TITLE: Effects of 12-week aerobic exercise on patient-reported outcomes in women with Systemic Lupus Erythematosus

ABSTRACT

Purpose: To evaluate the effects of aerobic exercise on patient-reported outcomes (PROs) in women with systemic lupus erythematosus (SLE), and whether changes in cardiorespiratory fitness (CRF) mediate the changes in PROs.

Methods: A total of 58 women with SLE were assigned to either an exercise group (EG;*n*=26) or a control group (CG;*n*=32) in this non-randomized clinical trial. The EG comprised 12 weeks of aerobic exercise (2 sessions/week) between 40%-75% of the individual's heart rate reserve. At baseline, and at week 12, CRF (Bruce test) and PROs were assessed including psychological stress (Perceived Stress Scale), sleep quality (Pittsburg Sleep Quality Index), fatigue (Multidimensional Fatigue Inventory), depressive symptoms (Beck Depression Inventory), and quality of life (36-item Short-Form Health Survey).

Results: In comparison to the CG, the EG showed a significant reduction in general fatigue (mean difference(MD) -2.86 units; 95%CI -5.70 to -0.01; *P*=0.049), physical fatigue (MD -4.33 units; 95%CI -7.02 to -1.65; *P*= 0.002) and a non-significant reduction of reduced motivation (MD – 1.29 units; 95%CI -2.60 to 0.03; *P*=0.055). There were no significant between-group differences in the changes in psychological stress, sleep quality, depressive symptoms, quality of life, or other fatigue dimensions (all *P*>0.05). The percentage of the total effect of exercise on general fatigue mediated by CRF was 53.81%.

Conclusion: The results suggest that 12 weeks of progressive aerobic exercise might improve relevant dimensions of fatigue in women with SLE, despite the absence of effects

on other PROs. Improvements in CRF seem to mediate the effect of exercise on general fatigue.

Keywords: physical activity, quality of life, aerobic capacity, SLE, mental health, fatigue,

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with variable multi-system involvement predominantly affecting young adult women [1]. The survival rate of patients with SLE has significantly improved along the years [2], yet longer disease duration leads to greater disease burden [3]. As a result, health-related quality of life (HRQoL) and other patient-reported outcomes (PROs), that represent individuals' perception of a widely variety of health aspects, are highly deteriorated in these patients [4]. While physicians have typically focused on reducing disease activity and damage as their primary therapeutic goal [4], this not necessarily translates to improvements in how patients feel or function [5]. Optimizing HRQoL and other PROs is considered an emerging complementary goal that must be addressed for a successful management of the disease [6].

Non-pharmacologic therapies, in conjunction with conventional medical treatments, are promising options for SLE patients [7]. Specifically, exercise has demonstrated to be a safe strategy to improve several health outcomes in SLE [8–10], including HRQoL [11–14], depressive symptoms [11,12] or, even more importantly, fatigue [9,14–19]. Fatigue is the most prevalent complaint among patients [4] and it affects individuals physically, emotionally, cognitively, and behaviorally [20]. However, previous research on exercise in SLE have used single scales to assess fatigue, limiting a complete description of the fatigue experience of patients that could be better captured by multidimensional

questionnaires [20]. Poor sleep quality is another common symptom that considerably contribute towards the burden of SLE [4]. Benefits of exercise in this regard are equivocal: while physical activity counselling might lead to better sleep quality in these patients [21], other exercise interventions have not shown any amelioration in this outcome [19,22]. In addition, it is unclear how exercise could affect other relevant PROs such as psychological stress, which can negatively influence function of these patients [23], HRQoL [24] or provoke disease activity exacerbation [24].

A recent meta-analysis pointed out that exercise interventions in SLE have considerable limitations including insufficiently detailed protocols, unsupervised and under-dosed programs, or lack of reports regarding adherence rates [8]. Because there is insufficient evidence to describe the optimal exercise prescription protocol in SLE [8,9], following exercise-related guidelines from international institutions would be advisable. This study was designed so that participants meet the current physical activity guidelines of the American College of Sport Medicine (ACSM), which indicate that a minimum of 150 min/week of moderate-to-vigorous physical activity (MVPA) are needed for health benefits [25]. Although previous cross-sectional studies revealed an association of greater MVPA with lower fatigue and better physical function in SLE [26], it is unclear the extent to which the minimal amount of aerobic exercise recommended for the general population might improve PROs in this group of patients. Also, given the potential relationship between fitness levels and HRQoL in addition to other health outcomes in SLE [27,28], it is of interest to assess how the improvements in CRF driven by this intervention [29] might mediate improvements in PROs.

This study aimed to assess: i) the effect of a 12-week aerobic exercise intervention following the ACSM guidelines on PROs (psychological stress, sleep quality, fatigue, depressive symptoms, and HRQoL) in women with SLE compared to usual care, and ii)

whether changes in CRF mediate the changes in the outcomes. It was hypothesized that aerobic exercise would improve PROs and that CRF would mediate these changes. These are secondary analyses from a clinical trial [29] which main results revealed that, in comparison to a control group, the aerobic exercise intervention did not reduce either arterial stiffness or inflammation, although a clinically relevant increase in cardiorespiratory fitness (CRF) was found.

METHODS

Design and Protocol Registration

The protocol of this non-randomized controlled clinical trial was registered at clinicaltrials.gov [NCT03107442] on 11 April 2017, before the enrolment of participants started.

