



Systemic Lupus Erythematosus and the Evaluation of Poor Sleep (SLEEPS): A Prospective Longitudinal Study

Philip Chu¹, Alicia Hinze², Nancy Mathis¹, Lacey Feigl¹, Ashley Peterson¹, Noor Al-Hammadi³, Deepali Sen¹, Seth Eisen¹, Yo-el Ju⁴, Alfred H. Kim¹

¹Department of Medicine, Division of Rheumatology, Washington University, St Louis, MO, ²Division of Rheumatology, Johns Hopkins University, Baltimore, MD

³Division of Biostatistics, ⁴Department of Neurology, Division of Sleep Medicine, Washington University, St Louis, MO



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INTRODUCTION

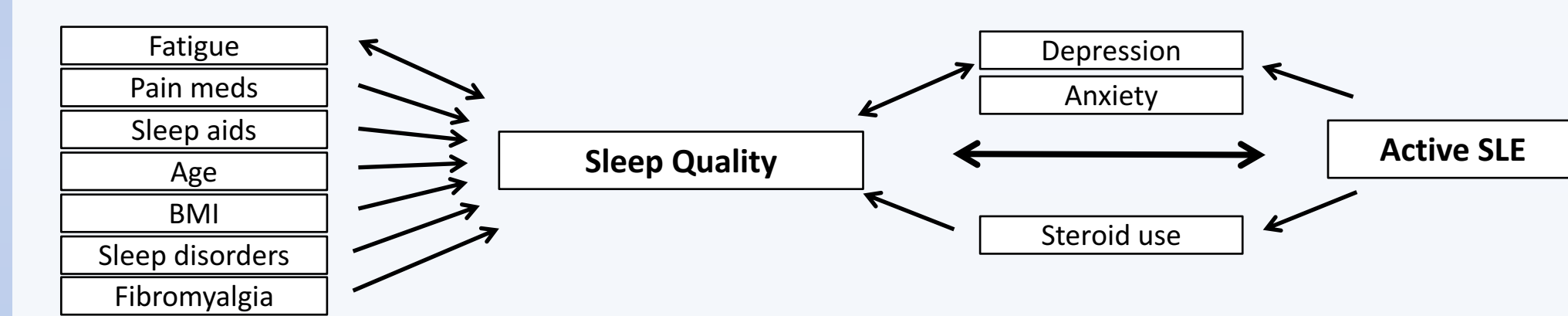
- Circadian rhythm influences immune responses, modulating innate and adaptive immune responses (1-2).
- In a mouse model, sleep deprivation accelerated SLE disease onset (3).
- Patients with sleep disorders have a higher incidence of autoimmune disease (4).
- An underappreciated complaint observed in patients with SLE is poor sleep quality (5), but the association between poor sleep and SLE disease is unclear (6-10).
- The impact of sleep on SLE disease activity may provide important therapeutic implications.

AIMS

We hypothesize that poor sleep quality and active SLE correlate.

- Aim I. Evaluate the relationship between subjective sleep measures and active SLE.
- Aim II. Evaluate the relationship between objective sleep actigraphy and active SLE.

Figure 1. SLEEPS model: proposed relationship between sleep quality, active SLE, and confounding variables



METHODS

SLEEPS is a prospective, longitudinal observational study designed to evaluate the relationship between sleep quality and SLE disease activity. Subjects are from WashU Lupus Clinic. Inclusion criteria: > age 18, Systemic Lupus International Collaborating Clinics (SLICC) or American College of Rheumatology (ACR) criteria for SLE. Exclusion criteria: Hepatitis B/C, HIV, cirrhosis, ESRD, or pregnancy.

Sleep surveys

- Pittsburgh Sleep Quality Index (PSQI): Evaluates multiple components. Score > 5 considered poor sleep (max score 21).
- Epworth Sleepiness Scale (ESS) Evaluates daytime sleepiness. ESS score >9 indicates hypersomnolence (max score 24)
- Patient Reported Outcomes Measurement Instrument System (PROMIS). General population standardized to a mean score of 50 and standard deviation of 10, maximum 100.
 - Sleep Related Impairment (SRI) evaluates perceptions of alertness, sleepiness, tiredness and perceived functional impairments during usual waking hours.
 - Sleep Disturbance (SD) evaluates perceptions of staying asleep, adequacy, satisfaction with sleep.

