Doctoral Thesis / Tesis Doctoral

# ARTERIAL STIFFNESS, INFLAMMATION, FITNESS AND PSYCHOLOGICAL STRESS IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS: ROLE OF PHYSICAL ACTIVITY AND AEROBIC EXERCISE

RIGIDEZ ARTERIAL, INFLAMACIÓN, FITNESS Y ESTRÉS PSICOLÓGICO EN MUJERES CON LUPUS ERITEMATOSO SISTÉMICO: ROL DE LA ACTIVIDAD FÍSICA Y EL EJERCICIO AERÓBICO


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**A cada una de las personas que me han acompañado**
**en todos los momentos, buenos y no tan buenos,**
**durante este largo pero productivo recorrido**

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# ARTERIAL STIFFNESS, INFLAMMATION, FITNESS AND PSYCHOLOGICAL STRESS IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS: ROLE OF PHYSICAL ACTIVITY AND AEROBIC EXERCISE

RIGIDEZ ARTERIAL, INFLAMACIÓN, FITNESS Y ESTRÉS PSICOLÓGICO EN MUJERES CON LUPUS ERITEMATOSO SISTÉMICO: ROL DE LA ACTIVIDAD FÍSICA Y EL EJERCICIO AERÓBICO

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## Research Projects and Funding

The present Doctoral Thesis was performed as a result of the following research projects:

**- Project 1:** Physical activity, subclinical arteriosclerosis and inflammation in patients with systemic lupus erythematosus (Actividad física, arteriosclerosis subclínica e inflamación en pacientes con lupus eritematoso sistémico). Subvenciones para la financiación de la I+d+i biomédica y en ciencias de la salud en Andalucía. BOJA nº 98, de 25 de mayo 2016. Duration: from 15-09-2016 to 14-06-2017. No funding. Principal investigator: José Antonio Vargas Hitos. [This Project led to Studies I and II of the present Doctoral Thesis]

**- The EJERCITALES Project:** Effects of a physical exercise program on subclinical arteriosclerosis and inflammation of patients with systemic lupus erythematosus **(**Efectos de un programa de ejercicio físico sobre la arteriosclerosis subclínica y la inflamación de pacientes con lupus eritematoso sistémico). Resolución de 20 de diciembre de 2016, de la Secretaría General de Investigación, Desarrollo e Innovación en Salud, publicada en B.O.J.A. nº 33, de 17 de febrero de 2017. Duration: from 01/09/2017 to 30/06/2018. Principal investigator: José Antonio Vargas Hitos. [This Project led to Study III of the present Doctoral Thesis]

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## Abbreviations

**SLE,** systemic lupus erythematosus

**CVD,** cardiovascular diseases

**PA,** physical activity

**MVPA,** moderate-to-vigorous physical activity

**PWV,** pulse wave velocity

**TNF-α,** tumor necrosis factor alpha

**IL-6,** interleukin-6

**ACSM,** American College of Sports Medicine

**CRP,** C-reactive protein

**SLEDAI,** systemic lupus erythematosus disease activity index

**SDI,** damage index for systemic lupus erythematosus

**BMI,** body mass index

**HRR,** heart rate reserve

**$HR_{max}$,** maximal heart rate

**tHR,** training heart rate

**RPE,** rating of perceived exertion

**CV,** coefficient of variation

**MPO,** myeloperoxidase

**SD,** standard deviation

**BOCF,** baseline observation carried forward

**hsCRP,** high-sensitivity C-reactive protein

## Resumen

El lupus eritematoso sistémico (LES) es una enfermedad autoinmune de causa desconocida que afecta predominantemente a mujeres adultas jóvenes. El LES representa una gran carga para el sistema de salud. Identificar factores asociados con una menor sintomatología y severidad de la enfermedad es de interés clínico y de salud pública. Los objetivos principales de esta Tesis Doctoral fueron: examinar la asociación entre los niveles de actividad física, valorada de forma objetiva mediante acelerometría, con la rigidez arterial en mujeres con LES, así como explorar si las mujeres que cumplen con las recomendaciones de actividad física del *American College of Sport Medicine* presentan una menor rigidez arterial respecto a las que no cumplen con dichas recomendaciones; evaluar la asociación de los niveles de intensidad de actividad física, medidos objetivamente con acelerometría, y el tiempo sedentario con el estrés psicológico en mujeres con LES; y mostrar el efecto de 12 semanas de ejercicio aeróbico sobre la rigidez arterial (resultado principal), la inflamación, el estrés oxidativo y la capacidad cardiorrespiratoria (resultados secundarios) en mujeres con LES. Para abordar estos objetivos, se llevaron a cabo tres estudios en el contexto de dos proyectos.

Proyecto I (Estudios I y II). Cuarenta y siete mujeres con LES se incluyeron en ambos estudios, donde la actividad física y el tiempo sedentario se midieron objetivamente mediante acelerometría triaxial. La rigidez arterial se obtuvo midiendo la velocidad de onda de pulso (VOP) mediante el dispositivo Mobil-O-Graph® 24h y el estrés psicológico se registró mediante la escala de estrés percibido.

Proyecto II (Estudio III). Un total de cincuenta y ocho mujeres con LES se incluyeron y asignaron a un grupo que realizó ejercicio aeróbico supervisado en tapiz rodante durante 12 semanas (*n=26*) o a un grupo control que recibió recomendaciones para llevar un estilo de vida saludable (*n=32*). La rigidez arterial se evaluó mediante la VOP mediante el dispositivo Mobil-O-Graph® 24h. La PCR ultrasensible sérica se evaluó mediante un método inmunoturbidimétrico utilizando los sistemas ARCHITECT cS. La interleuquina 6 (IL-6) y el factor de necrosis tumoral alfa (TNF-α), así como la mieloperoxidasa (MPO; como marcador de estrés oxidativo), se midieron mediante inmunoradioanálisis utilizando kits comerciales y siguiendo las instrucciones del fabricante. La capacidad cardiorrespiratoria se evaluó con el protocolo de Bruce.

Los principales hallazgos de esta Tesis indican que: **I)** Los niveles de actividad física y el tiempo sedentario no están asociados con la rigidez arterial en mujeres con LES; **II)** Niveles más bajos de actividad física moderada o actividad física moderada-vigorosa se asocian con un mayor estrés psicológico en mujeres con LES. Las mujeres que no cumplieron con las recomendaciones internacionales de actividad física presentaban mayor estrés psicológico que aquellas que sí las cumplieron; y **III)** 12 semanas de ejercicio aeróbico progresivo en tapiz rodante, siguiendo las recomendaciones del *American College of Sport Medicine*, aumenta la capacidad cardiorrespiratoria sin exacerbar la rigidez arterial, la inflamación o el estrés oxidativo en mujeres con LES, en comparación con el grupo de control.

Los resultados de esta Tesis Doctoral incrementan nuestro conocimiento sobre la asociación de la actividad física/ejercicio físico y tiempo sedentario con síntomas clave del LES, como la rigidez arterial, el estrés psicológico, la inflamación y la capacidad cardiorrespiratoria. Estos resultados ayudarán a generar futuros estudios que evalúen el valor preventivo y terapéutico de la actividad física/ejercicio físico en esta población.

## Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology that predominantly affects young adult women. SLE represents a heavy burden for the health care system. Identifying factors associated with lower symptomatology and disease severity is of clinical and public health interest. The major aims of this Doctoral Thesis were: to examine the association of physical activity levels, assessed by accelerometry, with arterial stiffness in women with SLE, as well as to explore whether women meeting the physical activity guidelines of the American College of Sport Medicine have lower arterial stiffness than those not meeting these recommendations; to evaluate the association of physical activity intensity levels, measured with accelerometry, and sedentary time with psychological stress in women with SLE; and to show the effect of 12-week aerobic exercise on arterial stiffness (primary outcome), inflammation, oxidative stress and cardiorespiratory fitness (secondary outcomes) in women with SLE. To address these aims, three studies were conducted in the context of two projects.

Project I (Studies I and II). Forty-seven women with SLE were included in both studies, where physical activity and sedentary time were measured by triaxial accelerometry. Arterial stiffness was obtained by measuring the pulse wave velocity (PWV) using the device Mobil-O-Graph® 24h pulse wave monitor and psychological stress was recorded using the perceived stress scale.

Project II (Study III). A total of fifty eight women with SLE were included and assigned to a group that performed supervised aerobic exercise on treadmill for 12 weeks (*n=26*) or to a control group that received healthy lifestyle recommendationsto (*n=32*). Arterial stiffness was assessed by PWV using the Mobil-O-Graph® 24h device. Ultrasensitive serum CRP was evaluated by an immunoturbidimetric method using the ARCHITECT cSystems. Interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α), as well as myeloperoxidase (MPO; as marker of oxidative stress), were measured by immunoradioassay using commercial kits and following the manufacturer's instructions. Cardiorespiratory fitness was assessed with the Bruce protocol.

The main findings of this Thesis indicate that: **I)** Physical activity levels and sedentary time are not associated with arterial stiffness in women; **II)** Lower levels of moderate physical activity or moderate-to-vigorous physical activity are associated with higher psychological stress in women with SLE. Women who did not meet the international physical activity guidelines presented higher psychological stress than those meeting them; and **III)** 12 weeks of progressive treadmill aerobic exercise following the American College of Sport Medicine guidelines increases cardiorespiratory fitness without exacerbating arterial stiffness, inflammation, or oxidative stress in women with SLE, in comparison to the control group.

The results of this Doctoral Thesis enhance our understanding about the association of physical activity/physical exercise and sedentary time with key symptoms of SLE, such as arterial stiffness, psychological stress, inflammation and cardiorespiratory fitness. These results will help to generate future studies that evaluate the preventive and therapeutic value of physical activity/physical exercise in this population.

# INTRODUCTION

# INTRODUCTION

## 1. SLE: definition, epidemiology and burden for the health care system

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown aetiology characterized by multiorgan involvement and persistent systemic inflammation[1] that predominantly affects young adult women with a prevalence of 20-150 cases/10.000 inhabitants[2]. Although there is no curative treatment for SLE, the prognosis of SLE has improved significantly in recent decades[3] and has led to new comorbidities, such as clinical and subclinical atherosclerotic cardiovascular diseases (CVD)[4]. In fact, CVD, which are characteristically of early presentation and accelerated evolution[5], have become one of the main causes of mortality in this population[5]. SLE has a negative impact in all spheres of the patient's life: professional (higher unemployment and lower labor productivity)[6], physical (fatigue, pain, insomnia) and mental (depression, anxiety)[7], among others. It is important to note that SLE implies a heavy burden for National Health Systems, with an average annual cost per patient in treatments of 2650 € in non-severe cases and 4700 € in severe cases[8].

## 2. PA and sedentary time: association with arterial stiffness in SLE (Study I)

Physical activity (PA) is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. PA in daily life can be categorized into occupational, sports, conditioning, household, or other activities[9]. The term 'sedentary' can operationally be defined as any waking sitting or lying behavior with low energy expenditure[10]. The term 'sedentary behavior' therefore typically refers to sitting/lying behavior rather than a simple absence of moderate-to-vigorous PA (MVPA)[10]. Arterial stiffness is a marker of subclinical atherosclerosis that allows the detection of mechanical changes in the distensibility of the arteries previous to the onset of atherosclerosis, and is a powerful predictor of CVD independently of the presence of other cardiovascular risk factors[11,12]. Arterial stiffness, measured by pulse wave velocity (PWV), is significantly increased in patients with SLE[13,14] and is associated with the development of CVD[15]. There is enough information about exercise physiology to support the well-documented public health guidelines promoting at least 150 min/week of moderate-vigorous leisure-time PA aimed at decreasing risks for metabolic diseases[16]. In addition, current PA guidelines recommend 150 minutes per week of MVPA in periods of at least 10 minutes in patients with rheumatic diseases[17]. In patients with SLE, it has been found that low PA levels were associated with increased subclinical atherosclerosis[18], and more severe organ damage was associated with less physical activity on "low to moderate" intensity, compared to general population[19]. In addition, it has been suggested that in adults, long lasting periods of sedentary time are associated with a worse cardiometabolic risk profile, and greater risk for clinical and subclinical atherosclerosis[20]. It has been evidenced that endothelial function declines with age and sedentary lifestyle, and this is associated with an increased risk for CVD in general population[21]. Most of previous research has been conducted in the general population or in patients with CVD. However, no prior study has examined the extent to

which PA or sedentary time (measured by accelerometry) might be associated with arterial stiffness in patients with SLE.

### 3. PA and sedentary time: association with psychological stress in SLE (Study II)

Psychological stress is an environmental factor that has been associated with several immunological diseases in the general population[22]. Psychological stress is present in many chronic diseases both as a risk factor and as a trigger of physical and mental symptoms[23]. The daily psychological stress of patients with SLE is higher than in the general population[24] and different studies have shown that the symptoms of the disease worsen due to psychological stress[25-28]. Emotional support is considered one of the most important aspects as a moderator of psychological stress in patients with SLE[25]. In addition, there are other factors such as physical exercise to reduce psychological stress in these patients[29,30]. Therefore, implementing strategies or lifestyle modifications to prevent psychological stress is of major interest in this population. Previous studies have investigated the effects of increasing PA levels on health-related quality of life of patients with SLE[31]. Bostrom et al. described that these patients showed improved mental health. Furthermore, patients with SLE who did not perform a PA program had a worse impact on fatigue and depressive symptomatology compared to general population, as well as that PA improved health-related quality of life in patients with SLE[32]. Furthermore, it has been suggested that in adults, greater sedentary time is associated with higher psychological stress[33]. Mancuso et al. evaluated PA through questionnaires[34], comparing PA levels with clinical and psychosocial variables, such as fatigue, depressive symptoms, and psychological stress, in patients with SLE. However, to the best of our knowledge, no prior study examined the extent to which PA or sedentary time (i.e. measured by accelerometry) might be associated with psychological stress in patients with SLE.

### 4. 12-week aerobic exercise: effects on arterial stiffness, inflammation and cardiorespiratory fitness in SLE (Study III)

Arterial stiffness is a marker of subclinical atherosclerosis that increases with age and is significantly elevated in patients with SLE compared to the general population[13]. Arterial stiffness reveals structural changes in the elasticity of the arteries prior to the development of clinical atherosclerosis, and is a powerful predictor of CVD independently of other cardiovascular risk factors, both in the general population[11] and in patients with SLE[15]. Therefore, attenuating the increase of arterial stiffness in this population is of clinical relevance for the early prevention of CVD. In SLE, inflammation and tissue damage are mediated by pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), released by recruited inflammatory cells (macrophages, myeloid dendritic cells, pathogenetic T and B cells) and immune complexes-induced complement activation[35]. These markers of systemic inflammation, as well as C-reactive protein (CRP), are known to independently predict cardiovascular events[36,37], and represent potential mechanisms explaining the excess cardiovascular morbi-mortality in SLE[38]. Oxidative stress (i.e. an imbalance in the cells

due to an increase in free radicals or a decrease in antioxidants) has also shown to be involved in the development of CVD in patients with SLE[39]. Although behavioral interventions, such as regular exercise, might elicit significant cardiovascular benefits without many of the side effects of pharmacological treatments, they are understudied and hardly appear in the British Society for Rheumatology guidelines for the management of SLE[40]. Exercise has been shown to increase physical fitness and reduce CVD risk in many populations across the whole lifespan. The American College of Sports Medicine (ACSM) highlights the need to undertake a minimum of 150 min/week (i.e., accumulated in bouts of ≥10 min) of aerobic exercise of moderate to vigorous intensity in adults[17]. Although aerobic exercise has a promising role attenuating arterial stiffness in the general population[41], its effects in women with SLE have not been previously investigated. Perandini et al. observed that a single bout (i.e., 30 min) of aerobic exercise (i.e., either at 50% or 70% of $VO_{2peak}$) did not increase inflammation in women with either active or inactive SLE[42], and that 12 weeks of aerobic training (*n=8*) tended to reduce inflammation in comparison to a control group (*n=10*)[43]. Timoteo et al.[44], however, did not observe changes in IL-6 or TNF-α in the combined exercise (i.e., flexibility, resistance and aerobic training) group (*n=5*) compared to the control group (*n=9*). Overall, these studies had a small sample size and the exercise programs were not comprehensively described to allow replication or application in clinical practice.

# OBJETIVOS/AIMS

## OBJETIVOS

El objetivo general de esta Tesis Doctoral fue examinar el rol de la actividad física y el ejercicio aeróbico sobre parámetros clave de mujeres con LES, tales como la rigidez arterial, la inflamación, el fitness cardiorrespiratorio y el estrés psicológico. Los resultados de esta Tesis Doctoral están organizados en forma de tres estudios, basados en los siguientes objetivos específicos:

1. Estudio I. Examinar la asociación de diferentes niveles de actividad física, valorada de forma objetiva mediante acelerometría, con la rigidez arterial en mujeres con lupus eritematoso sistémico. Este objetivo se investigó adicionalmente evaluando si aquellas mujeres que cumplieron con las recomendaciones de actividad física del *ACSM* presentaban una menor rigidez arterial respecto a las que no cumplieron con dichas recomendaciones.

2. Estudio II. Evaluar la asociación de diferentes niveles de actividad física, medidos objetivamente con acelerometría, y el tiempo sedentario, con el estrés psicológico en mujeres con lupus eritematoso sistémico. Este objetivo se investigó adicionalmente evaluando si aquellas mujeres que cumplieron con las recomendaciones de actividad física del *ACSM* presentaban menor estrés psicológico respecto a las que no cumplieron con dichas recomendaciones.

3. Estudio III. Evaluar el efecto de una intervención de ejercicio aeróbico de intensidad moderada a vigorosa en una cinta de correr [dos sesiones de 75 min por semana durante un total de 12 semanas (es decir, 24 sesiones)], siguiendo las pautas de ACSM, sobre rigidez arterial en mujeres con LES en comparación con la atención habitual (objetivo principal), y evaluar los efectos de la intervención de ejercicio sobre la inflamación, el estrés oxidativo y la capacidad cardiorrespiratoria (objetivos secundarios).

## AIMS

The general aim of this Doctoral Thesis was to examine the role of PA and aerobic exercise on key parameters of women with SLE, such as arterial stiffness, inflammation, cardiorespiratory fitness and psychological stress. The results of this Doctoral Thesis are organized in three studies, based on the following specific aims:

1. Study I. To examine the association of different levels of PA, assessed by accelerometry, with arterial stiffness in women with SLE. This aim was additionally investigated evaluating whether those women meeting the PA guidelines of the ACSM had lower arterial stiffness than those not meeting these recommendations.

2. Study II. To evaluate the association of different levels of PA, measured with accelerometry, and sedentary time, with psychological stress in women with SLE. This aim was additionally investigated evaluating whether those women meeting the PA guidelines of the ACSM have lower psychological stress than those not meeting these recommendations.

3. Study III. To assess the effect of a moderate to vigorous intensity aerobic exercise intervention on a treadmill [two 75-min sessions per week during a total of 12 weeks (i.e., 24 sessions)], following the ACSM guidelines, on arterial stiffness in women with SLE in comparison with usual care (primary aim), and to assess the effects of the exercise intervention on inflammation, oxidative stress, and cardiorespiratory fitness (secondary aims).

