Exercise and physical activity in systemic lupus erythematosus: A systematic review with meta-analyses

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ABSTRACT

Systemic lupus erythematosus (SLE) associates with enhanced cardiovascular (CV) risk frequently unexplained by traditional risk factors. Physical inactivity, common in SLE, likely contributes to the burden of CV risk and may also be a factor in co-morbid chronic fatigue. This systematic review evaluates whether exercise has a deleterious effect on disease activity in SLE, and explores effects on CV function and risk factors, physical fitness and function and health-related measures.

Materials and methods: A systematic review, with meta-analyses, was conducted; quasi-randomised and randomised controlled trials in SLE comparing at least one exercise group to controls were included. MEDLINE/PubMed, EMBASE, PEDro, AMED, CINAHL, The Cochrane Central Register of Controlled Trials, and relevant conference abstracts were searched. Random-effects meta-analyses were used to pool extracted data as mean differences. Heterogeneity was evaluated with χ^2 test and I^2, with $p < 0.05$ considered significant.

Results: The search identified 3068 records, and 31 full-texts were assessed for eligibility. Eleven studies, including 469 participants, were included. Overall risk of bias of these studies was unclear. Exercise interventions were reported to be safe, while adverse effects were rare. Meta-analyses suggest that exercise does not adversely affect disease activity, positively influences depression, improves cardiorespiratory capacity and reduces fatigue, compared to controls. Exercise programmes had no significant effects on CV risk factors compared to controls.

Conclusion: Therapeutic exercise programmes appear safe, and do not adversely affect disease activity. Fatigue, depression and physical fitness were improved following exercise-based interventions. A multimodal approach may be suggested, however the optimal exercise protocol remains unclear.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease which, despite advances in therapy, continues to associate with premature mortality, largely attributable to cardiovascular (CV) causes [1,2]. The excess CV morbidity in SLE is multifactorial, contributed to by disease and treatment-specific features, in addition to both traditional and non-traditional CV risk factors. Notwithstanding innumerable advances in SLE therapy over the past six decades, including corticosteroids, immunosuppressives, immunomodulators, improved antibiotics and angiotensin converting enzyme inhibitors, CV outcomes remain unchanged [3,4].

Myocardial infarction, the leading cause of death in people with SLE, occurs on an average at 49 years of age, 20 years earlier than the general population [5]. Patients with SLE also have significantly increased subclinical atherosclerosis, measured as carotid artery plaque or coronary artery calcification [6,7]. Of further concern is the fact that medications, proven in primary and secondary prevention in the general population, such as HMG-CoA reductase inhibitors, are yet to be shown to be beneficial in SLE [8].

Individuals with SLE have many actual and perceived barriers to exercise [9]. Physical impediments include arthritis, arthralgias and avascular necrosis, serositis, pulmonary involvement and anaemia. Fatigue, depression and co-morbid fibromyalgia are contributing factors. Furthermore, individuals with SLE appear to have lower cardiovascular capacity [10,11] and diminished muscular strength [11] compared to controls. These barriers mean that patients are often reluctant to exercise and it is likely that

their sedentary lifestyle is infrequently addressed by clinicians despite the numerous health benefits associated with physical activity [12].

Physical inactivity is an independent risk factor for cardiovascular events [13] and is highly prevalent in SLE [9,14]. Exercise and physical activity decrease cardiovascular morbidity and mortality in the general population [12,15]. Data from the Framingham Heart Study indicate that high levels of physical activity (in those over the age of 50) associate with an increased life expectancy of 3.7 years in men and 3.5 years in women [16]. In women with SLE, decreased physical activity has been shown to associate with pro-inflammatory high-density lipoprotein (HDL) and with increased carotid plaque [17].

Exercise is an important component of the management of a number of rheumatic conditions, and associated co-morbidities (RA [18], AS [19] and OA [20]). However, exercise has not traditionally been part of the care plans for individuals with SLE. Despite minimal SLE-specific evidence, in 2008 EULAR made recommendations for the management of SLE [21]. Physical activity, weight control and smoking cessation were identified as positive lifestyle modification strategies, particularly for individuals with increased CVD risk. In the years since, researchers have investigated the impact of therapeutic exercise on various outcomes in SLE. To date, only fatigue has been the subject of a systematic review; del Pino-Sedeño et al. [22] and Yuen and Cunningham [23] concluded that aerobic exercise appears effective in reducing fatigue in individuals with SLE. Other narrative reviews have suggested that habitual exercise has a role in preventing cardiovascular risks [24–26], in addition to reducing physical and psychological symptoms of SLE [24], enhancing physical fitness [25,26] and improving health-related quality of life [25,26]. There is a need for a systematic synthesis of studies to date to evaluate current evidence regarding the role of exercise in managing SLE.

This systematic review with meta-analyses aimed to establish the effect of exercise and physical activity on disease activity in adults with SLE, including any deleterious effects. Additionally, this study evaluated the effects of exercise interventions on (1) cardiovascular function and risk factors, (2) physical fitness and function, (3) health-related measures and (4) habitual physical activity levels, in adults with SLE. A final objective was to explore the effects of different types of exercise programmes.

Materials and methods

A protocol outlining the planned search strategy and methods of analysis for this review was registered online with a registry of systematic reviews (available at http://www.crd.york. ac.uk/prospero/display_record.asp?ID=CRD42016036407). The reporting was guided by the 'Preferred Reporting Items for Systematic Reviews and Meta-analyses' (PRISMA) recommendations [27].

Eligibility criteria

Studies evaluating adults diagnosed with SLE by established criteria [28,29] were eligible. Those with participants under 18 years of age were excluded. Review articles, observational studies, case reports, commentaries and studies with ≤ 5 participants were also excluded. Quasi-randomised and randomised controlled trials (RCTs) in which at least one of the groups received exercise therapy were included. This included studies comparing exercise to no intervention controls, studies comparing different exercise or physical activity protocols (e.g., aerobic exercise versus strengthening exercise), and studies comparing an exercise-based intervention to another treatment approach (e.g., relaxation).

Exercise-based interventions comprised one or more of the following components: range of motion (stretching), resistance training, or aerobic exercise. Any dosages of exercise prescription were considered (i.e., any frequency, intensity, mode, or duration). Behaviour change interventions targeting habitual physical activity were also eligible for inclusion. However, interventions offering general advice to exercise or to be active, without prescribing specific exercises, were excluded. Studies in which exercise-based interventions were administered in conjunction with other modalities (e.g., manual therapy) were excluded.

