's scale:** ratings of perceived exertion with the Borg 15-grade scale (range 6–20) within the last 30 s of each stage of walking recorded. Higher scores indicate higher perceived exertion. Outcome measured at weeks 0 and 12. 15. **Smartwatch data:** evaluation of the physical strain and performance during the weekly training sessions measured by heart rate and distance covered during running. Outcome measured at weeks 0 and 12.
Notes	**Country:** Germany **Funding:** University of Mainz, Germany **Trial registration:** DERR1-10.2196/18291 **Serious adverse events:** none reported **Other adverse events:** none reported **Total adverse events:** not reported

ACR: American College of Rheumatology; anti-dsDNA: antidouble stranded DNA; EULAR: European League Against Rheumatism; min: min; SLE: systemic lupus erythematosus.

Appendices

Appendix 1. CENTRAL (via Ovid) search strategy

1.	Lupus.mp.
2.	exp Lupus Erythematosus, Systemic/

3.	SLE.mp.
4.	or/1-3
5.	Exercise Therapy/ or Exercise/ or exercis*.mp.
6.	physical activity.mp. or Exercise/
7.	physical activities.mp. or Exercise/
8.	exp Physical Therapy Modalities/
9.	or/5-8

Appendix 2. MEDLINE (via Ovid) search strategy

1.	Lupus.mp.
2.	exp Lupus Erythematosus, Systemic/
3.	SLE.mp.
4.	or/1-3
5.	Exercise Therapy/ or Exercise/ or exercis*.mp.
6.	physical activity.mp. or Exercise/
7.	physical activities.mp. or Exercise/
8.	exp Physical Therapy Modalities/
9.	or/5-8
10.	randomized controlled trial.pt
11.	controlled clinical trial.pt
12.	randomized.ab
13.	placebo.ab
14.	drug therapy.fs
15.	randomly.ab
16.	trial.ab
17.	groups.ab
18.	or/10-17
19.	exp animals/ not humans.sh
20.	18 not 19
21.	9 AND 20

Appendix 3. Embase (via Ovid) search strategy

1 lupus.mp.

2 systemic lupus erythematosus.mp. or exp systemic lupus erythematosus/

3 SLE.mp.

4 or/1-3

5 Exercise Therapy.mp.

6 exp exercise/ or exercis*.mp.

7 physical activity.mp. or exp physical activity/

8 physical activities.mp.

9 Physical Therapy Modalities.mp.

10 or/5-9

11 random$.tw.

12 factorial$.tw.

13 crossover$.tw.

14 cross over.tw.

15 cross-over.tw.

16 placebo$.tw.

17 (doubl$ adj blind$).tw.

18 (singl$ adj blind$).tw.

19 assign$.tw.

20 allocat$.tw.

21 volunteer$.tw.

22 crossover procedure/

23 double blind procedure/

24 randomized controlled trial/

25 single blind procedure/

26 or/11-25

27 4 and 10 and 26

Appendix 4. CINAHL (via EBSCO) Search strategy

(Lupus OR SLE OR "systemic Lupus Erythematosus") AND (exercis* OR "physical activity" OR "physical activities)

Appendix 5. SPORTDiscus (via EBSCO) Search strategy

(Lupus OR SLE OR "systemic Lupus Erythematosus") AND (exercis* OR "physical activity" OR "physical activities)

Appendix 6. Web of Science Search strategy

1.	lupus.mp.
2.	systemic lupus erythematosus.mp. or exp systemic lupus erythematosus/
3.	SLE.mp.
4.	or/1-3
5.	Exercise Therapy.mp.
6.	exp exercise/ or exercis*.mp.

7.	physical activity.mp. or exp physical activity/
8.	physical activities.mp.
9.	Physical Therapy Modalities.mp.
10.	or/5-9

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Additional tables

Table 1

Characteristics of interventions in included studies

Study ID	Description of usual care	Description of exercise group	Description of control group
Trials with a placebo plus usual care control			
Lopes-Souza 2021	The SLE treatment outlined at baseline for each intervention group included: **Exercise group (n = 11)** 1. Mean lupus treatment prednisone (change in daily dose) 5.3 (SD 5.3) mg 2. Mean lupus treatment prednisone (change in cumulative dose 6 months) 896 (SD 337) months 3. Mean lupus treatment time of prednisone use: 13.3 (SD 5.4) years Number (%) of participants on the following medications: 1. hydroxychloroquine: 8 (73%) 2. immunosuppressants: 10 (90%) **Control group (n = 10)** 1. Mean lupus treatment prednisone (change in daily dose) 5.0 (SD 1.9) mg 2. Mean lupus treatment prednisone (change in cumulative dose 6 months) 963 (SD 950) months 3. Mean lupus treatment time of prednisone use: 14.8 (SD 7.1) years Number (%) of participants on the following medications: 1. Hydroxychloroquine: 7 (70%) 2. Immunosuppressants: 7 (70%) No further information about their usual care was reported.	Participants received usual care and whole body vibration exercise 2 times/week (24 hours between sessions) for 12 weeks. WBVE is a subgroup of resistance training, better classified as muscle activation or neuromuscular training complementary to resistance training. The participants were positioned on the vibrating platform (turned on) with 130° of knee flexion. It is unclear whether this was supervised. **Intensity of exercise** **Week 1–4:** 10 bouts of 30 s, frequency 30 Hz, D 1.23 mm, and a peak of 2.22 g. **Week 5–8:** 10 bouts of 60 s, frequency 40 Hz, D 0.95 mm, and a peak of 3.06 g. **Week 9–12:** 10 bouts of 60 s, frequency 50 Hz, D 0.88 mm, and a peak of 4.40 g. **Time of exercise session** **Week 1–4:** 2-min warm-up, 5-min WBVE. **Week 5–12:** 2-min warm-up, 10-min WBVE. 3 participants dropped out; 1 withdrew before 6-week analysis due to low back pain ("not related directly with the intervention"), and 2 withdrew before 12-week analysis for personal reasons.	Participants received usual care and isometry[a] (they did not receive any vibration), 2 times/week (24 hours between sessions) for 12 weeks. [a]Participants were requested to maintain stance with 130° of knee flexion on the same vibrating platform (vibration turned off). It is unclear whether this was supervised. **Intensity of exercise:** light-to-moderate intensity, warm-up performed in the same way as in WBVE group. Cycles, working, and rest times corresponded to the weeks, consistent with the WBVE group, but without vibration. **Time of exercise session** **Week 1–4:** 2-min warm-up, 5-min stood on platform. **Week 5–12:** 2-min warm-up, 10-min stood on platform. 1 participant withdrew before the 6-week analysis for personal reasons.
Trials with a usual care alone control			
Avaux 2016	No information about their usual care was reported.	Participants received usual care plus an exercise programme that was supervised or performed independently at home. All participants were asked to perform 3 hours of exercise per week for 12 weeks. At start of programme, the home-training group and supervised training group participated in a multidisciplinary information session about the benefits of exercise in SLE, during which practical information was also delivered. Participants in both groups were asked to record their number of training hours. **Exercise group 1: home training** Participants performed endurance exercise (walking or bicycle) and strengthening exercises (elastic band or weights for upper and lower limbs), at home unsupervised. The targeted intensity was moderate (60–80% of theoretical maximal HR). The modified Borg scale was used to determine participant's perception of exertion at PWC75%. **Exercise group 2: supervised training** Participants performed the same exercise programme; endurance exercise (walking or bicycle) and strengthening exercises (elastic band or weights for upper and lower limbs), in the hospital-based revalidation centre under the supervision of the multidisciplinary team. Targeted intensity was moderate (60–80% of theoretical maximal HR). The modified Borg scale was used to determine participant's perception of exertion at PWC75%.	Participants did not attend the information session and were asked not to change their level of physical activity. No further information reported.

Benatti 2015	The SLE treatment outlined at baseline for each intervention group. **Exercise group (n = 17)** 1. Mean cumulative prednisone dose: 31.2 (SD 33.7) g 2. Mean prednisone dose: 11.5 (SD 12.8) mg 3. Number of participants on the following medications: a. Prednisone: 12 (70.6%) b. Azathioprine: 9 (52.9%) c. Chloroquine: 11 (64.7%) d. Methotrexate: 1 (5.9%) e. Mycophenolate mofetil: 5 (29.4%) f. Cyclophosphamide: 2 (11.8%) **Control group (n = 16)** 1. Mean cumulative prednisone dose: 21.8 (SD 15.6) g 2. Mean prednisone dose: 7.2 (SD 8.6) mg 3. Number of participants on the following medications: a. Prednisone: 10 (62.5%) b. Azathioprine: 7 (43.7%) c. Chloroquine: 10 (62.5%) d. Methotrexate: 4 (25.0%) e. Mycophenolate mofetil: 2 (12.5%) f. Cyclophosphamide: 0 (0%) No further information about their usual care reported.	Participants received usual care plus a combined resistance and cardiovascular supervised exercise training programme for 12 weeks. Participants performed approximately 30 min of cardiovascular endurance exercise and strength exercise, 2 times/week. Intensity was set at the HR corresponding to the interval between ventilatory anaerobic threshold and 10% below respiratory compensation point.	Participants remained physically inactive. No further information reported.
Benatti 2018	The SLE treatment outlined at baseline for each intervention group. **Exercise group (n = 9)** 1. Mean cumulative glucocorticoid dose: 42.1 (SD 31.8) g/kg 2. Mean current glucocorticoid dose: 1.7 (SD 3.5) mg 3. Number participants on the following medications: a. Glucocorticoid: 2 (22%) b. Hydroxychloroquine: 5 (56%) c. Methotrexate: 2 (22%) d. Azathioprine: 5 (56%) e. Mycophenolate: 1 (11%) f. Cyclophosphamide: 0 (0%) g. Oral contraceptive: 6 (67%) **Control group (n = 10)** 1. Mean cumulative glucocorticoid dose: 32.4 (SD 19.1) g/kg 2. Mean current glucocorticoid dose: 2.0 (SD 4.2) mg 3. Number of participants on the following medications: a. Glucocorticoid: 2 (20%) b. Hydroxychloroquine: 7 (70%) c. Methotrexate: 2 (20%) d. Azathioprine: 4 (40%) e. Mycophenolate: 2 (20%) f. Cyclophosphamide: 0 (0%) g. Oral contraceptive: 6 (60%) No further information about their usual care reported.	Participants received usual care plus a supervised aerobic exercise programme in an intrahospital gymnasium for 12 weeks. Participants performed 40–60 min of aerobic exercise (5-min warm-up, followed by 30–50 min of treadmill walking, and 5-min cool-down), 2 times/week. Walking duration was gradually increased every 4 weeks, from 30 min to 50 min. Intensity was set at the HR corresponding to the interval between ventilatory anaerobic threshold and 10% below respiratory compensation point.	Participants were strongly instructed to maintain their usual living activities throughout the study. No further information reported.

Bostrom 2016	The SLE treatment outlined at baseline for each intervention group. **Exercise group (N=18)** 1. Median prednisolone: 3.1 (quartiles Q1–Q3 0–5) mg 2. Number of participants who are on: a. Beta-blockers: 3 **Control group (n = 17)** 1. Median prednisolone: 1.3 (quartiles Q1–Q3 0–5) mg 2. Number of participants who are on: a. beta-blockers: 1 No further information about their usual care reported.	Participants received usual care plus a supervised combined aerobic and resistance exercise programme for 12 weeks. Participants performed 60-min exercise programme 2 times/week. Participants were also followed up with exercise for 12 months; however the level of exercise supervision decreased over time. Programme consisted of 3 phases **Phase 1 (0–3 months)** Consisted mainly aerobic exercise (about 20 min) and muscle strength and endurance exercise (about 15 min). Intensity was set as high (65–80% of maximum HR or a rating of 13–16 out of 20 on the BORG rating of perceived exertion scale) *Note: participants could alternatively choose any preferred self-managed high-intensity physical activity, as some participants lived far from the hospital.* Phase also included a 1-hour education session held by a rheumatologist and another by a physiotherapist to educate them on: their disease, the risk for cardiovascular disease, the treatment of the disease, and the importance of, and how to perform, physical activity and exercise. It also included education on how to use a HR monitor, how to assess intensity according to RPE scale, and how to document physical activity with modes, frequency, durations, and intensities. This phase also included supervised exercise training, 30 min of individual coaching of physical activity at 6 and 12 weeks, loan and use of HR monitor, and use of a physical activity diary. **Phase 2 (4–9 months)** During this period, the physical activity was self-managed with the help of videotapes or sound cassettes (or both) from the high-intensity aerobic group exercise programme performed during the first 3 months. As an alternative, any physical activity at high intensity could be chosen. This phase included: 30-min of individual coaching of physical activity at 6 and 9 months, use of HR monitor, and use of the physical activity diary. Participants also received 10 min of telephone support which reduced towards the end of the 12 months. **Phase 3 (9–12 months)** This phase included: use of the HR monitor, and use of physical activity diary.	Participants were asked not to change their physical activity lifestyle during the study period. They were not given any specific information related to the study. No further information reported.
Hashemi 2022	No information about their usual care described.	Participants received usual care plus a combined aerobic and anaerobic supervised exercise programme for 8 weeks. Participants performed 60 min of exercise (commencing with 40 min in week 1), 3 times/week. The exercise programme included a 10-min warm-up, 10-min of running on a treadmill, and 10 min of cycling, both at an intensity of 50–60% of their VO_{2max}, followed by 60 min of Pilates training uses bodyweight resistance, and a 10-min cool-down.	No information about the control group reported. Assumed that control group continued with their usual care alone.
Tench 2003	No information about their usual care described.	Participants received usual care plus a partially supervised aerobic exercise programme for 12 weeks. Participants were encouraged to perform 30–50 min of aerobic exercise (consisting of walking, cycling, or swimming) 3 times/week. The target intensity was moderate; HR corresponding to 60% of peak oxygen consumption. Participants were seen by an exercise professional every 2 weeks for a supervised exercise session. Comparator group included participants who received usual care plus a different non-pharmacological intervention (relaxation practice). Participants listened to a relaxation audiotape in a quiet, warm, and darkened room for 30 min, 3 times/week. Participants were seen by an exercise professional every 2 weeks for a supervised relaxation session. This intervention is included as a control group comparator in the description below under 'trials with another non-pharmacological intervention plus usual care control.'	Participants were asked to continue with their normal daily activity pattern and specifically asked to avoid doing any extra physical activities. They were reviewed at follow-up but not seen at any other times. No further information reported.
Trials with another non-pharmacological intervention plus usual care control			

Abrahão 2016	There was no clear information about their usual care, including the medications taken by participants. However, authors reported that there were changes in the use of medication to control disease activity in the control group, but without significant differences amongst groups (P = 0.34). It is also reported that the 2 exercise intervention groups (group 1: cardiovascular training, group 2: resistance training) had no changes in the use of medications.	Participants in the 2 exercise groups received their usual care plus they performed 1 type of exercise, described below, 3 times/week, for 50 min for 12 weeks. Both exercise groups were supervised by trained professional in the Rheumatology Services at the Interlagos Specialty Outpatient Clinic. **Exercise group 1: cardiovascular training group** Participants received walking and bicycle ergometer interventions (Model CLB 10 Classic, Caloi, São Paulo, Brazil) consisting of a 10-min warm-up, 30 min of exercise at target HR, and 10-min cool-down. The targeted intensity was moderate (65–75% of maximum HR according to the ACSM guidelines), determined by the HR reserve. **Exercise group 2: resistance training group** Participants received a resistance training programme comprised of 8 exercises; holds (crucifix) with free weights, extension-machine exercises, rowing exercise with an elastic band, knee flexion with ankle weights, 2-arm biceps curls, adduction exercises with an elastic band, French curls, and abdominal exercises. The training involved small and large muscle group exercises. Participants performed 3 sets of 15 repetitions with rest intervals of 1 min between sets. The targeted intensity was moderate (65–75% of 1 repetition maximum according to the ACSM guidelines). To establish the training intensity for each participant, their 1 repetition maximum for each exercise was determined. Training intensity changed over time as the participants progressed.	Participants received usual care and information about the disease, but no exercise intervention. They were informed that they would receive the intervention after the study was finished, and they would be invited to participate in the intervention that proved the most effective. No further information reported.
Daltroy 1995	The SLE treatment outlined at baseline for each intervention group. **Exercise group (n = 16)** 1. % of participants taking steroids: 38% 2. % of participants taking NSAIDs: 31% **Control group (n = 18)** 1. % of participants taking steroids: 61% 2. % of participants taking NSAIDs: 67% No further information about their usual care described.	Participants received usual care plus unsupervised home aerobic exercise for 12 weeks. Participants performed 30 min of aerobic exercise (cycling on a stationary bike that was set up in their home) 3 times/week. The target intensity was moderate to high (60–80% of maximum HR achieved on the exercise tolerance test). A physiotherapist contacted the participant once a week to update their exercise log, report any symptoms, and ask about their perceived fatigue. Pulse oximeters were provided to help participants monitor their heart rates and as a compliance-enhancing strategy. The physiotherapist instructed the participant at home when setting up the bike, and made a second visit 2–3 weeks later at an exercise session to check the participants' ability to follow the regimen correctly.	Participants received usual care plus they were contacted by the research team oncer per week as an attention control group. They were also asked to fill out questionnaires, and were encouraged to maintain their current level of activity during the 12-week programme. No further information reported.
Dos Reis-Neto 2013	The SLE treatment outlined at baseline for each intervention group. **Exercise group (n = 18)** Number (%) of participants on the following medications: 1. Prednisone: 10 (55%) a. Median current prednisone dose: 2 (minimum–maximum 0–40) mg 2. Antimalarials: 13 (72.2%) 3. Immunosuppressives: 8 (44.4%) 4. Antihypertensives: 3 (16.7%) 5. Aspirin: 2 (11.1%) 6. Contraceptives: 3 (16.7%) **Control group (n = 20)** Number (%) of participants on the following medications: 1. Prednisone: 13 (65%) a. Median of current prednisone dose: 5 (minimum–maximum 0–30) 2. Antimalarials: 16 (80%) 3. Immunosuppressives: 14 (70%) 4. Antihypertensives: 7 (35%) 5. Aspirin: 3 (15%) 6. Contraceptive: 8 (40%) No further information about their usual care reported.	Participants received usual care plus an aerobic exercise programme for 16 weeks. Participants performed 60 min of outdoor walking (10-min warm-up, 40 min of walking, 10-min cool-down), 3 times/week. Target intensity set at a HR corresponding to the ventilatory 1 threshold obtained from ergospirometry and monitored by frequency meter. Participants met in the morning at a public park, supervised by a physical educator or physician.	Participants received usual care and information about the disease, but no exercise intervention. They received clear instruction not to start any exercise programme for the next 16 weeks. No further information reported.

Kao 2021	No information about their usual care reported.	Participants received usual care plus a home-based exercise programme for 12 weeks. Participants performed approximately 40 min of combined aerobic and resistance exercise (3–5 min warm-up, 30 min combined aerobic and resistance exercises, 5 min relaxation and stretching; the exercise programme comprised a 7- to 8-min set of combined aerobic and resistance exercise such as high knees/shuffle runs/biceps curls etc., and participants had to perform 4 sets). The target intensity was moderate, determined by the HR reserve. The research team member contacted participants periodically by telephone or text messages to ensure their compliance. Each week the participants reported their maximal HR after each exercise session using written logs. Instructed by an exercise physiologist/professional exercise instructor on the performance of aerobic exercise combined with resistance training and the skills of HR measurement at rest and after exercise.	Participants received usual care and information about the disease, but no exercise intervention. They were to maintain their usual lifestyle. No further information reported.
Keramiotou 2020	The SLE treatment outlined at baseline for each intervention group. **Exercise group (n = 32)** Number (%) of participants on the following medications: 1. Corticosteroids: 20 (54.1%) **note that the percentage seems to be reported incorrectly in the study.* a. Mean prednisolone dosage: 4.63 (SD 5.55) mg 2. Hydroxychloroquine: 26 (81.3%) 3. Immunosuppressive agents: 15 (46.9%) 4. Biological agents: 1 (3.1%) **Control group (n = 30)** Number (%) of participants on the following medications: 1. Corticosteroids: 17 (46%) **note that the percentage seems to be reported incorrectly in the study.* a. Mean prednisolone dosage: 4.97 (SD 5.80) mg 2. Hydroxychloroquine: 25 (83.3%) 3. Immunosuppressive agents: 15 (50%) 4. Biological agents: 3 (10%) No further information about their usual care reported.	Participants received usual care plus an upper limb combined resistance and stretching exercise programme for 12 weeks, and were followed up at 24 weeks. Participants performed 30 min of upper limb exercises (9 strengthening and stretching exercises for the upper extremities with a stick, 10 strengthening and stretching exercises for the fingers, and 11 strengthening exercises against resistance with therapeutic putty) daily. The initial intensity was set at a moderate level, and the programme was reassessed using a modified Borg Scale (a tool to measure a persons' perception of their effort and exertion, breathlessness, and fatigue during physical work) to maintain the same intensity, in every face-to-face session with the hand therapist at 0, 3, 6, and 9 weeks. It is unclear whether this programme was supervised.	Participants received usual care plus they 4 sessions of training in alternative methods of performing daily activities, use of aids, joint protection, and energy conservation, additionally to assessment at baseline, 6, 12, and 24 weeks, in order to keep them committed and motivated. All participants received the same training in alternative methods of performing daily activities, use of aids, joint protection and energy conservation.
Miossi 2012	The SLE treatment outlined at baseline for each intervention group. **Exercise group (n = 14)** Number of participants on the following medications: 1. Prednisone: 10 (66.7%) 2. Prednisone ≥ 20 mg/day: 2 (12.3%) 3. Azathioprine: 8 (53.3%) 4. Chloroquine: 12 (80%) 5. Methotrexate: 1 (6.7%) 6. Mycophenolate mofetil: 4 (26.7%) 7. Cyclophosphamide: 1 (6.7%) 8. Drug medroxyprogesterone: 4 (26.7%) **Control group (n = 10)** Number of participants on the following medications: 1. Prednisone: 8 (61.5%) 2. Prednisone ≥ 20 mg/day: 1 (7.1%) 3. Azathioprine: 5 (38.4%) 4. Chloroquine: 12 (92.3%) 5. Methotrexate: 3 (23.0%) 6. Mycophenolate mofetil: 2 (15.3%) 7. Cyclophosphamide: 0 (0%) 8. Medroxyprogesterone: 7 (53.8%) No further information about their usual care described.	The participants received usual care plus a supervised combined resistance and aerobic exercise programme for 12 weeks. Participants performed approximately 80 min of exercise (5-min treadmill warm-up, 35–40 min of resistance training, 30 min of treadmill aerobic training, and 5 min of stretching. Resistance training included 7 exercises for the main muscle groups (e.g. bench press, leg press, leg extension); 2 sets of 15–20 repetition maximum for each exercise in week 1, and 4 sets of 8–12 repetitions maximum every week after that, 2 times/week. Intensity was set at a HR corresponding to the interval between Ventilatory anaerobic threshold and 10% below respiratory compensation point. All sessions were monitored by 1 fitness professional.	Participants received usual care plus information about their disease, but no exercise intervention. They were advised to remain physically inactive. No further information reported.

Tench 2003	No information about their usual care described.	Participants received usual care plus a partially supervised aerobic exercise programme for 12 weeks. Participants were encouraged to perform 30–50 min of aerobic exercise (consisting of walking, cycling, or swimming) 3 times/week. Target intensity was moderate; HR corresponding to 60% of peak oxygen consumption. Participants were seen by an exercise professional every 2 weeks for a supervised exercise session.	Participants received usual care plus a different non-pharmacological intervention (relaxation practice). Participants listened to a relaxation audiotape in a quiet, warm, and darkened room for 30 min, 3 times/week. Participants were seen by an exercise professional every 2 weeks for a supervised relaxation session. This intervention was included as a control group comparator in the description above under ' Trials with a usual care alone control. '

ACSM: American College of Sports Medicine; HR: heart rate; NSAID: non-steroidal anti-inflammatory; PWC75%: 75% of the predicted maximal heart rate; RPE: rating of perceived exertion; SD: standard deviation; SLE: systemic lupus erythematosus.

Table 2

Characteristics of exercise intervention in included studies

Study ID	Dosage of exercise (frequency, intensity, time, type), duration of exercise intervention, progressions to programme (if any), and equipment used	Setting of exercise (supervision, provider expertise, setting of exercise, individual or group)	Country
Trials that compared exercise plus usual care to a placebo plus usual care			
Lopes-Souza 2021	**Frequency of exercise sessions:** 2 times/week (24 hours between sessions). **Intensity of exercise** 1. Week 1–4: 10 bouts of 30 s, frequency 30 Hz, D 1.23 mm, and a peak of 2.22 g. 2. Week 5–8: 10 bouts of 60 s, frequency 40 Hz, D 0.95 mm, and a peak of 3.06 g. 3. Week 9–12: 10 bouts of 60 s, 50 Hz, D 0.88 mm, and a peak of 4.40 g. The "low" amplitude was maintained in all sessions. **Time of exercise session** 1. Week 1–4: 2-min warm-up on a cycle ergometer pedalling continuously with no defined load, and 5-min WBVE. 2. Week 5–12: 2-min warm-up on a cycle ergometer pedalling continuously with no defined load, and 10-min WBVE. **Type of exercise:** WBVE is a subgroup of resistance training, better classified as muscle activation or neuromuscular training complementary to resistance training. The participants were positioned on the vibrating platform with 130° of knee flexion. **Duration of intervention:** 12 weeks **Progressions:** described above **Equipment used:** vertical vibrating platform used in the study was of the triaxial type, where the base moves vertically and horizontally directions (with predominantly vertical displacement), model Power Plate Pro5®(Power Plate International, Performance Health Systems, USA).	**Supervision:** unclear if there was supervision present during the intervention. **Provider:** not reported. **Setting of exercise:** not clearly reported. **Individual or group:** given that participants were positioned on a single vibration platform, this exercise intervention was performed individually; however, it was unclear whether multiple participants performed this together in a clinic, or unsupervised at home.	Brazil
Trials that compared exercise plus usual care to usual care alone			

Avaux 2016	At the start of the programme, the 2 groups (supervised training group and home training group) participated in a multidisciplinary information session about the benefits of exercise in SLE, during which practical information was also delivered. **Frequency of exercise sessions:** not clearly reported. However, participants were advised to perform 3 hours of exercise per week. **Intensity of exercise:** moderate to high (60–80% of predicted maximal heart rate) **Time of exercise session:** not clearly reported. However, participants were advised to perform 3 hours of exercise per week. **Type of exercise:** participants were advised to perform cardiovascular endurance exercise (walking or cycling), or strengthening exercises. **Duration of intervention:** 12 weeks **Progression:** not clearly reported. **Equipment used:** 1. Endurance exercises (walking or bicycle) 2. Strengthening exercises (elastic band or weights for both upper and lower limbs) Note that the intervention dosage were the same in both groups. The groups only differed by the level of supervision and setting of exercise.	**Exercise intervention group 1 (supervised training group)** 1. **Supervision:** yes 2. **Provider:** participant were supervised by a multidisciplinary team in the hospital 3. **Place of exercise:** hospital-based revalidation centre 4. **Individual or group:** not clearly reported **Exercise intervention group 2 (home training group)** 1. **Supervision:** no 2. **Place of exercise:** home 3. **Individual or group:** not clearly reported	Belgium
Benatti 2015	**Frequency of exercise sessions:** 2 times/week **Intensity of exercise:** heart rate corresponding to the interval between ventilatory anaerobic threshold and 10% below respiratory compensation point. **Time of exercise session:** cardiovascular endurance exercise = 30 min and strength exercise = time not specified, per session. **Type of exercise:** cardiovascular endurance exercise (treadmill walking) and strength exercises (7 exercises for major muscle groups: 4 sets of 8–12 repetitions maximum for each exercise) **Duration of intervention:** 12 weeks **Progression:** not reported. **Equipment used:** not reported.	**Supervision:** yes **Provider:** not reported **Place of exercise:** not reported **Individual or group:** not reported	Brazil
Benatti 2018	**Frequency of exercise sessions:** 2 times/week **Intensity of exercise:** heart rate corresponding to the interval between ventilatory anaerobic threshold and 10% below respiratory compensation point. **Time of exercise session:** 40–60 min (including a 5-min warm-up and 5-min cool-down). **Type of exercise:** cardiovascular endurance (treadmill walking) **Duration of exercise intervention:** 12 weeks **Progression:** walking duration gradually increased every 4 weeks, from 30 min to 50 min. **Equipment used:** treadmill	**Supervision:** yes **Provider:** not reported **Place of exercise:** intrahospital gymnasium (Laboratory of Assessment and Conditioning in Rheumatology, School of Medicine, University of São Paulo) **Individual or group:** not clearly reported. However, given that participants were walking on a treadmill, it was assumed to be individual. Whether participants performed treadmill walking with other participants in the clinic was not clear.	Brazil

Bostrom 2016	**Frequency of exercise sessions:** 2 times/week (supervised) **Intensity of exercise:** high (65–80% of MHR, or 13–16 rate of perceived exertion) **Time of exercise session:** 60 min (20 min aerobic and 15 min strength) **Type of exercise** 1. **0–3 months:** education about the disease and exercise (1-off 1-hour workshop), supervised aerobic and strength exercise, individual coaching of physical activity (30 min of individual coaching at the start and after 6 weeks and 12 weeks), loan and use of heart rate monitor, and use of a physical activity diary. 2. **4–9 months:** individual coaching of physical activity, use of heart rate monitor, and the use of a physical activity diary, self-managed aerobic and strength exercise. 3. **10–12 months:** use of heart rate monitor and the use of a physical activity diary, self-managed aerobic and strength exercise. **Duration of exercise intervention** 1. Phase 1: 0–3 months 2. Phase 2: 4–12 months **Progression:** participants were asked to successively increase their physical activity during the programme to achieve: 1. high intensity, ≥ 30 min per session, 2–3 days/week, and 2. low-to-moderate intensity, ≥ 30 min per session, 4–5 days/week. **Equipment used:** treadmill, heart rate monitor, activity diary.	**Supervision/support** 1. Phase 1: more supervision; education about the disease and exercise was offered in a 1-hour workshop at the start. 2 supervised high-intensity aerobic exercise sessions were offered during the first 3 months in the hospital gymnasium. However, participants could choose to perform their own 2 high-intensity exercise sessions if the hospital was not convenient for them to get to. Participants were also encouraged to perform low-to-moderate exercise 4–5 days per week on their own during this time. Individual coaching for 30 min was offered at the start, and 6 and 12 weeks. 2. Phase 2: less supervision; this was assisted by videotapes and cassettes of the 2 high-intensity exercise sessions performed during phase 1. Participants were also encouraged to perform low-to-moderate exercise 4–5 days/week on their own during this time. Individual coaching for 30 min was also offered at months 6 and 9. They also received telephone support for approximately 10 min and the frequency of this was reduced during the 4- to 12-month period (months 4–6, every third week; months 7–9, once per month; months 10–12, no support). 3. **Provider:** physiotherapist provided the education, individual coaching, and the supervision of the exercise. A rheumatologist was also present during the education session at the start of the programme. 4. **Place of exercise:** hospital gymnasium, at home/their choice of location. 5. **Individual or group:** group-based when under supervision, individual or group if they were performing exercise at home/their choice of location.	Sweden
Hashemi 2022	**Frequency of exercise sessions:** 3 times/week **Intensity of exercise:** stage 2 of the session (aerobic exercise programme, including 10 min of cycling and 10 min of running, both at intensity of 50–60% maximum, as predetermined in the peak oxygen uptake measurements). **Time of exercise session:** 60 min per session (40 min for the first week, to allow for acclimatisation, but increased thereafter) **Type of exercise:** Pilates exercise, which is classified as low-intensity resistance exercise. Each exercise session consisted of 4 stages, including 10-min warm-up, 10-min aerobic exercise programme (10 min cycling and 10 min running), 60-min Pilates training using bodyweight as the resistive load, and 10-min cool-down. Borg's scale was used to assess the participants' perceptions of physical exertion during the aerobic exercises that were used in stage 2. **Duration of intervention:** 8 weeks	**Supervision:** not reported **Provider:** not reported **Setting of exercise:** not reported **Individual or group:** not reported	Iran
Tench 2003	**Frequency of exercise sessions:** 3 times/week **Intensity of exercise:** heart rate corresponding to 60% of peak oxygen consumption **Time of exercise session:** 30–50 min **Type of exercise:** home-based cardiovascular exercise (mainly walking, swimming, or cycling) with a supervised exercise session every 2 weeks **Duration of exercise intervention:** 12 weeks **Progression:** not reported. **Equipment used:** not reported.	**Supervision:** yes **Provider:** not clearly reported. **Place of exercise:** home-based, with a supervised exercise session every 2 weeks. **Individual or group:** not clearly reported	UK
Trials that compared exercise plus usual care to another non-pharmacological intervention plus usual care			

Abrahão 2016	**Frequency of exercise sessions:** 3 times/week **Intensity of exercise:** moderate intensity (65–75% of MHR according to the ACSM guidelines). Exercise intensity was determined by HRR, which was calculated by HRR = MHR – RHR. MHR determined using: MHR = 205 − (0.42 × age). **Time of exercise session:** 50 min per session **Type of exercise** 1. Cardiovascular exercise; walking and bicycle ergometry interventions. Each training session consisted of a 10-min warm-up followed by 30 min of exercise at the target heart rate, and 10-min cool-down. 2. Resistance training exercise. Each session consisted of 8 exercises, including holds (crucifix) with free weights, extension-machine exercises, rowing exercise with an elastic band, knee flexion with ankle weights, 2-arm biceps curls, adduction exercises with an elastic band, French curls, and abdominal exercises. The training involved small and large muscle group exercises. Participants performed 3 sets of 15 repetitions with rest intervals of 1 min between sets. **Duration of exercise intervention:** 12 weeks **Progression:** training intensity changed over time as the participants progressed. Progression unknown. **Equipment used:** bicycle ergometry (Model CLB 10 Classic, Caloi, Sao Paulo, Brazil), free weights, extension-machine, and elastic bands.	**Supervision:** yes **Provider:** trained professional (profession unknown) **Place of exercise:** in the Rheumatology Services at the Interlagos Specialty Outpatient Clinic. **Individual or group:** not clearly reported.	Brazil
Daltroy 1995	**Frequency of exercise sessions:** 3 times/week **Intensity of exercise:** moderate–high (60–80% of MHR achieved on the exercise tolerance test) **Time of exercise session:** 30 min per session **Type of exercise:** aerobic exercise performed on a stationary bike that was set up in their home. **Duration of exercise intervention:** 12 weeks **Progression:** not reported **Equipment used: s**tationary bike	**Supervision:** yes **Provider:** a physiotherapist contacted the participant once a week to update logs of exercise, report of symptoms, and perceived fatigue. The physiotherapist instructed the participant at home when setting up the bike, and made a second visit 2–3 weeks later at an exercise session to check the participants' ability to follow the regimen correctly. **Place of exercise:** participants' homes **Individual or group:** individual (participants completed their sessions in their own homes, independently)	US
Dos Reis-Neto 2013	**Frequency of exercise sessions:** 3 times/week **Intensity of exercise:** heart rate corresponding to the ventilatory 1 threshold obtained from ergospirometry and monitored by frequency meter (Poland Electro, Kempele, Finland). **Time of exercise session:** 60 min per session (10-min warm-up, 40-min of walking and 10-min cool-down). **Type of exercise:** walking, outdoors in the morning **Duration of exercise intervention:** 16 weeks **Progression:** not reported **Equipment used:** none	**Supervision:** yes **Provider:** physical educator or physician **Place of exercise:** park, outdoors **Individual or group:** not clearly reported	Brazil
Kao 2021	**Frequency of exercise sessions:** 5 times/week **Intensity of exercise:** moderate intensity determined by HRR 50–50%, according to the ACSM guidelines. HRR = MHR − RHR. MHR determined using formula: MHR = 205 − (0.42 × age). **Time of exercise session:** 30 min per session (3- to 5-min warm-up session, 4 sets of combined exercise session for approximately 30 min in total, and a final set of 3- to 5-min of relaxation and stretching). Each set of combined exercise lasting for 7 min 15 s, with a brief break between sets. **Type of exercise:** aerobic exercise combined with bodyweight or 500–620 mL of dumbbell water weights for resistance training. Combined exercise sessions consisted of various styles of basic exercises, alternating workouts of legs with trunk movement, and arm exercises. **Duration of exercise intervention:** 12 weeks **Progression:** not reported. **Equipment used:** 500–620 mL of dumbbell water weights	**Supervision:** yes **Provider:** instructed by an exercise physiologist/professional exercise instructor on the performance of aerobic exercise combined with resistance training and the skills of heart rate measurement at rest and after exercise. The research team member contacted participants periodically by telephone or text message to ensure their compliance. Each week, the participants reported their maximal heart rate after each exercise session by written logs. **Place of exercise:** participant's home **Individual or group:** individual (considering each participant was performing the exercise intervention in their own home)	Taiwan

Keramiotou 2020	**Frequency of exercise sessions:** 7 days/week **Intensity of exercise:** moderate intensity. The initial intensity of exercise was set at a moderate level and the programme was reassessed, using a modified Borg Scale (a tool to measure a persons' perception of their effort and exertion, breathlessness, and fatigue during physical work) to maintain the same intensity, in every face-to-face session with the hand therapist at 0, 3, 6, and 9 weeks. **Time of exercise session:** 30 min per session **Type of exercise:** upper limb resistance and range of motion exercise (9 strengthening and stretching exercises for the upper extremities with a stick, 10 strengthening and stretching exercises for the fingers and 11 strengthening exercises against resistance with therapeutic putty). **Duration of exercise intervention:** 12 weeks (with a follow-up assessment at 24 weeks) **Progression:** not reported **Equipment used:** therapeutic putty (soft or medium resistance)	**Supervision:** not reported **Provider:** team of hand therapists. Frequency of visits to the hand therapist, unknown. **Place of exercise:** home-based programme **Individual or group:** individual (taking into account participants were performing their exercise programme at home)	Greece
Miossi 2012	**Frequency of exercise sessions:** 2 times/week **Intensity of exercise:** heart rate corresponding to the interval between ventilatory anaerobic threshold and 10% below respiratory compensation point. **Time of exercise session:** 80 min per session (5-min treadmill warm-up, 35–40 min of resistance training, 30 min of treadmill aerobic training, and 5-min of stretching). **Type of exercise:** cardiovascular exercise (treadmill walking for 30 min), and resistance training included 7 exercises for the main muscle groups (e.g. bench press, leg press, leg extension). **Duration of exercise intervention:** 12 weeks **Progression:** participants were required to perform 4 sets of 8–12 repetitions maximum, except during the first week, when a reduced volume of 2 sets of 15–20 repetitions maximum for each exercise was performed (as an adaptation period to resistance training). Overload progression was implemented when the participant could perform > 12 repetitions on the last training set for 2 consecutive workouts. Aerobic training intensity was set at the corresponding heart rate between the ventilatory anaerobic threshold and 10% below the respiratory compensation point. Cardiorespiratory exercise test was performed on a treadmill (Centurion, Model 200, Micromed) using a maximal-graded exercise protocol. The recovery period was set at 2 min using the initial workload (1.7 miles per hour). **Equipment used:** treadmill and resistance training equipment (e.g. machine weights or dumbbells); however, this was not clearly reported.	**Supervision:** yes **Provider:** 1 fitness professional **Place of exercise:** hospital gymnasium **Individual or group:** not clearly reported	Brazil
Tench 2003	**Frequency of exercise sessions:** 3 times/week **Intensity of exercise:** heart rate corresponding to 60% of peak oxygen consumption **Time of exercise session:** 30–50 min **Type of exercise:** home-based cardiovascular exercise (mainly walking, swimming, or cycling) with a supervised exercise session every 2 weeks. **Duration of exercise intervention:** 12 weeks **Progression:** not reported. **Equipment used:** not reported.	**Supervision:** yes **Provider:** not clearly reported. **Place of exercise:** home-based, with a supervised exercise session every 2 weeks **Individual or group:** not clearly reported	UK

ACSM: American College of Sports Medicine; HRR: heart rate reserve; MHR: maximum heart rate; RHR: resting heart rate; SLE: systemic lupus erythematosus; WBVE: whole body vibration exercise.

