[Intervention Protocol]

Exercise as adjunctive therapy for systemic lupus erythematosus

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To evaluate the safety and effectiveness of structured exercise interventions for adults with systemic lupus erythematosus.

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. 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 among 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 comparison 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. For people with SLE, their usual care may involve regular use of pharmaceutical treatments including hydroxychloroquine, glucocorticoids, immunosuppressive drugs, biological agents, or a combination of these. 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, non-steroidal anti-inflammatory drugs (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 will focus on studies that examine 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. Resistance training is a type of physical exercise specialising in the use of resistance to induce muscular contraction that builds the strength, anaerobic endurance, and size of skeletal muscles that can be structured or unstructured, for example, sitting to standing, walking upstairs, and lifting groceries. 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 (HRmax) OR a rating of perceived exertion (RPE) value of 5 to 7/10), moderate (55% to less than 70% HRmax OR an RPE value of 3 to 4/10), or light (40% to less than 55% HRmax OR an RPE value of 1 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 two systematic reviews that assess the safety and effectiveness of exercise in adults with SLE, both of which were published in 2017 (O'Dwyer 2017; Wu 2017).

Exercise was found to improve depression and fatigue and not alter disease activity in adults with SLE compared to control groups (O'Dwyer 2017). Meta-analyses of seven studies (Abrahão 2016; Boström 2016; Carvalho 2005; Dos Reis-Neto 2013; Miossi 2012; Robb-Nicholson 1989; Tench 2003) found that disease activity was not significantly changed following exercise interventions (MD = 0.01; 95% CI: -0.54 to 0.56), fatigue significantly decreased in the exercise intervention group compared to controls (MD = -0.52; 95% CI:–0.91 to –0.13), and depression scores significantly 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.

Similarly, a 12-week supervised aerobic exercise program reduced fatigue for SLE patients with mild disease activity (Wu 2017). Meta-analysis of three trials (Carvalho 2005; Ramsey-Goldman 2000; Tench 2003) 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 SF36 vitality subscale (MD = 14.98; 95% CI: 7.45, 22.52). However, the quality of evidence assessed using PEDro was downgraded to fair (Tench 2003) or poor (Ramsey-Goldman 2000).

These two reviews identified that exercise is effective in managing concerning symptoms of SLE including fatigue and depression. However, 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. This review will be conducted according to the guidelines recommended by the Cochrane Musculoskeletal Editorial Board (Ghogomu 2014).

OBJECTIVES

To evaluate the safety and effectiveness of structured exercise interventions for adults with systemic lupus erythematosus.

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

We will include trials with adults (aged 18 years or greater), diagnosed with SLE according to the study author's report. We will include trials using American College of Rheumatology (ACR) criteria and European League Against Rheumatism (EULAR) criteria, and with systemic disease involving at least two body sites or organ systems. We will include trials that define SLE according to incomplete or partial diagnostic criteria, and provide notes to identify possible weaknesses in selection. We will exclude trials including 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 cannot be determined on the participants with SLE alone. We will include intervention trials without regard to race, gender, or disease duration of participants.

Types of interventions

We will include any RCT that evaluates the effect of an exercise programme compared with usual care (no exercise/wait list control), active control (education/counselling), or placebo in adults with SLE. We will include studies in which exercise is used as an adjunct to pharmacological management if the effect of the exercise can be determined. Exercise interventions may be performed at any intensity, in any environment, and can include an individual type of exercise or a combination of various types. Exercise interventions must be structured, recurring, and prescriptions should include specific dosage information (i.e. frequency, intensity, timing, type). Aerobic exercise may include, but not limited to, walking (treadmill or free), cycling (stationary or free), swimming, or aerobics classes. Range of movement exercise may 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 may also be included. Exercise environments may include water- or, land-based exercise, indoor or outdoor settings, home-based or community led, supervised or unsupervised, face-to-face or telehealth.

Control groups receive usual care (no exercise/wait list control), an active control where participants receive an alternative intervention such as education about exercise or counselling about exercise, or a placebo control.

