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Monitoring of Sleep Indicators, Physical Activity, Pain, and Fatigue in Patients with Systemic Lupus Erythematosus and Relations among These Variables: A Pilot Study

Mitsuyo Inoue[1], Kazuko Shiozawa[2], Ryosuke Yoshihara[2], Yoshihito Shima[3], Toru Hirano[4], Kiyoko Makimoto[5]

[1]School of Nursing, Hyogo Medical University, Kobe, Japan
[2]Rheumatology & Collagen Disease Center, Hyogo Prefectural Kakogawa Medical Center, Kakogawa, Japan
[3]Laboratory of Thermo-Therapeutics for Vascular Dysfunction, Graduate School of Medicine, Osaka University, Suita, Japan
[4]Division of Rheumatology, Nishinomiya Municipal Central Hospital, Nishinomiya, Japan
[5]Graduate School of Medicine, Osaka University, Suita, Japan
Email: inoue@hyo-med.ac.jp

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Abstract

Background: Poor sleep, fatigue, and pain are major health problems in patients with systemic lupus erythematosus (SLE). However, only cross-sectional surveys on these health outcomes have been conducted, and the association between day-to-day fluctuations remains unknown. **Objectives:** We aimed to characterize daily fluctuations in sleep quality, physical activity, pain, and fatigue in patients with SLE. **Method:** Exploratory study with a cross-sectional design. Two rheumatology centers (a university hospital and a prefectural hospital) in Japan between September 2017 and May 2019. The sample size was set to 20. Demographic and clinical data were collected. Sleep and physical activity were measured with monitoring devices; pain and fatigue levels were recorded daily during the 4-week period. The Pittsburgh Sleep Quality Index, Short Form Health Survey-12, the Japanese version of the Lupus Patient Outcome, and SLE Disease Activity Index 2000 were collected at the start and end of the study. Descriptive statistics and coefficients of variation (CV) were tabulated to examine daily fluctuations. Pearson correlation coefficients were obtained for monitored variables. **Results:** The mean age was 43.7 ± 8.5 years, and the mean SLE duration was 16.0 ± 7.2 years. The mean moderate-to-vigorous physical activity (MVPA) duration was 7.8 ± 5.8 min/day, and the mean total sleep duration was 391.8 ± 65.3 min, with a mean sleep efficiency of 88.6% ± 6.1%. Daily fluctuations were high for leaving the bed frequency, MVPA duration, pain, and waking after sleep onset. Seventeen participants showed correlations between some of the variables, such as fatigue or longer MVPA duration and poorer sleep outcomes; longer sleep latency and increased frequency of leaving the bed; and higher physical activity and increased pain and fatigue. **Conclusion:** The quality of sleep and fatigue fluctuated daily, and correlations existed between these variables, as well as for pain and physical activity. The impact of MVPA duration on pain and fatigue is of concern as increased physical activity may worsen the quality of life patients with SLE. The monitoring of sleep and physical activity using the device seems feasible for SLE symptom management.

Keywords

Daily Fluctuation, Sleep Indicator, Physical Activity, Pain, Fatigue

1. Introduction

Poor sleep, fatigue, and pain are major health problems in patients with systemic lupus erythematosus (SLE) [1] [2]. The prevalence of sleep disorders ranges from 55% to 81% [3], and fatigue is reported in 67% - 90% of patients with SLE [4]. To our knowledge, four studies on the quality of sleep in patients with SLE have been conducted within the past 10 years [3] [5] [6] [7] (**Table A1**). These studies focused on the predictors of the quality of sleep measured by the Pittsburgh Sleep Quality Index (PSQI), which focuses on the quality of sleep, such as sleep latency and sleep efficiency, within the previous month [3]. Factors associated with sleep quality were pain, SLE duration, comorbidity, medication, and side effects [3] [5]. In two small-scale studies, actigraphy was used to objectively measure the quality of sleep, such as time in bed and actual sleep [6] [7].

Fatigue has become an important clinical outcome for patients with SLE [8]. Over 20 types of self-administered questionnaires have been used to measure fatigue [9], but fatigue assessment remains difficult. Pain, medication, disease activity, and mental health are contributors to fatigue [1] [8]. Poor sleep quality, obesity, and reduced physical activity are also included in the risk factors for fatigue [4].

Physical activity in patients with SLE is drawing attention in recent years as they are at high risk of cardiovascular disease [10]. Eight studies on physical activity or physical function in patients with SLE, conducted within the past 10 years, have been identified [11]-[18] (**Table A2**). Among them, five were cross-sectional studies on physical activity. Interestingly, these studies reported that patients with SLE tended to have longer sedentary hours than healthy controls or had lower activity levels than those recommended by the World Health Organization [16] [17]. Three small-scale intervention studies examined the effect of physical activity on quality of life and reported significant improvements in fatigue level, mental health, or physical functions [11] [12] [13]. The scales used to measure physical activity varied. ActiGraph GT3X was used in four studies to objectively measure physical activity. However, the ActiGraph GT3X's monitoring period is short (1 - 7 days).

These monitoring studies used the mean values of indicators to examine the association between the main outcomes (sleep or physical activity) and factors of interest. A recent systematic review on sleep consistency (day-to-day variability) and health outcomes reported that higher sleep variability was associated with adverse health outcomes, such as mental and cardiometabolic health [19]. Day-to-day variability in sleep indicators in patients with SLE has not been documented, although they have a high prevalence of sleep problems. Understanding day-to-day fluctuations in these parameters provide useful information for symptom management in patients with SLE.

The aims of this pilot study were 1) to document the daily fluctuations in the device-monitored sleep indicators and physical activity in addition to the pain and fatigue levels in patients with SLE during 4-week and, and 2) to examine how the daily fluctuations in these variables affect one another.

2. Materials and Methods

2.1. Participants

Patients were not involved in the development of the research question, the design of the study, or the selection of outcome measures.

We recruited outpatients at two rheumatology centers (a university hospital and a prefectural hospital) in western Japan between September 2017 and May 2019. Primary physicians (rheumatologists) screened outpatients who met the following eligibility criteria: 1) were adults aged ≥ 20 years and were registered in the national SLE registry program, meeting the American College of Rheumatology classification criteria for SLE, and 2) had the ability to self-administer the questionnaires in Japanese. The exclusion criteria were as follows: 1) major comorbidity that would affect quality of life (QoL), such as terminal-stage cancer; and 2) overlap with other autoimmune diseases, such as rheumatoid arthritis or fibromyalgia. The first author contacted outpatients at the clinic to explain the research protocol and obtain written informed consent.