Participants

A telephone screening was conducted among potential participants from the Systemic Autoimmune Diseases Unit of the "Virgen de las Nieves" and the "San Cecilio" University Hospitals (Granada, Spain). The inclusion criteria were: i) women with a diagnosis of SLE [30], ii) a follow-up of ≥12 months, iii) clinical and treatment stability during the 6 previous months, and iv) not performing regular exercise. Exclusion criteria were: i) to have had biological treatment in the previous 6 months or to need a prednisone dose of >10 mg/day or equivalent, ii) a background of clinical cardiovascular disease in the previous year, iii) to present contraindications to perform exercise, and iv) other associated rheumatic disease, pregnancy, active acute or chronic infection, neoplasms, acute renal failure, cardiac or pulmonary involvement, or body mass index (BMI) >35 kg/m^2, to avoid the influence of other conditions. All participants received information about the study procedures and signed written informed consent before being included in

the trial. The Research Ethics Committee of Granada approved the study protocol on 11 November 2016 [reference nº: 10/2016].

Procedures

The baseline examinations were carried out in 2 days. On day 1, CRF was assessed, socio-demographic information was collected, and patients were instructed in how to fill the questionnaires at home. On day 2, participants returned to the Unit and the research team checked questionnaires. This article follows the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) statement [31], included in supplementary table 2. The funding source had no role in the investigation.

Interventions

Exercise Group

Patients assigned to exercise performed two 75-min sessions per week during a total of 12 weeks of moderate to vigorous intensity aerobic exercise on a treadmill (BH, Series, i.RC12 Dual, Vitoria-Gasteiz, Spain) from 24 April to 14 July 2017. To maximize replicability of the procedures, the exercise program has been comprehensively described elsewhere [29], following the Consort of Exercise Reporting Template [32]. In brief, weekly volume of MVPA progressively ranged from 90-145 min (week 1 to 4) to 150 min (week 5 to 12). A progression from only continuous exercise (week 1 to 6), to continuous + interval exercise (week 6 to 8) and, eventually, only interval exercise (week 9 to 12) was planned.

The exercise sessions were carried out in groups ≤ five persons in a quiet room of the "Virgen de las Nieves" Hospital, Granada (Spain). All sessions were supervised by exercise professionals and residents from the Internal Medicine Department. Attendance at the sessions was registered daily and patients were contacted upon any missing session

to ask for the reason and motivate them to replace it on a day of the same week. Adherence to exercise is reported as the median attendance frequency and the proportion of patients attending >75% (18 sessions; the minimum attendance to assess efficacy) and >90% of the sessions.

All the sessions included a 3-4 min warm-up on the treadmill at 35-40% of the heart rate reserve (HRR= maximum heart rate [HRmax] – resting heart rate [RHR]), and 3–4 min of active stretching of major muscle groups and ended with a cool down phase of static stretching of major muscle groups. Exercise was individually prescribed, with training intensity ranging from 40 to 75% of each patient's HRR, to represent moderate-to-vigorous intensity. The maximum heart rate (HRmax) was estimated as 208 - (0.7 × age) [33]. The training (or target) heart rate (tHR) was calculated with the formula tHR = RHR + (%HRR). Heart rate was continuously monitored during all sessions (Polar V800, Kempele, Finland), and the session rating of perceived exertion was additionally used[34].

Potential adverse effects that might occur during the intervention (i.e., cardiovascular effects including chest pain, dizziness, arrhythmia, or hypotension related to effort, osteoarticular injuries, and falls) were foreseen and minimized through constant supervision and heart rate monitoring, performance of warm-up and cool down in all sessions, and the inclusion of a familiarization phase with the treadmill.

Control Group

After the baseline evaluation, the patients assigned to the control group (usual care) received verbal information about a healthy lifestyle, which included physical activity guidelines and basic nutritional information.

Outcome measures

In a previous research work of this non-randomized controlled trial [29] the results of the primary outcome (arterial stiffness) were reported. These are secondary analysis of the exercise intervention including several measures of PROs.

Psychological stress

Psychological stress was measured with the Perceived Stress Scale (PSS), a 14-item self-report global measure designed to assess the degree to which situations in one's life are appraised as stressful [35]. The PSS have shown to be a valid and reliable measure in patients with SLE [36]. According to how patients felt during the last month, each item is rated from 0 (never) to 4 (very often). The PSS provides a single overall score (0-56) where higher score represents greater perceived stress.

Sleep quality

Sleep quality over the last month interval was assessed with the Pittsburg Sleep Quality Index (PSQI)[37], a widely-used instrument in SLE [38]. This questionnaire is composed of 19 questions addressing a variety of factors related to sleep quality. The sleep quality global score is the sum of all components, that ranges from 0 to 21, with higher scores indicating worse sleep quality.

Fatigue

Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI) [20], which is a well-established instrument previously used in SLE [39,40]. This questionnaire includes 5 subscales of fatigue severity: general, physical, and mental fatigue as well as reduced activity, and reduced motivation. Each subscale consists of four items ranging from 4 to 20, with higher scores indicating greater fatigue on that subscale.