# MATERIALS AND METHODS

## MATERIALS AND METHODS

### Project I (Studies I and II)

*Design and Participants*

In this cross-sectional study, a total of 144 women with SLE were invited to participate through the Systemic Autoimmune Diseases Unit of the "Virgen de las Nieves" University Hospital and the "San Cecilio" University Hospital (Granada, Spain). The inclusion criteria were: i) women aged 18–60 years), ii) with ≥4 SLE classification criteria according to the American College of Rheumatology[45], and iii) with a minimum medical follow-up of 1 year at the units and presenting clinical stability, defined as no changes in the systemic lupus erythematosus disease activity index (SLEDAI) and/or the treatment during 6 months before the study. Exclusion criteria were as follows: not being able to read, understand and/or sign the informed consent; CVD in the previous year; receiving a biological treatment or required doses of prednisone (or equivalent) greater than 10 mg/day in the last 6 months. Furthermore, in the accelerometry analysis, a minimum of ten or more hours of registration per day during the seven days of recording was necessary to be included in the study[46]. The patients signed written informed consent after receiving detailed information about the study procedures. The study protocol was reviewed and approved by the Research Ethics Committee of Granada.

*Protocol*

Each patient received a dossier with detailed information about the study design and evaluation protocols, as well as the objectives and purpose of the study. The patients were evaluated in October 2016 at the "Virgen de las Nieves" University Hospital (Granada, Spain), where sociodemographic data and clinical history were obtained, anthropometric measures and body composition were assessed, PWV was measured by a pulse wave analysis monitor, and the perceived stress scale was registered. Finally, an accelerometer was given to each participant to record PA. They were informed to wear the accelerometers for the next 9 days and were instructed on how to fill out a sleep diary (see **Annexe**, page 119).

*Sociodemographic variables and clinical history*

Age, educational level, occupational status, family history of CVD, personal history of cardiovascular risk factors and treatments, and SLE data (diagnostic criteria, year of diagnosis, time of evolution and treatments) were registered by questionnaires. The disease activity was measured by the SLEDAI[47]. SLEDAI is a global score system which provides an overall measure of disease activity within the last 10 days and includes 24 weighted objective clinical and laboratory variables[47]. Disease activity can range from 0 to 105: no activity (SLEDAI = 0), mild activity (SLEDAI = 1–5), moderate activity (SLEDAI = 6–10), high activity (SLEDAI = 11–19), very high

activity (SLEDAI ≥ 20)[47]. Accumulated organ damage was assessed by the damage index for systemic lupus erythematosus (SDI) scale[48]. SDI is defined as damage in an organ or system that occurred since the onset of SLE, ascertained by clinical assessment, and is present for at least 6 months. It includes 42 items encompassing 12 organ systems. Repeat episodes require at least 6 months between them to score 2. The same lesion cannot be scored twice[48].

*Anthropometric measures and body composition*

Weight was measured in kilograms (InBody R20, Biospace, Seoul, Korea) and height in centimeters using a stadiometer (SECA 222, Hamburg, Germany). Body mass index (BMI; $kg/m^2$) was calculated. Body fat percentage and muscle mass was measured by Bioelectrical impedance (InBody R20, Biospace, Seoul, Korea). Waist circumference (at the umbilical level) and hip circumference (at the level of the iliac crest) were measured by non-elastic anthropometric tape (SECA 200).

*Pulse wave velocity*

The Mobil-O-Graph® 24h pulse wave monitor (IEM GmbH, Stolberg, Germany), which is based on the oscillometry recorded by a blood pressure cuff placed on the brachial artery[49], was used to measure PWV. Data obtained by the recorder can be easily transferred to a computer-based central database by use of a Blue-tooth interface. The central database is a hypertension management software (IEM GmbH, Stolberg, Germany)[50]. This device has been largely shown to be valid and reliable for measuring PWV in different populations[51,52], met the accuracy requirements of the British Hypertension Society[53-55], and can be recommended for clinical use[50].

*Psychological stress*

Psychological stress was measured with the perceived stress scale, a 14-item self-report global measure designed to assess psychological stressful symptomatology[56]. Each psychological stressful symptom is rated from 0 (not present) to 4 (very often) according to how patients felt during the last month. The total score was obtained by adding all the values (direct and inverse), after transforming the inverse items: 4, 5, 6, 7, 9, 10, 13 (0=4; 1=3; 2=2; 3=1; 4=0). The perceived stress scale provides a single overall score (ranging from 0 to 56) where higher score represents higher psychological stress. This self-report instrument has a Spanish version that demonstrates adequate reliability (internal consistency 1⁄4 0.81, test – retest reliability 1⁄4 0.73) and good concurrent validity and sensitivity (test validity and sensitivity 1⁄4 0.72)[57].

*PA intensity levels and sedentary time*

PA was measured by accelerometry[58]. Data was collected using triaxial accelerometer GT3X+ (Actigraph, Pensacola, Florida, USA), stored at an epoch length of 60 seconds and with a frequency rate of 30 Hz[59]. Participants wore the accelerometer on the hip

secured with an elastic tape. The device was carried over the whole day for seven consecutive days except when bathing, swimming or sleeping, because non sleep patterns were measured. PA was recorded up to seven days, starting from the day the participants received the accelerometers until the day that they were instructed to return the device. It was necessary a minimum of ten or more hours of registration per day during the seven days of recording to be included in the study[46]. It was considered as non-wearing time and consequently excluded from the analysis bouts of 90 continuous minutes (30 minutes small window length and 2 minutes skip tolerance) of 0 activity intensity counts[60]. Furthermore, values with recording of more than 20000 counts per minute were excluded from the analyses (potential malfunction). Accelerometer wearing time was calculated by subtracting the non-wear time and the sleeping time (obtained from the sleep diary where patients wrote time they went to bed and time they woke up) from the total registered time for each day. Sedentary time was estimated as the amount of time accumulated below 200 counts per minute (cpm) in the PA vector magnitude during periods of wear time[61]. PA intensity levels (light, moderate and vigorous) were calculated based upon recommended PA vector magnitude cut points[59-61]: 200-2689, 2690-6166 and ≥6167cpm, respectively. All values were expressed in min/day. MVPA intensity level was obtained through the sum of moderate and vigorous PA. The average time per week of MVPA in bouts of ≥10 minutes (bouted MVPA) was calculated (up to 2 minutes below the cut point allowance) according to the PA recommendations for adults[17]. However, recent evidence also supports health benefits with MVPA performed in bouts shorter than 10 min[62]. It was required the ActiGraph software (Actilife version 6.11.9) for data download, reduction, cleaning and analyses.

## The EJERCITALES project (Study III)

*Design and Participants*

Participants were recruited from the Systemic Autoimmune Diseases Unit of the "Virgen de las Nieves" and the "San Cecilio" University Hospitals. Women with a diagnosis of SLE according to the American College of Rheumatology criteria[45], a follow-up of ≥12 months, clinical and treatment stability during the previous six months, and not performing regular exercise (defined as ≥60 min/week of structured exercise) were included. Exclusion criteria were to have been under biological treatment in the previous six months or to need a prednisone dose of >10 mg/day; a background of CVD in the previous year; to present contraindications to perform exercise; other associated rheumatic conditions; pregnancy; active acute or chronic infection; neoplasms; acute renal failure; cardiac or pulmonary involvement; BMI >35; or not being able to read, understand, and sign written informed consent. All participants received detailed information about the study procedures and signed written informed consent. The Research Ethics Committee of Granada approved the protocol on 11 November 2016 (reference No.: 10/2016).

*Protocol*

This non-randomized controlled trial was registered at clinicaltrials.gov [https://clinicaltrials.gov/ct2/show/NCT03107442] on 11 April 2017, before the enrolment of participants started (i.e., on 12 April), and no deviations occurred regarding the primary outcome and the secondary outcomes.
A telephone screening was conducted. Potentially eligible participants were invited to a personal screening and, if included, day 1 of the baseline examination was performed. The baseline examination comprised two assessment days. On day 1, PWV was assessed. Thereafter, cardiorespiratory fitness testing was performed, and socio-demographic and clinical information was collected. On day 2 (i.e., between two and four days after day 1), 8-h fasting blood samples were collected between 8:00 a.m. and 10:00 a.m. This work follows the TREND statement for improving the reporting of non-randomized experiments of behavioral and public health interventions (see **table 13**; pages 72-74)[63]. The funding source had no role in the study.

*Exercise group*

To maximize transparency and replicability, the exercise program described in this manuscript follows the Consensus on Exercise Reporting Template (CERT; see **table 14**; page 75)[64]. The patients assigned to exercise performed two 75-min sessions per week during a total of 12 weeks (i.e., 24 sessions) of moderate to vigorous intensity aerobic exercise on a treadmill (BH, Serie i.RC12 Dual, Vitoria-Gasteiz, Spain) from 24 April to 14 July 2017. A scheme of the prescribed exercise intervention is presented in **table 1**.
The sessions took place in a quiet room of the "Virgen de las Nieves" Hospital, Granada (Spain). All sessions were performed in groups of a maximum of five persons (depending on the patients' schedule preferences) and were supervised by both exercise professionals with a degree in Sports Sciences 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 an alternative day of the same week. Adherence to exercise is reported as the median attendance frequency and the proportion of patients attending ≥75% (i.e., 18 sessions; the minimum pre-defined attendance to assess efficacy) and ≥90% of the sessions. All the sessions began with a warm-up comprising 3–4 min of activation on the treadmill at about 35–40% of the heart rate reserve (HRR) 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 and relaxation. Exercise was individually prescribed to represent moderate-to vigorous intensity, with training intensity ranging from 40% to 75% of each patient's HRR. The maximum heart rate ($HR_{max}$) was estimated with the formula by Tanaka et al. ($HR_{max}$ = 208 - (0.7 x age))[65]. The training (or target) heart rate (tHR) was calculated with the formula tHR = $HR_{rest}$ + (%HRR). Heart rate was continuously monitored during all sessions (Polar V800, Kempele, Finland). The session rating of perceived

exertion (RPE) was used as a measure of subjective training load[66], and the feeling scale to assess positive affective responses experienced before and after each session[67].
The starting level was specific for each individual according to her previous exercise experience and physical fitness. During the first half of the program, only continuous exercise was performed so that the patients got used to the treadmill and felt confident at increasing intensities. Continuous sessions comprised several bouts of exertion at constant intensity, followed by a couple of minutes of recovery (i.e., rest) to drink water. During month 2, there were alternated continuous and interval sessions, and at month 3, the patients undertook interval training sessions, where there were periods of lower and periods of higher intensity efforts followed by some minutes of rest for hydration (**table 1**).

**Table 1.** Summary of the prescribed training program.

| Month | Week | Weekly MVPA (min) | Session (No.) | Training Type | Total Session Time (min) | Estimated Session Time at Target Intensity (min) | Intensity (% HRR) | | Series/Workout |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 90 | 1 | Continuous | 55 | ≈40 | 35–45 | | 7,5′ Warm-up + 15′ 35–45% + 3′ rec + 10′ 35–45% + 3′ rec + 10′ 35–45% + 7,5′ Cool down |
| | | | 2 | Continuous | 65 | ≈50 | 35–45 | | 7,5′ Warm-up + 2 × (15′ 35–45%/3′ rec) + 15′ 35–45% + 7,5′ Cool down |
| | 2 | 105 | 3 | Continuous | 65 | ≈50 | 40–50 | | 7,5′ Warm-up + 20′ 40–50% + 3′ rec + 15′ 40–50% + 3′ rec + 10′ 40–50% + 7,5′ Cool down |
| | | | 4 | Continuous | 75 | ≈60 | 40–50 | | 7,5′ Warm-up + 2 × (20′ 40–50%/3′ rec) + 15′ 40–50% + 7,5′ Cool down |
| | 3 | 130 | 5 | Continuous | 75 | ≈60 | 45–55 | | 7,5′ Warm-up + 25′ 45–55% + 3′ rec + 20′ 45–55% + 3′ rec + 10′ 45–55% + 7,5′ Cool down |
| | | | 6 | Continuous | 85 | ≈70 | 45–55 | | 7,5′ Warm-up + 2 × (25′ 45–55%/3′ rec) + 15′ 45–55% + 7,5′ Cool down |
| | 4 | 145 | 7 | Continuous | 85 | ≈70 | 45–55 | | 7,5′ Warm-up + 30′ 45–55% + 3′ rec + 25′ 45–55% + 3′ rec + 10′ 45–55% + 7,5′ Cool down |
| | | | 8 | Continuous | 90 | ≈75 | 45–55 | | 7,5′ Warm-up + 1 × (40′ 45–55%/3′ rec) + 30′ 45–55% + 7,5′ Cool down |
| | | | | | | | Interval lower bound | Interval higher bound | |
| 2 | 5 | 150 | 9 | Continuous | 90 | ≈75 | 50–60 | | 7,5′ Warm-up + 30′ 50–60% + 2.5′ rec + 25′ 50–60% + 2.5′ rec + 15′ 50–60% + 7,5′ Cool down |
| | | | 10 | Continuous | 90 | ≈75 | 50–60 | | 7,5′ Warm-up + 1 × (40′ 50–60%/5′ rec) + 30′ 50–60% + 7,5′ Cool down |
| | 6 | 150 | 11 | Continuous | 90 | ≈75 | 55–60 | | 7,5′ Warm-up + 1 × (40′ 55–60%/5′ rec) + 30′ 55–60% + 7,5′ Cool down |
| | | | 12 | Interval | 90 | ≈75 | 50–55 | 60–65 | 7,5′ Warm-up + 1 × (25′ 50–55%+10′ 60–65%+5′ rec) + 1 × (25′ 50–55%+10′ 60–65%) + 7,5′ Cool down |
| | 7 | 150 | 13 | Continuous | 90 | ≈75 | 57.5–62.5 | | 7,5′ Warm-up + 1 × (45′ 57.7–62.5%/5′ rec) + 25′ 57.5–62.5% + 7,5′ Cool down |
| | | | 14 | Interval | 90 | ≈75 | 52.5–57.5 | 60–65 | 7,5′ Warm-up + 1 × (20′ 52.5–57.5%+15′ 60–65%+5′ rec) + 1 × (20′ 52.5–57.5%+15′ 60–65%) + 7,5′ Cool down |
| | 8 | 150 | 15 | Continuous | 90 | ≈75 | 55–60 | | 7,5′ Warm-up + 1 × (40′ 55–60%/5′ rec) + 30′ 55–60% + 7,5′ Cool down |
| | | | 16 | Interval | 90 | ≈75 | 50–55 | 60–65 | 7,5′ Warm-up + 1 × (30′ 55–60%+5′ 60–65%+5′ rec) + 1 × (30′ 55–60%+5′ 60–65%) + 7,5′ Cool down |
| | | | | | | | Interval lower bound | Interval higher bound | |
| 3 | 9 | 150 | 17 | Interval | 90 | ≈75 | 55–60 | 65–70 | 7,5′ Warm-up + 2 × (15′ 55–60%+3′ 65–70%) + 5′ rec + 15′ 55–60% + 3′ 65–70% + 12′ 55–60% + 3′ 65–70% + 7,5′ Cool down |
| | | | 18 | Interval | 90 | ≈75 | 55–60 | 65–70 | 7,5′ Warm-up + 2 × (15′ 55–60%+3′ 65–70%) + 5′ rec + 15′ 55–60% + 3′ 65–70% + 12′ 55–60% + 3′ 65–70% + 7,5′ Cool down |
| | 10 | 150 | 19 | Interval | 90 | ≈75 | 57.5–62.5 | 65–70 | 7,5′ Warm-up + 3 × (11′ 57.5–62.5% + 3′ 65–70%) + 5′ rec + 2 × (11′ 57.5–62.5% + 3′ 65–70%) + 7,5′ Cool down |
| | | | 20 | Interval | 90 | ≈75 | 57.5–62.5 | 70–75 | 7,5′ Warm-up + 3 × (11′ 57.5–62.5% + 3′ 70–75%) + 5′ rec + 2 × (11′ 57.5–62.5% + 3′ 70–75%) + 7,5′ Cool down |
| | 11 | 150 | 21 | Interval | 90 | ≈75 | 60–65 | 70–75 | 7,5′ Warm-up + 2 × (15′ 60–65%+3′ 70–75%) + 5′ rec + 15′ 60–65% + 3′ 70–75% + 12′ 60–65% + 3′ 70–75% + 7,5′ Cool down |
| | | | 22 | Interval | 90 | ≈75 | 60–65 | 70–75 | 7,5′ Warm-up + 2 × (15′ 60–65%+3′ 70–75%) + 5′ rec + 15′ 60–65% + 3′ 70–75% + 12′ 60–65% + 3′ 70–75% + 7,5′ Cool down |
| | 12 | 150 | 23 | Interval | 90 | ≈75 | 60–65 | 70–75 | 7,5′ Warm-up + 5 × (5′ 60–65%+3′ 70–75%) + 5′ rec + 2 × (11′ 60–65%+3′ 70–75%) + 7,5′ Cool down |
| | | | 24 | Interval | 90 | ≈75 | 60–65 | 70–75 | 7,5′ Warm-up + 5 × (5′ 60–65%+3′ 70–75%) + 5′ rec + 3 × (6′ 60–65%+4′ 70–75%) + 7,5′ Cool down |

MVPA, moderate-to-vigorous physical activity; HRR, heart rate reserve; Rec, recovery.

The progression in volume and/or intensity was patient-limited and was undertaken by increasing the treadmill speed (first) or inclination according to the symptoms and perceived exertion. There were no home-based or non-exercise components within this intervention. However, if a participant was eventually not able to attend a particular session, we provided her with a heart rate monitor and allowed recovery of that session out of the Hospital (a total of seven sessions were recovered in this fashion). Finally, the exercise intensity progressions had to be slightly modified from the initial plan. For instance, several patients perceived a 5% HRR intensity increase (i.e., from one week to another) as very heavy and difficult-to-follow. Consequently, there were weeks in which exercise intensity increased by 2.5% instead of 5% (**table 1**).

*Control group*

After the baseline evaluation, the SLE patients assigned to the (usual care) control group received verbal information about a healthy lifestyle, including PA guidelines and basic nutritional information.

*Arterial Stiffness*

Arterial stiffness was assessed in a sitting position by PWV[13], using the Mobil-O Graph 24 h pulse wave analysis monitor (IEM GmbH, Stolberg, Germany), whose operation is based on oscillometry recorded by a blood pressure cuff placed on the brachial artery. The coefficient of variation (CV) of Mobil-O-Graph for consecutive PWV analyses is 3.4% and its intraclass correlation coefficient is 0.98 [0.96–0.99][68]. This device has been largely shown to be valid a reliable for measuring PWV in different populations[51,52], met the accuracy requirements of the British Hypertension Society[53-55] standard, and can be recommended for clinical use[50].

*Blood samples and biochemical analyses*

Blood specimens (after 12-hour fast period) for biochemical and immunological tests were collected and routinely processed by the central laboratory of our hospital. Among other measurements, they included lipids, insulin (BioRad, Marne-la-Coquette, France), and a routine biochemical profile. The homeostatic model assessment for insulin resistance (HOMA-IR) was calculated (HOMA-IR = glucose (mmol/L) x insulin (μU/L)/22.5).