A sample size of 12 patients was recommended for a pilot study to investigate continuous variables [20]. As we planned to investigate multiple continuous variables and since the use of monitoring devices as well as daily reporting pain and fatigue scales were demanding for the participants, the sample size was set to 20 individuals.

2.2. Instruments

2.2.1. Quality of Sleep Monitoring Device

The body vibrometer device (Nemuri SCAN, PARAMOUNT BED Co., LTD, Tokyo, Japan) objectively measured various sleep indicators. This device (78 cm × 24.5 cm, 1.5 cm high) was placed under the mattress to measure the following 11 sleep indicators [21] [22]: total sleep time [min] (total time scored as "sleep" relative to the time inside the bed), time in bed [min], sleep latency [min] (elapsed time from when the participant got into bed to the beginning of the first interval containing 10 min scored as "sleep" with not more than 1 min of wakefulness), sleep efficiency [%] (total sleep time divided by total time in bed), wake after sleep onset [min] (total time scored as "wake" during the period scored as "sleep"), frequency of leaving the bed [times], respiratory disorder index [count/hour], periodic body movement index [count/hour] (Number of times the amplitude of respiratory movement decays per hour of sleep), activity score [count/min] (the intensity and frequency of large body movements, excluding smaller movements, such as breathing and heartbeat), respiratory rate [count/min], and heart rate [count/min] [23].

2.2.2. Physical Activities

Physical activity was measured using a 3-axis accelerometer (Medi-Walk MT-KTODZ, TERUMO Co., LTD, Tokyo, Japan). The participants were asked to wear the device, except when bathing or sleeping. The following three parameters measuring physical activities were used: the number of steps, mean-to-vigorous physical activity (MVPA) [min], and total daily energy expenditure [kcal].

2.2.3. Patient-Reported Outcomes (PRO)

1) PSQI [24]: The PSQI is an 18-item self-report scale of sleep quality during the previous month. The PSQI evaluates seven components of sleep quality: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction due to poor sleep. The PSQI score ranges from 0 to 21 points.

2) The Lupus Patient-Reported Outcome—Japanese version (LupusPRO) [25]: The LupusPRO is a disease-specific QoL scale that consists of 43 items (eight health-related QoL subcategories with 30 items and four non-health-related QoL subcategories with 13 items) related to the QoL of the SLE patient's daily life during the last 4-week.

3) Short Form Health Survey-12 (SF-12) [26]: The SF-12 is a globally used, non-disease-specific QoL scale. It comprises the following eight domains: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health.

2.3. Data Collection

This was a pilot study with a cross-sectional design. The data collection was labor-intensive and required the participants' full cooperation in setting up a sleep monitoring device, wearing an accelerometer, and recording fatigue and pain levels for 4 weeks. To the best of our knowledge, this type of prospective data collection in patients with SLE has not been previously reported, and a small convenience sample is appropriate for the study objectives. The participants were asked to fill out a set of QoL questionnaires and mail them back to the first author at the beginning and end of the 4-week study period. Demographic data were obtained from the questionnaire, while clinical data were extracted from medical records. Rheumatologists evaluated the SLE Disease Activity Index 2000 (SLEDAI-2K) at the beginning and end of the 4-week study period. A flare was defined as an increase of ≥3.0 points in the total SLEDAI-2K score between the previous visit and survey data [27].

Two types of devices were given to the participants to monitor their quality of sleep and physical activity. The first author explained to the patients how to use the devices and made follow-up phone calls to enquire about any problems related to them.

2.4. Data Analysis

Descriptive statistics were obtained for all variables. Imputation was not used for missing values. To examine day-to-day fluctuations in the monitored variables, the coefficient of variation (CV) was tabulated to determine changes in physical activity and sleep indicator scores. The CV was also obtained for self-reported daily pain and fatigue. The Shapiro-Wilk test was used to test the normal distribution of all variables, as the CV uses the mean as the denominator. Spearman's rank correlation coefficients between all daily monitoring variables were calculated to explore the association between day-to-day fluctuations of some of these variables.

We grouped the participants into good and poor sleepers according to the PSQI values, using a cutoff point of ≥5.5 to categorize poor sleepers [24]. Statistical significance was set at $p < 0.05$. Correlation coefficients between the total PSQI score and subscales of the two QoL scales were obtained to examine sleep-related factors. JMP 15 software (SAS, Inc., Cary, NC, USA) was used for all statistical analyses.

3. Results

3.1. Participant Demographics

Outpatients with SLE from two rheumatology departments were screened for eligibility. A sample size of 21 outpatients was judged eligible by the primary physician; however, one patient declined to participate as she considered that it was difficult to use monitoring devices for 4 weeks. Thus, 20 eligible outpatients provided informed consent, completed self-administered questionnaires, and underwent sleep monitoring. Seventeen patients monitored physical activity for 4 weeks. Three participants failed to return the 3-axis accelerometer for measuring physical activities when returning the questionnaires and the body vibrometer device for measuring sleep indicators. The accelerometer automatically recorded null values daily, even when it was not used. Thus, physical activity data were replaced with null values by the time the researcher received the device.

Table 1 displays the demographic and clinical characteristics of the participants. Specifically, 80%, 60%, and 20% of the participants had at least a junior college education, part-time employment, and were unemployed, respectively.

Table 1. Demographic and clinical characteristics of the participants (n = 20).

Variables	Mean	(SD)
Age (mean, SD) years	43.7	(8.5)
Female (%)	95.0	
Education (mean, SD) years	14.8	(1.9)
Education attainment (%)		
<High school	0.0	
High school	20.0	
Junior College	35.0	
College	35.0	
More than college	10.0	
Living alone (%)	0.0	
Employment status (%)		
Full time employed	20.0	
Part time employed	60.0	
Unemployed	20.0	
Body mass index	21.7	(4.0)
Disease duration (mean, SD) years	16.0	(7.2)
SLEDAI-2K (mean, SD) start	5.0	(4.3)
SLEDAI-2K (mean, SD) last p = 0.33	5.4	(5.4)
moderate flare (%)	10.0	
Medications (%)		
Sleep aid	40.0	
Corticosteroids	75.0	
(Corticosteroid; PSL equivalent), mg/day (mean, SD)	6.1	(2.7)
Mycophenolate mofetil	40.0	
Cyclosporine	15.0	
Hydroxychloroquine	15.0	
PSQI (mean, SD) start	6.8	(3.1)
PSQI (mean, SD) last p = 0.28	7.1	(3.3)

SD: standard deviation; PSQI: Pittsburgh Sleep Quality Index; SLEDAI-2K: Systemic lupus erythematosus Disease Activity Index 2000.