The primary outcomes of interest were condition-related outcomes, cardiovascular risk factors, and habitual physical activity or energy expenditure collected over at least 24 h. These included both self-report methods (e.g., questionnaires) and objective measures (e.g., pedometry). Secondary outcome variables were health-related fitness (aerobic capacity, muscular strength and body composition), depression, physical function and quality of life. Outputs expressed as continuous variables [e.g., body mass index (BMI), VO_{2MAX}] or categorical variables (e.g., high/moderate/low physical activity level) were eligible (Supplement 1).

Information sources and study selection

Studies were retrieved by searching six electronic databases (MEDLINE/PubMed, EMBASE, PEDro, AMED, CINAHL and The Cochrane Central Register of Controlled Trials) from their inception to October 2016. Search terms were adapted for use with each database, and consisted of common keywords and medical subject headings related to SLE and exercise (Supplement 2). No search restrictions were imposed. The electronic database search was supplemented by searching abstracts from the annual congresses of the World Confederation for Physical Therapy (2003–2015), the American College of Rheumatology (2006–2015), the European League Against Rheumatism (2002–2015) and the American Physical Therapy Association (2002–2015). When only abstracts were available in the published literature, authors were contacted seeking full-text manuscripts of relevant studies. Finally, a hand search of the reference lists of included studies was conducted.

Two reviewers (T.O.D. and F.W.) independently screened titles and abstracts to identify studies that potentially met the eligibility criteria using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Full-texts of these reports were retrieved and assessed for eligibility (T.O.D. and F.W.); inter-reviewer disagreements on inclusion were resolved by discussion to achieve consensus and, failing agreement, a third reviewer (L.D.) was consulted.

Data collection and analysis

A standardised data extraction template based on Cochrane recommendations was piloted on five randomly selected studies, and modified accordingly for this review [30]. The review team recorded the following: (1) study characteristics, (2) participant characteristics, (3) features of the intervention and control groups and (4) relevant outcome data. In cases where elaboration on published material was needed or further data was required, study authors were contacted requesting the pertinent information. In trials comparing two exercise groups with one control group, the exercise group results were pooled for comparative purposes, when appropriate [31].

For suitable outcomes, random-effects model meta-analyses were conducted to pool extracted data as mean differences (MD) with 95% confidence intervals; for continuous data reported on different scales standardised mean differences (SMD) with 95%

confidence intervals were used. Heterogeneity of studies was evaluated with χ^2 test and I^2, with $p < 0.05$ considered significant. For comparisons unsuitable for meta-analysis, narrative summaries of outcomes were conducted. Statistical analysis was conducted using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and SPSS 22 (IBM, Armonk, NY).

Risk of bias and levels of evidence

A risk of bias appraisal of included studies was performed independently by two reviewers (T.O.D. and F.W.). Disagreements between the reviewers were resolved through discussion to achieve consensus. Failing agreement, a third reviewer (L.D.) arbitrated. The Cochrane Collaboration's risk of bias tool rated risk of bias across six domains as low, high, or unclear [32]; the domains included selection bias, performance bias, detection bias, attrition bias, reporting bias and other sources of bias. Each study was ascribed a level of evidence according to the criteria of the Oxford Centre for Evidence-based Medicine [33] (level I: systematic review of randomised trials or n-of-1 trial; level II: randomised trial or observational study with dramatic effect; level III: non-randomised controlled cohort/follow-up study; level IV: case-series, case–control, or historically controlled studies; and level V: mechanism-based reasoning). These levels of evidence

provide a hierarchy of the likely best evidence. Quality of evidence for key outcomes across comparisons was evaluated following the GRADE levels of evidence [34].

Results

Study selection

A total of 10 studies, reported across 11 articles published between 1989 and 2016, were included in this review. The search strategy is summarised in Figure 1. The electronic database search returned 3143 records and an additional 151 reports were identified from the conferences abstracts search. Of the 3068 records screened for eligibility, 31 titles were considered for full-text review. Studies were excluded for not meeting study design criteria ($n = 1$), not investigating a discrete SLE cohort ($n = 2$) and not including an exercise intervention ($n = 2$). Twelve records did not exist as full-text manuscripts, and three records were duplicates of included titles. When multiple articles reported different data from the same study, results were pooled under a primary study. As such, data reported by Benatti et al. [35] are included with the data from Miossi et al. [36]. Avaux et al. [37] provided additional unpublished detail of their intervention protocol.
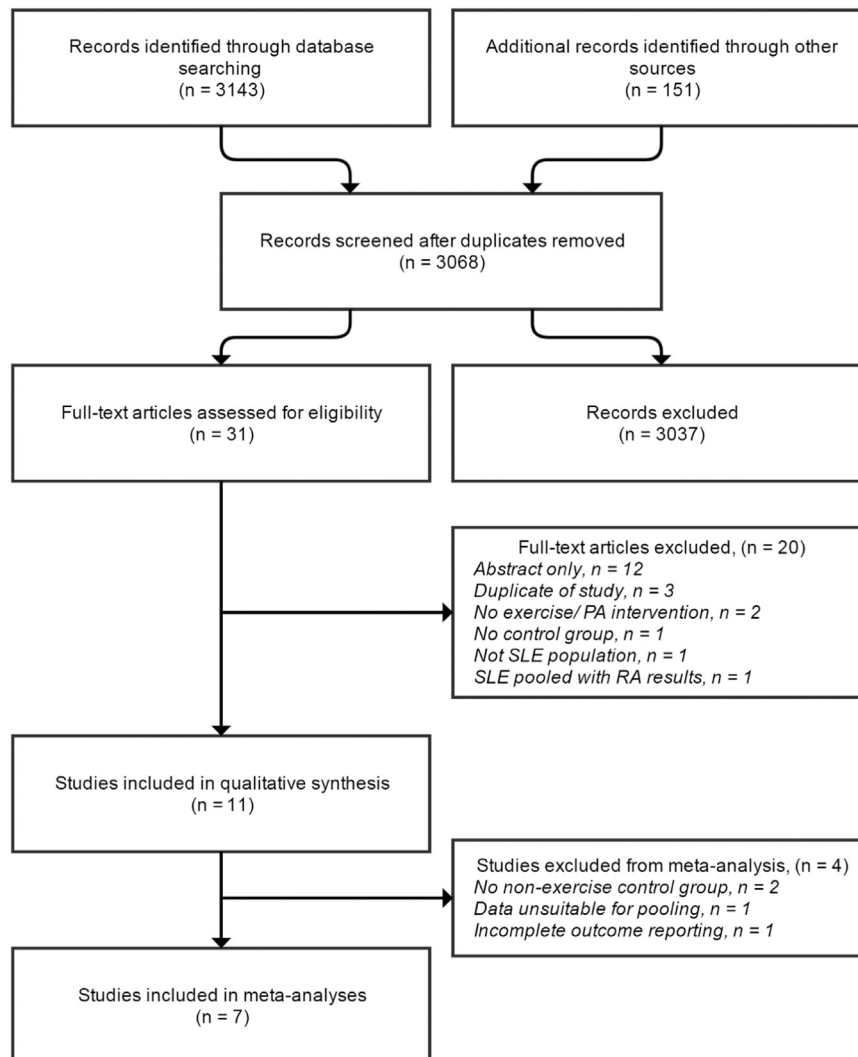

Fig. 1. PRISMA flow diagram of search strategy and study selection process.