*Inflammatory markers*

Serum high-sensitivity CRP was assessed by an immunoturbidimetric method using the ARCHITECT cSystems (MULTIGENT CRP Vario assay); the limit of quantitation was 0.2 mg/L and the upper limit for normal serum was 5 mg/L (CV<6%). IL-6 and TNF-α, as well as myeloperoxidase (MPO; as marker of oxidative stress), were measured in plasma. Serum was initially separated by centrifugation and stored at -70ºC. Bioserum concentrations of IL-6/TNF-α (pg/mL) and MPO (ng/mL) were measured by an

immunoradiometric assay using commercial kits (MILLIPLEX MAP Kit Human High Sensitivity T Cell Magnetic Bead Panel (HSTMAG-28SK) and Human Cardiovascular Disease Magnetic Bead Panel 2 (HCVD2MAG-67K)), Millipore) following the manufacturer's instructions. Quantitative data were obtained by using the Luminex-200 system (Luminex Corporation, Austin, TX, USA), and data analysis was performed on XPonent 3.1 software (Austin, TX, USA). The detections limits were 0.73 pg/mL for IL-6, 0.43 pg/mL for TNF- α, and 0.024 ng/mL for MPO.

*Cardiorespiratory fitness*

Cardiorespiratory fitness was assessed with the Bruce submaximal treadmill protocol[69]. The test comprised five increasing workload stages of 3 min each (stage 1: 2.7 km/h and 10% inclination; stage 2: 4 km/h and 12% inclination; stage 3: 5.5 km/h and 14% inclination; stage 4: 6.8 km/h and 16% inclination; stage 5: 8 km/h and 18% inclination). The test concluded when the participant achieved 85% of the individual's $HR_{max}$, as estimated with the formula by Tanaka et al.[65]. As validated SLE-specific formulas to estimate $VO_{2max}$ are not available, we used the total time to reach 85% $HR_{max}$ as the outcome of interest.

*Other measurements*

All participants filled out a socio-demographic and clinical data questionnaire. Height (cm) was measured using a height gauge, weight (kg) with a bioimpedance device (InBody R20, Biospace, Seoul, Korea), and BMI was calculated ($kg/m^2$). Blood pressure was measured with Mobil-O-Graph® (IEM GmbH, Stolberg, Germany)[50]. Lupus disease activity was assessed through the SLEDAI (range 0–105 where a higher score indicates higher degree of disease activity)[47] and damage accrual by means of SDI[48]. PA was self-reported at baseline and at week 12 with the International Physical Activity Questionnaire[70].

*Sample size*

The sample size was calculated for the primary outcome (i.e., PWV). Ashor et al. found an average effect of aerobic exercise on PWV of - 0.63 m/s in adults aged ≥18 years[41]. A total of 52 patients (26 per group) were needed to detect an effect of - 0.63 (SD 0.75) m/s, with a power of 85% and an α error of 0.05. Anticipating a maximum loss to follow-up of 15%, we aimed at recruiting a total of 60 patients.

*Treatment allocation and blinding*

Randomization was not feasible because more than half of the patients who regularly attend the Autoimmune Disease Units lived far from the Hospital and were not able to attend twice per week in case of being randomized to exercise. Therefore, participants from the city of Granada were included in the exercise group and participants living outside Granada were included in the control group. To minimize potential selection

bias, we aimed to match the groups by age (±2 years), BMI (±1 kg/m$^2$), and SLEDAI (±1 unit). The data analyzer was blinded to the patient allocation.

The variables included in each of the three studies comprising the present Doctoral Thesis are presented in **table 2**.

The questionnaires used in the present Doctoral Thesis are presented as **Annexes** (page 117 et seq.).

**Table 2.** Summary table of the methods used in this Doctoral Thesis.

| Project | Study | Design | Participants | Main variables | Methods |
|---|---|---|---|---|---|
| Project I | I. Association of PA levels, assessed by accelerometry, with arterial stiffness in women with SLE | Cross- sectional | *n= 49* | PWV, PA levels, sedentary time, and SLEDAI | Mobil-O Graph 24 h pulse wave analysis monitor, triaxial accelerometer GT3X+, and clinical data questionnaire |
| Project I | II. Association of PA levels, measured with accelerometry, and sedentary time with psychological stress in women with SLE | Cross- sectional | *n= 49* | Psychological stress, PA levels, sedentary time, and SLEDAI | Perceived stress scale, triaxial accelerometer GT3X+, and clinical data questionnaire |
| The EJERCITALES project | III. Effect of 12-week aerobic exercise on arterial stiffness, inflammation, oxidative stress, and cardiorespiratory fitness in women with SLE | Non-Randomized Controlled Trial | *n= 58* | HR, $HR_{max}$, RPE, PWV, CRP, IL-6, TNF-α, MPO, cardiorespiratory fitness, and SLEDAI | Pulsometer Polar V800, Mobil-O Graph 24 h pulse wave analysis monitor, immunoturbidimetric method using the ARCHITECT cSystems, immunoradiometric assay using commercial kits, the Bruce submaximal treadmill protocol, and clinical data questionnaire |

PA, physical activity; SLE, systemic lupus erythematosus; PWV, pulse wave velocity; SLEDAI, systemic lupus erythematosus disease activity index; HR, heart rate; RPE, rating of perceived exertion; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha; MPO, myeloperoxidase.

**Statistical analysis**

Summary statistics are presented as means (standard deviation; SD), unless otherwise indicated. The normality, linearity and homoscedasticity assumptions of the linear regression models used in the Studies I and II were checked and reasonably met. Confounders were selected after examining their influence on the estimates analyzed in each study. Studies I and II were analyzed with the Statistical Package for the Social Sciences, version 23.0 for Windows (SPSS, IBM, Armonk, NY, USA), while the study III was analyzed with Stata v.13.1 (StataCorp LP., College Station, TX, USA). Statistical significance was set at $P<0.05$.

The statistical approach undertaken to accomplish the aims of this Doctoral Thesis is presented below and is summarized in **table 3** (page 53).

*Analyses conducted for Study I*

Normality of the main variables was checked using histograms and the Shapiro-Wilk test. The association of PA intensity levels (light PA, moderate PA, MVPA, total PA and bouted MVPA) and sedentary time with arterial stiffness was analyzed using linear regression models, with PWV as dependent variable and PA levels and sedentary time as independent variables in separate models. The low levels of vigorous PA of the participants (2.5 min/day) did not allow assessing its effects on PWV. The association of PA intensity levels (light PA, moderate PA, MVPA, total PA and bouted MVPA) and sedentary time with arterial stiffness was analyzed using linear regression models, with PWV as dependent variable and PA levels and sedentary time as independent variables in separate models. Three adjustment models were made: model 1 was adjusted for accelerometer-wear time; model 2 added BMI, smoking habit, blood pressure to model 1; model 3 added age to model 2. Further adjusting for SLEDAI did not change the coefficients. Normality of the residuals was analyzed and was reasonably met. Differences in PWV of participants meeting vs. not meeting the PA guidelines were calculated with analysis of covariance (ANCOVA), where PWV was entered as dependent variable, the group (0 = not meeting the guidelines; 1 = meeting the guidelines) was entered as independent variable, and accelerometer-wear time, BMI, smoking habit, blood pressure and age were entered as covariates.

*Analyses conducted for Study II*

Linear regression models were used to assess the association of PA intensity levels (light PA, moderate PA, MVPA, total PA and bouted MVPA) and sedentary time (i.e. included as independent variables in separate models) with perceived stress scale (dependent variable) in women with SLE. The low levels of vigorous PA of the participants (2.5 min/day) did not allow assessing its effects on psychological stress. Potential confounding was controlled by three consecutive models: model 1 was adjusted for accelerometer-wear time; model 2 added adherence to the Mediterranean diet and depression to model 1; model 3 added age to model 2. The selection of these

confounding variables was based on previous literature[71,72-75]. Normality of the residuals was reasonably met. Bouted MVPA, associated with psychological stress in regression analyzes, was categorized as binary variables (0 = not meeting the guidelines; 1 = meeting the guidelines). The level of psychological stress of participants with "low" vs "high" PA levels were compared with analysis of covariance (ANCOVA), with the aforementioned confounders included in model 3.

*Analyses conducted for Study III*

The distribution of the main study variables was assessed through histogram and Q-Q plots. As the main outcomes were non-normally distributed, their descriptive characteristics were presented using the median and interquartile range instead of the mean and SD and we used non-parametric tests for the main analyses. Between-group 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 between group differences in the studied outcomes were assessed through quantile regression with baseline values, resting heart rate (bpm)[76], and changes in PA (min/week; since the change in self-reported PA at week 12 was >60 min higher in the control compared to the exercise group and this change was associated with changes in PWV; $r_{Pearson} = -0.27$, $P = 0.048$) as potential confounders, after checking baseline group comparisons. As we aimed at assessing efficacy, the primary analyses were defined as per-protocol, where patients from the exercise group were included if attendance at the exercise sessions was ≥75%. To assess the robustness of the results, subsequent sensitivity analyses (i.e., baseline observation carried forward (BOCF) imputation; per-protocol with minimum attendance of ≥90%, and complete-case analyses) were conducted.

**Table 3.** Summary table of the statistical approach used in each study included in the present Doctoral Thesis.

| Study | Statistical analysis |
|---|---|
| I. Association of PA levels, assessed by accelerometry, with arterial stiffness in women with SLE | Objective 1: 3 LR models (dependent variable: PWV; independent variables: PA levels and sedentary time). Confounders/covariates: accelerometer-wear time, BMI, smoking habit, blood pressure, and age. Objective 2: Differences in PWV of participants meeting vs. not meeting the PA guidelines → ANCOVA |
| II. Association of PA levels, measured with accelerometry, and sedentary time with psychological stress in women with SLE | Objective 1: 3 LR models (dependent variable: perceived stress scale; independent variables: PA levels and sedentary time). Confounders/covariates: accelerometer-wear time, adherence to the Mediterranean diet, depression, and age. Objective 2: level of psychological stress of participants with "low" vs "high" PA levels → ANCOVA |
| III. Effect of 12-week aerobic exercise on arterial stiffness, inflammation, oxidative stress, and cardiorespiratory fitness in women with SLE | Quantile regression for between-group differences. Pearson's correlation for changes in PA and PWV. BOCF imputation to assess the robustness of the results |

PA, physical activity; SLE, systemic lupus erythematosus; LR, linear regression; PWV, pulse wave velocity; BMI, body mass index; ANCOVA, analysis of covariance; BOCF, baseline observation carried forward

# RESULTS

## RESULTS

The results of each individual study comprising the present Doctoral Thesis are presented below.

### Study I. Association of PA levels, assessed by accelerometry, with arterial stiffness in women with SLE.

The participant's flow diagram is presented in **figure 1**. Of the 144 patients initially invited, 81 refused to participate (i.e. 41 patients reported living too far from the hospital; 36 were unable to find time to perform the evaluations; and 4 were not interested), 12 patients did not present clinical stability during the 6 months prior to the beginning of the study, and 2 patients had CVD during the previous year. A total of 49 participants were finally included in the study. However, 2 patients refused wearing the accelerometer during one week. Thus, the final sample size for this study was 47 women with SLE.

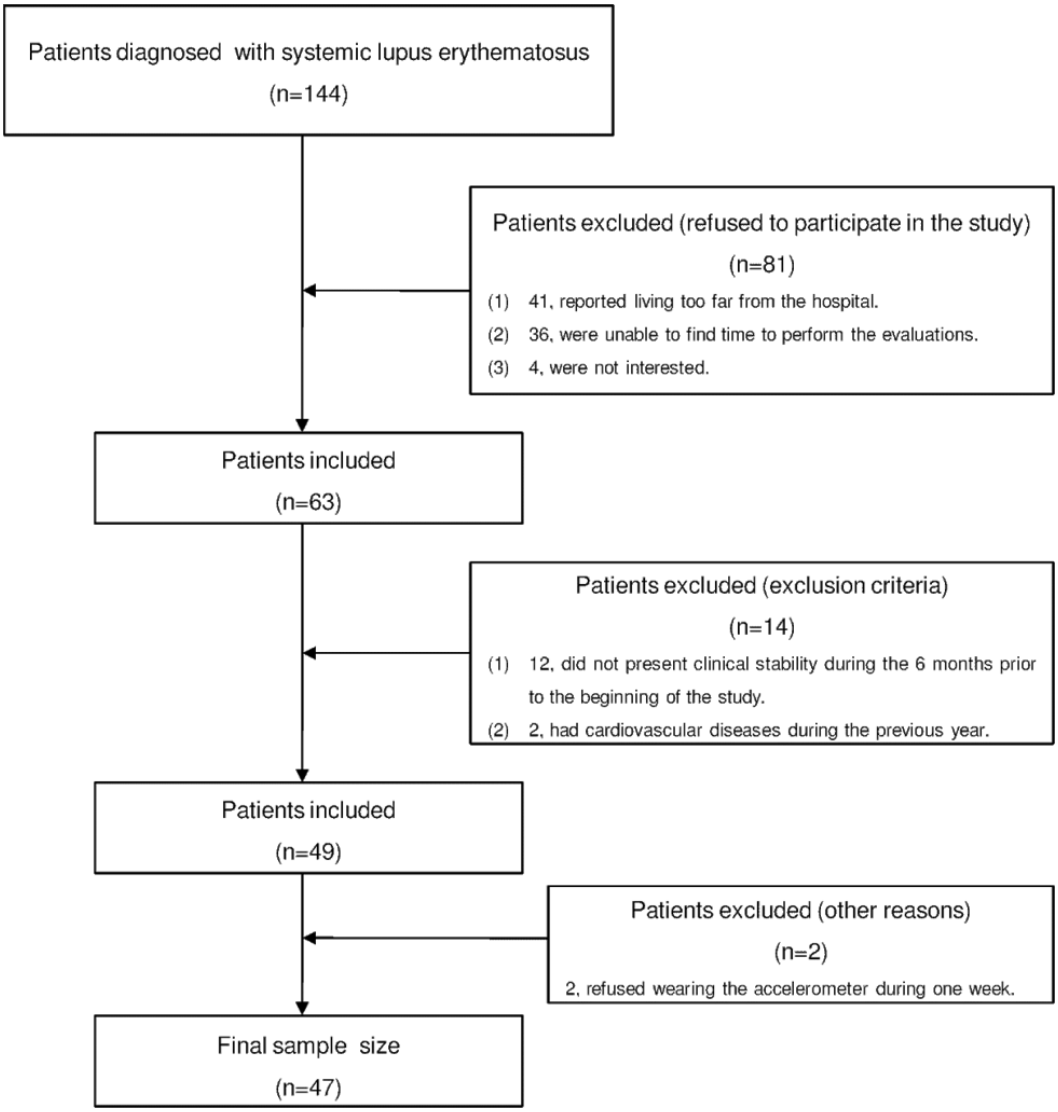


**Figure 1.** The flowchart of the selection of the patients with SLE (*n=47*).

The sociodemographic and clinical characteristics of the study participants are presented in **table 4**. Participants meeting the PA guidelines presented a higher percentage of renal (57.1 %) and hematologic (57.1 %) disease than participants not meeting the PA guidelines (30.3 % and 36.4 %, respectively). ANOVA analysis did not show significant differences in renal and hematologic disease between the two groups.

The PA intensity levels and sedentary time in women with SLE are shown in **table 5**. The average accelerometer-wear time result of the included participants was 928.2 (SD 67.2) min/day. Participants showed sedentary time and light PA of 451.4 (SD 104.7) and 425.7 (SD 96.5) min/day, respectively. Furthermore, participants showed MVPA (min/day) and bouted MVPA (min/week) of 51.1 (SD 31.3) and 135.1 (SD 151.8), respectively. Besides, participants meeting the PA guidelines performed 221 min/week of bouted MVPA more than participants not meeting the PA guidelines.

The CVD risk factors in women of the study are presented in **table 6**. 28 % of participants reported being current smokers and 16.4 % of the study participants had arterial hypertension. Furthermore, study participants presented a BMI of 26.1 (SD 5.1) $kg/m^2$ and a PWV of 6.2 (SD 1.4) m/s. Besides, participants meeting the PA guidelines presented a lower BMI (24.5 $kg/m^2$) and body fat (32.9 %) than participants not meeting the PA guidelines (26.8 $kg/m^2$ and 38.1 %, respectively). ANOVA analysis showed significant differences in dyslipemia between the two groups ($P$=0.026).

The association of PA intensity levels and sedentary time with PWV is shown in **table 7**. There was no association of PA intensity levels and sedentary time with arterial stiffness, either in model 1 or after controlling for additional potential confounders (i.e. models 2 and 3). There was no bouted MVPA x age interaction on PWV (b= -0.00001; 95% CI: -0.00003 to 0.00001; $P$=0.263). Further adjustment for SLEDAI, SDI and DMARD (hydroxychloroquine and immunosuppressants) did not modify the results and (with the aim to provide parsimonious models) we did not include these variables in the final model. As a higher proportion of physically active patients presented dyslipemia, we also included dyslipemia as a covariate but the results were unaltered.

**Table 4.** Socio-demographic and clinical characteristics in women with SLE *(n=47)*

| Characteristics | Total *(n=47)* | | Meeting PA guidelines *(n=14)* | | Not meeting PA guidelines *(n=33)* | |
|---|---|---|---|---|---|---|
| Age (years; mean, SD) | 41.2 | 13.9 | 46.1 | 12.2 | 39.1 | 14.2 |
| Educational level (n, %) | | | | | | |
| No education | 4 | 8.2 | 3 | 21.4 | 1 | 3 |
| Primary and secondary education | 19 | 36.8 | 6 | 42.8 | 13 | 39.4 |
| Higher education | 24 | 55.1 | 5 | 35.7 | 19 | 57.6 |
| Duration of SLE (years; mean, SD) | 11.7 | 9.3 | 15.9 | 8.2 | 10.2 | 9.4 |
| Criteria for SLE (n, % yes) | | | | | | |
| Erythema | 22 | 46.9 | 5 | 35.7 | 17 | 51.5 |
| Discoid lupus | 3 | 6.1 | 1 | 7.1 | 2 | 6.1 |
| Photosensitivity | 15 | 32.2 | 4 | 28.6 | 10 | 30.3 |
| Oral ulcer | 14 | 30.1 | 4 | 28.6 | 9 | 27.3 |
| Arthritis | 31 | 63.3 | 9 | 64.3 | 20 | 60.6 |
| Serositis | 15 | 32.2 | 4 | 28.6 | 10 | 30.3 |
| Renal | 19 | 40.6 | 8 | 57.1 | 10 | 30.3 |
| Neurological | 4 | 8.2 | 1 | 7.1 | 3 | 9.1 |
| Hematological | 21 | 44.8 | 8 | 57.1 | 12 | 36.4 |
| DNA | 43 | 87.8 | 11 | 78.6 | 30 | 90.9 |
| ANA | 46 | 98 | 13 | 92.9 | 33 | 100 |
| Total criteria for SLE (mean, SD) | 5 | 0.8 | 5.1 | 0.1 | 4.9 | 0.8 |
| SLEDAI (mean, SD) | 1.9 | 3.7 | 1.6 | 1.9 | 0.9 | 1.7 |
| SDI (mean, SD) | 0.5 | 0.9 | 0.3 | 0.5 | 0.6 | 1 |
| Corticorteroids consumption (n, % yes) | 33 | 70.2 | 9 | 64.3 | 24 | 72.7 |
| Cumulative corticorteroids exposure, mg (mean, SD) | 2864 | 2696 | 3131 | 3244 | 2752 | 2477 |
| Drugs consumption (n, % yes) | | | | | | |
| Hydroxychloroquine | 45 | 95.9 | 13 | 92.9 | 30 | 90.9 |
| Immunosuppressants (current) | 21 | 44.8 | 8 | 57.1 | 13 | 39.4 |
| Immunosuppressants (previous) | 20 | 42.7 | 7 | 50 | 13 | 39.4 |
| Antihypertensive drugs | 15 | 32.2 | 5 | 35.7 | 10 | 30.3 |
| Statins | 8 | 16.4 | 5 | 35.7 | 3 | 9.1 |

SD: Standard Deviation; PA: Physical Activity; SLE: Systemic Lupus Erythematosus; DNA: Double Native Antibodies; ANA: Antinuclear Antibodies; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Damage Index for Systemic Lupus Erythematosus.