We will exclude studies if the exercise intervention is not structured (i.e. the exercise intervention does not have a dosage for frequency, intensity, or duration of exercise) or if the exercise intervention is an acute bout of exercise (i.e. one individual session of exercise or one exercise test).

Types of outcome measures

Studies will not be excluded on basis of outcome reporting.

Major outcomes

1. 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. 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. 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. 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. 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), number of SAEs, or number of people with one or more SAE.
7. Withdrawals due to adverse events.

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. Mean or mean change in aerobic fitness assessed by predicted or absolute value of maximum rate of oxygen consumption (VO_{2max}).
3. 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. Mean or mean change in anxiety assessed by Hospital Anxiety and Depression Scale (HADS) or other relevant anxiety scales.
5. Withdrawals from the interventions for any reasons.

We will analyse all exercise interventions in the pooled primary analysis, and explore exercise setting (supervised, unsupervised/home-based) and types of exercise (aerobic, resistance, relaxing) in subgroup analyses. For efficacy outcomes, we will extract data from the end of intervention time point. We will extract 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 will search the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, CINAHL, SPORTDiscus, Embase, and Web of Science. We will also conduct a search of ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO trials portal (www.who.int/ictrp/en/). We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

See Appendix 1 for the MEDLINE search strategy. We will adapt this search strategy for the other databases.

Searching other resources

We will not contact organisations to obtain additional references. We will search for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed), and report the date this was done within the review. We will handsearch the reference lists of included trials to identify any additional studies.

Data collection and analysis

Selection of studies

Two review authors (SF, MC) will independently screen titles and abstracts for inclusion of all the potentially relevant studies we identify as a result of the search, and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publication and two review authors (SF, MC) will independently screen the full text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (SO). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (PRISMA Group 2009; prisma-statement.org/PRISMAStatement/Default.aspx) and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. One review author (SF) will extract study characteristics from included studies. A second review author (MC) will spot-check study characteristics for accuracy against the trial report. We will extract the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run-in' period, 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 is supervised.
4. Outcomes: primary and secondary 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) will independently extract outcome data from included studies. We will extract the number of events and number of participants per treatment group for dichotomous outcomes, and means, standard deviations, and number of participants per treatment group for continuous outcomes. We will note 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 will resolve disagreements by consensus or by involving a third review author (SO). One review author (SF) will transfer data into Review Manager 5 (Review Manager 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports.

We will use Plot Digitiser (computer program) to extract data from graphs or figures (Plot Digitizer). These data will also be extracted in duplicate.

If more than one measure for an outcome (i.e. fatigue, quality of life) is reported, we will extract only the one reported by most of the included trials. In the event of multiple outcome reporting, if both final values and change from baseline values are reported for the same outcome, we will extract the final values, as reported in the publication. Similarly, if data are analysed based on an intention-to-treat (ITT) sample and another sample (e.g. per-protocol, as-treated), we will extract the ITT sample for both outcomes assessing benefits and outcomes assessing harms. If data for more than one time point are provided, we will use the longest time point for the meta-analysis.

Assessment of risk of bias in included studies

Two review authors (SF, MC) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 8; Higgins 2020). We will resolve any disagreements by discussion or by involving another review author (SO). We will assess 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 will grade each potential source of bias as high, low, or unclear risk, and provide a quote from the study report together with a justification for our judgement in the risk of bias table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for objective outcome measures may be different than for a participant-reported scale). In addition, we will consider the impact of missing data by key outcomes.

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

When considering treatment effects, we will consider the risk of bias for the studies that contribute to that outcome.

We will present the figures generated by the risk of bias tool to provide summary assessments of the risk of bias.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratios or Peto odds ratios when the outcome is a rare event (approximately less than 10%), with 95% confidence intervals (CIs). We will analyse continuous data as mean difference (MD; if studies use the same scale) or standardised mean difference (SMD; if studies use different scales) with 95% CIs. We will enter data presented as a scale with a consistent direction of effect across studies.

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

For dichotomous outcomes, we will calculate the number needed to treat for an additional beneficial outcome (NNTB), or the number needed to treat for an additional harmful outcome (NNTH) from the control group event rate and the risk ratio using the Visual Rx NNT calculator (Cates 2008).