Table 1
Study characteristics.

Study	Location	Study design; evidence level	Duration (mo)	Inclusion/exclusion criteria	Outcomes
Robb-Nicholson et al. [38]	USA	Quasi-RCT Level III	2	*Inclusion:* SLE (American Rheumatism Association preliminary criteria for SLE), fatigue *Exclusion:* serum creatinine $\geq$ 265 μmol/l, haematocrit $\leq$ 30%, previous MI, CVA, severe cognitive impairment, diastolic BP $\geq$ 100 mmHg, severe arthritis in ≥ 3 weight-bearing joints, beta-blocker therapy	SLE-AI, aerobic capacity, hours of sleep, NIMH Depression Scale, POMS Fatigue subscale, BP, HR
Ramsey-Goldman et al. [39]	USA	Quasi-RCT Level III	9	*Inclusion:* SLE (ACR), female *Exclusion:* significant functional impairments due to heart, neurologic or chronic pulmonary disease; cognitive impairment; conditions of the hip or knee preventing exercise; symptomatic anaemia; advanced renal insufficiency, or thrombocytopenia	SLAM, aerobic capacity, FSS, SF-36 (physical function subscale), isometric strength (knee flexors/extensors), BMD (lumbar and hip), bone biochemical markers (PTH, osteocalcin)
Tench et al. [11]	UK	RCT Level II	3 + 3 mo follow-up	*Inclusion:* SLE (ACR) *Exclusion:* < 16 or > 55 y; active severe myositis, nephritis, neurological involvement or cardiac or pulmonary disease; pregnancy	FFS, Chalder Fatigue Scale, Fatigue VAS, PSQI, SLAM, SLICC/ACR Damage Index, HADS, aerobic capacity, BMI, SF-36 (physical function, vitality, role physical)
De Carvalho et al. [40]	Brazil	Quasi-RCT, with matching Level III	3	*Inclusion:* SLE (ACR), female, 18–55 y *Exclusion:* neurologic, cardiovascular, rheumatic or respiratory disease; heart insufficiency (functional class $\geq$ II), history of MI or ischaemic heart disease, or diastolic BP > 100 mmHg; haemoglobin < 10 gm/dl; psychosis, a diagnosis of depression and/or under psychiatric care; active nephritis (creatine > 3.0 mg/dl), SLEDAI score > 8, thyroid dysfunction, diabetes mellitus; hip and/or knee joint prosthesis or aseptic bone necrosis, DVT in lower limb, severe arthritis in ≥ 3 weight-bearing joints; pregnancy; practicing regular PA (≥ 3 times per wk)	FFS, HAQ, BDI, aerobic capacity, pain, SF-36
Miossi et al. [36] Benatti et al. [35]	Brazil	RCT Level II	3	*Inclusion:* SLE (ACR), SLEDAI score $\leq$ 4, female, 20–40 y, physically inactive for ≥ 6 mo *Exclusion:* cardiovascular dysfunction, rhythm and conduction disorders; musculoskeletal disturbances; kidney and pulmonary involvements; peripheral neuropathy; fibromyalgia; use of tobacco; treatment with lipid-lowering, chronotropic or antihypertensive drugs	Chronotropic reserve, response to exercise [ΔHRR1, ΔHRR2, HR$_{VAT}$, HR$_{RCP}$, HR$_{PEAK}$, cholesterol (total, HDL, LDL, VLDL)], triglyceride, insulin, glucose, apolipoprotein A-I, apolipoprotein A-II, apolipoprotein B, apolipoprotein E, SLEDAI
Reis-Neto et al. [41]	Brazil	Quasi-RCT Level III	4	*Inclusion:* SLE (ACR), female, 18–45 y *Exclusion:* haemoglobin < 10 mg/dl; neuropsychiatric, pulmonary, articular or vascular damage that would not allow the practice of exercise; coronary disease; heart failure (functional class $\geq$ II); pulmonary hypertension; uncontrolled hypertension; creatinine $\geq$ 1.4 mg/dl; BMI $\geq$ 35 kg/m^2; diabetes mellitus; uncontrolled hypothyroidism; smoking in the last 12 mo; pregnancy; menopause; use of statins or regular practice of exercise; overlap with other autoimmune rheumatic diseases, except anti-phospholipid syndrome	Endothelial function (US brachial artery), aerobic capacity, SLEDAI
Bogdanovic et al. [14]	Serbia	RCT Level II	6 wk	*Inclusion:* SLE (ACR), female *Exclusion:* not specified	SLEDAI, BDI, SF-36, FSS
Abrahão et al. [31]	Brazil	RCT Level II	3	*Inclusion:* SLE (ACR), $\geq$ 18 y *Exclusion:* absolute or relative contraindications to physical exercise (ACSM guidelines); unavailable for two consecutive weeks during the study period; regular physical activity in the past 6 mo	SLEDAI, SF-36, 12-min walk test, BDI

Table 1 (continued)

Study	Location	Study design; evidence level	Duration (mo)	Inclusion/exclusion criteria	Outcomes
Boström et al. [43]	Sweden	RCT Level II	12	*Inclusion:* SLE (ACR), haemoglobin > 100, creatinine < 300, DBP < 100, prednisone dose < 15, ability to follow instructions and perform ergometer test. *Exclusion:* stroke with complications; arthroplastic complications; pregnancy	Aerobic capacity, SF-36, SLEDAI, SLICC/ACR Damage Index, self-reported physical activity
Avaux et al. [37]	Belgium	Quasi-RCT Level III	3 + 6 mo follow-up	*Inclusion:* SLE (ACR), FFS ≥ 3.7. *Exclusion:* fatigue due to anaemia, iron deficiency, hypothyroidism, or any other organics cause; physical disability compromising exercise	FSS, aerobic capacity (W/kg body weight and Borg scale at 75% of predicted HR_{MAX}: data not reported)