**Table 5.** PA intensity levels and sedentary time in women with SLE *(n=47)*

| Variables | Total *(n=47)* | | Meeting PA guidelines *(n=14)* | | Not meeting PA guidelines *(n=33)* | |
|---|---|---|---|---|---|---|
| PA and sedentary time (min/day) | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** |
| Accelerometer-wear time | 928.2 | 67.2 | 946.7 | 64.3 | 920.4 | 67.8 |
| Sedentary Time | 451.4 | 104.7 | 392.5 | 111.8 | 476.4 | 92.3 |
| Light PA | 425.7 | 96.5 | 472.7 | 106.7 | 405.8 | 85.1 |
| Moderate PA | 48.5 | 29.5 | 75.8 | 36.7 | 36.9 | 16.7 |
| Vigorous PA | 2.5 | 6.9 | 5.3 | 11.7 | 1.3 | 3 |
| MVPA | 51.1 | 31.3 | 81.6 | 35.6 | 38.2 | 17.7 |
| Bouted MVPA (min/week) | 135.1 | 151.8 | 289.9 | 197.8 | 69.4 | 48.1 |

PA: Physical Activity; SLE: Systemic Lupus Erythematosus; SD: Standard Deviation; MVPA: Moderate-to-Vigorous Physical Activity.

**Table 6.** Cardiovascular risk factors in women with SLE *(n=47)*

| Variables | Total *(n=47)* | | Meeting PA guidelines *(n=14)* | | Not meeting PA guidelines *(n=33)* | | *P* |
|---|---|---|---|---|---|---|---|
| Weight (kg; mean, SD) | 66.4 | 12.7 | 61.1 | 6 | 68.5 | 14.4 | 0.071 |
| Body fat (%; mean, SD) | 36.5 | 8.6 | 32.9 | 9.4 | 38.1 | 8.2 | 0.066 |
| Waist circumference (cm; mean, SD) | 83.6 | 10.1 | 80.8 | 8.8 | 84.5 | 11.6 | 0.284 |
| Hip circumference (cm; mean, SD) | 100.9 | 9.9 | 97.5 | 6.8 | 102.5 | 10.8 | 0.118 |
| Waist/Hip ratio (mean, SD) | 0.8 | 0.06 | 0.8 | 0.07 | 0.8 | 0.06 | 0.799 |
| BMI ($Kg/m^2$; mean, SD) | 26.1 | 5.1 | 24.5 | 3.2 | 26.8 | 5.8 | 0.184 |
| Tobacco consumption (n, % yes) | 13 | 28 | 3 | 21.4 | 10 | 30.3 | 0.115 |
| HTA (n, % yes) | 8 | 16.4 | 2 | 14.3 | 6 | 18.2 | 0.752 |
| Dyslipemia (n, % yes) | 8 | 16.4 | 5 | 35.7 | 3 | 9.1 | 0.026 |
| Diabetes (n, % yes) | 1 | 2 | 0 | 0 | 1 | 3 | 0.521 |
| Obesity (n, % yes) | 6 | 12.2 | 1 | 7.1 | 5 | 15.2 | 0.463 |
| Pulse wave velocity (m/s; mean, SD) | 6.2 | 1.4 | 6.5 | 1.2 | 6.1 | 1.5 | 0.421 |

SLE: Systemic Lupus Erythematosus; SD: Standard Deviation; BMI: Body Mass Index; HTA: Hypertension.

**Table 7.** Linear regression models examining the association of PA intensity levels and sedentary time with PWV in women with SLE *(n=47)*

| Pulse wave velocity | β* | b* | (95 % CI) | $P^1$ | $P^2$ | $P^3$ |
|---|---|---|---|---|---|---|
| Sedentary time | 0.034 | 0.001 | (-0.001, 0.002) | 0.597 | 0.367 | 0.484 |
| Light PA | -0.014 | -0.001 | (-0.002, 0.001) | 0.467 | 0.290 | 0.776 |
| Moderate PA | -0.067 | -0.003 | (-0.008, 0.001) | 0.639 | 0.757 | 0.164 |
| MVPA | -0.072 | -0.003 | (-0.008, 0.001) | 0.683 | 0.879 | 0.132 |
| Total PA | -0.036 | -0.001 | (-0.002, 0.001) | 0.597 | 0.367 | 0.484 |
| Bouted MVPA | -0.051 | -0.001 | (-0.001, 0.0004) | 0.474 | 0.343 | 0.291 |

PA: Physical Activity; PWV: Pulse Wave Velocity; SLE: Systemic Lupus Erythematosus; β: standardized regression coefficient; b: non-standardized regression coefficient; CI: Confidence Interval; MVPA: Moderate-to-Vigorous Physical Activity.

β*, b*: these values correspond to the complete model (model 3).

[1]Model 1: adjusted for accelerometer-wear time.

[2]Model 2: model 1 plus body mass index, smoking habit and blood pressure.

[3]Model 3: model 2 plus age.

The comparison of the average PWV between participants meeting and not meeting the PA guidelines of 150 min/week of bouted MVPA is shown in **figure 2**. ANCOVA analysis showed no significant differences in PWV between the two groups (b= -0.169; 95% CI: -0.480 to 0.143; *P*=0.280).

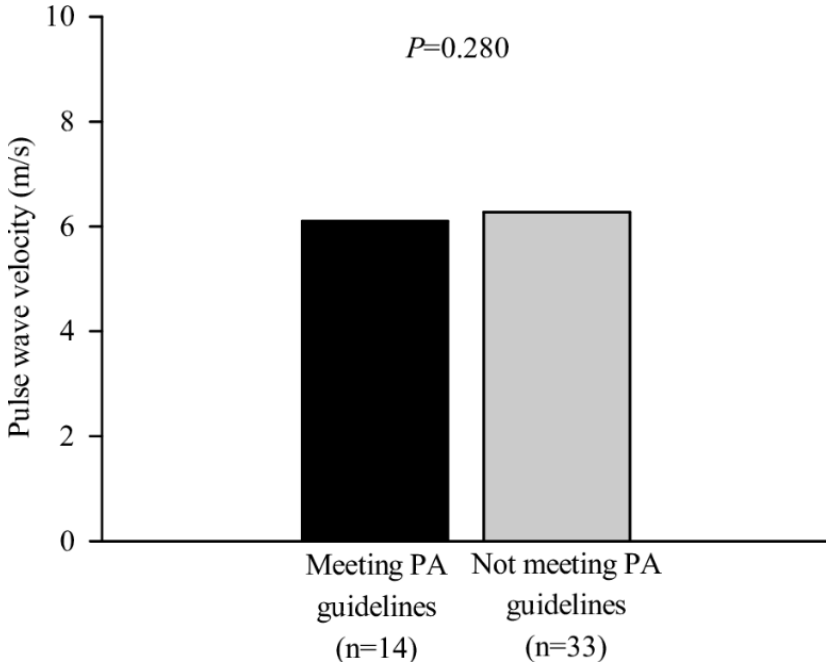


**Figure 2.** Means (95 % confidence interval) of PWV in participants meeting and not meeting the PA guidelines.

**Study II. Association of PA levels, measured with accelerometry, and sedentary time with psychological stress in women with SLE.**

The participants flowchart is presented in **figure 3**. Of the 144 patients initially invited, 81 refused to participate (i.e. 41 patients reported living too far from the hospital; 36 were unable to find time to perform the evaluations; and 4 were not interested), 12 patients did not present clinical stability during the 6 months prior to the beginning of the study, and 2 patients had CVD during the previous year. Furthermore, 2 patients refused wearing the accelerometer during one week. A total of 47 participants with SLE met inclusion criteria and were finally included in the study.

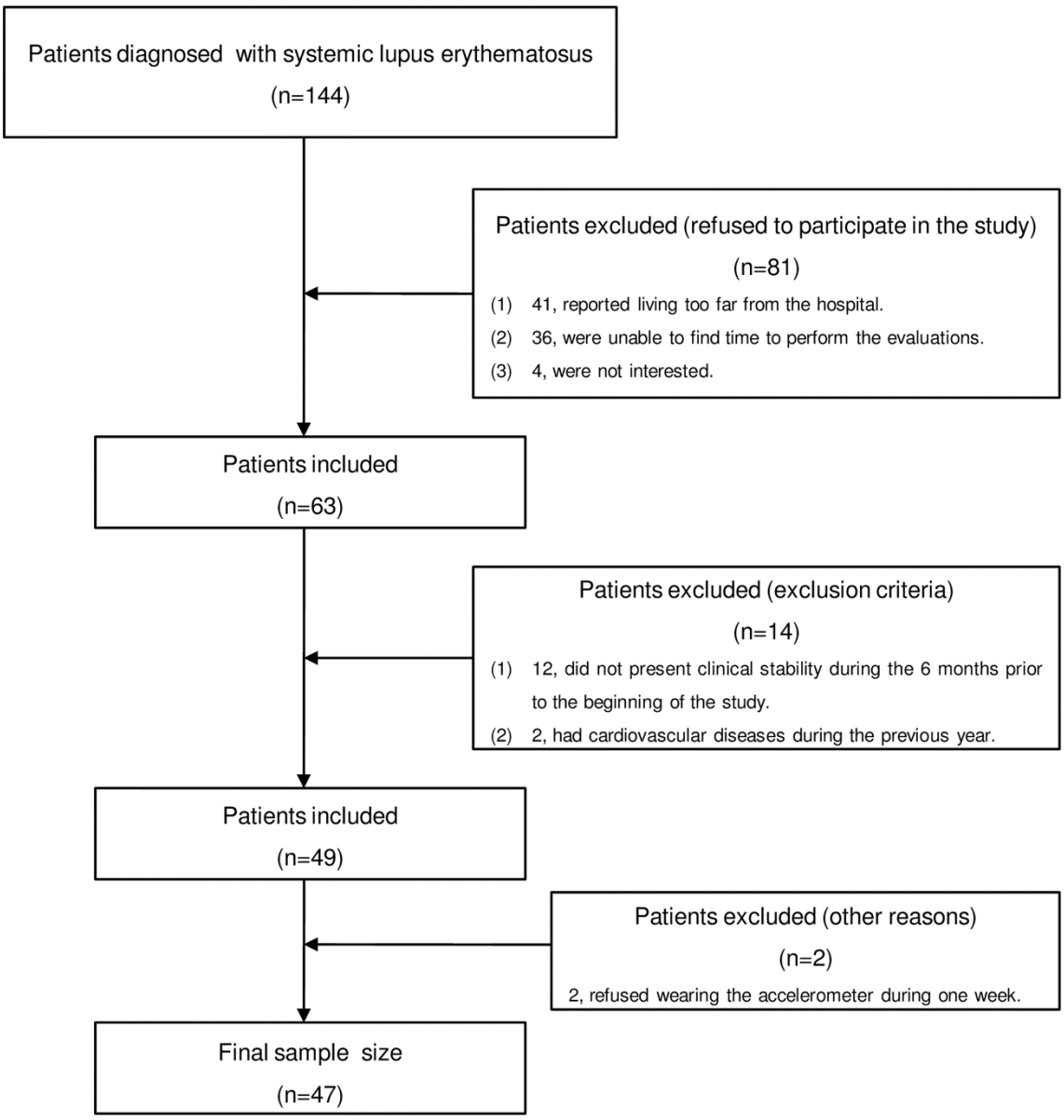


**Figure 3.** The flowchart of the inclusion of the participants with SLE (*n=47*).

The socio-demographic and clinical characteristics of the study participants are presented in **table 8**. Participants were, on average, 41 (SD 13.9) years old. The average accelerometer-wear time result of the included participants was 928.2 (SD 67.2) min/day and the average sedentary time was 451.4 (SD 104.7) min/day. In average, participants engaged in bouted MVPA 135.1 (SD 151.8) min/week. The average in the perceived stress scale was 24.9 (SD 9.0) units. Furthermore, the average adherence to the Mediterranean diet was 31.1 (SD 6.3) points, and the average BDI-II score was 13.2 (SD 9.5) points.

**Table 8.** Clinical, psychological and socio-demographic characteristics of the study participants (*n=47*)

| **Variables** | **Mean** | **SD** |
|---|---|---|
| Age (years) | 41.2 | 13.9 |
| Weight (kg) | 66.3 | 12.9 |
| BMI (kg/m$^2$) | 26.1 | 5.1 |
| Disease duration (years) | 11.7 | 9.3 |
| SLEDAI | 1.9 | 3.7 |
| Adherence to the Mediterranean diet | 31.1 | 6.3 |
| Depression | 13.2 | 9.5 |
| PA and sedentary time (min/day) | | |
| Accelerometer-wear time | 928.2 | 67.2 |
| Sedentary time | 451.4 | 104.7 |
| Light PA | 425.7 | 96.5 |
| Moderate PA | 48.5 | 29.5 |
| Vigorous PA | 2.5 | 6.9 |
| MVPA | 51.1 | 31.3 |
| Bouted MVPA (min/week) | 135.1 | 151.8 |
| Perceived stress scale | 24.9 | 9.0 |
| | **n (%)** | |
| Perceived stress categorization | | |
| Mild stress (0-10) | 3 (6.4) | |
| Moderate stress (11-21) | 15 (31.9) | |
| High stress (22-40) | 27 (57.4) | |
| Severe stress (41-56) | 2 (4.3) | |
| Tobacco consumption | 13 (28) | |

SD: standard deviation; BMI: body mass index; SLEDAI: systemic lupus erythematosus disease activity index; PA: physical activity; MVPA: moderate-to-vigorous physical activity; Bouted MVPA: MVPA in bouts of ≥10 consecutive minutes.

The association of PA intensity levels and sedentary time with psychological stress is shown in **table 9**. Sedentary time was not associated with psychological stress in either model. There was an inverse association of PA intensity levels (moderate PA and MVPA) with psychological stress, either in model 1 or after controlling for additional potential confounders (i.e. models 2 and 3). Regarding bouted MVPA, it showed a significant association in model 1 that became non-significant in models 2 and 3. Further adjustment for SLEDAI and tobacco consumption did not modify these results and, with the aim to provide parsimonious models, we did not include these variables in the final model.

**Table 9.** Linear regression models examining the association of PA intensity levels and sedentary time with psychological stress in women with SLE (*n=47*).

| Psychological stress | β* | b* | SE* | (95 % CI)* | $P^a$ | $P^b$ | $P^c$ |
|---|---|---|---|---|---|---|---|
| Sedentary time | 0.112 | 0.010 | 0.009 | (-0.009, 0.028) | 0.098 | 0.307 | 0.300 |
| Light PA | -0.040 | -0.004 | 0.010 | (-0.025, 0.017) | 0.283 | 0.733 | 0.723 |
| Moderate PA | -0.251 | -0.075 | 0.031 | (-0.137, -0.013) | 0.019 | 0.018 | 0.019 |
| MVPA | -0.262 | -0.075 | 0.029 | (-0.133, -0.017) | 0.016 | 0.012 | 0.013 |
| Total PA | -0.118 | -0.010 | 0.009 | (-0.028, 0.009) | 0.098 | 0.307 | 0.300 |
| Bouted MVPA | -0.203 | -0.012 | 0.006 | (-0.025, 0.001) | 0.022 | 0.069 | 0.063 |

PA: physical activity; SLE: systemic lupus erythematosus; β: standardized regression coefficient; b: non-standardized regression coefficient; SE: standard error; CI: confidence interval; MVPA: moderate-to-vigorous physical activity.

β*, b*, SE*, (95 % CI)*: these values correspond to the complete model (model 3).

[a]Model 1: adjusted for accelerometer-wear time.

[b]Model 2: model 1 plus adherence to the Mediterranean diet and depression.

[c]Model 3: model 2 plus age.

The comparison of the average perceived stress scale between participants meeting and not meeting the PA guidelines is shown in **figure 4**. 33 participants did not meet PA guidelines. ANCOVA analysis showed that participants not meeting the PA guidelines presented 4.3 (95% CI 0.311 to 8.242; *P*=0.035) units higher psychological stress than those meeting the guidelines.

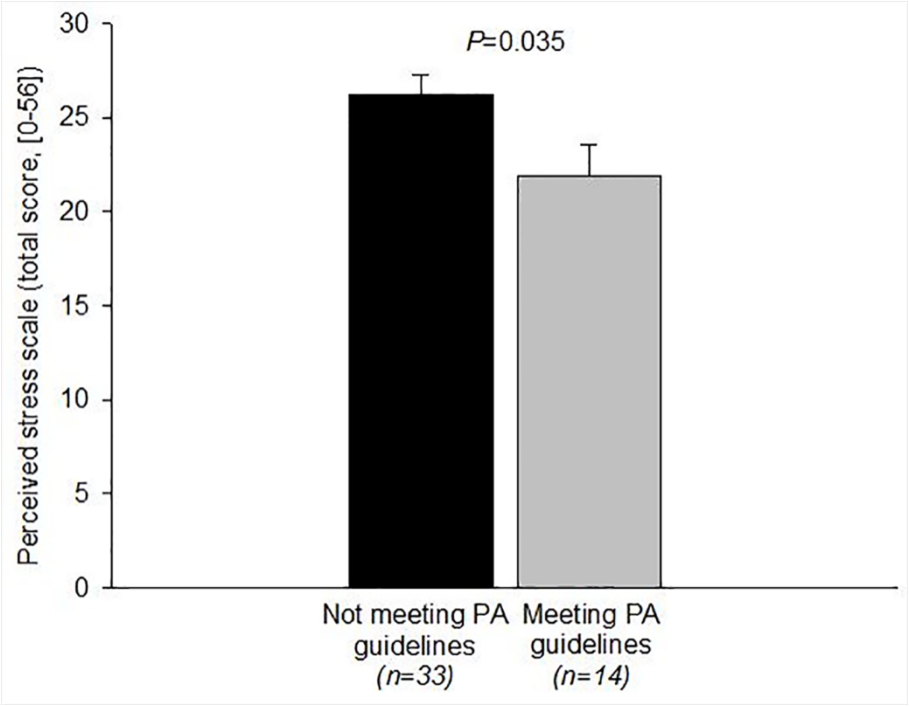


**Figure 4.** Means (95 % confidence interval) of perceived stress scale in participants meeting and not meeting the PA guidelines (≥150 min/week of bouted MVPA).

