

RESEARCH ARTICLE

Association of objectively measured physical activity and sedentary time with arterial stiffness in women with systemic lupus erythematosus with mild disease activity

Pablo Morillas-de-Laguno^{1*}, José A. Vargas-Hitos², Antonio Rosales-Castillo³, Luis Manuel Sáez-Urán³, Cristina Montalbán-Méndez³, Blanca Gavilán-Carrera¹, Carmen Navarro-Mateos¹, Pedro Acosta-Manzano¹, Manuel Delgado-Fernández¹, José M. Sabio², Norberto Ortego-Centeno⁴, José L. Callejas-Rubio⁴, Alberto Soriano-Maldonado^{5,6}

1 Department of Physical Education and Sport, Faculty of Sport Sciences, University of Granada, Granada, Spain, **2** Systemic Autoimmune Diseases Unit, Department of Internal Medicine, “Virgen de las Nieves” University Hospital, Granada, Spain, **3** Fellows of Systemic Autoimmune Diseases Unit, Department of Internal Medicine, “Virgen de las Nieves” University Hospital, Granada, Spain, **4** Systemic Autoimmune Diseases Unit, Department of Internal Medicine, “San Cecilio” University Hospital, Granada, Spain, **5** Department of Education, Faculty of Education Sciences, University of Almería, Almería, Spain, **6** SPORT Research Group (CTS-1024), CERNEP Research Center, University of Almería, Almería, Spain

✉ These authors contributed equally to this work.

* pmorillasdelaguno@correo.ugr.es



OPEN ACCESS

Citation: Morillas-de-Laguno P, Vargas-Hitos JA, Rosales-Castillo A, Sáez-Urán LM, Montalbán-Méndez C, Gavilán-Carrera B, et al. (2018) Association of objectively measured physical activity and sedentary time with arterial stiffness in women with systemic lupus erythematosus with mild disease activity. PLoS ONE 13(4): e0196111. <https://doi.org/10.1371/journal.pone.0196111>

Editor: Xu-jie Zhou, Peking University First Hospital, CHINA

Received: October 24, 2017

Accepted: April 8, 2018

Published: April 25, 2018

Copyright: © 2018 Morillas-de-Laguno et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This work was supported by Fundación para la Investigación Biosanitaria de Andalucía Oriental, Grant numbers: PI-0525-2016 (<http://www.fibao.es/>; <http://www.ibsgranada.es/>) to JAVH. The funder had no role in study design, data

Abstract

Objectives

To examine the association of objectively measured physical activity (PA) intensity levels and sedentary time with arterial stiffness in women with systemic lupus erythematosus (SLE) with mild disease activity and to analyze whether participants meeting the international PA guidelines have lower arterial stiffness than those not meeting the PA guidelines.

Methods

The study comprised 47 women with SLE (average age 41.2 [standard deviation 13.9]) years, with clinical and treatment stability during the 6 months prior to the study. PA intensity levels and sedentary time were objectively measured with triaxial accelerometry. Arterial stiffness was assessed through pulse wave velocity, evaluated by Mobil-O-Graph® 24h pulse wave analysis monitor.

Results

The average time in moderate to vigorous PA in bouts of ≥ 10 consecutive minutes was 135.1 \pm 151.8 minutes per week. There was no association of PA intensity levels and sedentary time with arterial stiffness, either in crude analyses or after adjusting for potential

collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

confounders. Participants who met the international PA guidelines did not show lower pulse wave velocity than those not meeting them ($b = -0.169$; 95% CI: -0.480 to 0.143 ; $P = 0.280$).

Conclusions

Our results suggest that 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 the PA guidelines. Future prospective research is needed to better understand the association of PA and sedentary time with arterial stiffness in patients with SLE.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown aetiology that predominantly affects young adult women. The prognosis of SLE has improved significantly in recent decades [1] and has led to new comorbidities, such as clinical and subclinical atherosclerotic cardiovascular diseases (CVD) [2]. In fact, CVD, which are characteristically of early presentation and accelerated evolution [3], have become the main cause of mortality in this population [3].

Arterial stiffness is a marker of subclinical atherosclerosis that allows the detection of mechanical changes in the distensibility of the arteries previous to atherosclerosis development, and is a powerful predictor of CVD independently of the presence of other cardiovascular risk factors [4,5]. Arterial stiffness, measured by pulse wave velocity (PWV), is significantly increased in patients with SLE [6,7] and is associated with the development of CVD [8]. Therefore, understanding potential modifiable factors that might be associated with lower arterial stiffness in patients with SLE is of clinical and public health interest.