ACR, American College of Rheumatology; ACSM, American College of Sports Medicine; BDI, Beck Depression Inventory; BMD, bone mineral density; BMI, body mass index; BP, blood pressure; CVA, cerebrovascular accident; DBP, diastolic blood pressure; DVT, deep vein thrombosis; FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; HAQ, Health Assessment Questionnaire; HDL, high-density lipoprotein; HR, heart rate; HR_{VAT}, heart rate at ventilator anaerobic threshold; HR_{RCP}, heart rate at 10% below the respiratory compensation point; LDL, low-density lipoprotein; MI, myocardial infarction; NIMH, National Institutes of Health; PA, physical activity; POMS, profile of mood states; PSQI, Pittsburgh Sleep Quality Index; PTH, parathyroid hormone; RCT, randomised controlled trial; SF-36, Medical Outcomes Study Shot Form 36; SLAM, Systemic Lupus Activity Measure; SLE, systemic lupus erythematosus; SLE-AI, Systemic Lupus Erythematosus Activity Index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC, Systemic Lupus International Collaboration Clinics; US, ultrasound; VAS, visual analogue scale; VLDL, very low-density lipoprotein; ΔHRR1, difference between HR at peak exercise and the first minute after exercise; ΔHRR2, difference between HR at peak exercise and the second minute after exercise.

Study characteristics

Six RCT and five quasi-RCT were included in this review [11,31,35–43] (Table 1). Two studies included a follow-up period (3 and 6 months) [11,37]. The median study sample size was 40 (IQR: 28.75). A total of 469 participants with SLE (ACR criteria except Robb-Nicholson et al. [38]) were included (F:M, 425:2). Mean age ranged from 30.5 years (SD = 5.6) to 52.5 years (SD = 9.4), and disease duration ranged from a median of 30 months (IQR: 74) to a mean of 17.9 years (SD = 11.9). Participant characteristics are summarised in Table 2.

Study interventions are described in Table 3. Five studies [36,38,40,41,43] compared an exercise intervention to a control group (usual care, or unchanged physical activity status) and two studies [39,42] compared an aerobic exercise programme to a ROM/muscle strengthening programme. Three three-armed studies were included: Tench et al. [11] compared an exercise intervention, a relaxation intervention and a control group, Abrahão et al. [31] compared aerobic exercise, resistance training and a control group, and Avaux et al. [37] compared the effects of supervised exercise training, unsupervised exercise training and a control group. Intervention duration ranged from 6 weeks to 52 weeks. Frequency of exercise varied from 3 days per week to 5 days per week, with session duration ranging from 15 to 85 min. The components of individuals exercise interventions varied across studies. Boström et al. [43] implemented a physical activity programme inspired by social cognitive theory. Compliance with exercise programmes was seldom specified [11,37,41]. Table 1 summarises the relevant standardised outcomes used in each study.

Risk of bias within studies

The methodological quality of included studies was mixed, with a large number of domains unreported (Fig. 2). Two studies were deemed to have a low risk of selection bias [11,31], five were high [35,38,39,41] and four reports were unclear [36,40,42,43]. There was a high risk of performance bias due to the inherent difficulties in blinding participants to exercise-based treatments. Five studies met the criteria for blinding of outcome assessments [31,38,40,41,43]. Reporting bias across studies was generally unclear; only three studies pre-registered their study protocols [31,35,41].

Synthesis of results

Meta-analyses were deemed appropriate for four outcomes: disease activity, fatigue, aerobic capacity and depression. A narrative synthesis is presented for outcomes for which data could not be pooled due to heterogeneity of study characteristics (participants and exercise intervention), data type (e.g., median IQR), or when only a single study was available for a particular outcome.

Comparison 1: Therapeutic exercise compared to controls

Condition-related outcomes
Disease activity and disease damage. A meta-analysis of disease activity including three studies is presented in Figure 3 [31,36,41]. Disease activity was not significantly changed following exercise interventions [MD = 0.01 (95% CI: −0.54 to 0.56)]. Two further studies (data unsuitable for pooling) also reported no significant between-group differences post-intervention [11,43]. No significant differences between exercise and control groups in SLE-related damage were reported by Boström et al. [43] following a year-long intervention.

Table 2
Participant characteristics.

Study	Participants (n)	Age (y), mean (SD)	Disease activity mean (SD)	Disease duration (y), mean (SD)	Medication use, n (%)
Robb-Nicholson et al. [38]	20	39.9 (10.3)	SLEDAI 6.4 (2.4)	8 (6.3)	Hydroxychloroquine 57% Prednisone 39% NSAIDS 40% Antihypertensives 26%
Ramsey-Goldman et al. [39]	10	38.5 (21.1)	SLAM 5.0 (1.6)	8.52 (6.24)	Prednisone dose (mg): 2.8 (1.9)
Tench et al. [11]	93	39 (7.7)	SLAM score 5 (IQR: 3–8) SLICC/ACR Damage Index 0 (IQR: 0–0)	30 mo (IQR: 74)	Predinisolone ($\leq$ 7.5 mg) 29 (31.2) Hydroxychloroquine 53 (57.0) Azathioprine 21 (22.6)
De Carvalho et al. [40]	72	35.9 (10.2)	SLEDAI 1.3 (2.2)	6.01 (4.5)	Prednisone ($\geq$ 5 mg/d) 24 (40) Hydroxychloroquine (250 mg/d) 24 (40) Predinisone and hydroxychloroquine 13 (22) Methotrexate $>$ 7.5 mg/wk 6 (10) Antihypertensive drugs 8 (13)
Miossi et al. [36]	28	31.2 (5.4)	SLEDAI 0.95 (1.4)	6.25	Predinisone 18 (60) Prednisone $\geq$ 20 mg/d 3 (10) Azathioprine 13 (43.3) Chloroquine 24 (80) Methotrexate 4 (13) Mycophenolate mofetil 6 (20) Cyclophosphamide 1 (3.3) Medroxyprogesterone 11 (36.7)
Benatti et al. [35]	33	30.5 (5.6)	SLEDAI 1.0 (1.4)	6.1 (3.9)	Predinisone 22 (66.7) Azathioprine 16 (48.5) Chloroquine 21 (63.6) Methotrexate 5 (15.2) Mycophenolate mofetil 7 (21.2) Cyclophosphamide 2 (6.0)
Reis-Neto et al. [41]	38	33.2 (7.8)	SLEDAI 2.2 (2.2)	94.2 mo (80.5)	Prednisone 23 (60.5) Antimalarial 29 (76.3) Immunosuppressive 22 (57.8) Aspirin 5 (13.1) Antihypertensive 10 (26.3)
Bogdanovic et al. [42]	60	43.4 (12.8)	SLEDAI $<$ 5	6.8 (2.9)	NR
Abrahão et al. [31]	63 (F: 61, M: 2)	42.9 (14.4)	SLEDAI 1.8 (1.1)	3.8 (3.3)	NR
Boström et al. [43]	35	52.5 (9.4)	Intervention SLEDAI 1 (IQR: 0–8) SLICC 0 (IQR: 0–1) control SLEDAI 2 (IQR: 0–3) SLICC 0 (IQR 0–2)	17.9 (11.9)	Betablockers 4 (11.4) Corticosteroid 13 (51.4)
Avaux et al. [37]	42 (F: 40, M: 2)	41.1 (8.6)	SLEDAI 2.7 (3.6) SLICC 0.5 (0.8)	14.3 (8.8)	NR

ACR, American College of Rheumatology; F, female; IQR, interquartile range; M, male; NR, not reported; NSAIDS, nonsteroidal anti-inflammatory drugs; SD, standard deviation; SLAM, Systemic Lupus Activity Measure; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC, Systemic Lupus International Collaboration Clinics.

