UNIVERSIDADE ESTADUAL DE CAMPINAS
SISTEMA DE BIBLIOTECAS DA UNICAMP
REPOSITÓRIO DA PRODUÇÃO CIENTIFICA E INTELECTUAL DA UNICAMP

Versão do arquivo anexado / Version of attached file:

Versão do Editor / Published Version

Mais informações no site da editora / Further information on publisher's website:
https://link.springer.com/article/10.1007/s00296-023-05370-x

DOI: https://doi.org/10.1007/s00296-023-05370-x

Direitos autorais / Publisher's copyright statement:
©2023 by Springer. All rights reserved.

DIRETORIA DE TRATAMENTO DA INFORMAÇÃO

Cidade Universitária Zeferino Vaz Barão Geraldo
CEP 13083-970 – Campinas SP
Fone: (19) 3521-6493
http://www.repositorio.unicamp.br

Rheumatology International (2023) 43:1799–1810
https://doi.org/10.1007/s00296-023-05370-x

Rheumatology
INTERNATIONAL

PROTOCOLS

A randomized controlled trial of an intervention promoting physical activity and healthy eating recommendations in systemic lupus erythematosus: the protocol study "Living Well with Lupus"

Sofia Mendes Sieczkowska[1] · Fabiana Infante Smaira[1] · Bruna Caruso Mazzolani[1] · Marina Romero[1,3] · Sandra Gofinet Pasoto[2] · Ana Lúcia de Sá Pinto[1,2] · Fernanda Rodrigues Lima[1,2] · Victor Rodrigues De Oliveira[2] · Serli Ueda[2] · Fabiana Braga Benatti[1,3] · Hamilton Roschel[1] · Bruno Gualano[1,2]

Received: 2 June 2023 / Accepted: 8 June 2023 / Published online: 24 June 2023
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2023

Abstract

There is a paucity of studies assessing multidisciplinary interventions focused on tackling physical inactivity/sedentary behavior and poor dietary habits in SLE. The Living well with Lupus (LWWL) is a randomized controlled trial to investigate whether a six-month lifestyle change intervention will improve cardiometabolic risk factors (primary outcome) among systemic lupus erythematosus (SLE) patients with low disease activity (SLEDAI score ≤ 4) and with high cardiovascular risk. As secondary goals, we will evaluate: (1) the intervention's safety, efficacy, and feasibility in promoting lifestyle changes, and (2) the effects of the intervention on secondary outcomes (i.e., clinical parameters, functional capacity, fatigue, psychological aspects, sleep quality and health-related quality of life). Patients will be randomly allocated to either a control (i.e., standard care) or a lifestyle intervention group using a simple randomization (1:1 ratio, blocks of 20). Mixed Model analyses will be conducted for comparing groups following an intention-to-treat approach. A per protocol analysis will also be conducted. This study has the potential to generate new, clinically relevant data able to refine the multidisciplinary management of SLE patients. Protocol version number: NCT04431167 (first version).

Keywords Systemic lupus erythematosus · Lifestyle · Behavior change

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune and multisystemic rheumatic disease characterized by the presence of autoantibodies and immune complexes that activate the immune response in various tissues, resulting in several clinical and laboratory manifestations, chronic inflammation, and tissue damage. SLE patients can present with skin lesions, osteoarthritis, renal and neurological disorders, hematological changes, among other complications [1, 2].

Patients with SLE can also exhibit reduced physical, functional and aerobic capacity, increased fatigue, and higher prevalence of sleep, neurological and/or psychiatric (i.e., anxiety and depression) disorders [3–5]. Furthermore, they are often affected by cardiovascular diseases, which are the main cause of morbidity and mortality in this population [6, 7]. This cluster of abnormalities leads to a prominent reduction in the quality of life in SLE.

Sofia Mendes Sieczkowska, Fabiana Infante Smaira and Bruna Caruso Mazzolani have contributed equally to this work.

✉ Bruno Gualano
gualano@usp.br

[1] Applied Physiology and Nutrition ResearchGroup, Center of Lifestyle Medicine, Faculdade de Medicina FMUSP, Universidade de São Paulo, Av. Dr. Arnaldo, 455, 3° Andar, São Paulo, SP 01246-903, Brazil

[2] Rheumatology Division, Faculdade de Medicina FMUSP, Universidade de São Paulo, Av. Dr. Arnaldo, 455, Sao Paulo, SP 05403-900, Brazil

[3] School of Applied Sciences, Universidade Estadual de Campinas, Campinas, São Paulo 13484-350, Brazil

Atherosclerosis, dyslipidemia, diabetes mellitus, hypertension, obesity, hyperhomocysteinemia, vascular inflammation, and endothelial dysfunction are cardiometabolic alterations reported in SLE [6, 8, 9]. However, the increased cardiometabolic risk in these patients is not fully explained by the presence of these risk factors [10], implying that some factors inherent to the disease (e.g., disease duration and activity, chronicity, medications, genetic factors and immunological mechanisms), in addition to direct damage to organs and tissues, may also underly the cardiovascular burden in SLE [6, 7, 11–14].

Pharmacological treatment (e.g., hydroxychloroquine, corticosteroids, immunosuppressants, biological agents) is the main strategy to control disease activity, alleviate symptoms and improve patients' quality of life [15]. Although effective, these therapies are not free of adverse effects (e.g., nausea, hepatotoxicity, leukopenia, anemia, infections, glucose intolerance, and osteoporosis) [16–18]. Considering the variety and complexity of the factors that negatively affect these patients, adjuvant, non-pharmacological therapies (e.g., physical activity and dietary interventions) become potentially relevant to improve disease symptoms, patients' quality of life and reduce cardiometabolic risk factors [19–23].

Even with the disease in remission, physical activity is below the recommended levels in SLE patients [21, 24]. These patients also spend more time in sedentary behaviors than the general population [21, 25]. Food consumption and eating aspects of SLE patients remain largely unexplored in the literature. The few existing studies are controversial, with one study showing inadequate intake of some micronutrients (i.e., calcium, iron, vitamin B12 and fiber) [26] and another showing a high consumption of fruits, milk, vegetables, meat and rice (i.e., foods rich in micronutrients) in SLE patients [27]. A recent review emphasized that an adequate food intake in SLE patients can help preserve the body's homeostasis, increase the period of remission, prevent adverse effects of medication and improve the patient's physical and mental well-being [28]. It is known that isolated interventions to promote physical activity or healthy eating among SLE patients have resulted in improvements in inflammation, symptoms (e.g., fatigue, anxiety and depression), quality of life and cardiovascular risk factors (e.g., weight loss, blood pressure, dyslipidemia, insulin resistance [22, 29]. However, existing studies are limited by short-term follow-ups, small samples, and interventions that are difficult to implement in the clinical setting [22, 30]. Furthermore, although the literature shows that separate interventions of physical activity or diet may provide some health benefits, co-interventions focused on tackling physical inactivity/sedentary behavior and poor dietary habits are still lacking in SLE, to our knowledge [31].