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 behaviour with low energy expenditure [10]. The term 'sedentary behaviour' therefore typically refers to sitting/lying behaviour rather than a simple absence of moderate-to-vigorous PA (MVPA) [10]. 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 [11]. Moreover, current physical activity guidelines, including patients with rheumatic diseases, recommend a minimum of 150 minutes of MVPA per week accumulated in bouts lasting at least 10 minutes [12]. In patients with SLE, it has been observed that low PA levels were associated with increased subclinical atherosclerosis, and more severe organ damage was associated with less PA of "low to moderate" intensity, compared to general population [13,14]. 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 of clinical and subclinical atherosclerosis [15]. Furthermore, in general population, daily sitting time or low non-exercise activity levels may have a significant direct relationship with each of these medical concerns: mortality, CVD, type 2 diabetes, metabolic syndrome risk factors and obesity [11]. 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 [16]. 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 physical activity or sedentary time (objectively

measured by accelerometry) might be associated with arterial stiffness in patients with SLE. We hypothesized that lower levels of PA and higher sedentary time would be associated with higher arterial stiffness in patients with SLE.

Therefore, the present study aimed to examine the association of objectively measured PA intensity levels and sedentary time with arterial stiffness in patients with SLE and whether participants meeting the international PA guidelines present lower arterial stiffness than those not meeting the PA guidelines.

Materials and methods

Study design and participants

In this cross-sectional study, a total of 144 women with SLE were invited to participate in the study from the Systemic Autoimmune Diseases Unit of the “Virgen de las Nieves” University Hospital or the “San Cecilio” University Hospital.

Inclusion criteria were: fulfilling ≥ 4 ACR classification criteria [17], at least 1 year of follow-up at the respective autoimmune unit and presenting clinical stability (defined as no changes in Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and/or the treatment) during the 6 months prior to the beginning of the study. Exclusion criteria were: not being able to read, understand and/or sign the informed consent, personal history of CVD in the previous year and having received a biological treatment or the need of prednisone (or equivalent) higher than 10 mg / day in the past 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 [18].

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.

Procedures

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, where sociodemographic data and clinical history were recorded, anthropometric measures and body composition were assessed, and PWV was measured. Finally, an accelerometer was given to each participant. They were asked to wear the accelerometers for the following 9 days, and were instructed on how to fill out the sleep diary.

Measurements

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 [19]. Accumulated organ damage was assessed by the Damage Index for Systemic Lupus Erythematosus (SDI) scale [20].

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 [21], 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) [22]. This device has been largely shown to be valid a reliable for measuring PWV in different populations [23,24], met the accuracy requirements of the British Hypertension Society (BHS) [25–27] standard, and can be recommended for clinical use [22].

PA levels and sedentary time. PA was objectively measured by accelerometry [28]. 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 [29]. 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 [18]. 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 [30]. 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 [31]. PA intensity levels (light, moderate and vigorous) were calculated based upon recommended PA vector magnitude cut points [29–31]: 200–2689, 2690–6166 and ≥ 6167 cpm, respectively. All values were expressed in min/day. Moderate-to-vigorous PA (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 [12]. However, recent evidence also supports health benefits with MVPA performed in bouts shorter than 10 min [32]. It was required the ActiGraph software (Actilife version 6.11.9) for data download, reduction, cleaning and analyses.

Statistical analysis

Descriptive statistics are provided as mean and standard deviation for quantitative variables and percentages for categorical variables. 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. Three adjustment models were conducted: 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 assessed 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. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 23.0 for Windows (SPSS, IBM, Armonk, NY, USA), and statistical significance was set at $P < 0.05$.

Results

The flowchart of the participants included in this cross-sectional study is presented in Fig 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