Fatigue. Data from two studies assessing fatigue were included in a meta-analysis presented in Figure 4 [11,40]. Fatigue was significantly improved in the exercise intervention group compared to controls [MD = −0.61 (95% CI: −1.19 to −0.02)]. Tench et al. [11]. 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 no significant difference measured on visual analogue scale (VAS) (p = 0.11). Robb-Nicholson et al. [38] did not report any statistically significant differences in fatigue on the Profile of Mood States (POMS) fatigue subscale (p > 0.05). Avaux et al. [37], reporting within-group changes only, found that both supervised and unsupervised exercise interventions resulted in a significant decrease in fatigue score post-intervention, which were sustained at 6-month follow-up; no significant changes were observed within the control group.

Pain. No significant difference in post-intervention pain measured on a VAS was reported by de Carvalho et al. [40] [MD = −1.31 (95% CI: −3.06 to 0.44)].

Cardiovascular function and risk factors
Chronotropic incompetence and HR recovery. A multimodal exercise training programme was effective in promoting significant increases in chronotropic reserve (p = 0.007, effect size = 1.21), heart rate recovery ΔHRR1 (p = 0.009, ES = 1.18), ΔHRR2 (p = 0.002, ES = 1.16) compared to the control group [36]. The exercise training programme was also effective in promoting a significant increase in relative change in HR from rest to ventilatory anaerobic threshold (p = 0.01, ES = 0.96), rest to respiratory compensation point (RCP) (p = 0.004, ES = 1.15) and rest to peak of exercise (p = 0.001, ES = 1.20) compared to the control group. The exercise group also showed increased HRR1.

Lipid profile. A multimodal exercise intervention did not result in any change in lipid profile (HDL, LDL, VLDL, total cholesterol and triglyceride), composition of HDL subfractions (HDL_2 and HDL_3) and serum levels of glucose and insulin compared to a control group [35].

Endothelial function. There were no significant differences in flow-mediated dilation [MD = 4.7% (95% CI: −0.19 to 9.59), MD =

Table 3
Description of the intervention.

Study	Description of intervention	Level of exercise supervision	Duration	Frequency (d/wk)	Time (min)	Intensity	Mode	Compliance with intervention
Robb-Nicholson et al. [38]	*EG*: 5 min warm-up, 20 min CV exercise, 5 min cool down *CG*: Non-aerobic stretching exercise	None	8 wk	3	30	60–80% of HR_{MAX}	Walk, cycle or jog	NR
Ramsey-Goldman et al. [39]	*PHASE 1* (2 mo) *CV group:* 5–10 min warm-up, 20–30 min CV exercise, 5–10 min cool down *ROM/RT:* isolated upper and lower extremity joint ROM and limb movement patterns *PHASE 2* (7 mo) *CV group:* as in phase 1 *ROM/RT:* stretching, isometric and progressive resistive exercises, stretching cool down	Supervised Mixed	9 mo	3	40–50	*CV group:* 70–80% of HR_{MAX} *ROM/RT:* 2–3 sets of 10 reps isotonic contraction per muscle groups using increasing 1–2 pound weights	NR	NR
Tench et al. [11]	*EG:* aerobic HEP; supervised exercise session every 2 wk *Relaxation group:* listen to relaxation audiotape in a darkened, warm quiet room; supervised session every 2 wk *CG:* continue with normal activity and avoid extra physical activity	Mixed	12 wk	≥ 3	30–50	*EG:* 60% of HR at $VO2_{PEAK}$	Self-selected: primarily walking, with cycling and swimming encouraged	Compliance with supervised sessions: *EG* 5 (4–5)[a]; *Relaxation group:* 4 (2–5)[a] Compliance with unsupervised sessions: *EG* 35 (25–40)[a]; *Relaxation group* 33 (12–36)[a]
Carvalho et al. [40]	*EG:* 10-min warm-up/stretching, 40 min walking, 10-min cool down *CG:* no training	Supervised	12 wk	3	60	Ventilatory anaerobic threshold	Walking	NR
Miossi et al. [36] Benatti et al. [35]	*EG:* 5 min treadmill warm-up, 35–40 min resistance training, 30 min aerobic training, 5 min cool down *CG:* remain inactive	Supervised	12 wk	2	80–85	*Resistance:* 2 sets of 15–20 RM in the first week, 4 sets of 8–12 RM thereafter *Aerobic:* between ventilatory anaerobic threshold and 10% below the respiratory compensation point	*Resistance:* bench press, leg press, latissimus dorsi pull-down, leg extension, seated row, squat and sit-up *Aerobic:* Treadmill	NR
Reis-Neto et al. [41]	*EG:* 10 min warm-up, 40 min aerobic exercise, 10 min cool down *CG:* no exercise	Supervised	16 wk	3	40	Ventilatory 1 threshold	Walking	Adherence: ≥ 75% of exercise sessions
Bogdanovic et al. [42]	*CV group:* cycle ergometer *ROM/RT:* ROM and muscle strengthening, with emphasis on abdominal and back muscles, and with focus on concentration, balance, breathing and relaxation	Supervised	6 wk	3	*CV:* 15 *ROM/RT:* 30	NR	Cycle ergometer	NR
Abrahão et al. [31]	*CV Group:* 10 min warm-up, 30 min aerobic exercise, 10 min cool down *RT Group:* 3 sets × 15 reps of eight exercises at 65–75% of 1 RM, with 1 min rest in between exercises *CG:* Usual care and information about the disease	Supervised	12 wk	3	50	*CV group:* 65–75% HRR *RT group:* 3 sets × 15 reps at 65–75% of 1 RM	*CV group:* walking and bicycle ergometer *RT group:* holds (crucifix) with free weights, extension machine exercises, rowing exercises with an elastic band, knee flexion with	NR