There has been a growing interest in multidisciplinary interventions aimed at promoting healthy lifestyle habits, based on encouraging physical activity and healthy and sustainable eating habits [32]. More comprehensive lifestyle interventions, that combine multifaceted strategies aimed at promoting physical activity and healthy food consumption, are capable improving cardiometabolic health parameters [33–35] and health-associated quality of life in various chronic diseases [36–38]. Thus, it becomes relevant to investigate whether new interventions focused on promoting lifestyle changes can also improve cardiometabolic risk factors, symptoms, and quality of life in SLE.

Materials and methods

Objectives and hypotheses

The goal of the proposed intervention is promoting lifestyle changes through recommendations of structured and unstructured physical activity and health eating. The primary aim of the study is to investigate whether such an intervention will improve cardiometabolic risk factors among SLE patients with high cardiovascular risk. Also, as secondary aims, we will evaluate: (1) the intervention's safety, efficacy, and feasibility, in promoting lifestyle changes, and (2) the effects of the intervention on secondary outcomes (i.e., clinical parameters, functional capacity, fatigue, psychological aspects, sleep quality and health-related quality of life).

Our main hypotheses are that (1) the intervention will improve cardiometabolic risk factors; (2) the intervention will be safe, effective, and feasible in promoting lifestyle changes; and (3) the intervention will improve secondary outcomes.

Experimental design

We will conduct a 6-month, parallel-group, randomized controlled trial, in which patients will be assessed for a cardiovascular risk score (primary outcome), physical activity levels and sedentary behavior; food consumption and eating behavior; clinical parameters; cardiometabolic risk factors (i.e., adiposity, aerobic fitness, blood pressure, serum blood lipid profile, insulin resistance and endothelial dysfunction); sleep quality; fatigue; functional capacity; psychological aspects and health-related quality of life.

After baseline assessments, patients will be randomly allocated to either a control or intervention group using a simple randomization (1:1 ratio, blocks of 20) procedure, by computer-generated random numbers in SAS 9.3 (SAS Institute Inc., Cary, NC, USA) for Windows. An external researcher will generate the allocation sequence and results will be placed sequentially numbered in opaque, sealed

envelopes so that the allocation stays concealed until randomization. All assessors will be blinded to patients' exam, except for the cardiopulmonary exercise, functional capacity tests and food consumption analyses. The cardiopulmonary and functional capacity tests will be analyzed before randomization by the researcher responsible for the intervention physical activity construct, as this is a criterion for performing the structured physical exercise program. Food consumption will be analyzed by the research responsible for conducting the nutritional counseling, but data collection will be self-reported with no interference of the researcher. All assessors will be responsible for patients' recruitment and enrollment. The control group will receive standard care, as described below.

The current study is registered in an international database of clinical research studies (clinicaltrials.gov, NCT04431167). This manuscript is described according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [39] and the findings from this study will be reported according to the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) guidelines [40] (Fig. 1).

Patient recruitment and selection

Patient recruitment and selection will take place at the Clinical Hospital (School of Medicine, University of Sao Paulo). Patients will be recruited directly from the SLE Outpatient Clinic of the Rheumatology Division. Inclusion criteria will be: (1) females; (2) that meet classification criteria according to the Systemic Lupus International Collaborating Clinics classification criteria (SLICC) (37); (3) aged between 18 and 65 years; (4) with SLEDAI score ≤ 4 at the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) [41], (5) under treatment with prednisone at a dose < 10 mg/day and with antimalarials at a stable dose; (6) with BMI between 25 e 40 kg/m^2 and/or high cardiovascular risk, which will be defined by the presence of one of the following criteria: dyslipidemia (i.e., plasma total cholesterol > 200 mg/dL, high density lipoprotein (HDL) < 40 mg/dL, low density lipoprotein (LDL) > 130 mg/dL or triglycerides > 150 mg/dL) [42], hypertension or diabetes. Exclusion criteria will include: (1) participation in structured physical activity programs and/or reporting dieting in the last 12 months; (2) having any physical disability that prevents the performance of the cardiopulmonary exercise test or the structured physical exercise program; (3) illiterate patients or with cognitive impairments that impede the understanding of the intervention recommendations; (4) patients with musculoskeletal impairments that potentially impede participation in the intervention.

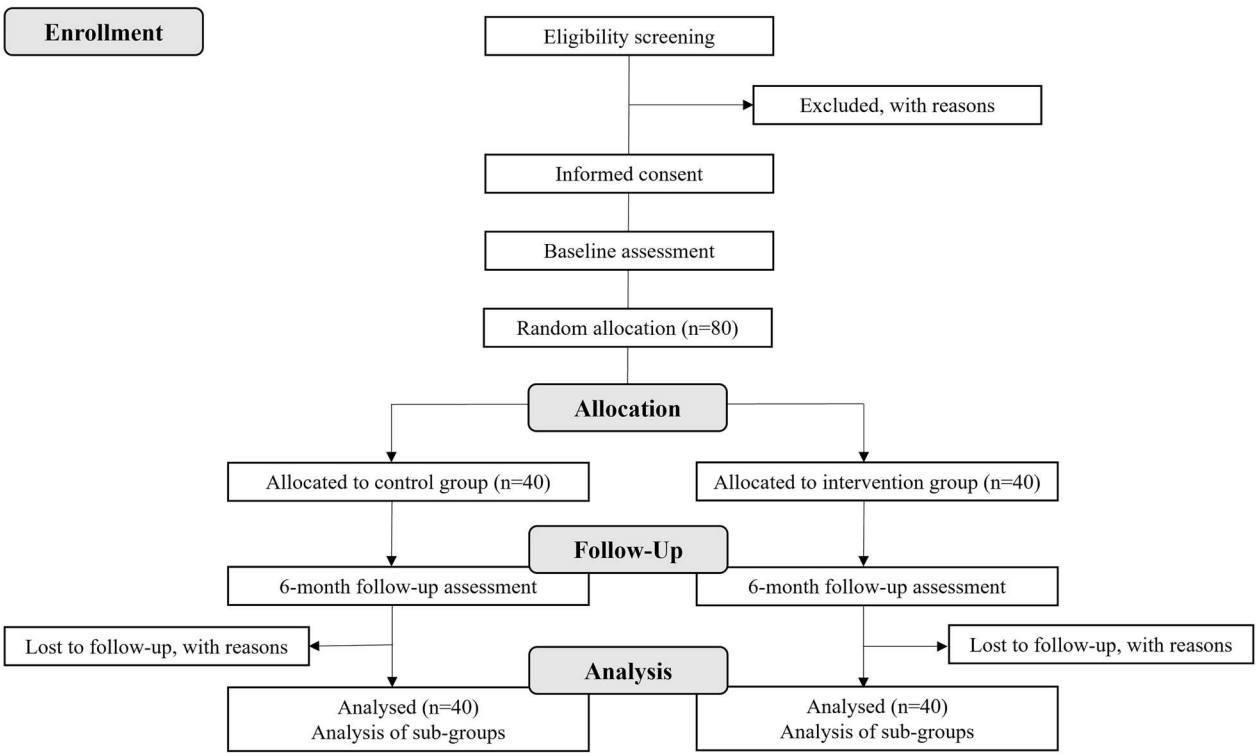

Fig. 1 Planned flow diagram

Sample size

The sample size was determined by feasibility criteria, following previous recommendations [43, 44]. Namely, we considered: (1) the number of potentially eligible patients from our outpatient clinic; (2) our staff capacity (number of technicians, assistants, students and researchers), and (3) the availability of financial resources to conduct the study. This feasibility analysis led us to determine a sample of 80 patients in total.