We will use the minimal clinical important difference (MCID) in the calculation of NNTB or NNTH; we will assume an 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-F scale in people with SLE. 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 will consider 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 will use the SMD interpretation where values greater than 0.8 will be considered clinically significant (large effect).

For dichotomous outcomes, we will calculate 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 will calculate the absolute percent change by dividing the MD by the scale of the measure and expressed as a percentage.

In the 'Effects of interventions' results section and the 'What happens' column of the summary of findings table, we will provide the absolute percent change and the NNTB or NNTH (the NNTB or NNTH will be provided only when the outcome shows a clinically significant difference).

Unit of analysis issues

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting. We will list all treatment arms in the 'Characteristics of included studies' table, even if they are not used in the review.

We will analyse non-standard designs (i.e. cluster-randomised trials and crossover trials) 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 will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when data are not available for all participants). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. We will clearly describe any assumptions and imputations to handle missing data and explore the effect of imputation using sensitivity analyses.

For dichotomous outcomes (e.g. number of withdrawals due to adverse events), we will calculate 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 will calculate the MD or SMD based on the number of participants analysed at that time point. If the number of participants analysed is not presented for each time point, we will use the number of randomised participants in each group at baseline.

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

Assessment of heterogeneity

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

As recommended in *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 will keep 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 will be interpreted where a $P \leq 0.10$ will indicate evidence of statistical heterogeneity.

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

Assessment of reporting biases

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

To assess outcome reporting bias, we will check trial protocols against published reports. For studies published after 1 July 2005, we will screen 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 will evaluate whether selective reporting of outcomes is present.

Data synthesis

We will undertake meta-analyses only where this is meaningful (i.e. if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense). We anticipate that the following comparisons will be used.

1. Exercise versus usual care (no exercise/wait list control).
2. Exercise versus active control (education/counselling).
3. Exercise versus placebo.

We will use a random-effects model. We will analyse all types of exercise interventions in the pooled primary analysis. All trials will be included in the primary analysis. Sensitivity analyses will be undertaken using a fixed-effect model on trials with low risk of bias.

Subgroup analysis and investigation of heterogeneity

If there are sufficient data, we will conduct subgroup analyses for fatigue according to components of exercise. We will restrict 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 will use the formal test for subgroup interactions in Review Manager 5 (Review Manager 2014), and will 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 will 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 plan 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 will assess the certainty of the supporting evidence behind each estimate of treatment effect using the GRADE approach. We will use methods and recommendations described in *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 14; Schünemann 2020). We will use 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 contribute data to the meta-analyses for the prespecified outcomes, and report the certainty of evidence as high, moderate, low, or very low.

We will use GRADEpro GDT software to prepare and display the summary of findings tables (GRADEpro GDT). We will justify all decisions to downgrade the certainty of evidence for each outcome using footnotes, and we will make comments to aid the reader's understanding of the review where necessary. We will provide the NNTB or NNTH and absolute percent change in the 'What happens' column of the summary of findings table as described in the 'Measures of treatment effect' section.

We have 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 adverse events.

We will produce three summary of findings tables for the following comparisons.

1. Exercise versus usual care (no exercise/wait list control).
2. Exercise versus active control (education/counselling).
3. Exercise versus placebo.

For efficacy outcomes, we will extract data at the end of intervention time point. We will extract 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 will follow the guidelines in *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 15; Schünemann 2020), for interpreting results, and will be aware of distinguishing a lack of evidence of effect from a lack of effect. We will base 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 will suggest priorities for future research and outline what the remaining uncertainties are in the area.

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APPENDICES

Appendix 1. MEDLINE search strategy

1. Lupus

2. SLE

3. "systemic Lupus Erythematosus"

4. or/1-3

5. exercis*

6. "physical activity"

7. "physical activities"

8. or/5-7

9. 4 AND 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

HISTORY

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CONTRIBUTIONS OF AUTHORS

All authors contributed to each stage of the protocol, including conceiving the protocol; designing the protocol; planning the search strategy; designing data extraction methods; planning data management and analysis; writing, proof-reading, and editing the protocol; and responding to critique from peer reviewers.

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SF: none.

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