Study	Description	Mode	Duration	Frequency	Session duration	Intensity	Exercises	
							ankle weights, two-arm biceps curls, adduction exercises with an elastic band, French curls and abdominal exercises	
Boström et al. [43]	*Physical activity group:* mo 0–3: individual coaching, education, supervised aerobic exercise at high intensity, use of heart rate monitor, self-managed low-to-moderate intensity physical activity	Mixed	52 wk	High intensity: 2–3	High intensity: > 30	High intensity: 13–16 RPE (65–80% HR_{MAX})	Self-selected mode of physical activity	NR
	Month 4–12: tapering of coaching, self-managed physical activity *CG:* usual lifestyle			Low-to-moderate intensity: 4–5	Low-to-moderate intensity: 30	Low-to-moderate intensity: 9–12 RPE (45–60% HR_{MAX})		
Avaux et al. [37][b]	*Supervised EG:* one MDT exercise information session; aerobic and resistance exercise programme conducted in hospital-based rehabilitation centre	Supervised	12 wk	*Supervised EG:* 2	*Supervised EG:* 90	*Supervised EG Resistance:* 2 sets of 10 reps	*Supervised EG Resistance:* body weight, handweights (1–2 kg) and elastoband exercises	*Supervised EG:* 47% of programme
	HEP: One MDT exercise information session; aerobic, resistance and stretching exercise programme conducted at home	Unsupervised		*HEP:* 3	*HEP:* 60	*HEP Resistance:* 2 sets of 8 reps	*HEP Resistance:* 20 × body weight and elastoband exercises for upper and lower limbs and trunk	*HEP:* 54% of programme
	CG: usual physical activity					*Aerobic:* 60–80% HR_{MAX}	*Aerobic:* walking or bicycle	

1 RM, one repetition maximum; CG, control group; CV, cardiovascular; EG, exercise group; HEP, home exercise programme; HR, heart rate; HRR, heart rate reserve; HR_{MAX}, maximum heart rate; NR, not reported; ROM, range of motion; RPE, rated perceived exertion; RT, resistance training; VO_{2PEAK}, peak oxygen consumption.

[a] Median (interquartile range).
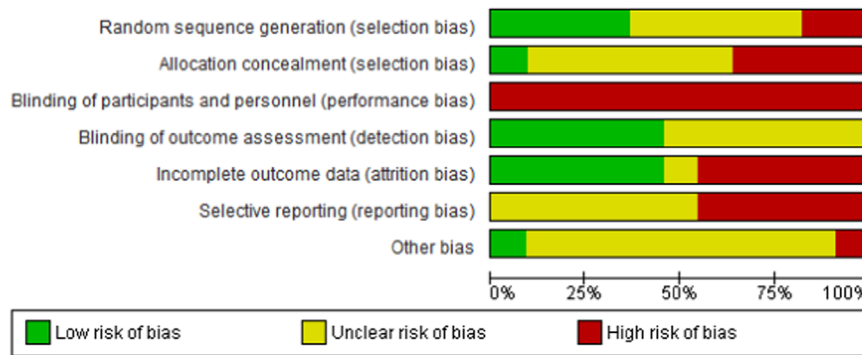[b] Additional unpublished details provided by author.

Fig. 2. Summary of risk of bias of included studies.

0.09 mm (95% CI: −0.03 to 0.21)], basal diameter [MD = −0.17 (95% CI: −0.52 to 0.18)], or nitroglycerin-mediated dilation (NitroMD) [MD = −0.07 mm (95% CI: −0.21 to 0.07), MD = −1.8 % (95% CI: −6.57 to 2.97)] between the exercise group compared to the control group [41].

Heart rate and blood pressure. No significant change in resting blood pressure or resting HR following 8 weeks of exercise training [38].

Physical fitness and function

A meta-analysis of aerobic capacity data from five studies (Fig. 5) demonstrated a significant difference favouring exercise compared to controls [MD = 1.85 ml/kg/min (95% CI: 1.12 to 2.58)]. Abrahão et al. [31] reported a significantly higher functional performance in a 12 minute walk test among exercisers than controls [MD = 205.7 m (95% CI: 94.7 to 316.8)]. Functional capacity, assessed on the health assessment questionnaire (HAQ), was found to be improved in the exercise group compared to controls [40]. Tench et al. [11] found no significant difference in body composition between exercise and control groups.

Health-related quality of life

Four studies used the SF-36 to evaluate health-related quality of life. Carvalho et al. [40] and Abrahão et al. [31] reported that following aerobic exercise interventions, physical role functioning and vitality subscales were significantly improved compared to controls. This was not supported by Tench et al. [11] or Boström et al. [43]; these authors found no significant differences in any SF-36 subscales, except for mental health, which was significantly improved in the exercise group compared to the control group at 6 months in the study by Boström et al. [43].

Depression and anxiety. A meta-analysis including three studies (Fig. 6) found significantly lower depression scores in the exercise groups compared to controls (SMD = −0.40 SD; 95% CI: −0.71 to −0.09) [11,31,40]. However, no significant between-group differences in depression were reported by Robb-Nicholson et al. [38] (data not reported). Results from a single study did not report any significant between-group differences in anxiety [11].

Sleep. No significant between-group differences in sleep were observed in two studies [11,38].

Physical activity. Boström et al. [43] reported a significant increase from self-reported high-intensity physical activity following a physical activity programme, however, this was not significantly different to the control group.

Summary

Therapeutic exercise does not adversely affect SLE disease activity with a low level of evidence from five studies. There is moderate level evidence from six studies that therapeutic exercise significantly improves aerobic capacity. There is low-level evidence from three studies that therapeutic exercise positively influences depression. Very low-level evidence from four studies favours exercise over controls in lowering symptoms of fatigue; with fatigue inconsistently lowered across different fatigue scales. There is also conflicting evidence from four studies as to the effect of therapeutic exercise on quality of life. Single studies found no differences between exercise and a control group for disease damage, pain, cardiovascular function and risk factors, body composition, anxiety, or habitual physical activity.

Comparison 2: Aerobic exercise compared to ROM/resistance training

Three studies compared aerobic exercise with ROM/resistance training programmes [31,39,42]. Abrahão et al. [31] found significant differences between physical role functioning and vitality subscales of the SF-36 favouring aerobic exercise training [MD = 22.1 units (95% CI: 5.9–38.3), MD = 36.9 units (95% CI: 25.2–48.6)] [31]. Participants in the aerobic exercise group also had a significant increase in aerobic capacity compared to the resistance training group [MD = 265.9 m (95% CI: 133.7–398.1)]. There were no significant between-group differences in disease activity, medication use, or depression.