Moreover, 60% and 50% of the participants had poor sleep quality, as measured by the total PSQI score, and had SLEDAI-2K < 4.0 points, indicating remission or a mild disease form, respectively. Approximately 75% of the participants used corticosteroids, while 40% used immunosuppressive drugs.

QoL measured using the SF-12 showed low mean scores on the general health and vitality subscales. Among the LupusPRO subscales, the social support and coping subscale scores were low (≤25).

3.2. Descriptive Statistics of 4-Week Monitoring of the Quality of Sleep Indicators, Physical Activity, Fatigue, and Pain

The descriptive statistics of the daily monitoring variables are presented in Table 2. The mean number of steps taken (range: 2287.0 - 8018.0) and MVPA duration (range: 0.0 - 19.0 minutes) showed substantial variability among participants. The majority of the participants had a mean sleep duration of <7 h. Sleep

Table 2. Descriptive statistics of daily monitoring of physical activity, quality of sleep, pain, and fatigue in this study.

Variables	Mean of the mean of each sample		Median of the median of each sample		(Min-Max)	Coefficient of variation		
	Mean	(SD)	Median	IQR		Median	IQR	(Min-Max)
Physical activities measured by accelerometer (n = 17)								
Number of steps a day	5452.6	(1923.0)	4571.0	3861.0	(2287.0 - 8018.0)	0.40	0.25	(0.25 - 1.04)
Moderate-to vigorous physical activity (MVPA) [min/day]	7.8	(5.8)	5.5	8.3	(0.0 - 19.0)	0.80	0.54	(0.38 - 2.10)
Moving distance [km/day]	3.6	(1.2)	3.1	2.4	(1.6 - 5.0)	0.38	0.24	(0.24 - 1.01)
Sleep indicators measured by body vibrometer device (n = 20)								
Total sleep time [min]	391.8	(65.3)	398.5	117.3	(217.0 - 488.0)	0.18	0.13	(0.05 - 0.50)
Time in bed [min]	443.2	(71.6)	441.5	133.1	(240.0 - 572.5)	0.18	0.14	(0.04 - 0.48)
Sleep latency [min]	18.6	(6.6)	11.0	11.8	(8.0 - 26.5)	0.59	0.16	(0.26 - 1.16)
Sleep efficiency [%]	88.6	(6.1)	91.1	4.4	(73.0 - 96.2)	0.04	0.05	(0.02 - 0.16)
Wake after sleep onset [min]	30.7	(26.5)	17.3	17.0	(2.0 - 105.5)	0.72	0.48	(0.35 - 1.29)
Frequency of leaving bed [times]	0.8	(0.8)	0.0	1.0	(0.0 - 3.0)	1.48	2.39	(0.00 - 3.74)
Respiratory disorder index [count/hour]	9.0	(3.3)	8.0	5.0	(4.4 - 15.3)	0.28	0.10	(0.20 - 0.40)
Periodic body movement index [count/hour]	7.3	(4.5)	5.6	5.7	(1.9 - 18.5)	0.53	0.26	(0.27 - 0.90)
Activity score [count/min]	40.0	(16.2)	37.7	17.9	(20.0 - 78.0)	0.26	0.12	(0.15 - 0.42)
Respiratory rate [count/min]	16.8	(1.6)	16.8	2.1	(13.9 - 20.0)	0.03	0.01	(0.02 - 0.09)
Heart Rate [count/min]	64.1	(8.6)	63.0	13.0	(45.6 - 79.4)	0.05	0.03	(0.03 - 0.11)
Pain: Visual analogue scale[a]	25.2	(25.0)	10.0	28.8	(0.0 - 75.0)	0.74	1.43	(0.00 - 3.71)
Fatigue: Four Likert scale[b]	2.8	(0.7)	3.0	1.5	(1.0 - 4.0)	0.28	0.15	(0.09 - 0.55)

SD: standard deviation; Min: minimum; Max: maximum; IQR: interquartile range; min: minute; CV: coefficient of variation; MVPA; moderate-to-vigorous physical activity; [a]: pain was recorded from 0 (none) to 100 (strong); [b]: fatigue was recorded from 1 (none) to 4 (strong).

efficiency for most participants exceeded 85%, a cutoff point for the lower normal range [28], and sleep latency for most of the participants was within the normal range of 10 - 20 min [29]. The majority of the participants did not leave the bed most of the nights (0.8 times/night). The median pain score was also low (10 out of 100 points). Regarding CV, the indicator of daily fluctuation within the individual, the greatest CV among the 11 sleep indicators was the number of times leaving the bed (1.48), followed by "waking after sleep" (0.72), and sleep latency (0.59). Most other sleep variables had a CV of <0.3. The median CV of MVPA was twice as large as that of the number of steps (0.8 and 0.40, respectively). The median CV for the pain score was much higher than that for fatigue (0.74 and 0.28, respectively). The interquartile range of CV, an indicator of variability among individuals, was the highest for "frequency of leaving bed" (2.39), followed by pain (1.43) and MVPA (0.54). In short, day-to-day variability was high for "frequency of leaving bed," pain, and MVPA within an individual as well as among individuals.

3.3. Association between Sleep Indicators, Fatigue, Pain, and Physical Activity

Table 3 shows statistically significant correlation coefficients between variables monitored daily in each participant as well as the mean and SD of these monitored variables.

The fatigue levels were moderately correlated with poor sleep quality indicators in all five participants (range: r = −0.40 to −0.52). Higher fatigue levels showed a moderate correlation with slower heart and/or respiratory rates in three participants (range: r = −0.40 to −0.50) and were correlated with elevated respiratory distress index scores in two participants (r = 0.40 and 0.61, respectively).