Table 3

Major outcomes reported in included studies

Study ID	Fatigue	Functional capacity	Disease activity	Quality of life	Pain	Serious adverse events	Withdrawals due to adverse events
Trials that compared exercise plus usual care to placebo plus usual care							

Lopes-Souza 2021	**Yes** **The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)** 1. Score range: score 0–52, higher scores indicate less fatigue. SF-35 Vitality domain was also used; however, this was not used in our analyses.	**Yes** **SF-36 Functional Capacity domain** 1. Score range 0–100, higher scores indicate better functional capacity. HAQ and TUG test were also used to assess functional capacity; however, these were not used in our analyses.	Not measured.	Partially reported. SF-36 was used to measure quality of life; however, authors did not report the MCS and PCS scores, so this was not used in our analyses.	**Yes** **SF-36 Pain domain** 1. Score range 0–100, higher scores indicate less pain.	No serious adverse events were reported.	No withdrawals due to adverse events were reported.
Trials that compared exercise plus usual care to usual care alone							
Avaux 2016	**Yes** **Krupp FSS** 1. Score range: 1–7, lower score indicates less fatigue.	Not measured.	Not measured.	Not measured.	Not measured.	No serious adverse events were reported.	Yes. 1 participant withdrew from study due to a disease flare; however, unclear which group they were part of, and, therefore, unable to be included in meta-analysis. It is also important to note that it is unclear whether the disease flare was due to the intervention, the severity of the disease flare, or whether they were hospitalised.
Benatti 2015	Not measured.	Not measured.	Not measured.	Not measured.	Not measured.	No serious adverse events were reported.	No withdrawals due to adverse events were reported.
Benatti 2018	Not measured.	Not measured.	Not measured.	Not measured.	Not measured.	No serious adverse events were reported.	**Yes** **2 participants withdrew from the study.** 1. 1 from the control group due to a disease flare. 2. 1 from the exercise group due to a disease flare. However, it is important to note that it was unclear whether the disease flare was due to the intervention, the severity of the disease flare, or whether they were hospitalised.
Bostrom 2016	Not measured. SF-36 Vitality domain was used; however this was not used in our analyses.	**Yes** **SF-36 Physical Function domain** 1. Score range 0–100, higher scores indicate better functional capacity.	**Yes** **SLEDAI** 1. Score range: 0–105, lower scores indicate less disease activity.	Partially reported. Used SF-36 to measure quality of life; however, authors did not report MCS and PCS scores, and, therefore, this was not used in our analyses.	**Yes** **SF-36 Pain** 1. Score range 0–100, higher scores indicate less pain.	No serious adverse events were reported.	No withdrawals due to adverse events were reported.

Hashemi 2022	Not measured.	Not measured.	Not measured.	Not measured.	Not measured.	No serious adverse events were reported.	No withdrawals due to adverse events were reported.
Tench 2003	**Yes** **Krupp FSS** 1. Score range 1–7, lower score indicates less fatigue. Chalder Fatigue Scale, Visual Analogue Scale, and SF-36 Fatigue and Vitality domains were also used; however, these were not used in our analyses.	**Yes** **SF-36 Physical Function domain** 1. Score range 0–100, higher scores indicate better functional capacity.	**Yes** **Systemic Lupus Activity Measure** 1. Score range 0–83, lower scores indicate less disease activity.	Partially reported. Used SF-36 to measure quality of life; however, authors did not report the MCS score, PCS score, and all 8 domains, and, therefore, this was not used in our analyses.	Not reported. Used SF-36 to measure quality of life, but authors did not report the Pain domain, and, therefore, this was not used in our analyses.	No serious adverse events were reported.	No withdrawals due to adverse events were reported.
Trials that compared exercise plus usual care to another nonpharmacologic intervention plus usual care							
Abrahão 2016	Not measured.	**Yes** **SF-35 Physical Function domain** 1. Score range 0–100, higher scores indicate better functional capacity.	**Yes** **SLEDAI** 1. Score range: 0–105, lower scores indicate less disease activity.	Partially reported. SF-36 used to measure quality of life; however, authors did not report the MCS and PCS scores, and, therefore, this was not used in our analyses.	**Yes** **SF-36 Pain domain** 1. Score range 0–100, higher scores indicate less pain.	No serious adverse events were reported.	No withdrawals due to adverse events were reported.
Daltroy 1995	Yes, the Mental Adjustment to Cancer questionnaire, and the Profile Of Moods State Fatigue questionnaire were used; however, these were not included in our analyses because the results for the participants with SLE were not presented separately from the results for participants with rheumatoid arthritis.	Not measured.	Not measured.	Not measured.	Not measured.	No serious adverse events were reported.	No withdrawals due to adverse events were reported.
Dos Reis-Neto 2013	Not measured.	Not measured.	**Yes** **SLEDAI** 1. Score range: 0–105, lower scores indicate less disease activity.	Not measured.	Not measured.	No serious adverse events were reported.	No withdrawals due to adverse events were reported.
Kao 2021	Not measured.	Not measured.	Yes, used SLEDAI; however, authors did not report the mean and standard deviation, and, therefore, we were unable to use in our analyses.	Not measured.	Not measured.	No serious adverse events were reported.	No withdrawals due to adverse events were reported.

Keramiotou 2020	**Yes** **Lupus quality of life Fatigue domain** 1. Score range 0–100, higher scores indicate less fatigue.	Not measured.	Yes, used SLEDAI; however, authors do not report the mean and standard deviation, and, therefore, we were unable to use in our analyses.	Partially reported Used Lupus Quality of Life questionnaire; however, only Physical Health and Fatigue domains were reported, and, therefore, this was not used in our analyses.	**Yes** **Visual Analogue Scale Pain** 1. Score range 0–10, lower scores indicate less pain.	No serious adverse events were reported.	No withdrawals due to adverse events were reported.
Miossi 2012	Not measured.	Not measured.	**Yes** **SLEDAI** 1. Score range: 0–105, lower scores indicate less disease activity.	Not measured.	Not measured.	No serious adverse events were reported.	No withdrawals due to adverse events were reported.
Tench 2003	**Yes** **Krupp FSS** 1. Score range 1–7, lower score indicates less fatigue. Chalder Fatigue Scale, Visual Analogue Scale, and SF-36 Fatigue and Vitality domains were also used; however, these were not used in our analyses.	**Yes** **SF-36 Physical Function domain** 1. Score range 0–100, higher scores indicate better functional capacity.	**Yes** **Systemic Lupus Activity Measure** 1. Score range 0–83, lower scores indicate less disease activity.	Partially reported. SF-36 was used to measure quality of life; however, authors did not report MCS score, PCS score, and all 8 domains, and, therefore, this was not used in our analyses.	Not reported. SF-36 was used to measure quality of life but authors did not report the Pain domain, and, therefore, this was not used in our analyses.	No serious adverse events were reported.	No withdrawals due to adverse events were reported.

FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; FSS: Fatigue Severity Scale; HAQ: Health Assessment Questionnaire; MCS: Mental Component Score; PCS: Physical Component Score; SF-36: 36-item Short Form; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; TUG: Timed Up and Go.

Table 4

Minor outcomes reported in included studies

Study ID	Composite responder rate	Aerobic capacity	Depression	Anxiety	Withdrawals due to any reason
Trials that compared exercise plus usual care to placebo plus usual care					
Lopes-Souza 2021	Not measured.	Not measured.	Not measured.	Not measured.	**Yes** **4 participants withdrew from the intervention** 1. 3 from the exercise group (1 before the 6-week analysis due to low back pain, and 2 before the 12-week analysis for personal reasons). 2. 1 from the control group before the 6-week analysis due to personal reasons.
Trials that compared exercise plus usual care to usual care alone					
Avaux 2016	Not measured.	Not measured.	Not measured.	Not measured.	Yes, 2 participants withdrew from the intervention for personal reason; however, it is unclear which group they were part of, and, therefore, not included in our analyses.

Benatti 2015	Not measured.	Not measured.	Not measured.	Not measured.	No withdrawals for any reason reported.
Benatti 2018	Not measured.	Not measured.	Not measured.	Not measured.	**Yes** **8 participants withdrew from the intervention.** 1. 4 from the control group (1 pregnant, 3 for personal reasons) 2. 4 from the exercise group (1 fractured limb outside of training sessions, 3 for person reasons)
Bostrom 2016	Not measured.	**Yes** **Maximum oxygen consumption (VO_{2max} in L/min)** 1. Higher scores indicate better aerobic capacity.	Not measured.	Not measured.	**Yes** **3 participants withdrew from the control group (1 depression/cognitive impairment, 1 untreated dementia, 1 suspected relapse breast cancer)**
Hashemi 2022	Not measured.	Not measured.	Not measured.	Not measured.	No withdrawals for any reason reported.
Tench 2003	Not measured.	**Yes** **Peak oxygen consumption (VO_{2peak} in mL/kg/min)** 1. Higher scores indicate better aerobic capacity.	**Yes** **Hospital Anxiety and Depression Scale – Depression subscale** 1. Score range 0–21, lower scores indicate a better outcome.	**Yes** **Hospital Anxiety and Depression Scale – Anxiety subscale** 1. Score range 0–21, lower scores indicate a better outcome.	**Yes** **14 participants withdrew from the study.** 1. 4 from the exercise group. 2. 5 from the active control group (relaxation). 3. 5 from the usual care control group. Note that 6 participants dropped out of treatment and 8 participants completed the study but did not wish to repeat the walking test to exhaustion at the end of the intervention.
Trials that compared exercise plus usual care to another nonpharmacologic intervention plus usual care					
Abrahão 2016	Not measured.	Not measured.	**Yes** **Beck-Depression Inventory** 1. Score range 0–63, lower scores indicate a better outcome.	Not measured.	**Yes** **2 participants withdrew from the control group for an unknown reason.**
Daltroy 1995	Not measured.	Yes, the 12-min walking test was used to measure aerobic capacity; however, this was not used in our analyses.	**Yes** **Center for Epidemiologic Studies – Depression Scale** 1. Score range 0–60, lower scores indicate a better outcome.	Not measured.	No withdrawals for any reason were clearly reported.
Dos Reis-Neto 2013	Not measured.	**Yes** **Peak oxygen consumption (VO_{2peak} in mL/kg/min)** 1. Higher scores indicate better aerobic capacity.	Not measured.	Not measured.	No withdrawals for any reason were clearly reported.
Kao 2021	Not assessed.	Not measured.	Not measured.	Not measured.	No withdrawals for any reason were reported.
Keramiotou 2020	Not measured.	Not measured.	Not measured.	Not measured.	**Yes** **2 participants from the exercise intervention group withdrew; however, the reasons were not reported.**
Miossi 2012	Not measured.	Not measured.	Not measured.	Not measured.	No withdrawals for any reason were reported.

Tench 2003	Not measured.	**Yes** **Peak oxygen consumption (VO_{2peak} in mL/kg/min)** 1. Higher scores indicate better aerobic capacity.	**Yes** **Hospital Anxiety and Depression Scale – Depression subscale** 1. Score range 0–21, lower scores indicate a better outcome.	**Yes** **Hospital Anxiety and Depression Scale – Anxiety subscale** 1. Score range 0–21, lower scores indicate a better outcome.	**Yes** **14 participants withdrew from the study.** 1. 4 from the exercise group. 2. 5 from the active control group (relaxation). 3. 5 from the usual care control group. Note that 6 participants dropped out of treatment and 8 participants completed the study but did not wish to repeat the walking test to exhaustion at the end of the intervention.

Figure 1

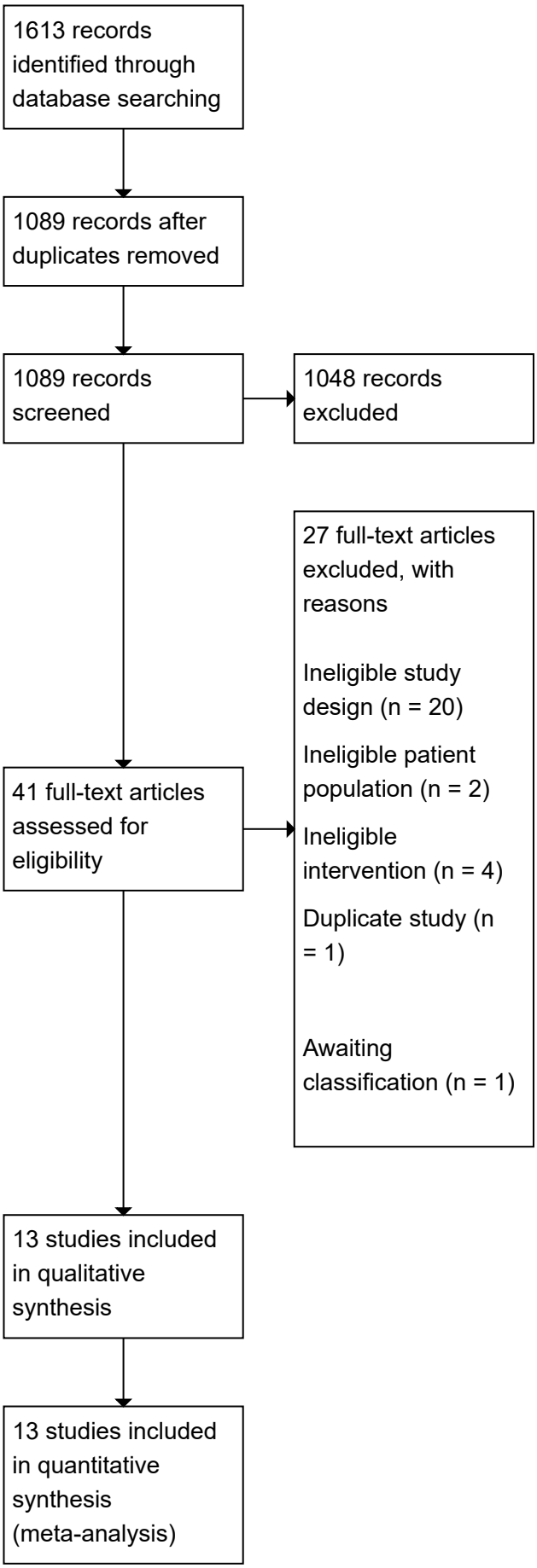
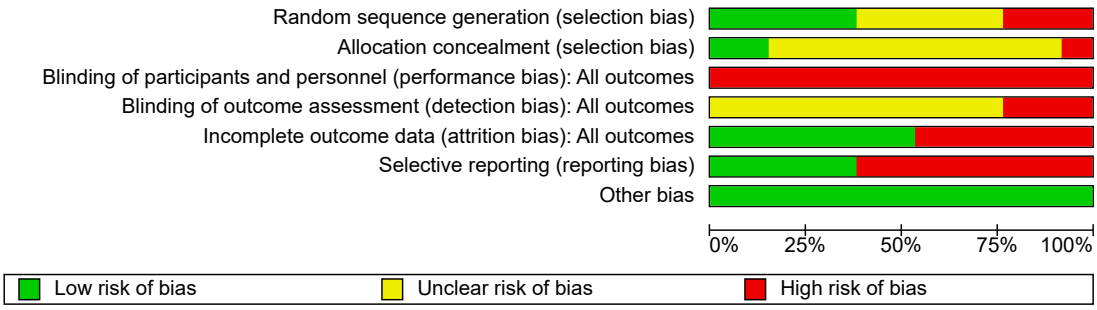
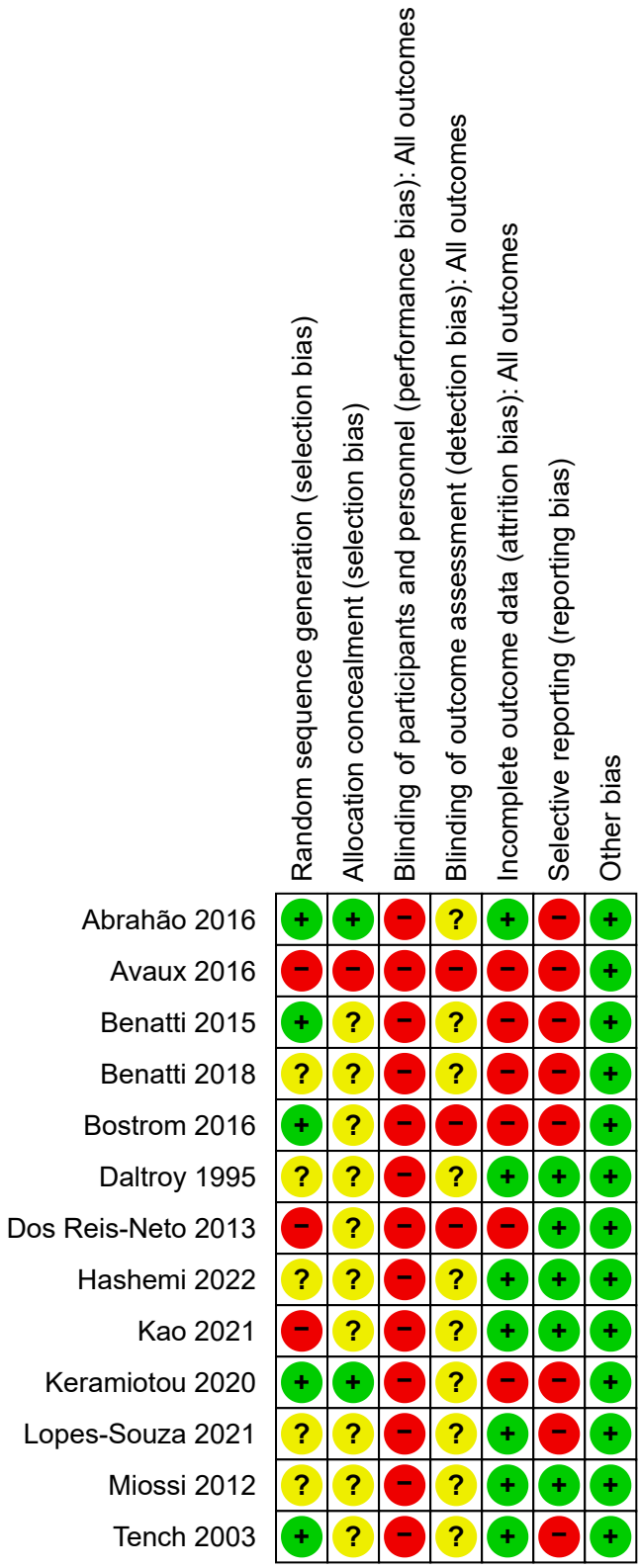

1613 records identified through database searching
1089 records after duplicates removed
1089 records screened
1048 records excluded
27 full-text articles excluded, with reasons
Ineligible study design (n = 20)
Ineligible patient population (n = 2)
Ineligible intervention (n = 4)
Duplicate study (n = 1)
Awaiting classification (n = 1)
41 full-text articles assessed for eligibility
13 studies included in qualitative synthesis
13 studies included in quantitative synthesis (meta-analysis)

Figure 2



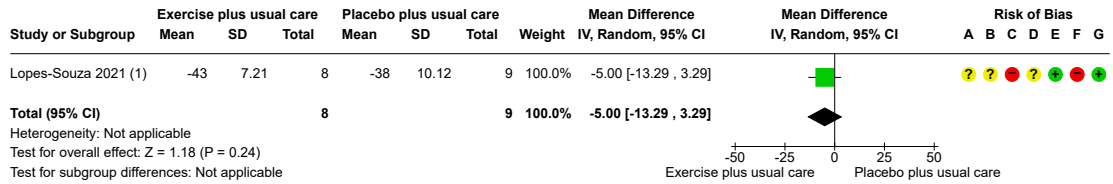
Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3



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

Analysis 1.1



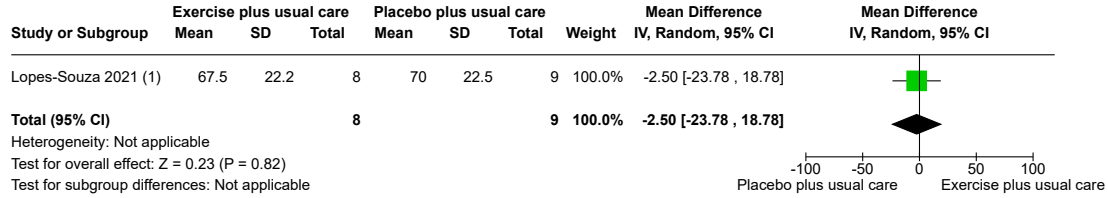
Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Not applicable

Footnotes
(1) FACIT: Functional Assessment of Chronic Illness Therapy.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 1: Exercise plus usual pharmacological care versus placebo plus usual pharmacological care (exercises versus placebo), Outcome 1: Fatigue (FACIT fatigue, score 0–52, lower scores indicate less fatigue)

Analysis 1.2

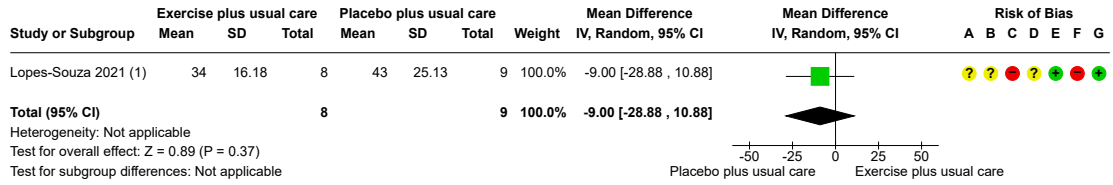


Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable

Footnotes
(1) SF-36: 36-item Short Form questionnaire.

Comparison 1: Exercise plus usual pharmacological care versus placebo plus usual pharmacological care (exercises versus placebo), Outcome 2: Functional capacity (SF-36 Function Capacity domain, score 0–100, higher scores indicate better functional capacity)

Analysis 1.3



Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)
Test for subgroup differences: Not applicable

Footnotes
(1) SF-36: 36-item Short Form.

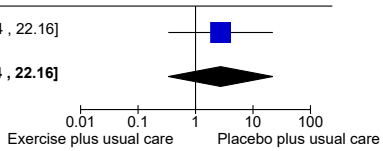
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 1: Exercise plus usual pharmacological care versus placebo plus usual pharmacological care (exercises versus placebo), Outcome 3: Pain (SF-36 Pain domain, score 0–100, lower scores indicate less pain)

Analysis 1.4

Study or Subgroup	Exercise plus usual care Events	Total	Placebo plus usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lopes-Souza 2021 (1)	3	11	1	10	100.0%	2.73 [0.34 , 22.16]
Total (95% CI)		**11**		**10**	**100.0%**	**2.73 [0.34 , 22.16]**
Total events:	3		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



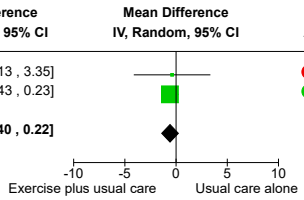
Footnotes
(1) Exercise plus usual care group: 1 discontinued due to low back pain, and 2 for personal reasons. Placebo plus usual care: 1 discontinued for personal reasons.

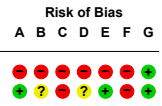
Comparison 1: Exercise plus usual pharmacological care versus placebo plus usual pharmacological care (exercises versus placebo), Outcome 4: Withdrawals for any reason

Analysis 2.1

Study or Subgroup	Exercise plus usual care Mean	SD	Total	Usual care alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Avaux 2016 (1)	5.11	5.39	31	5.5	4.65	8	4.7%	-0.39 [-4.13 , 3.35]
Tench 2003	4.8	1.723369	33	5.4	1.697056	32	95.3%	-0.60 [-1.43 , 0.23]
Total (95% CI)			**64**			**40**	**100.0%**	**-0.59 [-1.40 , 0.22]**

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.15)
Test for subgroup differences: Not applicable





Footnotes
(1) Result is the combined mean and standard deviation of the two exercise groups.

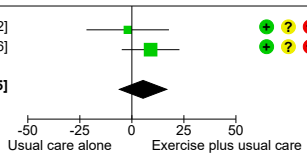
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

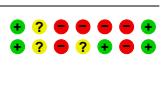
Comparison 2: Exercise plus usual pharmacological care versus usual pharmacological care alone (exercise versus usual care alone), Outcome 1: Fatigue (Fatigue Severity Scale, score 1–7, lower score indicates less fatigue)

Analysis 2.2

Study or Subgroup	Exercise plus usual care Mean	SD	Total	Usual care alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bostrom 2016 (1)	63	25.93	17	65	29.63	14	32.8%	-2.00 [-21.82 , 17.82]
Tench 2003 (1)	69	28.73	33	60	28.28	32	67.2%	9.00 [-4.86 , 22.86]
Total (95% CI)			**50**			**46**	**100.0%**	**5.39 [-5.97 , 16.75]**

Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable





Footnotes
(1) SF-36 Physical Function domain (higher value = better function (scale 0–100)).

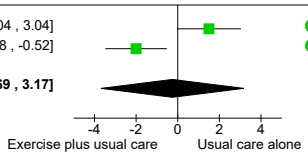
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2: Exercise plus usual pharmacological care versus usual pharmacological care alone (exercise versus usual care alone), Outcome 2: Functional capacity (SF-36 Physical Function domain, score 0–100, higher scores indicate better functional capacity)

Analysis 2.3

Study or Subgroup	Exercise plus usual care Mean	SD	Total	Usual care alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bostrom 2016 (1)	2	2.96	18	0.5	1.48	17	49.8%	1.50 [-0.04 , 3.04]
Tench 2003 (2)	4	3.7	33	6	2.22	32	50.2%	-2.00 [-3.48 , -0.52]
Total (95% CI)			**51**			**49**	**100.0%**	**-0.26 [-3.69 , 3.17]**

Heterogeneity: Tau² = 5.53; Chi² = 10.34, df = 1 (P = 0.001); I² = 90%
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable



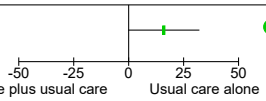
Footnotes
(1) SLEDAI: Systemic Lupus Erythematosus Disease Activity Index (lower scores indicate less disease activity (score range 0–105).
(2) SLAM: Systemic Lupus Activity Measure (lower scores indicate less disease activity (score range 0–83).

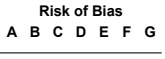
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2: Exercise plus usual pharmacological care versus usual pharmacological care alone (exercise versus usual care alone), Outcome 3: Disease activity (various scales, lower scores indicate less disease activity)

Analysis 2.4

Study or Subgroup	Exercise plus usual care Mean	SD	Total	Usual care alone Mean	SD	Total	Mean Difference IV, Random, 95% CI
Bostrom 2016 (1)	54	21.91	17	38	23.64	14	16.00 [-0.18 , 32.18]





Footnotes
(1) SF-36 Pain (higher score indicates less pain; score range 0–100). We inversed this to match other comparisons. Data extracted from 3-month analyses.

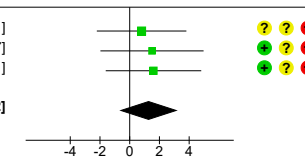
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

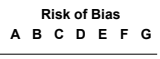
Comparison 2: Exercise plus usual pharmacological care versus usual pharmacological care alone (exercise versus usual care alone), Outcome 4: Pain (SF-36 Pain domain, score 0–100, lower scores indicate less pain)

Analysis 2.5

Study or Subgroup	Exercise plus usual care Mean	SD	Total	Usual care alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Benatti 2018 (1)	24.6	2.99	9	23.8	3.7	10	38.0%	0.80 [-2.21 , 3.81]
Bostrom 2016 (2)	23.7	4.16	12	22.2	4.69	13	28.6%	1.50 [-1.97 , 4.97]
Tench 2003 (3)	23.8	5.74	33	22.2	7.35	32	33.4%	1.60 [-1.61 , 4.81]
Total (95% CI)			**54**			**55**	**100.0%**	**1.27 [-0.59 , 3.12]**

Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.34 (P = 0.18)
Test for subgroup differences: Not applicable



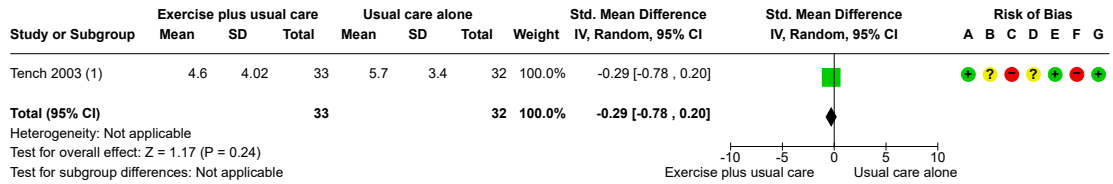


Footnotes
(1) VO_{2peak} (mL/kg/min) used (higher scores indicate better aerobic capacity).
(2) VO_{2max} (mL/kg/min) used (higher scores indicate better aerobic capacity).
(3) Peak oxygen uptake (mL/kg/min) used (higher scores indicate better aerobic capacity).

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2: Exercise plus usual pharmacological care versus usual pharmacological care alone (exercise versus usual care alone), Outcome 5: Aerobic capacity (peak oxygen uptake, higher scores indicate better aerobic capacity)

Analysis 2.6



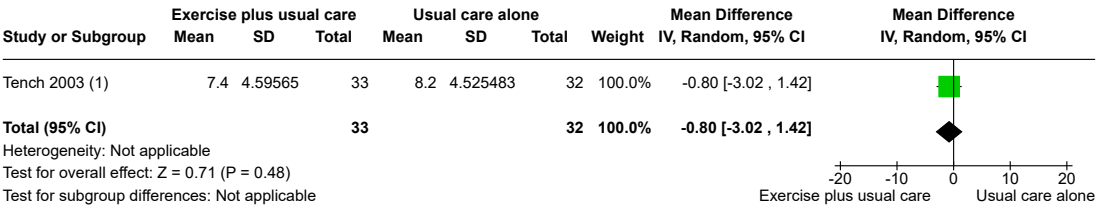
Heterogeneity: Not applicable
Test for overall effect: Z = 1.17 (P = 0.24)
Test for subgroup differences: Not applicable

Footnotes
(1) Hospital Anxiety and Depression Scale – Depression used (lower scores indicate less depression (score range 0–21)).

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2: Exercise plus usual pharmacological care versus usual pharmacological care alone (exercise versus usual care alone), Outcome 6: Depression (various scales, lower score indicates less depression)

Analysis 2.7

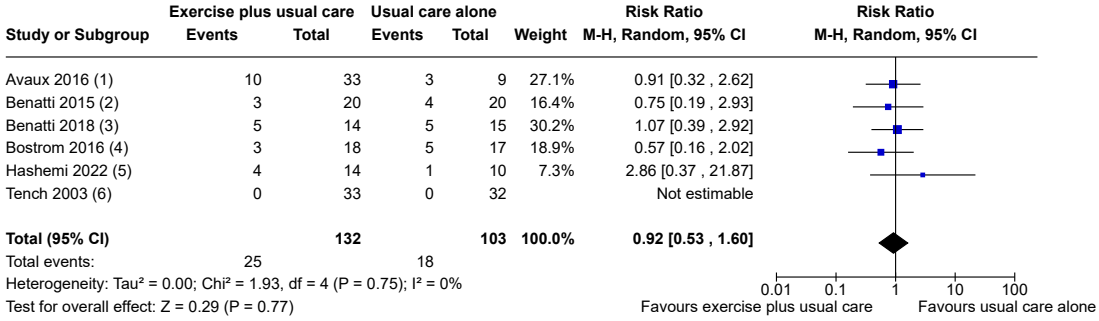


Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable

Footnotes
(1) Hospital Anxiety and Depression Scale – Anxiety.

Comparison 2: Exercise plus usual pharmacological care versus usual pharmacological care alone (exercise versus usual care alone), Outcome 7: Anxiety (HADS Anxiety, score 0–21, lower score indicates less anxiety)

Analysis 2.8

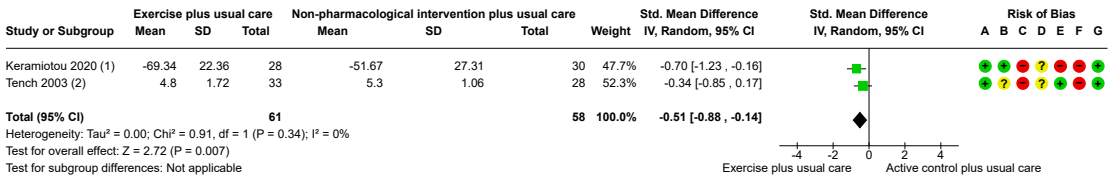


Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 4 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.77)
Test for subgroup differences: Not applicable

Footnotes
(1) Exercise plus usual care: reasons for withdrawal not clear for each group.
(2) Exercise plus usual care: 3 withdrew for personal reasons; usual care alone: 4 withdrew for personal reasons.
(3) Exercise plus usual care: 5 withdrew (see text); usual care alone: 5 withdrew (see text).
(4) Exercise plus usual care: 3 withdrew (see text); usual care alone: 3 withdrew after 2 weeks, and then another 2 withdrew (see text).
(5) Authors did not report why 5 participants (1 in usual care alone, and 4 in exercise plus usual care) were not included in analyses.
(6) Authors did not clearly report how many withdrew from each group.

Comparison 2: Exercise plus usual pharmacological care versus usual pharmacological care alone (exercise versus usual care alone), Outcome 8: Withdrawals for any reason

Analysis 3.1



Footnotes

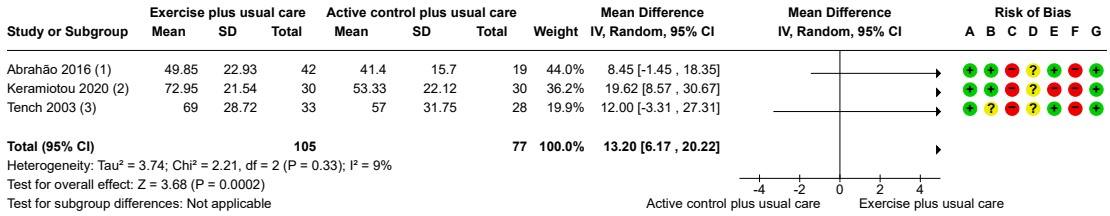
(1) Lupus QOL Fatigue used (higher score indicates less fatigue (scale 0–100)). Control group received joint aids and information about their disease.
(2) Krupp Fatigue Severity Scale used (lower scores indicate less fatigue severity (scale 1–7)). Control group received relaxation therapy.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3: Exercise plus usual pharmacological care versus another non-pharmacological intervention plus usual pharmacological care (exercise versus active control), Outcome 1: Fatigue (various scales, lower score indicate less fatigue)

Analysis 3.2



Footnotes

(1) SF-36 Physical Function domain used (higher scores indicate better functional capacity (scale 0–100)). Control group included education.
(2) LupusQOL physical domain used (higher scores indicate better functional capacity (scale 0–100)). Control group received joint aids and information about their disease.
(3) SF-36 Physical Function domain used (higher scores indicate better functional capacity (scale 0–100)). Control group received relaxation therapy.