Ethical compliance

This trial has been approved by the local Ethical Committee (Commission for Analysis of Research Projects, CAPPesq; approval: 19554719.5.0000.0068). Patients will be required to sign an informed consent form before participation and all the procedures will be conducted in accordance with the Declaration of Helsinki revised in 2008.

The Living Well with Lupus intervention

The Living Well with Lupus program is a newly developed, goal setting, behavioral intervention aimed at changing lifestyle behaviors (i.e., increasing physical activity levels, decreasing time spent in sedentary behaviors and improving eating aspects).

The constructs of Living Well with Lupus

Changing behaviors is a process, which imply the existence of different stages, and it is multifactorial, which means it is affected by physical, psychological, and socioeconomic aspects, among others [45]. The present intervention is based on three main pillars: (1) there are different stages in the behavior changing process; (2) behaviors, especially physical activity and eating aspects, are multifactorial and shall be addressed in different fronts; and (3) there are individual characteristics and needs that can be fostered to enhance this process. Based on these assumptions, two models will be used as a theoretical basis for the intervention: the transtheoretical behavior change model and the behavior change wheel [46, 47].

This lifestyle intervention will involve two constructs: (1) to increase physical activity level and reduce sedentary behavior, and (2) to improve eating aspects. The first construct will be a 3-times-a-week, home-based, structured physical activity program composed by ten exercises focused on different muscle groups (e.g., chest, back, abdomen, quadriceps femoris and biceps femoris), with duration of approximately 40 min per session. Progression will occur in terms of volume, duration, intensity, and difficulty of the exercises depending on the developments of the patient over the period. Furthermore, individualized goals will be established in common agreement between patient and researcher to reduce sedentary behavior and increase unstructured physical activity during transport (e.g., "get off the bus one stop before or after your destination and walk the rest of the way at least 3 times a week"), leisure (e.g., "stay standing while talking on the phone or cell phone") and work (e.g., "stop using your computer and get up every 60 min for at least 3 min").

The second construct that aims to improve eating behaviors will be based on nutritional counseling, a technique defined as a meeting between two people to carefully examine, look with respect, and deliberate with prudence and fairness about the eating habits of one of them [48], which is in line with Expanded Clinical Nutrition concepts [49]. Patients will be encouraged to autonomously make desired and/or necessary changes related to any eating aspect, and the nutritionist will facilitate the process, using knowledge about nutrition and strategies based on behavior change theories [50] to define priorities, setting goals, and creating individualized actions [51]. The Dietary Guidelines for the Brazilian Population [52] will guide the recommendations as follows: (1) to have unprocessed or minimally processed foods as the basis of your diet; (2) to use cooking ingredients in small amounts when seasoning, cooking, and creating culinary preparations; (3) to limit the consumption of processed foods by consuming them as ingredients in culinary preparations or as part of meals based on unprocessed or minimally processed foods; and (4) to avoid ultra-processed foods. In addition to the recommendations focused on food consumption, orientations that cover other aspects of eating will be presented, namely: shopping in places that offer a variety of unprocessed or minimally processed foods; developing, exercising and sharing cooking skills; planning the use of time dedicated to eating; eating regularly and with attention; eating in appropriate environments and in company; being critical about information and messages about food conveyed. In this context, the goals established will aim to promote changes both in food consumption and eating aspects (i.e., structure, behavior, and attitudes). The detailed exercise program and nutritional counseling materials can be found in the supplementary material.

Sessions aims and structure

Over the 6-month intervention, eight meetings will be held, the first two fortnightly and the others monthly. The meetings will be personalized and will last approximately 60 min. The recommendations will be carried out by 3 members of the research team with background in Nutrition and/or Exercise Science and an ongoing PhD in these areas, following a specific training for standardizing the intervention. In the first session, patients will: (1) be inquired about their daily

activities' routine; (2) select viable goals to reduce sedentary behavior time; (3) be guided for the practice of the home-based, exercise program; (4) set goals to promote changes on eating aspects; (5) receive a booklet of the selected goals, the material for carrying out the home-based exercise program (including a video) and a log diary for monitoring the compliance with the goals. In the subsequent sessions, we will (1) assess whether patients accomplished the defined goals; (2) increment the physical exercise program; (3) discuss strategies to deal with potential barriers encountered by patients, exclude or replace unmet goals, set new goals and/or increase their frequency and intensity. Recommendations made during the sessions will be reinforced and monitored by text messages and phone calls every single week (Fig. 2).

Control group

The control group will receive standard care at the SLE outpatient clinic from our hospital, which includes the pharmacological management of SLE disease and its comorbidities, with general medical recommendations about a healthy lifestyle (e.g., "engage in more physical activities", "restrict calorie intake", "control your weight"). After 3 months of the randomization, the control group will be contacted to report changes in medications, lifestyle, and routine.

Study procedures

Cardiometabolic risk factors

Cardiovascular risk score (primary outcome) The metabolic syndrome risk score will be used to evaluated cardiovascular risk [53]. It considers the measurement of HDL cholesterol, triglycerides, fasting glucose, waist circumference and blood pressure (mean of diastolic and systolic blood pressure); reference values for the population studied were equivalent to 50 mg/dL, 150 mg/dL, 100 mg/dL, 88 cm and 115 mmHg, respectively. The five variables will default to:

$$Z = \text{(subject data} - \text{reference value)/SD).}$$

Except HDL values, for which, as a protective cardiovascular risk (e.g., values below the recommended levels may contribute to an increased risk of cardiovascular diseases), the z-score will be inverted. The score will be calculated for each variable using individual subject data and standard deviations (SD) will be calculated for the entire group. The sum of the z-scores will be the value of the cardiovascular risk score:

$$\begin{aligned} &Z\text{-score} \\ &= [(50 - HDL)/SD + (TG{-}150)/SD] \\ &\quad + [(\textit{fasting}\ \text{glucose-100/SD}] + [(\text{waist circumference-88})/\text{SD}] \\ &\quad + [(\text{mean diastolic and systolic blood pressure-115})/\text{SD}]. \end{aligned}$$

Anthropometry and visceral fat Height will be measured with a stadiometer and weight by a calibrated scale. Waist circumference will be measured using a plastic tape (i.e., midpoint between the last floating vertebra and the iliac crest). All assessments will be performed by the same trained technician. Visceral fat will be assessed through computer tomography, with the patient in the supine position and shoulders extended with their hands above the head. Examinations will be performed by radiology specialized technicians under medical supervision. Three