Reporting change scores from a two-phase study, Ramsey-Goldman et al. [39] found no significant between-group differences after either phase in disease activity or symptoms, physical fitness (aerobic or muscle strength), physical function, bone mineral density and bone biochemical markers. Bogdanovic
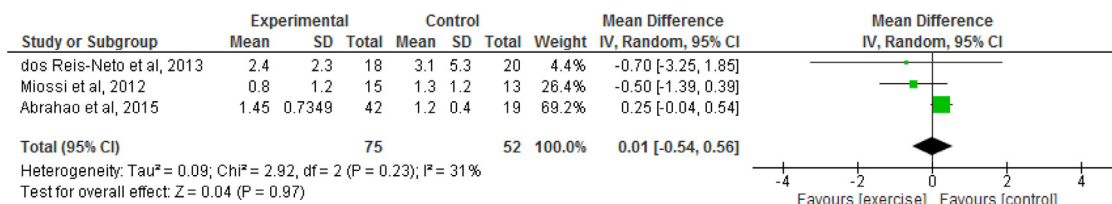

Fig. 3. Forest plot comparing disease activity outcomes of exercise groups and controls.
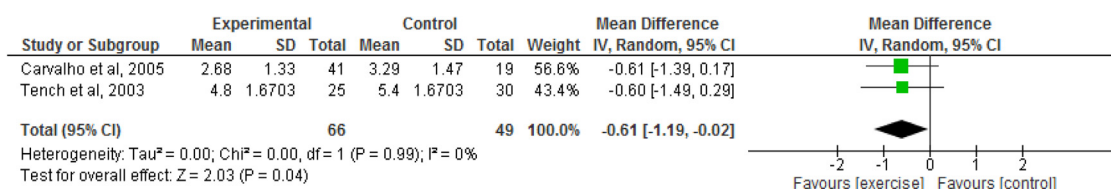
Fig. 4. Forest plot comparing fatigue outcomes of exercise groups and controls.

et al. [42] did not observe any significant between-group differences in fatigue, depression or HRQoL post-intervention.

Comparison 3: Therapeutic exercise compared to relaxation

A single study by Tench et al. [11] compared the effects of an aerobic exercise programme with a relaxation programme. No significant between-group differences were observed post-intervention or at follow-up in condition-related outcomes (disease activity and disease damage, fatigue and sleep quality and depression and anxiety) and physical fitness (cardiovascular fitness and body composition) or functional status.

Dropouts and adverse events

Transient join pain was the most frequently reported adverse event ($n = 5$), although this did not cause affected participants to dropout across two [38,40]. Avaux et al. [37] and Tench et al. [11] each reported one withdrawal due to disease flare; the latter also reported one dropout due to worsening fatigue. Boström et al. [43] reported three dropouts due to unspecified illness (one from exercise group and two from control group). Other medical reasons for dropouts, unrelated to the exercise interventions, included musculoskeletal injuries and pericarditis [41], dementia, systemic sclerosis with alveolitis, suspected breast cancer relapse and depression/cognitive impairment [43]. The remaining reasons for withdrawal from studies included pregnancy [39], lack of time [11,39,41], amotivation [43], personal reasons [36,37,40] loss to follow-up [36,41], or no reason stated [31]. One study did not report dropouts or adverse events [42] and one study reported dropouts but did not specify the reasons [38].

Discussion

This systematic review investigated the effects of exercise and physical activity interventions on adults with SLE. No studies reported any deleterious effect on disease activity measured on the SLE disease activity index (SLEDAI); five studies [11,31, 36,41,43] reported disease activity to be unchanged following exercise, with four of these demonstrating a non-significant trend towards improvement following exercise intervention. Only one study measured the influence of exercise on pain, demonstrating no change in this outcome [40]. It was noted that three participants dropped out of studies due to disease or symptom flare-up. In addition, five participants reported transient musculoskeletal pain, but continued with their respective programmes. The impact of exercising on disease activity has been a concern for both individuals with SLE and their treating clinicians, and this review indicates that exercise is safe and well tolerated by the vast majority of individuals with SLE. Pre-participation screening of risk factors, and monitoring by a healthcare professional may further enhance safety and minimise the risk of adverse reactions to exercise programmes.

Exercise is proposed as an important intervention in the management of SLE due to the risk of associated CV disease. This review aimed to clarify the effect of exercise on cardiovascular function and risk factors in this population. Results demonstrated that with exercise, individuals with SLE experience, for the most part, similarly positive effects on the cardiovascular system as healthy individuals. Studies showed significant increases in chronotropic reserve and heart rate recovery compared to a non-exercise control group [36]. Exercise training was also effective in promoting a significant increase in relative change in HR from rest to ventilatory anaerobic threshold, rest to respiratory compensation point and rest to peak of exercise. Unlike a non-SLE cohort [44], a multimodal exercise intervention did not result in any change in lipid profile (HDL, LDL, VLDL, total cholesterol and triglyceride), composition of HDL subfractions (HDL_2 and HDL_3), or serum levels of glucose and insulin compared to a control group [35]. In addition to potential features inherent to the disease, dietary intake and medication usage may be confounders. Likewise, change in endothelial function as a response to exercise was not significant in flow-mediated dilation, basal diameter, or nitroglycerin-mediated dilation [41]. A single study reported no significant changes in resting
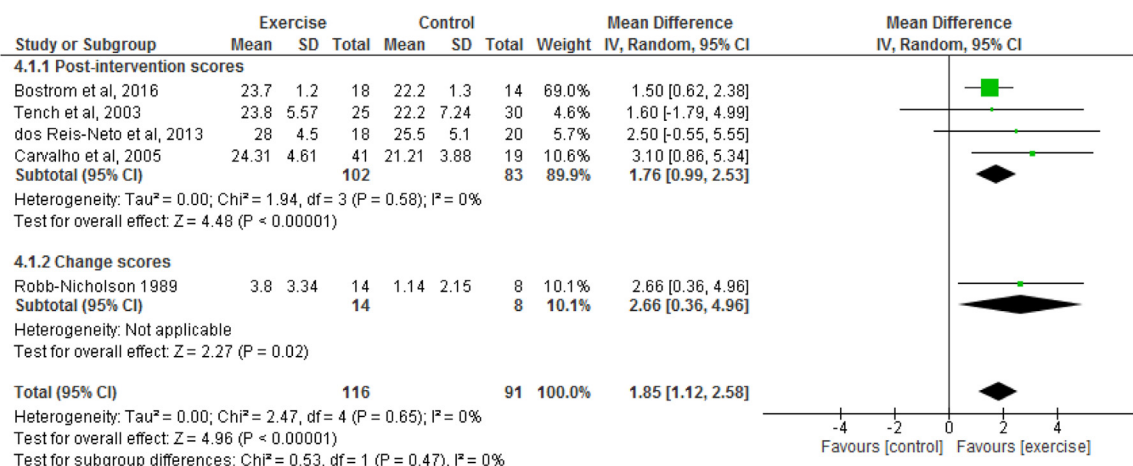

Fig. 5. Forest plot comparing aerobic capacity outcomes of exercise groups and controls.