Risk of bias legend

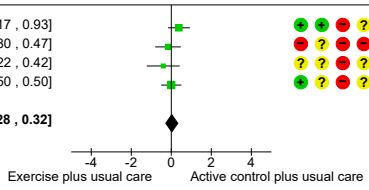
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3: Exercise plus usual pharmacological care versus another non-pharmacological intervention plus usual pharmacological care (exercise versus active control), Outcome 2: Functional capacity (various scales, higher scores indicate better functional capacity)

Analysis 3.3

Study or Subgroup	Exercise plus usual care Mean	SD	Total	Active control plus usual care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Abrahão 2016 (1)	1.45	0.73	42	1.2	0.4	19	29.8%	0.38 [-0.17 , 0.93]
Dos Reis-Neto 2013 (1)	2.4	2.3	18	3.1	5.3	20	21.9%	-0.16 [-0.80 , 0.47]
Miossi 2012 (1)	0.8	1.2	14	1.3	1.2	10	13.3%	-0.40 [-1.22 , 0.42]
Tench 2003 (2)	4	12.85	33	4	10.58	28	35.0%	0.00 [-0.50 , 0.50]
Total (95% CI)			**107**			**77**	**100.0%**	**0.02 [-0.28 , 0.32]**

Heterogeneity: Tau² = 0.00; Chi² = 3.02, df = 3 (P = 0.39); I² = 1%
Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Not applicable



Footnotes
(1) SLEDAI used (lower scores indicate less disease activity (scale 0–105)). Control group received information about their disease.
(2) SLAM used (lower scores indicate less disease activity (score 0–83)). Control group received relaxation therapy.

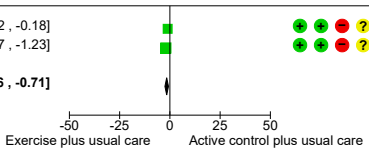
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3: Exercise plus usual pharmacological care versus another non-pharmacological intervention plus usual pharmacological care (exercise versus active control), Outcome 3: Disease activity (various scales, lower scores indicate less disease activity)

Analysis 3.4

Study or Subgroup	Exercise plus usual care Mean	SD	Total	Active control plus usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Abrahão 2016 (1)	6.4	2.3	42	7.5	1.4	21	46.1%	-1.10 [-2.02 , -0.18]
Keramiotou 2020 (2)	2.97	1.45	28	4.97	1.56	30	53.9%	-2.00 [-2.77 , -1.23]
Total (95% CI)			**70**			**51**	**100.0%**	**-1.59 [-2.46 , -0.71]**

Heterogeneity: Tau² = 0.22; Chi² = 2.16, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 3.53 (P = 0.0004)
Test for subgroup differences: Not applicable

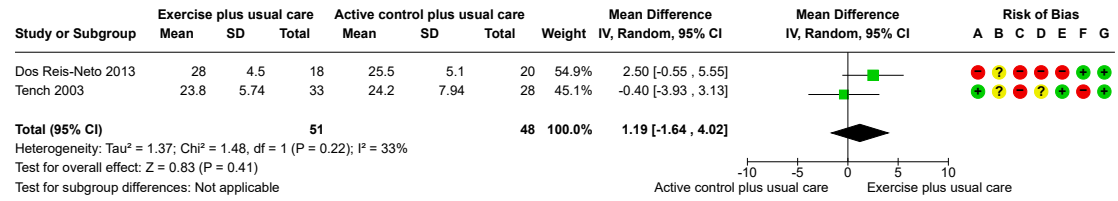


Footnotes
(1) SF-36 Bodily Pain domain used (lower scores indicates less pain (score 0–100)). Control group received information about their disease.
(2) VAS Pain used (lower scores indicate less pain (scores 0 to 10)). Control group received joint aids and information about their disease.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3: Exercise plus usual pharmacological care versus another non-pharmacological intervention plus usual pharmacological care (exercise versus active control), Outcome 4: Pain (various scales, lower score indicates less pain)

Analysis 3.5



Heterogeneity: Tau² = 1.37; Chi² = 1.48, df = 1 (P = 0.22); I² = 33%
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3: Exercise plus usual pharmacological care versus another non-pharmacological intervention plus usual pharmacological care (exercise versus active control), Outcome 5: Aerobic capacity (peak oxygen uptake, higher scores indicate better aerobic capacity)

Analysis 3.6

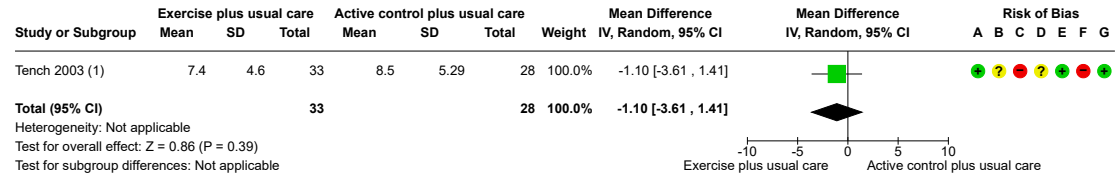
Heterogeneity: Not applicable
Test for overall effect: Z = 0.85 (P = 0.39)
Test for subgroup differences: Not applicable

Footnotes
(1) BDI: Beck Depression Inventory.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3: Exercise plus usual pharmacological care versus another non-pharmacological intervention plus usual pharmacological care (exercise versus active control), Outcome 6: Depression (BDI, score 0–63, lower scores indicate less depression)

Analysis 3.7



Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable

Footnotes
(1) HADS: Hospital Anxiety and Depression Scale – Anxiety.

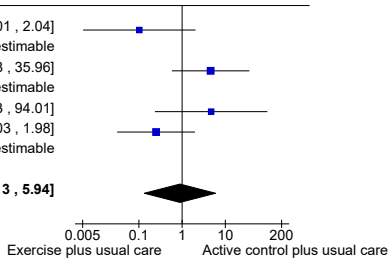
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3: Exercise plus usual pharmacological care versus another non-pharmacological intervention plus usual pharmacological care (exercise versus active control), Outcome 7: Anxiety (HADS Anxiety, score 0–21, lower score indicates less anxiety)

Analysis 3.8

Study or Subgroup	Exercise plus usual care Events	Total	Active control plus usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abrahão 2016 (1)	0	42	2	21	21.0%	0.10 [0.01 , 2.04]
Daltroy 1995 (2)	0	16	0	18		Not estimable
Dos Reis-Neto 2013 (3)	5	23	1	21	29.0%	4.57 [0.58 , 35.96]
Kao 2021 (4)	0	12	0	11		Not estimable
Keramiotou 2020 (5)	2	32	0	30	21.0%	4.70 [0.23 , 94.01]
Miossi 2012 (6)	1	15	4	15	28.9%	0.25 [0.03 , 1.98]
Tench 2003 (7)	0	33	0	28		Not estimable
Total (95% CI)		**173**		**144**	**100.0%**	**0.89 [0.13 , 5.94]**
Total events:	8		7			

Heterogeneity: Tau² = 2.12; Chi² = 7.04, df = 3 (P = 0.07); I² = 57%
Test for overall effect: Z = 0.12 (P = 0.91)
Test for subgroup differences: Not applicable



Footnotes

(1) Active control plus usual care: 2 people abandoned the study without reason. Control group received information about their disease.
(2) Authors did not clearly report dropouts for participants with SLE alone. Control group received information about their disease.
(3) Exercise plus usual care: 5 withdrew. Control group received information about their disease.
(4) No withdrawals reported. Control group received information about their disease.
(5) Exercise plus usual care: 2 people withdrew after 6 weeks for no reported reason. Control group received joint aids and information about their disease.
(6) Control group received information about their disease.
(7) Authors did not clearly report dropouts within each group. Control group received relaxation therapy.

Comparison 3: Exercise plus usual pharmacological care versus another non-pharmacological intervention plus usual pharmacological care (exercise versus active control), Outcome 8: Withdrawals for any reason

2.3. Links and implications for next study

This is the first systematic review to evaluate the effectiveness of *exercise as adjunctive therapy* in comparison to 1) placebo plus usual care, 2) usual care alone, or 3) another non-pharmacological intervention plus usual care, for people with SLE. The reason for referring to exercise as an adjunctive therapy is because exercise is usually recommended or prescribed in conjunction with other therapies (described in section 1.4.2) (Fanouriakis et al., 2019). For all three comparisons, the results are equivocal, and the quality of evidence is low due to methodological biases and lack of participant numbers, suggesting that we cannot be confident about the true effects of exercise on fatigue, functional capacity, disease activity, quality of life, and pain. However, these findings highlight the need for greater quality trials of exercise in SLE, with more SLE participants, and a focus on rigorous methodology (randomised, controlled, double-blinded), which will increase our confidence in the effects of exercise for this population. In the included studies there was a lack of sufficient detail in exercise dosage reporting to allow for reproducibility and the development of specific exercise guidelines for this population. Qualitative studies to explore the perception of exercise for this population in rheumatology practitioners (study 3), and patients (study 4), have been developed to help inform key considerations for exercise interventions. A protocol for a double-blinded, randomised comparison of two different types of exercise (aerobic exercise versus resistance exercise) in SLE has been developed (appendix 7.4). However, this exercise intervention was unable to be conducted during the period of candidature due to the COVID-19 pandemic and lockdown restrictions in Sydney, Australia where the research was undertaken. In lieu of the original research design, an individualised telehealth-supervised exercise intervention was conducted, taking into consideration some of the limitations identified in this review (study 5).

2.4. Study 2: Exercise and physical therapy for systemic sclerosis

This systematic review protocol was published in the Cochrane Database of Systemic Reviews on the 3rd of March 2022 and is presented in its original published format. Due to external collaboration, we were bound by differing timeframes and unable to complete the review in time for completion of this thesis.

2.5. Links and implications for future research and clinical practice

This will be the first systematic review to explore the safety and effectiveness of both exercise and physical therapy in SSc. To date, we have screened title and abstracts for inclusion, and are in the process of screening the full text (Figure 1) (Page et al., 2021). The completed systematic review will contribute to the advancement of the research area by providing evidence on the safety and effectiveness of exercise on outcomes of importance to people with SSc (For example, hand mobility, skin thickness, pain, and aerobic capacity), and help. This evidence will help inform future the development of rigorous exercise intervention studies and clinical practice exercise recommendations for people with SSc.

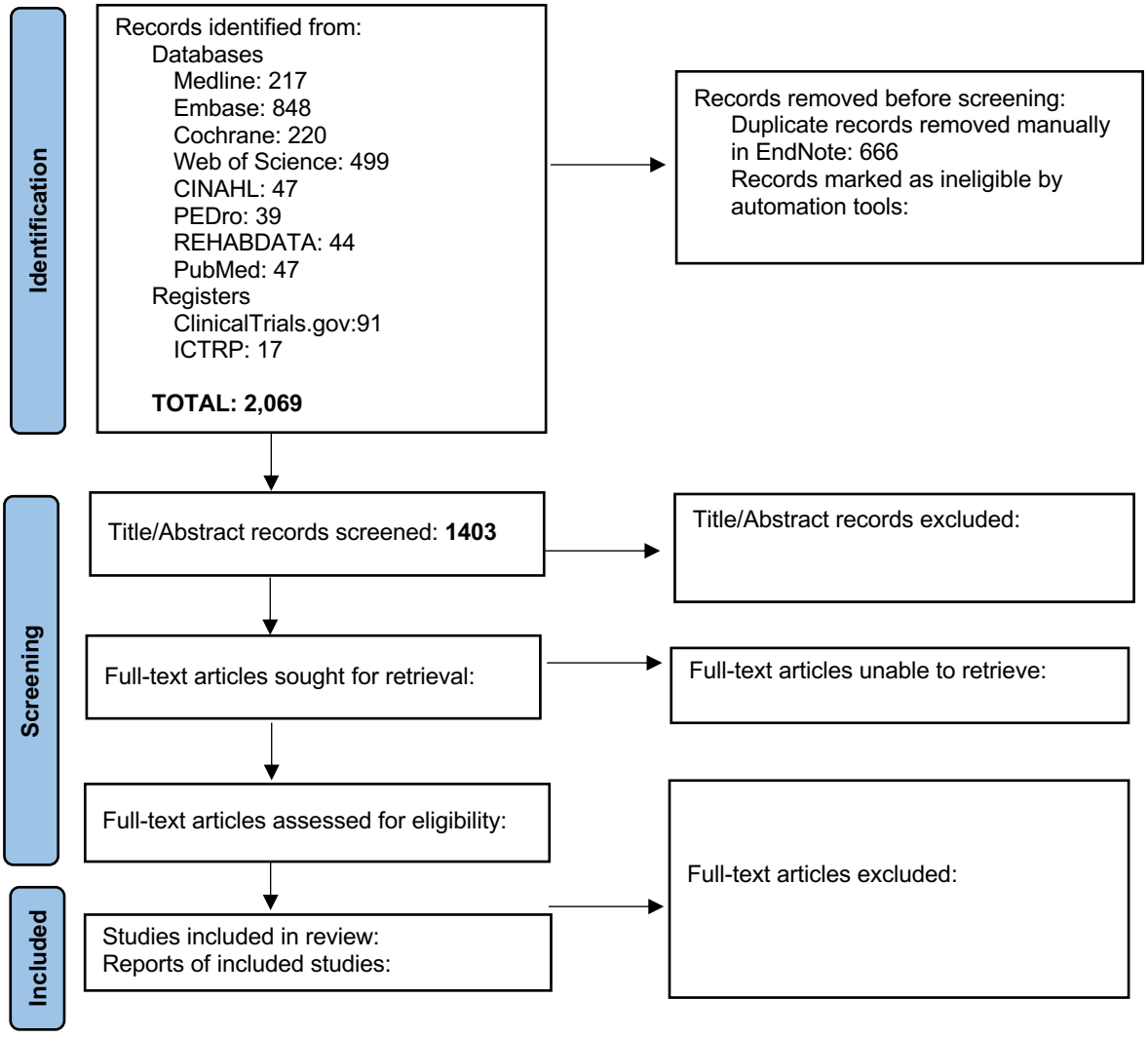


Figure 1. PRISMA flow diagram

CHAPTER 3: STUDY 3 - RHEUMATOLOGY PRACTITIONERS VIEW OF EXERCISE IN ADULTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS OR SYSTEMIC SCLEROSIS

3.1. Overview of the chapter

This chapter includes study 3, a qualitative study that explores rheumatologists' and rheumatology nurses' perspectives of exercise for people with SSc and SLE. These two diseases affect joints and surrounding tissues, and in this regard, fall within the purview of rheumatologists. Rheumatology practitioners were interviewed because they are the primary care specialists for this population and the key source of health care information identified by their patients (Farina et al., 2022; Schouffoer et al., 2011) It is therefore important to understand more about what rheumatology practitioners think about exercise or whether they recommend it routinely to their patients with SLE or SSc. Furthermore, this study took place during COVID-19 lockdown restrictions that were occurring in Sydney, Australia, thus the design had been amended to be conducted online using Zoom, rather than in-person as originally intended. As a result, recruitment for this study differed to the original plan. We had planned to attend the Australian Rheumatology Association national conference to approach clinicians in-person inviting them to participate in interviews. This event was canceled due to the lockdown restrictions; therefore, we recruited participants online via email, social media, or through word of mouth. We aimed to recruit a diverse participant cohort from hospitals and private practices within Australia. This study has been published in the Journal of Clinical Exercise Physiology (JCEP) on the 14$^{th\ of}$ December 2021.

3.2. Links and implications to next study

This is the first study to qualitatively explore and describe rheumatology clinicians and nurses' perspectives and routine use of exercise for people with SLE and SSc in private and public settings in New South Wales, Australia. Importantly, rheumatology practitioners view exercise as an important component of care for SLE and SSc, due to its beneficial effects, with little concern about its safety implications for people with SLE or SSc. The rheumatology practitioners offered advice to ensure exercise safety including the need for supervision, close monitoring, individualisation, and a graded approach to exercise. These considerations were implemented in the design of the original (appendix D) and adapted (study 5) exercise intervention study. For both planned exercise intervention studies, participants were supervised 1 on 1 by an exercise physiologist, in person (appendix D) or virtually in real-time (study 5). To supplement supervision during telehealth sessions, the exercise physiologist knew the participants telephone number and home address in case of an emergency (e.g., to direct emergency services). To monitor exercise, the visual analogue scale (VAS) for pain (Appendix C-19) and fatigue (Appendix C-20) was used at the start and end of each exercise session, with exercises adapted accordingly. The exercise physiologist also monitored the technique of each exercise, providing verbal feedback for correction as needed. For the originally designed study (appendix D), the exercise physiologist would monitor the participants' heart rate and oxygen, and for the amended study design (study 5), the participant was taught how to manually check their own heart rate. All participants were prescribed the same exercises, to individualise the intervention, rating of perceived exertion (RPE) (Appendix C-18) was used to ensure the participant achieved moderate intensity exercise (i.e., 3 to 4/10 RPE). For example, the exercise intensity was increased when the participant reported an RPE <3 or made easier if they reported an RPE of ≥5. A graded approach to maintaining the desired RPE as the exercise became more tolerable (e.g., increasing repetitions completed or resistance used) was utilised based upon subjective feedback from the participant. This involvement of the participant facilitates a person-centred approach to the progression and modification of their own exercise program.

CHAPTER 4: STUDY 4 - BARRIERS AND FACILITATORS TO EXERCISE FOR PEOPLE WITH SYSTEMIC SCLEROSIS: A QUALITATIVE STUDY

4.1. Overview of the chapter

This chapter includes study 4, a qualitative focus group study that explores and describes the perspectives and experiences of exercise in adults with SSc. This study was developed in succession to the findings derived from study 3, following the suggestions made by rheumatology practitioners to explore the views of those with lived experience. This study was conducted during the COVID-19 lockdown restrictions that were occurring in Sydney, Australia, thus the original face-to-face focus group design has been amended to online focus groups. This change of implementation allowed us to recruit far flung participants within NSW and other states within Australia, adding to the diversity of participants included in the study. This study was submitted to *Journal of Clinical Exercise Physiology* on the 25th of September 2022, accepted for publication on the 1st of December 2022, and will be published in September 2023.

4.2. Abstract

Introduction. Systemic sclerosis (SSc) is a connective-tissue autoimmune disease that results in significant reduction in physical function and quality of life. Exercise may offer health benefits in people with autoimmune disease, yet approximately 50% of people with SSc are physically inactive and experience a wide array of barriers that may impede their exercise engagement. Currently, there are no exercise recommendations or guidelines for this population. In this qualitative study, we explore and describe barriers and facilitators to exercise in adults with SSc, aiming to provide person-centred exercise recommendations for people with SSc.

Methods. Adults with SSc were purposefully recruited to represent diversity in disease type, duration, and manifestations. Three online focus groups were conducted to explore barriers and facilitators to exercise in people with SSc, transcribed, and thematically analysed.

Results. Twenty-three adults with SSc (mean age 59 ±11 years, 91% female) participated. Four themes emerged: 1) disease-related and general barriers to

exercise, 2) perceived change in personal exercise capacity post-diagnosis, 3) beneficial effects of exercise, 4) preference for modified supervised exercise.

Conclusion. SSc imposes disease-related barriers that, combined with general barriers, impede exercise engagement. People with SSc understand that exercise is potentially beneficial. Key recommendations and advice to counter these barriers include 1) ensuring a comfortable temperature to exercise, 2) utilising modified equipment (e.g., adjustable weighted straps), 3) individually supervising and modifying exercise as required, and 4) keeping people with SSc accountable and motivated to exercise.

Keywords: Systemic sclerosis. Scleroderma. Exercise. Physical activity. Exercise physiology

4.3. Introduction

Systemic sclerosis (SSc), also called scleroderma, is a heterogeneous connective-tissue autoimmune disease characterised by excessive collagen production and infiltration causing organ and skin fibrosis, and vascular injury (1, 2). Physical function can be severely diminished by tendon and skin contractures, myositis or myopathies, as well as diverse impairments arising from ischemic circulatory dysfunction, leading to painful skin ulceration and calcinosis, and pulmonary hypertension causing severe dyspnoea (1, 2). SSc is a rare and unpredictable illness that is currently not curable, and results in significant morbidity and mortality (2-4). People with SSc describe debilitating physical limitations due to skin hardening, painful skin ulcerations, and pervasive exhaustion (5, 6). SSc can also result in distressing appearance transformation because of radical facial changes and subsequent identity loss (5, 6). SSc can hinder ones' ability to perform activities of daily living (ADLs) and disrupts three critical life areas: work, family, and social/leisure, and impacts on psychological well-being and health-related quality of life (5).

Although physical activity (PA) is considered important for health benefits in all people (7), and those with an autoimmune disease (8), data from a large SSc national cohort demonstrated that approximately 50% of people with SSc are physically inactive (9), and among those who reported to be exercising, walking was most

reported (9). Another study comparing all PA (including sport, commuting, work or school, household, and leisure) in people with SSc to their healthy counterparts, demonstrated a significant difference in time spent in all PA (1704 minutes/week vs 2614 minutes/week, respectively, p>0.001) (10). Notably, PA and "exercise" are often used interchangeably in the literature, however, are different concepts (11). Exercise is a subset of PA that is planned, structured and repetitive, and usually includes a dosage (frequency, intensity, time, and type) and an objective to improve and/or maintain one or more components of physical fitness (11).

People with SSc experience a wide array of barriers that may impede their engagement in PA/exercise (12, 13); Skin tightening and stiffness, shortness of breath, painful digital ulcerations, tiredness and fatigue, have been identified as disease consequence barriers (12, 13). The risk of adverse effects from PA/exercise including resultant "pain" and "severe muscle soreness" are also reported to barriers (13). Furthermore, the aerobic capacity, measured by Vo2 peak, was demonstrated to be significantly lower (p=0.04) in those with SSc (without pulmonary or cardiac involvement), compared to healthy controls (14). Although the evidence is scarce in exercise safety and effectives in SSc, we do know that exercise is safe, with no reported adverse events associated with exercise (15-19), and beneficial for adults with SSc with and without lung involvement (14), including improvements in the peak amount of oxygen utilised during intense exercise (Vo2 peak) (16-18) and aerobic capacity (15), self-reported quality of life (17), muscle strength and function (15), and a reduction in self-reported fatigue (15).

Considering the wide array of barriers that impede PA and exercise engagement in adults with SSc, in conjunction with the scarcity of exercise trials, absence of clinical exercise guidelines, and promising benefits of exercise in people with SSc (10, 20), tailored exercise advise for this population is warranted. In this qualitative study, we explore and describe barriers and facilitators to exercise in adults with SSc, aiming to provide person-centred and tailored exercise recommendations and advice for people with SSc.

4.4. Methods

Study Design. A qualitative research study comprising online participant focus groups, with adults with SSc, was developed and conducted to capture barriers and facilitators to exercise experience by people with SSc. This study was approved by the University of Southern Queensland (USQ) Human Research Ethics Committee [Ethics approval number: H21REA094, approved June 2021].

Participants. The study inclusion criteria included participants aged ≥ 18 years old, English speaking, access to a laptop/tablet/mobile phone device, ability to provide informed consent, and diagnosed with SSc according to the European League Against Rheumatism (EULAR) and America College of Rheumatology (ACR) classification criteria for SSc (3, 4). Enrolment decisions were guided by a purposive sampling framework (21), developed by the research team, to ensure a representative participant cohort with respect to disease subtype (mixture of limited and diffuse), disease duration (<10 and ≥ 10 years), demographic location within Australia (mixture between states), and exercise participation (mixture between "exercisers" and "non-exercisers"). Participants were recruited via snowball sampling through advertisement in the Scleroderma New South Wales (NSW) and Scleroderma Australia social media groups, websites, and newsletters. Each focus group was limited to a maximum of 8 participants to ensure all participants had the opportunity to express their personal views and could confidently challenge alternate or opposing experiences expressed within the group. A minimum of one focus group was originally planned, with an intention to undertake additional focus groups until thematic saturation was achieved (22).

Data collection. Participant demographic information was collected by the principal investigator (SF) prior to the focus groups to guide purposive sampling. Information included demographics such as age, sex, work status, home location, disease type, duration, and manifestations, and exercise participation. Each of the three focus groups lasted approximately 1 hour in duration, were conducted on Zoom (online video communication software) between August 2021 and September 2021, led by SF, and were audio-recorded, transcribed, and anonymised. An interview guide was developed by the research team (SF, MC) and reviewed by a third-party investigator who is a registered psychologist.

Data analysis. Qualitative analysis of the focus group transcripts was undertaken by all members of the research team (SF, CC, SB, MC) to ensure a fair and an unbiased appraisal of the experiences expressed. Reflexive thematic analysis was adopted in accordance with qualitative research guidelines, ensuring findings were grounded in shared person experiences rather than imposed from existing concepts (23-26). Data analysis software (NVivo QSR international, release 1.5.1 (940) was used to facilitate qualitative analysis. During the transcription phase, participants were de-identified using alphanumeric codes, characterised by disease duration. (For example, F01). Initially, anonymized transcripts were read multiple times independently by SF and CC, and initial words/phrases (codes) that captured important experiences derived from the research questions were. independently applied to each transcript to ensure a rigorous analysis and to minimize researcher bias. The codes were then explored and refined during several discussions between SF and CC to see how conceptually related codes could be grouped to form themes and subthemes (23). This process was an iterative one, undertaken concurrently with data collection, allowing emerging themes to be explored in subsequent groups. After a preliminary independent analysis of the data and several discussions, revisions of the themes were conducted by the research team (SF, CC, MC, SB) to derive consensus. De-identified key quotations from the transcripts were selected to illustrate themes and subthemes (tables 2 to 5).

4.5. Results

Participants. Twenty-three adults with SSc met study inclusion criteria and participated in one online focus group (Group 1, n=8; Group 2, n=8; Group 3, n=7). Following a total of three focus groups, including 23 participants, thematic saturation was reached. The mean age of participants was 59 ± 11 years, ranging from 36 to 77 years, and 91% (n=21) were female. Purposive sampling ensured broad and representative participation in terms of SSc disease type (diffuse SSc n=14, 61%; limited SSc n=9, 39%), disease duration (< 10 years n= 11, 48%; ≥ 10 years n=12, 52%) and lung involvement (n=12, 52%); however, most participants were currently engaged in exercise (n=20, 87%) and from NSW, Australia (n=16, 70%). See table 1 for further details about individual participant characteristics.

Table 1: Participant characteristics (n=23)

Participant	Sex	Age (yrs.)	Disease duration(yrs.)	Disease Type	Lung involvement	Currently exercising	Currently working	Location
A29	F	72	29	Limited	No	Yes	No	NSW
B47	F	65	47	Diffuse	Yes	Yes	No	NSW
C9	F	68	9	Diffuse	No	Yes	No	NSW
D13	M	51	13	Diffuse	Yes	Yes	Yes	NSW
E4	F	50	4	Limited	No	No	No	QLD
F9	F	63	9	Limited	Yes	Yes	No	NSW
G20	F	68	20	Diffuse	Yes	No	No	QLD
H8	F	66	8	Limited	No	Yes	No	SA
I7	F	56	7	Diffuse	Yes	Yes	Yes	NSW
J21	F	77	21	Limited	No	No	No	NSW
K13	F	67	13	Limited	No	Yes	Yes	SA
L25	F	75	25	Limited	Yes	Yes	No	NSW
M3	F	54	3	Diffuse	Yes	Yes	Yes	WA
N1	F	48	1	Diffuse	No	Yes	Yes	ACT
O12	F	46	12	Diffuse	Yes	Yes	No	NSW
P9	F	48	9	Diffuse	Yes	Yes	Yes	NSW
Q25	F	59	25	Limited	No	Yes	Yes	NSW
R1	F	58	1	Diffuse	Yes	Yes	Yes	WA
S12	F	36	12	Diffuse	No	Yes	Yes	NSW
T7	M	60	7	Diffuse	Yes	Yes	No	NSW
U32	F	56	32	Limited	Yes	Yes	No	NSW
V1	F	46	1	Diffuse	No	Yes	Yes	NSW
W30	F	76	30	Diffuse	No	Yes	Yes	NSW

a We limited the description of organ involvement in this table to “lung”. Note that all participants each experienced multiple symptoms and all participants had one or more organ involvement, including the skin. All participants had Raynaud’s phenomenon (RP).

b Exercise dosage included various frequencies, intensities, time, and type; settings including group-based or 1:1, in-person or online, home-based or in-clinic, water or land-based, supervised, or unsupervised. Variations of exercise described included walking, aerobics (e.g., Zumba), resistance training (e.g., TheraBand and free weights), Bikram yoga, chair yoga, tai chi, Pilates, hydrotherapy, stretch therapy, golf, dancing.

Themes. Four themes emerged following thematic analysis of the focus group data, that together constitute barriers and facilitators to exercise in adults with SSc. The themes identified are 1) disease-related and general barriers to exercise, 2) perceived change in personal exercise capacity post-diagnosis, 3) beneficial effects of exercise, and 4) preference for modified supervised exercise. Each theme and subtheme are described in further detail below. Illustrative quotations for each subtheme are included in tables 2 to 5, and a thematic schema summarising the relationship between the themes are presented in figure 1.

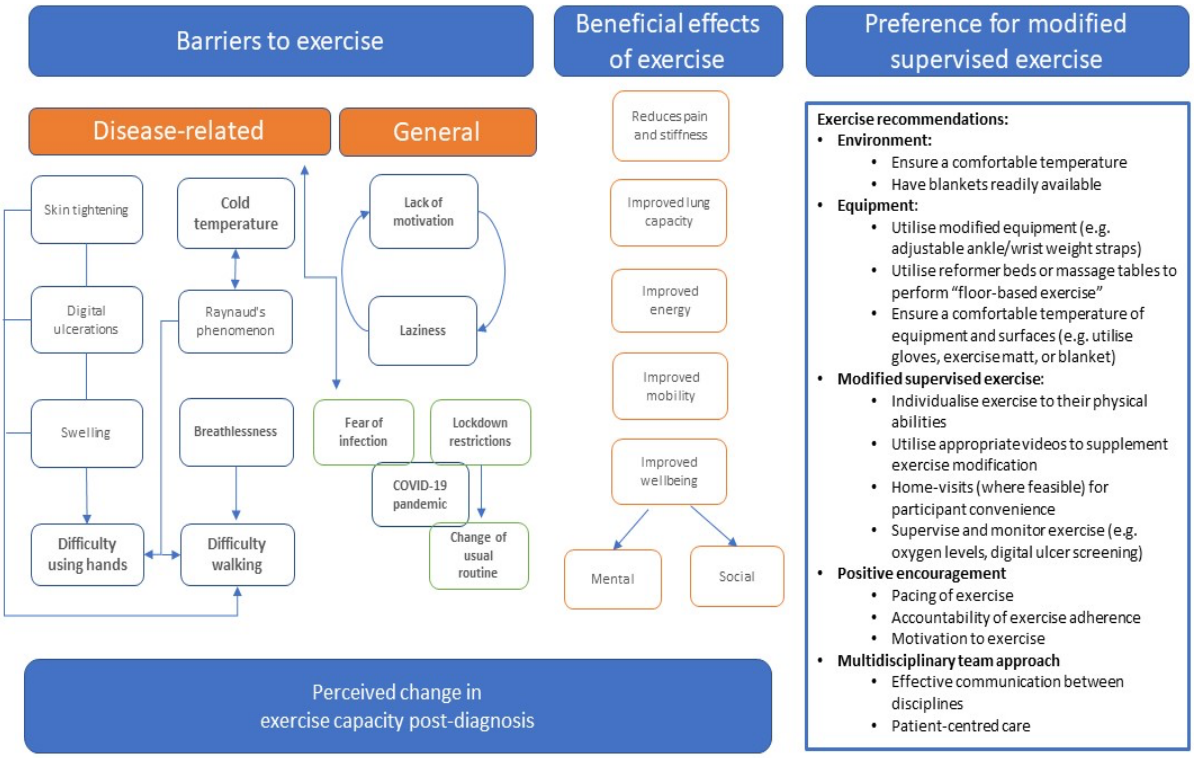


Figure 1. Thematic Schema: Barriers and facilitators to exercise for people with SSc

Disease-related and general barriers to exercise. Participants reported several barriers and challenges to engaging in, adhering to, and performing exercise, with this being the loudest theme amongst all three focus groups. The subthemes are further illustrated using key quotations in table 2.

Disease-related barriers. The cold weather (Q1-5) pertaining to Raynaud's phenomenon (RP), which was a disease manifestation experienced by all participants in our study, was expressed as "a huge factor", and "…stops me doing a lot",

affecting exercise. Though this barrier was described to affect exercise engagement all year around, RP was described to be particularly problematic during the winter months and was influenced by where participants lived in Australia i.e., participants who live in Queensland (QLD) did not report the cold weather as a significant barrier for them to exercise because the average temperature is generally higher than other states in Australia (27). Skin tightening causing difficultly or the inability to perform exercises that involved gripping objects with their hands (for example, holding a dumbbell or the handle of a gym-based machine), or bearing weight down onto their hands (for example, a floor push-up position), largely attributed to disease manifestations such as hand and/or finger ulcerations, calcinosis, or sclerodactyly (Q8-14). Further, digital ulcerations on the feet were also hindrances to do certain exercise such as meaningful walking. Lung capacity restrictions due to pulmonary fibrosis or interstitial lung disease were reported to cause" shortness of breath" while trying to perform aerobic exercise such as walking long distances and/or walking up a hill (Q15-19), making it difficult to engage in exercise. Fatigue and exhaustion before and resulting from exercise (Q20-22), and skin and tendon tightening/restrictions (Q23-27) were other deterrents to engage in exercise.

General barriers. The following barriers are categorised independent to the disease-related barriers because they are not considered to be related to manifestations of the disease itself and could apply to people without SSc. Participants transparently expressed "laziness" and a lack of motivation (Q28-32) as reasons for not exercising or being a barrier to exercise. A "new" barrier to exercise expressed strongly by participants was the recent COVID-19 outbreak and subsequent lockdown restrictions (Q33-35). This barrier was twofold; participants were fearful of being exposed to the community and contracting the virus, "I'm being extra careful", and because the lockdown restrictions meant that their usual exercise routine was compromised. Other barriers included the "expensive" cost of exercise, and difficultly in "accessing" exercise because of a lack of services available for those who live in rural and remote areas of Australia.

Table 2. Disease-related and general barriers to exercise

Cold temperature	
Participant	*Quote*
1: C9	… if it's raining, or cold or windy, I don't get out.
2: F9	The only thing that gets in the way for me is if it's really cold and windy
3: K13	I used to swim a lot. It was most my favourite thing. But once the Raynaud's came, you can't. The water is too cold
Difficultly using hands	
Participant	*Quote*
4: E4	The problem is if I went to a gym, I wouldn't be able to grip things because the weakness and the constriction in the hands makes it really hard to do stuff like that.
5: M3	Some yoga positions I'm not able to do and I'll find a can't make a fist or grip anything. I used to do weight training and I can't actually do that anymore because I just don't have the grip strength to be able to hold anything
6: S12	I find it really difficult with grip strength and anything like that. I love lifting weights at the gym and things like that. But I don't have the strength in the hands. I can't do anything on my hands. So, things like push ups, I can't do, because the hands are a big impact for me.
Digital ulcerations	
Participant	*Quote*
7: A29	Because I've got ulcers on my feet, I can't do meaningful walking
8: B47	I had fingers that will clawed and ulcers on the fingertips
9: S12	Very often, I have bandaged fingers like I have now because of digital ulcers. So that for me is a big barrier
Breathlessness	
Participant	*Quote*
10: F9	My breathing is impacted by walking up hills.
11: J21	Things were going really well until I started feeling really breathless. … if I walk a block, I'm panting hard. So, I'm not exercising anymore.
12: M3	I was diagnosed a couple of years ago, and I've lost my breath a lot, it's climbing stairs for me and walking up slight inclines

Swelling and skin tightening	
Participant	*Quote*
15: E4	What I experienced now is the swelling and the tightness in my legs. I don't have full movement in my knees and my ankles.
16: R1	I'm really restricted by the swelling and the skin tightening. So, for me, really, the only exercise I do is walking. I can't always do that. Sometimes I get swelling in my feet, and pain in my shins
17: P9	I find it really unpredictable as well because some days my legs feel like lead
Laziness and lack of motivation	
Participant	*Quote*
18: B47	Let's be honest. Straight out laziness
19: E4	For me it's just laziness and the fear of pain
20: L25	But I find with exercise, being motivated is a bit hard.
COVID-19	
Participant	*Quote*
21: B47	…I would say though, last year in lockdown, I did not do any exercise.
22: P9	.. I'm not doing [reformer] at the moment because I'm in lockdown, even though I could potentially do it. But just because I'm being extra careful, I'm not going
23: S12	. …. being in lockdown for most of the days of the last few years, I've really struggled.

Perceived change in personal exercise capacity post-diagnosis. A discussion that formed within each of the focus groups was a perceived change in their exercise participation and capacity following their diagnosis with SSc (table 3). Participants described exercise/s that they used to do before they were diagnosed with SSc and commented on how it has significantly differed following their diagnosis (Q1-9). Sport such as tennis, squash, dancing, athletics or soccer used to be played, and since diagnosis they have stopped because of reasons such as "joints are no good", "tightness and swelling in legs", and descriptions such as "but that's all gone now", "… but no longer", and "not as strong as I used to be" were made. There was a mixed description between acceptance of this change, and conversely, disappointment and

frustration that they could no longer do what they used to do. An expectation that they "should" be able to do more than what they can currently do, and expressions such as "I'll cry because I should be able to do this stuff" were made. On the contrary, comments such as "accepting our bodies limits" and self-talk to remind themselves that "whatever we're doing is sufficient" were described. Remarks were made about the importance of having a "different mental attitude" and changing their own mindset from "I should be able to do it" to "at least I do it" were highlighted. Furthermore, participants suggested to one another that they should "try and pace" and understand when they can "keep going" and when to "pull back".