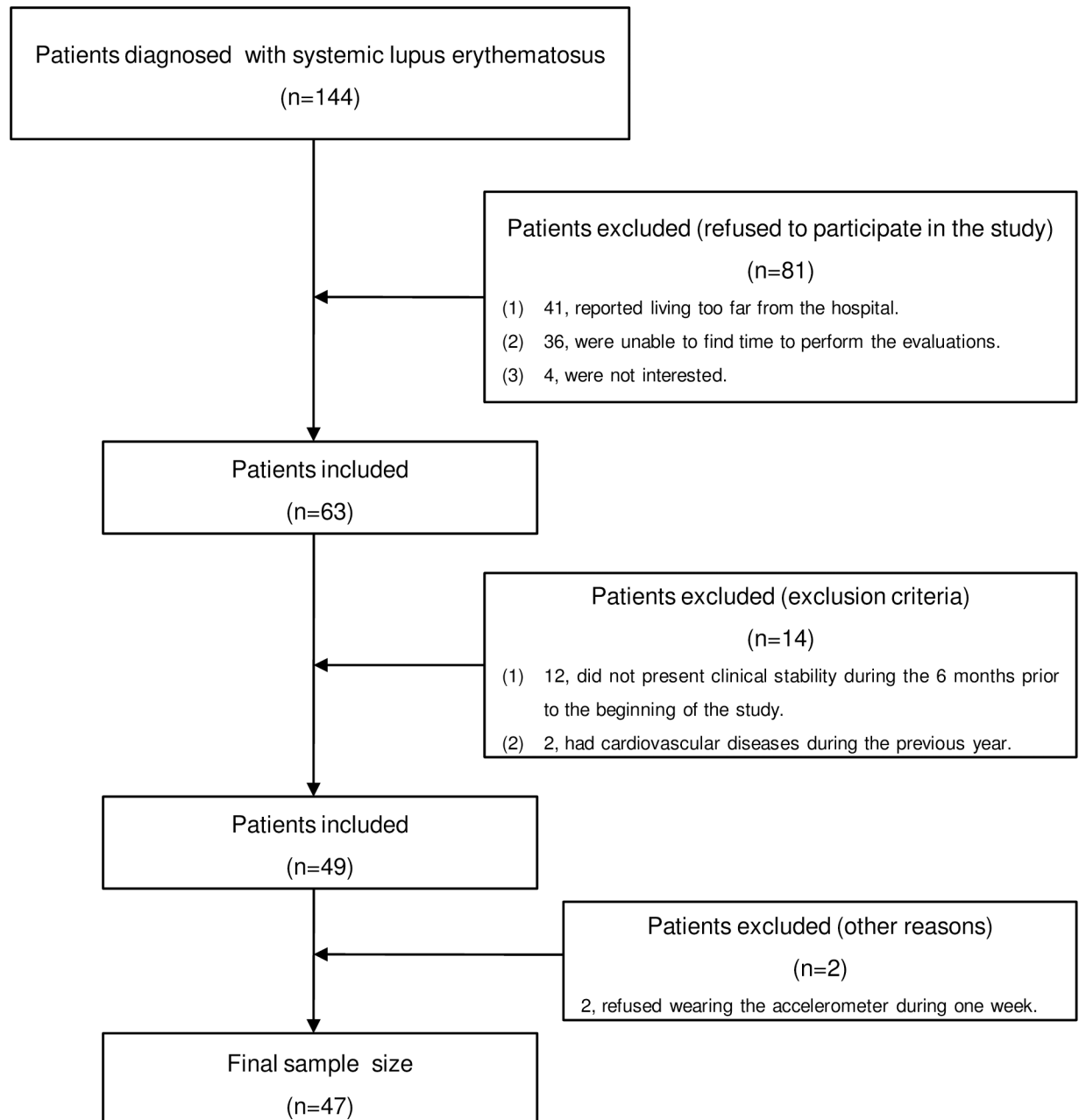


Fig 1. The flowchart of the selection of the patients with systemic lupus erythematosus with mild disease activity ($n = 47$).

<https://doi.org/10.1371/journal.pone.0196111.g001>

Table 1. Socio-demographic and clinical characteristics in women with systemic lupus erythematosus (n = 47).

Characteristics	Total (n = 47)		Meeting PA guidelines (n = 14)		Not meeting PA guidelines (n = 33)	
	n	%	n	%	n	%
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
Corticosteroids consumption (n, % yes)	33	70.2	9	64.3	24	72.7
Cumulative corticosteroids 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.

<https://doi.org/10.1371/journal.pone.0196111.t001>

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.

The sociodemographic and clinical characteristics of the study participants are presented in Table 1. The quantitative variables were presented as mean (standard deviation; SD) and the qualitative variables as frequency and percentage (n, %). Participants were, on average, 41 years old, and 45% of participants reported an educational level of no studies or secondary school. Study participants presented a SLEDAI of 1.9 (SD 3.7) and a SDI of 0.5 (SD 0.9), and a total criteria for SLE of 5 (SD 0.8). The majority of participants (96%) were consuming hydroxychloroquine. 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), although these differences were not significant.