**Study III. Effect of 12-week aerobic exercise on arterial stiffness, inflammation, oxidative stress, and cardiorespiratory fitness in women with SLE.**

A total of 190 women with SLE were invited to participate. The flowchart of the study participants throughout the trial is presented in **figure 5**. A total of 58 patients volunteered to participate, met the inclusion criteria, signed informed consent, and were finally included and assigned to either the exercise group (*n=26*) or the control (*n=32*) group. The median attendance to the exercise intervention was 22.5 (out of 24; i.e. ~94%) sessions. A total of 22 participants (~85%) attended ≥75% of the sessions (i.e. and were 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 4 participants (i.e. 6.8% of the total sample) were lost to follow-up in the control group at week 12 and none in the exercise group. A summary of the average exercise intensity achieved at each session, RPE and pre- and post-session feeling scale scores are presented in **figure 6**. There were no adverse events occurring during the exercise sessions.

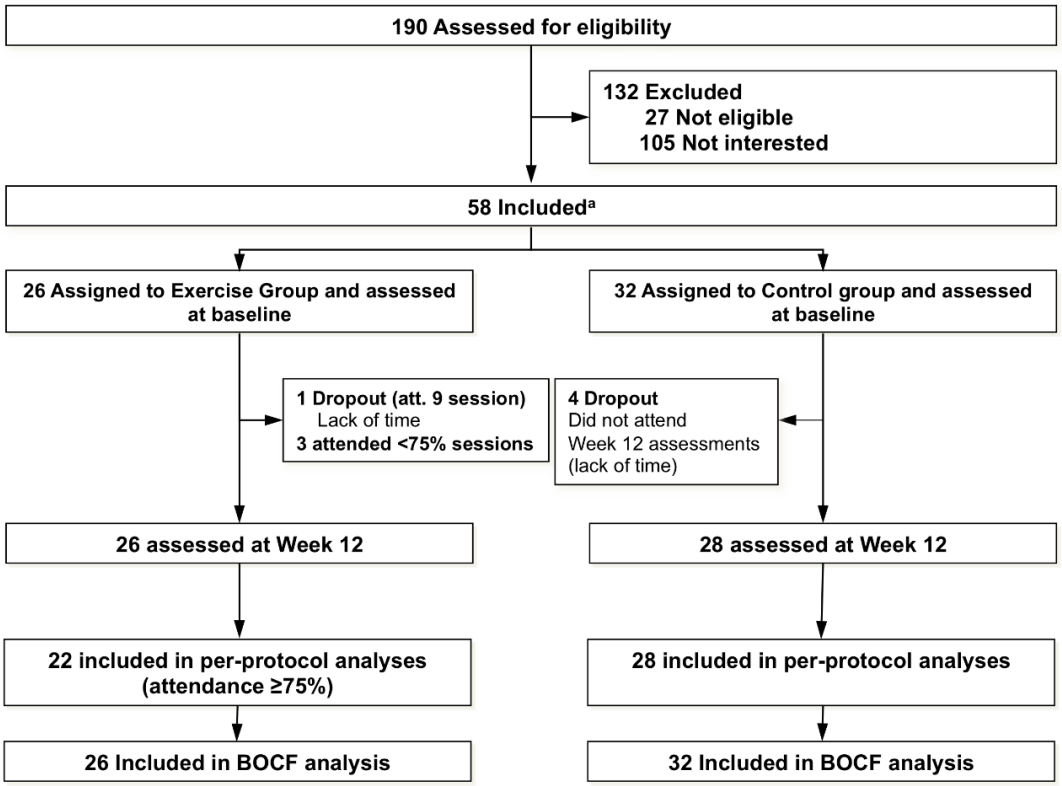


**Figure 5.** Flow chart of the study participants throughout the study.

At baseline (**table 10**), the control group showed lower resting heart rate (mean difference -9.6 bpm; *P*=0.002), and higher IL-6 levels (median difference 3.09 mg/dL; *P*=0.026) than the exercise group. There were no other significant between-group differences at baseline (all *P*>0.05).

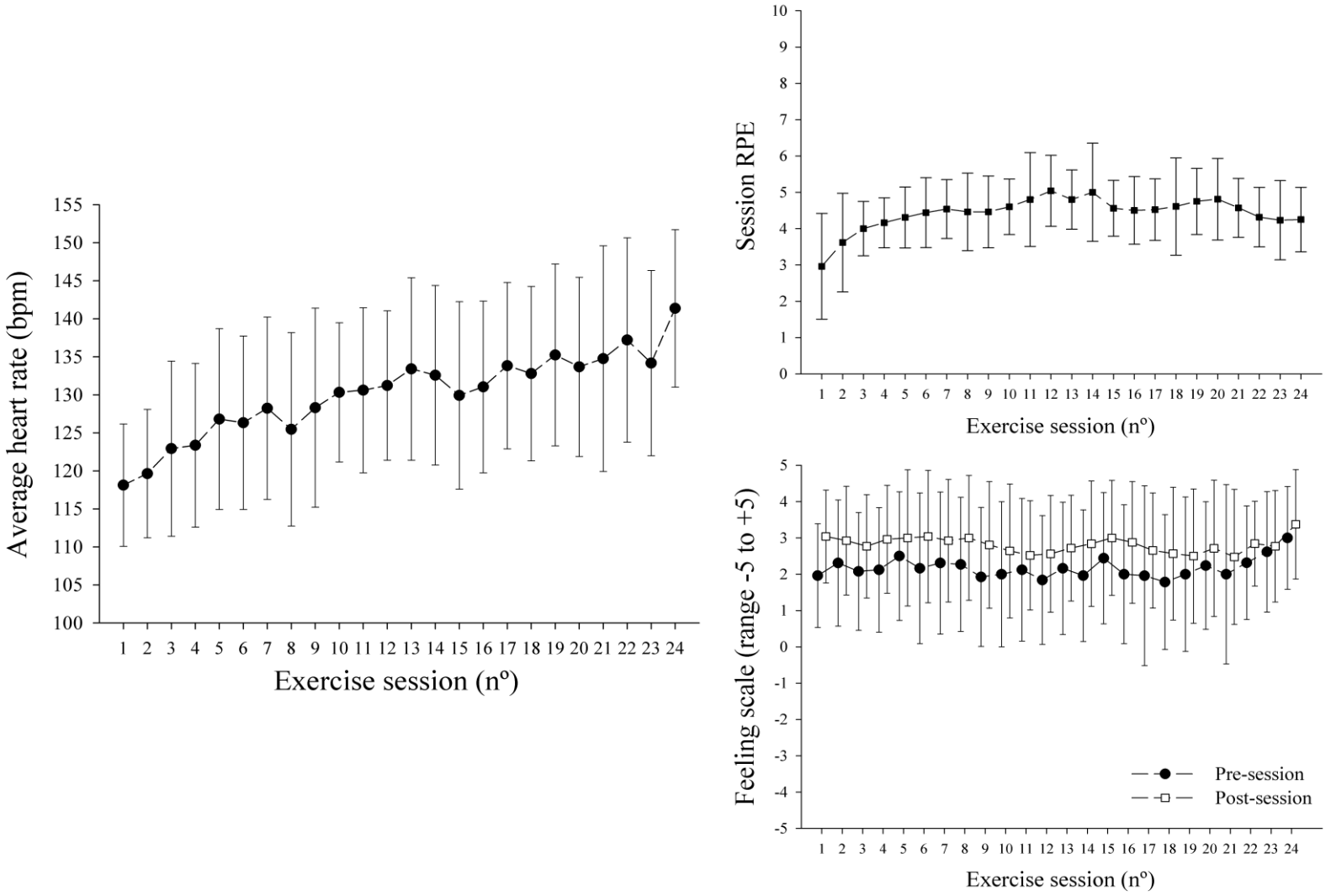


**Figure 6.** Summary of objective (i.e., heart rate) exercise intensity, session rating of perceived exertion (RPE), and (pre- and post-session) possitive affect (feeling scale) during each session of the exercise program. Bpm, beats per minute.

**Table 10**. 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 |
| BMI, $kg/m^2$ | 25.2 (4.7) | 25.9 (3.4) | 24.7 (5.6) | 0.336 |
| SBP, mm/Hg | 117.7 (10.3) | 116.8 (10.0) | 118.4 (10.6) | 0.567 |
| DBP, mm/Hg | 75.5 (9.5) | 75.6 (8.8) | 75.4 (10.1) | 0.937 |
| MBP, mm/Hg | 94.8 (8.8) | 94.5 (8.3) | 95.0 (9.3) | 0.821 |
| RHR, bpm | 81.6 (11.8) | 86.9 (11.0) | 77.3 (10.7) | 0.002 |
| Insulin, mg/dL | 7.6 (3.5) | 7.7 (4.2) | 7.5 (2.8) | 0.809 |
| BP lowering drugs (%) | 15.5 | 7.7 | 21.9 | 0.138 |
| Smoke (%) | 25.9 | 15.4 | 34.4 | 0.166 |
| Alcohol (yes/no; %) | 5.2 | 7.7 | 3.2 | 0.435 |
| Menopause (%) | 39.7 | 38.5 | 40.6 | 0.867 |
| History of CVD (%) | 12.1 | 15.4 | 9.4 | 0.485 |
| Dislipemia | 17.2 | 19.2 | 15.6 | 0.718 |
| Statins | 17.2 | 23.1 | 12.5 | 0.289 |
| Hydroxicloroquine (%) | 89.7 | 96.1 | 84.4 | 0.143 |
| Dosis of Hydroxicloroquine, mg/d | 189.4 (115.8) | 187.4 (94.1) | 191.1 (132.3) | 0.905 |
| Immunosupressants (%) | 44.8 | 46.1 | 43.7 | 0.874 |
| Current corticosteroid intake (mg/d) | 3.9 (5.1) | 4.1 ( 6.1) | 3.7 (4.1) | 0.760 |
| Cumulative corticosteroid intake (mg) | 2947 | 2696 | 3164 | 0.511 |
| Disease duration, years | 15.4 (10.5) | 14.5 (10.4) | 16.1 (10.6) | 0.570 |
| Total PA, min/week | 90.9 (92.2) | 96.8 (97.9) | 86.3 (88.8) | 0.646 |
| SLEDAI | 0.22 (0.90) | 0.04 (0.20) | .38 (1.18) | 0.158 |
| SDI | 0.47 (1.11) | 0.19 (0.63) | 0.69 (1.35) | 0.092 |
| Pulse wave velocity, m/s (median, IQR) | 6.3 (5.3 - 7.4) | 6.3 (5.1 - 7.8) | 6.4 (5.5 - 7.3) | 0.696 |
| hsCRP, mg/L (median, IQR) | 1.46 (0.84 - 4.37) | 2.18 (1.2 - 4.37) | 1.21 (0.73 - 4.35) | 0.161 |
| TNF-alpha, pg/mL (median, IQR) | 15.95 (12.02 - 21.9) | 16.48 (12.48 - 21.46) | 15.18 (11.4 - 21.93) | 0.487 |
| IL-6, pg/mL (median, IQR) | 10.33 (7.07 - 13.67) | 8.18 (5.82 - 11.89) | 11.27 (9.21 - 14.14) | 0.026 |
| MPO, ng/mL (median, IQR) | 71.8 (42.8 - 127.1) | 60.15 (40.08 - 113.54) | 79.00 (56.65 - 161.1) | 0.241 |
| Cardiorespiratory fitness (Bruce test, min) | 8.2 (2.8) | 8.1 (2.2) | 8.3 (3.2) | 0.763 |

Values are mean (standard deviation; SD), unless otherwise indicated. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; CVD, cardiovascular disease; RHR, resting heart rate; PA, physical activity; MD, Mediterranean diet; SLEDAI, systemic lupus erythematosus disease activity index; SDI, systemic damage index; PWV, pulse wave velocity; hsCRP, high sensitivity C-reactive protein; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; MPO, myeloperoxidase.

The baseline and (adjusted) follow-up values on the main study outcomes, and between-group comparisons are presented in **figure 7**. The primary analyses revealed no significant group differences between changes in PWV (primary aim) at week 12 (median difference -0.034, 95% CI -0.42 to 0.36 m/s; *P*=0.860; **table 11**), and these results were consistent across sensitivity analyses (**tables 12**, **15** and **16**). Regarding the secondary study aim, there were no between-group differences in the changes in hsCRP, TNF-α, IL-6, and MPO at week 12 (all *P*>0.05; **table 11**). **Table 17** shows lack of between-group differences in the change from baseline to week 12 for traditional CVD risk factors such as blood pressure, insulin resistance, or BMI. In comparison to the control group, the exercise group experienced a significant increase in cardiorespiratory fitness (median difference 2.26 minutes, 95% CI 0.98 to 3.55; *P*=0.001; **table 11**). Overall, sensitivity analyses corroborated these results (**tables 12**, **15** and **16**).

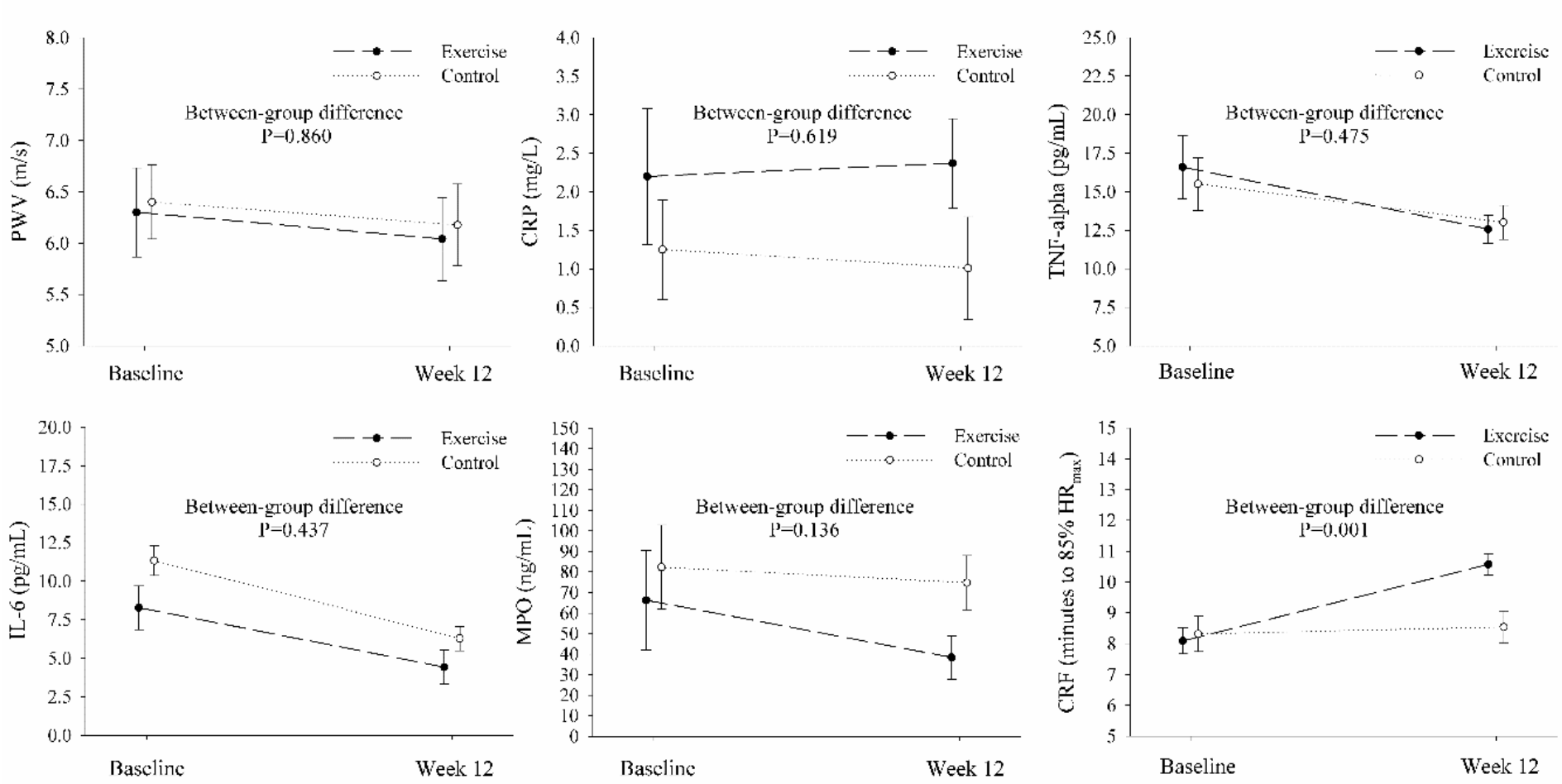


**Figure 7.** Graphical representation of the effects of the 12-week progressive aerobic exercise intervention. Results derived from the primary analyses (i.e., per-protocol with a minimum attendance of 75% for participants in the exercise group to be included). PWV, pulse wave velocity; hsCRP, high sensitivity C-reactive protein; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; MPO, myeloperoxidase; CRF, cardiorespiratory fitness; $HR_{max}$, maximal heart rate.

**Table 11.** Per-protocol (primary) analyses assessing the effects of 12-week progressive aerobic exercise on arterial stiffness, inflammation, oxidative stress, and cardiorespiratory fitness in women with systemic lupus erythematosus (participants in the exercise group were included if attendance was ≥75%).

| Change from baseline at Week 12 | Intervention | | Mean difference (95%CI) | *P* |
|---|---|---|---|---|
| | Exercise (*n=22*) Median (SE) | Control (*n=28*) Median (SE) | | |
| PWV, m/s | -0.26 (0.14) | -0.22 (0.13) | -0.034 (-0.42 to 0.36) | 0.860 |
| hsCRP, mg/L | 0.17 (0.59) | -0.24 (0.55) | 0.411 (-1.25 to 2.07) | 0.619 |
| TNF-α, pg/mL | -4.04 (1.53) | -2.49 (1.41) | -1.55 (-5.87 to 2.78) | 0.475 |
| IL-6, pg/mL | -3.86 (1.04) | -5.05 (0.99) | 1.19 (-1.86 to 4.25) | 0.437 |
| MPO, ng/mL | -27.84 (9.61) | -7.49 (9.02) | -20.35 (-47.38 to 6.68) | 0.136 |
| Cardiorespiratory fitness (Bruce), min | 2.49 (0.44) | 0.22 (0.41) | 2.26 (0.98 to 3.55) | 0.001 |

The analyses were adjusted for baseline values, resting heart rate and changes in self-reported physical activity during the study period. SE, standard error; CI, confidence interval; PWV, pulse wave velocity; hsCRP, high sensitivity C-reactive protein; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; MPO, myeloperoxidase.