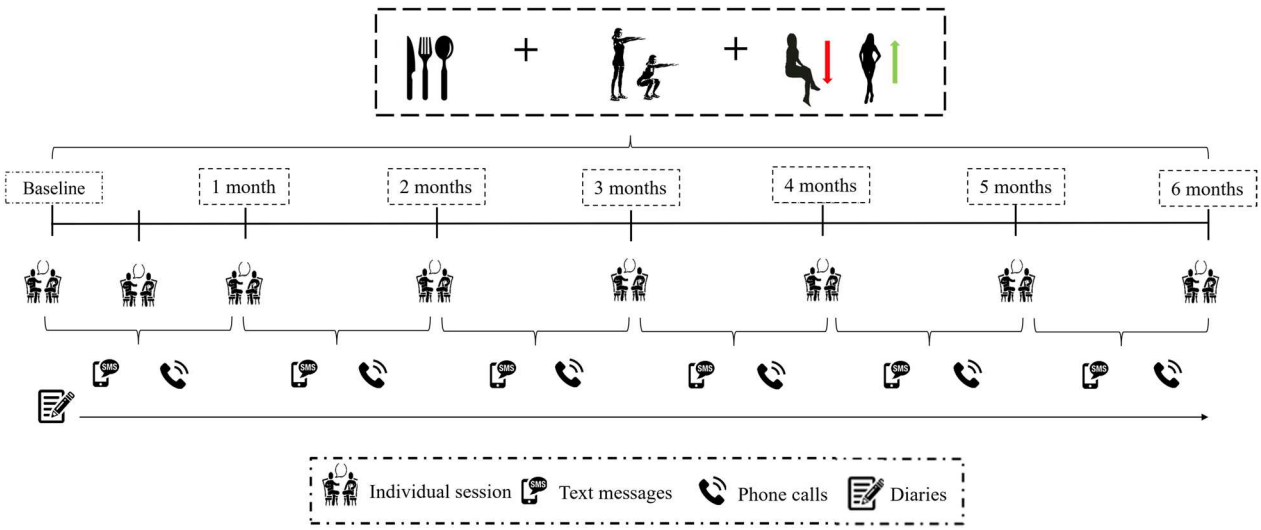

Fig. 2 Overall design of The Living Well with Lupus Intervention

acquisitions will be performed: umbilicus, greater trochanter and the upper third of the thigh. The image acquisition parameters will be: slice thickness = 10 mm; table increment = 10 mm, 0.70 rev/s, 120 kV, 68 mAs per slice and field of view = 500. The density values used will be from − 30 to − 190 for adipose tissue and 30–100 for muscle tissue [54].

Aerobic conditioning During the cardiopulmonary exercise test, cardiovascular behavior will be continuously evaluated using an electrocardiograph, with 12 simultaneous leads. Heart rate and blood pressure will be recorded at rest, and at the end of the effort. The assessment of maximal aerobic capacity will be performed through the direct measurement of oxygen consumption at peak exercise (VO2peak) by a sensor system that allows measurement of pulmonary ventilation at each expiration (Metalyzer model III b/breath-by-breath). From the analysis of ventilatory equivalent (VE) and concentrations of expired gases, oxygen consumption (VO2) and production of carbon dioxide (VCO2) will be calculated. The VO2peak will be considered as the average values in the last 30 s of effort [55]. The test will be considered maximal when two of the following four criteria are met: (1) incidence of a plateau in VO2; (2) respiratory exchange ratio above 1.10; (3) heart rate greater than 90% of the maximum predicted for age; (4) perceived exertion ≥ 17. Metabolic thresholds will be determined by a single experienced evaluator based on the responses of the ventilatory equivalents of O2 (VE/VO2) and CO2 (VE/VCO2). Ventilatory anaerobic threshold will be considered as the point where there was an abrupt increase in VE/VO2, without a concomitant increase in VE/VCO2. Respiratory compensation point will be considered as the moment in which both ventilatory equivalents showed a similar increase [56]. All tests will be conducted under the supervision of a physician. Before the exercise test, participants will be instructed not to drink caffeinated beverages, and not to do vigorous physical activity in the 24 h prior the exam.

Blood pressure Resting blood pressure will be measured by an automatic monitor (SPACELABS, São Paulo, Brazil). Before measurement, patient should rest for 5 min. During the measurement, patient should be in a sitting position, with legs uncrossed, feet flat on the floor, arms slightly flexed and forearms in a supine position. The cuff will be positioned on the participant's left arm, 2–3 cm above the cubital fossa, with the compressive portion under the brachial artery. The use of antihypertensive drugs will be monitored.

Blood sampling and oral glucose tolerance test (OGTT) Blood samples with 15 mL will be collected after a 12-h overnight fast from the median or cephalic basilic vein for further analysis. Serum concentrations of fasting glucose, fasting insulin, total cholesterol and fractions, triglycerides, protein-C reactive (PCR), erythrocyte sedimentation rate (ESR), markers of oxidative stress (Superoxide Dismutase—SOD 1 e 2) and inflammatory cytokines (TNF-α, IL-6, IL-10, IL-1ra, IL-1B e IL4) will be measured.

A 2-h oral glucose tolerance test will be performed at PRE and POST. Blood samples will be collected after a 12-h overnight fast, and at 30, 60, 90, and 120 min after ingestion of 75 g of glucose. Area under the curve (AUC) for glucose, insulin, and C-peptide, and Matsuda index, homeostatic model assessment-insulin resistance (HOMA-IR) and HOMA-B cell function (HOMA-B) will be calculated as surrogates of insulin resistance.

Blood flow and endothelial function Flow-mediated dilatation (FMD) will be evaluated as a measure of endothelial function according to current guidelines [57] using a high-resolution ultrasound machine (LOGIQ e PRO—GE Healthcare, Chicago, IL, US) equipped with a 4.0–12.0 MHz linear transducer.

Initially, participants will be positioned in the supine position with their right arm extended at an angle of ~ 80° from the torso. Longitudinal images of the brachial artery diameter will be taken using the B-mode ultrasound, and simultaneous pulse-waved Doppler blood flow velocity will be obtained using a 60° insonation angle with the sample volume placed in mid-artery and aligned with the blood flow. Initially, a 1-min baseline recording of the brachial artery diameter and blood flow velocity will be performed. Then, the ischemic stimulus will be performed by inflating a cuff placed in the forearm to 50 mmHg above the patient's resting systolic pressure for 5 min. Recordings will be resumed 60 s before cuff deflation and continued for 3 min thereafter. Artery diameter and shear rate (4 × mean blood velocity/internal diameter) will be analyzed by a blinded evaluator using a semi-automatic edge-detection and wall-tracking software (Cardiovascular Suite, Quipu®, Pisa, Italy). FMD will be calculated as the percentage change of the brachial artery diameter after cuff release in relation to baseline brachial artery diameter.

$$\mathrm{FMD} = (\textit{baseline}\ \text{diameter} - \text{peak diameter / baseline diameter}) \times 100].$$

Clinical assessment

Disease parameters (i.e., age of onset, time of disease since diagnosis, current medications) will be obtained by reviewing medical records and interviewing patients. The

evaluation of drug therapy will include the drugs used to control the disease and associated comorbidities.

Disease activity will be evaluated using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) questionnaire [41], which includes clinical and laboratory parameters considering the organ affected. Higher scores represent greater disease activity Damage indices will be measured with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology—Damage Index (SLICC/ACR-DI) created by the American College of Rheumatology [58], which assesses the damage in 12 organ systems. Global patients' health status will be assessed using the Visual Analog Scale (VAS) in which patients grade their health status using a 10-point scale.