Table 2. Physical activity intensity levels and sedentary time in women with systemic lupus erythematosus (n = 47).

Variables	Total (n = 47)		Meeting PA guidelines (n = 14)		Not meeting PA guidelines (n = 33)	
	Mean	SD	Mean	SD	Mean	SD
PA and sedentary time (min/day)						
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

SD: Standard Deviation; PA: Physical Activity; MVPA: Moderate-to-Vigorous Physical Activity.

<https://doi.org/10.1371/journal.pone.0196111.t002>

The PA intensity levels and sedentary time in women with SLE are shown in Table 2. 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 3. 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/m² and a PWV of 6.2 (SD 1.4) m/s. Participants meeting the PA guidelines presented a lower BMI (24.5 kg/m²) and body fat (32.9%) than participants not meeting the PA guidelines (26.8 kg/m² and 38.1%, respectively). Women meeting the PA guidelines presented a higher proportion of dyslipemia than those not meeting them (P = 0.026).

The association of PA intensity levels and sedentary time with PWV is shown in Table 4. 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).

Table 3. Cardiovascular risk factors in women with systemic lupus erythematosus (n = 47).

Variables	Total (n = 47)		Meeting PA guidelines (n = 14)		Not meeting PA guidelines (n = 33)		P
	Mean	SD	Mean	SD	Mean	SD	
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

SD: Standard Deviation; BMI: Body Mass Index; HTA: Hypertension.

<https://doi.org/10.1371/journal.pone.0196111.t003>

Table 4. Linear regression models examining the association of physical activity intensity levels and sedentary time with pulse wave velocity in women with systemic lupus erythematosus (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

β : standardized regression coefficient; b: non-standardized regression coefficient; CI: Confidence Interval; PA: Physical Activity; MVPA: Moderate-to-Vigorous Physical Activity.

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

¹Model 1: adjusted by accelerometer-wear time.

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

³Model 3: model 2 plus age.

<https://doi.org/10.1371/journal.pone.0196111.t004>

There was no bouts 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.

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

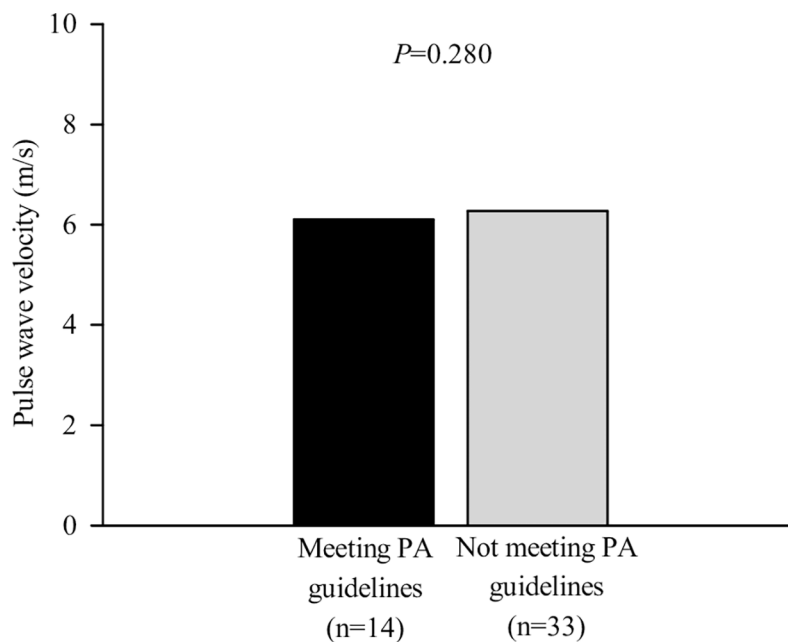


Fig 2. Average PWV (95% confidence interval) in women with SLE meeting and not meeting the PA guidelines.

<https://doi.org/10.1371/journal.pone.0196111.g002>

Discussion

The main findings of the present study indicate a lack of 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 PA for general health are well documented [33]. Parsons et al. showed that low levels of PA and high levels of sedentary time are associated with higher CVD risk among older people [34]. Furthermore, Matthews et al. evidenced that time spent in sedentary behaviours 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 [35,36]. Although the sedentary time in our study was similar to that found in the general population and in patients with Sjögren's syndrome (451.4 min/day in average) [34,37], 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 accelerometry) [38], while Mahieu et al. observed a total of 38.4 (SD 29.6) min/day of MVPA [39]. These numbers are tentative to think that in the present study, participants performed 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 [38,39], 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 [38].