Table 3. Perceived change in personal exercise capacity post-diagnosis

Participant	*Quote*
1: C9	I used to like in tennis and squash but nowadays my joints are no good.
2: E4	Prior to being diagnosed I could walk for three hours problem without anything being sore, or anything afterwards. What I experienced now is the swelling and the tightness in my legs. I don't have full movement in my knees and my ankles
3: B47	I found that I'm not as strong as I used to be. And I have slowed right down with my gardening.
4: N1	I can still probably do 2km but very slowly, and it that's all I can do for the day. Whereas I used to walk about eight to 10k a day last years locked down before scleroderma hit.
5: K1	I used to swim a lot. It was most my favourite thing. But once the Raynaud's came, you can't.
6: U32	The strength you know, like, I'm just finding find it's lessening. And it's affecting my mental health because my whole life I've been a fairly active person, a maniac in the garden, and spend hours out there, and now because of a combination of things, like heart stuff, lung stuff, joints, whatever. It is extremely depressing, and just a feeling of hopelessness and why bother?
7: M3	I was diagnosed a couple of years ago, and I've lost my breath a lot, it's climbing stairs for me and walking up slight inclines
8: S12	I was a really good swimmer when I was a young kid, I love swimming, I was part of a Swim Club. I was up early every morning swimming. And since been diagnosed just don't even step into your pool anymore. Very often, I have bandaged fingers

	like I have now because of digital ulcers. So that for me is a big barrier. I just don't get in the water anymore

Beneficial effects of exercise. Participants acknowledge that exercise is beneficial in countering their disease-related barriers and have been categorised into several subthemes for a more comprehensive view (table 4). An improvement in mental wellbeing and physical mobility were described to be beneficial from engaging in regular exercise (Q1-5). Participants' also described exercise to be beneficial in improving their lung capacity and fitness (Q6-8), and in improving their energy levels and sleep, with some describing exercise as "invigorating", and expressed that not exercising can make them feel "more fatigued" (Q9-11). Participants also described exercise to help reduce overall pain and stiffness, improve circulation, and make them feel "warmer internally", "feel accomplished", and that exercising regularly also helped them to "eat healthier" (Q12-16). Participants who performed group exercise expressed that the social aspect was a benefit to exercising, with descriptions such as "it's a good social outlet" and that exercise gives you a sense of "togetherness" (Q17-19), highlighting the social benefit of exercise.

Table 4. Beneficial effects of exercise

Improvements in mental wellbeing	
Participant	*Quote*
1: F9	So physical exercise for me is parallel to my mental wellbeing my emotional wellbeing.
2: S12	I love it when you get to walk out of the gym because that means you are finished, and that endorphin hit that you get, it certainly does have a big impact on my mental health, a big impact on just how I feel.
3: W30	I think it's also got a lot to do with mental health as well, you can become more and more depressed if you're not moving if you're not active. I think even if you're active around your own home, set yourself some goals to do in your own home, I think that helps you a lot, including the mental health and positivity

Improvements in lung capacity	
Participant	*Quote*
4: T7	I suppose my exercise experience stemmed out of the fact to improve my lung capacity, my lung function DLCO was down to 27. Now, I'm back up to around 43.
5: I7	The class would start with a breathing exercise in the beginning and a breathing exercise at the end, which I found very, very good because I've got lung fibrosis, and just with the breathing and concentrating on my breathing, I think it just helped me.
6: Q25	So, on the days that you do it, you feel great, and in fact, if you do it you just find that your breathing actually benefits from it
Improvements in energy	
Participant	*Quote*
7: F9	I am fortunate that I can exercise, not at the moment, but I usually can, and it's just invigorating. You come out with high energy, if you're like, you have more energy than before you walk in the door.
8: S12	So, fatigue for me, if I don't exercise, I get really fatigued.
9: O12	Even though I would get up every morning or afternoon, extremely tired and fatigued. By the end of the day, I find that if I don't do my exercises and stretches, I don't rest as well. And I find even if I'm really tired, like dragging my feet around, if I do them, I actually rest and sleep better
Reduction in pain and stiffness, and improved mobility	
Participant	*Quote*
10: C9	I think it's beneficial for my joints. Especially stretches, they are good.
11: G20	I also think like we all get the joint pain and the aches and all the rest of it. But if we just sit immobile all day, I find I'm worse. You've got to move a bit, you've got to keep moving, not necessarily do great hours of physical exercises or gym work but keep lubricated or keep active
12: U32	We know that we need to move our joints and everything. And if we don’t, we feel the ceasing up and the tightening

Improvements in social wellbeing	
Participant	*Quote*
13: H8	I've been doing an exercise class twice a week for an hour a session. I really enjoy, it's been really good for me. It's a good social outlet. We always have lots of laughs.
14: F9	For me, any form of exercise, it's always nice doing with someone else. Because when you're in a class, it gives you a sense of togetherness which is important for me.

Preference for modified supervised exercise. This theme was categorised into several subthemes according to participants specific suggestions that would facilitate their engagement in exercise (table 5), however, the consensus was that participants expressed the importance of and preference for modified supervised exercise. Participants conveyed the need for accountability to keep them "motivated" (Q1-3). A lack of interest in going to a gym or performing exercise that was "structured" were described, and participants reported a preference in incidental exercise such as walking, or gardening, especially if it's walking outdoors in the fresh air and sunlight, or with a friend. A preference to exercising in a group or with a partner was highlighted, or having a health professional come to their house, again keeping them "accountable". An emphasis was placed on exercises and/or environments to exercise that were modified to suit their needs (Q4-6). For example, performing Pilates on a reformer bed or standing to perform an exercise, instead of getting on the floor, or turning on the heater before they commence exercise. Suggestions such as having exercise videos online was described as an effective strategy in assisting exercise engagement (Q7-9). For example, using "YouTube" and performing "chair yoga" online, for example, to engage in exercise at home effectively. This theme was enhanced by the recent COVID-19 pandemic, where, for many, exercising in a gym or clinic was either not an option due lockdown restriction, or they were fearful of being exposed to infection. Another suggestion to facilitate exercise was to come prepared in suitable clothing for the cold (Q10-11), for example, wearing "hoodies", "gloves", or "orthopaedic boots", with comments such as "being appropriately clothed adds to the benefit of the exercise". Participants also held high value in the health professional team having a good understanding about their disease and

pointing them in the right direction with exercise (Q12-13). Other suggestions about ways to exercise effectively included finding the right balance, pacing, and knowing "...when to pull back and when to just push yourself".

Table 5. Preference for modified supervised exercise

Accountability	
Participant	*Quote*
1: C9	I got an EP into the house. And I got a structured programme and I'm supposed to continue. She comes [to my] house, once a week, and it's very beneficial. She works me very hard. I think it's beneficial for my joints.
2: A29	Because when you're in a class, it gives you a sense of togetherness which is important for me.
3: S12	I'm the type of person who loves exercise when I've got somewhere to go and be accountable to someone.
Suitable modifications	
Participant	*Quote*
4: T7	There is a chair yoga group that I do online. And that's been quite good because it's actually set up for people in situations where they're not as mobile.
5: H8	So, the girls working [at the gym I go to], they always put the heaters on about 10 minutes before our group starts. So, by the time I get in there, it's warm.
6: L25	I do the same thing with Pilates. We have three in a class. But she does it exactly for what you need. She's very encouraging to do just that little bit further forward, and maybe challenge you a little bit more than perhaps you would do normally.
Suitable exercise videos	
Participant	*Quote*
7: H8	Just go to YouTube and just type in chair exercises for chronic disease o or scleroderma. And you'll be surprised what comes up.
8: F9	I am OK to step out and to try something new. And I usually try to look on YouTube first.
9: P9	I've actually found a lot on YouTube, there's actually quite a lot available.

Suitable clothing/equipment	
Participant	*Quote*
10: A29	Working out what exercises to do and where to put your hands, and being appropriately clothed adds to the benefit of the exercise.
11: U32	I have had orthotics made, and they work a treat. It improved my balance, and because it improved my balance, it lessened my foot pain, there's still foot pain there, but it's nowhere near what it was early on.
Guidance and information about exercise	
Participant	*Quote*
12: N1	I don't expect her to know how to advise me on exercise. If she could at least point me to the right kind of specialists that I can go and see, who can advise me, and particularly if there was a register of advisors, exercise physiologist and physios in Canberra who actually know something about scleroderma
13: M3	I think if they could point us in the direction of maybe doing stretching, or you know, maybe go and have a look at something to do with your hands if your hands are tight, things like that that would be helpful

4.6. Discussion

For adults with SSc, disease-related barriers were amongst the most impeding factors to exercise and were highlighted in our study findings. Cold temperature, described as “more” problematic during the winter months, was a major deterrent for people with SSc to engage in exercise, often making it difficult to exercise comfortably, or exercise at all. This is not a surprising finding from this study considering Raynaud’s phenomenon (RP) occurs in virtually all patients (~96%) with SSc (28, 29), and in fact, all participants in our study reported RP as a disease manifestation (see table 1). Furthermore, typical descriptors of RP are episodic vasospasm occurring in response to cold exposure (30). This barrier may have been pronounced in our findings because the focus groups took place in winter. A small (n = 18) longitudinal study identified “RP attacks” to double in frequency (2.9 *vs* 1.5 attacks/day) during winter compared with summer despite similar rates of outdoor exposure across seasons (31). It is therefore imperative that exercise professionals acknowledge that the cold temperature is a barrier to exercise and address this accordingly. For example, warm up the temperature of the environment in which your patient will be

exercising and/or use blankets to keep surfaces or equipment warm before use. One participant in our study explained that her exercise instructor would always turn on the heaters in the room prior to commencing their group exercise class to ensure the room was comfortable. Other participants also explained that wearing appropriate clothing (thermal underlayers, heated jackets, gloves, long socks) is paramount for them to be able to engage in exercise, especially during winter. Exercise professionals can encourage and/or remind people with SSc to come prepared to exercise with warmer clothing, particularly when controlling the temperature is beyond our control (e.g., community-based gym). Importantly, participants in our study described exercise to improve "circulation" and "body warmth", consistent with other qualitative findings (13), and to quantitative results that demonstrated improvements in microvascular endothelial function following upper body high intensity interval training in adults with limited SSc (16, 17). Furthermore, consistent with other quantitative findings of exercise in SSc (14-18), participants described a reduction in pain and stiffness, and improved lung capacity, aerobic fitness, strength, and mental wellbeing following exercise. Furthermore, people with Sc consider PA/exercise to be an effective treatment, reduces fear of deterioration, and makes them feel healthy and satisfied with themselves (13). To enhance the benefits of exercise in people with SSc, a suitable strategy is to ensure that there is clear communication between the multidisciplinary team (MDT). The MDT for someone with SSc usually comprises, but not limited to, a rheumatologist, pulmonologist, cardiologist, gastroenterologist, physiotherapists, hand therapist, and specialised nurse (32). Significant improvements in grip strength ($p=0.001$), aerobic/walking capacity measured by a 6-minute walking test ($p=0.021$), and functional ability measured by the health assessment questionnaire (HAQ) ($p=0.0025$), have been demonstrated in people with who underwent an MDT program 1 day/week including individualised treatments, group exercise and education, compared to usual outpatient clinic care (33).

Other disease-related barriers that were pronounced in our findings were physical disabilities associated with SSc (e.g., digital ulcerations, skin tightening, swelling), making it difficult to use their hands effectively to exercise, or do meaningful walking. For example, participants with sclerodactyly reported it to be difficult, painful, and merely impossible to hold exercise equipment (e.g., dumbbells, barbells,

resistance bands) because of the "curling" of the fingers and lack of mobility. Sclerodactyly, among other physical disabilities such as widespread skin tightening, digital ulcerations located on feet/hands/elbows/ knees, and pervasive fatigue, were also expressed as particularly impeding factors to exercise in another qualitative study (13). Participants in our study shared a consistent view amongst each other that their ability to perform exercise "now" (post diagnosis) is very different to "before" (pre-diagnosis). This theme did not constitute a barrier to exercise, per se, it was a distinctive perception that many of the participants shared in the group discussions. Focus groups encourage open discussion and debate among participants, allowing convergent and divergent views to be clarified where necessary during the discussion (34). The dynamic nature of focus group interactions, particularly with people who share a rare disease, facilitates unique patient experiences that may not always be expressed in one-on-one interview settings.

Participants in our study expressed the importance of modified supervised exercise, consistent with recommendations from rheumatology practitioners who strongly advised that exercise is individualised and supervised for this population (35). Participants in our study also provided suggestions on how to facilitate exercise. For example, there was a preference for exercise professionals to provide a home-visit to exercise as this would alleviate the additional stress and energy required to commute to a clinic or gym. Participants also suggested the use of modified equipment (e.g., "reformer bed or massage table to perform floor-based exercise"), and to adapt the exercise to suit their physical abilities (e.g., "standing to perform an exercise instead of having to get down on the floor"). Participants also valued the use of modified exercise videos so that they could perform exercise comfortably at home, with some suggesting "YouTube" to perform modified exercises such as chair yoga.

Interpretation of results should consider our study strengths and limitations. Our study sampling method allowed us to include diversity of views amongst participants, with varying types of SSc, duration of disease, and manifestations. However, despite a purposive sampling framework, this study only included individuals with SSc from Australia, and therefore it is not representative of adults

with SSc worldwide, who may have provided other views of exercise. Also, this study included mostly female (n=21, 91%) participants who exercise (n=20, 87%), perhaps inherent due to the gender bias of SSc (36, 37), and the nature of the study. We performed online focus groups, which although is becoming increasingly common as a cost-effective method and opportunity to recruit geographically far-flung participants (38), online interviews pose some limitations including not being able to respond easily to participants' body language and emotional cues, as well as technological difficulties (39). However, the gathered data provided rich content that summarised barriers and facilitators to exercise and fulfilled the aims of the study.

SSc imposes disease-related barriers that, combined with general barriers, impede exercise engagement. People with SSc understand that exercise is potentially beneficial. Key recommendations and advice to counter these barriers include 1) ensuring a comfortable temperature to exercise, 2) utilising modified equipment (e.g., adjustable weighted straps), 3) individually supervising and modifying exercise as required, and 4) keeping people with SSc accountable and motivated to exercise. To improve our understanding about the barriers, facilitators, and benefits to exercise in people with SSc, exercise trials using mixed methodology that captures both quantitative and qualitative outcomes, is recommended.

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Author contributions

SF and MC conceived the study design. SF acquired the data, and all authors contributed to data analysis and interpretation. All authors were involved in drafting or revising this study critically for important intellectual content, and all authors approved the final version to submit for publication. Stephanie Frade had full access to all the data in the study and takes responsibility for the integrity of the data.

Study conception and design: Stephanie Frade and Dr Melainie Cameron

Acquisition of data: Stephanie Frade.

Analysis and interpretation of data: Stephanie Frade, Chloe Campbell, Dr Stephen Bird, and Dr Melainie Cameron.

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4.8. Links and implications for future research and clinical practice

This is the first focus group study to explicitly explore the barriers and facilitators to exercise in Australian adults with SSc. Many of the barriers to exercise that were described by participants centred around their disease-specific physical limitations (e.g., curling of the fingers, skin tightness, digital ulcerations, shortness of breath). Future exercise interventions should include individualised exercise programs that consider the participants unique disease manifestations and adapt exercise accordingly. Participants in our study offered key considerations for the development of exercise programs, including supervision of exercise sessions, ensuring exercise is performed in a comfortable room temperature, and the use of appropriate equipment that is suited to their physical abilities (e.g., weighted wrist straps if participant is unable to hold a dumbbell or TheraBand). These considerations should be used in future exercise intervention studies and clinical practice to facilitate person-centred exercise prescription which may subsequently increase adherence and comfort of exercise for people with SSc.

CHAPTER 5: STUDY 5 - TELEHEALTH-SUPERVISED EXERCISE IN SYSTEMIC LUPUS ERYTHEMATOSUS: A PILOT STUDY

5.1. Overview of the chapter

This chapter includes study 5, a mixed method investigation that explores the feasibility and effectiveness of telehealth-supervised exercise in adults with SLE. This study was developed and conducted following the findings from study 1 and 3, aiming to fill the gaps found in exercise intervention studies in SLE and taking into consideration the advice from rheumatology practitioners and nurses. This study took place during the COVID-19 lockdown restrictions that were occurring in Sydney, Australia, thus this study design differs from the original plan (see Appendix D for the original study protocol). Furthermore, this telehealth-supervised intervention study was designed as a single group study, however, following feedback from peer reviewers', a control group was included. Thus, the exercise and control groups are performed asynchronously, and consequently, not randomized. This study was submitted to the LUPUS journal on the 17th of June 2022, received consideration with major revisions (e.g., advice to include a control group), re-submitted on the 17th of January 2023, and accepted for publication on the 24th of January 2023.

Paper

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Telehealth-supervised exercise in systemic lupus erythematosus: A pilot study

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Abstract

Objectives: To explore the feasibility and effectiveness of telehealth-supervised exercise for adults with Systemic lupus erythematosus (SLE).

Methods: This was a non-randomised controlled pilot trial comparing telehealth-supervised exercise (8 weeks, 2 days/week, 45 min, moderate intensity) plus usual care with usual care alone. Mixed methods were used to assess change in fatigue (FACIT-fatigue), quality of life (SF36), resting fatigue and pain (11-point scale), lower body strength (five-time sit-to-stand) and endurance (30 s sit-to-stand), upper body endurance (30 s arm curl), aerobic capacity (2 min step test), and experience (survey and interviews). Group comparison was performed statistically using a two-sample T-test or Mann–Whitney U-test. Where known, we used MCID or MCII, or assumed a change of 10%, to determine clinically meaningful change within groups over time. Interviews were analysed using reflexive thematic analysis.

Results: Fifteen female adults with SLE were included (control group $n = 7$, exercise group $n = 8$). Statistically significant differences between groups, in favour of the exercise intervention, were noted for SF36 domain emotional well-being ($p = 0.048$) and resting fatigue ($p = 0.012$). There were clinically meaningful improvements over time for FACIT-fatigue (+6.3 ± 8.3, MCID >5.9), SF36 domains physical role functioning (+30%), emotional role functioning (+55%), energy/fatigue (+26%), emotional well-being (+19%), social functioning (+30%), resting pain (−32%), and upper body endurance (+23%) within the exercise group. Exercise attendance was high (98%, 110/112 sessions); participants *strongly agreed* ($n = 5/7$, 71%) or *agreed* ($n = 2/7$, 29%) they would do telehealth-supervised exercise again and were satisfied with the experience. Four themes emerged: (1) ease and efficiency of exercising from home, (2) value of live exercise instruction, (3) challenges of exercising at home, and (4) continuation of telehealth-supervised exercise sessions.

Conclusion: Key findings from this mixed-method investigation suggest that telehealth-supervised exercise was feasible for, and well-accepted by, adults with SLE and resulted in some modest health improvements. We recommend a follow-up RCT with more SLE participants.

Keywords

systemic lupus erythematosus, exercise, autoimmune disease, telehealth, COVID-19

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, multi-system, autoimmune disease characterised by an immune response to self-antigens.[1,2] Common manifestations of SLE include fatigue, affecting up to 80% of patients,[3] arthritis, myalgia, serositis, and nephritis.[1] People with SLE are less physically active than people without SLE.[4] Sixty percent of people with SLE do not meet World Health Organisation (WHO) recommendations for physical activity

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(PA).[4] Additionally, physical inactivity increases the risk of developing common comorbidities such as osteoporosis[5] and atherosclerotic cardiovascular disease (CVD).[6,7] Regular, moderate intensity exercise is demonstrated to be a safe and effective adjunctive therapy to improve aerobic capacity, fatigue, depression, and physical function in people with SLE.[2,8,9] Jeyasingham and colleagues surveyed 55 adults with SLE[10] and found that most (n = 49, 89%) reported some barriers to engagement in regular exercise; reasons included fatigue (n = 39, 71%), lack of time (n = 27, 49%), weather conditions (n = 18, 33%), and lack of motivation (n = 17, 31%). Promisingly, most participants (n = 48, 87%) were willing to change their daily routine to include more exercise.[10] Additionally, Dickson and colleagues[11] surveyed 1113 adults with rheumatologic diseases to assess perceived influences of the COVID-19 pandemic on PA, revealing additional barriers. Over half of participants (55.5%) reported engaging in less PA, followed by unchanged PA (26.6%), and increased PA (15.3%) since the start of the pandemic; reasons included increased overall fear/anxiety (33.5%), lack of motivation (32.4%), and contracting coronavirus infection (32.1%). Most participants reported that they did not meet their exercise goals during the 2020/2021 years of COVID-19 pandemic (67.2%).[11]

Telehealth is a possible strategy for delivering exercise interventions for people with SLE that may alleviate some of the reported barriers (i.e. exercise performed in the comfort of the participants' home, requiring no additional travel time and energy, and supervised to ensure safety, and increase motivation). Telehealth exercise interventions targeting fitness have proved effective and safe in other populations, including cardiopulmonary diseases[12] and multiple sclerosis.[13] Galloway and colleagues[14] trialled telehealth using real-time video as an exercise delivery mode for twenty-one people recovering from stroke and found that feasibility and satisfaction were high; 95% of participants rated usability favourably, and 95% 'enjoyed' telehealth exercise sessions and 'would recommend them to others'.[14] Telehealth-supervised exercise does not appear to have been trialled for people with SLE. Therefore, in this pilot study we aimed to explore the feasibility and effectiveness of individually supervised telehealth exercise for adults with SLE adjunctive to their usual care.

Methods

Study design

This study was a non-randomised controlled pilot trial conducted between September 2021 and December 2022. This study was approved by the University of Southern Queensland (USQ) Human Research Ethics Committee (ethics application number: H21REA052) and registered with Australia and New Zealand Clinical trial registry (ACTRN12622000063718).

Participants

Participants were recruited through advertisement within a tertiary hospital rheumatology department and the Lupus New South Wales (NSW) association. Following initial screening, those who met the inclusion criteria and signed consent were included in the study. Inclusion criteria were age ≥ 18 years, diagnosis of SLE according to the European League Against Rheumatism (EULAR)[15] or American College of Rheumatology (ACR) criteria for SLE,[16] and deemed safe to exercise by principal investigator (SF) who is an accredited exercise physiologist (AEP). Exclusion criteria were those who were pregnant, or had active lupus nephritis, myocarditis, or pericarditis, or otherwise deemed unsafe to exercise.

Interventions

Participants in the exercise group underwent an 8 week, 2 days per week, 45 min, individually supervised telehealth exercise program. All sessions were conducted in real-time on Zoom (Zoom Video Communications, Inc, CA, USA) by an AEP (i.e. SF delivered one session per week, and a trained research assistant delivered one session per week). Exercise was performed at moderate intensity, with a rating of perceived exertion (RPE) between 3 and 4 out of 10, in accordance with the American College of Sports Medicine (ACSM) intensity guidelines,[16] which was monitored through-out the program. All participants were allocated 48 hours of relative rest (i.e. no structured exercise) between the two sessions. The session comprised of a 10 -min seated mobility warm up, 30-min strength circuit, and a 5-min static stretching and breathing cool down. The circuit was designed in accordance with the ACSM resistance training guidelines[16] for muscular strength, with exercise volume comprising 2–4 sets and 8–12 repetitions, 1 min rest between each set, and inclusion of 6–8 exercises focusing on major muscle groups. The program was structured as a circuit, with 6–8 exercises comprising 1 set, incorporating fundamental movements: push, pull, squat, lunge, locomotion, and rotation. Resistance included body weight, available items in participants' home, and two resistance bands which were sent to participants. Exercise volume progressed over the 8 weeks consistently between participants (i.e. 2 sets progressed to 3 sets, 8 repetitions progressed to 12 reps); however, RPE was used as the primary tool to substantiate an increase or decrease in intensity (i.e. increasing tension on the resistance bands) to ensure participants maintained the desired RPE. All participants maintained their usual care during the

duration of the intervention. Participants in the control group continued with their usual care; we did not ask control participants to stop their usual exercise routines, nor did we prescribe any new exercises.

Outcomes

Baseline and post-intervention testing were conducted by a blinded investigator (SW), also an AEP. Self-reported questionnaires were sent to the participants to complete, and exercise tests were conducted in real-time on Zoom. Data were stored electronically on a university password-secured OneDrive folder.

Pain and fatigue. An 11-point scale (e.g. 0 = no pain to 10 = maximum pain) was used to measure participants' self-reported resting pain and fatigue. Lower scores indicate less pain and fatigue (lower scores are better). This scale has been visually adapted from the 10-point Borg RPE scale, with good reliability (0.898) and correlation to the visual analogue scale (rs = 0.754, $p < 0.01$).[17] Each number on the scale included a description (e.g. 1 = just noticeable, 'my pain is hardly noticeable'). This scale was also used to monitor the exercise program. A change of 15% (mean change/baseline × 100) has been identified as the minimally clinically importance difference (MCID) for pain in people with chronic musculoskeletal pain.[18]

Fatigue. The Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) was used to measure self-reported fatigue. Functional Assessment of Chronic Illness Therapy Fatigue Scale is reliable ($\alpha > 0.95$) and has been validated in SLE (ρ 0.81).[19] Functional Assessment of Chronic Illness Therapy Fatigue Scale-F (version 4) is a 13-item questionnaire that uses a 5-point Likert-type response scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; and 4 = very much), with scores ranging from 0 to 52 (higher scores indicating less fatigue). Goligher et al.[20] derived 5.9 points as the MCID for the FACIT-F scale in SLE.[20]

Quality of life

The RAND 36-Item Health Survey (version 1.0)[21] (SF36) was used to measure self-reported quality of life (QOL) on eight health domains including physical and emotional limitations, fatigue/energy, emotional well-being, social functioning, pain, and general health. SF36 has good reliability as a measure of QOL[21] and has been used to measure QOL in various exercise intervention studies in SLE.[22–27] Scores for each domain range from 0 to 100, with a higher score defining a more favourable health state.[28] An MCID has not been identified for each individual domain.

Lower body endurance. A 30-second sit-to-stand (30sSTS) test was used to measure lower body muscular endurance because of its reliability in telehealth (ICC 0.989),[29] excellent test–retest reliability in community-dwelling older adults (men, ICC 0.84 and women, ICC 0.92),[30] and validity correlating to weight-adjusted leg press performance (men, $r = 0.78$ and women, $r = 0.71$).[30] Lower limb muscular endurance is the ability of the lower limb muscles to perform repetitive contractions against a force for an extended period of time.[16] This test involves the participant standing up and sitting down as many times as possible in 30-seconds, whereby the greater number of repetitions completed indicates greater lower limb muscular endurance (higher scores are better). The minimal clinically important improvement (MCII) for a 30sSTS is 2.6.[31]

Lower body strength. A five-time STS (5TSTS) was used to measure lower body muscular strength because of its reliability in telehealth (ICC 0.990),[29] excellent test–retest reliability in older adults with hip or knee osteoarthritis (ICC 0.96),[32] and good validity when compared to the timed up and go (TUG) test in older adults ($r = 0.64$).[33] Lower limb strength is the ability of the lower limb muscles to exert a maximum force against an object external to the body, or own body weight, in one maximum effort of the lower body muscles.[16] This test assesses the time it takes to stand up and sit down five times, whereby the less time it takes to complete five repetitions, the greater the lower limb strength (lower scores are better). The MCID for a 5TSTS is 2.3 s.[34]

Upper body endurance. A 30-second arm curl test (30sAC) was used to measure upper body muscular endurance because of its reliability in telehealth (ICC 0.992),[29] good test–retest reliability (ICC 0.80–0.81) in an older population,[35] and good validity ($r = 0.84$ for men and $r = 0.79$ for women) when compared to composite strength measures (1-repetition max biceps, chest, and upper back).[36] Upper body endurance is the ability for upper body muscles to continue contracting against external resistance for an extended period.[37] To perform this test successfully via telehealth, participants were instructed to do as many arm curls (bending the arms simultaneously towards the body at the elbow) as they could using available household items (e.g. dumbbell, water jug, and cans) in 30-seconds. The greater number of repetitions completed indicates greater upper limb endurance (higher scores are better). An MCID has not been identified for this test.

Aerobic capacity. The 2 minute step test (2MST) was used to measure aerobic capacity because of its reliability in telehealth (ICC 0.999),[29] excellent test–retest reliability (ICC = 0.95),[38] and validity correlating to the 6-min walking test ($p = 0.04$).[39] Aerobic capacity is the measure of the body's ability to use oxygen from the atmosphere and produce

energy for muscle cells.[16] For this test, participants were instructed to stand perpendicular to the wall and march in one place as many times as they could in 2 min, whereby the higher number of repetitions indicates greater aerobic capacity (higher scores are better). The number of knee lifts performed on the right leg in 2 min was recorded. An MCID has not been determined for this test.

Participant feedback. Participants who completed the exercise program provided quantitative feedback about the telehealth-supervised exercise program via a face-validated questionnaire used by Galloway and colleagues in stroke,[14] with minor modifications made to better reflect our study design and participants. The questionnaire was sent electronically to participants post-intervention, and data were generated using Qualtrics XM® software (Provo, UT, USA), presented as the number and percentage of respondents. Participants also provided qualitative feedback during a 15-minute semi-structured interview (Figure 1), conducted and audio-recorded on Zoom, transcribed using Otter.ai transcription software (Mountain View, CA), and analysed using NVivo software (QSR International Pty Ltd, VIC, AUS). A six-phase reflexive thematic methodology was used to analyse themes.[40] Key quotations from the transcripts were selected to illustrate themes and de-identified by an alphanumeric code that represents their disease duration (i.e. F12), consistent with the reporting of quantitative data.

Attendance

Attendance to the exercise intervention was calculated by taking the number of attended sessions as a percentage of the total number of scheduled sessions.[41]

Statistical analysis

The sample size was calculated using SF36 fatigue/energy domain results from Tench (2003)[27] who explored the effect of exercise on fatigue; considering an effect size (Cohen's d) of 2.18, alpha level of 0.05, and a power of 90%, a minimum of 6 participants per group (total of 12 participants) was required. Missing data were imputed using the last measure carried forward method. Descriptive (mean, standard deviation, median, and interquartile ranges) and statistical analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA). Shapiro–Wilks test was used to examine distribution of data. End of intervention measures are reported as change scores from baseline. Comparisons between groups were performed using a two-sample t-test for normally distributed data and a Mann–Whitney U test for non-normally distributed data. Alpha (α) level of 0.05 was pre-determined as the arbiter of statistical significance ($p \leq 0.05$) for inferential tests. Where known, we used MCID or MCII, or assumed a change of 10% (mean change/baseline ×100),[42] to determine clinically meaningful change within groups.

Results

Participant characteristics

Fifteen adults with SLE expressed interest in the study and were all eligible (control group $n = 7$, exercise group $n = 8$); one participant in the exercise group withdrew due to other health complications. All control group participants engaged in regular exercise (e.g. walking, resistance, and yoga), $n = 4/7$ had fibromyalgia overlap, medications included $n = 5/7$ hydroxychloroquine, $n = 3/7$ immunosuppressants, and $n = 1/7$ corticosteroids. Most ($n = 5/7$) exercise group participants engaged in regular exercise (e.g. walking, running, and stationary cycling), $n = 4/7$ had fibromyalgia overlap, medications included $n = 6/8$ hydroxychloroquine, $n = 4/8$ immunosuppressants, and $n = 3/8$ corticosteroids. There were no reported changes to their prescribed medication upon completion of the exercise program. No participants were on biologic therapies. All participants had joint ($n = 15/15$), skin ($n = 11/15$), and/or renal involvement ($n = 8/15$). The four most common symptoms reported were fatigue ($n = 14/15$), joint pain ($n = 12/15$), muscle aches ($n = 10/15$), and brain fog ($n = 12/15$) (Table 1).

Quantitative results

Pain and fatigue (11-point scale). There was no statistically significant difference between the exercise and control group for resting pain ($p = 0.633$). There was a statistically significant difference in resting fatigue ($p = 0.012$) between the exercise (mean change −0.8 ± 1.5) and control group (mean change +1.4, ±1.4), favouring the exercise intervention. There was a clinically meaningful improvement in resting pain (−32%) over time within the exercise group (mean change −0.6 ± 0.7). There was no clinically meaningful improvement in resting pain over time for the control group and resting fatigue over time within both groups (Table 2).

Fatigue (FACIT-F). There was no statistically significant difference between the exercise and control group ($p = 0.128$). There was a clinically meaningful improvement in fatigue over time within the exercise group (mean change +6.3 ± 8.5). However, the median change (+4 ± 12.3) did not meet this MCID. There was no clinically meaningful improvement over time within the control group (Table 2).

- *Explain interview process and aim of the interview questions (interview approximately 10-15minutes)*
- *The aim of this interview is to explore your experiences of the 8-week telehealth exercise program.*
- *Re-assure ethics has been approved. Provide ethics number = H21REA052*
- *Ask permission to record. Turn on recording device. Ask participant to verbally confirm consent.*

Part 1: Exercise program

Tell us about your experience with the supervised exercise program? (Exercise program itself)

- What are some aspects of the exercise program that you enjoyed?
- What are some aspects of the exercise program that you did not enjoy?

What benefits did you experience following the exercise program? Tell me about those benefits that you experienced?

- Were there any changes in yourself that you noticed following the exercise program? Have you noticed any changes within yourself? *For example, your ability to walk further or perform daily tasks better?*

Tell us about any challenges you experienced with the exercise program?

- **Were there any specific aspects of the program that you found difficult?**
  For example, holding the band or the weights, performing the lower body exercises. The number of exercises within the session? The number of repetitions you did in a row. The style of the session? The time of the day the session was performed.

Is there anything that we could do to improve the exercise program? Or make it more challenging? i.e., variety, more cardio?

Part 2: Exercise delivery via telehealth

Tell us about your experience with the exercise program delivered online?

- How was your experience with using a live video conferencing platform, **Zoom?**
- How was your experience with the online **supervision** of exercise?
- What are some aspects of telehealth delivered exercise that you liked?
- What are some aspects of telehealth delivered exercise that you did not like?

Tell us about any challenges you experienced with the program delivered online?

How likely would you be to continue with this delivery of exercise?

- Would you be able to tell me a little more about why you would/would not continue with this type of exercise program delivered online?
- How likely would you be to continue with supervised exercise online?
- Is there anything that we could do to improve the delivery of the exercise program?

Figure 1. Post-intervention interview framework.

Table 1. Demographic characteristics and baseline data for the two groups.

	Control group (n = 7)				Exercise group (n = 8)				
Variable	Mean	SD	Median	IQR	Mean	SD	Median	IQR	p-Value
Age (years)	41	11	38	8	48	18	48	30	0.352
Disease duration (years)	7	6	7	9	12	8	11	11	0.222
RHR (beats/min)	65	5	66	8	70	11	68	18	0.312
Rpain (0–10 scale)	3	1	3	2	2	1	2	2	0.304
Rfatigue (0–10 scale)	3	2	3	3	3	2	3	3	0.441
FACIT-F (0–52 scale)	22	9	24	13	26	15	24	24	0.518
FTSTS (seconds)	12	2	13	4	13	4	13	5	0.656
30sSTS (repetitions)	13	3	12	4	13	3	13	4	0.873
30sAC (repetitions)	16	4	15	5	16	5	16	6	0.916
2MST (repetitions)	62	19	65	32	70	17	73	24	0.43

RHR: resting heart rate; Rpain: resting pain; Rfatigue: resting fatigue; FACIT-F: functional assessment of chronic illness therapy (fatigue measurement system); 5TSTS: five-time sit to stand test; 30sSTS: 30 s sit to stand test; 30sAC: 30 s bicep/arm curl test; 2MST: 2 min step test.

Table 2. Comparison of exercise versus control group changes from baseline.

	Control group (n = 7)				Exercise group (n = 8)				
Variable	Mean	SD	Median	IQR	Mean	SD	Median	IQR	p-Value
RHR (beats/min)	6.9	11.7	4	15	−3.8	7.8	−4	7.3	**0.057**
Rpain (0–10 scale)	−0.3	1.8	−1	3	−0.6[a]	0.7	−0.5	1	0.633
Rfatigue (0–10 scale)	1.4	1.4	1	2.5	−0.8	1.5	−0.5	3	0.012[b]
FACIT-F (0–52 scale)	−0.6	7.9	−1	16	6.3[c]	8.3	4	12.3	0.128
5TSTS (seconds)	−1.5	1.8	−2	3	−1	1.7	−1	2.7	0.574
30sSTS (repetitions)	1	2.8	1	5	1.1	3.2	1	2.5	0.937
30sAC (repetitions)	1.7	1.5	2	3	3.8	2.9	3.5	4.5	0.121
2MST (repetitions)	5	8.8	8	15	3	12.5	−2.5	23.3	0.745

RHR: resting heart rate; Rpain: resting pain; Rfatigue: resting fatigue; FACIT-F: functional assessment of chronic illness therapy (fatigue measurement system); 5TSTS: five-time sit to stand test; 30sSTS: 30 second sit to stand test; 30sAC: 30 second bicep/arm curl test; 2MST: 2 minute step test.
[a]Clinically meaningful improvement over time within group (>15% change).
[b]Statistically significant difference between groups ($p < 0.05$).
[c]Clinically meaningful improvement over time within group (MCID >5.9 points).

Quality of life (SF36). There was a statistically significant difference between groups, in favour of the exercise intervention, for the SF36 domain emotional well-being (p = 0.048) only. There were clinically meaningful improvements in physical role functioning (+30%), emotional role functioning (+55%), energy/fatigue (+26%), emotional well-being (+19%), and social functioning (+30%), over time within the exercise group. There were clinically meaningful improvements in physical role functioning (167%) and energy/fatigue (11.6%) over time within the control group (Table 3).

Lower body strength (5TSTS). There was no statistically significant difference between the exercise and control group for lower body strength (p = 0.574). There were no clinically meaningful improvements over time within each group (Table 2).

Lower body endurance (30sSTS). There was no statistically significant difference between the exercise and control group for lower body endurance (p = 0.937). There were no clinically meaningful improvements over time within each group (Table 2).

Upper body endurance (30sAC). There was no statistically significant difference between the exercise and control group for upper body endurance (p = 0.121). There were clinically meaningful improvements over time within the exercise (+23%) and control group (+10.7%) (Table 2).