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Abrahao et al, 2015	18.7	6.0035	42	20.1	5.9	21	35.1%	-0.23 [-0.76, 0.29]
Carvalho et al, 2005	2.9	3	41	6.63	8.5	19	31.0%	-0.69 [-1.25, -0.13]
Tench et al, 2003	4.6	3.5	25	5.7	3.2863	30	33.9%	-0.32 [-0.85, 0.21]
Total (95% CI)			108			70	100.0%	-0.40 [-0.71, -0.09]

Heterogeneity: Tau² = 0.00; Chi² = 1.50, df = 2 (P = 0.47); I² = 0%
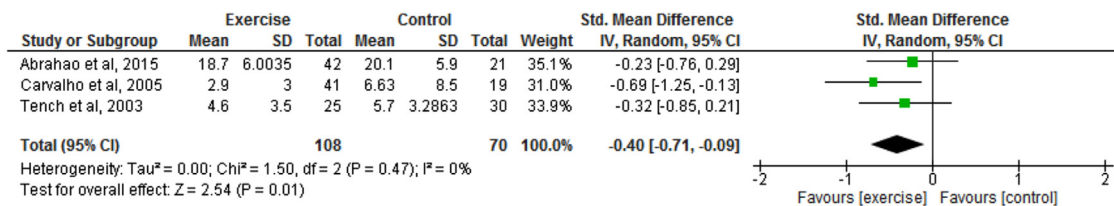Test for overall effect: Z = 2.54 (P = 0.01)

Fig. 6. Forest plot comparing depression outcomes of exercise groups and controls.

blood pressure or resting HR following exercise training [38]. As hypertension was an exclusion criterion for most studies it is unlikely that any significant changes would be noted in this category.

Fatigue is common in SLE, and a frequently cited barrier to exercise [9]. This review found that exercise improves fatigue. However, findings varied between favouring exercise and no-different depending on the outcome measurement tool used [11,38,40]. The complex, multifactorial nature of fatigue, and a reliance on self-reported measurement, may account for the inconsistent evidence identified. Importantly, no studies reported any adverse effects on fatigue. Clinical features of SLE such as disease activity and inflammation contribute to fatigue [45]; this review suggests that exercise has no deleterious effects on these and indeed may improve them. Furthermore, secondary features which contribute to fatigue such as deconditioning and quality of life are improved with exercise. Thus, exercise interventions appear beneficial for fatigue in this SLE cohort.

Exercise was shown to have significant positive effects on physical fitness and function in an SLE cohort. Pooled results demonstrated that exercise programmes significantly improve fitness as measured by aerobic capacity, and other measures of performance (HAQ and 12MWT). Only one study examined the effect of exercise on body composition [11]. Unsurprisingly the study found no significant change in BMI; the aerobic nature of the exercise intervention, without controlling for dietary effect, is unlikely to have been sufficient to elicit changes to BMI. Further research is required to profile adiposity in this cohort, and to evaluate the effects on fat and lean mass.

In SLE, depression is common. The prevalence has been reported to range from 17% to 75% [46]. The effect of exercise interventions on quality-of-life outcomes varied depending on the outcome used. Three out of four studies demonstrated that exercise had a significant effect on improving depression [11,31,40], with one study reporting no significant between-group differences [38]. In this latter study, data were not reported and the authors stated that '70% of the exercise group noted improved psychological well-being after exercise.' Tench et al. [11] reported no significant between-group differences in anxiety although those in the exercise group reported better scores compared to the control group.

This review aimed to examine the roles of different types of exercise in the management of SLE. In general, there was a paucity of studies making these comparisons and it appears that those that examined a strengthening protocol are likely to have under-dosed. Abrahão et al. [31] reported the correct intensity for improving strength according to ACSM guidelines [47]; however, Ramsay-Goldman et al. [39] reported a programme that is unlikely to improve strength or endurance [47], and Bogdanovic et al. [42] did not report components of the programme. Although the consensus from studies was that aerobic exercise was superior to other type, this was measured in outcomes directly linked to aerobic capacity. There is clearly a need for well-constructed studies which implement appropriate intensity, frequency, and duration of exercise for ROM and strength exercises. Resistance and ROM exercise have

been shown to be beneficial in other cohorts with systemic disease [48–50] and it is likely to be similar in SLE.

Review limitations and future studies

Anticipating a relatively small number of eligible RCTs on this topic, this review included quasi-randomised trials; this increased the evidence base, while simultaneously raising the risk of selection bias within studies. In many studies the risk of bias was unclear due to underreporting of key methodological features; following the CONSORT guidelines for reporting RCTs would improve this feature of future studies [51]. The focus of this review was on the effects of therapeutic exercise programmes; studies examining exercise therapy in combination with other modalities were excluded, as the relative effect of exercise therapy would be unknown. Combining exercise prescription with other modalities may yield different outcomes. Due to the relatively small sample sizes of included studies, extrapolation of findings should be undertaken cautiously. It is important that future exercise interventions meet the recommended dosage to achieve physiological changes; while in general the aerobic components of included interventions were adequately prescribed, other components such as flexibility and resistance training were in sufficient. Furthermore, comprehensive reporting of exercise protocols and participant adherence rates is essential to understanding the effectiveness of exercise therapy. Additionally, reporting of adherence data is essential to appraise the efficacy of exercise-based programmes; this has been inconsistently reported. The optimal exercise protocol remains unclear, and exact recommendations for therapeutic exercise in SLE cannot be made.

Conclusions

This systematic review reports an emerging evidence-base broadly favouring therapeutic exercise interventions among individuals with SLE. Within this cohort, exercise was reported to be safe and well tolerated, while adverse effects were rare. Furthermore, meta-analysis suggests that exercise does not deleteriously effect disease activity. SLE associates with enhanced CV risk; although exercise programmes significantly improved aerobic capacity and cardiovascular function, cardiovascular risk factors appeared unchanged following exercise interventions compared to controls. Meta-analyses found that exercise interventions positively influenced depression, and lowered symptoms of fatigue, compared to control groups. Although a multimodal approach may be suggested, the optimal exercise protocol remains to be determined.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.semarthrit.2017.04.003.

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