SLE disease activity assessment

- Measured with the Systemic Lupus Erythematosus Disease Activity Index 2000 Responder Index -50 (S2K RI-50).
- Scores calculated from a combination of clinical and laboratory variables.
- Scores > 4 indicate active SLE.

Sleep actigraphy

- Involves wearing a device on the wrist to measure gross motor activity. Validated to correlate well with polysomnography, and provides feasibility of home administration, extended periods of time, less expense.
- Actigraphs are distributed to patients on the day of their lupus clinic visit, and worn for seven days, a concurrent sleep diary is filled out to confirm the indicated sleep and wake times. Sleep efficiency from downloaded actigraphs is generated by ACTMe software (Figure 2).

Statistical Analyses

- Pearson Correlation analysis was performed to measure correlation between individual measures of sleep quality (sleep surveys and sleep efficiency by actigraphy) and lupus disease activity.
- Univariate and multivariate logistic regression analyses were performed to explore predictors of active SLE and worsening SRI.

Results

Table 1. Patient Characteristics at Study Enrollment (N=127)

Age (mean±SD)	42±13
Female	89%
African American	55%
Overweight/Obese	62%
Fibromyalgia	16%
Depression (CESDR)	19%
Anxiety	5%
Sleep comorbidities (OSA, PLMD)	8%
Tobacco Use	25%
Prednisone (>7.5 mg/day)	25%

Depression is a categorical variable, determined by the Center for Epidemiologic Studies Depression Scale Revised (CES-D-R) survey.

Table 2. Sleep characteristics in the lupus clinic population at baseline

Sleep Survey	Mean ± SD	% hypersomnolence	% poor sleep
PROMIS SRI	58 ± 11		
PROMIS SD	56 ± 12		
ESS	8.5 ± 5.6	62%	
PSQI	9.5 ± 4.4	54%	

A PROMIS-SRI and PROMIS-SD T-score of 50 is the average for the US general population with a standard deviation of 10. Poor sleep or daytime sleepiness is defined as ESS >9, PSQI >5.

Table 3. Univariate and Multivariate Logistic Regression of Variables Predicting Active SLE – Cross-sectional

Predictors	Univariate Regression				Multivariate Regression			
	Estimate	95% CI	R ²	P-value	Estimate	95% CI	R ²	P-value
Active SLE	4.36	0.36-8.36	0.037	0.03	0.13	-0.12-0.39		0.31
Fatigue	0.97	0.85-1.08	0.69	<.00	0.87	0.71-1.03	0.70	<.00
Anxiety	0.52	0.39-0.66	0.35	<.00	0.06	-0.07-0.18		0.37
Depression	10.4	5.7-15.1	0.14	<.00	1.41	-2.0-4.8		0.42
Prednisone	1.28	-3.2-5.7	0.003	0.57				
Age	-0.11	-0.25-0.04	0.017	0.15				
BMI	-0.16	-0.44-0.12	0.010	0.26				
Narcotics	-0.60	-4.9-3.7	0.0006	0.79				
Sleep Aids	1.26	-2.8-5.3	0.003	0.54				
Sleep Comorb	1.08	-5.8-8.0	0.0008	0.76				
Fibromyalgia	0.31	-5.0-5.6	0.0001	0.91				

- Active SLE disease, Fatigue, Anxiety, and Depression significantly predict worse sleep.
- Active SLE predicts a 4.36 higher SRI T-score compared to inactive SLE.
- Meeting criteria for Depression (by CESDR) predicts a 10.4 higher SRI T-score compared to those who do not meet criteria for Depression.
- An increase in Fatigue T-score by 1 unit predicts an increase of SRI T-score by 0.97.
- Univariate and Multivariate analyses of predictors of PROMIS-SD (not shown) showed similar estimates and Confidence Intervals.

Table 4. Univariate and Multivariate Linear Regression of Variables Predicting Sleep Related Impairment – Cross-sectional

Predictors	Univariate (OR)		Multivariate Regression (OR)	
	Estimate	95% CI	Estimate	95% CI
SRI	1.04	1.002-1.08	0.97	0.90-1.05
SD*	1.03	1.002-1.07	1.02	0.97-1.07
PSQI	1.02	0.92-1.12		
ESS	1.01	0.95-1.08		
Fatigue	1.05	1.01-1.10	1.08	0.98-1.18
Anxiety	1.03	0.99-1.06	1.04*	0.97-1.11
Depression	2.23	0.92-5.4		
Prednisone	2.17	0.96-4.9		
Age	0.97	0.94-1.0		
BMI	0.97	0.92-1.02		
Narcotics	1.06	0.47-2.4		
Sleep aids	1.11	0.52-2.4		
Sleep comorbidities	1.52	0.44-5.3		
Fibromyalgia	0.50	0.17-1.4		