**Table 12.** Sensitivity analyses: Baseline-observation carried forward imputation assessing the effects of 12-week progressive aerobic exercise on arterial stiffness, inflammation, oxidative stress, and cardiorespiratory fitness in women with systemic lupus erythematosus.

| Change from baseline at Week 12 | Intervention | | Mean difference (95%CI) | *P* |
|---|---|---|---|---|
| | Exercise (*n=26*) Median (SE) | Control (*n=32*) Median (SE) | | |
| PWV, m/s | -0.25 (0.12) | -0.09 (0.12) | -0.16 (-0.51 to 0.19) | 0.365 |
| hsCRP, mg/L | -0.04 (0.36) | -0.09 (0.34) | 0.06 (-0.95 to 1.06) | 0.913 |
| TNF-α, pg/mL | -4.14 (1.85) | -3.88 (1.76) | -0.26 (-5.51 to 5.00) | 0.923 |
| IL-6, pg/mL | -3.81 (1.34) | -5.02 (1.31) | 1.22 (-2.79 to 5.22) | 0.545 |
| MPO, ng/mL | -17.11 (11.01) | -10.52 (10.84) | -6.58 (-37.97 to 24.80) | 0.676 |
| Cardiorespiratory fitness (Bruce), min | 2.71 (0.38) | 0.29 (0.36) | 2.42 (1.31 to 3.52) | <0.001 |

The analyses were adjusted for baseline values, resting heart rate and changes in self-reported physical activity during the study period. SE, standard error; CI, confidence interval; PWV, pulse wave velocity; hsCRP, high sensitivity C-reactive protein; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; MPO, myeloperoxidase.

**Table 13**. TREND Statement for improving the reporting of non-randomized experiments.

| Paper Section/ Topic | Item No. | Descriptor | Reported? | Pg # |
|---|---|---|---|---|
| | | **Title and Abstract** | | |
| Title and Abstract | 1 | Information on how unit were allocated to interventions | ✓ | 66 |
| | | Structured abstract recommended | ✓ | n/a |
| | | Information on target population or study sample | ✓ | 66 |
| | | **Introduction** | | |
| Background | 2 | Scientific background and explanation of rationale | ✓ | 30,31 |
| | | Theories used in designing behavioral interventions | ✓ | 30,31 |
| | | **Methods** | | |
| Participants | 3 | Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects) | ✓ | 43 |
| | | Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented | ✓ | 44 |
| | | Recruitment setting | ✓ | 44 |
| | | Settings and locations where the data were collected | ✓ | 44 |
| Interventions | 4 | Details of the interventions intended for each study condition and how and when they were actually administered, specifically including: | ✓ | 43-47 |
| | | o Content: what was given? | ✓ | 43-44 |
| | | o Delivery method: how was the content given? | ✓ | 44,47 |
| | | o Unit of delivery: how were the subjects grouped during delivery? | ✓ | 44,47 |
| | | o Deliverer: who delivered the intervention? | ✓ | 44,47 |
| | | o Setting: where was the intervention delivered? | ✓ | 44 |
| | | o Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last? | ✓ | 44-47 |
| | | o Time span: how long was it intended to take to deliver the intervention to each unit? | ✓ | 46 |
| | | o Activities to increase compliance or adherence (e.g., incentives) | ✓ | 44,45 |
| Objectives | 5 | Specific objectives and hypotheses | ✓ | 36-37 |
| Outcomes | 6 | Clearly defined primary and secondary outcome measures | ✓ | 47,48, 30,31 |
| Sample Size | 7 | Methods used to collect data and any methods used to enhance the quality of measurements | ✓ | 47,48 |
| | | Information on validated instruments such as psychometric and biometric properties | ✓ | 47,48 |
| | | How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules | ✓ | 48 |
| Assignment Method | 8 | Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community) | ✓ | 48,49 |
| | | Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization) | ✓ | 48,49 |
| | | Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching) | ✓ | 48,49 |

| | | | | |
|---|---|---|---|---|
| Blinding (masking) | 9 | Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed. | ✓ | 48,49 |
| Unit of Analysis | 10 | Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community) | ✓ | 48 |
| | | 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 of correlated data | ✓ | 52 |
| | | Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis | | 52 |
| | | Methods for imputing missing data, if used | ✓ | 52 |
| | | Statistical software or programs used | ✓ | 52 |
| | | **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) | ✓ | 66 |
| | | o Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study | ✓ | 66 |
| | | o Assignment: the numbers of participants assigned to a study condition | ✓ | 66 |
| | | o Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention | ✓ | 66 |
| | | o 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 | ✓ | 66 |
| | | o Analysis: the number of participants included in or excluded from the main analysis, by study condition | ✓ | 66 |
| | | Description of protocol deviations from study as planned, along with reasons | ✓ | 43,44, 47 |
| Recruitment | 13 | Dates defining the periods of recruitment and follow-up | ✓ | 43,44 |
| Baseline Data | 14 | Baseline demographic and clinical characteristics of participants in each study condition | ✓ | 68 |
| | | Baseline characteristics for each study condition relevant to specific disease prevention research | ✓ | 68 |
| | | 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 | ✓ | 68 |
| Baseline equivalence | 15 | Data on study group equivalence at baseline and statistical methods used to control for baseline differences | ✓ | 52 |

| | | | | |
|---|---|---|---|---|
| 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 | ✓ | Tables 11,12, 15,16, Fig. 7 |
| | | Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses | ✓ | 52, Tables 11,12, 15,16, Fig. 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 | ✓ | Tables 11,12, 15,16, Fig. 7 |
| | | Inclusion of null and negative findings | ✓ | 69-77 |
| | | Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any | | n/a |
| Ancillary analyses | 18 | Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory | | n/a |
| 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) | ✓ | 52 |
| | | **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 | ✓ | 84-86 |
| | | Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations | ✓ | 84-86 |
| | | Discussion of the success of and barriers to implementing the intervention, fidelity of implementation | ✓ | 86 |
| | | Discussion of research, programmatic, or policy implications | ✓ | 86 |
| 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 | ✓ | 86 |
| Overall Evidence | 22 | General interpretation of the results in the context of current evidence and current theory | ✓ | 84-86 |

Reference: Des Jarlais DC, Lyles C, Crepaz N, The Trend Group. Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: The TREND statement. *American Journal of Public Health.* 2004;94:361-366.

**Table 14.** CERT checklist from *the EJERCITALES Study* physical exercise program

| | Item | Checklist Item | Identification |
|---|---|---|---|
| **WHAT: materials** | 1 | Detailed description of the type of exercise equipment | *Pages 43 and 44* |
| **WHO: provider** | 2 | Detailed description of the qualifications, expertise and/or training | *Page 44* |
| **HOW: delivery** | 3 | Describe whether exercises are performed individually or in a group | *Page 44* |
| | 4 | Describe whether exercises are supervised or unsupervised; how they are delivered | *Pages 44, 45 and 47* |
| | 5 | Detailed description of how adherence to exercise is measured and reported | *Page 44* |
| | 6 | Detailed description of motivation strategies | *Pages 45 and 47* |
| | 7[a] | Detailed description of the decision rule (s) for determining exercise progression | *Pages 44, 45 and 47* |
| | 7b | Detailed description of how the exercise program was progressed | *Pages 43, 44, 45, 47 and table 1* |
| | 8 | Detailed description of each exercise to enable replication | *Pages 43, 44, 45, 47 and table 1* |
| | 9 | Detailed description of any home programme component | *Pages 44, 45 and 47* |
| | 10 | Describe whether there are any non-exercise components | *Pages 44, 45 and 47* |
| | 11 | Describe the type and number of adverse events that occur during exercise | Page 66 |
| **WHERE: location** | 12 | Describe the setting in which the exercises are performed | *Page 43* |
| **WHEN, HOW MUCH: dosage** | 13 | Detailed description of the exercise intervention | *Pages 44, 45 and 47 and table 1* |
| **TAILORING: what, how** | 14[a] | Describe whether the exercises are generic (one size fits all) or tailored | *Pages 44, 45 and 47* |
| | 14b | Detailed description of how exercises are tailored to the individual | *Pages 44, 45 and 47* |
| **HOW WELL: planned, actual** | 15 | Describe the decision rule for determining the starting level | *Page 45* |
| | 16[a] | Describe how adherence or fidelity is assessed/measured | *Page 44* |
| | 16b | Describe the extent to which the intervention was delivered as planned | *Page 47* |

**Table 15**. Per-protocol analyses assessing the effects of 12-week progressive aerobic exercise on arterial stiffness, inflammation, oxidative stress, and cardiorespiratory fitness in women with systemic lupus erythematosus (participants in the exercise group were included if attendance ≥90%).

| Change from baseline at Week 12 | Intervention | | Mean difference (95%CI) | *P* |
|---|---|---|---|---|
| | Exercise (*n=18*) Median (SE) | Control (*n=28*) Median (SE) | | |
| PWV, m/s | -0.26 (0.14) | -0.25 (0.11) | -0.010 (-0.38 to 0.36) | 0.958 |
| hsCRP, mg/L | -0.12 (0.58) | -0.183 (0.48) | 0.064 (-1.50 to 1.62) | 0.934 |
| TNF-α, pg/mL | -4.15 (1.69) | -2.49 (1.41) | -1.65 (-6.28 to 2.97) | 0.475 |
| IL-6, pg/mL | -4.22 (1.13) | -5.64 (0.96) | 1.41 (-1.77 to 4.59) | 0.375 |
| MPO, ng/mL | -29.30 (11.45) | -8.95 (9.56) | -20.35 (-51.25 to 10.54) | 0.191 |
| Cardiorespiratory fitness (Bruce), min | 2.42 (0.50) | 0.28 (0.41) | 2.14 (0.75 to 3.54) | 0.003 |

The analyses were adjusted for baseline values, resting heart rate and changes in self-reported physical activity during the study period. SE, standard error; CI, confidence interval; PWV, pulse wave velocity; hsCRP, high sensitivity C-reactive protein; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; MPO, myeloperoxidase.

**Table 16**. Sensitivity analyses: Complete case analyses assessing the effects of 12-week progressive aerobic exercise on arterial stiffness, inflammation, oxidative stress, and cardiorespiratory fitness in women with systemic lupus erythematosus (only participants with valid data were included).

| Change from baseline at Week 12 | Intervention | | Mean difference (95%CI) | *P* |
|---|---|---|---|---|
| | Exercise (*n=26*) Median (SE) | Control (*n=28*) Median (SE) | | |
| PWV, m/s | -0.24 (0 .12) | -0.21 (0.12) | -0.03 (-0.39 to 0.32) | 0.838 |
| hsCRP, mg/L | 0.08 (0.61) | -0.17 (0.62) | 0.25 (-1.52 to 2.03) | 0.777 |
| TNF-α, pg/mL | -3.51 (1.69) | -2.72 (1.73) | -0.79 (-5.73 to 4.15) | 0.749 |
| IL-6, pg/mL | -3.40 (0.90) | -5.24 (0.92) | 1.84 (-0.830 to 4.51) | 0.172 |
| MPO, ng/mL | -16.61 (8.44) | -10.44 (8.85) | -6.18 (-30.90 to 18.55) | 0.618 |
| Cardiorespiratory fitness (Bruce), min | 2.72 (0.38) | 0.19 (0.39) | 2.54 (1.39 to 3.68) | <0.001 |

The analyses were adjusted for baseline values, resting heart rate, and changes in self-reported physical activity during the study period. SE, standard error; CI, confidence interval; PWV, pulse wave velocity; hsCRP, high sensitivity C-reactive protein; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; MPO, myeloperoxidase.

**Table 17**. Between-group comparison of the change in traditional cardiovascular disease risk factors from baseline at week 12.

| Change from baseline at Week 12 | Intervention | | Mean difference (95%CI) | *P* |
|---|---|---|---|---|
| | Exercise (*n=22*) Median (SE) | Control (*n=28*) Median (SE) | | |
| BMI, kg/m$^2$ | -0.37 (0.21) | -0.33 (0.19) | -0.05 (-0.64 to 0.54) | 0.863 |
| SBP, mm/Hg | -5.9 (2.4) | -5.7 (2.2) | -0.26 (-7.13 to 6.61) | 0.939 |
| DBP, mm/Hg | -2.6 (1.9) | -4.9 (1.8) | 2.30 ( -3.2 to 7.8) | 0.403 |
| MBP, mm/Hg | -4.1 (2.0) | -5.5 (1.8) | 1.46 (-4.2 to 7.1) | 0.605 |
| Insuline, mg/dL | -0.58 (0.76) | -0.95 (0.68) | 0.37 (-1.78 to 2.53) | 0.729 |
| HOMA-IR | 0.07 (0.16) | -0.22 (0.15) | 0.30 (-0.16 to 0.75) | 0.197 |

BMI, body mass index; SBP, systolic blood pressure; DBP, distolic blood pressure; MBP, mean blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance.

# DISCUSSION

# DISCUSSION

## 1. Summary of main findings.

The main findings of the present Doctoral Thesis suggest that **I)** PA intensity levels and sedentary time are not associated with arterial stiffness in patients with SLE. Further analyses revealed that patients with SLE meeting international PA guidelines did not present lower arterial stiffness than those not meeting them; **II)** Lower levels of moderate PA or MVPA are associated with higher psychological stress in women with SLE. Women who did not meet the international PA guidelines presented higher psychological stress than those meeting them; **III)** 12 weeks of progressive treadmill aerobic exercise following the ACSM guidelines significantly increases cardiorespiratory fitness without exacerbating arterial stiffness, inflammation, or oxidative stress in women with SLE, in comparison to a control group that received recommendations for a healthy lifestyle.

## 2. Discussion of main findings.

### *2.1. Association of PA levels, assessed by accelerometry, with arterial stiffness in women with SLE (Study I)*

The main findings of the present study indicate that there is no association of PA intensity levels and sedentary time with arterial stiffness in women with SLE. Participants who met the international PA guidelines did not show lower PWV than those not meeting them.

Benefits of regular practice of PA for general health are well documented[77]. Parsons et al. showed that low levels of PA and high levels of sedentary time are associated with higher CVD risk among older people[78]. Furthermore, Matthews et al. evidenced that time spent in sedentary behaviors was positively associated with CVD incidence and mortality in general population, and participation in high levels of MVPA did not fully mitigate health risks associated with prolonged time watching television[79,80]. Although the sedentary time in our study was similar to that found in general population and patients with Sjögren´s syndrome (451.4 min/day in average)[78,81], the time spent in PA of our participants differed from those observed in previous studies.

Several studies have analyzed the amount of MVPA performed by patients with SLE. For instance, Ahn et al. observed that patients with SLE performed 39.6 (SD 29.9) min/day of MVPA (measured by accelerometery)[58], while Mahieu et al. observed a total of 38.4 (SD 29.6) min/day of MVPA[82]. These numbers are tentative to think that in the present study, participants greater PA (i.e. 51.1 (SD 31.3) min/day of MVPA). However, these differences in PA levels might be explained by the use of an older version of accelerometer in previous studies[58,82], the GT3X ActiGraph instead of GT3X+, and because the vector magnitude from the triaxial accelerometry was computed using a different algorithm on a minute-by-minute basis to classify activity as

MVPA by Ahn et al[58]. Furthermore, differents accelerometer cut-off points to determine PA levels could explain these differences[46].

There is enough information about exercise physiology to support the well-documented public health guidelines promoting at least 150 min/week of moderate-vigorous leisure-time PA aimed at decreasing risks for metabolic diseases[16]. In addition, García-Hermoso et al. found that, in adults, long lasting periods of sedentary time were associated with a worse cardiometabolic risk profile, and greater risk for with clinical and subclinical atherosclerosis[20]. Pedersen and Febbraio confirmed that physical inactivity probably leads to an altered myokine response, which could provide a potential mechanism for the association between sedentary behavior and many chronic diseases[83].

However, it is currently uncertain whether there is a link between the levels of PA, measured by accelerometry, and subclinical atherosclerosis in women with SLE. Implementing strategies or lifestyle modifications to prevent CVD development is of major interest in this population. Previous studies have investigated the relationship between PA levels and sedentary lifestyle, measured by accelerometry, and clinical parameters in other autoimmune disease populations[81]. Dassouki et al. described that patients with primary Sjögren's syndrome showed reduced physical capacity and function[81]. The results of PA of this study were 26.3 (SD 13.6) min/day of MVPA. Therefore, the time engage in MVPA of this study differed from our results (51.1 (SD 31.3) min/day of MVPA).

In patients with SLE, it has been found that low PA levels were associated with more severe organ damage compared to general population[19]. Volkmann et al. found that low PA levels were associated with increased subclinical atherosclerosis, but this association did not remain significant after controlling for traditional cardiovascular factors[18]. Moreover, unlike our study, subclinical atherosclerosis was assessed by intima media thickness and PA was investigated from self-reports questionnaires (the Medical Outcomes Study Short Form 36, SF-36, and the MESA Typical Week Physical Activity Survey). In addition, it is important to note that Kruse and Scheuermann evidenced that endothelial function declines with age and sedentary lifestyle, and this is associated with an increased risk for CVD in general population[21].

The use of questionnaires to assess PA levels has shown significant differences in the estimation of PA in other populations compared to a measure such as accelerometry[84]. In SLE patients, accelerometer measures and IPAQ energy expenditure estimates showed a moderate grade of agreement since individuals tend to underestimate their daily walking distance, overestimate their energy expenditure and overestimate time spent in MVPA with patient-reported PA instruments[58]. Despite accelerometers did not capture PA time spent in water activities, a review of the activity logs showed that this time was very low.

To the best of our knowledge, our study is the first to examine the association of

measured PA levels and sedentary time with PWV in a cohort of women with SLE. Based on previous literature in the general population[20,78-80], it was hypothesized that there would be a significant association between PA levels and sedentary time and arterial stiffness, measured by PWV. However, contrary to our hypothesis, the results of the study showed lack of association of either PA intensity levels or sedentary time with PWV. These negative results could be due to the fact that daily PA might not be sufficient to produce changes in PWV and it is necessary to perform a supervised cardiovascular training to reduce arterial distensibility in this population.

### *2.2. Association of PA levels, measured with accelerometry, and sedentary time with psychological stress in women with SLE (Study II)*

The main findings of the present study indicate that low levels of moderate PA or MVPA are associated with higher psychological stress in women with SLE. Participants who did not meet the international PA guidelines showed higher psychological stress than those meeting them. However, contrary to the a priori hypothesis, sedentary time was not associated with psychological stress in this population.

Recently, psychological stress-related disorders seem to be significantly associated with an increased risk of subsequent autoimmune disease[85]. In patients with SLE, there is scientific evidence of the deleterious effect of psychological stress both on their clinical manifestations[25-28], that may worsen in up to 74.1% of patients[86], and on their cognitive functioning[87]. To the best of our knowledge, our study is the first to examine the association of PA levels measured by accelerometry and sedentary time with psychological stress in a cohort of women with SLE. Our results suggest that higher MVPA is related to lower psychological stress, concurring with several studies in different populations.