Depressive symptoms

Depressive symptomatology was assessed through the Beck Depression Inventory-second edition (BDI-II) [41]. This questionnaire has been used extensively in research, including SLE [42]. It is a 21-item self-report measure where, according to how patients felt during the past 2 weeks, each depressive symptom is rated from 0 (not present) to 3 (severe). The BDI-II provides an overall score (0–63) where higher score indicates higher depressive symptomatology.

Health-related quality of life

The Spanish version of the 36-item Short-Form Health Survey (SF-36)[43] was used to assess HRQoL. This questionnaire is validated for patients with SLE [44] and it assesses eight health dimensions that define two global domains: the physical and mental component scales (PCS and MCS, respectively). Only the global domains were used for the present work, which scores range from 0 (worst possible health status) to 100 (the best possible health status).

Cardiorespiratory Fitness

The Bruce submaximal treadmill protocol [45] was used to estimate CRF and was undertaken as reported elsewhere [29]. This test consisted of five increasing workload stages of 3 min each (stage 1: 2.7 km/h + 10% inclination to stage 5: 8 km/h + 18% inclination). The total time to reach 85% of their HRmax was registered and the test was then concluded.

Treatment Allocation and Blinding

Randomization was not possible as a considerable number of the patients lived far from the Hospital and were not able to attend exercise sessions. To minimize selection bias, groups were matched by age (±2 years), BMI (±1 kg/m2), and SLEDAI (±1 unit). The data analyzer was blinded to the patient allocation.

Statistical Analysis

The sample size was calculated for the primary trial outcome (i.e. arterial stiffness), as reported elsewhere [29]. Histogram and Q-Q plots were used to assess the normal distribution of the main outcomes. For those outcomes that were non-normally distributed, their descriptive characteristics were presented using the median and interquartile range instead of the mean and standard deviation. Between-groups baseline characteristics were compared with the Student t-test (when normally distributed) or Kruskal-Wallis test (when non-normally distributed) for continuous variables and the Chi-square test for categorical variables. The differences in the changes from baseline at week 12 between groups in the studied outcomes were analyzed through quantile regression with baseline outcomes as covariates. The primary analyses were defined as per-protocol in order to assess efficacy, with patients from the exercise group being included if attendance was ≥75%. The Cohen's d was used to calculate the standardized effect size in primary analyses and was interpreted as small (~0.2), medium (~0.5) or large (~0.8 or greater). Three different sensitivity analyses were carried out to assess the robustness of the results: i) baseline observation carried forward (BOCF) imputation; ii) per-protocol with minimum attendance of ≥90%; and iii) Complete-case analyses.

As an ancillary aim, it was analyzed whether changes in those PROs that improved after the intervention were mediated by changes in CRF. The mediation analyses followed the approach described by Baron and Kenny [46]. The following linear regression models were built to check each of the conditions to accept mediation hypothesis: Equation 1: the predictor is associated with the hypothesized mediator; Equation 2: the predictor is associated with the outcome; Equation 3: the hypothesized mediator is associated with the outcome; and Equation 3': the effect of the predictor on the outcome decreases or completely diminishes after adjusting for the hypothesized mediator. To test if this

attenuation was significant, the Sobel test was performed[47]. Finally, the percentage of the total effect that is mediated by changes in CRF was estimated by multiplying the unstandardized coefficients of equation 1 and 3 and dividing it by the unstandardized coefficient of equation 2. All analyses were adjusted for baseline outcomes.

All the analyses were conducted with Stata v.13.1 (StataCorp LP., College Station, Texas, USA). Statistical significance was set at $P< 0.05$.

RESULTS

The flowchart of the participants is shown in Figure 1. The median attendance to the exercise intervention was 22.5 (~94%) sessions. A total of 22 participants (~85%) attended ≥75% of the sessions (included in primary analyses) and 18 (~69%) attended ≥90% of the sessions. One participant withdrew at week 5 due to severe sciatica (not associated with the exercise program). A total of four participants were lost to follow-up in the control group at week 12 and none in the exercise group. There were no adverse events occurring during the exercise sessions.

Table 1 presents the characteristics of the sample at baseline. The exercise group showed better HRQoL in physical (P=0.037) and mental (P=0.035) domains, and lower depressive symptoms (P=0.008). There were no other significant between-group differences at baseline (all $P> 0.05$).

The between-group differences in the mean change from baseline at week 12 are presented in Table 2. The primary analyses revealed no significant between-group differences between changes in psychological stress (mean difference=-0.40; 95 % IC -3.64 to 2.84; P=0.805; Cohen's d=0.07) or sleep quality (0.32; -1.67 to 2.32; P=0.744; Cohen's d=0.10). Regarding fatigue domains, the exercise group experienced a significant reduction of general fatigue (-2.86; -5.70 to -0.01; P=0.049; Cohen's d=0.57)

and physical fatigue (-4.33; -7.02 to -1.65; *P*=0.002; Cohen's d=0.92), a non-significant reduction of reduced motivation (-1.29; -2.60 to 0.03; *P*=0.055; Cohen's d=0.60) and no effects on reduced activity (*P*=0.837; Cohen's d=0.06) or mental fatigue (*P*=0.285; Cohen's d=0.31) domains. There were no significant between-group differences between changes in depressive symptoms (-1.78; -6.74 to 3.19*; P*=0.475; Cohen's d=0.21), the PCS (2.341; -3.83 to 8.52), *P*=0.448; Cohen's d=0.25) or the MCS (4.39; -3.00 to 11.78; *P*=0.237; Cohen's d=0.39) of HRQoL. The sensitivity analyses shown in Tables 3-4 and supplementary table 1 generally corroborated per-protocol findings.