A longer duration of MVPA was significantly correlated with poor sleep outcomes, such as shorter sleep time (r = −0.50) (n = 1), longer sleep latency (r = 0.40 and 0.61) (n = 2), higher respiratory distress scores (range: r = 0.40 - 0.46) (n = 3), and higher heart rate (r = 0.60 and 0.62) (n = 2). In contrast, a higher number of steps was significantly correlated with better sleep outcomes, such as a lower heart rate (r = −0.41) (n = 1), respiratory distress index score, and activity score (r = −0.64, and −0.47) (n = 1). However, a higher number of steps was associated with worse pain (range: r = 0.52 - 0.63) and fatigue scores (range: r = 0.41 - 0.54) (n = 3).

Higher pain scores showed moderate correlations with higher physical activity levels in three participants and positive correlations with respiratory and/or cardiovascular system indicators in two. In contrast, negative correlations between pain scores and respiratory indicators or activity scores were observed in three participants. These statistically significant associations were even observed in participants with lower mean pain scores (<20 points). In short, 28-day monitoring revealed individual differences in the impact of daily fluctuations in physical activity level and/or fatigue on the quality of sleep.

Table 3. Correlation coefficients between factors related to daily fluctuations in fatigue in each participant and descriptive statistics (n = 20).

ID	*Age*	*Employment status*	*Correlation coefficient* (p < 0.05)				*Number of steps (No. of steps)*	*SLEDAI-2K*	*Sleep aid Yes (Y), No (N)*	*Corticosteroids* [g/day]	*MVPA* [min]	*Total sleep time (ST)* [*min*]	*Sleep efficiency (SE)* [*%*]	*Out-of-bed* [times]	*Respiratory disorder index (RDI)* [*count/hour*]	*Activity score (AS)* [*count/min*]	*Pain*	*Fatigue*	*PSQI score*
			Pain	*Fatigue*	*No. of steps*	MVPA													
1	47	Part time	-	-	-	-	8328.7 (5476.6)	0	N	7.0	11.0 (10.8)	379.4 (73.8)	85.1 (8.1)	0.6 (1.1)	6.2 (2.1)	53.4 (18.4)	17.1 (12.5)	3.1 (0.8)	8
2	55	Part time	-	-	-	-	8175.9 (2937.8)	0	Y	0.7	10.3 (6.6)	309.6 (70.5)	73.4 (7.1)	1.2 (1.4)	8.9 (2.1)	77.6 (15.4)	36.3 (25.5)	3.1 (1.0)	11
3	44	Part time		ST (−0.48)	HR (−0.41)		7626.4 (2652.9)	1	Y	3.0	17.8 (13.2)	426.4 (74.5)	91.7 (3.0)	0.9 (0.6)	6.7 (2.0)	30.7 (7.6)	0.7 (2.6)	3.3 (0.7)	9
4	51	Part time	MVPA (0.56) No. of steps (0.52)	MVPA (0.51) No. of steps (0.42)	Pain (0.52) Fatigue (0.42)	RDI (0.43) HR (0.62) Pain (0.56) Fatigue (0.51)	7538.0 (2539.3)	1	N	5.0	19.9 (13.5)	321.3 (80.1)	91.5 (3.2)	0.7 (0.7)	6.1 (1.6)	27.4 (6.6)	6.9 (13.5)	2.0 (1.1)	2
5	48	Part time	MVPA (0.62) No. of steps (0.63) Fatigue (0.50)	MVPA (0.46) No. of steps (0.49) Pain (0.50)	ST (−0.47) Pain (0.63) Fatigue (0.49)	ST (−0.50) Pain (0.62) Fatigue (0.46)	7399.0 (4537.5)	2	N	4.0	14.2 (13.9)	314.5 (49.1)	93.4 (2.3)	0.0 (0.0)	7.9 (3.0)	24.5 (6.2)	90.0 (10.4)	3.6 (0.5)	11
6	25	Full time		No. of steps (0.41)	Fatigue (0.41)	SL (0.40)	7134.6 (2005.6)	2	N	5.0	10.0 (3.7)	283.5 (139.5)	88.6 (5.0)	0.1 (0.3)	10.8 (3.1)	41.0 (12.2)	2.5 (9.1)	3.1 (0.6)	9
7	41	Part time	Out-of-bed (0.80) RDI (−0.36)				6247.8 (1477.2)	0	N	7.5	4.6 (2.4)	364.0 (87.5)	91.0 (4.1)	0.1 (0.3)	12.3 (4.5)	38.8 (10.3)	11.1 (3.1)	2.0 (1.1)	3
8	32	Part time	-	-	-	-	4951.6 (4410.4)	8	Y	10.0	6.4 (6.1)	475.9 (68.6)	84.2 (6.2)	2.4 (1.1)	7.0 (1.8)	46.7 (15.4)	32.9 (33.2)	3.1 (0.8)	10
9	40	Part time		RDI (0.40)		RDI (0.46)	4925.9 (1572.9)	10	N	6.0	3.3 (2.2)	470.7 (59.5)	91.2 (3.3)	0.2 (0.4)	10.6 (2.1)	40.4 (6.0)	25.0 (16.1)	3.0 (0.3)	5
10	53	NA	AS (−0.48)			HR (0.60)	4639.3 (1811.6)	16	Y	10.0	3.9 (3.5)	337.8 (75.0)	88.9 (6.7)	0.9 (1.5)	6.8 (1.9)	31.3 (11.5)	66.4 (29.1)	3.6 (0.8)	12