Physical activity level and sedentary behavior

Physical activity level will be objectively measured using a triaxial ActivPAL® accelerometer (PAL Technology), which allows the evaluation of the time spent in sedentary behavior and in light and moderate-to-vigorous intensity physical activities. All patients will be instructed to wear the accelerometer for 7 days, removing it only during submerged water activities (swimming pool). The accelerometer will be positioned on the medial portion of the right thigh using a waterproof bandage. Patients will have to accumulate at least 10 h of valid activity per day for at least 4 days. Additionally, patients must fill in a device use diary, which will include day, time of insertion and removal of the device, if necessary. The collected data will be downloaded to the computer through the ActivPAL® software. The following data will be reported: (1) sitting time (hours/day); 2) standing time (hours/day); (3) light-intensity physical activity (hours/day), moderate-to-vigorous physical activity (minutes/day), and moderate-to-vigorous physical activity (minutes/day); and (4) number of steps.

Food consumption and eating aspects

Food consumption will be assessed by means of three 24-h food recalls undertaken on separate days, two weekdays and one weekend day. Data will be evaluated using Dietbox® software (online version). Food preparations (e.g., soups, puree, pies, sandwiches) were broken down into foods and ingredients, according to standardized recipes. For characterization purposes, the total energy intake (kcal) and macronutrients consumption (grams and percentage of total energy intake [%TEI]) were calculated.

The absolute amount (g/day), energy contribution (%TEI), and frequency of food consumption (portions/day) were calculated for each processing level in accordance with the NOVA classification [59]. Food processing levels were classified as follows: Group 1: Unprocessed or minimally processed foods, which include plants or animals after separation from nature and natural foods altered by the processes designed to preserve natural foods, to make them suitable for storage, safe, and edible or more pleasant to consume, such as drying, fractioning, and filtering (e.g., seeds, fruits, roots, milk). Group 2: Culinary ingredients, which are substances derived from Group 1 or from nature by processes that include pressing, refining, grinding, milling, and drying (e.g., oils, sugar, and salt). Group 3: Processed foods, which are made essentially by adding salt, oil, sugar, and other substances or foods from Groups 1 and 2 (e.g., homemade breads, cheeses, dried meats). Group 4: Ultra-processed foods, which are formulations made mostly or entirely from substances derived from foods and additives, with little, if any, intact food from Group 1 (e.g., sausages, candies, snacks).

Eating aspects will be evaluated only in the intervention group. Changes in eating structure, behavior and/or attitudes during the 6-month intervention analyzed through nutritionist sessions record and patient's fulfillment of defined goals in each aspect (monitored through diaries and nutritionist text messages) will be reported.

Safety, efficacy, and feasibility of the intervention

Safety, defined as whether the intervention is plausible to be implemented without damaging patient's health condition, will be assessed through disease activity evaluation using the SLEDAI/2K questionnaire [60]. In addition, laboratory serum markers associated with kidney, liver, immune, muscle and heart health will be analyzed.

Efficacy, which refers to the effects caused by the intervention in a controlled context for a certain population [61], will be evaluated through quantitative data related to the two constructs aimed at this lifestyle promotion program, namely: (1) levels of physical activity obtained by accelerometry: time spent in sedentary behavior, light and moderate-to-intense physical activities; and (2) "quality" of food consumption, inferred from data obtained from 24-h recalls and analyzed regarding the degree of food processing as well as positive changes in other eating aspects.

To assess the feasibility of the study, which is defined as the ability to carry out the intervention with patient engagement, knowledge, acceptance and satisfaction [62], we will rely on data obtained by a specific questionnaire to evaluate the program, and data from a focus group as described below.

Focus group

Focus groups will be conducted by trained researchers for collecting qualitative experiences and impressions of

patients regarding the intervention. The aim of the focus group is to broaden the understanding intervention process and effects. A semi-structured script with open questions will be used to stimulate patients to talk about: positive and negative aspects of the intervention; any barriers to changes physical activity and eating aspects; changes in perceptions of health and well-being (physical and psychological aspects); motivation to maintain the achieve changes in behavior. Each focus group will accommodate 4–6 participants; therefore, 4–6 focus groups will be held in total. A moderator will lead the group and an observer will take notes. The discussions will be recorded and transcribed for later analysis through the content analysis method, which is "a set of communication analysis techniques that aim to obtain, through systematic procedures and description of the content of the messages, indicators that allow inferring related knowledge to the conditions of production/reception of these messages" [63]. The MAXQDA software (Verbi, Berlin, Germany, 2015) will be used to facilitate the analysis.

Health-related quality of life

Quality of life will be assessed by two questionnaires: Systemic Lupus Erythematosus Quality of Life (SLEQOL) and the SF-36 (Medical Outcomes Study 36—Short-Form Health Survey). The SLEQOL consists of 40 items divided into six domains: physical function, occupational activities, symptoms, treatment, mood and self-image [64]. Score ranges from 40 to 280, with each question having scores between 1 and 7. The SF-36 is composed of 36 items that assess the following domains: functional capacity, physical aspects, pain, general health status, vitality, aspects social, emotional aspects and mental health [65]. The maximum score is 100, with higher scores representing better quality of life.

Functional capacity

Timed-stands, timed up-and-go and handgrip tests will be used to assess functional capacity. All patients will undergo a familiarization session, held at least 48 h before the actual test, to ensure data reliability.

The timed-stands test consists in counting the number of times the patient can get up and sit down from a chair using only the lower limbs for 30 s [66]. The timed up-and-go test assesses the time required for the patient to get up from a chair, walk 3 m, turn 180°, and return to the chair [67]. In both assesses, the patient will make two attempts and the average will be considered for analyzes.

Handgrip strength will be evaluated using a hand dynamometer. The test will be performed with the participant's dominant hand and during the test the participant must remain in an upright position with the arm extended along the body. Participants will perform maximum handgrip strength on the device for 5 s. The average value obtained among three attempts, separated by a one-minute interval, will be considered the handgrip strength [68].

Fatigue

The FACIT Fatigue Scale, which contains13 items ranging from 0 to 4 (e.g., not at all to very much), will be used to assess fatigue. Final score can range from 0 to 52, where higher scores represent higher fatigue levels. Items on this scale have been previously considered relevant to measure fatigue in SLE [69]

Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) [70], which is composed by 14 items, 7 for anxiety (HADS-A) and 7 for depression (HADS-D), will be used to assess anxiety and depression symptoms. Items can be scored from 0 to 3, making up a maximum score of 21 points for each subscale. The cut-off points are: 0–8 without the symptom (i.e., anxiety or depression) and ≥ 9 with the symptom (i.e., anxiety or depression) for each subscale.