Aerobic capacity (2MST). There was no statistically significant difference between the exercise and control group for aerobic capacity (p = 0.745). There were no clinically meaningful improvements over time within each group (Table 2).

Participant feedback

Participants either strongly agreed or agreed that Zoom was easy to learn and use after the first few sessions. Participants strongly disagreed that they needed someone at home to help them use the system, strongly agreed they were able to use the system by themselves, and rated the audio and video quality as acceptable either all the time or most of the time. Feasibility of telehealth-supervised exercise was high; participants either strongly agreed or agreed they would use it again, were satisfied with the experience, felt safe, and would recommend telehealth to others with SLE. Over half of the participants strongly disagreed or disagreed that they would have preferred to do the exercise sessions on their own without telehealth supervision, and there were mixed responses about whether they would have preferred to go to a central venue instead. Participants strongly agreed or agreed that the exercise program had enough variety, was challenging enough to improve their strength, and that they had sufficient space to perform the exercises at home. The preferred dose parameters were 2 sessions/week (n = 5/7, 71%), 30–45 min (n = 4/7, 57%) per exercise session, and 8–12 weeks in duration (n = 4/7, 57%) (Table 4).

Attendance

Attendance to the exercise program was high (110/112, 98%), with two sessions missed: one due to general malaise, and the other due to a suspected UTI.

Qualitative results

Interviews

Four common themes emerged (Table 5).

Theme 1. *Ease and efficiency of exercising at home.* Participants reported that not having to commute to a central venue to exercise was convenient; noting that they would have been more likely to cancel various sessions due to bouts of fatigue. Participants also commented on the positives of being in a comfortable and familiar environment which correlated to high adherence and participant satisfaction. Furthermore, participants who may have been feeling unwell or fatigued prior to an exercise session were still able to safely proceed with their allocated session due to the convenience of it being supervised online, at home.

Table 3. SF36 domain score for the two groups before and after 8 weeks of intervention.

	Control group (n = 7)								Exercise group (n = 8)								
	Baseline		Post		Change				Baseline		Post		Change				
SF36 domain	Mean	SD	Mean	SD	Mean	SD	Median	IQR	Mean	SD	Mean	SD	Mean	SD	Median	IQR	p-Value
Physical functioning	65.7	33.2	66.4	30.6	0.7	44.8	5	10	68.1	30.9	67.5	34.7	−0.6	6.8	0	8.75	0.105*
Physical role functioning	10.7	19.7	28.6	41.9	17.9[a]	53.5	0	100	31.3	43.8	40.6	44.2	9.4[a]	29.7	0	18.75	0.862*
Emotional role functioning	61.9	48.8	52.4	50.4	−9.5	49.9	0	33.34	37.6	45.2	58.3	42.7	20.8[a]	35.4	16.5	58.34	0.193
Energy/ fatigue	25	12.9	27.9	18.9	2.9[a]	19.8	10	40	36.3	25.6	45.6	25.7	9.4[a]	17.2	10	22.5	0.506
Emotional well-being	60.6	18.7	59.4	20.6	−5.7	14.9	−8	16	57	15.8	68	14.8	11[a]	14.6	10	27	0.048[b]
Social functioning	39.3	32.6	41.1	35.9	1.8	26.4	0	50	42.2	24.9	54.7	32	12.5[a]	23.1	6.25	21.88	0.418
Pain	51.8	33	51.1	18.3	−0.7	23.8	−10	35	64.4	24.4	60.9	22	−3.4	18.4	−6.25	36.88	0.806
General health	35.5	15.3	34.1	15.7	−1.4	13.9	−5	22.5	39.8	17.3	42.4	19.4	2.6	17.1	3.75	19.69	0.633

SF36: 36-Item Short Form Health Survey, SD: standard deviation.
*Mann–Whitney U test used for non-normally distributed data.
[a]Clinically meaningful improvement overtime within group (>10% change).
[b]Statistically significant improvement between groups (p < 0.05).

Table 4. Quantitative feedback following the telehealth-supervised exercise program (n = 7).

Question	Response	*n*, Percentage
Quality of telehealth delivery		
The video quality was acceptable	All of the time	4/7, 57%
	Most of the time	3/7, 43%
The audio quality was acceptable	All of the time	3/7, 43%
	Most of the time	4/7, 57%
Usability of telehealth delivery		
Zoom was easy to learn	Strongly agree	4/7, (57%)
	Agree	3/7, (43%)
After the first few sessions, Zoom was easy to use	Strongly agree	4/7, (57%)
	Agree	3/7, (43%)
I was able to use Zoom on my own.	Strongly agree	7/7, (100%)
I needed someone at home to help me use Zoom.	Strongly disagree	7/7, (100%)
Exercise program satisfaction		
I found the exercises difficult to perform due to my physical ability	Strongly disagree	4/7, (57%)
	Disagree	2/7, (29%)
	Agree	1/7, (14%)
The exercise program was challenging enough to improve my strength	Strongly agree	4/7, (57%)
	Agree	2/7, (29%)
	Agree nor disagree	1/7, (14%)
The exercise program had enough variety	Strongly agree	4/7, (57%)
	Agree	3/7, (43%)
I felt safe doing the exercises	Strongly agree	6/7, (86%)
	Agree	1/7, (14%)
I had enough equipment at home to do the exercises	Strongly agree	7/7, (100%)
I had enough space at home to perform the prescribed exercise program and see the instructor at the same time	Strong agree	6/7, (86%)
	Agree	1/7, (14%)
I would have preferred to do the exercises by myself without being supervised by telehealth	Strongly disagree	2/7, (29%)
	Disagree	3/7, (43%)
	Neither agree nor disagree	2/7, (29%)
Exercise preferences (frequency, time, and duration)		
Preferred length of time for a telehealth-supervised exercise session	30–45 min	4/7, (57%)
	45+ min	3/7, (43%)
Preferred number of telehealth-supervised sessions per week	1 session/week	1/7, (14%)
	2 session/week	5/7, (71%)
	3 sessions/week	1/7, (14%)
Preferred length of time for a telehealth-supervised exercise program	6–8 weeks	1/7, (14%)
	8–12 weeks	4/7, (57%)
	12+ weeks	2/7, (29%)
Satisfaction with telehealth delivery of exercise		
If I had transport, I would have preferred going to a central venue for the sessions (e.g. clinic, community centre, and gym) instead of doing them at home via telehealth	Agree nor disagree	4/7, (57%)
	Strongly agree	1/7, (14%)
	Agreed	1/7, (14%)
	Strongly disagree	1/7, (14%)
Overall, I was satisfied with the telehealth experience	Strongly agree	6/7, (86%)
	Agree	1/7, (14%)
I would recommend telehealth exercise to others who have SLE	Strongly agree	6/7, (86%)
	Agree	1/7, (14%)
I would use telehealth exercise sessions again	Strongly agree	5/7, (71%)
	Agree	2/7, (29%)

Additional information: Note that only the responses that were selected by participants are included in this table for brevity.

Table 5. Qualitative feedback following the telehealth-supervised exercise program (n = 7).

Theme: Ease and efficiency of exercise at home	
Participant	*Quote*
8A	'Not having to commute or travel anywhere, that can take a lot of energy out of me personally, and I'm sure other people with lupus as well. I think that's a massive positive for telehealth exercise intervention'
17D	'When you've got something like lupus in particular and if you're immunosuppressed, because I'm on steroids and other people are on those chemo tablets, you don't really want to be getting public transport into gyms and mingling with lots of people'
17D	'I had quite a few times where I was really ill and if it was in a different venue other than home, it would have not been happening'
10F	'Usually, I have to cancel a lot, or I'm too tired, but because I had more energy, I was more alert or felt more awake and I felt like I was able to have a better time with friends'
8A	'I found the intervention really flexible. So, I think it was really good they were able to accommodate to my preferences and my needs in terms of my scheduling'
29C	'I think being able to be at home and not having to travel especially with COVID and that kind of thing, knowing you have to get onto public transport just adds that stressful bit right at the beginning'
3E	'The convenience of it, I suppose, and particularly in light of COVID and getting out and about while having something like lupus, one tends to want to avoid that exposure as much as possible, so that was a big plus'
Theme: Value of live instruction	
Participant	*Quote*
10F	'I feel a lot more safe and secure in what I'm doing, I'm not doubting if it's wrong because I'm being watched'
	'Having the exercises two times a week was really helpful, it kind of carries you through'
8A	'I found the instructors really good, knew what they were doing and knew how to instruct the exercises and do it in a safe way'
	'Regular sessions pushed me to attend each week'
12B	'Knowing somebody was going to ask you made you think about your day and how you could fit more exercise into your day'
12G	'Having the girls ask me twice a week, what have I been doing, made me motivated to actually do things and not just have lazy days all the time'
17D	'I enjoyed that the sessions were supervised and therefore you had personal encouragement'
3E	'I was very impressed with the way in which it was executed. The instructors understanding of my particular situation and how they took that into account'
Theme: Challenges of exercising at home	
Participant	*Quote*
8A	'You're limited with some of the exercises that you can do purely based on what equipment is available'
	'More variety in the program would be nice'
	'I think just to have a bit more exposure to different equipment, also potentially having more weights or resistance applied'
12B	'If we do meet physically, in a different sort of environment, maybe physical contact will actually make me work harder, probably will be more challenging'
	'The weight I have which is the water bottle could be improved a bit'
	'I would prefer the exercises to be even more challenging'
10F	'One thing that I would really like is if you could do a mixture of online and in person'
	'Maybe I could push myself harder'
	'I didn't have proper weights and so it would be nice to have something to hold that's comfortable'
29C	'Probably for somebody like me, making it more challenging as we go along, I would have easily coped with that'
3E	'The only aspect of this delivery is the social contact, not having other people around, that is why I'd like to go to a gym, I feel I really need that social interaction'
12G	'It took me a while to find a space that would work'
Theme: Continuation of telehealth-supervised exercise sessions	
Participant	*Quote*
8A	'It's really easy to do, it's like you can just quickly get changed and be able to do it from home'
12B	'The convenience of time and flexibility'
29C	'I think I would probably prefer it versus going to the gym especially with COVID still being the situation it is'
12G	'I'd like to do it again. It's easy for me to do because it's at home'
10F	'I would be very likely to continue, I asked the instructor if there was any way I could continue'

Theme 2. *Value of live instruction.* Participants reported feeling safe and confident performing the exercises while being supervised online by knowledgeable practitioners. Participants found the practitioners' communication was clear and encouraging throughout the program. High levels of enjoyment experienced by participants were strongly influenced by the accountability and motivation provided by the individually supervised sessions.

Theme 3. *Challenges of exercising at home*. Participants reported some challenges to exercising at home: lack of physical space in their home and limitations to exercise variability due to lack of equipment. Participants also commented that their personally owned hand weights that they used for the exercise program were either difficult to hold comfortably, or were inadequate in providing enough resistance, emphasising the limitation of exercise equipment.

Theme 4. *Continuation of telehealth-supervised exercise sessions.* Participants reported that they would continue with this exercise delivery mode due to its ease and efficiency. Participants were satisfied with the convenience and flexibility of being able to exercise from home. There were participants who would prefer supervised telehealth exercise over a face-to-face session.

Discussion

Our main qualitative and quantitative findings suggest that an individually telehealth-supervised exercise program was suitable to and well-accepted by adults with SLE. However, due to a limited number of participants and the possibility that they were more likely to be motivated to exercise and/or have more stable disease, results could exaggerate the true efficacy of the exercise program itself. Recruiting SLE participants was difficult because COVID-19 was of particular concern in Australia during the time of the study, and people with SLE may have been apprehensive about engaging in an exercise trial during this time. It is unclear why there was a lack of male recruitment; however, this is likely because more women have SLE.[43] Home-based exercise has gathered popularity among practitioners in the past few years due to the COVID-19 pandemic, where this was the only form of exercise delivery, at times. Rapid advancements in mobile technologies have allowed for improvements in intervention delivery and supervision.[44] Furthermore, face-to-face exercise interventions have shown positive effects on outcomes such as fatigue and QOL in SLE,[24,27,45] and so, when face-to-face exercise supervision is not an option, it is important that there are feasible alternatives. A decrease in PA and increase in sedentary behaviour during respective lockdowns in response to the COVID-19 pandemic were seen across several populations,[46] another potential reason for difficulty in recruitment (i.e. less motivation to engage in exercise). Our study, therefore, highlights the potential beneficial effect of telehealth-supervised exercise on outcomes such as fatigue, QOL, and strength in people with SLE. Fatigue is particularly problematic for people with SLE,[3] with most participants in our study reporting fatigue as a symptom. FACIT-F[47] was chosen in addition to the SF36 fatigue/energy domain[21] because FACIT-F is more sensitive to detecting changes in fatigue for people with chronic disease.[19] Promisingly, both fatigue questionnaires showed a clinically meaningful improvement over time within the exercise group.

To our knowledge, this is the first study to explore telehealth-supervised exercise in SLE using a live video platform. A similar study using a live video to supervise people who have suffered a stroke found high levels of satisfaction with the delivery mode and a high likelihood of participants partaking in supervised telehealth sessions again,[14] the same result shown in our study. An important theme that emerged from our qualitative assessment was the value of live instruction, enabling safe guidance of exercise and the opportunity for the patient and practitioner to build a rapport. Gherman et al.[48] indicated that patients who had a good and regular bond with healthcare workers were better at following advice and contributing to their treatment. Another study reveals a strong correlation between higher levels of PA in adults with rheumatoid arthritis when there is live exercise instruction,[49] which is consistent with our high adherence rate (98%, 110/112 sessions). Furthermore, Wilcox et al.[49] also highlight the importance of having an instructor who is knowledgeable in the patients' disease as this is likely to further encourage exercise participation.

An important theme that emerged in our study was the ease and efficiency of exercising at home, with most participants valuing the convenience of not commuting to a centre-based venue. Galloway et al.[14] indicated that participants favoured the convenience of telehealth as it decreased the burden of transport, a commonly reported barrier for exercise participation in clinical populations. Another study revealed that people with SLE found exercising at home a more comfortable experience.[50] In our study, we identified a beneficial effect of the exercise program on emotional well-being – it is unclear whether this result can be attributed to the exercise itself, or perhaps because participants received personalised care, attention, and investment from a practitioner during a pandemic lockdown. Regardless of the mechanism of this effect, we suggest that supervised home exercise delivered by telehealth offers holistic benefits for people with a rare disease.

Limitations of this study include low sample size, limiting the statistical credibility of quantitative and qualitative findings; limited number of validated assessments via telehealth, including the SLE disease activity index (SLEDAI) to measure the change in disease activity; non-randomised methodology; inherent lack of blinding; and short duration

of exercise, limiting the potential for physiological adaptions.

In this small, exploratory mixed-methods pilot study, we identified that individually supervised telehealth exercise was acceptable, feasible, and satisfying for adults with SLE during a pandemic lockdown. The intervention demonstrated a trend to improvement in perceived QOL, fatigue, and strength outcomes. Although we used data from a previous study to estimate the sample required, our study is underpowered. The effect sizes obtained are modest, and the results, although encouraging, need to be corroborated in a larger, confirmatory investigation, ideally undertaken without the confounding influence of a pandemic and lockdown so that there may be controlled comparison with face-to-face supervised exercise. We recommend that future telehealth-supervised studies include more SLE participants, longer exercise intervention duration, and adopt a randomised and longitudinal study design to measure long-term outcomes.

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Author contributions

All authors were involved in drafting or revising this study critically for important intellectual content, and all authors approved the final version to submitted for publication. SF had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: • Conduct of interviews, questionnaires, and exercise tests: Samantha Walsh. • Transcriptions of interviews: Stephanie Frade. • Coding questionnaires: Stephanie Frade.

Analysis and interpretation of data: • Quantitative data: Stephanie Frade, Samantha Walsh, and Melainie Cameron. • Qualitative data: Stephanie Frade, Chloe Campbell, and Melainie Cameron.

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CHAPTER 6: DISCUSSION AND CONCLUSION

6.1. Overview of the chapter

The purpose of this chapter is to interpret and discuss the significance of these thesis findings considering the wider evidence-base, and to synthesis the current literature, patient experiences, feasibility, and preference for telehealth in people with SLE and SSc. First, a summary of key research findings is presented, followed by implications and recommendations for future research and clinical practice. Thereafter, the strengths and limitations of the research are discussed, followed by an overall conclusion of the research.

6.2. Summary of aims and key research findings

The primary aim of this research was to better understand the safety, effectiveness, and experience of exercise in adults with SLE and SSc. To meet this aim, this research included five individual research studies. The first study comprised a systematic review of randomised controlled trials (RCTs) of exercise in systemic lupus erythematosus to synthesise the most up-to-date highest-quality evidence (Burns, Rohrich, & Chung, 2011). Originally, this systematic review was planned as an adjoined systematic review of exercise in both SLE and SSc, however, following careful consideration, and advice provided by the Cochrane collaboration, we developed two distinct systematic review protocols, including one titled: *exercise as adjunctive therapy in systemic lupus erythematosus.* This review specifically focused on exercise as an adjunctive therapy because most people with SLE are prescribed pharmaceutical drugs to manage their disease and are therefore undergoing usual care (Fanouriakis et al., 2019). The purpose of this review was to further improve the understanding about exercise safety and effectiveness in SLE and include any new RCTs following previously published systemic reviews (Lu & Koo, 2021; O'Dwyer et al., 2017; Wu et al., 2017). During the process of conducting this systematic review, another systematic review in exercise for SLE was published, however, this review only assessed the effectiveness of exercise on health-related quality of life (Lu & Koo, 2021).

For our systematic review, a total of 13 RCTs (540 adults with SLE) were included. We are uncertain of the effectiveness of exercise on fatigue, disease activity, quality

of life, and functional capacity, and pain because of a high risk of bias, small number of participants, and heterogenous measurement tools. This review highlighted gaps in the literature, including a lack of rigorous and good quality designed studies of exercise in SLE, a lack of homogeneity in measurement tools used to assess important outcomes relating to SLE, and limited reporting of exercise components (e.g., dosage of exercise).

The second systematic review is titled: *Exercise and physical therapy in systemic sclerosis*. The aim of this review was to capture the highest quality evidence in all physical therapies, including exercise, in SSc. To our knowledge, this is the first review that has combined both physical therapy and exercise. The protocol for this review has been developed, in collaboration with the co-authors, and is published in the Cochrane Database of Systematic Reviews. Screening articles for inclusion is currently underway, and this project is likely to continue following the period of candidature.

To further explore the safety and effectiveness of exercise in SLE and SSc, study 3, titled: *rheumatology practitioners' perspectives and use of exercise in systemic sclerosis or systemic lupus erythematous*, was conducted. This study was originally planned to be conducted in-person at the Australian rheumatology association conference in 2020, however, due to COVID-19 lockdown restrictions, this study was amended to be completed online via zoom. In total, 12 rheumatologists and 5 rheumatology nurses were interviewed and included in the study. Overall, rheumatology practitioners and nurses highly value exercise for people with SSc and SLE, with many perceived benefits, some specific barriers for exercise engagement, and limited safety concerns specific to their disease. They also expressed the idea of interviewing people living with SSc or SLE to hear their personal experiences with exercise, to gain a further understanding about potential barriers and facilitators to exercise. Rheumatology practitioners and nurses offer recommendations to facilitate safe exercise for people with SLE and SSc, expressing the need for exercise professionals to provide rheumatology practitioners with information and options for their patients to engage in long-term and affordable exercise. Rheumatology practitioners also emphasize the importance of exercise being supervised and

individually tailored. See table 6.1 for a summary of themes extracted from individual interviews.

Table 6.1 Summary of themes extracted from individual interviews (study 3)

Theme	Summary
Benefits of exercise	• Feeling better about themselves generally. • Improvements in energy, bone density, metabolism, sleep, muscular strength, cardiovascular health, joint range of motion, exercise tolerance, activities of daily living, blood flow, breathing, weight loss. • Reduced feelings of depression and anxiety. • Helping to cope with their illness, a sense of empowerment, encourage social wellbeing.
Barriers to exercise	General barriers • Conflicting commitments in life, lack of motivation, cultural restrictions, reduce exercise capacity, time of year or day (i.e., too cold) Structural • Cost • limited sustainable and long-term options to engage in exercise readily Disease-related • pain, fear of disease worsening, fatigue, physical deformities such as finger ulcerations or skin tightening, general malaise, breathlessness, muscle weakness. • Overwhelmed due to diagnosis and coping with new illness
Confidence in exercise advice but lack time and confidence in exercise prescription	• Confident in providing general exercise advice (goal setting, light intensity exercise such as walking and balance) • Time is a barrier • Lack of expertise and knowledge in exercise prescription • Main role is to identify those who are not exercising and offer advice accordingly • Exercise is often not prioritised because they need to focus on disease management • Hard to discuss when there is significant disease manifestations • Hospital-based practitioners usually refer to in-house physiotherapists, and private practitioners usually refer to external exercise physiologists. • Would value more exercise information and referral guidance

Concerns for exercise	• Overall exercise was not viewed as problematic • Individualisation and supervision is important because of the heterogeneity of the diseases • High-impact exercise may be of concern for people with aches and pains • Guidance is important so that people feel safe • Sunlight exposure • Cold environments • Severe disease manifestation: Pulmonary hypertension, pulmonary fibrosis, interstitial lung disease, skin and joint contractures, ulcerations • Poor proprioception due and risk of falls
Facilitators to exercise	• Sustainable, long-term exercise • Exercise is treatment • Support from medical and allied health care team • Supervision was highly emphasized • A group of allied health practitioners who are versed in SSc and SLE • For those with Raynaud's phenomenon, choose exercise on warmer times of the day • For those with SLE, choose exercise where UV light is low when exercising outdoors • Pacing, rest when needed, manageable exercise

Study 4, titled: *barriers and facilitators to exercise for people with systemic sclerosis: A qualitative study,* originally planned to be conducted in-person at a hired venue in Sydney, though amended to be conducted online using Zoom, instead. Furthermore, only one focus group was originally considered, however, saturation of themes was not reached with one focus group alone, and purposive sampling suggested a wider range of disease durations, types, and symptoms to be included in the sample. More participants were recruited, and an additional two focus groups were conducted. In total, 23 participants with SSc were included in the study. Overall, adults with SSc perceive exercise to be effective in improving their mental wellbeing and physical mobility, however, also express disease-related and general barries to engaging in exercise. SSc participants suggested ways to facilitate their engagement and comfort to exercise (e.g., support and guidance from their health care team, accountability, temperate environments, modifications to exercise). These findings have improved our understanding about the barriers people with SSc face to exercise, and ways to facilitate a person-centred approach to exercise that ultimately improves exercise adherence and comfort. Further exploratory studies of

people with SSc, worldwide, could be conducted to capture a wider perspective of experiences. See table 6.2 for a summary of themes extracted from the focus groups.

Table 6.2 Summary of themes extracted from focus groups (study 4)

Theme	Summary
Barriers to exercise	Disease-related barriers • Cold weather, particularly Raynaud's phenomena • Difficulty gripping exercise equipment due to finger ulcerations, hand contractures, lack of grip strength. • Breathing difficulty especially walking up hills or climbing stairs. • Fatigue • Swelling and tightening causing movement restrictions General barriers • Laziness and lack of motivation • COVID-19 lockdown restrictions making it difficult to resume their regular exercise, and fear of the virus.
Perceived change in personal exercise capacity post-diagnosis	• Unable to play sport because joints are no longer "any good" • Unable to walk for as long and far • Slowed down with gardening due to lack of strength • Unable to swim anymore because of Raynaud phenomenon and/or ulcerations. • Difficult climbing stairs and walking up inclines because of breathing difficulties • Change in strength and subsequent feelings of "hopelessness"
Beneficial effects of exercise	• Improved mental wellbeing • Improvements in lung capacity and breathing • Improvements in energy and vitality • Reductions in overall pain and stiffness, and improvements in mobility. • Improvements in social wellbeing
Preference for modified supervised exercise.	• Accountability to exercise (e.g., Exercise professional coming to their home, exercising with a friend) • Suitable modifications to exercise to meet their physical abilities (e.g., Sitting instead of standing) • Exercise videos that are suitable and can be performed independently from home (| chair yoga) • Suitable clothing and equipment (e.g., warm clothing, gloves, socks, weighted wrist straps) • More guidance and information from their health care team about where to access exercise.

The next study titled: *Telehealth-supervised exercise in systemic lupus erythematosus: A pilot study*, was conducted online using Zoom. This study was an amended study of an originally planned face-to-face exercise intervention (appendix 7.4). The original study design was a two-group comparison of aerobic exercise and resistance exercise. This was a double blinded study, where both the participants and assessor were blinded to the intent of the study and the exercise group they were allocated. The exercise interventions were prescribed according to the ACSM guidelines, at moderate intensity (3 to 4 out of 10 on the modified Borg rating of perceived exertion (RPE) scale), and individually supervised and tailored to the participants RPE. This study was subsequently developed following the findings derived from study 1 and study 3 of this thesis. However, due to the COVID-19 pandemic and uncertainty of when lockdown restrictions would ease in the community, we were unable to conduct this originally planned study.

The amended and conducted study (study 5) was a single group, individually supervised, telehealth exercise intervention study. The single group study design was originally developed because to our knowledge, this was the first telehealth-supervised exercise intervention study in SLE, and thus we wanted to explore the feasibility of its implementation. Following feedback from peer reviewers, a control group was included in the study, and therefore the design became a non-randomised trial of telehealth-supervised exercise in SLE and conducted asynchronously at two different time points (intervention group was conducted in 2021 and control group was conducted in 2022). This study accounts for findings derived from study 1 and 3, with the implementation of individual supervision, a graded exercise program over the 8-weeks, and supervision by an exercise physiologist.

At present, there is paucity of exercise intervention studies in adults with SLE, with this study being the first telehealth-supervised exercise intervention in SLE. This study adds to the limited literature base on exercise in SLE, with the novel findings showing a trend to improvement in participants' self-reported fatigue, pain, and quality of life including emotional wellbeing following 8-weeks of telehealth-supervised exercise (50mins, 2 times/week). Our study findings also suggest that telehealth-supervised exercise is a suitable delivery mode that is feasible for adults with SLE, with survey and interview findings suggesting that participants would

engage in this delivery mode again. Importantly, participants also explained that they "felt safe" performing the exercises because they were being supervised in real-time by experience trainers. See table 6.3 for a summary of themes extracted from individual interviews post-intervention.

Through a telehealth-exercise intervention, we were able to engage adults with SLE in supervised exercise during a pandemic, where, for some time, attending an exercise clinic or gym was not possible in Sydney, Australia, because of lockdown restrictions. The COVID-19 pandemic created an environment that promoted reduced amounts of habitual physical activity because of self-isolation and quarantine requirements, reduced opportunities to remain physically active (i.e., attend a gym or regular dance class), and there was fear of being infected, particularly for those with an underlying health conditions such as SLE (A. J. Pinto, Dunstan, Owen, Bonfá, & Gualano, 2020).

As such, this is a novel approach to encourage adults with SLE to exercise, with our findings indicating that it is acceptable, feasible, and satisfying for adults with SLE. However, this study is underpowered, and the results need to be corroborated in a larger, confirmatory investigation, ideally undertaken without the confounding influence of a lockdown so that there may be controlled comparison with face-to-face supervised exercise. We recommend that future telehealth-supervised studies include more SLE participants from around the world, longer exercise intervention duration, greater variety in exercises and equipment, and adopt a longitudinal study design to measure long-term outcomes.

Table 6.3 Summary of themes extracted from individual interviews (study 5)

Theme	Summary
Ease and efficiency of exercising at home	• Not having to commute or travel anywhere • Being immunocompromised, you don't want to be getting public transport into gyms and mingling. • Still able to exercise even when feeling unwell • Less cancelation • Convenience
Value of live instruction	• Felt safe and secure because you are being watched • Two times per week kept you accountable • Good instructors that were accommodating and understanding

	• Having instructors ask you what you have done over the week keep you accountable • Enjoyed the supervision
Challenges of exercising at home	• Limited with equipment variability • Less variety • Potential for face to face to work you harder • Exercises could be more challenging • Missing social interaction • Difficulty with space in the house
Continuation of supervised telehealth sessions	• Efficient to do from home • Convenience of time and flexibility • Preferred over going to a gym, especially with COVID • Likely to do it again • Keen for seeking ways to continue

6.3. Interpretation of findings

The key findings have already been discussed within each manuscript above in section 6.2, however, it is important to provide further insight into novel findings of this thesis in the context of current literature.

Firstly, consistent with previously published systematic reviews in the effectiveness of exercise in SLE (O'Dwyer et al., 2017; Wu et al., 2017), the current research highlighted the potential benefits of exercise in improving outcomes such as fatigue, functional capacity, and pain, however, the quality of evidence was either low or very low. Our research findings for safety of exercise, based on changes in disease activity, is similar to other findings (O'Dwyer et al., 2017); whereby disease activity did not worsen in people with low to moderate SLE disease activity. Overall, meta-analysis of outcomes, including fatigue, functional capacity, quality of life, and disease activity, have low quality of evidence due to a high risk of bias and imprecision; including a lack of blinding of assessors and participants, and a small number of participants included in the studies. Furthermore, there is a lack of homogeneity in outcome measurement tools used to assess key outcomes. It is important to know that within individual trials of exercise, exercise has proven effective on key outcomes (Abrahão et al., 2016; Clarke-Jenssen et al., 2005; dos Reis-Neto et al., 2013; Gavilán-Carrera et al., 2022), emphasising the need for

studies on exercise in SLE to use consistent outcome tools to measure key outcomes such as fatigue, functional capacity, disease activity, and quality of life. Furthermore, we are unable to apply the results to all people with SLE because most of the studies included participants with relatively low disease activity (<4 on SLEDAI). Our current research has highlighted the need for more studies on exercise in SLE, using standardised outcomes to measure key outcomes, are conducted to improve our confidence in these results. The magnitude of the estimated effects may change with larger and more studies.

Prior to commencing the qualitative study to explore rheumatology practitioners and nurses' view of exercise (Study 3), it was unclear what practitioners thought about exercise for their patients with SSc or SLE, and whether they had concerns about the safety and effectiveness of exercise. To my knowledge, this was the first study to explore rheumatology practitioners' perspectives and use of exercise in SLE and SSc. A similar study was conducted to explore the views of orthopaedic surgeons and rheumatologists on osteoarthritis management (Wallis et al., 2021). One of the themes revealed in the study was that clinicians recognised the importance of nonsurgical management of hip and knee OA, including exercise therapy. Comparably, one of the themes of our study was that practitioners perceived there to be many benefits of exercise and highly valued exercise for their patients with SLE and SSc. Another theme of our study revealed that although practitioners reported a lack of time and expertise in exercise prescription, they often provided some general exercise advice or referral to exercise. These findings align with the findings from Wallis et al., 2021, where several medical professionals also recognised that education can be challenging to deliver effectively due to time constraints (e.g., general practice consultations) and patient language barriers (Wallis et al., 2021). In our study, there were expressions of interest by practitioners to have information about exercise readily available. Exercise and Sports Science Australia (ESSA) have resources available on the exercise right website, www.exerciseright.com.au, specifically on autoimmune disease and exercise, in which rheumatology practitioners could access. However, this information does not provide individualised exercise advice, and therefore highlights the need for exercise professionals to work closely with hospital-based rheumatology departments and rheumatology clinics, to offer individualised exercise for their patients.

Through qualitative exploration of the barriers and facilitators to exercise in people with SSc (study 4), we were able to provide further insight into the emerging views of exercise in people with SSc, during a pandemic. To date, only one other study has explored the experiences of exercise in people with SSc (Henrik Pettersson et al., 2020). Disease-related barriers to exercise, such as shortness of breath, tight skin and stiffness, and digital ulcerations described in Petterson, et al (2019) are also expressed in our study, though digital ulcerations were correlated to pain and social stigmatisation in the former study, whereas our study participants expressed difficulty with gripping exercise equipment more commonly due to finger ulcerations. Another study (Harb et al., 2020) explored the perceived barriers and facilitators to exercise for people with SSc through quantitative exploration and found similar findings to our conclusions. Health and medical barriers were rated as the "most important" to people with SSc regarding being physically active. when thinking about or being physically active. Fatigue was also described as the "most important" barrier to engaging in exercise, followed by Raynaud's phenomenon, joint stiffness and contractures, shortness of breath, difficulty gripping objects, and gastrointestinal problems. Other barriers to exercise included a lack of motivation, difficulty, feeling embarrassed or discouraged due to physical ability and appearance, judgement from others, and a fear of injury or extended recovery time (Harb et al., 2020).

There are few exercise intervention studies in SLE that use mixed method investigation to explore quantitatively measured outcomes (e.g., fatigue), and qualitative experiences of exercise (i.e., how participants felt following an exercise intervention). Based on the current findings presented in our mixed method investigation of telehealth-supervised exercise in adult with SLE, we found a correlation between improvements in quantitively measured fatigue, quality of life, and strength, and the qualitative themes derived from out interviews with participants following the intervention, with reported improvements in their energy levels, strength, and fitness. Similarly, exercise had positive reported outcomes on flexibility, energy, pain, and symptoms for people with SLE following an interview with participants after a yoga exercise intervention (Middleton et al., 2018).

The silver lining of the amendments made to the original exercise intervention study design (Appendix D) was that we were able to explore the feasibility of a novel telehealth-exercise delivery mode, which to my knowledge, has not been explored in adults with SLE. A similar study, published in 2022, was a home-based exercise intervention in juvenile SLE, which involved one live online exercise session and two unsupervised home exercise sessions per week, for 12-weeks (S. M. Sieczkowska et al., 2022). The measurement tools (30-second sit-to-stand, Five-time sit-to-stand, 30-sec arm curls, and 2-minute step test) to assess strength and aerobic capacity following the exercise intervention were selected based on previous validation via telehealth (Holland et al., 2020; Ogawa et al., 2021). To date, only a limited number of published telehealth-supervised exercise studies include the use of real-time video conferencing as their "telehealth option". For example, a review exploring the feasibility of exercise interventions delivered via "telehealth" for people with cancer (Morrison, Paterson, & Toohey, 2020), included studies that used web based or mobile applications, such as text messaging and phone calls as their telehealth intervention. However, no studies included in this review used real-time video conferencing as their exercise intervention. We found one study that used video-conferencing as their telehealth-intervention for people following a stroke, (Galloway et al., 2019) and this helped guide our methodology and post-intervention questionnaire.

In our study findings (study 5), participants expressed the use of telehealth exercise to be convenient, more time efficient, and still allowed them to exercise even on the days they were feeling more fatigued. By being able to exercise at home, without the need to travel, allowed participants to expend their energy on the exercise rather than commuting. These findings are similar to the home-based exercise intervention performed on JSLE, described above, where a home-based exercise training program was suitable and well-accepted by adolescents with JSLE during the COVID-19 pandemic (S. M. Sieczkowska et al., 2022). However, authors also conclude that adherence was not high, and suggest that facilitators and barriers identified in the current study should be explored to improve the quality of new home-based exercise programs implementation, particularly in a future emerging crisis. The barriers that stood out in their study were 1) Patients reporting pain when exercising, and 2) perceiving that they were not doing the exercises the right way and afraid that

exercising incorrectly could worsen usual pain (S. M. Sieczkowska et al., 2022). The benefits to our study design being performed in real-time is that the instructors were able to closely monitor and correct exercise technique. When our study participants were asked about their preferred frequency for this type of exercise delivery, 2 times per week was voted as the most preferred by 5 out of the 7 participants (71%). In fact, this was one of the themes that was derived from our study, that participants felt safe and well guided by the instructors. Participants from our telehealth-intervention study expressed feeling "safe" when performing the exercises as they felt "well guided" by the instructors. Also, participants were individually supervised by trained exercise physiologists who understood SLE, and participants in our study highly valued the trainers, similar to the theme derived from the former study (S. M. Sieczkowska et al., 2022), where participants reported the "trainer to be very good and explained the exercises very well".

6.4. Implications and recommendations for future research and practice

This research has implications for strategies aimed at influencing clinical practice guidelines, such as the inclusion of exercise considerations for people with SSc and SLE. There are, of course, more questions to answer from this research. We have yet to complete the systematic review of exercise interventions and physical therapies for people with SSc, and so we remain uncertain about the possible effects of exercise in this disease. Secondly, we did not interview people with SLE in the same depth as we did those with SSc, and so we do not really know what people with SLE think about exercise, including their specific barriers and facilitators to exercise. Thirdly, we did not conduct a telehealth-supervised exercise intervention on people with SSc, and so we do not know whether people with SSc would also find this type of intervention feasible, effectives, and safe.

There are implications for future research projects, which have been identified following the completion of study 1. Further intervention studies on exercise in SLE are warranted, including more participants with moderate to high disease activity, and a focus on rigorous methodologies (e.g., comparative study design with blinding of assessors and participants to group allocation. No exercise studies in SLE have compared different intensities of exercise, and few studies have compared different types of exercise and therefore there is the need for future development of these types

of research studies.). Longitudinal studies of exercise in SLE that report harms data (adverse events and withdrawals, with reason) followed for long durations (more than 6 months) are needed to improve our understanding of the benefit: risk ratio of long-term exercise adherence. More studies that include functional resistance training are needed, as most of the current intervention studies are predominately aerobic exercise. This would provide further insight into exercise guidelines for people with SLE. The inclusion of homogonous outcomes and measurement tools are needed in exercise intervention studies in SLE for consistency across studies. To provide more information about the "safety" and disease response to exercise, studies of exercise in SLE should report disease activity and serological markers (anti-dsDNA, complement levels C3 and C4, ESR, CRP, and IL-6) before and following the exercise intervention. All exercise intervention studies should clearly report exercise components: type of exercise, frequency of exercise, intensity of exercise, time of exercise session, duration of the exercise intervention, progression of exercise intervention, equipment used, whether the exercise intervention was supervised or not and who it was supervised by, and a breakdown of the exercises included in the program, according to the consensus n exercise reporting template (Slade, Dionne, Underwood, & Buchbinder, 2016).