There is strong evidence supporting 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 [11]. 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 of clinical and subclinical atherosclerosis [15]. 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 behaviour and many chronic diseases [40].

However, it is currently uncertain whether there is a link between the levels of PA, measured objectively 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 [37].

In SLE patients, it has been observed that more severe organ damage was associated with less PA of "low to moderate" intensity, compared to general population [14]. 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 CVD risk factors [13]. Moreover, unlike our study, subclinical atherosclerosis was assessed by intima media thickness (IMT) 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, which are associated with an increased risk for CVD in general population [16].

The use of questionnaires to assess PA levels has shown significant differences in the estimation of PA in other populations compared to an objective measure such as accelerometry

[41]. In SLE patients, accelerometer measures and IPAQ energy expenditure estimates showed a moderate agreement since individuals tend to underestimate daily walking distance, overestimate energy expenditure and overestimate time spent in MVPA with patient-reported PA instruments [38]. 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 objectively measured PA levels and sedentary time with PWV in a cohort of women with SLE. Based on previous literature in the general population [15,34–36], it was hypothesized that PA levels (inversely) and sedentary time (directly) would be associated with arterial stiffness. However, contrary to our hypothesis, the results of the study showed lack of association of either PA intensity levels or sedentary time with arterial stiffness. 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 supervised exercise training to reduce arterial distensibility in this population.

This study has limitations that might partially explain the unexpected results. The cross-sectional nature of the present study precludes establishment of causality. The participants in our study showed higher PA levels than those observed in previous studies [38,39]. Different accelerometer algorithms and/or cutoff points to determine PA intensity levels could explain these differences [18]. 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, just like the low average of SLEDAI and SDI showed. Furthermore, the women meeting the PA guidelines were older and presented a higher prevalence of comorbidities (such as dyslipidemia) than those not meeting the guidelines. This might be due to a higher degree of motivation to move, or a more intensive and strict cardiovascular recommendations by their physicians, which might have influenced our results. 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 influence on PWV.

Conclusions

Our results suggest that PA intensity levels 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. Future prospective research is needed to better understand the association of PA and sedentary time with arterial stiffness in patients with SLE.

Future research

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 [42]. Clinical trials should also address the extent to which meeting the minimum amount of aerobic exercise might positively influence arterial stiffness this population.

Supporting information

S1 File. Database.
(XLSX)

Acknowledgments

The authors would like to gratefully acknowledge all the patients who participated in the study for their collaboration and enthusiasm. We also thank Germán Prados García, nurse of the Internal Medicine Service at the Virgen de las Nieves University Hospital, for his help during the drawing blood process.

Author Contributions

Conceptualization: Pablo Morillas-de-Laguno, José A. Vargas-Hitos, Manuel Delgado-Fernández, Alberto Soriano-Maldonado.

Data curation: Pablo Morillas-de-Laguno, José A. Vargas-Hitos, Alberto Soriano-Maldonado.

Formal analysis: Pablo Morillas-de-Laguno, Alberto Soriano-Maldonado.

Funding acquisition: José A. Vargas-Hitos, Alberto Soriano-Maldonado.

Investigation: Pablo Morillas-de-Laguno, José A. Vargas-Hitos, Antonio Rosales-Castillo, Luis Manuel Sáez-Urán, Cristina Montalbán-Méndez, Blanca Gavilán-Carrera, Carmen Navarro-Mateos, Pedro Acosta-Manzano, Manuel Delgado-Fernández, José M. Sabio, Alberto Soriano-Maldonado.

Methodology: Pablo Morillas-de-Laguno, José A. Vargas-Hitos, Antonio Rosales-Castillo, Luis Manuel Sáez-Urán, Cristina Montalbán-Méndez, Blanca Gavilán-Carrera, Pedro Acosta-Manzano, Manuel Delgado-Fernández, Alberto Soriano-Maldonado.

Project administration: Manuel Delgado-Fernández, Alberto Soriano-Maldonado.

Resources: Manuel Delgado-Fernández, José M. Sabio, Alberto Soriano-Maldonado.

Software: Pablo Morillas-de-Laguno, Pedro Acosta-Manzano, Alberto Soriano-Maldonado.