Results of the mediation analyses are shown in figure 2. For general fatigue, regression models 1, 2, and 3 were significant (all, *P*<0.05) and the regression coefficient in model 3' was no longer significant (*P*=0.186) compared to model 2. The percentage of the total effect of exercise on general fatigue that is mediated by changes in CRF was 53.81 % (z=-2.455, *P*=0.014). For physical fatigue, regression models 1 and 2 were significant (*P*<0.010) but not regression model 3 (*P*=0.719). Therefore, the mediation hypothesis was not accepted, and no additional tests were carried out.

DISCUSSION

The results of this study suggest that, in comparison to a usual care control group, 12 weeks of progressive treadmill aerobic exercise following the ACSM guidelines improved several fatigue-related domains such as general fatigue, physical fatigue and, less consistently, reduced motivation in women with SLE. However, exercise did not significantly affect psychological stress, sleep quality, depressive symptoms nor HRQoL. In addition, improvements in CRF mediated the effects of exercise on general fatigue but not on physical fatigue.

To our knowledge, no previous studies have addressed the effects of an exercise program on psychological stress in SLE. A previous cross-sectional investigation found that lower social stress was associated with greater self-reported exercise and sport participation in these patients [48]. In other mental outcomes closely related to stress such as anxiety, it was found an absence of effect of a 12-week aerobic exercise program among patients with SLE [16]. HRQoL or depression have been proposed as determinants of psychological stress in SLE [24], and the lack of effect of the current intervention in these outcomes is in line with the absence of effect on psychological stress as well. Longer duration of the exercise program could have potentially yielded more favorable changes and further research exploring the effects of exercise on stress is needed.

Only two previous interventions have analyzed the effect of exercise on sleep in SLE [16,19] showing that 8 [19] or 12 weeks [16] of aerobic exercise did not improve sleep quality [16] or duration [19]. Although these previous studies were mainly unsupervised, this supervised exercise program reported similar findings. According to previous evidence [49], the most important determinants of sleep quality in SLE are depressed mood along with prednisone use and, importantly, exercise engagement [49]. Exercise participation was, however, inaccurately defined in this prior observational publication [49]. The exercise protocol here reported as well as those from previous interventions [16,19] only included aerobic training and could have been more effective if other fitness components (strength, flexibility) that generate physiologic and psychologic adaptations in relation to sleep [50] would have been included. Also, recent publications in other clinical populations have describe the potential of novel exercise approaches such as whole-body vibration to improve sleep quality parameters [51]. Future research comparing different exercise protocols and using other measures of sleep quality (i.e.,

polysomnography or actigraphy) could help to better understand the effects of exercise on sleep quality in SLE.

Fatigue is a major complaint among SLE and one of the most studied outcomes in relation to exercise. Programs including aerobic exercise [11–13,16,19], strength training [11,14] or a combination of both [15,18] have shown benefits on fatigue as assessed by single domain scales such as the Fatigue severity scale by Korp [11,15,18], the visual analogue scale [16], the Chalder Fatigue Scale [16], the vitality subdomain of SF-36[12,13], the Profile of Mood States [19], or the LupusQoL fatigue subscale [14]. However, fatigue is a multifaceted phenomenon that might affect to different dimensions of health and could be better captured by multidimensional questionnaires such as the one used in the present study. For instance, benefits of exercise were found for general fatigue, physical fatigue and, less consistently, reduced motivation but not for reduced activity nor mental fatigue. Different peripheral and central mechanisms seem to be involved in the perception of fatigue [52] and could explain the findings. Depression, sleep and inflammatory markers are related to fatigue in SLE [52] and might be improved through exercise. However, the explanatory capacity of these factors is limited as no improvements on these variables either in this report or in the parent trial were observed[29]. Other more plausible hypothesis would include the role of aerobic capacity and deconditioning [52]. The exploratory analyses revealed that improvements in CRF mediated the effects of exercise on general fatigue. Increased blood flow, more optimal oxygen utilization and conditioning in peripheral musculature [53] could be changes related to exercise and increased fitness that could explain, in turn, improvements in general fatigue. The relationship between exercise, CRF, and fatigue in SLE is ambiguous according to previous literature [54]. Indeed, there was no association between changes in CRF and changes in other domains of fatigue. Also, fatigue improvements have been described in

SLE independently of changes in fitness levels [54]. The differences in tests used to estimate aerobic capacity, exercise protocols, type of supervision during the program [54] or the inclusion of patients with concomitant diseases hinder interpretation of the results available so far. In this regard, the present supervised exercise protocol contributes to current literature providing novel evidence for a possible mediating role of CRF in the reduction observed in general fatigue following aerobic exercise in SLE.