Sleep quality

Sleep quality will be measured with the triaxial accelerometer Actigraph GT3x® (Actigraph®) in conjunction with a diary of device use. The accelerometer will be used on the non-dominant wrist for 10 nights, with a minimum of 7 valid nights being required. The diary will include the day, time they went to bed and got out of bed (i.e., time in bed). Collected data will be downloaded to the computer using the ActiLife software version 6.11.2. Periods of accelerometer use will be classified as sleep or wakefulness using a software automatic algorithm and will be checked based on patients' sleep diary. Total sleep time, sleep effectiveness, sleep latency and time between sleep onset and awakening will be reported. Total sleep time is the sum of minutes slept during the period that individual is lying down. Sleep efficiency is sleep time percentage during which the individual is lying down. Sleep latency is the time it takes the individual to fall asleep from the moment he is lying down. Time between sleep onset and awakening is the time between the onset of sleep and the first awakening [71].

Statistical analysis

Before inferential analysis, the presence of outliers will be verified and sphericity, homoscedasticity and normality of the data will be tested. Having guaranteed the fundamental assumptions for variance analysis, Mixed Model analysis will be used for repeated measures using the Kenward–Roger method and, when a significant value of F is observed, Tukey post hoc will be performed for multiple comparisons. For all dependent variables (i.e., cardiometabolic risk factors, sedentary behavior, physical activity level, food consumption, clinical parameters, quality of life, psychological aspects, and sleep quality), the group (i.e., intervention and control) and time (i.e., pre and post) will be considered fixed factors, and subjects will be defined as random factors. A per protocol analysis will also be conducted. All data will be expressed as mean ± standard deviation, 95% confidence intervals and effect size. The significance level adopted to reject the null hypothesis will be $p \leq 0.05$. Analyses will be performed in RStudio version 4.02.

Trial status

Protocol version number: NCT04431167 (first version). Date of protocol registration, June 16, 2020. P Patients' recruitment began in September 2020 and finished in August 2022. We expect to conclude the 6-month follow-up assessments by March 2023.

Discussion

Patients with SLE have low levels of physical activity and high levels of sedentary behavior when compared to the general population [21, 25]. Also, these patients may consume inadequate levels of nutrients [26, 72]. Exercise interventions may promote benefits for SLE patients, such as improvements in fatigue and depression, physical conditioning, inflammation, cardiorespiratory capacity, autonomic function and quality of life [73–76]. Moreover, a few studies have shown that specific dietary interventions may also be beneficial for this population. For instance, vitamin D supplementation decreased inflammation and improved bone mass density, while omega-3 supplementation improved lipid profile and endothelial function, reduced oxidative stress, fatigue and depressive symptoms in SLE patients [77, 78]. In addition, both a low-glycemic index diet and a calorie-restricted diet reduced weight and improve fatigue in this group [22]. In this study, we hypothesize that a multidisciplinary intervention focused on improving physical activity and eating aspects concomitantly will improve cardiovascular risk factor and SLE-associated symptoms and comorbidities.

The main strengths of this study are the assessment of a newly developed intervention that is tailored to improve both physical activity levels and eating aspects; and the use of a qualitative–quantitative approach and a plethora of valid methods to test the safety, efficacy, and feasibility of the intervention, having a randomized controlled design.

This study has the potential to generate new, clinically relevant data able to refine the multidisciplinary management of SLE patients, with emphasis on the prevention of cardiovascular burden, symptomatology and poor quality of life frequently seen in this disease.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00296-023-05370-x.

Acknowledgements B.C.M., F.I.S., S.M.S. and B.G. were supported by São Paulo Research Foundation—FAPESP (Grants #2019/14820-6, #2019/14819-8, #2019/15231-4 and #2017/13552-2),MR was supported by Support fund to education, research and extension at the State University of Campinas—FAEPEX accord 519.292 (98082-22) and SGP was supported by National Council for Scientific and Technological Development—CNPq (#303116/2022-6).

Declarations

Conflict of interest The authors declare no conflict of interest.

References

1. Hartman EAR, van Royen-Kerkhof A, Jacobs JWG et al (2018) Performance of the 2012 Systemic Lupus International Collaborating Clinics classification criteria versus the 1997 American College of Rheumatology classification criteria in adult and juvenile systemic lupus erythematosus. A systematic review and meta-an. Autoimmun Rev 17:316–322. https://doi.org/10.1016/j.autrev.2018.01.007
2. Yu C, Gershwin ME, Chang C (2014) Diagnostic criteria for systemic lupus erythematosus: a critical review. J Autoimmun 48–49:10–13. https://doi.org/10.1016/j.jaut.2014.01.004
3. Palagini L, Mosca M, Tani C et al (2013) Depression and systemic lupus erythematosus: a systematic review. Lupus 22:409–416. https://doi.org/10.1177/0961203313477227
4. Ahn GE, Ramsey-Goldman R (2012) Fatigue in systemic lupus erythematosus. Int J Clin Rheumtol 7:217–227. https://doi.org/10.2217/ijr.12.4
5. Palagini L, Tani C, Mauri M et al (2014) Sleep disorders and systemic lupus erythematosus. Lupus 23:115–123. https://doi.org/10.1177/0961203313518623
6. Giannelou M, Mavragani CP (2017) Cardiovascular disease in systemic lupus erythematosus: a comprehensive update. J Autoimmun 82:1–12. https://doi.org/10.1016/j.jaut.2017.05.008
7. Sitia S, Atzeni F, Sarzi-Puttini P et al (2009) Cardiovascular involvement in systemic autoimmune diseases. Autoimmun Rev 8:281–286. https://doi.org/10.1016/j.autrev.2008.08.004
8. McCarthy EM, Wilkinson FL, Parker B, Alexander MY (2016) Endothelial microparticles: pathogenic or passive players in endothelial dysfunction in autoimmune rheumatic diseases? Vascul Pharmacol 86:71–76. https://doi.org/10.1016/j.vph.2016.05.016