Supervision: Pablo Morillas-de-Laguno, José A. Vargas-Hitos, Antonio Rosales-Castillo, Luis Manuel Sáez-Urán, Cristina Montalbán-Méndez, Blanca Gavilán-Carrera, Carmen Navarro-Mateos, Pedro Acosta-Manzano, Manuel Delgado-Fernández, José M. Sabio, Norberto Ortego-Centeno, José L. Callejas-Rubio, Alberto Soriano-Maldonado.

Validation: Pablo Morillas-de-Laguno, José A. Vargas-Hitos, Antonio Rosales-Castillo, Luis Manuel Sáez-Urán, Cristina Montalbán-Méndez, Blanca Gavilán-Carrera, Carmen Navarro-Mateos, Pedro Acosta-Manzano, Manuel Delgado-Fernández, José M. Sabio, Alberto Soriano-Maldonado.

Visualization: Pablo Morillas-de-Laguno, José A. Vargas-Hitos, Antonio Rosales-Castillo, Luis Manuel Sáez-Urán, Cristina Montalbán-Méndez, Blanca Gavilán-Carrera, Carmen Navarro-Mateos, Pedro Acosta-Manzano, Manuel Delgado-Fernández, José M. Sabio, Norberto Ortego-Centeno, José L. Callejas-Rubio, Alberto Soriano-Maldonado.

Writing – original draft: Pablo Morillas-de-Laguno, Alberto Soriano-Maldonado.

Writing – review & editing: Pablo Morillas-de-Laguno, José A. Vargas-Hitos, Blanca Gavilán-Carrera, Pedro Acosta-Manzano, Manuel Delgado-Fernández, José M. Sabio, Norberto Ortego-Centeno, José L. Callejas-Rubio, Alberto Soriano-Maldonado.

References

1. Nikpour M, Urowitz MB, Gladman DD. Premature atherosclerosis in systemic lupus erythematosus. *Rheum Dis Clin North Am*. 2005; 31(2):329–54. PMID: [15922149](https://pubmed.ncbi.nlm.nih.gov/15922149/)