No differences between-group were found in depressive symptoms. A previous non-controlled trial [11] showed a reduction of depression after a 6 weeks of aerobic or strength exercise [11]. Another investigation consisting of 12-week aerobic exercise [12] also found reductions in depression vs. a controlled group. In contrast, no effects on depression were found in other controlled trials following 6 [19] or 12 weeks [13,16] of strength [13] or aerobic [13,16,19] exercise. It must be noted that, although the imbalanced levels of depressive symptoms between groups was controlled in the analyses, residual confounding cannot be discarded due to the non-randomized design. In addition, the groups in the study showed only minimal to mild symptoms of depression according to reference values [41], which limit the ability of the intervention to provide benefits similar to those seen in patients with higher levels of depression [12]. Recent systematic reviews have also suggested that benefits in depressive symptoms are achieved with exercise of low to moderate intensity [55,56], which differs from moderate-to-vigorous intensity level performed in this trial. Light physical activity might also improve adherence [56] and be a safe initial strategy for highly sedentary patients [57].

Regarding HRQoL, two previous non-controlled trials [11,18] observed improvements in some domains of the SF-36 following a 6-week aerobic or strength [11] and a 8-month aerobic [18] exercise program. Keramiotou et al.[14] recently demonstrated that 12 weeks of upper limb exercise involving strength and stretching improved different measures of

HRQoL compared a control group. Prior interventions by Abrahao et al. [13] and Carvalho et al. [12] also showed that a 12-week aerobic exercise program improved physical role and vitality domains of the SF-36 vs. a control group. Compared to the intervention reported here, a similar weekly volume of exercise (150-180 min/week) was accumulated in these prior studies [12,13], but training frequencies were higher (65-75% HRR [13]) which could explain the disagreement between findings. Another interesting intervention by Bostrom et al. revealed that after 6 months of exercise and coaching, mental health domain of the SF-36 was improved compared to the control group [58]. More in agreement with our findings, Tench et al. [16] observed no effect on SF-36 domains after a mainly home-based 12-week walking aerobic exercise vs. a control group. Therefore, the lack of effect of exercise in this and previous studies [16] could indicate that a protocol of exercise with more frequent sessions, progressively moving to vigorous intensities when tolerated, and in combination with other behavioral approaches, might be more beneficial for HRQoL in SLE. Exercising in other settings (e.g., water-based) and the inclusion of other types of exercise (e.g., whole-body vibration) might also hold potential to improve HRQoL according to previous research in other populations [59,60].

This study has several limitations. First, the final sample size was relatively small and was calculated to assess the between-group change in arterial stiffness as the primary trial outcome [29]. Consequently, the power to detect significant between-group differences in the outcomes reported here was checked. For instance, for the outcomes in which we detected an effect of exercise (general, physical and motivation dimensions of fatigue), the power was 0.50, 0.89 and 0.54, respectively. For the remaining outcomes, the power ranged from 0.06 to 0.27. As the effect size for certain outcomes was rather small (i.e. stress or sleep quality), the evidence derived from this study suggests no effects of 12 weeks of aerobic exercise with the above-mentioned intensities and dose. However,

regarding HRQoL in which the sample size was specially reduced due to missing data and the standardized effect size was small to moderate, increasing the sample size would actually be advisable to clarify the short term effects of aerobic exercise in these outcomes. Second, the non-randomized design might compromise the between-groups comparability. Third, the results are not generalizable to men or patients with higher disease activity. The work also has strengths that need to be highlighted. First, the adherence to the exercise intervention was very high and accurately reported. Second, the intervention is described transparently and in a replicable manner [29] following the CERT guidelines [32], and may serve practitioners for implementation in clinical practice.

CONCLUSION

This study suggests that 12 weeks of progressive aerobic exercise on a treadmill following ACSM recommendations might significantly improve general and physical fatigue and, to a lesser extent, reduced motivation in women with SLE. Improvements in CRF mediated the effects of exercise on general fatigue. However, no effects on other aspects of fatigue, psychological stress, sleep quality, depressive symptoms or HRQoL were experienced by participants.

Conflicts of Interest: The authors declare no conflicts of interests

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Table 1. Baseline descriptive characteristics of the study participants

	All (*n*=58)	Exercise (*n*=26)	Control (*n*=32)	*P*
	Mean (SD)	Mean (SD)	Mean (SD)	
Age, years	44.0 (13.9)	43.0 (15.1)	44.8 (13.1)	0.618
Marital status (Single/Married/Divorced; %)	44.8/50.0/5.2	53.8/42.3/3.9	37.5/56.3/6.2	0.455
Educational level (No studies/Primary/Secondary/University; %)	3.4/36.2/22.4/37.9	0/38.5/26.9/34.6	6.3/34.4/18.7/40.6	0.521
Occupational status (Working/housewife/Not working; %)	41.4/24.1/34.5	42.3/19.2/38.5	40.6/28.1/31.3	0.706
Disease duration, years	15.4 (10.5)	14.5 (10.4)	16.1 (10.6)	0.570
SLEDAI	0.22 (0.90)	0.04 (0.20)	0.38 (1.18)	0.158
SDI	0.47 (1.11)	0.19 (0.63)	0.69 (1.35)	0.092
Cardiorespiratory fitness (Bruce test, min)	8.2 (2.8)	8.1 (2.2)	8.3 (3.2)	0.763
BMI, kg/m2	25.2 (4.7)	25.9 (3.4)	24.7 (5.6)	0.336
Smoke (%)	25.9	15.4	34.4	0.166
Menopause (%)	39.7	38.5	40.6	0.867
Total PA, min/week	90.9 (92.2)	96.8 (97.9)	86.3 (88.8)	0.646
Psychological Stress (PSS; 0-56; median, IQR)	31 (28-33)	30 (27 - 32)	31.5 (29-34)	0.087
Sleep Quality (PSQI; 0-21)	7.8(4.1)	6.7(3.5)	8.7(4.3)	0.062
Fatigue (MFI-S; 0-20)				
General Fatigue (median, IQR)	15 (11-17)	14.5 (11-17)	15.5 (11.5-16.5)	0.588
Physical fatigue	12.8(4.7)	12.4(4.6)	13.1(4.6)	0.572
Reduced Activity (median, IQR)	9 (6-12)	8 (6-12)	10.5 (5.5-13)	0.719
Reduced Motivation	9.6 (3.7)	8.5(3.4)	10.4(3.9)	0.054
Mental Fatigue	12.4(2.9)	12.0(3.0)	12.6(2.9)	0.453
Depressive symptoms (BDI-II; 0-63)	13.0 (9.0)	9.6(7.7)	15.7(9.0)	**0.008**
Health-related quality of life (SF-36; 0-100)*				
Physical Summary Component	42.9(8.2)	45.5(8.5)	40.6(7.4)	**0.037**
Mental Summary Component	43.8(11.7)	47.5(11.7)	40.4(10.9)	**0.035**