This research also has implications for clinical practice. Rheumatology practitioners (study 3) and people with SSc (study 4) provided advice on ways to facilitate safe and effective exercise, suggesting that exercise should be structured with an appropriate dose for the individual and progressed using a graded approach. Given the scarcity of evidence on high-intensity exercise in SLE, it is implicated that exercise commences at low to moderate intensity, and progress accordingly and within the individual's limits, with close monitoring of physiological responses to exercise (e.g., heart rate or RPE). Exercise should be individualised and supervised by exercise practitioners (e.g., exercise physiologists) who understand SSc and SLE. There a simple ways to learn about the disease including accessing information from websites such as https://arthritisaustralia, https://www.sclerodermaaustralia.com.au. For adults with SLE, exercise should be performed during times of the day when ultraviolet rays are lower, and this can be monitored using apps such as https://www.sunsmart.com.au/uvalert/. For adults with SSc or SLE who experience Raynaud's phenomenon, exercise should be performed in temperate and comfortable

environments, and avoid times of the day or places when and where it is too cold. For adults with SSc who experience digital ulcerations, it is advised to avoid engaging in water-based exercise where they could be exposed to infections. For adults with SLE or SSc with joint pain or contractures, it is advised to avoid high-impact exercise that may exacerbate their pain. For adults with SSc that experience sclerodactyly (curling of the fingers), it is suggested to use exercise equipment such as ankle or wrist straps as an alternative to handheld weight to still encourage resistance training. It is important that exercise prescribed for someone with SLE or SSc is suited to their individual abilities and advised to pace exercise appropriately.

Participants with SLE provided positive feedback about the telehealth-supervised exercise program (study 5) and selected some preferred dose parameters for the telehealth exercise program; 2 sessions/week, 30-45minutes per exercise session, and program length between 8-12 weeks. This mixed method explorative study was small, however it identified that individually supervised exercise was acceptable, feasible, and satisfying for adults with SLE during a pandemic lockdown. The results need to be corroborated in a larger, confirmatory investigation, ideally undertaken without the confounding influence of a lockdown so that there may be controlled comparison with face-to-face supervised exercise. Future telehealth-supervised studies should include more SLE participants from around the world, longer exercise intervention duration, greater variety in exercises and equipment, and adopt a longitudinal study design to measure long-term outcomes. Importantly, more studies are needed to validate outcome measures online using video conferencing software's to allow for more comprehensive exercise capacity measurement following a telehealth-exercise intervention. Also, the outcome tool SLEDAI, to measure disease activity in SLE, has not yet been validated online. This would be beneficial for future researchers to consider, as telehealth-exercise is becoming increasingly popular in clinical practice and research, especially since COVID-19 pandemic and because people with SLE are often immune compromised.

6.5. Strengths and limitations

The integration of quantitative and qualitative methods to systematically investigate the effectiveness and safety of exercise in SLE and SSc is a key strength of this thesis. Conducting qualitative individual interviews with rheumatology practitioners

who primarily care for people with SLE and SSc provided an insight into how medical professionals view and use exercise with their patients, and new insights into exercise considerations for this population. Conducting qualitative focus group discussions with participants with SSc provided even further insights into the specific barriers and challenges people face with exercise, a deeper understanding about their perceived beneficial effects of exercise, and ideas on ways to facilitate a person-centred approach to exercise. Conducting qualitative individual interviews on participants with SLE post-intervention, in conjunction with quantitative outcome measures, allowed us to understand more about the effectiveness of exercise based on personal experiences and perceived response to the telehealth-supervised exercise program, and whether there was a correlation between personal experience and measured effect. Including interviews and focus groups of health professionals, and people living with the disease/s, allowed for a more comprehensive insight into exercise considerations for this population.

There are some limitations of this thesis and the included studies. For the systematic review *exercise as adjunctive therapy in SLE* (study 1), we only included RCTs. Despite RCTS providing the highest quality of evidence (Burns et al., 2011), it also limits the number of included studies that could have potentially important outcomes. A limitation to the study *rheumatology practitioners' views of exercise in SLE and SSc* (study 3) was that data was drawn from Australian rheumatology practitioners and nurses only, potentially limiting the generalisability of the results. A wider participatory approach, including the views of other medical and allied health professionals who may also consult people with SLE and SSc, (e.g., immunologists, exercise physiologists, physiotherapists) will provide more comprehensive findings of the perspectives of exercise for people with SLE and SSc.

A major limitation to this research project overall was the COVID-19 pandemic, with all three studies (study 3, 4, and 5) included in this thesis, impacted. The first two studies (study 3 and 4), although impacted by COVID-19, only experienced changes to the way data were collected (face-to-face to online), however, did not undergo any modifications to the research question and aims of the study. The exercise intervention study (study 5), however, underwent changes to the study design, research questions, and aims. The original aims of the intervention study

were to compare the effectiveness and experience of aerobic exercise to resistance exercise. Qualitative and quantitative data was to be collected in a gymnasium by two blinded assessors, a rheumatologist and exercise physiologist research assistant. The exercise programs were also to be delivered in a gymnasium by another exercise physiologist research assistant, with participants blinded to the intent of the study. With uncertainty and anticipation about COVID-19 and lockdown restrictions, a decision was made to change the study design and re-commence as an online intervention as soon as possible. This decision was made for several reasons; 1) there were currently five interested participants and we did not want to lose their interest, 2) if restrictions did ease, the participants include in our study are immunosuppressed and raised concern about attending a gymnasium in the current climate, 3) there was uncertainty around COVID-19 and how long the restrictions were going to last, 4) a telehealth-exercise delivery mode was novel and seemed to be the way our exercise physiology profession was moving in the current times, with an opportunity to pilot this mode of delivery for people with SLE; creating an opportunity for further research and practice for this population.

Another limitation to the intervention study (study 5) was a lack of available funding, limiting the applicability of rigorous methodology. In the original intervention study design, a private exercise physiology provided enough funding to hire two research assistants; one who was blinded to the study intent and would perform the baseline and post-intervention assessments, and the other who would run all exercise sessions for the duration of the study, allowing the principal investigator to be blinded from the allocation of participants.

6.6. Conclusions

Exercise is undoubtedly a highly valued intervention by rheumatology practitioners, nurses, and people living with SLE and SSc, with several measured and perceived benefits and barriers to exercise. Overall, exercise is ‘safe’, with no reported adverse effects or worsening of disease activity and is effective in reducing levels of fatigue and depression and improving physical fitness and physical functioning in people with SLE. Furthermore, exercise has the potential to improve aerobic capacity, exercise tolerance, muscular endurance, fatigue, pain, and life satisfaction in people with SSc. This thesis featured a novel exercise intervention study that investigated

the effectiveness and experience of an individually supervised functional resistance and mobility exercise program, conducted real-time on Zoom by exercise physiologists. Key findings from this mixed-method investigation suggest that telehealth-supervised exercise was feasible for, and well-accepted by, adults with SLE, and resulted in some modest health improvements. This intervention, and its findings, has provided an innovative way for people with SLE to conveniently engage in exercise, and improve quality of life and strength, and reduce fatigue. This thesis provides researchers, exercise professionals, rheumatology practitioners and nurses, and people with SLE and SSc, a more comprehensive knowledge base about exercise in SLE and SSc, and opportunity for further research.

CHAPTER 7: INSIDER PERSPECTIVE

7.1. Overview of the chapter

This is a short concluding chapter to provide insight into my personal experience with the research topic and throughout the period of candidature.

7.2. My personal story

My thesis is inspired by my lived experience with systemic lupus erythematosus (SLE or "lupus"), and my mum's life and passing away with systemic sclerosis (scleroderma). My personal story begins in 2007, when I was hospitalized during my preliminary year 11 exams with what they first thought was leukemia, and then later, idiopathic thrombocytopenia. I spent the final year of high school fatigued, counting medication, and attending monthly medical appointments. I then started to experience joint pain in my wrists and fingers, more fatigue, and after further medical appointments and tests, I was diagnosed with SLE in 2008. I thought, "What is this disease?." A few years prior to my diagnosis, my mum had been diagnosed with scleroderma. I remember she felt very scared, isolated, and uncertain about her prognosis. As did I. Mum and I lived with similar, yet different diseases, and for this reason we shared a very special bond and always understood each other.

Living with SLE for over 14 years has had its ups and downs. It has taught me to be kind to myself, resilient, and strong. I was able to complete my higher school certificate, bachelor's degree in Exercise and Sports Science, Master's degree in Exercise Physiology, and now, a research degree and thesis. I also managed to work full-time as an exercise physiologist straight out of university. I was always a big fan of exercise and loved to push my body to its limits, competing in running events and adventure races. In June 2015, after 5 years of university and 2 years working full-time, I decided to travel through South and Central America for 6 months. I spent the first few months backpacking through South America with a best friend, hiking the Inka trail, white water rafting in Peru, visiting remote places in Bolivia, and living with local families. Simultaneously, my partner (now husband) Andrew was cycling mountains in Italy with his friends, and then represented Australia in the 2015 dodgeball world championships. After 2 months of independent travel, Andrew and I continued our adventures together in Central America, with what started off to

be a fun-filled adventure, that very quickly turned into a frightening experience, for both of us, and our family. Every day for me became more exhausting and painful, and although I thought this was a normal response after months of backpacking, I soon realized that I was potentially having a "lupus flare?". Admittedly in denial, I kept pushing through. I was young and full of life. I didn't want "lupus" to stop me. We were in Antigua, Guatemala, when I finally phoned a local doctor - a call that saved my life. I say this literally because we were due to go to Belize islands the next day, with limited reception, and far from the mainland. Instead, Andrew and I were driven to Guatemala City by this same doctor, where I was seen by a rheumatologist specialist. I will never forget the words the rheumatologist said to me that day, "If you were my daughter, I would want you back home in Australia, right away". I was having a severe lupus flare; my kidneys, lungs, skin, and other systems of my body were being attacked. I was immediately admitted to hospital upon my return to Antigua, where I was medicated, well-taken care of, and after a few days of ensuring I was safe enough to travel, flown back home to Australia. My family, filled with relief, met Andrew and I at Sydney airport and took us straight to our local hospital. A kidney biopsy, the very next morning, confirmed that I had lupus nephritis stage 4. It was at this moment where I felt as though my life was turned upside down. From an adventurous holiday of a lifetime to a life I did not recognize. I was house bound, unable to go out into the sun, unable to exercise like I used to, unable to work, and having to say "no" to social activities. I began to focus on calculating my daily medication, monitoring my diet, and finding new ways of reducing my level of stress to keep my disease activity down. I was doing everything I could to get better. After 6 months of recovering and living life a little different to what I was used to, I started teaching at the Australian Catholic University as a sessional tutor, and soon after, as a casual exercise physiologist. Life was becoming normal again… until 2 years later.

Mum started to become very ill around November 2017. I thought that her scleroderma was progressing, and day by day she seemed to be getting worse. Mum spent months in and out of hospital, seeing several doctors, getting multiple tests, and experiencing a roller coaster of emotions. On the 23rd of January 2018, a moment I will never forget, mum was diagnosed with stage 4, grade 3, metastatic breast cancer of an unknown primary cause. Not only was this diagnosis heart breaking, but mum was also left feeling even more isolated knowing that not only did she have

scleroderma, a disease most people have never heard of, she now had a cancer that is “unknown”. The life of my beautiful mum ended on the 15th of February 2018, the hardest day of my life. My mum was my best friend, my biggest cheerleader, and my rock. She was the most bubbly and energetic person that I have ever known, despite being so sick with scleroderma. She lived every day to the fullest, always smiling, offering help to others in need. She showed so much love to those around her. Not only is she my inspiration, but she also left a mark on everyone she touched. It is her strength, passion, and zest for life that inspired me to not only start a PhD, but to finish it. With her, my thesis begins and ends.

7.3. My PhD journey

Like others undergoing a PhD, it’s been a rollercoaster ride and juggling act of commitment, work, and play. Part of the unique journey that I have had in doing so is the recent heart break of losing my mum, managing a chronic disease of my own, and balancing all of this through a pandemic – the infamous COVID-19. This has certainly brought some challenges that have tested my health, patience, and resilience, and taught me to be a better person and researcher.

Firstly, recruitment and interviews for Study 3 of my thesis, were planned to be conducted face-to-face at a rheumatology conference, which was cancelled due to lockdown restrictions. I transitioned this investigation to be online. At the time, performing interviews on zoom was fairly new, but has very quickly become a norm. Study 4 was also affected by lockdown restrictions. I had planned to host a focus group session face-to-face at Club York in Sydney with people with scleroderma. Again, I transitioned this study design to online focus groups, which allowed me to recruit more participants from far-flung regional NSW and other states in Australia. Study 5 was the study impacted most significantly. My original study design was going to be face-to-face, comparing different types of exercise. For this study, I was provided funding from an exercise physiology company; everything was on track and running smoothly. Unfortunately, one week into the study, I had to make the tough decision to cancel this intervention because Sydney went into another lockdown that continued with no certainty of end date. I amended the study design to be online, a novel exercise delivery mode at the time. With major amendments to design, outcomes, and delivery mode, I pushed on and made this study continue,

however, the change of circumstances and study design meant that the exercise physiology company withdrew most of their funding. Returning research funding was a difficult experience at the time and did limit Study 5 somewhat because I had to cap recruitment based upon funding available to pay the exercise physiologists leading the intervention.

The pandemic has significantly impacted my studies; however, the silver lining is that I was able to explore novel ways of interviewing busy clinicians, people with SSc, and delivering a feasible exercise intervention to people with SLE. It has been a challenging, yet rewarding, journey having to go back and forth to change study designs, amend ethics applications, and make tough decisions. Simultaneous to this, I got married, renovated our newly bought apartment, got a new job as a research manager in the rheumatology department at Liverpool hospital, all whilst managing my health and like others, living day-by-day with the uncertainty of the pandemic. This PhD journey, and everything along the way, has taught me to be a more patient, creative, and resilient person and researcher. For this, I am grateful.

7.4. My personal investment in the research topic

This research topic is very close to my heart, and I am aware of the potential influences of my own personal interest and values to the research. For this reason, I designed my research studies to include other researchers who could offer less biased or different perspectives. For the systematic review (Study 1), my principal supervisor, Melainie Cameron, associate supervisors Sean O'Neill and David Greene, and Honours student Elise Nutter, worked collaboratively with me on data extraction, assessment of risk of bias, and meta-analysis. I also had support from two Cochrane managing editors, Renea Johnston and Sheila Cyril, who offered their expertise in data extraction and meta-analysis. For study 4, my principal supervisor, Melainie Cameron, associate supervisor Stephen. P Bird, and another Honours student Chloe Campbell, were involved in the qualitative thematic analysis. Samantha Walsh (research assistant) conducted the quantitative and qualitative assessments on participants in Study 5, ensuring that I, principal investigator, was blinded to baseline and post-intervention testing.

An important skill that I have acquired in this PhD, because of my personal investment in this research topic, is how to dissociate my experience and perspectives from the research. I have also learnt that exercise evidence in SLE and scleroderma is limited, and despite me wanting to find positive results, this wasn't the case in the systematic review because of limited studies and participants, and insufficient study design. I now understand the challenges in funding good quality and large studies and have taken away skills that will enable me to continue to develop as a researcher. I have also grown an appreciation for the challenges that people living with scleroderma and lupus face, more than I had ever realised. And for this reason, I am excited to continue my research journey and help improve the lives of people living with scleroderma and lupus, one study at a time.

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APPENDICES

Appendix A: Study 3

Appendix A-1: Advertisement Flyer

Rheumatology practitioners' and nurses'
understanding, knowledge, and use of exercise for people with

Systemic Sclerosis &
Systemic Lupus Erythematosus

The research team highly values your responses for this Master of Research Project, and for future research opportunities in exercise for this population.

Your involvement will include participation in a **semi-structured** interview that will take approximately **20 minutes of your time.**
This interview will be guided questions around exercise for people with Systemic Sclerosis and Systemic Lupus Erythematosus.

All interviews will be anonymous.
Responses will be collated, analyzed for themes and reported in a journal article that will be submitted for publishing.

If you are interested in participating please contact Stephanie to arrange an online interview at your preferred date and time.

Contact Stephanie Frade:
p: 0412567110
e: u1128449@umail.usq.edu.au

USQ Student Researcher: Stephanie Frade
USQ Research Supervisor: A/Prof Lainie Cameron, Prof David Greene, Dr. Sean O'Neill.

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Appendix A-2: Information sheet

Project Details

Title of Project: Rheumatology practitioners' and nurses' understanding, knowledge, and use of exercise interventions for people with Systemic Sclerosis and Systemic Lupus Erythematosus.

Human Research Ethics Approval Number: H20REA009

Research Team Contact Details

Principal Investigator
Ms Stephanie Frade
Email: stephanie.frade@usq.edu.au
Telephone: +61 0412 567 110

Associate supervisor
Professor Dr David Greene
Email: David.Greene@acu.edu.au
Telephone: +61 0418411433

Principal Supervisor
Associate professor Dr. Melainie Cameron
Email: Lainie.Cameron@usq.edu.au
Telephone: +61 0412 852 956

Associate supervisor:
Dr. Sean O'Neill
Email: Sean.ONeill@health.nsw.gov.au
Telephone : +61 0413 629 272

Description

This project is being undertaken as part of Master of Research Project. The purpose of this project is to explore your understanding, knowledge, and use of exercise interventions for people with Systemic Sclerosis and Systemic Lupus Erythematosus. The research team requests your assistance because you are the prime clinician for people with Systemic Sclerosis or Systemic Lupus Erythematosus and your responses are highly valued for this project.

Participation

- Your involvement will include participation in an interview that will take approximately 20 minutes of your time.
- The interview will take place at a time and venue that is convenient to you and can be either face to face or via teleconference, depending on your availability and preference.
- A semi-structured interview plan will be used to guide each interview. This plan includes guided questions around exercise, and yet remains sufficiently open-ended.
- The interview will be audio recorded and transcribed. If you do not wish to be audio-recorded, please advise the research team and you will be withdrawn from the study.
- Your participation in this project is entirely voluntary. If you do not wish to take part, you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. If you do wish to withdraw from this project, please contact the research team.
- Your decision whether you take part, do not take part, or to take part and then withdraw, will in no way impact your current or future relationship with the University of Southern Queensland or the research team.

Expected Benefits

It is expected that this project may indirectly benefit your patients with Systemic Sclerosis or Systemic Lupus Erythematosus.

Risks

There will be no risks associated with this project.

Privacy and Confidentiality

All comments and responses will be treated confidentially unless required by law.

- Interviews will be audio recorded and transcribed verbatim using voice to text software.
- Full transcripts will be returned to you for memory-checking, allowing a two-week period for review.
- At the memory-checking stage you may make modifications to the transcript of your audio recording or withdraw part or all of the interview from the data set. All modifications and withdrawals will be honoured without prejudice.
- After memory-checking is complete, all transcripts will be de-identified using alphanumeric codes, and these finalized transcripts will form the data set.

Any data collected as a part of this project will be stored securely as per University of Southern Queensland's Research Data Management policy.

Consent to Participate

We would like to ask you to sign a written consent form (enclosed) to confirm your agreement to participate in this project. Please return your signed consent form to a member of the Research Team prior to participating in your interview.

Questions or Further Information about the Project

Please refer to the Research Team Contact Details at the top of the form to have any questions answered or to request further information about this project.

Concerns or Complaints Regarding the Conduct of the Project

If you have any concerns or complaints about the ethical conduct of the project, you may contact the University of Southern Queensland Manager of Research Integrity and Ethics on +61 7 4631 1839 or email researchintegrity@usq.edu.au. The Manager of Research Integrity and Ethics is not connected with the research project and can facilitate a resolution to your concern in an unbiased manner.

Thank you for taking the time to help with this research project. Please keep this sheet for your information.

Appendix A-3: Consent form

Project Details

Title of Project: Rheumatology practitioners' and nurses' understanding, knowledge, and use of exercise interventions for people with Systemic Sclerosis and Systemic Lupus Erythematosus.

Human Research Ethics Approval Number: H20REA009

Research Team Contact Details

Principal Investigator
Ms Stephanie Frade
Email: stephanie.frade@usq.edu.au
Telephone: +61 0412 567 110

Associate supervisor
Professor Dr David Greene
Email: David.Greene@acu.edu.auTelephone: +61 0418411433

Principal Supervisor
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Telephone: +61 0412 852 956

Associate supervisor:
Dr. Sean O'NeillEmail:
Sean.ONeill@health.nsw.gov.au
Telephone : +61 0413 629 272

Statement of Consent

By signing below, you are indicating that you:

- Have read and understood the information document regarding this project. ☐Yes / ☐No
- Have had any questions answered to your satisfaction. ☐Yes / ☐No
- Understand that if you have any additional questions, you can contact the research team. ☐Yes / ☐No
- Understand that the interview will be audio recorded. ☐Yes / ☐No
- Are over 18 years of age. ☐Yes / ☐No
- Understand that any data collected may be used in future research activities [all future research activities OR only those related to this field] ☐Yes / ☐No
- Agree to participate in the project. ☐Yes / ☐No

Participant Name	
Participant Signature	
Date	

Please return this sheet to a Research Team member prior to undertaking the interview.

Appendix A-4: Interview guide

- Explain interview process.
- Give ethics approval number.
- Ask permission to record.
- Turn on recording device.
- Ask participant to verbally confirm consent for recording.
- Thank participant.
- Confirm memory checking process: verbatim transcript, allow 2 weeks to review / change it / withdraw it.
- If no response, you will assume transcript is acceptable for use.

Interview questions

- Tell me about your experiences of working with people with SS and SLE?
- What are your experiences and thoughts about exercise for people with SS and SLE?
- Where do you currently work? *Public Hospital – private hospital - Private practice – Combination – Academic – Not currently practicing (days/week)*
- Would you consider your practice to have a special focus on SLE and SS?
- Do you currently work with an exercise practitioner of any type?
- How confident are you with prescribing exercise?

Positives toward exercise "believers"	Negatives toward exercise "non-believers"
• Could you tell me about a time when you have used exercise with your clients?	• Could you tell me about a time where you have seen issues arising related to exercise in your clients?
• Can you tell me about any changes you have seen in your clients with exercise?	• Can you tell me about any changes you have seen in your clients with exercise?
• What do you think are some of the barriers that may exist to prescribing or promoting exercise to your clients?	• What do you think are some of the barriers that may exist to prescribing or promoting exercise to your clients?
• Could you tell me about any benefits or positive experiences of exercise with your clients?	

Appendix B: Study 4

Appendix B-1: Advertisement flyer

FOCUS GROUP
Talking about....

EXERCISE

Do you have Systemic Sclerosis?

Are you 18+ years old?

Physically active or not, please join!

What is involved?

- 60-minute small group discussion about exercise (6-8 people).
- This event is FREE, and it will be conducted online, via Zoom.
- The focus group discussion will be audio-recorded.
- We can share a virtual tea together as we talk about "exercise".

Outcomes of interest: Personal experience and view of exercise.

Where & When?

- When: A day and time will be booked in once I have interested participants.
- Where: ONLINE via Zoom, in the comfort of your own home :)

The research team highly values your participation in this Doctor of Philosophy research project.

How to join?

If you are interested in participating, please contact Stephanie Frade.

P: 0412567110 e: stephanie.frade@usq.edu.au

Stephanie Frade is an Accredited Exercise Physiologist and PhD candidate.

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Supported by scleroderma nsw Supporting the Scleroderma Community in NSW

Appendix B-2: Information sheet

Project Details

Project title: View of exercise in people with systemic sclerosis

Ethics approval number: H21REA094

Research Team Contact Details:

Principal investigator
Mrs. Stephanie Frade
Email: stephanie.frade@usq.edu.au
Telephone: 0412567110

Principal supervisor
Associate professor Dr. Melainie Cameron
Email: Lainie.Cameron@usq.edu.au

Associate supervisor
Professor Dr. David Greene
Email: David.Greene@acu.edu.au

Associate supervisor:
Associate professor Dr. Sean O'Neill
Email: Sean.ONeill@health.nsw.gov.au

Associate supervisor:
Associate professor Dr. Stephen Bird
Email : Stephen.Bird@usq.edu.au

Description

- This project is being undertaken as part of **Doctor of Philosophy.**
- The purpose of this project is to explore your view and personal experience with exercise.
- You can either be currently engaging in exercise, never engaged in exercise, hate or love exercise. We want to hear it all.
- This focus group will be a **small group discussion** (6-8people with Scleroderma) done **online on Zoom**. You will receive a Zoom link with a day and time that this focus group session will run (pending everyone's availability).
- The focus group will run for approximately **60-minutes**.
- The focus group will be semi-structured, with some prompting questions about your experience with exercise. Some examples of the questions in the focus group will include:
  - Tell us a little bit about the current exercise you are participating in?
  - What are some aspects that you like/ don't like about exercise?
  - What are some benefits that you experience with exercise?
  - What are some barriers or challenges that you experience with exercise?

Participation

- The 60-minute focus group discussion will be **audio-recorded**, transcribed, and used for data analysis. **You will be de-identified.**
- There are **no costs** associated with participating in this research project, nor will you be paid.

- Your participation in this project is **entirely voluntary**. If you do not wish to take part, you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. If you do wish to withdraw from this project or withdraw data collected about you (i.e., you want to remove something you said in the focus group), please contact the research team (contact details at the top of this form). Please do note that you will be de-identified, and your personal information will not be used for data collection.
- Your decision whether you take part, do not take part, or to take part and then withdraw, will in no way impact your current or future relationship with the University of Southern Queensland or Scleroderma NSW.

Expected Benefits

This project will indirectly benefit you and other people with Systemic Sclerosis by improving qualitative evidence on the views of exercise in people with systemic sclerosis. Subsequently, this may improve the development of future exercise interventions for people with systemic sclerosis.

Risks

There may be a risk that the focus group discussion may cause you some distress if any information is said that you are not comfortable with or you are worried that others will be offended by what you say. To minimize this risk, I will advise all participants that your responses will be de-identified during the analysis of this data to ensure confidentiality.

Privacy and Confidentiality

All comments and responses will be treated confidentially unless required by law.

The 60-minute focus group will be audio recorded on Zoom and transcribed using Otter (voice to text software), following your verbal and written consent. The transcription will be de-identified. Only the investigators of this project will have access to the recording and transcription, and it will be safely stored in the University of Southern Queensland OneDrive and CloudStor storage. Once the audio recording has been uploaded into the two storage folders, the audio recording will be removed from my personal mobile device. The results of this study will be likely published in a journal and presented at conferences.

Please be advised that although the research team will take every precaution to maintain the confidentiality of the data, the nature of focus groups prevents the research team from guaranteeing confidentiality. Please respect the privacy of other participants and not repeat what is said during the focus group to others.

Any data collected as a part of this project will be stored securely as per University of Southern Queensland's Research Data Management policy.

Consent to Participate

We would like to ask you to sign the written consent form that has been sent to you to confirm your agreement to participate in this project. Please return your signed consent form via email (scanned or photographed) to Stephanie Frade prior to participating in your focus group.

Questions or Further Information about the Project

Please refer to the Research Team Contact Details at the top of the form to have any questions answered or to request further information about this project.

Concerns or Complaints Regarding the Conduct of the Project

If you have any concerns or complaints about the ethical conduct of the project, you may contact the University of Southern Queensland Manager of Research Integrity and Ethics on +61 7 4631 1839 or email researchintegrity@usq.edu.au. The Manager of Research Integrity and Ethics is not connected with the research project and can facilitate a resolution to your concern in an unbiased manner.

Thank you for taking the time to help with this research project. Please keep this sheet for your information.

Appendix B-3: Consent form

Project Details
Title of Project: Views of exercise in people with Systemic sclerosis. **Human Research Ethics Approval Number:** H21REA094

Research Team Contact Details	
Principal investigator Mrs. Stephanie Frade Email: stephanie. frade@usq.edu.au Telephone: 0412567110	**Associate supervisor** Professor Dr. David Greene Email: David.Greene@acu.edu.au
Principal supervisor Associate professor Dr. Melainie Cameron Email: Lainie.Cameron@usq.edu.au	**Associate supervisor:** Associate professor Dr. Sean O'Neill Email: Sean.ONeill@health.nsw.gov.au
	Associate supervisor: Associate professor Dr. Stephen Bird Email : Stephen.Bird@usq.edu.au

Statement of Consent

By signing below, you are indicating that you:

• Have read and understood the information document regarding this project.	☐Yes / ☐No
• Have had any questions answered to your satisfaction.	☐Yes / ☐ No
• Understand that if you have any additional questions, you can contact the research team.	☐Yes / ☐No
• Understand and consent for the focus group to be audio recorded.	☐Yes / ☐No
• Are over 18 years of age.	☐Yes / ☐No
• Agree to maintain the confidentiality of the information discussed by other participants and researchers during the focus group.	☐Yes / ☐No
• Understand that you may decline or withdraw from this project at any time leading up to the focus group, without prejudice.	☐Yes / ☐No

Participant name:

Participant signature

Date:

Please return this sheet via email to Stephanie Frade prior to the focus group.

Appendix B-4: Participant screening and baseline information

CONTACT INFORMATION	
Full name:	
Contact number:	
Email address:	
How did you hear about this study?	
Regular treating practitioner?	**Specialist:** Name: Role? **General Practitioner:** Name?
INCLUSION CRITERIA	
Diagnosis of Systemic Sclerosis	Yes ☐ No ☐
Age ≥ 18 years	Yes ☐ No ☐
DEMOGRAPHY	
Date of birth (DD/MM/YYYY)	
Sex	Male ☐ Female ☐ Prefer not to say ☐
Age (years)	
What suburb do you live in?	
Are you currently working?	Yes ☐ No ☐ What is your work? How many days per week do you work? What is your level of stress at work? ☐ Very stressful ☐ Moderately stressful ☐ Not stressful at all
Do you have any children?	Yes ☐ No ☐ How many children do you have? What age are your children?
Do you live with anyone else?	Yes ☐ No ☐ Relationship to them?
Systemic Sclerosis INFORMATION	
When were you diagnosed with Systemic Sclerosis? (year)	
What type of Systemic Sclerosis do you have?	☐ Diffuse ☐ Limited ☐ Other
What secondary manifestations do you have from Systemic Sclerosis?	☐ Pulmonary fibrosis ☐ Pulmonary hypertension ☐ Raynaud's phenomenon ☐ Digital ulcerations

	☐ Skin tightness ☐ Joint and tendon contractures ☐ Other:
What symptoms do you CURRENTLY experience from Systemic Sclerosis?	☐ Joint pain ☐ Muscle aches ☐ Fatigue ☐ Brain fog ☐ Raynaud's phenomenon ☐ Other:
Have you been hospitalised in the last 12 months due to a Systemic Sclerosis 'flare'?	Date hospitalised: _____ Time spent in hospital: ____ months and/or ____days
Are you getting any support for Systemic Sclerosis? (e.g. NDIS funding: cleaner/gardener/carer/social worker)	Yes ☐ No ☐ If yes, please list:

MEDICATIONS

Medication (name)	Frequency	Dose (mg)

OTHER MEDICAL CONDITIONS

Cardiac Chest pain: Yes ☐ No ☐ Heart disease: Yes ☐ No ☐ Raised cholesterol: Yes ☐ No ☐ Hypertension: Yes ☐ No ☐ Uncontrolled BP: Yes ☐ No ☐ Pacemaker/Defib: Yes ☐ No ☐ If yes to any above, provide details:	**Muscle/Bone** Arthritis: Yes ☐ No ☐ Painful muscle/joints: Yes ☐ No ☐ Osteoporosis: Yes ☐ No ☐ Previous facture: Yes ☐ No ☐ If yes, where: If yes, when: If yes to any above, provide details:
Neural Seizures, faints, dizziness: Yes ☐ No ☐ Overall bodily pain: Yes ☐ No ☐ Open sore or wound: Yes ☐ No ☐ If yes to any above, provide details:	**Other** Allergies: Yes ☐ No ☐ Asthma: Yes ☐ No ☐ Cancer: Yes ☐ No ☐ Diabetes: Yes ☐ No ☐ Reduced kidney function: Yes ☐ No ☐ Ulcers: Yes ☐ No ☐ Other: Yes ☐ No ☐ If yes to any above, provide details:

CURRENT EXERCISE STATUS	
Current activity level	Meeting 150min/week ☐ 100-150min/week ☐ 50-100min/week ☐ >50min/week ☐ How many days per week do you engage in structured exercise?
What types of activity are completed?	Walking ☐ Swimming ☐ Cycling ☐ Pilates ☐ Yoga ☐ Gym-based strength training ☐ Other: ☐
Are you sleeping well?	How many hours of sleep are you getting each day? _____ Is this sleep broken? Yes ☐ No ☐ Do you feel refreshed when you wake up? Yes ☐ No ☐

Appendix B-5: Focus Group Script

Step 1. Welcome participants.

"Firstly, thank you for agreeing to be part of the focus group and volunteering your time to be here today. I appreciate your willingness to participate". The reason we are having this focus groups is to explore your views and personal experience with exercise. We need your input and want you to share your honest and open thoughts with us".

Step 2. Set ground rules for the focus group.

1. Please ensure you minimise any background noise where you are located. You can set the viewing option to a grid so that you can see everyone. Please mute while others are speaking, and then un-mute when you are ready to speak.
2. "We want you to do the talking". I will be providing some prompting questions to guide the conversation.
2. We would like everyone to participate. I may call on you if I have not heard from you in a while. I may also ask you to let other people speak.
3. There are no right, or wrong answers, every person's experiences and opinions are important. Speak up whether you share the same or differing thoughts. We want to hear a wide range of opinions. However, I will not allow anyone, including myself, to give health advice to anyone in this discussion.
4. We want you to feel comfortable sharing when sensitive issues come up. Please feel free to leave the focus group session at any point during the session if you do not feel comfortable.
5. We will be audio-recording the focus group discussion. We want to capture everything you have to say. We will not be identifying anyone by name in our report. You will remain anonymous.

Step 3. Set the agenda.

"Today's focus group will be 60-minutes in duration. This will involve a discussion about your general thoughts, experiences, and views of exercise. I will be facilitating this discussion with prompting questions".

Step 4. Commence focus group discussion & audio-recording (60-minutes).

1. Ask permission to record.
2. Start audio-recording.
3. Ask permission to record again.
4. Read the questions.

Interview Questions

“Do you all consent to audio-recording this meeting today? I will ask again once I press record if you could please all repeat your response”.

- Would anyone like to share their experiences with exercise?

- Could you tell us some positive experiences that you get from exercise?
  - What aspects of exercise do you enjoy?
  - What exercises have worked for you?
  - What aspects of exercise do you get benefits from?

- Could you tell us about negative experiences that you have had with exercise?
  - What aspects of exercise do you not enjoy?
  - What aspects of exercise have not worked for you?
  - What aspect of exercise do you not get benefits from?

- Could you tell us about any barriers that you have experienced with exercise?
  - What stops you from exercising?
  - What makes it harder to exercise?

- Could you tell us some reasons why you participate in exercise?
  - How was your experience in engaging with exercise?

- Could you tell us about the support you receive from your medical health care team regarding exercise?

- Could you share with the group how exercise makes your feel?

- Could you describe ways that would facilitate your engagement in exercise?

Step 5. Thank participants.

Appendix C: Study 5

Appendix C-1: Advertisement flyer (intervention group)

FREE ONLINE
Exercise intervention

Do you have Systemic Lupus Erythematosus?

Are you 18+ years old?

Currently physically active or not, please join!

What is involved?

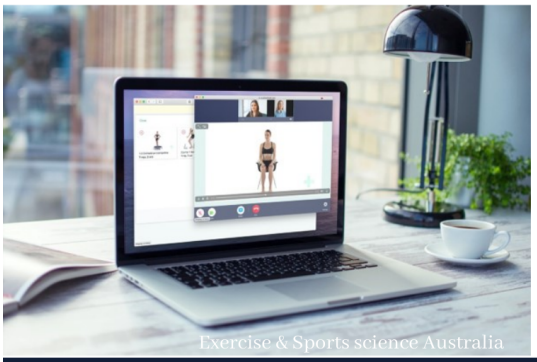
1. Pre-exercise screening phone call (30min)
2. Initial assessment: exercise tests & questionnaires (30min)
3. Individually supervised exercise (45 min, 2 times/week, 8-weeks)
4. Final assessment: exercise tests & questionnaires (30min)

Where?

The comfort of your own home!

Online using Zoom

(online video communication software)



When?

- Initial assessment: Mid-late September 2021
- 8-week intervention: Sep - Oct - Nov 2021
- Final assessment: Mid-late Nov 2021

The research team will contact you to book in session days and times.

How to join?

If you are interested in participating, please contact Stephanie Frade.

Phone: 0412567110 Email: stephanie.frade@usq.edu.au

Stephanie Frade is an Accredited Exercise Physiologist and Doctor of philosophy student.

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Supported by Lupus Australia

Appendix C-2: Advertisement flyer (control group)

Usual care in SLE

Do you have Systemic Lupus Erythematosus?

Are you 18+ years old?

Currently physically active or not, please join!

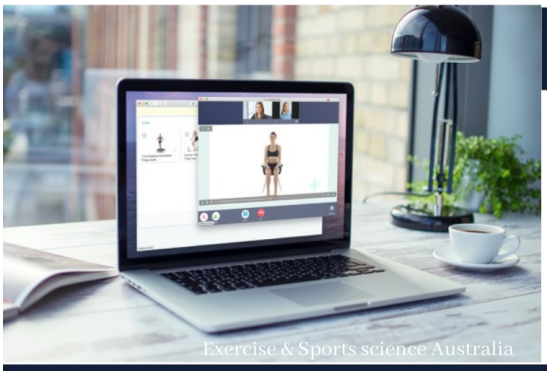
What is involved?