Continued

11	46	Part time				RDI (0.40)	4577.3 (2224.1)	6	Y	0.0	10.5 (7.5)	425.1 (64.3)	93.7 (2.7)	0.2 (0.4)	4.3 (1.0)	31.7 (6.6)	53.2 (18.1)	2.7 (0.9)	10
12	53	Part time	RR (−0.38)		Out-of-bed (0.58)	SL (0.39)	4424.6 (1461.8)	0	N	0.0	1.6 (1.1)	455.3 (46.3)	95.7 (1.7)	0.1 (0.3)	13.1 (2.8)	25.2 (5.6)	53.2 (18.1)	3.1 (0.9)	2
13	41	Part time		RR (−0.45) HR (−0.50)			4364.6 (2467.1)	12	Y	0.0	10.6 (7.9)	377.8 (108.4)	72.1 (11.8)	3.3 (3.1)	16.2 (5.9)	82.2 (31.0)	0.0 (0.0)	1.8 (0.9)	8
14	53	Full time	RDI (0.42)	ST (0.49) RR (−0.40)			3747.3 (2051.4)	4	Y	7.5	2.2 (3.9)	402.8 (21.9)	90.8 (3.5)	0.1 (0.3)	9.2 (1.9)	42.5 (8.7)	16.6 (11.7)	3.1 (0.8)	9
15	42	NA	MVPA (0.38) No. of steps (0.53) Fatigue (0.38)	MVPA (0.51) No. of steps (0.54) Out-of-bed (0.44) Pain (0.38)	Pain (0.53) Fatigue (0.54)	Pain (0.38) Fatigue (0.51)	3039.2 (1175.3)	3	N	3.0	1.8 (4.0)	476.7 (29.5)	91.6 (2.9)	1.3 (1.0)	7.2 (1.4)	31.4 (5.2)	8.6 (16.4)	1.4 (0.5)	4
16	48	NA	Fatigue (0.49)	Pain (0.49)	RDI (−0.64) AS (−0.47)		2890.3 (1124.3)	2	N	0.0	1.8 (2.4)	338.3 (61.6)	91.0 (2.0)	1.0 (0.6)	13.9 (3.4)	25.1 (6.0)	14.0 (10.1)	3.3 (0.5)	8
17	48	NA		SE (−0.37)			2683.5 (1564.7)	4	Y	7.5	2.6 (3.9)	478.5 (59.4)	89.7 (1.9)	1.0 (0.2)	4.9 (1.1)	37.6 (4.6)	46.4 (25.4)	3.1 (0.9)	8
18	43	Part time		ST (−0.52) RDI (0.61) HR (0.51)	NA	NA	NA	18	N	10.0	NA	417.7 (113.8)	92.2 (4.7)	1.2 (1.6)	9.1 (3.1)	22.4 (9.4)	4.6 (8.7)	2.8 (0.8)	5
19	37	Full time	RR (0.60) HR (0.56)	Out-of-bed (0.39)	NA	NA	NA	12	N	5.0	NA	462.0 (1461.8)	91.0 (2.0)	0.2 (0.6)	13.4 (3.3)	41.9 (8.6)	14.6 (9.8)	3.1 (0.9)	2
20	26	Full time	Fatigue (0.52)	Pain (0.52) RR (−0.43)	NA	NA	NA	6	N	0.0	NA	322.7 (60.7)	86.1 (6.1)	0.9 (1.5)	6.3 (2.1)	48.6 (12.8)	4.3 (11.5)	1.6 (0.9)	5

SLEDAI-2K, systemic lupus erythematosus disease activity index 2000; MVPA, moderate-to-vigorous; PSQI, Pittsburgh Sleep Quality Index; NA, not applicable; SL, sleep latency; RR, respiratory rate; HR, heart rate; letters in blue, sleep indicators; letters in red, pain and fatigue.

Figure 1 illustrates the daily fluctuations in the number of steps/100, pain score, and sleep time in minutes in identification number 5 (ID 5). The number of steps was converted to per 100 steps to use the same second X-axis as the pain score. The increased number of steps was job-related, and the peaks in the pain score seemed to correspond to the number of steps. To a lesser extent, sleep time tended to be lower when the number of steps peaked.

Higher fatigue levels were moderately correlated with higher activity levels (MVPA or the number of steps/day) in four participants (range: r = 0.41 - 0.54) and were associated with higher pain levels in three participants (range: r = 0.42 - 0.60). Negative correlations between the fatigue level and the respiratory/cardiovascular systems were observed in three participants (range: r = −0.40 - −0.50).

As a summary of the correlations between variables, a conceptual framework of the associations among the four daily measured factors is presented in Figure 2. Fatigue levels in the evening and physical activity levels during the day were significant predictors of sleep quality. Predictors of fatigue were pain and physical activity levels in four participants, and these three factors were correlated with each other in three participants. To a lesser extent, pain level was a predictor of the quality of sleep.

3.4. Association between Sleep Indicators, Fatigue, Pain, and Physical Activity

The total PSQI score at the end of the monitoring period was significantly and negatively correlated with four SF-12 subscales (role physical, role emotional, vitality, and mental health) (range: r = −0.57 to −0.67). It was also associated with three LupusPRO subscales (cognition, physical health, pain, and vitality) (range: r = −0.51 to −0.57) (Table 4). Regarding the daily monitored variables,

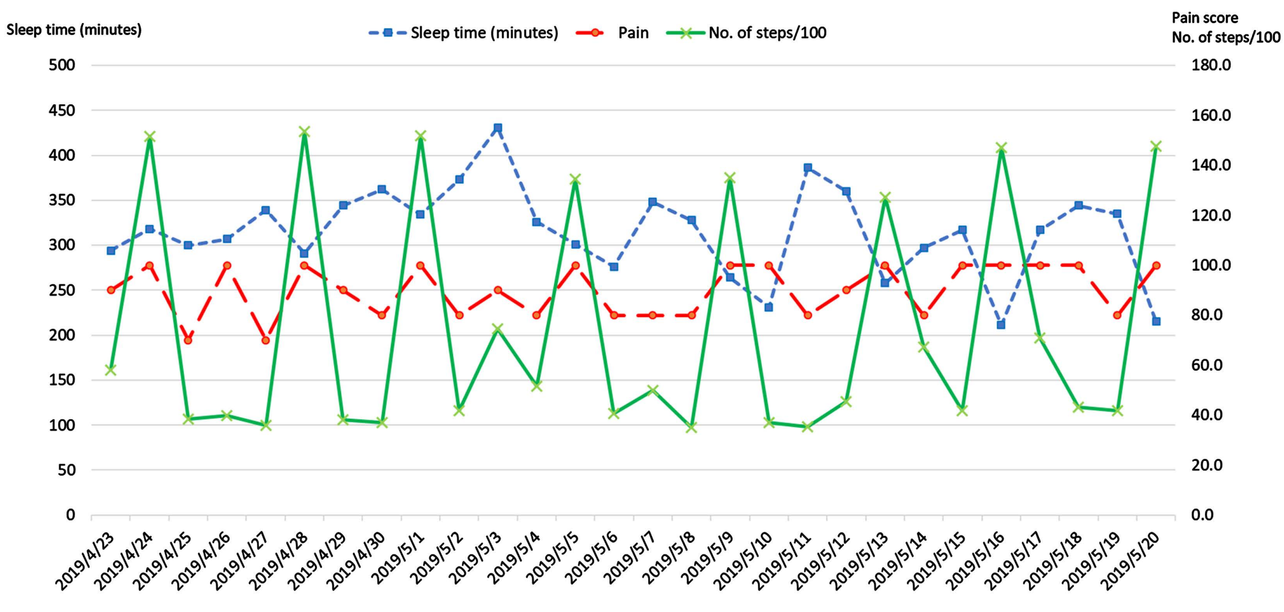

Figure 1. Daily fluctuations in the number of steps/100, pain score, and sleep time in minutes for ID 5.