*For SF-36 domains total sample size was *n*=41 due to missing data

BDI-II: Beck Depression Inventory-second edition; BMI: Body Mass Index; MFI: Multidimensional Fatigue Inventory; IQR: Interquartile range; PSQI: Pittsburgh Sleep Quality Index; PSS: Perceived Stress Scale; PA: physical activity; SD: Standard Deviation; SDI, systemic damage index; SF-36: Short-Form Health Survey; SLEDAI: systemic lupus erythematosus disease activity index,

Figure 1. Flowchart of the participants throughout the study.

BOCF: Baseline-observations carried forward.

Table 2. Per-protocol (primary) analyses assessing the effects of 12-week progressive aerobic exercise on patient-reported outcomes in women with systemic lupus erythematosus (participants in the exercise group were included if attendance was ≥75%).

Patient-reported outcomes	Change from Baseline at Week 12 (Final - Baseline)				
	Exercise (*n*=22) median (SE)	Control (*n*=28) median (SE)	Mean difference (95%CI)	*P*	Cohen's *d*
Psychological stress (PSS)	-1.6 (1.20)	-1.2 (1.06)	-0.4 (-3.64 to 2.84)	0.805	0.07
Sleep Quality (PSQI)	-0.63 (0.73)	-0.96 (0.66)	0.32 (-1.67 to 2.32)	0.744	0.10
Fatigue (MFI)					
General Fatigue	-2.57 (1.07)	0.29 (0.94)	-2.86 (-5.70 to -0.01)	**0.049**	**0.57**
Physical Fatigue	-3.33(1.00)	1.00 (0.88)	-4.33 (-7.02 to -1.65)	**0.002**	**0.92**
Reduced Activity	-1.00 (0.92)	-0.75 (0.84)	-0.25 (-2.68 to 2.18)	0.837	0.06
Reduced Motivation	-1.43 (0.47)	-0.14(0.43)	-1.29 (-2.60 to 0.03)	0.055	0.60
Mental Fatigue	-1.00 (0.69)	0.00 (0.61)	-1.00 (-2.86 to 0.86)	0.285	0.31
Depressive symptoms (BDI-II)	-4.03 (1.81)	-2.25 (1.59)	-1.78 (-6.74 to 3.19)	0.475	0.21
Health-related Quality of life (SF-36)*					
Physical Summary Componer	2.83 (2.15)	0.49 (2.06)	2.34 (-3.83 to 8.52)	0.448	0.14
Mental Summary Component	6.51 (2.63)	2.12 (2.47)	4.39 (-3.00 to 11.78)	0.237	0.27

* For SF-36 variables *n*=18 exercise group and *n*=22 control group.

BDI-II: Beck Depression Inventory-second edition; HRQoL: Health-related quality of life; MFI: Multidimensional Fatigue Inventory; PSQI: Pittsburgh Sleep Quality Index; PSS: Perceived Stress Scale; SF-36: Short-Form Health Survey.

Models were adjusted for outcome at baseline

Table 3. Sensitivity analyses: Baseline-observation carried forward imputation assessing the effects of 12-week progressive aerobic exercise on patient-reported outcomes in women with systemic lupus erythematosus.

Patient-reported outcomes	Change from Baseline at Week 12 (Final - Baseline)			
	Exercise (*n*=26) median (SE)	Control (*n=32*) median (SE)	Mean difference (95%CI)	*P*
Psychological stress (PSS)	-1.6 (1.13)	-1.2 (1.00)	-0.40 (-3.45 to 2.65)	0.794
Sleep Quality (PSQI)	-0.96 (0.84)	-0.32 (0.65)	-0.64 (-2.80 to 1.51)	0.552
Fatigue (MFI)				
General Fatigue	**-3.0 (0.74)**	**-0.01 (0.66)**	**-3.0 (-4.96 to -1.04)**	**0.003**
Physical Fatigue	-2.00 (0.93)	0.00 (0.83)	-2.00 (-4.50 to 0.50)	0.114
Reduced Activity	-1.25 (0.78)	-0.25 (0.72)	-1.00 (-3.10 to 1.10)	0.345
Reduced Motivation	**-1.25 (0.37)**	**0.00 (0.33)**	**-1.25 (-2.27 to -0.23)**	**0.017**
Mental Fatigue	-1.00 (0.67)	0.00 (0.61)	-1.00 (-2.80 to 0.80)	0.271
Depressive symptoms (BDI-II)	-3.32 (1.74)	-1.32 (1.56)	-2.00 (-6.83 to 2.83)	0.411
Health-related Quality of life (SF-36)*				
Physical Summary Component	3.82 (2.07)	0.21 (1.63)	3.61 (-1.94 to 9.16)	0.196
Mental Summary Component	6.52 (3.23)	1.94 (2.64)	4.58 (-4.05 to 13.21)	0.289