1. Initial assessment: Screening, 4 exercise tests & 2 questionnaires (45min)
2. Continue with your usual care for 8-weeks
3. Final assessment: 4 exercise tests & 2 questionnaires (45min)

Where & How?

The comfort of your own home!

Online using Zoom (online video communication software)



When?

- Screening + Initial assessment: October / November 2022
- Final assessment: December 2022/ January 2023

How to join?

If you are interested in participating, please contact Stephanie Frade.

Phone: 0412567110 Email: stephanie.frade@usq.edu.au

Stephanie Frade is an Accredited Exercise Physiologist and Doctor of philosophy student.

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Appendix C-3: Information sheet (Intervention group)

Project Details

Title of Project: Feasibility and effectiveness of individually supervised telehealth exercise in systemic lupus erythematosus.

Human Research Ethics Approval Number: H21REA052

Research Team Contact Details

Principal Investigator
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Principal Supervisor
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Associate supervisor:
Associate professor Dr. Stephen Bird
Email: Stephen.Bird@usq.edu.au

Associate supervisor
Professor Dr. David Greene
Email: David.Greene@acu.edu.au

Associate supervisor: Associate professor rheumatologist Dr. Sean O'Neill
Email: Sean.ONeill@health.nsw.gov.au

Description

- This project is being undertaken as part of a **Doctor of Philosophy**.
- The purpose of this project is to assess 1) the feasibility of individually supervised telehealth exercise (real-time) and 2) the effectiveness of home-based functional resistance exercise on fatigue, quality of life, disease activity, functional strength, and individual experience. With your consent, the research team would like to obtain your most recent blood reports before and following the exercise intervention to explore changes in your disease activity. The research team may also contact your regular treating physician to obtain any further information about your health history, if needed.
- The exercise program will be **prescribed** and **individually supervised telehealth exercise, real-time using Zoom (video communication software)** by an Accredited Exercise Physiologist**. An email link will be sent to you to access the sessions.** You do not need to download the software. You can simply access it on a web browser by clicking the link in the email. *Please let the research team know if you have any difficulty accessing or using Zoom.*
- The intention of this project is to determine whether individually supervised exercise via telehealth is a feasible and effective adjunct intervention for the management of systemic lupus erythematosus.

Participation

- Your involvement will include participation in a FREE **8-week individually supervised exercise intervention**.

- You will be required to attend **2 x 45-minute exercise sessions per week, online on Zoom.**
  You will be responsible for your own laptop/computer/phone device and internet connection.
- The intervention is anticipated to take place during October – early December 2021.
- Each exercise session will be **45 minutes in duration** (5-minute warm-up, 30 minutes of moderate intensity exercise [3 to 4 out of 10 based on your rating of perceived exertion, which is referred to as "somewhat hard"] and a 10-minute cool down).
- To assess the effectiveness of the program, you will be required to attend a **20-minute phone screening** and a **30-minute initial and final assessment**, which will take place online on Zoom the week before and after your 8-week exercise intervention. The research team will contact you to book this in.
- Please know that your participation in this project is entirely voluntary. There is no obligation to participate. There will be **no financial cost to you**, and **you will not be paid for participating in this project**.
- If you decide to take part and later change your mind, **you are free to withdraw from the project at any stage**. If you do wish to withdraw from this project, please contact the research team.
- Your decision whether you take part, do not take part, or to take part and then withdraw, will in no way impact your current or future relationship with the University of Southern Queensland or the research team.

Expected Benefits

It is expected that this exercise program may directly benefit your health by improving your muscular strength and endurance, fatigue, and quality of life. It may also improve your motivation to engage in further exercise, as well as continue to explore the use of online exercise delivery as part of your exercise routine. It may also indirectly benefit you by contributing to further knowledge on the effectiveness and feasibility of exercise interventions for people with systemic lupus erythematosus.

Risks

There are some risks involved in this project, and from exercise in general.

- You may experience muscle soreness or fatigue following an exercise session.
- You may experience a musculoskeletal injury during a session if your exercise technique is not performed correctly.
- You may experience an exacerbation of symptoms related to your condition.

To mitigate these risks, your exercise session will be individually supervised online by an accredited exercise physiologist who will be monitoring your rating of perceived exertion and exercise technique through-out the entirety of the exercise session. If at any point during the exercise intervention you experience any abnormal symptoms or discomfort, please inform the exercise physiologist immediately, and contact your regular treating physician for advice as soon as possible. The exercise physiologist may ask you to cease the exercise session and take 5-10 minutes of supervised rest, and if symptoms persist or worsen, an ambulance will be called

immediately. The exercise physiologist will have their mobile phone device available throughout the entire session to ensure action is taken promptly if needed.

Privacy and Confidentiality

- All comments and responses will be treated confidentially unless required by law.
- Any data collected as a part of this project will be stored securely as per University of Southern Queensland's Research Data Management policy.

Consent to Participate

We ask you to sign a written consent form (enclosed) to confirm your agreement to participate in this project. Please return your signed consent form via email to the principal investigator, Stephanie Frade, prior to participating in this study.

Email: stephanie.frade@usq.edu.au

Questions or Further Information about the Project

If you have any questions or require further information about this project, please feel free to email the principal investigator.

Email: stephanie.frade@usq.edu.au

Concerns or Complaints Regarding the Conduct of the Project

If you have any concerns about the ethical conduct of the project, you may contact the University of Southern Queensland Manager of Research Integrity and Ethics on +61 7 4631 1839 or email researchintegrity@usq.edu.au. The Manager of Research Integrity and Ethics is not connected with the research project and can facilitate a resolution to your concern in an unbiased manner.

Thank you for taking the time to help with this research project. Please keep this sheet for your information.

Appendix C-4: Information sheet (control group)

Project Details

Title of Project: Feasibility and effectiveness of individually supervised telehealth exercise in systemic lupus erythematosus.

Human Research Ethics Approval Number: H21REA052

Research Team Contact Details

Principal Investigator
Mrs. Stephanie Frade
Email: stephanie.frade@usq.edu.au
Telephone: 0412567110

Principal Supervisor
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Professor Dr. David Greene
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Associate supervisor:
Associate professor rheumatologist Dr. Sean O'Neill
Email: Sean.ONeill@health.nsw.gov.au

Description

- This project is being undertaken as part of a **Doctor of Philosophy**.
  The purpose of this overall research study is to assess the feasibility and effectiveness of individually supervised telehealth exercise in adjunction to usual care in SLE, compared with usual care alone **(control group).**
- As part of the **control group**, you will be involved in the initial and post-8-week assessment. In between the assessments you will carry out your usual care and activities. Nothing is required of you during this 8-week time period.
- The assessments will be conducted online on Zoom. **You do not need to download the software. You can simply access it on a web browser by clicking the link in the email.** ***Please let the research team know if you have any difficulty accessing or using Zoom.***
- The intention of this project is to determine whether individually supervised exercise via telehealth is a feasible and effective adjunct intervention for the management of systemic lupus erythematosus compared to a control group performing their usual care.

Participation

- As part of the **control group,** you will be required to attend a **15-minute phone screening** and a **30-minute initial and final assessment**, which will take place online on Zoom the week before and after 8-weeks. The research team will contact you to book this in.
- Please know that your participation in this project is entirely voluntary. There is no obligation to participate. There will be **no financial cost to you**, and **you will not be paid for participating in this project**.

- If you decide to take part and later change your mind, **you are free to withdraw from the project at any stage**. If you do wish to withdraw from this project, please contact the research team.
- Your decision whether you take part, do not take part, or to take part and then withdraw, will in no way impact your current or future relationship with the University of Southern Queensland or the research team.

Expected Benefits

Indirect benefits to the participants may include an improvement in their motivation to engage in exercise, as well as continue to explore the use of telehealth exercise delivery as part of their exercise routine. This will also improve research knowledge for exercise practitioners on the application of telehealth for a clinical population.

Risks

- Muscle soreness or fatigue following an exercise test
- Emotional distress following discuss their disease during the screening.
- Time imposition due to the exercise tests (2 times pre and post, 30min each test)

(However, this time imposition is minimized by having the intervention delivered online).

Privacy and Confidentiality

- All comments and responses will be treated confidentially unless required by law.
- Any data collected as a part of this project will be stored securely as per University of Southern Queensland's Research Data Management policy.

Consent to Participate

We ask you to sign a written consent form (enclosed) to confirm your agreement to participate in this project. Please return your signed consent form via email to the principal investigator, Stephanie Frade, prior to participating in this study.

Questions or Further Information about the Project

If you have any questions or require further information about this project, please feel free to email the principal investigator. **Email: stephanie.frade@usq.edu.au**

Concerns or Complaints Regarding the Conduct of the Project

If you have any concerns about the ethical conduct of the project, you may contact the University of Southern Queensland Manager of Research Integrity and Ethics on +61 7 4631 1839 or email researchintegrity@usq.edu.au. The Manager of Research Integrity and Ethics is not connected with the research project and can facilitate a resolution to your concern in an unbiased manner.

Thank you for taking the time to help with this research project. Please keep this sheet for your information.

Appendix C-5: Consent form

Project Details:

Title of Project: Feasibility and effectiveness of individually supervised exercise via telehealth in systemic lupus erythematosus.

Human Research Ethics Approval Number: H21REA052

Research Team Contact Details

Principal investigator
Mrs. Stephanie Frade
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Associate supervisor:
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Associate supervisor
Professor Dr. David Greene
Email: David.Greene@acu.edu.au

Associate supervisor:
Associate professor rheumatologist Dr. Sean O'Neill
Email: Sean.ONeill@health.nsw.gov.au

Statement of Consent

By signing below, you are indicating that you:

- Have read and understood the information sheet regarding this project. ☐Yes / ☐No
- Have had any questions answered to your satisfaction. ☐Yes / ☐No
- Understand that if you have any additional questions, you can contact the research team. ☐Yes / ☐No
- Are over 18 years of age. ☐Yes / ☐No
- Understand that you can withdraw from this project at any time without prejudice. ☐Yes / ☐No
- Agree for the research team to contact your regular treating physician to request any further information regarding your health history, if needed. ☐Yes / ☐No
- Agree for the research team to obtain your most recent blood reports from you or your regular treating physician. ☐Yes / ☐No

Participant name:
Participant signature:
Date:

Please return this sheet to the principal investigator, Stephanie Frade, prior to undertaking the study.

Appendix C-6: Screening and baseline information

CONTACT INFORMATION	
Date of screening:	
Full name:	
Contact number:	
Email address:	
Regular treating physician: (General practitioner/rheumatologist/ immunologist, etc)	Name: Role? Contact number:
Emergency contact Details:	Name: Relationship: Contact number:

DEMOGRAPHY	
Date of birth (DD/MM/YYYY)	
Sex	Male ☐ Female ☐ Prefer not to say ☐
Age (years)	
Are you currently working?	Yes ☐ No ☐ …… What is your work: _____ How many days per week do you work? _____ What is your level of stress at work? ☐ Very stressful ☐ Moderately stressful ☐ Not stressful at all
Do you have any children? Do you live with anyone else?	Yes ☐ No ☐ …… How many children do you have? _____ What age are your children? _____ Yes ☐ No ☐ Relationship to them? _____

Systemic Lupus Erythematosus INFORMATION	
When were you diagnosed with SLE? (year)	
What body systems **have been** affected since being diagnosed with Systemic Lupus Erythematosus?	☐ Kidneys ☐ Lungs ☐ Heart ☐ Skin ☐ Blood ☐ Brain ☐ Joints ☐ Other:

	Have you had joint pain? Yes ☐ No ☐ Have you had skin rashes? Yes ☐ No ☐ Has it affected your kidneys? Yes ☐ No ☐
What symptoms do you **CURRENTLY** experience from Systemic Lupus Erythematosus?	☐ Joint pain ☐ Muscle aches ☐ Fatigue ☐ Brain fog ☐ Skin rashes ☐ Raynaud's phenomenon ☐ Other:
Have you been hospitalised in the last 12 months due to a SLE 'flare'?	Yes ☐ No ☐ Date hospitalised: Time spent in hospital: months and/or days
Are you getting any support for Systemic Lupus Erythematosus? *(e.g., NDIS funding)*	Yes ☐ No ☐ If yes, please list:

MEDICATIONS		
Medication (name)	Frequency	Dose (mg)

OTHER MEDICAL CONDITIONS
Heart disease: Yes ☐ No ☐ Raised cholesterol: Yes ☐ No ☐ Hypertension: Yes ☐ No ☐ Arthritis (including OA): Yes ☐ No ☐ Osteoporosis: Yes ☐ No ☐ Allergies: Yes ☐ No ☐ Asthma: Yes ☐ No ☐ Cancer: Yes ☐ No ☐ Diabetes: Yes ☐ No ☐ Other: If yes to any above, provide details:

CURRENT EXERCISE STATUS	
Current physical activity /exercise level	Type: Intensity: Time: Frequency:
Sleep	How many hours of sleep are you getting on average each day? Is this sleep broken? Yes ☐ No ☐ Do you feel refreshed when you wake up? Yes ☐ No ☐

Appendix C-7: Fibromyalgia questionnaire

I. Using the following scale, indicate for each item the level of severity over the past week by checking the appropriate box.

0 No problem

1 Slight or mild problems, generally mild or intermittent

2 Moderate; considerable problems; often present and/ or at a moderate level

3 Severe continuous, life disturbing problems

Fatigue	☐0	☐1	☐2	☐3
Trouble thinking or remembering:	☐0	☐1	☐2	☐3
Waking up tired (unrefreshed):	☐0	☐1	☐2	☐3

II. During the past 6 months have you had any of the following symptoms?

Pain or cramps in lower abdomen	Yes ☐	No ☐
Depression	Yes ☐	No ☐
Headache	Yes ☐	No ☐

III. Joint/body pain:
Please indicate below if you have had pain or tenderness over the past 7 days in each of the areas listed below. Be sure to mark both right side and left side separately.

☐ Shoulder, left	☐ Upper leg, left	☐ Lower back
☐ Shoulder, right	☐ Upper leg, right	☐ Upper back
☐ Hip, left	☐ Lower leg, left	☐ Neck
☐ Hip, right	☐ Lower leg, right	
☐ Upper arm, left	☐ Jaw, left	
☐ Upper arm, right	☐ Jaw, right	
☐ Lower arm, left	☐ Chest	
☐ Lower arm, right	☐ Abdomen	☐ No pain in any of these areas

IV. Overall, were the symptoms listed in I-III above generally present for at least 3 months?

Yes ☐	No ☐

Appendix C-8: Scoring sheet: baseline and post-assessment.

Participant name: **Date of test:**			
RESTING MEASURES			
Outcome Measure			**Result**
Resting Heart rate **(bpm)** ➔ Educate on how to take radial pulse heart rate, manually.			
RPE **(0/10)** ➔ Educate on the scale, tell them the intervention is 3-4/10, moderate intensity.			
EXERCISE MEASURES			
Outcome Measure	**Test**	**Result**	**RPE (/10)**
Lower body muscular strength	Five times sit-to-stand Test **(time in sec)** *ESSA outcome measures: pg. 252 (Marlow, Hastings, Hansson, 2014)		
Lower body muscular endurance	30 second sit-to-stand test **(repetitions)** *ESSA outcome measures: pg. 216 (Marlow, Hastings, Hansson, 2014)		
Upper body muscular endurance	30sec arm curl test **(repetitions)** *ESSA outcome measures: pg. 260 (Marlow, Hastings, Hansson, 2014)		
Aerobic capacity / lower body muscular endurance	2min step test **(Step count)** *ESSA outcome measures: pg. 103 (Marlow, Hastings, Hansson, 2014)		
SELF-REPORTED QUESTIONNAIRES			
Outcome & assessment tool	**Component**	**Result**	
Fatigue (FACIT-fatigue: 40-item questionnaire)	FACIT-F Trial outcome Index (score range 0-108)		
	FACT-G total score (score range 0-108)		
	FACIT-F total score (score range 0-160)		

Quality of life (RAND 36-item Short-Form Survey)	Physical functioning	
	Role limitations due to physical health	
	Role limitations due to emotional problems	
	Energy/fatigue	
	Emotional well-being	
	Social functioning	
	Pain	
	General health	

Appendix C-9: Five Times Sit-to-Stand (Marlow, Hastings, Hansson, 2014)

Purpose of test: To evaluate functional lower limb muscle strength.

Equipment required:

- Stopwatch
- Armless chair (43 cm standard height)

Test procedure:

Ensure the back of the chair is against a wall so that the chair doesn't slip. Before completing the test ensure that the client can complete a single sit to stand. Then instruct the client: 'I'd like you to fold your arms across your chest and when I say go, I want you to stand up and sit down as quickly as you can five times in a row.'

Ensure that:

- the client sits with the back against the chair.
- the arms are folded across the chest.
- the feet remain on the floor throughout the test.
- when the client stands the knees and hips are extended.

Record the time, in seconds, from 'go' to when the client is seated after the fifth sit-to stand.

Appendix C-10: The 30-second Sit-to-Stand Test (Marlow, Hastings, Hansson, 2014)

Purpose of test: To evaluate lower limb muscular endurance and the ability to perform activities of daily living.

Equipment required:

- Stopwatch
- Armless chair (43 cm standard height)

Test procedure

Ensure the back of the chair is against a wall so that the chair doesn't slip. Before completing the test, ensure that the client can complete a single sit to stand. Then instruct the client to fold their arms across their chest when you say 'go', ask them to stand up and sit down as many times as they can in 30 seconds.

Ensure that:

- The client sits when their back against the chair
- The arms are folded across the chest.
- The feet remain on the floor through the test.
- When the client stands, the knees and hips are extended.

Record the time when 'go' is said and say 'stop' when 30 seconds have passed.

Note: If a client uses their hands during the test, to push off their thighs on the chair, the test can continue' however, the results cannot be compared to age-related norms.

Appendix C-11: Bicep/arm curl Test (Marlow, Hastings, Hansson, 2014)

Purpose of test: To assess upper body strength.

Equipment required:

- Straight-back chair
- Stopwatch
- Dumbbell or any item at home with weight (as long as they use the same weight pre and post assessment)

Test procedure:

The client sits in the chair with the back straight and feet flat on the floor.

Have the client hold the dumbbell with a neutral (handshake grip) and let arm hang down by the side.

Ensure that the clients elbow stays against trunk as they curl the weight by fully flexing the elbow while supinating the forearm and then returning the weight to the starting position.

Scoring: Count the number of repetitions executed in 30 seconds.

Note if the forearm is more than halfway to the supine position when time expires, count the move as a complete repetition.

Appendix C-12: Two Minute Step Test (Marlow, Hastings, Hansson, 2014)

Purpose of Test: To assess aerobic endurance and lower body muscle endurance.

Equipment required:

- Stopwatch
- Tape measure
- Masking tape or marker

Test procedure:

Step 1: Establish the knee lift height.

- Mark a point on the participant's thigh, halfway between the participant's patella and iliac crest.
- Measure from this point to the ground with a tape measure.
- Place a mark on the wall with masking tape at the height from the ground to the participant's mid-thigh position.

Step 2: Give the participant these instructions.

- On the instruction to start, step up and down on the spot.
- Lift your knees to the indicated mark on the wall.
- Continue to step as fast as you can for 2 minutes.
- If you tire, slow down or stop and rest.

Scoring: Count the number of times the right knee is raised to the level of the mark on the wall. If either knee is not raised to the correct level, do not count the step. Encourage the participant to continue to raise both knees to the correct level.

Appendix C-13: Functional assessment of chronic illness therapy (FACIT-FATIGUE)

Below is a list of statements that other people with your illness have said are important**.**
Please mark <u>one number per line</u> to indicate your response as it applies to the <u>past 7 days</u>.

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
G	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the*					
G	I am satisfied with my sex life	0	1	2	3	4

Please mark <u>one number per line</u> to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very muc**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF	I am content with the quality of my life right now	0	1	2	3	4

Please mark <u>one number per line</u> to indicate your response as it applies to the <u>past 7 days</u>.

	<u>ADDITIONAL CONCERNS</u>	**Not at all**	**A little**	**Some -what**	**Quite a bit**	**Very much**
HI 7	I feel fatigued	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
An 1	I feel listless ("washed out")	0	1	2	3	4
An 2	I feel tired	0	1	2	3	4
An 3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An 4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An 5	I have energy	0	1	2	3	4
An 7	I am able to do my usual activities	0	1	2	3	4
An 8	I need to sleep during the day	0	1	2	3	4
An 12	I am too tired to eat	0	1	2	3	4

An 14	I need help doing my usual activities	0	1	2	3	4
An 15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An 16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix C-14: FACIT-Fatigue Scoring Guidelines (Version 4)

Instructions:

1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FACIT-F).
5. The higher the score, the better the QOL.

Subscale	Item Code	Reverse item?		Item response		Item Score
PHYSICAL	GP1	4	-	_____		=_____
WELL-BEING	GP2	4	-	_____		=_____
(PWB)	GP3	4	-	_____		=_____
	GP4	4	-	_____		=_____
Score range: 0-28	GP5	4	-	_____		=_____
	GP6	4	-	_____		=_____
	GP7	4	-	_____		=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered:

_____=**PWB subscale score**

SOCIAL/FAMILY	GS1	0	+	_____	=_____
WELL-BEING	GS2	0	+	_____	=_____
(SWB)	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered:

_____=**SWB subscale score**

EMOTIONAL	GE1	4	-	_____	=_____
WELL-BEING	GE2	0	+	_____	=_____
(EWB)	GE3	4	-	_____	=_____
Score range: 0-24	GE4	4	-	_____	=_____
	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____

Multiply by 6: _____

Divide by number of items answered:

_____=**EWB subscale score**

FUNCTIONAL	GF1	0	+	_____	=_____
WELL-BEING	GF2	0	+	_____	=_____
(FWB)	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered:

_____=**FWB subscale score**

FACIT-F Scoring Guidelines (Version 4) – Page 2

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
FATIGUE	HI7	4	-	_____	=_____

SUBSCALE	HI12	4	-	_____	=_____
(FS)	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
Score range: 0-52	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores: _____

Multiply by 13: _____

Divide by number of items answered: _____ **=F**

Subscale score

To derive a FACIT-F Trial Outcome Index (TOI):
Score range: 0-

_____ + _____ + _____
=_____ **=FACIT-F TOI**

(**PWB** score) (**FWB** score) (**FS** score)

To Derive a FACT-G total score:
Score range: 0-

_____ + _____ + _____ +
_____ = _____ **=FACT-G Total score**

(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FACIT-F total score:
Score range:

_____ + _____ + _____ + _____ + _____
=_____ **=FACIT-F Total score**

(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**FS** score)

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

Appendix C-15: 36-Item Short Form Survey

Please take the time to read and answer every question carefully by marking the number that best represents your response.

1. In general, would you say your health is? (Mark one number for this question).

Excellent	Very Good	Good	Fair	Poor
1	2	3	4	5

2. Compared to one year ago, how would you rate your health in general now? (Mark one number for this question).

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
1	2	3	4	5

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much: (mark one number on each line).

	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
3. Vigorous activities, such as running, lifting heavy objects participating in strenuous sports	1	2	3

4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5. Lifting or carrying groceries	1	2	3
6. Climbing **several** flights of stairs	1	2	3
7. Climbing **one** flight of stairs	1	2	3
8. Bending, kneeling, or stooping	1	2	3
9. Walking **more than a mile**	1	2	3
10. Walking **several blocks**	1	2	3
11. Walking **one block**	1	2	3
12. Bathing or dressing yourself	1	2	3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **because of your physical health**? **(Mark one number on each line).**

	Yes	**No**
13. Cut down on the **amount of time** you spend on work or other activities	1	2
14. Accomplished less than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **because of any emotional problems** (such as feeling depressed or anxious)?

(Mark one number on each line)

	Yes	**No**
17. Cut down on the **amount of time** you spend on work or other activities	1	2

18. Accomplished less than you would like	1	2
19. Didn't do work or other activities as carefully as usually	1	2

20. During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your social activities with family, friends, neighbours, or groups? <u>(Mark one number for this question).</u>

Not at all 1	Slightly 2	Moderately 3	Quite a bit 4	Extremely 5

21. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>? <u>(Mark one number for this question).</u>

None 1	Very Mild 2	Mild 3	Moderate 4	Severe 5	Very Severe 6

22. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)? <u>(Mark one number for this question)</u>

Not at all 1	Slightly 2	Moderately 3	Quite a bit 4	Extremely 5

These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>? <u>(Mark one number on each line).</u>

	All the time	**Most** of the time	**A good bit** of the time	**Some** of the time	**A little** of the time	**None** of the time
23. Did you feel full of pep (life)?	1	2	3	4	5	6
24. Have you been very nervous?	1	2	3	4	5	6
25. have you felt so down in the dumps nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and depressed?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been happy?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?
<u>(Mark one number for this question).</u>

All of the Time	Most of the Time	Some of the Time	A Little of the Time	None of the Time
1	2	3	4	5

How TRUE or FALSE is each of the following statements for you? <u>(Mark one number on each line)</u>

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

Appendix C-16: Telehealth Usability and Satisfaction Questionnaire

Quality	
The video quality was acceptable.	All the time
	Most of the time
	Some of the time
	Rarely
	Never
The audio quality was acceptable.	All the time
	Most of the time
	Some of the time
	Rarely
	Never
Usability	
The system was easy to learn.	Strongly agree
	Agree
	Neither agree nor disagree
	Disagree
	Strongly disagree
After the first few sessions the system was easy to use.	Strongly agree
	Agree
	Neither agree nor disagree
	Disagree
	Strongly disagree
I was able to use the technology on my own.	Strongly agree
	Agree
	Neither agree nor disagree
	Disagree
	Strongly disagree
I needed someone at home to help me use the system.	Strongly agree
	Agree
	Neither agree or disagree
	Disagree
Exercise Program	
I found the exercises difficult to perform due to my physical ability (e.g., fatigue, or pain).	Strongly agree
	Agree
	Neither agree or disagree
	Disagree
	Strongly disagree
The exercises were challenging enough to improve my	Strongly agree

strength.

Agree
Neither agree or disagree
Disagree
Strongly disagree

The exercise program had enough variety.

Strongly agree
Agree
Neither agree or disagree
Disagree
Strongly disagree

I felt safe doing the exercises.

Strongly agree
Agree
Neither agree or disagree
Disagree
Strongly disagree

I had enough equipment at home to do the exercises.

Strongly agree
Agree
Neither agree or disagree
Disagree
Strongly disagree

I had enough space at home to both do the exercises and see the instructor at the same time.

Strongly agree
Agree
Neither agree or disagree
Disagree
Strongly disagree

I would have preferred to do some of the exercise sessions by myself without being supervised by telehealth.

Strongly agree
Agree
Neither agree or disagree
Disagree
Strongly disagree

Which heart rate monitor (s) did you use?

Chest strap and watch (Garmin)
Finger clip (Pulse oximeter)
Both
Neither

The heartrate monitor I used the most was easy to use.

Strongly agree
Agree
Neither agree or disagree

	Disagree
Exercise preference **If you had a choice:**	
What is your preferred length of time for a telehealth supervised exercise session?	Less than 15 minutes 15-20 minutes 20-30 minutes 30-45 minutes More than 45 minutes
What is your preferred number of telehealth supervised exercise sessions per week?	None 1 2 3 4 5 or more
What is your preferred length of time for a telehealth supervised exercise program?	Less than 4 weeks 4-6 weeks 6-8 weeks 8-12 weeks
Satisfaction	
If I had transport, I would have preferred going to a central venue for the sessions (e.g., physio clinic, community Centre, gym) instead of doing them at home via telehealth.	Strongly agree Agree Neither agree or disagree Disagree Strongly disagree
Overall, I was satisfied with the telehealth exercise experience.	Strongly agree Agree Neither agree nor disagree Disagree
I would recommend telehealth exercise sessions to other people who have had a stroke.	Strongly agree Agree Neither agree nor disagree Disagree Strongly disagree
I would use telehealth exercise sessions again	Strongly agree Agree Neither agree nor disagree Disagree Strongly disagree

Appendix C-17: Post-intervention Interview framework

1. *Explain interview process and aim of the interview questions (interview approximately 10-15minutes)*
    a. *The aim of this interview is to explore your experiences of the 8-week telehealth exercise program.*
    b. *Re-assure ethics has been approved. Provide ethics number = H21REA052*
2. *Ask permission to record. Turn on recording device. Ask participant to verbally confirm consent for recording.*

Interview questions

Part 1: Exercise program

- **Tell us about your experience with the supervised exercise program? (Exercise program itself)**
    - What are some aspects of the exercise program that you enjoyed?
    - What are some aspects of the exercise program that you did not enjoy?
    - **What benefits did you experience following the exercise program? Tell me about those benefits that you experienced?**
    - Were there any changes in yourself that you noticed following the exercise program? Have you noticed any changes within yourself? *For example, your ability to walk further or perform daily tasks better?*

- **Tell us about any challenges you experienced with the exercise program?**
    - **Were there any specific aspects of the program that you found difficult?** *For example, holding the band or the weights, performing the lower body exercises. The number of exercises within the session? The number of repetitions you did in a row. The style of the session? The time of the day the session was performed.*

- **Is there anything that we could do to improve the exercise program? Or make it more challenging?** i.e., variety, more cardio?

Part 2: Exercise delivery via telehealth

- **Tell us about your experience with the exercise program delivered online?**
  - How was your experience with using a live video conferencing platform, **Zoom?**
  - How was your experience with the online **supervision** of exercise?
  - What are some aspects of telehealth delivered exercise that you liked?
  - What are some aspects of telehealth delivered exercise that you did not like?

- **Tell us about any challenges you experienced with the program delivered online?**

- **How likely would you be to continue with this delivery of exercise?**
  - Would you be able to tell me a little more about why you would/would not continue with this type of exercise program delivered online?
  - How likely would you be to continue with supervised exercise online?
  - Is there anything that we could do to improve the delivery of the exercise program?

Appendix C-18: Rating of Perceived Exertion (RPE)

Please rate how difficult the exercise felt to you.

0	**Nothing at all**	E.g., sleeping or watching TV.
1	**Very light**	Hardly anything at all. E.g., walking around the house.
2	**Light**	Very comfortable. E.g., Walking around the shops.
3	**Moderate**	Feeling as though your breathing is getting heavier, muscles are starting to work, but you are mostly comfortable.
4	**Moderate to somewhat hard**	Breathing is getting even heavier, and muscles are working harder, but you can still speak. Somewhat comfortable.
5	**Somewhat hard to hard**	Borderline uncomfortable, getting short of breath and muscles getting sore, but can still speak and carry on if needed.
6	**Hard**	Getting uncomfortable, shorter of breath, muscles getting very sore. Harder to speak.
7	**Very hard**	Getting very uncomfortable and difficult to maintain. Can only speak a few words without gasping for air. Muscles very sore.
8	**Very hard to extremely hard**	Very uncomfortable. Can only speak a few words without gasping for air. Muscles starting to cramp.
9	**Extremely hard**	Extremely uncomfortable. Cannot talk. Muscles are very sore.
10	**Absolute maximum**	Almost impossible, unbearable.

Appendix C-19: Rating of Bodily Pain

Please rate how much <u>overall bodily pain</u> you are experiencing <u>right now.</u>

0	**None**	I have no pain at all.
1	**Just noticeable**	My pain is hardly noticeable.
2	**Minimal**	I am aware of my pain only when I pay attention to it.
3	**Mild**	My pain bothers me, but I can ignore it.
4	**Mild to moderate**	I am constantly aware of my pain, but I can continue most activities.
5	**Moderate**	I think about my pain most of the time and cannot do some activities.
6	**Moderate to high**	I think about my pain all the time and give up of many activities.
7	**High**	I am in pain all the time. It keeps me from doing most activities.
8	**Very high**	My pain is so severe that it is hard to think of anything else.
9	**Extremely high**	My pain is all I can think about. I can barely move or talk.
10	**Absolute maximum**	I feel like I need to be in bed and cannot move due to my pain.

Appendix C-20: Rating of Overall Fatigue

Please rate how much <u>overall physical and mental fatigue</u> you are experiencing <u>right now.</u>

0	**None**	Not tired at all.
1	**Just noticeable**	Slightly tired, but still able to carry on as normal with little to no difficulty.
2	**Minimal**	Finding everything more effort than usual, but still able to carry on.
3	**Mild**	Tiredness makes it hard to enjoy activities. Still able to work with some difficulty.
4	**Mild to moderate**	Possibly able to do some work, can go out to buy food, but only if essential.
5	**Moderate**	Mostly unable to work, can go out to buy food, but only if essential.
6	**Moderate to high**	Too tired to go out. Able to move around the house and do activities that require little energy and focus. Cannot work.
7	**High**	Can walk around the house but cannot stand for more than a few minutes without resting. Cannot focus on anything easily.
8	**Very high**	Able to sit up for a while and walk around the house if necessary. Conversing is hard.
9	**Extremely high**	Able to sit up for a short time and can walk around the house (with difficulty). Too tired to eat.
10	**Absolute maximum**	Can barely sit up. Need assistance getting out of bed. Cannot think properly.

Appendix D: Original study design for study 5

Title: Effectiveness of individually supervised exercise in Systemic Lupus Erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune disease characterised by an immune response to self-antigens, inflammation of joints, tissues, and internal organs, and consequent damage (Fanouriakis et al., 2019; O'Dwyer et al., 2017). The manifestations of SLE vary markedly and can be intermittent, however common symptoms include a characteristic butterfly rash on the face, arthritis, myalgia, serositis, and nephritis, and is often characterized by periods of remission and exacerbation (Jakez-Ocampo et al., 2020). SLE has a severe and pervasive effect on those living with the disease, with patients reporting the disease to cause debilitating fatigue, mental deterioration, and widespread pain (Sutanto et al., 2013). SLE is associated with comorbidities such as osteoporosis (Gu et al., 2019) and atherosclerotic cardiovascular disease (CVD) (Manzi et al., 1997; Schoenfeld et al., 2013). CVD risk among SLE patients compared to the general population is at least doubled. While older SLE patients appear to have the highest absolute risks of CVD, young women have alarmingly high relative risks, given the rarity of CVD in the comparison general population (Schoenfeld et al., 2013).

SLE is a rare disease, with a worldwide prevalence varying from 4.3 to 150 persons in 100 000 (Nikpour et al., 2014), or approximately 5 million persons worldwide. The prevalence in Australia varies between 19.3-39 persons in 100 000 for non-Aboriginal Australians and 52.0-92.8 persons in 100 000 Aboriginal Australians (Bossingham, 2003; Segasothy & Phillips, 2001). SLE can affect both men and women of any age, with nine out of ten being female. For females, it is more prevalent between the ages of fifteen and forty-five. By age, the female: male ratio is 3:1 before puberty, 10–15:1 during childbearing years, with a slight decrease again after menopause, 8:1 (Askanase et al., 2012).

Patients with SLE are also less physically active than people without SLE (Margiotta et al., 2018), with 60% of patients not meeting sufficient physical activity guidelines according to the World Health Organisation (WHO) recommendations. Subsequent

inactivity may add to the heightened risk of comorbidities, as well as lead to physical de-conditioning and poor health-related quality of life. Regular exercise is readily available self-care, and at moderate intensity, appears to be safe and effective in SLE (Neill et al., 2006; O'Dwyer et al., 2017; Wu et al., 2017), although the quality of evidence is low and the risk of bias in the available studies is high. Exercise interventions are already understood to be beneficial in improving aerobic capacity, depression scores, and some of the most concerning symptoms of SLE such as fatigue (O'Dwyer et al., 2017; Wu et al., 2017), which is a commonly reported symptom experienced by people living with SLE (Sutanto et al., 2013), affecting up to 80% of SLE patients (Sharif et al., 2018). Furthermore, to our knowledge, the individuals' experiences following an exercise intervention has also not been explored in this population. This could provide comprehensive knowledge about the measured and perceived response to exercise, revealing potential barriers and benefits to the exercise program. The aim of this pilot exercise intervention is to compare the effectiveness of aerobic and resistance exercise on disease activity, perceived fatigue and quality of life, and individual experience, as a way of providing further insight into exercise components and quantifying appropriate dosage parameters.

Methods

Study Design. This study will be a single-centre, double-blind, randomised two group parallel trial conducted in Sydney, Australia, following the principles of the Declaration of Helsinki (Association, 2013) and in accordance with Australia's National Statement on Ethical Conduct in Human Research (CONSORT) (Schulz, Altman, & Moher, 2010). This study has been approved by the University of Southern Queensland (USQ) Human Research Ethics Committee [ethics application number: H21REA052].

Participants. In accordance with pilot study recommendations (Lancaster, Dodd, & Williamson, 2004), up to 30 participants are aimed to be recruited into this study. Inclusion criteria includes adults (18+ years), diagnosed with SLE, according to the American College of Rheumatology (ACR) and the 2019 European League Against Rheumatism criteria (EULAR) for SLE (Fanouriakis et al., 2019), and deemed safe to exercise according to an exercise pre-screening evaluation performed by the

research team. Exclusion criteria will include currently pregnant, or who have any contraindication to exercise such as active lupus nephritis, myocarditis, or pericarditis.

Recruitment. Participants will be recruited from the Royal North Shore Hospital, Sydney, Australia, through advertisement flyers located in the rheumatology department, and word of mouth by the staff. Participants will also be recruited from the Lupus NSW association through email, website, and Facebook support group advertisement. All participants will be informed that participation in this study is completely voluntary. The advertisement flyer will instruct interested participants to send an email to the principal investigator (SF). When an email is received from an interested participant, which will likely occur in a staggered approach between May and September 2021, the research team will send the participant an information letter to provide further details about the project, as well as a consent form for participants to sign and return at their convenience.