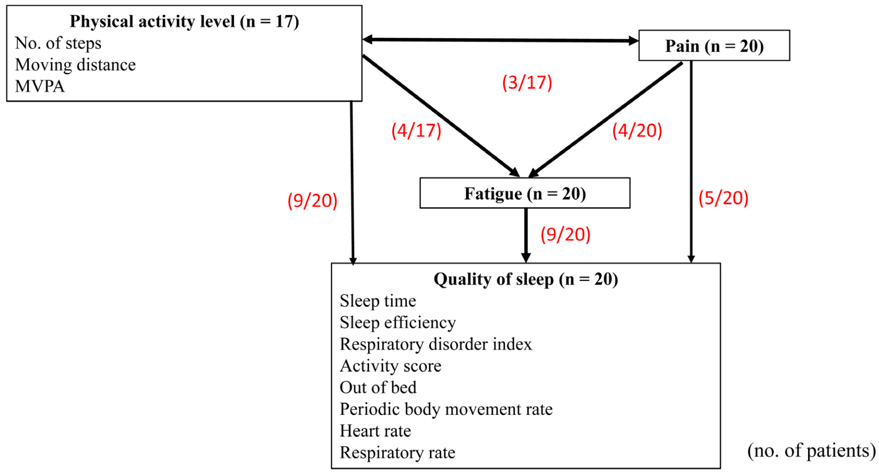

Figure 2. Conceptual framework of association among the four factors measured daily. No. of steps, number of steps, MVPA, moderate-to-vigorous physical activity.

Table 4. Descriptive statistics of PSQI and QoL (SF-12 and LupusPRO) and correlation between PSQI and QoL (n = 20).

Subscale of QoL instrument	Mean	(SD)	Correlation between PSQI and QoL domain	
			Coefficient	p value
		SF-12		
General Health	44.5	(21.8)	−0.31	0.190
Physical Function	73.8	(31.9)	−0.25	0.284
Role Physical	68.1	(26.1)	−0.63	0.003
Role Emotional	71.3	(28.1)	−0.67	0.001
Bodily Pain	70.0	(28.8)	−0.36	0.118
Vitality	50.0	(30.4)	−0.57	0.009
Mental Health	65.0	(22.1)	−0.59	0.006
Social Function	77.5	(29.1)	−0.39	0.091
		LupusPRO		
Lupus Symptoms	84.6	(18.8)	0.24	0.304
Cognition	85.6	(23.4)	−0.57	0.009
Lupus Medications	65.6	(32.2)	−0.22	0.350
Procreation	70.0	(43.8)	0.09	0.691
Physical Health	85.5	(17.1)	−0.56	0.010
Pain/Vitality	71.0	(24.6)	−0.51	0.021
Emotional Health	62.9	(29.0)	−0.24	0.311
Body Image	71.3	(28.6)	−0.32	0.174
Desires/Goals	72.2	(30.8)	−0.43	0.058
Social Support	16.9	(20.0)	0.33	0.157
Coping	25.0	(22.9)	0.37	0.104
Satisfaction with Care	54.7	(34.0)	0.40	0.080

PSQI: Pittsburgh Sleep Quality Index; QoL: quality of life; SD: standard deviation; SF-12: short-form health survey-12; LupusPRO, lupus patient-reported outcome.

the total PSQI score was positively correlated with the mean and median fatigue levels (r = 0.62, p = 0.004; r = 0.65, p = 0.002, respectively) in the 4-week period and was positively correlated with the CV of the mean number of steps (r = 0.53, p = 0.036). In short, the total PSQI score was negatively moderately correlated with the QoL and positively moderately correlated with fatigue and the mean number of steps.

4. Discussion

The current study examined day-to-day fluctuations in sleep indicators, physical activity level, pain, and fatigue and explored the association between these monitored variables among patients with SLE. The changes measured by CV were large for the frequency of leaving the bed, duration of MVPA, pain score, and waking after sleep onset in minutes. In nearly half of the participants, fatigue and MVPA duration were major factors associated with sleep duration and cardiopulmonary indicators at night. Physical activity, fatigue, and pain were correlated in less than a quarter of the participants.

The correlations between the fatigue levels measured in the evening and poor sleep outcomes are at variance with previous studies on fatigue, which suggest that poor quality of sleep itself is one of the contributory factors to fatigue [1] [4]. However, previous studies using instruments, such as the PSQI and the daily fluctuations in sleep indicators, were not examined. Our cross-sectional data using the PSQI are in agreement with review findings [1] [4], showing a negative association between the total PSQI score and the vitality subscale scores measured using SF-12 and LupusPRO.

The number of participants with significant correlations between pain, fatigue, and/or sleep quality is limited. Pain is regarded as a significant contributor to fatigue in patients with SLE as well as inflammation, corticosteroid use, and mental health issues [1] [4] [8]. Most participants had low mean pain scores, consistent with the fact that pain can be controlled more easily than fatigue. Detailed information on the use of pain medications was not available.

Corticosteroids are one of the contributors to fatigue [1] [4], and most participants were on corticosteroids. Nevertheless, the medication dosage does not change daily and is unlikely to affect the day-to-day fatigue levels. All participants were in a non-flare state, and inflammation itself was unlikely to affect the day-to-day fatigue level.

The moderate correlations between physical activity level and the other monitored variables in our study suggest that increased physical activity was detrimental to the physical and mental health of some participants. None of our participants attained the goal recommended by the WHO [30], and the MVPA duration in our study was one-third of that reported in North American studies [14] [16]. An exercise program is reported to be beneficial in reducing fatigue and improving mental health and cardiorespiratory capacity [31], although the evidence level is low. Caution is necessary to apply study findings to the clinical setting because patients participating in randomized control trials may not represent those in real-world settings. In conclusion, our findings suggest the need for daily monitoring of physical activity, fatigue, and pain before exercise is recommended.