2. Wu GC, Liu HR, Leng RX, Li XP, Li XM, Pan HF, et al. Subclinical atherosclerosis in patients with systemic lupus erythematosus: A systemic review and meta-analysis. *Autoimmun Rev*. 2016; 15(1):22–37. <https://doi.org/10.1016/j.autrev.2015.10.002> PMID: 26455562
3. Fors Nieves CE, Izmirly PM. Mortality in Systemic Lupus Erythematosus: an Updated Review. *Curr Rheumatol Reports*. 2016; 18(4):21.
4. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*. 2001; 37(5):1236–41. PMID: 11358934
5. Sacre K, Escoubet B, Pasquet B, Chauveheid M-P, Zennaro M-C, Tubach F, et al. Increased arterial stiffness in systemic lupus erythematosus (SLE) patients at low risk for cardiovascular disease: a cross-sectional controlled study. *PLOS ONE*. 2014; 9(4):e94511. <https://doi.org/10.1371/journal.pone.0094511> PMID: 24722263
6. Kerekes G, Soltesz P, Nurmohamed MT, Gonzalez-Gay MA, Turiel M, Vegh E, et al. Validated methods for assessment of subclinical atherosclerosis in rheumatology. *Nat Rev Rheumatol*. 2012; 8(4):224–34. <https://doi.org/10.1038/nrrheum.2012.16> PMID: 22349611
7. Sabio JM, Vargas-Hitos JA, Zamora-Pasadas M, Mediavilla JD, Navarrete N, Ramirez A, et al. Metabolic syndrome is associated with increased arterial stiffness and biomarkers of subclinical atherosclerosis in patients with systemic lupus erythematosus. *J Rheumatol*. 2009; 36(10):2204–11. <https://doi.org/10.3899/jrheum.081253> PMID: 19723903
8. Bjarnegrad N, Bengtsson C, Brodzki J, Sturfelt G, Nived O, Lanne T. Increased aortic pulse wave velocity in middle aged women with systemic lupus erythematosus. *Lupus*. 2006; 15(10):644–50. <https://doi.org/10.1177/0961203306071402> PMID: 17120590
9. Caspersen CJ, Powell KE, Christenson GM. Physical Activity, Exercise, and Physical Fitness: Definitions and Distinctions for Health-Related Research. *Public health reports*. 1985; 100(2):126–31 PMID: 3920711
10. Wilmot EG, Edwardson CL, Achana FA, Davies MJ, Gorely T, Gray LJ, et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. *Diabetologia*. 2012; 55(11):2895–905. <https://doi.org/10.1007/s00125-012-2677-z> PMID: 22890825
11. Hamilton MT, Hamilton DG, Zderic TW. Role of Low Energy Expenditure and Sitting in Obesity, Metabolic Syndrome, Type 2 Diabetes, and Cardiovascular Disease. *Diabetes*. 2007; 56(11):2655–67. PMID: 17827399
12. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: Updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007; 115(24):1423–1434.
13. Volkmann ER, Grossman JM, Sahakian LJ, Skaggs BJ, FitzGerald J, Ragavendra N, et al. Low Physical Activity Is Associated With Proinflammatory High-Density Lipoprotein and Increased Subclinical Atherosclerosis in Women With Systemic Lupus Erythematosus. *Arthritis Care Res*. 2010; 62(2):258–65.
14. Eriksson K, Svenungsson E, Karreskog H, Gunnarsson I, Gustafsson J, Möller S, et al. Physical activity in patients with systemic lupus erythematosus and matched controls. *Scand J Rheumatol*. 2012; 41(4):290–7. <https://doi.org/10.3109/03009742.2011.624117> PMID: 22651371
15. García-Hermoso A, Notario-Pacheco B, Recio-Rodríguez JI, Martínez-Vizcaino V, Rodrigo de Pablo E, Magdalena Belio JF, et al. Sedentary behaviour patterns and arterial stiffness in a Spanish adult population—The EVIDENT trial. *Atherosclerosis*. 2015; 243(2):516–22. <https://doi.org/10.1016/j.atherosclerosis.2015.10.004> PMID: 26523988
16. Kruse NT, Scheuermann BW. Cardiovascular Responses to Skeletal Muscle Stretching: “Stretching” the Truth or a New Exercise Paradigm for Cardiovascular Medicine? *Sport Med*. 2017:1–14.
17. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis and rheumatism*. 1997; 40(9):1725.
18. Migueles JH, Cadenas-Sánchez C, Ekelund Ulf, Nyström CD, Mora-González J, Löf M, et al. Accelerometer Data Collection and Processing Criteria to Assess Physical Activity and Other Outcomes: A Systematic Review and Practical Considerations. *Sports Med*. 2017.
19. Griffiths B, Mosca M, Gordon C. Assessment of patients with systemic lupus erythematosus and the use of lupus disease activity indices. *Best Pract Res Clin Rheumatol*. 2005; 19(5):685–708. <https://doi.org/10.1016/j.berh.2005.03.010> PMID: 16150398
20. Gladman DD, Urowitz MB, Rahman P, Ibanez D, Tam LS. Accrual of organ damage over time in patients with systemic lupus erythematosus. *J Rheumatol*. 2003; 30(9):1955–9. PMID: 12966597
21. Luzardo L, Lujambio I, Sottolano M, da Rosa A, Thijs L, Noboa O, et al. 24-h ambulatory recording of aortic pulse wave velocity and central systolic augmentation: a feasibility study. *Hypertension Res*. 2012; 35(10):980–7.