In the general population, it has been shown that PA positively affects psychological stress[88]. A systematic review that include eleven studies, observed an inverse association between psychological stress and PA[89]. Furthermore, in the general population, previous research evidences that sedentary behavior is associated with higher levels of psychological stress and risk of anxiety[33,90,91]. The average sedentary time in our study (451.4 min/day in average) differed from those observed in general population (510 min/day in average) and in patients with Sjögren´s syndrome (494 min/day in average)[81,92]. In addition, the time spent in MVPA of our participants (51.1 min/day in average) was different to that found in previous studies in SLE population[58,82]. Ahn et al. observed that patients with SLE performed 39.6 min/day of MVPA in average[58], while Mahieu et al. observed an average MVPA of 38.4 min/day[82]. These differences in sedentary time and MVPA time might be explained by the use of an older version of accelerometer in previous studies[58,82], the GT3X ActiGraph instead of GT3X+, and because the vector magnitude from the triaxial accelerometry was computed using a different algorithm on a minute-by-minute basis to classify activity as MVPA by Ahn et al[58]. Furthermore, differents accelerometer cut-off points to determine sedentary time and MVPA could explain these differences[46].

Dobkin et al. revealed that the daily psychological stress in patients with SLE is higher than in the general population[24]. Barnes et al. showed that physical exercise reduces psychological stress in SLE population[29], and Mancuso et al. evidenced that SLE patients with more social stress and more fatigue report less PA, but in this case PA was measured by questionnaire[34]. Pinto et al. found that SLE patients showed impaired aerobic capacity and health-related quality of life when compared with healthy controls matched by physical inactivity, age, sex, and BMI. These results reinforce the need of PA recommendations for SLE patients[1].

Previous studies have investigated the relationship between PA levels and sedentary lifestyle, measured by accelerometry, and clinical parameters in other autoimmune disease populations[81]. In addition, Ashdown-Franks et al. evidenced that a greater amount of sedentary behavior is associated with higher levels of psychological stress in adults[33]. However, it is currently uncertain whether there is a link between the levels of PA, sedentary time (i.e. measured by accelerometry) and psychological stress in women with SLE. Implementing strategies or lifestyle modifications to prevent psychological stress development is of major interest in this population. Based on previous literature in the general population[33,88-91], it was hypothesized that there would be a significant association between PA levels, sedentary time and psychological stress in women with SLE. However, contrary to our hypothesis, the results of the study showed lack of association of sedentary time with psychological stress. This negative result could be due to the fact that the study participants showed low sedentary time compared to previous research[81,92], and it is necessary to present higher sedentary time to increase psychological stress in this population.

### *2.3. Effect of 12-week aerobic exercise on arterial stiffness, inflammation, oxidative stress, and cardiorespiratory fitness in women with SLE (Study III)*

The main findings of this study suggest that 12 weeks of progressive treadmill aerobic exercise following the ACSM guidelines, performed between 40% and 75% of the HRR, increases cardiorespiratory fitness without exacerbating arterial stiffness, inflammation, or oxidative stress in women with SLE, in comparison to a control group of patients with SLE that received recommendations for a healthy lifestyle. Future clinical trials with larger sample sizes are needed to enhance our understanding on how different durations, types, volumes, and exercise intensities might affect vascular health and inflammation in this population.

To the best of our knowledge, this is the first study assessing the extent to which a progressive aerobic exercise intervention of moderate to vigorous intensity, following the ACSM guidelines for aerobic exercise, might influence arterial stiffness in women with SLE. Barnes et al.[93] cross-sectionally observed that participants (mainly women) with SLE who reported exercising regularly had lower central arterial stiffness than sedentary SLE subjects and similar to that of healthy individuals. By contrast, Morillas de-Laguno et al. observed a lack of association of accelerometer-based PA with PWV in women with SLE[71]. Our results did not evidence any significant change in arterial

stiffness following 12 weeks of aerobic exercise, which might have different explanations. Firstly, it is possible that aerobic exercise does not actually influence arterial stiffness, although this seems unlikely in light of recent evidence suggesting that this type of training reduces arterial stiffness[41,94,95]. As it has been suggested that the volume, duration, and intensity of exercise might play a relevant role in its effects on arterial stiffness[96], it seems plausible that 12 weeks of intervention might not have been enough time to modify the elasticity of the arteries. Therefore, longer interventions are warranted to unravel the effects of exercise on arterial stiffness in SLE. Secondly, the median baseline PWV in the present study (i.e., 6.3 m/s) was far from the levels considered harmful (i.e., 10 m/s)[96]. According to Ashor et al., the effects of exercise might be more pronounced in women with SLE with higher baseline PWV[41] (e.g., with older age or at higher CVD risk).

Barnes et al.[94] observed higher hsCRP and TNF-α levels in sedentary versus physically active patients with SLE. Perandini et al. observed that a single bout (i.e., 30 min) of aerobic exercise (i.e., either at 50% or 70% of $VO_{2peak}$) did not acutely increase inflammation in women with either active or inactive SLE[42], and that a 12-week aerobic exercise program reduced resting state inflammation. However, the sample size by Perandini et al. was rather low ($n$ = 8 SLE patients), the intervention was not described with complete detail to allow replication, and their results were derived from intra group (instead of between-group) comparisons, which might be misleading[98]. In line with our results, Timoteo et al. did not observe changes in IL-6 or TNF-α following combined (i.e., flexibility, resistance, and aerobic) exercise in a rather small study ($n$ = 14)[44]. The results of the present study, in sum to prior evidence, suggest that aerobic exercise training does not exacerbate inflammatory markers in women with SLE. As exercise has emerged in recent years as a highly beneficial intervention for the cardiovascular prevention of patients with SLE[99], future clinical trials should elucidate whether diverse exercise configurations might reduce inflammation in this population. It must be noted that, in animal models, aerobic exercise has been shown to protect against the cardiometabolic disturbances induced by the chronic use of corticosteroids, such as hyperglycemia, dyslipidemia, liver steatosis, and muscular hypotrophy[100]. In this line, a positive influence of exercise on the effect of corticosteroid use on CVD risk could similarly be expected in humans, although this far exceeds the purposes of the present study and is a matter of further investigation.

Oxidative stress has been implicated in the pathogenesis of CVD in both the general population and in patients with SLE[101]. MPO is a biomarker of oxidative stress that predicts CVD[102]. Although previous research has described an antioxidant effect of exercise[103], our results indicate no significant reduction of oxidative stress in the exercise group compared to the usual care group, although there seemed to be a non-significant trend towards reduction in the exercise group that might deserve further research. As the sample size was not calculated based on this outcome, increasing the number of participants and combining different intensity protocols would provide valuable information regarding the association of stress oxidative and exercise in SLE.

It must be noted that the exercise intensity gradually increased throughout the intervention period, and that participants' affective responses after each exercise session was better than before the session (**figure 7**). Importantly, the exercise program significantly increased cardiorespiratory fitness, as assessed by the time to achieve 85% of estimated $HR_{max}$ in the Bruce test[69]. As there are no SLE-specific validated formulas to estimate $VO_{2max}$, it is difficult to assess the effects of the program on $VO_{2max}$. However, as a reference, if we used the formula for estimating $VO_{2max}$ in a healthy adult population described by Bruce et al.[69], the 2.26 minutes increase in the exercise group would translate into approximately 7.6 mL/kg x $min^{-1}$ (95% CI 3.3 to 11.9; $P$ = 0.001), which means >2 metabolic equivalents (METs). This increase in fitness is clinically relevant since a 1-MET increase is associated with a 13% to 15% reduction in CVD and all-cause mortality[104], and with 10% to 30% lower adverse cardiovascular event rates[105]. Moreover, higher cardiorespiratory fitness has been shown to be related to a lower cardiovascular risk in patients with rheumatoid arthritis[106] and with lower age-related arterial stiffness in SLE[107], indicating that future studies should address the impact of long term changes in cardiorespiratory fitness on cardiovascular health in SLE and other rheumatic populations.

## Limitations and Strengths

### *Limitations*

The studies comprising this Doctoral Thesis have several limitations that must be underlined:

In regards to the **Study I**, the cross-sectional design precludes any establishment of causality and reverse causation cannot be discarded. The participants in this study showed higher PA levels than those observed in previous studies[58,82]. Different accelerometer algorithms and/or cutoff points to determine PA intensity levels could explain these differences[46]. However, it is also possible that our sample was more physically active than previous ones, as we required clinical stability during the previous 6 months to be included in the study, and the average SLEDAI and SDI indicated low disease activity. Furthermore, patients meeting the PA guidelines could be the result of an older age and a higher prevalence of comorbidities, such as dyslipidemia. In this group of patients, a higher degree of motivation to move, or even a more intensive and strict cardiovascular recommendations by physicians could have been present, and explain or influence this result. The relatively small sample size *(n=47)* yielded a power to detect a significant association of MVPA with PWV of ~45%. Therefore, these results must be understood as preliminary/exploratory until future research with larger sample sizes confirms or contrasts our findings. Finally, the low levels of vigorous PA observed in the participants (i.e. 2.5 min/day) did not allow assessing its potential effect on PWV.

In the **Study II**, the cross-sectional nature precludes establishment of causality. The participants in our study showed lower sedentary time than those observed in previous studies[81,92]. Different accelerometer algorithms and/or cut-off points to determine sedentary time could explain these differences[46], although it is also possible that the limited time spent in sedentary behaviour in our sample might partially explain the lack of association with psychological stress. However, our sample seemed to be more physically active than those in previous studies[58,82], as only patients with mild/inactive disease with clinical stability during the previous 6 months were included in the study. The relatively small sample size (*n=47*) did not allow us to adjusting for more potential confounders in the analyzes, which could have enriched the study findings. In addition, only women with mild disease activity were included and it remains to be investigated whether these results apply to men or women with higher disease activity. Therefore, these results must be understood as preliminary/exploratory until future longitudinal research with larger sample sizes confirms or contrasts our findings.

Lastly, in the **Study III**, the sample size was relatively small and future studies with larger samples are needed. Likewise, we undertook a non-randomized design, which limits the confidence about baseline groups comparability and, despite statistical adjustment, residual confounding cannot be discarded. Future studies could overcome this limitation by performing a more pragmatic trial with home-based exercise and

periodic visits to the clinic for outcome assessment. Furthermore, only women with mild/inactive disease were included. Consequently, the results are not generalizable to men or even women with medium-high disease activity. Finally, despite the importance of comparative studies to better understand the early onset of atherosclerosis in rheumatic diseases[108], the present study failed to gather data from healthy individuals. Therefore, future studies should assess the comparative effectiveness of exercise in healthy people and patients with SLE.

***Strengths***

The main strength of the **Study I** and **II** is that we used accelerometry (the gold standard) to measure PA levels and sedentary time. The use of questionnaires to assess PA levels has shown significant differences in the estimation of PA in other populations compared to an measure such as accelerometry[84].

The strengths of the **Study III** are: a) the adherence to the exercise intervention was very high (≥90% of the sessions), and the effects of the aerobic program on cardiorespiratory fitness underline that the program was effective; b) the intervention is described following the CERT guidelines[64], so as to enhance transparency and replicability, something that has been traditionally lacking in exercise-based clinical trials[109]. This allows any physician, physiotherapist, or exercise professional to use this exercise program in clinical practice or any other settings, thus increasing the transfer/dissemination of scientific knowledge to society.

## Future Research Directions

### Study I

Our results suggest that PA intensity levels and sedentary time are not associated with arterial stiffness in patients with SLE. Future prospective research is needed to better understand the association of PA and sedentary time with arterial stiffness in patients with SLE. Future studies should characterize the association of physical fitness with arterial stiffness in patients with SLE. Preliminary research from our group suggests that higher cardiorespiratory fitness could attenuate the age-related arterial stiffness in women with SLE[107].

### Study II

The study results must be understood as preliminary/exploratory until future longitudinal research with larger sample sizes confirms or contrasts our findings. Further prospective research with larger sample size is needed to better understand the direction of the association of PA and sedentary time with psychological stress in patients with SLE.

### Study III

Future clinical trials with larger sample sizes are needed to enhance our understanding on how different durations, types, volumes, and intensities of exercise might affect vascular health and inflammation in this population. In particular, it seems interesting to assess the extent to which resistance training alone or in combination with aerobic training[95] might influence these outcomes in patients with SLE.

Finally, it must be underlined that the findings of this Doctoral Thesis should be extended to investigate whether these results apply to men and/or women with higher disease activity.

# CONCLUSIONES / CONCLUSIONS

## CONCLUSIONES

Los resultados de la presente Tesis Doctoral sugieren que:

I. La actividad física y el tiempo sedentario no están asociados con la rigidez arterial en pacientes con LES. Además, las pacientes con LES que cumplieron con las recomendaciones internacionales de actividad física no mostraron menor rigidez arterial que aquellas que no cumplen con dichas recomendaciones.

II. Bajos niveles de actividad física moderada o de actividad física moderada a vigorosa se asocian con un mayor estrés psicológico en mujeres con LES. Las mujeres que no cumplieron con las recomendaciones internacionales de actividad física presentaron mayor estrés psicológico (4.3 unidades) que aquellas que sí cumplieron con las recomendaciones.

III. Un programa de 12 semanas de ejercicio aeróbico progresivo en tapiz rodante, siguiendo las recomendaciones del *ACSM*, pueden incrementar de forma significativa la capacidad cardiorrespiratoria sin exacerbar la rigidez arterial, la inflamación o el estrés oxidativo en mujeres con LES, en comparación con un grupo de control que recibió recomendaciones para un estilo de vida saludable.

## CONCLUSIONS

The results of the present Doctoral Thesis suggest that:

I. PA and sedentary time are not associated with arterial stiffness in patients with SLE. Moreover, patients with SLE meeting international PA guidelines did not show lower arterial stiffness than those not meeting the PA guidelines.

II. Lower levels of moderate PA or MVPA are associated with higher psychological stress in women with SLE. Women who did not meet the international PA guidelines presented higher psychological stress (4.3 units) than those meeting the guidelines.

III. A 12-week program of progressive aerobic exercise on treadmill, following the ACSM guidelines, can significantly increase cardiorespiratory fitness without exacerbating arterial stiffness, inflammation, or oxidative stress in women with SLE, in comparison to a control group that received recommendations for a healthy lifestyle.

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**Short CV**

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**Academic training**

- **2011-2015.** GRADUATE DEGREE IN SPORT SCIENCES. Faculty of Sport Sciences, University of Granada, Granada, Spain.
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- **2016-2017**. MASTER DEGREE IN RESEARCH ON PHYSICAL ACTIVITY AND SPORT. Faculty of Sport Sciences, University of Granada, Granada, Spain.

**Scientific Publications directly derived from the present Doctoral Thesis:**

1. [Study I] **Morillas-de-Laguno P**, Vargas-Hitos JA, Rosales-Castillo A, Sáez-Urán LM, Montalbán-Méndez C, Gavilán-Carrera B, Navarro-Mateos C, Acosta-Manzano P, Delgado-Fernández M, Sabio JM, Ortego-Centeno N, Callejas-Rubio JL, Soriano-Maldonado A. Association of objectively measured physical activity and sedentary time with arterial stiffness in women with systemic lupus erythematosus with mild disease activity. *PLOS ONE*. 2018;13(4). Accepted 08/04/2018. doi: 10.1371/journal.pone.0196111. IF: 2.77 (Q1 Multidisciplinary Sciences).

2. [Study II] **Morillas-de-Laguno P**, Vargas-Hitos JA, López-Berrocal JP, Gavilán-Carrera1 B, Peralta-Ramírez MI, Navarrete-Navarrete N, Sabio JM, Delgado-Fernández M, Soriano-Maldonado A. Physical activity, sedentary time, and psychological stress in women with systemic lupus erythematosus with mild disease activity. Ready to submit.

3. [Study III] Soriano-Maldonado A, **Morillas-de-Laguno P**, Sabio JM, Gavilán-Carrera B, Rosales-Castillo A, Montalbán-Méndez C, Sáez-Urán LM, Callejas-Rubio JL, Vargas-Hitos JA. Effects of 12-week Aerobic Exercise on Arterial Stiffness, Inflammation, and Cardiorespiratory Fitness in Women with Systemic LUPUS Erythematosus: Non-Randomized Controlled Trial. *Journal of Clinical Medicine*. 2018;7(12). Accepted 21/11/2018. doi: 10.3390/jcm7120477. IF: 5.58 (Q1 Medicine, General & Internal).

**Other scientific publications:**

4. Montalbán-Méndez C, Soriano-Maldonado A, Vargas-Hitos JA, Sáez-Urán LM, Rosales-Castillo A, **Morillas-de-Laguno P**, Gavilán-Carrera B, Jiménez-Alonso J. Cardiorespiratory fitness and age-related arterial stiffness in lupus. *European Journal of Clinical Investigation*. 2018;48(3). doi: 10.1111/eci.12885. IF: 3.09 (Q1 Medicine, General & Internal).

5. Gavilán-Carrera B, Garcia da Silva J, Vargas-Hitos JA, Sabio JM, **Morillas-de-Laguno P**, Rios-Fernández R, Delgado-Fernández M, Soriano-Maldonado A. Association of physical fitness components and health-related quality of life in women with systemic lupus erythematosus with mild disease activity. *PLOS ONE*. 2019;14(2). doi: 10.1371/journal.pone.0212436. IF: 2.77 (Q1 Multidisciplinary Sciences).

6. Sola-Rodríguez S, Gavilán-Carrera B, Vargas-Hitos JA, Sabio JM, **Morillas-de-Laguno P**, Soriano-Maldonado A. Physical Fitness and Body Composition in Women with Systemic Lupus Erythematosus. *Medicina*. 2019;55(2). doi: 10.3390/medicina55020057. IF: 1.43 (Q3 Medicine, General & Internal).

7. Gavilán-Carrera B, Vargas-Hitos JA, **Morillas-de-Laguno P**, Rosales-Castillo A, Sola-Rodríguez S, Callejas-Rubio JL, Sabio JM, Soriano-Maldonado A. Effects of 12-week aerobic exercise on patient-reported outcomes in women with Systemic Lupus Erythematosus: non-randomized controlled trial. Submitted to Rheumatology on 02/10/2019 (manuscript number RHE-19-1721)

**Research Projects:**

**1. PROJECT:** Physical activity, subclinical arteriosclerosis and inflammation in patients with systemic lupus erythematosus (Actividad física, arteriosclerosis subclínica e inflamación en pacientes con lupus eritematoso sistémico).
NO FUNDING.
DATE AND DURATION: 15-09-2016 to 14-06-2017.
PRINCIPAL INVESTIGATOR: José Antonio Vargas Hitos.

**2. PROJECT:** Effects of a physical exercise program on subclinical arteriosclerosis and inflammation of patients with systemic lupus erythematosus **(**Efectos de un programa de ejercicio físico sobre la arteriosclerosis subclínica y la inflamación de pacientes con lupus eritematoso sistémico).
FUNDING SOURCE: Consejería de salud, Junta de Andalucía, Spain (PI-0525-2016).
DATE AND DURATION: 01/09/2017 to 30/06/2018.
PRINCIPAL INVESTIGATOR: José Antonio Vargas Hitos.
FUNDING: 33679 €.

**Academic awards:**

- **2017.** Award to the best Master Work in the Master Degree in Research on Physical Activity and Sport. University of Granada.