The number of steps taken seems to have an impact on the pain, fatigue, and quality of sleep indicators in some participants. This appears to affect sleep indicators that differ from MVPA duration. Our participants' short duration of MVPA implies that most of the physical activity was of light intensity. Light-intensity physical activity is associated with reduced cardiometabolic risk factors and mortality [32] [33]. However, evidence for the appropriate level of light-intensity activity has not been established. Caution is necessary when increasing the number of steps because some participants showed positive correlations between the number of steps and increased pain, fatigue, and worse sleep indicators.

A moderate correlation between fatigue and physical activity level was observed, even in participants with low physical activity levels. This phenomenon may represent the concept of susceptibility to fatigue proposed by Cleanthous *et al.* [34]. Patients with SLE report a sudden onset of exhaustion after performing the minimal activity, such as taking a shower, which is defined as fatigue "disproportionate to the degree of activity or effort expended." Further studies are needed to understand the patterns of exhaustion onset for symptom management.

Some of the sleep indicators used in our study are not well documented. For example, only small-scale studies have reported respiratory distress index and activity scores [35] [36]. The mean activity score in our study is similar to a variable used for adults with sleep disorders [36] and was much higher than that in young adults [35]. As these two sleep indicators show significant correlations with pain, fatigue, and physical activity levels, future studies should explore the potential causal associations between them.

The association between physical activity and cardiopulmonary indicators was an unexpected finding. Heart and respiratory rates were measured only when participants were lying in bed. Future studies are needed to monitor 24-h changes in vital signs to examine the effects of MVPA on the cardiovascular and respiratory systems using smartwatch-type monitoring devices.

Various sleep indicators in our study showed correlations with physical activity and/fatigue level. Genetic and environmental factors probably account for individual variability. Genetic research has revealed the link between the clock genes and multiple health outcomes such as sleep disorders, hypertension, and metabolic disorders [37] [38]. Further, the clock genes modulate melatonin, which in turn affects the inflammatory pathways in patients with rheumatoid arthritis [38]. Studies are underway to examine the impact of time of medicine that affects disease outcomes, such as cardiovascular events or joint diseases. [38] [39]. For patients with RA, bedtime administration of corticosteroid is reported to reduce joint pain by reducing inflammation. For patients with SLE, self-monitoring of sleep indicators, physical activity, and fatigue may help identify factors that affect the quality of sleep and fatigue for symptom management.

5. Conclusions

We examined the day-to-day fluctuations in physical activity, pain, fatigue, and sleep indicators. Daily changes measured by CV were high for the frequency of leaving the bed, followed by MVPA duration, pain score, and duration of awakening after waking at night. Fatigue was a significant predictor of poor sleep. Among the two physical activity indicators, MVPA duration was associated with poor sleep outcomes. A longer MVPA duration was significantly correlated with shorter sleep time and increased cardiopulmonary output at night.

In contrast, a higher number of steps was associated with better cardiopulmonary outcomes at night in two participants. An association between fatigue, pain, and physical activity level was observed in several participants. The current study illustrates the importance of daily monitoring of physical activity, sleep quality, pain, and fatigue levels to examine the relationship between these variables for symptom management after a recommended monitoring duration of 4 weeks.

6. Limitations of This Study

The major limitation of this study was the small sample size, and type II errors were expected. However, the obtained correlations among well-known QoL scale data are consistent with those of previous studies, showing that the total PSQI score was correlated with the SF-12 and the LupusPRO subscales related to mental and physical health [1] [8]. The fatigue scale was based on a 4-point Likert scale, which may limit the classification of fatigue variability. Nevertheless, higher mean and median fatigue levels were associated with higher total PSQI scores and were considered adequate for this pilot study.

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Ethics Approval

This study was approved by the Ethics Committee of Hyogo Medical University and the two rheumatology centers (IRB no. 17012). At the initial contact with the participants, the first author provided a verbal and written explanation to confirm their willingness to participate. After obtaining written informed consent, the first author distributed a set of questionnaires and measurement devices.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix

Table A1. Studies of quality of sleep in patients with SLE.

Reference	Country	Objective	Study design	Scale for data collection: Sleep measurement	Scale for data collection: Scales to measure QoL, fatigue, and pain	Patients with SLE	Control group	SLEDAI mean ± SD	Main Results
[3]	Japan	1) To examine fluctuations in sleep quality at 2-week intervals; 2) To predict sleep quality measured by a SLE-specific QOL scale	Cross-sectional observational study × 2	Pittsburgh sleep quality index	• 12-Item Short-Form Health Survey (vitality domain) • LupusPRO	205 (Women 91.8%)	NA	3.9 ± 3.7	1) Low agreement rates for the PSQI-sleep latency and waking-up problems 2) LupusPRO-pain/vitality as a significant predictor of sleep quality
[5]	Turkey	To assess sleep quality and factors affecting sleep quality in patients with SLE.	Cross-sectional observational study	Pittsburgh sleep quality index	Patient description form (sociodemographic characteristics and characteristics relating to the disease and its effect.	105 (Women 93.3%)	NA	NA	1) Factors associated with sleep quality: duration of illness, presence of comorbidities, medication side effects, and sleep disturbances. 2) Sleep disturbances were significant predictors of the total PSQI score
[6]	Spain	To examine sleep quality measured by actigraphy and mobile systems.	A cross-sectional observational study (7-day monitoring)	• Pittsburgh sleep quality index, • Actigraphy	• Lupus Symptom Inventory • LupusQoL • McGill Pain Questionnaire-Short Form • Multidimensional Fatigue Inventory • Hospital Anxiety and Depression Scale	9 (Women)	11 (Healthy women)	NA	1) The SLE group had poorer sleep quality (sleep duration, sleep latency, subjective sleep quality, and use of sleeping medication) than the healthy controls. 2) Actigraphic measurements showed no significant differences between patients with SLE and healthy controls.