Screening and eligibility. Once a participant has signed the consent form, the research team will arrange a suitable time to conduct a 30-minute phone consultation with the participant to perform baseline screening and eligibility for inclusion. The pre-screening questionnaire will identify if participants are safe to exercise. Additional questions about whether they have a diagnosis with SLE, are current pregnant, and their availability to exercise will also be included, and this will assist in determining their eligibility to participate in the study.

Randomisation and allocation. Participants will be randomly allocated to either a resistance exercise program or aerobic exercise program by an independent research assistant with no involvement in the assessment or service delivery within this study. Randomisation will be performed using an online random generator (1= strength program, and 2=aerobic program). To reduce expectation bias, participants will be blinded to the use of different exercise modalities in this trial, with the two groups being conducted at different times or rooms in the gym, where possible. Allocation of participants to their respective group will be concealed from the investigators until all data collection is complete. The participants' allocated group will be communicated between the independent research assistant and the research assistant delivering the exercise sessions. Once allocation is complete, the participants'

contact phone number and email will be provided to the research assistants to book and manage their initial and final assessment, and exercise sessions.

Procedures. All participants are required to attend two 50-minute face to face sessions per week at the Australian Catholic University (ACU) gymnasium in North Sydney, Australia, for 8 weeks (i.e.: 16 sessions per participant, 30 participants, that is 480 exercise sessions for this study). All exercise sessions will be individually supervised by an Exercise Physiologist research assistant. All participants will be allocated at least 48 h of relative rest (i.e.: no structured exercise) between sessions. All research assistants will be trained in both exercise interventions, which will occur in a training session by the principal investigator (SF) leading up to the trial. The design of both exercise programs and training of instructors (but not participant training) will be performed by the principal investigator (SF) with over 7 years of experience as an Accredited Exercise Physiologist.

Outcome measures

Assessments will be conducted by an exercise physiologist research assistant who is blinded to the study intent and design, and who is not part of exercise delivery. Clinical outcomes of interest will be assessed before and after the completion of the 8-week intervention. Outcomes of interest include self-reported fatigue, self-reported quality of life, and disease activity. Disease activity will be assessed by the co-investigator of the project who is a trained rheumatology practitioner (SO). To accompany disease activity, inflammatory markers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complement components C3 and C4 and anti-double stranded DNA (anti-dsDNA) will be observed in pragmatic blood analyses obtained through the participants regular medical practitioner taken as close to the commencement and completion of the exercise intervention as possible. Additional outcomes that will be measured include aerobic capacity, upper and lower body strength, adherence to the exercise program, and individual experience of the exercise program. Safety of exercise will be assessed by exploring reasons for dropout from the exercise program and the number and type of adverse events that occurred during the exercise intervention.

Disease activity. Disease activity will be assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) at baseline and following the intervention, which is a commonly used instrument for detecting changes in disease activity in patients with SLE (Bombardier et al., 1992). The SLEDAI assesses 24 descriptors including clinical and laboratory measures of SLE activity, identifying a cumulative score ranging from 0 –105, with a higher score meaning higher disease activity. An increase >3 points is considered a flare of the disease. To accompany disease activity, elevations in inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), or a reduction in complement components C3, C4 and anti-double stranded DNA (anti-dsDNA) will be observed in pragmatic blood trials pre- and post- intervention, conducted during their usual practitioner consultations.

Fatigue. Fatigue will be measured by the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT) at baseline and following the intervention. The FACIT-Fatigue scale is a 13-item questionnaire, originally developed in cancer patients, that measures aspects of physical and mental fatigue and subsequent effects on daily living and functioning (Barbacki et al., 2019). Each item in the questionnaire is measured on a 4-point Likert scale. Thus, the total score ranges from 0 to 52, with higher scores representing less fatigue. The first validation study of FACIT-Fatigue scale in SLE was published in 2011 (Lai et al., 2011). The FACIT-Fatigue scale has been shown to have good psychometric properties, detect clinically meaningful and statistically significant differences in several studies in SLE, and is easy and quick to administer (< 5 min) (Barbacki et al., 2019).

Quality of life. Quality of life will be measured using the RAND 36-Item Short Form Health Survey 1.0 (Hays et al., 1993). The SF-36 is a 36-item patient-reported questionnaire that covers eight health domains: physical functioning (10 items), bodily pain (2 items), role limitations due to physical health problems (4 items), role limitations due to personal or emotional problems (4 items), emotional well-being (5 items), social functioning (2 items), energy/fatigue (4 items), and general health perceptions (5 items). Scores for each domain range from 0 to 100, with a higher score defining a more favourable health state (Ware, 2000).

Upper body grip strength. Upper body grip strength will be measured using a hand-grip strength test, which has been shown to serve as a useful tool to predict upper body muscle strength and endurance (Trosclair et al., 2011). Grip strength is a measure of muscular strength, or the maximum force generated by one's forearm muscles. It can be used as a screening tool for the measurement of upper body strength. To perform this test, the participant was standing with shoulder adducted, elbow flexed to 90 degrees, and forearm and wrist neutral. The research assistant will place the dynamometer in the participants' hand while gently supporting the base of the dynamometer, instructing the client to squeeze as hard as possible. The participant will be allowed three attempts of this test, per hand, and the average score of the three attempts per hand was recorded as their result.

Lower body muscular endurance. A 30-second timed sit-to-stand (STS) test will be used to measure participants' lower body muscular endurance because of its excellent test-retest reliability in community dwelling older adults (men, ICC 0.84 and women, ICC 0.92) (Jones et al., 1999), and validity correlating to weight adjusted leg press performance (men, r = 0.78 and women, r = 0.71) (Jones et al., 1999). This test will be performed at baseline and following the intervention. This test involves the participant standing up and sitting down as many times as possible in 30-seconds (higher scores are better). The minimal clinically important improvement (MCII) for a 30-second STS is 2.6 (Wright et al., 2011)

Lower body muscular endurance will be measured using a 30-second timed sit-to-stand (STS) test. This test will be performed at baseline and following the intervention. The STS test is designed to characterize the strength of the lower limbs, with its validity supported by its correlation with "leg-press" strength (0.78 for men and 0.71 for women) (Hays et al., 1993). This test is usually performed on older adults; however, it is a valid and easy test to administer given the limited testing equipment available in this study. The test, which typically incorporates a standard height armless chair, with the participant standing up and sitting down as many times as possible in the 30-seconds whilst their arms are folded over their chest. The number of repetitions completed was counted by the research assistant and recorded as their result.

Aerobic capacity. This will be measured using a sub-maximal treadmill walking test. This test will be performed at baseline and following the intervention and use the same protocol (speed and time intervals). Participants predicted maximum heart rate will be recorded at the start of the test using the formula HRmax = 2015 – (0.5 x age) and will be wearing a HR monitor during the duration of the test. Participants will commence walking at a comfortable speed (and this speed will be record), and every 3-minutes the speed of the treadmill will increase, until maximum walking speed is reached, and then the incline of the angle of the treadmill will be increased. Once participants reach 75% of their predicted maximum HR, the test will stop, and the total distance and time will be recorded. The more distance covered, the better the outcome.

Adherence. To evaluate adherence, attendance to the exercise sessions will be recorded by the research assistant supervising the exercise program. The adherence rate will be calculated by taking the number of attended sessions as a percentage of the total number of scheduled sessions for that participant (Munneke et al., 2003). If the participant attended a session and only participated in half of the session due to unforeseen circumstances, this session will still be recorded as attended. The research assistant accountable for supervising the student supervisors will be responsible for recording attendance and reported this information.

Individual experiences. To explore the individual experiences of the exercise program, participants will be interviewed following the completion of the program. A semi-structured interview with guided questions will be used to explore any changes experienced by the individual following the exercise program, any barriers or challenges to the exercise program, any comments on whether they would continue with this exercise program. This interview will form part of the participant's final assessment performed by the same research assistant who performed their baseline assessment.

Exercise programs

All exercise sessions will be moderate intensity, in accordance with the American college of sports medicine (ACSM) intensity guidelines, commonly reported as a rating of perceived exertion (RPE) between 3-4 out of 10 for moderate intensity. The

same RPE scale will be used for both exercise programs. All participants will be educated on this scale during baseline testing by the research assistant. All sessions will be 50 minutes in duration, inclusive of a 10-minute aerobic and mobility warm up, and 10 minutes static stretching cool down. An additional 10-minutes will also be allocated to allow for pre and post exercise session measurements, making the total time in the gym to be 60-minutes. The resting measures will include Heart rate, blood pressure, and oxygen saturation, as well as perceived level of fatigue and pain using a 10-point Likert numerical scale before commencing the exercise session, and what other physical activity the participant performed in the last 7 days. These results will be recorded as a way of monitoring participants. If the results obtained at the commencement of the session are considered unsafe to exercise (i.e., Blood pressure <90/60 or >150/110, or oxygen saturation <85%), the research assistant will be advised by SF to ask the participant to rest for approximately 5 minutes, and then to re-take the measurements. If results have not improved, the research assistant will advise the participant to not take part in the exercise session and to contact their regular treating physician to follow up.

Resistance training group. The resistance training group is designed in accordance with the ACSM resistance training guidelines. All participants will perform an 8-minute warm up which included a 5-minute light intensity (RPE 1-2/10) walk on the treadmill or rowing machine, followed by mobility and light resistance band exercises, replicable to the exercise session. The next 32-minutes is designed in accordance with ACSM resistance training guidelines for muscular strength, with exercise volume comprising of 3 sets and 10 repetitions, and rest periods of 15-30 seconds between each exercise, 1 minute rest between each set, and inclusion of 8 exercises focusing on major muscle groups. All exercises followed moderate intensity guidelines, with an RPE of 3-4/10 which was monitored through-out the session using a hard copy of the RPE scale. The program is structured as a circuit, with 8 exercises comprising 1 set. All exercises are functional movements that are replicable to activity of daily living such as push, pull, squat, lunge, locomotion, and rotation, using either their own body weight, exercise apparatus such as Thera Bands or external weights. The last 10 minutes include static stretches of major muscle groups and diaphragmatic breathing exercises to slowly return the body to resting state. To progress or regress the resistance program during the 8-weeks, the exercise

load may increase or decrease depending on the participants' rate of perceived of exertion (i.e., if the participants' RPE was below 3-4/10, the research assistant instructed increased the resistance of the TheraBand or added additional weight to a body weight exercise). The same principle will apply if the program needs to be regressed (i.e., if the participants' RPE is above 3-4/10, the research assistant will decrease the resistance of the TheraBand or remove additional weight of an exercise). See figure for the outline of the resistance exercise program.

Figure 1. Resistance exercise program

trength circuit program	Participant code:	Session number:	Precited HRmax: 205- (0.7*age)=				Date of session:
Pre and post measures & debrief (10minutes)	Pre-session measures (5 mins)						Post-session measures (5mins)
	HR:		Fatigue/10:				HR:
	*BP:		Pain/10:				*BP:
	*SaO2:		Sleep? Good / Fair / Poor				*SaO2:
	Other activities this week?						Other?
	*IF BP is too low (<90/60) or too high (>180/120), or O2 = <85%: Re-take, ask how they feel, rest.						Encourage to drink water & rest at the end.
Components	Exercise	Time (mins)	Notes				RPE (/10)
	Treadmill or rowing machine	5 mins					2-3
	Exercise	Reps	Sets	Load	Notes		RPE (/10)
Warm up (10 minutes)	Standing hip circles	10	1	body weight			2-3
	Standing crab walking (2 laps to the side/2 laps forward)	10 steps/side	1	Loop band (light)			2-3
	Standing arm circles (forward/backward)	10/direction	1	Body weight			2-3
	Standing band pull apart	10	1	Band (light)			2-3
	Exercise (Note: KB= kettle bells, DB= Dumbbells)	Reps	Sets	Load	Tempo	Rest (b/w sets)	RPE (/10)
trength circuit (32 minutes)	Banded sit to stand - banded box squat - squat - KB goblet squa	10	3	Loop band	0:1:0:1	15sec	3-4
	TheraBand standing or seated bicep curls - add resistance	10	3	TheraBand	0:1:0:1	15sec	3-4
	Step up on weight plates/donut - step up with DB	10/leg	3	Bodyweight (+DB)	0:1:0:1	15sec	3-4
	Standing Theraband bilateral row - add resistance	10	3	Band	0:1:0:1	15sec	3-4
	Farmers carry with KBs - increase weight of KB	4 laps	3	KB	0:1:0:1	15sec	3-4
	TRX supported lunge	10/leg	3	BW	0:1:0:1	15sec	3-4
	Wall push up - Incline push up on box - TRX push up (use stick)	10	3	BW	0:1:0:1	15sec	3-4
	Standing or seated Therband Paloff press	10	3	Band	0:1:0:1	15sec	3-4
	Exercise	Reps	Sets	Tempo	Notes		RPE (/10)
Cool Down (8 minutes)	Seated glute/piriformis stretch	1	1	30sec			2-3
	Standing calf stretch	1	1	30sec			2-3
	Pec wall stretch	1	1	30sec			2-3
	Standing quad stretch	1	1	30sec			2-3
Additional notes							

Aerobic training group. The aerobic training group is designed in accordance with the ACSM guidelines. All participants will perform an 8-minute warm up which includes a 5-minute light intensity (RPE 1-2/10) walk on the treadmill or rowing machine, followed by mobility and light resistance band exercises, replicable to the exercise session. The next 32-minutes of their aerobic exercise program is designed in accordance with moderate intensity interval training guidelines. All participants will perform 4 sets of 4-min intervals at 70% HR_{max}, or equivalent to an RPE of 3-4/10, with a recovery period of 4 min at 55% $HR_{max,}$ or equivalent to an RPE of 1-2/10, completing a total of 32 minutes. The last 10 minutes includes static stretches of major muscle groups and diaphragmatic breathing exercises to slowly return the

body to resting state. To progress or regress the aerobic exercise program over the 8-weeks, the speed or incline of walking either increased or decreased depending on the participants' RPE (i.e., if the participants' RPE was below 3-4/10, the research assistant will increase the speed on the treadmill from 4km/hour – 4.5km/hour or 2%-3% incline, for example). Only one of two of these components will be increased at one time. The same principle is applied if the program needs to be regressed (i.e., if the participants' RPE is above 3-4/10, the research assistant will decrease the speed on the treadmill from 4.5km/hour – 4km/hour or 4%-3% incline, for example). See figure 2 for the aerobic exercise program.

Figure 2. Aerobic exercise program

Aerobic exercise MIIT program	Participant code:	Session number:	Precited HRmax: 205- (0.7*age)=			Date of session:	
Pre and post measures & debrief (10minutes)	Pre-session measures (5 mins)					Post-session measures (5mins)	
	HR:	Fatigue/10:				HR:	
	*BP:	Pain/10:				*BP:	
	*SaO2:	Sleep? Good / Fair / Poor				*SaO2:	
	Other activities this week?					Other?	
	*IF BP is too low (<90/60) or too high (>180/120), or O2 = <85%: Re-take, ask how they feel, rest.					Encourage to drink water & rest at the end.	
Components	Exercise	Time (mins)	Notes				RPE (/10)
Warm up (10 minutes)	Treadmill or rowing machine	5 mins					2-3
	Exercise	Reps	Sets	Load	Notes		RPE (/10)
	Standing hip circles	10/side	1	BW			2-3
	Standing crab walking (2 laps to the side/2 laps	10 steps/side	1	Loop band			2-3
	Standing arm circles (forward/backward)	10/direction	1	BW			2-3
	Standing calf raises	10	1	BW			2-3
Aerobic moderate intensity interval training (32 minutes)	Exercise (Note: MHR=max heart rate)	Time (mins)	Speed (km/hr)	Incline (%)	HR zones	HR %	RPE (/10)
	Treadmill walking	4mins				55% MHR	2-3
		4mins				70% MHR	3-4
		4mins				55% MHR	2-3
		4mins				70% MHR	3-4
		4mins				55% MHR	2-3
		4mins				70% MHR	3-4
		4mins				55% MHR	2-3
		4mins				70% MHR	3-4
Cool Down (8 minutes)	Exercise	Reps	Sets	Tempo	Notes		RPE (/10)
	Seated glute/piriformis stretch	1	1	30sec			2-3
	Standing calf stretch	1	1	30sec			2-3
	Pec wall stretch	1	1	30sec			2-3
	Standing quad stretch	1	1	30sec			2-3
Additional notes							

Each of the two exercise programs are structured and consistent between participants, however, to ensure the exercise programs are safe and individualised, all participants will receive the same structured program with individualisation of the program limited to the participants' RPE. For example, for the aerobic training program, the structure and duration of the program is the same for all participants, except for speed or incline of the treadmill which will be individualised according to the patients RPE within moderate intensity (i.e., RPE equivalent to 3-4/10). For the resistance training program, the structure and duration of the program will be the same for all participants, except each exercise has regression and progression

options, which can be individualised according to the participants RPE i.e., one participant may perform a sit to stand, and another participant may perform a box squat with or without additional load. The research assistants will be trained on exactly how to modify, regress or progress, or cease the exercise program, if needed, and any changes will be clearly documented in their exercise program hard copy handout.

Statistical Analysis

Quantitative data analysis will include within and between group comparisons using an ANCOVA model. For within group analyses, participants will serve as their own controls, and post-intervention measures will be adjusted using baseline scores as covariates. Adverse events, withdrawals, and participants dropped out or lost to follow up will be reported as counts. Between group comparisons will include both per-protocol and intention to treat analyses to provide estimates of effect sizes regardless of dropouts, withdrawals, or non-compliance with the exercise program. Effect sizes will be calculated as Cohen's d for univariate effects within and between groups, and as eta squared for omnibus effect sizes (variance accounted for by group membership). Qualitative data analysis will be completed using NVivo to analyse themes and subthemes.

Appendix E: Poster Presentation ARA National

RHEUMATOLOGY PRACTITIONERS' VIEW OF EXERCISE

FOR PEOPLE WITH **SYSTEMIC SCLEROSIS OR SYSTEMIC LUPUS ERYTHEMATOSUS.**

This study aims to explore rheumatology practitioners' view and use of exercise interventions for people with Systemic sclerosis or Systemic lupus erythematosus.

FIVE THEMES identified in the interviews

1 Exercise has several benefits

- Joint range of motion
- Activities of daily living
- Energy
- Bone density & blood flow
- Muscular strength & aerobic fitness
- Coping with their illness

2 Exercise presents some barriers

- General: Lack of motivation, conflicting comitments, reduced exercise capacity.
- Structural: Cost, limited sustainable long-term exercise options.
- Disease-related: Fatigue, joint pain, fear of exacerbating disease.

3 Safety concerns limited to those with:

- Pulmonary hypertension
- Pulmonary fibrosis
- Severe skin & joint contractures
- Inflamed joints
- Ulcerated fingertips and toes

4 Practitioners offer some ideas on ways to increase safe exercise participation

- Individually tailored
- Proper guidance and supervision
- Comfortable & temperate environment
- Long-term and sustainable

5 Clinicians feel confident in providing general exercise advice, however, lack time and confidence in prescribing specific exercise.

UNIVERSITY OF SOUTHERN QUEENSLAND

Stephanie Frade, Melainie Cameron, Sean O'Neill, David Greene

Appendix F: Poster Scleroderma NSW newsletter

scleroderma new south wales

EXERCSE AND SCLERODERMA FOCUS GROUPS

Recently, twenty-three people with Systemic sclerosis voluntarily participated in online focus group sessions, as part of a PhD study titled "View of exercise in people with Systemic Sclerosis", hosted by Stephanie Frade from NSW. Stephanie Frade is an Accredited Exercise Physiologist, sessional lecturer at the Australian Catholic University, and PhD candidate from the University of Southern Queensland. She runs her own exercise physiology business "Immune Exercise Physiology", with a special focus on telehealth and home-delivered exercise for people living with an autoimmune disease, and specialising in Systemic sclerosis and Systemic Lupus Erythematosus. Stephanie is also a committee member for Scleroderma NSW.

Stephanie says "My passion in auto-immune disease sparked at a young age, when my mother was diagnosed with Scleroderma, and I was diagnosed with Systemic lupus erythematous. This triggered a desire in me to understand more about the diseases and how exercise could play a role in improving our quality of life, and share this knoweldge with others"

The main questions that were asked in the focus groups were:

- What are your barriers to engaging in exercise?
- What do you currently do for exercise?
- What benefits do you get out of exercising?
- What aspects of exercise do you enjoy?
- What aspects of exercise do you not enjoy or find difficult?
- Does your GP or specialists discuss exercise with you?
- How has exercise changed for you during COVID-19 and lockdown?

Everyone in the focus groups contributed equally to the discussion, bouncing ideas off each-other, and connecting over similar and differing views. Everyone shared their individual experience with exercise, the barriers they personally face in engaging in exercise, the benefits they feel from exercise, and how COVID-19 has impacted their exercise routine. Stephanie will be analysing the data, and upon completion, this will be likely published in an established journal. We will share this with all our members when available.

Since these focus group sessions were well received by the participants, and because our members live all over NSW, Scleroderma NSW intends to run more online focus group sessions (not research related) as part of our social networking.

As we know, we all experience different symptoms and manifestations from scleroderma, and what works for some does not always work for everyone. For this reason, it is important that you consult with your regular treating practitioner and an Exercise specialist, who can provide exercise advice and prescribe and modify a suitable exercise program for you.

Immune Exercise Physiology

If you would like to get in touch with Stephanie, her contact details are below:

P: 0412567110 E: contact@immuneep.com.au

W: www.immuneexercisephysiology.com.au

Appendix G: Factsheet for Exercise & Sport Science Australia

AUTOIMMUNE DISEASES

WHAT IS AN AUTOIMMUNE DISEASE?

The role of the immune system is to protect us and keep us healthy. If infectious agents such as bacteria or viruses get into our body, immune cells usually kill or overwhelm them, removing the infection or disease. This is known as the immune response. An autoimmune disease is when the immune system fails to recognize self from non-self, is chronically overactive, and mistakenly attacks its own healthy cells. Autoimmune rheumatic diseases (ARDs) are a group of systemic autoimmune disorders that mainly affect joints, bones and soft tissues and are associated with substantial morbidity and mortality. Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), idiopathic inflammatory myopathies (IIM), systemic sclerosis (SSc), and ankylosing spondylitis (AS) are autoimmune diseases that have been strongly related to sustained inflammation, and share common clinical features including periodic pain, chronic fatigue, depression, and, consequently, reduced physical activity and poor health-related quality of life.

TYPES OF AUTOIMMUNE DISEASES

There are more than 80 types of autoimmune diseases, with over half of them being considered rare. The overall estimated prevalence is 4.5%, with 2.7% for males and 6.4% for females, being more common in females and running in families. An autoimmune disease can either be organ-specific or systemic. There is an autoimmune disease specific for nearly every organ in the body, usually involving response to an antigen expressed only in that organ. Some organ-specific autoimmune diseases include coeliac disease, gastritis, graves' disease type 1 diabetes, and multiple sclerosis. In other autoimmune diseases the response seems to be directed against antigens that are widely expressed throughout the body. Some examples of systemic autoimmune diseases include systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis and polymyositis.

HOW DOES EXERCISE HELP WITH AUTOIMMUNE DISEASES?

Regular exercise appears to be safe and beneficial at a moderate intensity in modulating some of the most concerning symptoms, such as fatigue, in people with SLE, SSc, RA and MS. Fatigue is a commonly reported symptom experienced by people living with SSc and SLE, affecting up to 80% of SLE patients. Regular exercise training may lead to anti-inflammatory benefits in chronic diseases with systemic low-grade inflammation (i.e. type 2 diabetes) by reducing inflammatory markers, and is regarded as a valuable self-care intervention . Given the potential role of inflammation in the etiology and clinical symptoms of SLE, SSc, RA, and other autoimmune diseases, including pain, redness and swelling, it is postulated that exercise training, if able to alleviate the inflammatory process, could also be helpful in treating the symptoms related to inflammation in this population.

WHAT TYPE OF EXERCISE IS BEST FOR AUTOIMMUNE DISEASES?

Aerobic training combined with strength training is recommended as routine practice in patients with RA, with improvements in aerobic capacity, physical function, and fatigue. Exercise can be just as safe for people with an autoimmune disease as it is for people without, if there is a good understanding of the disease, symptoms, any side effects to medications and the person. It is important that if you have an autoimmune disease, your exercise program is supervised by an accredited exercise professional.

THINGS TO REMEMBER

You may have 'good days' and 'bad days' with your autoimmune disease, and there will be times when you will feel better and other times when you will have increased symptoms. For some, the illness can be mild, and symptoms appear to go away, whilst for others the symptoms can impact on their life considerably and require specialised treatment. Common treatments include different types of medication, which can compromise your immune system and make your body more prone to infection. It is important to ensure proper hygiene practices are in place during exercise, and that adequate rest is provided where needed.

PREPARED BY: *Prepared by Stephanie Frade* | SOURCE: Exercise is Medicine Australia
Always seek professional advice from an Accredited Exercise Physiologist. Find one here: www.essa.org.au/find-aep

Appendix H: Factsheet for Exercise & Sport Science Australia

EXERCISE PHYSIOLOGY AND RHEUMATOLOGY

ESSA
EXERCISE & SPORTS SCIENCE AUSTRALIA

What is an Accredited Exercise Physiologist?

An Accredited Exercise Physiologist (AEP) is a university-qualified allied health professional. They specialise in designing and delivering safe and effective exercise interventions for people with chronic medical conditions, injuries or disabilities. Services delivered by an AEP are also claimable under compensable schemes such as Medicare and covered by most private health insurers. When it comes to the prescription of exercise, they are the most qualified professionals in Australia.

An AEP is qualified to work with a range of Autoimmune & Rheumatic Disease, including, but not limited to:

- Systemic Sclerosis (Scleroderma)
- Systemic Lupus Erythematosus (Lupus)
- Osteoarthritis
- Rheumatoid Arthritis
- Ankylosing Spondylitis
- Sjogren's Syndrome
- Polymyalgia Rheumatica
- And many more...

An AEP can guide you with safe, graded, & individualised exercise to help manage:

- Fatigue
- Pain
- Inflammation
- Depression and anxiety
- Quality of life
- Cardiovascular fitness
- Functional strength
- Independence and activities of daily living

What makes an AEP different to other exercise professionals?

Accredited Exercise Physiologists are allied health professionals who have undergone a minimum of four years study at university. They use evidence-based movement and exercise intervention for chronic disease prevention and management, musculoskeletal injuries and weight management. AEPs often work as part of a team of doctors, physiotherapists and other allied health professionals to ensure the best results for their clients.

AEPs can help manage the health and well-being of those living with chronic autoimmune and rheumatic disease. AEPs also work within rebateable schemes such as Medicare, NDIS and private health insurance.

Why a Rheumatology practitioner or General practitioner may refer you to an AEP?

- To improve your quality of life
- To improve your quality of care
- To support you in managing your physical activity and exercise levels in a safe, supervised and individualised way

HOW CAN YOU FIND AN AEP TO SUPPORT YOU?

Visit www.essa.org.au/find-aep to locate an AEP in your local area.

Appendix I: Additional information

Appendix I-1: Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)

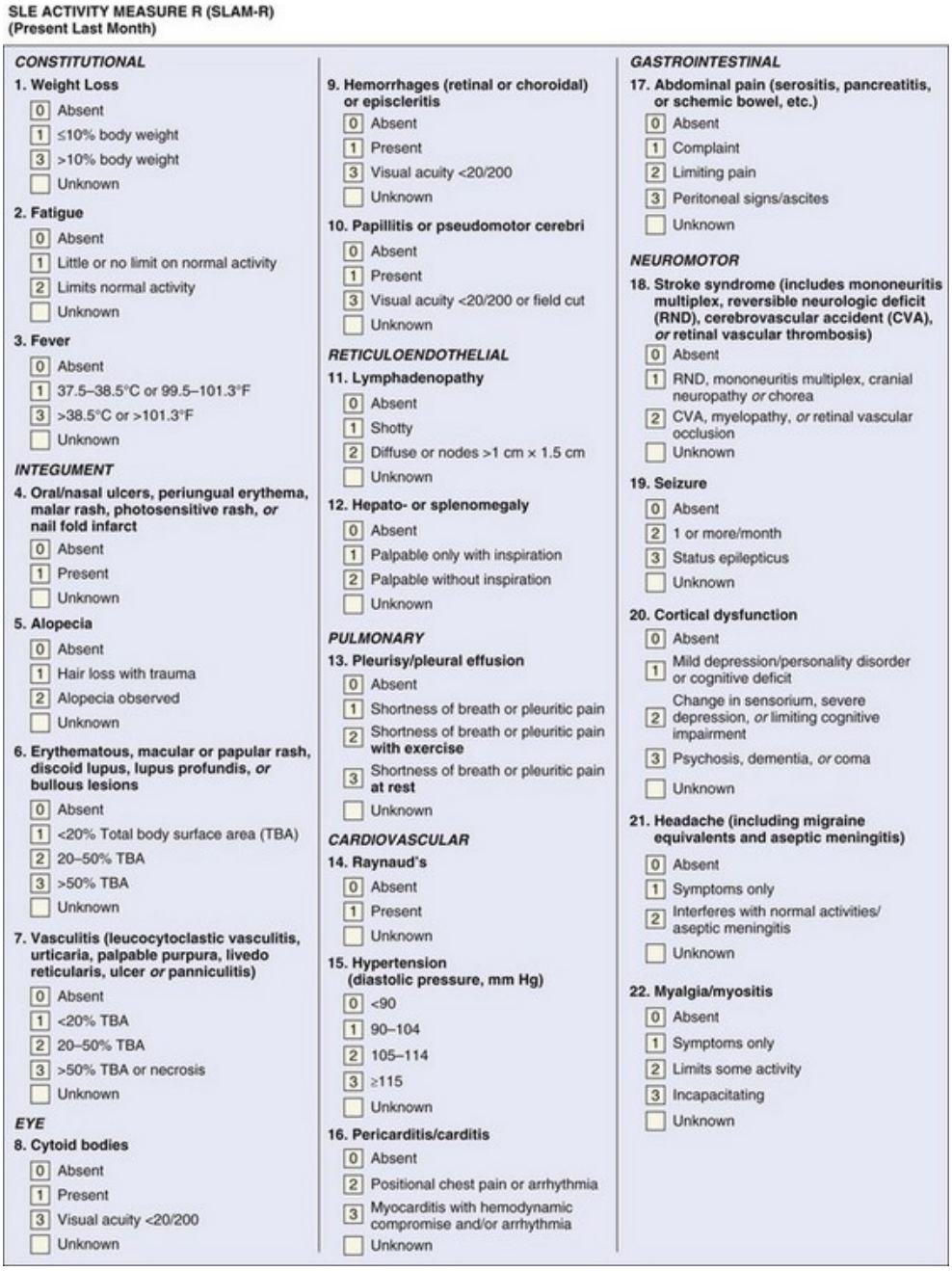
(Gladman, Ibañez, & Urowitz, 2002)

Study No.: _____ Patient Name: _____ _____ Visit Date: ___

(Enter weight in SLEDAI Score column if descriptor is present at the time of the visit or in the preceding 10 days.)

Weight	SLEDAI SCORE	Descriptor	Definition
8	_____	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	_____	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	>0.5 gram/24 hours
4	_____	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	_____	Rash	Inflammatory type rash.
2	_____	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____	Mucosal ulcers	Oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	>38° C. Exclude infectious cause.
1	_____	Thrombocytopenia	<100,000 platelets / $x10^9$/L, exclude drug causes.
1	_____	Leukopenia	< 3,000 white blood cells / $x10^9$/L, exclude drug causes.
TOTAL SLEDAI SCORE	_____		

Appendix I-2: Systemic Lupus Activity Measure (SLAM) (Bae et al., 2001b)



SLE ACTIVITY MEASURE R (SLAM-R)
(Present Last Month)

CONSTITUTIONAL

1. Weight Loss
- [0] Absent
- [1] ≤10% body weight
- [3] >10% body weight
- [ ] Unknown

2. Fatigue
- [0] Absent
- [1] Little or no limit on normal activity
- [2] Limits normal activity
- [ ] Unknown

3. Fever
- [0] Absent
- [1] 37.5–38.5°C or 99.5–101.3°F
- [3] >38.5°C or >101.3°F
- [ ] Unknown

INTEGUMENT

4. Oral/nasal ulcers, periungual erythema, malar rash, photosensitive rash, *or* nail fold infarct
- [0] Absent
- [1] Present
- [ ] Unknown

5. Alopecia
- [0] Absent
- [1] Hair loss with trauma
- [2] Alopecia observed
- [ ] Unknown

6. Erythematous, macular or papular rash, discoid lupus, lupus profundis, *or* bullous lesions
- [0] Absent
- [1] <20% Total body surface area (TBA)
- [2] 20–50% TBA
- [3] >50% TBA
- [ ] Unknown

7. Vasculitis (leucocytoclastic vasculitis, urticaria, palpable purpura, livedo reticularis, ulcer *or* panniculitis)
- [0] Absent
- [1] <20% TBA
- [2] 20–50% TBA
- [3] >50% TBA or necrosis
- [ ] Unknown

EYE

8. Cytoid bodies
- [0] Absent
- [1] Present
- [3] Visual acuity <20/200
- [ ] Unknown

9. Hemorrhages (retinal or choroidal) or episcleritis
- [0] Absent
- [1] Present
- [3] Visual acuity <20/200
- [ ] Unknown

10. Papillitis or pseudomotor cerebri
- [0] Absent
- [1] Present
- [3] Visual acuity <20/200 or field cut
- [ ] Unknown

RETICULOENDOTHELIAL

11. Lymphadenopathy
- [0] Absent
- [1] Shotty
- [2] Diffuse or nodes >1 cm × 1.5 cm
- [ ] Unknown

12. Hepato- or splenomegaly
- [0] Absent
- [1] Palpable only with inspiration
- [2] Palpable without inspiration
- [ ] Unknown

PULMONARY

13. Pleurisy/pleural effusion
- [0] Absent
- [1] Shortness of breath or pleuritic pain
- [2] Shortness of breath or pleuritic pain **with exercise**
- [3] Shortness of breath or pleuritic pain **at rest**
- [ ] Unknown

CARDIOVASCULAR

14. Raynaud's
- [0] Absent
- [1] Present
- [ ] Unknown

15. Hypertension (diastolic pressure, mm Hg)
- [0] <90
- [1] 90–104
- [2] 105–114
- [3] ≥115
- [ ] Unknown

16. Pericarditis/carditis
- [0] Absent
- [2] Positional chest pain or arrhythmia
- [3] Myocarditis with hemodynamic compromise and/or arrhythmia
- [ ] Unknown

GASTROINTESTINAL

17. Abdominal pain (serositis, pancreatitis, or schemic bowel, etc.)
- [0] Absent
- [1] Complaint
- [2] Limiting pain
- [3] Peritoneal signs/ascites
- [ ] Unknown

NEUROMOTOR

18. Stroke syndrome (includes mononeuritis multiplex, reversible neurologic deficit (RND), cerebrovascular accident (CVA), *or* retinal vascular thrombosis)
- [0] Absent
- [1] RND, mononeuritis multiplex, cranial neuropathy *or* chorea
- [2] CVA, myelopathy, *or* retinal vascular occlusion
- [ ] Unknown

19. Seizure
- [0] Absent
- [2] 1 or more/month
- [3] Status epilepticus
- [ ] Unknown

20. Cortical dysfunction
- [0] Absent
- [1] Mild depression/personality disorder or cognitive deficit
- [2] Change in sensorium, severe depression, *or* limiting cognitive impairment
- [3] Psychosis, dementia, *or* coma
- [ ] Unknown

21. Headache (including migraine equivalents and aseptic meningitis)
- [0] Absent
- [1] Symptoms only
- [2] Interferes with normal activities/ aseptic meningitis
- [ ] Unknown

22. Myalgia/myositis
- [0] Absent
- [1] Symptoms only
- [2] Limits some activity
- [3] Incapacitating
- [ ] Unknown

JOINTS

23. Joint pain

- [0] Absent
- [1] Arthralgia only
- [2] Objective synovitis
- [3] Limits function
- [ ] Not recorded

LABORATORY

25. Hematocrit (mL/dL)

- [0] >0.35
- [1] 0.30–0.35
- [2] 0.25–0.29
- [3] <0.25
- [ ] Not recorded

26. White blood cell count (per mm^3)

- [0] >3.5
- [1] 2.0–3.5
- [2] 1.0–1.9
- [3] <1.0
- [ ] Not recorded

27. Lymphocyte count (per mm^3)

- [0] 1.5–4.0
- [1] 1.0–1.49
- [2] 0.5–0.99
- [3] <0.5
- [ ] Not recorded

28. Platelet count (×1000 per mm^3)

- [0] >150
- [1] 100–150
- [2] 50–99
- [3] <50
- [ ] Not recorded

29. Westergren ESR (mm/hr)

- [0] <25
- [1] 25–50
- [2] 51–75
- [3] <75
- [ ] Not recorded

30. Serum creatinine (μmol/L) or creatinine clearance (% normal)

- [0] 44–123 or 80–100%
- [1] 124–185 or 60–79%
- [2] 186–354 or 30–59%
- [3] >354 or <30%
- [ ] Not recorded

31. Urine sediment (per hpf)

- [0] Normal
- [1] 6–10 RBC or 6–10 WBC;
  or 0–3 granular or 0–3 non RBC casts;
  or trace to 1+ (on dipstick)
  (<500 mg/L 24 urine protein)
- [2] 11–25 RBC or 11–25 WBC;
  or >3 granular or >3 non RBC casts;
  or 2 to 3+ (on dipstick)
  (500 mg–3.5 g/L 24 urine protein)
- [3] >25 RBC or >25 WBC;
  or any RBC casts;
  or 4+ (on dipstick)
  (>3.5 g/L urine protein)
- [ ] Not recorded

Total SLAM-R score: _____