9. Zardi EM, Afeltra A (2010) Endothelial dysfunction and vascular stiffness in systemic lupus erythematosus: are they early markers of subclinical atherosclerosis? Autoimmun Rev 9:684–686. https://doi.org/10.1016/j.autrev.2010.05.018
10. Esdaile JM, Abrahamowicz M, Grodzicky T et al (2001) Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 44:2331–2337. https://doi.org/10.1002/1529-0131(200110)44:10%3c2331::AID-ART395%3e3.0.CO;2-I
11. Miyake CNH, Gualano B, Dantas WS et al (2018) Increased insulin resistance and glucagon levels in mild/inactive systemic lupus erythematosus patients despite normal glucose tolerance. Arthritis Care Res (Hoboken) 70:114–124. https://doi.org/10.1002/acr.23237
12. Mocarzel LOC, Lanzieri PG, Montes RA et al (2015) Systemic lupus erythematosus: review of cardiovascular aspects. Int J Cardiovasc Sci. https://doi.org/10.5935/2359-4802.20150037
13. Negrón AM, Molina MJ, Mayor AM et al (2008) Factors associated with metabolic syndrome in patients with systemic lupus erythematosus from Puerto Rico. Lupus 17:348–354. https://doi.org/10.1177/0961203307086645
14. Tydén H, Lood C, Gullstrand B et al (2017) Endothelial dysfunction is associated with activation of the type I interferon system and platelets in patients with systemic lupus erythematosus. RMD Open 3:e000508. https://doi.org/10.1136/rmdopen-2017-000508
15. Golder V, Hoi A (2017) Systemic lupus erythematosus: an update. Med J Aust 206:215–220. https://doi.org/10.5694/mja16.01229
16 Costi LR, Iwamoto HM, de Neves ODC, Caldas CAM (2017) Mortalidade por lúpus eritematoso sistêmico no Brasil: avaliação das causas de acordo com o banco de dados de saúde do governo. Rev Bras Reumatol 57:574–582. https://doi.org/10.1016/j.rbr.2017.05.007
17. Monção CSA, Martins LN, Penteado MPS et al (2018) Incidence of cardiovascular risk factors in female patients with systemic lupus erythematosus: a 3-year follow-up cohort. Lupus 27:1790–1798. https://doi.org/10.1177/0961203318790676
18. Skare TL, Dagostini JS, Zanardi PI, Nisihara RM (2016) Infections and systemic lupus erythematosus. Einstein (São Paulo) 14:47–51. https://doi.org/10.1590/S1679-45082016AO3490
19. Perandini LA, de Sá-Pinto AL, Roschel H et al (2012) Exercise as a therapeutic tool to counteract inflammation and clinical symptoms in autoimmune rheumatic diseases. Autoimmun Rev 12:218–224. https://doi.org/10.1016/j.autrev.2012.06.007
20. Rodríguez Huerta MD, Trujillo-Martín MM, Rúa-Figueroa Í et al (2016) Healthy lifestyle habits for patients with systemic lupus erythematosus: a systemic review. Semin Arthritis Rheum 45:463–470. https://doi.org/10.1016/j.semarthrit.2015.09.003
21. Legge A, Blanchard C, Hanly JG (2020) Physical activity, sedentary behaviour and their associations with cardiovascular risk in systemic lupus erythematosus. Rheumatology 59:1128–1136. https://doi.org/10.1093/rheumatology/kez429
22. de Medeiros MCS, Medeiros JCA, de Medeiros HJ et al (2019) Dietary intervention and health in patients with systemic lupus erythematosus: a systematic review of the evidence. Crit Rev Food Sci Nutr 59:2666–2673. https://doi.org/10.1080/10408398.2018.1463966
23. Islam A, Khandker SS, Kotyla PJ, Hassan R (2020) Immunomodulatory effects of diet and nutrients in systemic lupus erythematosus (SLE): a systematic review. Front Immunol 11:1–17. https://doi.org/10.3389/fimmu.2020.01477
24. Legge A, Blanchard C, Hanly JG (2017) Physical activity and sedentary behavior in patients with systemic lupus erythematosus and rheumatoid arthritis. Open Access Rheumatol Res Rev 9:191–200. https://doi.org/10.2147/OARRR.S148376
25. Pinto AJ, Roschel H, de Sá Pinto AL et al (2017) Physical inactivity and sedentary behavior: overlooked risk factors in autoimmune rheumatic diseases? Autoimmun Rev 16:667–674. https://doi.org/10.1016/j.autrev.2017.05.001
26 Borges MC, dos Santos MMF, TellesRW et al (2012) Nutritional status and food intake in patients with systemic lupus erythematosus. Nutrition 28:1098–1103. https://doi.org/10.1016/j.nut.2012.01.015
27. Petric M, Bozic J, Radic M et al (2020) Dietary habits in patients with systemic lupus erythematosus. J Med Food 00:1–7. https://doi.org/10.1089/jmf.2019.0227
28. Constantin M, Nita I, Olteanu R et al (2018) Significance and impact of dietary factors on systemic lupus erythematosus pathogenesis (review). Exp Ther Med. https://doi.org/10.3892/etm.2018.6986
29. Mak A (2020) Physical exercise and systemic lupus erythematosus. Rheumatology 59:921–922. https://doi.org/10.1093/rheumatology/kez534
30. O'Dwyer T, Durcan L, Wilson F (2017) Exercise and physical activity in systemic lupus erythematosus: a systematic review with meta-analyses. Semin Arthritis Rheum 47:204–215. https://doi.org/10.1016/j.semarthrit.2017.04.003
31. Keefe FJ, Somers TJ, Martire LM (2008) Psychologic interventions and lifestyle modifications for arthritis pain management. Rheum Dis Clin N Am 34:351–368. https://doi.org/10.1016/j.rdc.2008.03.001
32. Khanji MY, van Waardhuizen CN, Bicalho VVS et al (2018) Lifestyle advice and interventions for cardiovascular risk reduction: a systematic review of guidelines. Int J Cardiol 263:142–151. https://doi.org/10.1016/j.ijcard.2018.02.094
33. Nanditha A, Snehalatha C, Raghavan A et al (2018) The post-trial analysis of the Indian SMS diabetes prevention study shows persistent beneficial effects of lifestyle intervention. Diabetes Res Clin Pract 142:213–221. https://doi.org/10.1016/j.diabres.2018.05.042
34. Lindström J, Ilanne-Parikka P, Peltonen M et al (2006) Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 368:1673–1679. https://doi.org/10.1016/S0140-6736(06)69701-8
35. Gill DP, Blunt W, Boa Sorte Silva NC et al (2019) The HealtheSteps™ lifestyle prescription program to improve physical activity and modifiable risk factors for chronic disease: a pragmatic randomized controlled trial. BMC Public Health 19:841. https://doi.org/10.1186/s12889-019-7141-2
36. Saboya PP, Bodanese LC, Zimmermann PR et al (2016) Lifestyle intervention on metabolic syndrome and its impact on quality of life: a randomized controlled trial. Arq Bras Cardiol 108:60–69. https://doi.org/10.5935/ABC.20160186
37. de Lima NR, dos Santos IK, Cobucci RN et al (2019) Lifestyle interventions and quality of life for women with polycystic ovary syndrome. Medicine (Baltimore) 98:e18323. https://doi.org/10.1097/MD.0000000000018323
38. Eaglehouse YL, Schafer GL, Arena VC et al (2016) Impact of a community-based lifestyle intervention program on health-related quality of life. Qual Life Res 25:1903–1912. https://doi.org/10.1007/s11136-016-1240-7
39. Chan AW, Tetzlaff JM, Altman DG et al (2013) SPIRIT 2013: new guidance for content of clinical trial protocols. Lancet 381:91–92. https://doi.org/10.1016/S0140-6736(12)62160-6
40. Boutron I, Altman DG, Moher D et al (2017) CONSORT Statement for randomized Trials of nonpharmacologic treatments: a 2017 update and a CONSORT extension for nonpharmacologic Trial Abstracts. Ann Intern Med 167:40–47. https://doi.org/10.7326/M17-0046