* For SF-36 variables n=25 exercise group and n=23 control group

BDI-II: Beck Depression Inventory-second edition; HRQoL: Health-related quality of life; MFI: Multidimensional Fatigue Inventory; PSQI: Pittsburgh Sleep Quality Index; PSS: Perceived Stress Scale; SF-36: Short-Form Health Survey.

Models were adjusted for outcome at baseline

Table 4. Per-protocol analyses assessing the effects of 12-week progressive aerobic exercise on patient-reported outcomes in women with systemic lupus erythematosus (participants in the exercise group were included if attendance ≥90%)

Patient-reported outcomes	Change from Baseline at Week 12 (Final - Baseline)			
	Exercise (*n*=18) median (SE)	Control (*n*=28) median (SE)	Mean difference (95%CI)	*P*
Psychological stress (PSS)	-0.25 (1.34)	0.5 (1.07)	-0.75 (-4.23 to 2.73)	0.666
Sleep Quality (PSQI)	-0.85 (0.86)	-0.96 (0.70)	0.10 (-2.15 to 2.37)	0.923
Fatigue (MFI)				
General Fatigue	**-3.89 (0.96)**	**0.22 (0.75)**	**-4.11 (-6.54 to -1.68)**	**0.001**
Physical Fatigue	**-3.67 (1.19)**	**1.00 (0.94)**	**-4.67 (-7.74 to -1.59)**	**0.004**
Reduced Activity	-1.23 (1.01)	-0.69 (0.83)	-0.54 (-3.12 to 2.05)	0.676
Reduced Motivation	-1.67 (0.68)	0.00 (0.54)	-1.67 (-3.46 to 0.13)	0.068
Mental Fatigue	-1.00 (0.76)	0.00 (0.61)	-1.00 (-2.96 to 0.96)	0.310
Depressive symptoms (BDI-II)	-4.22 (2.38)	-2.30 (1.88)	-1.92 (-8.19 to 4.36)	0.451
Health-related Quality of life (SF-36)*				
Physical Summary Component	2.83 (2.23)	0.50 (1.94)	2.34 (-3.91 to 8.60)	0.452
Mental Summary Component	5.96 (2.80)	1.57 (2.46)	4.39 (-3.31 to 12.09)	0.255

* For SF-36 variables n=16 exercise group and n=22 control group

BDI-II: Beck Depression Inventory-second edition; HRQoL: Health-related quality of life; MFI: Multidimensional Fatigue Inventory; PSQI: Pittsburgh Sleep Quality Index; PSS: Perceived Stress Scale; SF-36: Short-Form Health Survey.

Models were adjusted for outcome at baseline

Figure 2. Mediating effect of post-intervention changes in cardiorespiratory fitness (Δ CRF) in the effect of exercise on fatigue in women with systemic lupus erythematosus (n=50). Participants in the exercise group were included if attendance was ≥75%. B: Unstandardized regression coefficients.

Equation 1 includes the predictor (exercise intervention) and hypothesized mediator (changes in cardiorespiratory fitness) Equation 2 includes the predictor and the outcome changes in fatigue). Equation 3 includes the hypothesized mediator and the outcome. Equation 3' includes predictor, the outcome adjusted for the hypothesized mediator. All analyses were additionally adjusted by the baseline outcome.

*P< 0.05; **P< 0.01; ***P< 0.001

Supplementary table 1. Sensitivity analyses: Complete case analyses assessing the effects of 12-week progressive aerobic exercise on patient-reported outcomes in women with systemic lupus erythematosus (only participants with valid data were included)

Patient-reported outcomes	Change from Baseline at Week 12 (Final - Baseline)			
	Exercise (*n*=26) median (SE)	Control (*n*=28) median (SE)	Mean difference (95%CI)	*P*
Psychological stress (PSS)	-1.6 (1.16)	-1.2 (1.11)	-0.4 (-3.65 to 2.85)	0.806
Sleep Quality (PSQI)	-0.78 (0.69)	-0.89 (0.68)	0.11 (-1.87 to 2.08)	0.912
Fatigue (MFI)				
General Fatigue	**-3.00 (0.78)**	**0.00 (0.74)**	**-3.00 (-5.13 to -0.87)**	**0.007**
Physical Fatigue	**-2.57 (0.94)**	**1.00 (0.91)**	**-3.57 (-6.21 to -0.94)**	**0.009**
Reduced Activity	-1.0 (0.86)	-0.75 (0.85)	-0.25 (-2.60 to 2.10)	0.831
Reduced Motivation	-1.13 (0.40)	-0.13 (0.41)	-1.0 (-2.14 to 0.14)	0.085
Mental Fatigue	-1.5 (0.75)	-0.25 (0.72)	-1.25 (-3.33 to 0.83)	0.234
Depressive symptoms (BDI-II)	-2.97 (1.84)	-2.05 (1.77)	-0.92 (-6.22 to 4.40)	0.730
Health-related Quality of life (SF-36)*				
Physical Summary Component	2.83 (1.92)	0.49 (2.02)	2.34 (-3.38 to 8.07)	0.414
Mental Summary Component	5.41 (2.41)	1.02 (2.60)	4.39 (-2.84 to 11.61)	0.227