**Other merits:**

a) Reviewer for scientific journals: PLOS ONE.

b) **2014.** B2 diploma in English by Cambridge (FCE).

c) **2016.** B2 diploma in French by Language School.

d) **2016.** C1 diploma in French by "Alianza Francesa".

e) **2017.** B2 diploma in English by Language School.

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h) **Training courses:**

- "El tratamiento de los datos en Ciencias del Deporte". University of Sevilla (Sevilla, Spain). Duration: 12 hours.

- "Análisis estadístico de ensayos clínicos aleatorizados". iMUDS, University of Granada (Granada, Spain). Duration: 15 hours.

- "Herramientas de búsqueda y gestión de información para el desarrollo de la Investigación". University of Granada (Granada, Spain). Duration: 10 hours.

i) **Congresses:**

- I International Congress *Active brains for all: Exercise, Cognition and Mental Health*. iMUDS, University of Granada (Granada, Spain).

- XXXVIII National Congress of the Spanish Society of Internal Medicine (IFEMA, Madrid, Spain).

- I International Congress on Prevention and Interdisciplinary Physical Rehabilitation (Granada, Spain).

- VI EXERNET symposium. Research in Exercise, Health and Wellness: Exercise is Medicine.

- XXIV International Congress of the European College of Sport Science (Prague, Czech Republic).

- National days of Medicine and Sport Sciences (SAMEDE 2019).

- International Congress of Rheumatology – EULAR (Amsterdam, Netherlands).

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# Annexes

Nombre: _____

Fecha: _____ Código: _____

# DIARIO ACELEROMETRÍA

Deberá llevar el acelerómetro las 24 horas del día y, como norma general, **SOLO deberá quitárselo para ducharse.** Si usted realiza actividades acuáticas tales como la natación u otro tipo de actividad acuática, también deberá quitarse el aparato e indicar en esta hoja de registro la hora a la que se lo quitó y la hora a la que se lo volvió a poner, además de la actividad que realizó en ese periodo de tiempo. **Indique cada día la hora EXACTA a la que se acuesta por la noche y la hora EXACTA a la que se levanta por la mañana**.

**EJEMPLO:**

| | | |
|---|---|---|
| Hora levantarse: 08:13<br>Hora acostarse: 23:51 | Hora ducha inicio: 17:15<br>Hora ducha fin: 17: 37 | Act. Acuática: NATACIÓN<br>Inicio: 18:50 Fin: 20:05 |

**FECHA EN QUE SE HA PUESTO EL ACELERÓMETRO: _____**

| | | | | |
|---|---|---|---|---|
| Día 1 | $J_{23}$ | Hora acostarse: | Hora ducha inicio:<br>Hora ducha fin: | Act. Acuática:<br>Inicio: Fin: |
| Día 2 | $V_{24}$ | Hora levantarse:<br>Hora acostarse: | Hora ducha inicio:<br>Hora ducha fin: | Act. Acuática:<br>Inicio: Fin: |
| Día 3 | $S_{25}$ | Hora levantarse:<br>Hora acostarse: | Hora ducha inicio:<br>Hora ducha fin: | Act. Acuática:<br>Inicio: Fin: |
| Día 4 | $D_{26}$ | Hora levantarse:<br>Hora acostarse: | Hora ducha inicio:<br>Hora ducha fin: | Act. Acuática:<br>Inicio: Fin: |
| Día 5 | $L_{27}$ | Hora levantarse:<br>Hora acostarse: | Hora ducha inicio:<br>Hora ducha fin: | Act. Acuática:<br>Inicio: Fin: |
| Día 6 | $M_{28}$ | Hora levantarse:<br>Hora acostarse | Hora ducha inicio:<br>Hora ducha fin: | Act. Acuática:<br>Inicio: Fin: |
| Día 7 | $X_{29}$ | Hora levantarse:<br>Hora acostarse: | Hora ducha inicio:<br>Hora ducha fin: | Act. Acuática:<br>Inicio: Fin: |
| Día 8 | $J_{30}$ | Hora levantarse:<br>Hora acostarse: | Hora ducha inicio:<br>Hora ducha fin: | Act. Acuática:<br>Inicio: Fin: |

## Escala de Estrés Percibido

Marque con una "X" la opción que mejor se adecue a su situación actual, teniendo en cuenta **el último mes.**

| | Nunca | Casi nunca | De vez en cuando | A menudo | Muy a menudo |
|---|---|---|---|---|---|
| 1. En el último mes, ¿con qué frecuencia ha estado afectado por algo que ha ocurrido inesperadamente? | 0 | 1 | 2 | 3 | 4 |
| 2. En el último mes, ¿con qué frecuencia se ha sentido incapaz de controlar las cosas importantes en su vida? | 0 | 1 | 2 | 3 | 4 |
| 3. En el último mes, ¿con qué frecuencia se ha sentido nervioso o estresado? | 0 | 1 | 2 | 3 | 4 |
| 4. En el último mes, ¿con qué frecuencia ha manejado con éxito los pequeños problemas irritantes de la vida? | 0 | 1 | 2 | 3 | 4 |
| 5. En el último mes, ¿con qué frecuencia ha sentido que ha afrontado efectivamente los cambios importantes que han estado ocurriendo en su vida? | 0 | 1 | 2 | 3 | 4 |
| 6. En el último mes, ¿con qué frecuencia ha estado seguro sobre su capacidad para manejar sus problemas personales? | 0 | 1 | 2 | 3 | 4 |
| 7. En el último mes, ¿con qué frecuencia ha sentido que las cosas le van bien? | 0 | 1 | 2 | 3 | 4 |
| 8. En el último mes, ¿con qué frecuencia ha sentido que no podía afrontar todas las cosas que tenía que hacer? | 0 | 1 | 2 | 3 | 4 |
| 9. En el último mes, ¿con qué frecuencia ha podido controlar las dificultades de su vida? | 0 | 1 | 2 | 3 | 4 |
| 10. En el último mes, ¿con qué frecuencia se ha sentido al control de todo? | 0 | 1 | 2 | 3 | 4 |
| 11. En el último mes, ¿con qué frecuencia ha estado enfadado porque las cosas que le han ocurrido estaban fuera de su control? | 0 | 1 | 2 | 3 | 4 |
| 12. En el último mes, ¿con qué frecuencia ha pensado sobre las cosas que le quedan por lograr? | 0 | 1 | 2 | 3 | 4 |
| 13. En el último mes, ¿con qué frecuencia ha podido controlar la forma de pasar el tiempo? | 0 | 1 | 2 | 3 | 4 |
| 14. En el último mes, ¿con qué frecuencia ha sentido que las dificultades se acumulan tanto que no puede superarlas? | 0 | 1 | 2 | 3 | 4 |

A continuación le presentamos un cuestionario que pretende valorar la frecuencia con la que usted consume determinados tipos de alimentos. **Marque con una "X"** la casilla que corresponda. Si hay algunos alimentos que no aparecen en la lista, no se preocupe, **solo hay que tener en cuenta** los que aparecen aquí.

Tenga en cuenta las siguientes **notas aclaratorias:**

**1.-** En cereales integrales se incluye el consumo de pan, pasta, cous-cous, arroz, etc. en su forma **integral**.

**2.-** En carnes rojas y subproductos: incluir también embutidos grasos tipo chorizo, salchichón, jamón de york, etc, pero NO el pavo (el pavo no se incluye en ningún sitio).

**3.-** En lácteos enteros: incluir SOLO los que sean **enteros** (los semis o desnatados NO). El queso semicurado, de cabra, etc., sí son lácteos enteros.

**4.-** Consumo de vino: una copita de vino equivale a 75 ml.

| **CONSUMO DE ALIMENTOS (veces/MES)** | | | | | | |
|---|---|---|---|---|---|---|
| | **Nunca** | **1-4** | **5-8** | **9-12** | **13-18** | **>18** |
| **Cereales integrales** | | | | | | |
| **Patatas** | | | | | | |
| **Fruta** | | | | | | |
| **Verduras** | | | | | | |
| **Legumbres** | | | | | | |
| **Pescado** | | | | | | |
| **Carnes Rojas y Subproductos** | | | | | | |
| **Pollo** | | | | | | |
| **Lácteos enteros (queso, yogur, leche)** | | | | | | |
| **Uso de aceite de oliva para cocinar (veces/SEMANA)** | **Nunca** | **Ocasional-mente** | **<1** | **1-3** | **3-5** | **Diariamente** |
| | | | | | | |
| **Vino tinto (ml/día)** | **<300** | **300** | **400** | **500** | **600** | **>700 ó 0** |
| | | | | | | |

**Atención**: Si usted NO bebe vino, debe marcar la "X" en la casilla ">700 ó 0"

# PROTOCOLO MODIFICADO DE BRUCE

5 palieres incrementales (**3 minutos por palier**):

| Nº de Palier | Velocidad (km/h) | Inclinación (%) |
|---|---|---|
| **1** | 2.7 | 10 |
| **2** | 4 | 12 |
| **3** | 5.5 | 14 |
| **4** | 6.8 | 16 |
| **5** | 8 | 18 |

**FINALIZACIÓN DEL TEST** → Cuando la persona llega al 85% de su frecuencia cardíaca máxima teórica

(ver la tabla de FC Máxima según Edad en las hojas siguientes)

**IMPORTANTE → Apuntar el tiempo que tarda en llegar al 85% de la $FC_{máx}$.**

| EDAD | 85% FCMÁXIMA |
|---|---|
| 15 | 168 |
| 16 | 167 |
| 17 | 167 |
| 18 | 166 |
| 19 | 165 |
| 20 | 165 |
| 21 | 164 |
| 22 | 164 |
| 23 | 163 |
| 24 | 163 |
| 25 | 162 |
| 26 | 161 |
| 27 | 161 |
| 28 | 160 |
| 29 | 160 |
| 30 | 159 |
| 31 | 158 |
| 32 | 158 |
| 33 | 157 |
| 34 | 157 |
| 35 | 156 |
| 36 | 155 |
| 37 | 155 |
| 38 | 154 |
| 39 | 154 |
| 40 | 153 |
| 41 | 152 |
| 42 | 152 |
| 43 | 151 |
| 44 | 151 |
| 45 | 150 |

| EDAD | 85% FCMÁXIMA |
|---|---|
| 46 | 149 |
| 47 | 149 |
| 48 | 148 |
| 49 | 148 |
| 50 | 147 |
| 51 | 146 |
| 52 | 146 |
| 53 | 145 |
| 54 | 145 |
| 55 | 144 |
| 56 | 143 |
| 57 | 143 |
| 58 | 142 |
| 59 | 142 |
| 60 | 141 |
| 61 | 141 |
| 62 | 140 |
| 63 | 139 |
| 64 | 139 |
| 65 | 138 |
| 66 | 138 |
| 67 | 137 |
| 68 | 136 |
| 69 | 136 |
| 70 | 135 |
| 71 | 135 |
| 72 | 134 |
| 73 | 133 |
| 74 | 133 |
| 75 | 132 |
| 76 | 132 |

# BDI-II

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien | Mal (X) | Mal | Mal | Mal

CLAVE

| | | | | | |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | 2 | 2 | 2 | 2 | 2 |
| 3 | 3 | 3 | 3 | 3 | 3 |
| 4 | 4 | 4 | 4 | 4 | 4 |
| 5 | 5 | 5 | 5 | 5 | 5 |
| 6 | 6 | 6 | 6 | 6 | 6 |
| 7 | 7 | 7 | 7 | 7 | 7 |
| 8 | 8 | 8 | 8 | 8 | 8 |
| 9 | 9 | 9 | 9 | 9 | 9 |

Nº pág.

0 1 2 3 4 5 6 7 8 9

FECHA

NOMBRE.....

Este cuestionario consta de 21 grupos de enunciados. Por favor, lea cada uno de ellos cuidadosamente. Luego elija **uno** de cada grupo, el que mejor describa el modo como se ha sentido las **últimas dos semanas, incluyendo el día de hoy**. Marque el número correspondiente al enunciado elegido. Si varios enunciados de un mismo grupo le parecen igualmente apropiados, marque el número más alto. Verifique que no haya elegido más de uno por grupo, incluyendo el ítem 16 (Cambio en los Hábitos de Sueño) y el ítem 18 (Cambios en el Apetito).

**0 1 2 3**

**1. Tristeza.**

**0**= No me siento triste.
**1**= Me siento triste gran parte del tiempo.
**2**= Estoy triste todo el tiempo.
**3**= Estoy tan triste o soy tan infeliz que no puedo soportarlo.

**0 1 2 3**

**2. Pesimismo.**

**0**= No estoy desalentado respecto de mi futuro.
**1**= Me siento más desalentado respecto de mi futuro que lo que solía estarlo.
**2**= No espero que las cosas funcionen para mí.
**3**= Siento que no hay esperanza para mi futuro y que sólo puede empeorar.

**0 1 2 3**

**3. Fracaso.**

**0**= No me siento como un fracasado.
**1**= He fracasado más de lo que hubiera debido.
**2**= Cuando miro hacia atrás veo muchos fracasos.
**3**= Siento que como persona soy un fracaso total.

**0 1 2 3**

**4. Pérdida de placer.**

**0**= Obtengo tanto placer como siempre por las cosas de las que disfruto.
**1**= No disfruto tanto de las cosas como solía hacerlo.
**2**= Obtengo muy poco placer de las cosas que solía disfrutar.
**3**= No puedo obtener ningún placer de las cosas que solía disfrutar.

**0 1 2 3**

**5. Sentimiento de culpa.**

**0**= No me siento particularmente culpable.
**1**= Me siento culpable respecto de varias cosas que he hecho o que debería haber hecho.
**2**= Me siento bastante culpable la mayor parte del tiempo.
**3**= Me siento culpable todo el tiempo.

**0 1 2 3**

**6. Sentimiento de castigo.**

**0**= No siento que estoy siendo castigada.
**1**= Siento que tal vez pueda ser castigado.
**2**= Espero ser castigado.
**3**= Siento que estoy siendo castigado.

**0 1 2 3**

**7. Disconformidad con uno mismo.**

**0**= Siento acerca de mí lo mismo que siempre.
**1**= He perdido la confianza en mí mismo.
**2**= Estoy decepcionado conmigo mismo.
**3**= No me gusto a mí mismo.

# BDI-II

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien | Mal (X) | Mal | Mal | Mal

CLAVE

Nº pág.

NOMBRE.....

.....

.....

**8. Autocrítica.** 0 1 2 3

**0**= No me critico ni me culpo más de lo habitual.
**1**= Estoy más crítico conmigo mismo de lo que solía estarlo.
**2**= Me critico a mí mismo por todos mis errores.
**3**= Me culpo a mí mismo por todo lo malo que sucede.

**9. Pensamiento o deseos suicidas.** 0 1 2 3

**0**= No tengo ningún pensamiento de matarme.
**1**= He tenido pensamientos de matarme, pero no lo haría.
**2**= Querría matarme.
**3**= Me mataría si tuviera la oportunidad de hacerlo.

**10. Llanto.** 0 1 2 3

**0**= No lloro más de lo que solía hacerlo.
**1**= Lloro más de lo que solía hacerlo.
**2**= Lloro por cualquier pequeñez.
**3**= Siento ganas de llorar pero no puedo.

**11. Agitación.** 0 1 2 3

**0**= No estoy más inquieto o tenso que lo habitual.
**1**= Me siento más inquieto o tenso que lo habitual.
**2**= Estoy tan inquieto o agitado que me es difícil quedarme quieto.
**3**= Estoy tan inquieto o agitado que tengo que estar siempre en movimiento o haciendo algo.

**12. Pérdida de Interés.** 0 1 2 3

**0**= No he perdido el interés en otras actividades o personas.
**1**= Estoy menos interesado que antes en otras personas o cosas.
**2**= He perdido casi todo el interés en otras personas o cosas.
**3**= Me es difícil interesarme por algo.

**13. Indecisión.** 0 1 2 3

**0**= Tomo mis decisiones tan bien como siempre.
**1**= Me resulta más dificil que de costumbre tomar decisiones.
**2**= Encuentro mucha más dificultad que antes para tomar decisiones.
**3**= Tengo problemas para tomar cualquier decisión.

**14. Desvalorización.** 0 1 2 3

**0**= No siento que yo no sea valioso.
**1**= No me considero a mí mismo tan valioso y útil como solía considerarme.
**2**= Me siento menos valioso cuando me comparo con otros.
**3**= Siento que no valgo nada.

# BDI-II

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien | Mal (X) | Mal | Mal | Mal

CLAVE

Nº pág.

NOMBRE.....

.....

.....

**15. Perdida de Energía.** 0 1 2 3

**0**= Tengo tanta energía como siempre.
**1**= Tengo menos enrgía que la que solía tener.
**2**= No tengo suficiente energía para hacer demasiado.
**3**= No tengo energía suficiente para hacer nada.

**16. Cambios en los Hábitos de Sueño.** 0 1a 1b 2a 2b 3a 3b

**0** = No he experimentado ningún cambio en mis hábitos de sueño.
**1a**= Duermo un poco más que lo habitual.
**1b**= Duermo un poco menos que lo habitual.
**2a**= Duermo mucho más de lo habitual.
**2b**= Duermo mucho menos de lo habitual.
**3a**= Duermo la mayor parte del día.
**3b**= Me despierto 1-2 horas más temprano y no puedo volver a dormirme.

**17. Irritabilidad.** 0 1 2 3

**0**= No estoy más irritable que lo habitual.
**1**= Estoy más irritable que lo habitual.
**2**= Estoy mucho más irritable que lo habitual.
**3**= Estoy irritable todo el tiempo.

**18. Cambios en el apetito.** 0 1a 1b 2a 2b 3a 3b

**0** = No he experimentado ningún cambio en mi apetito.
**1a**= Mi apetito es un poco menor que lo habitual.
**1b**= Mi apetito es un poco mayor que lo habitual.
**2a**= Mi apetito es mucho menor que antes.
**2b**= Mi apetito es mucho mayor que lo habitual.
**3a**= No tengo apetito en absoluto.
**3b**= Quiero comer todo el tiempo.

**19. Dificultad de concentración.** 0 1 2 3

**0**= Puedo concentrarme tan bien como siempre.
**1**= No puedo concentrarme tan bien como habitualmente.
**2**= Me es difícil mantener la mente en algo mucho tiempo.
**3**= Encuentro que no puedo concentrarme en nada.

**20. Cansancio o Fatiga.** 0 1 2 3

**0**= No estoy más cansado o fatigado que lo habitual.
**1**= Me fatigo o me canso más facilmente que lo habitual.
**2**= Estoy demasiado fatigado o cansado para hacer muchas cosas de las que solía hacer.
**3**= Estoy demasiado fatigado o cansado para hacer la mayoria de las cosas que solía hacer.

**21. Pérdida de Interés en el Sexo.** 0 1 2 3

**0**= No he notado ningún cambio reciente en mi interés por el sexo.
**1**= Estoy menos interesado en el sexo de lo que solía estarlo.
**2**= Ahora estoy mucho menos interesado en el sexo.
**3**= He perdido completamente el interés en el sexo.