22. Wei W, Tölle M, Zidek W, van der Giet M. Validation of the mobil-O-Graph: 24 h-blood pressure measurement device. *Devices and technology*. 2010; 15(4):225–8.
23. Weber T, Wassertheurer S, Rammer M, Maurer E, Hametner B, Mayer CC, et al. Validation of a brachial cuff-based method for estimating central systolic blood pressure. *Hypertension*. 2011; 58:825–32. <https://doi.org/10.1161/HYPERTENSIONAHA.111.176313> PMID: 21911710
24. Weiss W, Gohlisch C, Harsch-Gladisch C, Tölle M, Zidek W, van der Giet M. Oscillometric estimation of central blood pressure: validation of the Mobil-O-Graph in comparison with the SphygmoCor device. *Blood Press Monit*. 2012; 17:128–31. <https://doi.org/10.1097/MBP.0b013e328353ff63> PMID: 22561735
25. O'Brien E, Petrie J, Littler W, de Swiet M, Padfield PL, O'Malley K, et al. The British Hypertension Society protocol for the evaluation of automated and semi-automated blood pressure measuring devices with special reference to ambulatory systems. *J Hypertens*. 1990; 8:607–619. PMID: 2168451
26. O'Brien E, Pickering T, Asmar R, Myers M, Parati G, Staessen J, et al. Working Group on Blood Pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults. *Blood Press Monit*. 2002; 7(1):3–17. PMID: 12040236
27. O'Brien E, Petrie J, Little W, de Swiet M, Padfield PL, Altma DG, et al. An outline of the revised British Hypertension Society protocol for the evaluation of blood pressure measuring devices. *J Hypertens*. 1993; 11(6):677–679. PMID: 8397248
28. Ahn GE, Chmiel JS, Dunlop DD, Helenowski IB, Semanik P a., Song J, et al. Self-Reported and Objectively Measured Physical Activity in Adults With Systemic Lupus Erythematosus. *Arthritis Care Res*. 2015; 67(5):701–7.
29. Sasaki JE, John D, Freedson PS. Validation and comparison of ActiGraph activity monitors. *J Sci Med Sports*. 2011; 14(5):411–6.
30. Choi L, Ward SC, Schnelle JF, Buchowski MS. Assessment of Wear/Nonwear Time Classification Algorithms for Triaxial Accelerometer. *Med Sci Sport Exercise*. 2012; 44(10):2009–16.
31. Aguilar-Farías N, Brown WJ, Peeters G.M.E.E. ActiGraph GT3X+cut-points for identifying sedentary behaviour in older adults in free-living environments. *J Sci Med Sports*. 2014; 17(3):293–9.
32. Glazer NL, Lyass A, Esliger DW, Blease SJ, Freedson PS, Massaro JM, et al. Sustained and shorter bouts of physical activity are related to cardiovascular health. *Med Sci Sports Exerc*. 2013; 45(1):109–115. <https://doi.org/10.1249/MSS.0b013e31826beae5> PMID: 22895372
33. Physical Activity Guidelines Advisory Committee Report, 2008. *Nutrition Reviews*. 2009; 67(2):114–20. <https://doi.org/10.1111/j.1753-4887.2008.00136.x> PMID: 19178654
34. Parsons TJ, Sartini C, Ellins EA, Halcox JPJ, Smith KE, Ash S, et al. Objectively measured physical activity, sedentary time and subclinical vascular disease: Cross-sectional study in older British men. *Prev Med*. 2016; 89:194–9. <https://doi.org/10.1016/j.ypmed.2016.05.031> PMID: 27261410
35. Matthews CE, George SM, Moore SC, Bowles HR, Blair A, Park Y, et al. Amount of time spent in sedentary behaviours and cause-specific mortality in US adults: The American Journal of Clinical Nutrition. 2012; 95(2):437–45. <https://doi.org/10.3945/ajcn.111.019620> PMID: 22218159
36. Kim Y, Wilkens LR, Park S, Goodman MT, Monroe KR, Kolonel LN. Association between various sedentary behaviours and all-cause, cardiovascular disease and cancer mortality: the Multiethnic Cohort Study. *Int. J. Epidemiol*. 2013; 42(4):1040–56. <https://doi.org/10.1093/ije/dyt108> PMID: 24062293
37. Dassouki T, Benatti FB, Pinto AJ, Roschel H, Lima FR, Augusto K, et al. Objectively measured physical activity and its influence on physical capacity and clinical parameters in patients with primary Sjögren's syndrome. *Lupus*. 2016; 26(7):1–8.
38. Ahn GE, Chmiel JS, Dunlop DD, Helenowski IB, Semanik PA, Song J, et al. Self-Reported and Objectively Measured Physical Activity in Adults With Systemic Lupus Erythematosus. *Arthritis Care Res*. 2015; 67(5):701–7.
39. Mahieu MA, Ahn GE, Chmiel JS, Dunlop DD, Helenowski IB, Semanik P, et al. Fatigue, patient reported outcomes, and objective measurement of physical activity in systemic lupus erythematosus. *Lupus*. 2016; 25(11):1–10.
40. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle. *Nat. Rev. Endocrinol*. 2012; 8:457–65. <https://doi.org/10.1038/nrendo.2012.49> PMID: 22473333
41. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003; 35(8):1381–95. <https://doi.org/10.1249/01.MSS.0000078924.61453.FB> PMID: 12900694
42. Montalbán-Méndez C, Soriano-Maldonado A, Vargas-Hitos JA, Sáez-Urán LM, Rosales-Castillo A, Morillas-de-Laguno P, et al. Cardiorespiratory fitness and age-related arterial stiffness in women with systemic lupus erythematosus. *Eur J Clin Invest*. 2018; 48(3):e12885.