* For SF-36 variables n=23 exercise group and n=22 control group

BDI-II: Beck Depression Inventory-second edition; HRQoL: Health-related quality of life; MFI: Multidimensional Fatigue Inventory; PSQI: Pittsburgh Sleep Quality Index; PSS: Perceived Stress Scale; SF-36: Short-Form Health Survey.

Models were adjusted for outcome at baseline

Supplementary table 2. TREND statement

Paper Section/Topic	Item No.	Descriptor	Reported?	
			✓	Pg #
TITLE and ABSTRACT				
Title and Abstract	1	• Information on how units were allocated to interventions	✓	1-2
		• Structured abstract recommended	✓	1-2
		• Information on target population or study sample	✓	1-2
INTRODUCTION				
Background	2	• Scientific background and explanation of rationale	✓	2-4
		• Theories used in designing behavioral interventions	✓	2-4
METHODS				
Participants	3	• Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)	✓	4
		• Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented	✓	4
		• Recruitment setting	✓	4
		• Settings and locations where the data were collected	✓	4
Interventions	4	• Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:		
		○ Content: what was given?	✓	5-6
		○ Delivery method: how was the content given?	✓	5-6
		○ Unit of delivery: how were subjects grouped during delivery?	✓	5-6
		○ Deliverer: who delivered the intervention?	✓	5-6
		○ Setting: where was the intervention delivered?	✓	5-6
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?	✓	5-6
		○ Time span: how long was it intended to take to deliver the intervention to each unit?	✓	5-6
		○ Activities to increase compliance or adherence (e.g., incentives)	✓	5-6
Objectives	5	• Specific objectives and hypotheses	✓	4
Outcomes	6	• Clearly defined primary and secondary outcome measures	✓	7
		• Methods used to collect data and any methods used to enhance the quality of measurements	✓	7-8
		• Information on validated instruments such as psychometric and biometric properties	✓	7-8
Sample size	7	• How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	✓	9
Assignment method	8	• Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)	✓	8
		• Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)	✓	8
		• Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)	✓	8
Blinding (masking)	9	• Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment;	✓	8

		if so, statement regarding how the blinding was accomplished and how it was assessed		
Unit of Analysis	10	• Description of the smallest unit that is being analysed to assess intervention effects (e.g., individual, group, or community)	✓	16
		• If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)		n/a
Statistical methods	11	• Statistical methods used to compare study groups for primary methods outcome(s), including complex methods for correlated data	✓	9
		• Statistical methods used for additional analyses, such as subgroup analyses and adjusted analysis	✓	9
		• Methods for imputing missing data, if used	✓	9
		• Statistical software or programs used	✓	9
RESULTS				
Participant flow	12	• Flow of participants through each stage of the study: enrollment, assignment, allocation and intervention exposure, follow-up, analysis (a diagram is strongly recommended)	✓	Fig 1
		○ Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study	✓	Fig 1
		○ Assignment: the numbers of participants assigned to a study condition	✓	Fig 1
		○ Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention	✓	Fig 1
		○ Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition	✓	Fig 1
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition	✓	Fig 1
		• Description of protocol deviations from study as planned, along with reasons		n/a
Recruitment	13	• Dates defining the periods of recruitment and follow-up	✓	7
Baseline data	14	• Baseline demographic and clinical characteristics of participants in each study condition	✓	Table 1
		• Baseline characteristics for each study condition relevant to specific disease prevention research	✓	Table 1
		• Baseline comparisons of those lost to follow-up and those retained, overall and by study condition	✓	-
		• Comparison between study population at baseline and target population of interest	✓	Table 1
Baseline equivalence	15	• Data on study group equivalence at baseline and statistical methods used to control for baseline differences	✓	Table 1
Numbers analyzed	16	• Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible	✓	Table 2, 3, 4, 5
		• Indication of whether the analysis strategy was “intention to treat” or, if not, description of how non-compliers were treated in the analyses	✓	Table 2, 3, 4, 5
Outcomes and estimation	17	• For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	✓	10-11
		• Inclusion of null and negative findings	✓	10-11
		• Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any	✓	10-11

Ancillary analyses	18	• Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory	✓	10-11
Adverse events	19	• Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)	✓	10-11
DISCUSSION				
Interpretation	20	• Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	✓	11-15
		• Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations	✓	11-15
		• Discussion of the success of and barriers to implementing the intervention, fidelity of implementation	✓	15
		• Discussion of research, programmatic, or policy implications	✓	15
Generalizability	21	• Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues	✓	15
Overall evidence	22	• General interpretation of the results in the context of current evidence and current theory	✓	15

From: Des Jarlais, D. C., Lyles, C., Crepaz, N., & the Trend Group (2004). Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: The TREND statement. *American Journal of Public Health*, 94, 361-366. For more information, visit: http://www.cdc.gov/trendstatement/