Continued

[7]	Spain	To compare sleep quality among three groups (FM, SLE, and healthy control) and to examine factors associated with sleep	Cross-sectional observational study (7-day monitoring)	• Pittsburgh sleep quality index • Actigraphy	• Multidimensional Fatigue Inventory • Hospital Anxiety and Depression Scale • McGill Pain Questionnaire-Short Form	19 (Women)	20 (Women with FM) 22 (Healthy women)	2.8 ± 3.1	1) Significant correlations between pain and sleep latency (−0.53, p < 0.05) and sleep disturbances 0.47, p < 0.05), depression and daytime sleepiness (0.49, p < 0.05) in patients with SLE. 2) Significant correlations between the PSQI and actigraphic measures (sleep latency and sleep efficiency) in patients with SLE

SLEDAI: Systemic Lupus Erythematosus Disease Index; SD: Standard Deviation; NA: Not Applicable; SLE: Systemic Lupus Erythematous; FM: Fibromyalgia.

Table A2. Studies of physical activity (PA) in patients with SLE.

Reference	Country	Objective	Study design	Scale for data collection		Patients with SLE	Control group	SLEDAI mean ± SD	Main results
				Sleep measurement	Other variables				
[11]	Taiwan	Evaluating the effect of PA counseling on PA and the association between PA changes and changes in fatigue, quality of sleep, and QoL	RCT (3 sessions of PA counseling at 1, 4, and 8 weeks and 3 telephone follow-ups over 13 weeks.	ActiGraph GT3X	• Fatigue Severity Scale • 36-Item Short-Form Health Survey • Pittsburgh sleep quality index	Stat point (38) Endpoint (31)	Stat point (38) End point (28)	Intervention group: 2.8 ± 2.0#; Control group: 3.4 ± 2.7#	1) Significant improvements in daily steps, quality of sleep, and vitality in the intervention group when compared with those in the control group at weeks 8 and 12. 2) A positive correlation between PA changes and changes in vitality and mental health

Continued

[12]	Egypt	To compare the effect of aerobic exercise with stretching and strengthening exercise on fatigue and PA in patients with SLE.	Invention study (50-min session × 3/week for 3 months)	• 6-min Walk Test (6 MWT) • 2-min (Min) step test • 30 S. chair stand test	• Fatigue Severity Scale • 36-Item Short-Form health Survey • Self-rating Depression Scale	40 Women Group 1: aerobic exercise (20), Group 2: strengthening exercise (20)	NA	NA	1) Significant improvements in SDS, SF-36, FSS, and physical functions (6 MWT and 2-min step test) in both groups 2) Both exercise methods were useful for improving fatigue, depression, and physical functions
[13]	Spain	To evaluate the effects of aerobic exercise on PROs and cardiopulmonary fitness	RCT (two aerobic sessions/ week for 2 weeks)	Cardiorespiratory fitness: The Bruce submaximal treadmill protocol	• Perceived Stress Scale • Pittsburgh sleep quality index • Multidimensional Fatigue Inventory • Beck Depression Inventory-second edition • 36-Item Short-Form Health Survey	Stat point (26) Endpoint (18)	Stat point (32) Endpoint (28)	Intervention group: 0.04 ± 0.20#; Control group: 0.34 ± 1.18#	Significant improvements in general fatigue and physical fatigue among the exercise group
[14]	USA	To examine the relationships between fatigue, other health status measures assessed with the PROM Information System instruments, and accelerometer-based PA measurements.	Cross-sectional observational study (7-day monitoring)	ActiGraph GT3X	• Patient Reported Outcomes Measurement Information System • Fatigue Severity Scale	123	NA	2.3 ± 2.8	1) Significant weak negative correlation between MVPA duration and the fatigue level 2) Significant weak positive correlation between MVPA duration and physical function 3) Significant negative correlation between MVPA duration and pain

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[15]	Spain	To compare the sedentary time between those who were physically active and those who were inactive based on the international PA guidelines	A cross-sectional observational study (1-day monitoring)	ActiGraph GT3X	• Heart rate (Mobil-O-Graph®) • Cardiovascular risk factors (waist/hip ratio, Body Mass Index, Tabaco consumption, hypertension, dyslipidemia, diabetes, and obesity)	47 women: active were those who met PA guidelines (14); inactive were those who failed to meet PA guidelines (33)	NA	Active: 1.6 ± 1.9 Inactive: 0.9 ± 1.7	1) Significant differences in the mean MVPA duration between the inactive (38.2 ± 17.7) and active (69.4 ± 48.1) groups. 2) Dyslipidemia was the only cardiovascular risk factor that differed significantly between active and inactive participants
[16]	Canada	To compare the PA levels among patients with SLE, patients with RA, and healthy participants	Cross-sectional observational study (7-day monitoring)	• ActiGraph GT3X • Framingham Physical Activity Index	• 36-Item Short-Form Health Survey • Health Assessment Questionnaire	20	RA (19) Healthy controls (20)	2.9 ± 2.1#	1) All three groups demonstrated longer sedentary hours (10.1 ± 1.3 h/day) 2) The mean MVPA duration for patients with SLE was significantly lower than that of the other two groups
[17]	Italy	Evaluating the proportion of patients with SLE who did not meet the WHO recommendations for PA and to evaluate the amount of time spent in sedentary behavior.	Cross-sectional observational study	International Physical Activity Questionnaire	• Functional Assessment of Chronic Illness Therapy-Fatigue • 36-Item Short-Form Health Survey • Beck Depression Inventory • Pittsburgh sleep quality index	93	NA	4.5 ± 5.0	1) 60% of the 93 patients did not meet the WHO recommended MVPA duration (>150 min/week) 2) 25% of the patients had sedentary time > 6 h/day. 3. Significant high correlation between sedentary hours and fatigue score

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[18]	Turkey	To investigate the relationship between kinesiophobia (excessive fear of movement or physical activity) and the level of PA, depression, disease activity, fatigue, pain, and QoL	Cross-sectional observational study	International Physical Activity Questionnaire	• Fatigue Severity Scale • Beck Depression Inventory • McGill Pain Questionnaire-Short Form • Nottingham Health Profile	69	NA	9.5 ± 5.2	1) Two-thirds of SLE patients had a kinisiophobia. 2) Significant weak correlations between kinisiophobia and quality of life (depression, r = 0.33; social isolation, r = 0.35; emotional reactions, r = 0.435).

SD: Standard Deviation; NA: Not Applicable; SLE: Systemic Lupus Erythematous; SLEDAI: Systemic Lupus Erythematosus Disease Index; RCT: Randomized Controlled Trial; RA: Rheumatoid Arthritis; MVPA: Moderate-to-Vigorous PA; WHO: World Health Organization. #SLEDAI-2K: Systemic Lupus Erythematosus Disease Index 2000.