41. Touma Z, Gladman DD, Ibañez D et al (2011) Systemic lupus erythematosus disease activity index 2000 responder index-50 enhances the ability of SLE responder index to identify responders in clinical trials. J Rheumatol 38:2395–2399. https://doi.org/10.3899/jrheum.110550
42. NATIONAL CEPN (2002) Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). Circulation
43. Bacchetti P, McCulloch CE, Segal MR (2008) Simple, defensible sample sizes based on cost efficiency. Biometrics 64:577–585. https://doi.org/10.1111/j.1541-0420.2008.01004_1.x
44. Bacchetti P (2010) Current sample size conventions: flaws, harms, and alternatives. BMC Med 8:17. https://doi.org/10.1186/1741-7015-8-17
45. Michie S, Johnston M (2012) Theories and techniques of behaviour change: developing a cumulative science of behaviour change. Health Psychol Rev. https://doi.org/10.1080/17437199.2012.654964
46. Michie S, van Stralen MM, West R (2011) The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci 6:42. https://doi.org/10.1186/1748-5908-6-42
47. Prochaska JO, Velicer WF (1997) The transtheoretical model of health behavior change. Am J Health Promot 12:38–48. https://doi.org/10.4278/0890-1171-12.1.38
48. Motta D (2009) Aconselhamento nutricional. In: Educação Nutricional e Diabetes tipo 2
49. Demetrio F, de Paiva JB, Goncalves Froes AA et al (2011) The extended nutritional clinic and humanization of patient-nutritionist relationship: contribution to reflection. Rev Nutr J Nutr 24:743–763
50. Ulian M, Sato P, Alvarenga M, Scagliusi F (2015) Aconselhamento nutricional versus prescrição. In: Nutrição Comportamental
51. Ulian MD, Gualano B, Benatti FB et al (2017) The design and rationale of an interdisciplinary, non-prescriptive, and Health at Every Size®-based clinical trial: the "Health and Wellness in Obesity" study. Nutr Health 23:261–270. https://doi.org/10.1177/0260106017731260
52. da Saúde M (2014) Guia alimentar para a população brasileira Promovendo a Alimentação Saudável. Ministério Da Saúde. https://doi.org/10.1111/j.1467-8624.2009.01380.x.How
53. Conceição M, Bonganha V et al (2013) Sixteen weeks of resistance training can decrease the risk of metabolic syndrome in healthy postmenopausal women. Clin Interv Aging. https://doi.org/10.2147/CIA.S44245
54. Kelley DE, Goodpaster BH (2001) Skeletal muscle triglyceride. Diabetes Care 24:933–941. https://doi.org/10.2337/diacare.24.5.933
55 Howley ET, Bassett DR, Welch HG (1995) Criteria for maximal oxygen uptake. Med Sci Sport Exerc 27:1292–1301. https://doi.org/10.1249/00005768-199509000-00009
56. Wasserman K (1984) The anaerobic threshold measurement to evaluate exercise performance 1, 2. Am Rev Respir Dis 129:S35–S40. https://doi.org/10.1164/arrd.1984.129.2P2.S35
57. Thijssen DHJ, Bruno RM, van Mil ACCM et al (2019) Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. Eur Heart J 40:2534–2547. https://doi.org/10.1093/eurheartj/ehz350
58. Gladman D, Ginzler E, Goldsmith C et al (1996) The development and initial validation of the systemic lupus international collaborating clinics/American college of rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 39:363–369. https://doi.org/10.1002/art.1780390303
59. Monteiro C, Cannon G, Levy R et al (2016) Food classification. Public health NOVA. The star shines bright. World Nutr 7:28–38
60. Touma Z, Urowitz MB, Taghavi-Zadeh S et al (2012) Systemic lupus erythematosus disease activity index 2000 responder index 50: sensitivity to response at 6 and 12 months. Rheumatology 51:1814–1819. https://doi.org/10.1093/rheumatology/kes146
61. Gottfredson DC, Cook TD, Gardner FEM et al (2015) Standards of evidence for efficacy, effectiveness, and scale-up research in prevention science: next generation. Prev Sci 16:893–926. https://doi.org/10.1007/s11121-015-0555-x
62. Durgante H, DalboscoDell'Aglio D (2017) Critérios metodológicos para a avaliação de programas de intervenção em psicologia. Rev Avaliação Psicológica 17:155–162. https://doi.org/10.15689/ap.2017.1701.15.13986
63. Bardin L (2011) Análise de Conteúdo
64. Freire EAM, Bruscato A, Leite DRC et al (2010) Translation into Brazilian Portuguese, cultural adaptation and validatation of the systemic lupus erythematosus quality of life questionnaire (SLEQOL). Acta Reumatol Port 35:334–339
65. Ciconelli RM, Ferraz MB, Santos W et al (1999) Brazilian-Portuguese version of the SF-36 questionnaire: a reliable and valid quality of life outcome measure. Rev Bras Reumatol 39:143–150
66. Newcomer KL, Krug HE, Mahowald ML (1993) Validity and reliability of the timed-stands test for patients with rheumatoid arthritis and other chronic diseases. J Rheumatol
67. Podsiadlo D, Richardson S (1991) The timed "up & go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. https://doi.org/10.1111/j.1532-5415.1991.tb01616.x
68. Innes E (1999) Handgrip strength testing: a review of the literature. Aust Occup Ther J 46:120–140. https://doi.org/10.1046/j.1440-1630.1999.00182.x
69. Kosinski M, Gajria K, Fernandes A, Cella D (2013) Qualitative validation of the FACIT-Fatigue scale in systemic lupus erythematosus. Lupus 22:422–430. https://doi.org/10.1177/0961203313476360
70. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x
71. Murray K, Godbole S, Natarajan L et al (2017) The relations between sleep, time of physical activity, and time outdoors among adult women. PLoS ONE 12:e0182013. https://doi.org/10.1371/journal.pone.0182013
72. Calzza JI, Muza LS, Gasparin AA et al (2021) Nutritional aspects and cardiovascular risk in systemic lupus erythematosus. Rev Assoc Med Bras 67:656–660. https://doi.org/10.1590/1806-9282.20200817
73. Abrahao MI, Gomiero AB, Peccin MS et al (2016) Cardiovascular training vs. resistance training for improving quality of life and physical function in patients with systemic lupus erythematosus: a randomized controlled trial. Scand J Rheumatol 45:197–201. https://doi.org/10.3109/03009742.2015.1094126
74. Benatti FB, Miyake CNH, Dantas WS et al (2018) Exercise increases insulin sensitivity and skeletal muscle AMPK expression in systemic lupus erythematosus: a randomized controlled trial. Front Immunol 9:1–10. https://doi.org/10.3389/fimmu.2018.00906
75. Perandini LA, Sales-de-Oliveira D, Mello SBV et al (2014) Exercise training can attenuate the inflammatory milieu in women with systemic lupus erythematosus. J Appl Physiol 117:639–647. https://doi.org/10.1152/japplphysiol.00486.2014
76. Prado DM, Benatti FB, Pinto ALS et al (2013) Exercise training in childhood-onset systemic lupus erythematosus: a controlled randomized trial. Lupus 22:95. https://doi.org/10.1186/ar4205

77. Duarte-García A, Myasoedova E, Karmacharya P et al (2020) Effect of omega-3 fatty acids on systemic lupus erythematosus disease activity: a systematic review and meta-analysis. Autoimmun Rev. https://doi.org/10.1016/j.autrev.2020.102688
78. Mok CC (2013) Vitamin D and systemic lupus erythematosus: an update. Expert Rev Clin Immunol 9:453–463. https://doi.org/10.1586/eci.13.19

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.