- PROMIS-SRI, SD, and Fatigue significantly predict active SLE in the baseline visit. An increase of SRI T-score by 1 unit increases the odds of having active SLE by 1.04. This effect is demonstrated in the univariate but not multivariate analysis.
- *SD is analyzed in separate multivariate analyses than SRI. Multivariate Odds Ratios for PROMIS-Fatigue are reported for analyses run with SRI and SD, respectively.

Figure 2. Revised model based on statistically observed relationships – cross-sectional

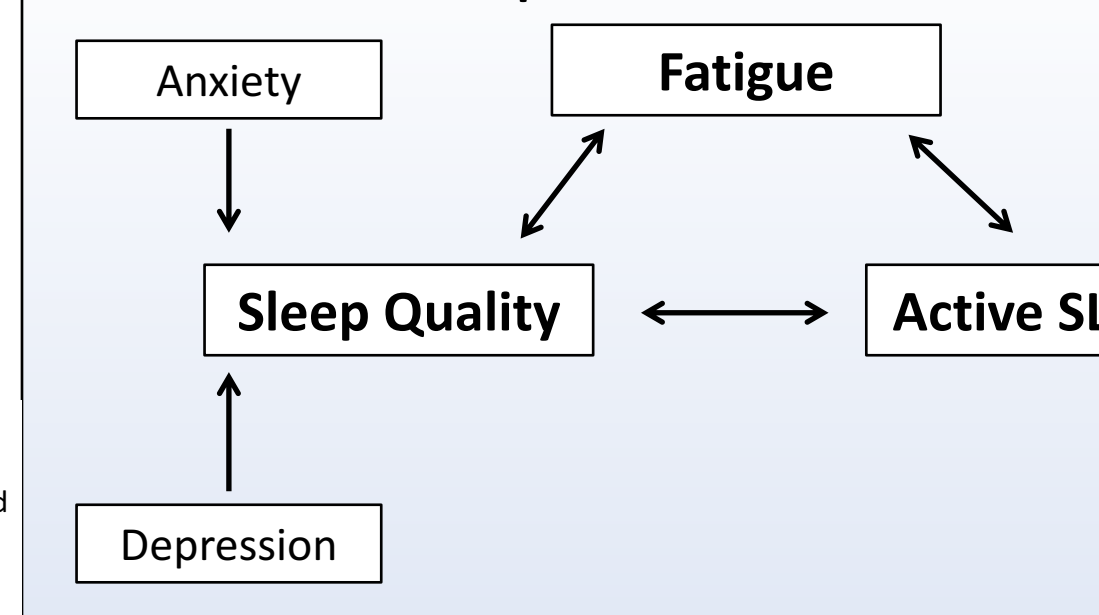


Table 5. Generalized Estimating Equation (GEE) predicting active SLE – Longitudinal

Predictors	Univariate (OR)		Multivariate (OR)	
	Estimate	95% CI	Estimate	95% CI
active SLE baseline	1.49	1.3-1.7	1.45	1.3-1.6
SRI baseline	1.01	1.003-1.02	1.02	1.001-1.03
SD	1.01	1.003-1.02	1.01	1.001-1.02
SD baseline	0.98	0.98-0.99	0.98	0.97-0.99
PSQI	1.00	0.99-1.003		
ESS	1.01	0.99-1.03		
Depression	0.96	0.81-1.1	1.1	0.92-1.3
Prednisone	1.17	0.93-1.5	1.1	0.89-1.4
Fatigue	1.01	0.99-1.02	0.99	0.99-1.01
Anxiety	1.00	0.99-1.01	1.00	0.99-1.01
Number of visits	1.05	0.99-1.1	1.06	0.99-1.1

- For the longitudinal analyses, up to visit # 5 was included.
- Active SLE at the baseline visit predicted active SLE in subsequent visits. Poor sleep (higher SRI/SD) predicted active SLE in longitudinal analyses. Interestingly, better sleep at baseline (lower SRI/SD T-score) predicted active SLE significantly. These effects remained significant in the multivariate analysis.
- Fatigue does not predict active SLE in the longitudinal analyses as in cross-sectional analyses (Table 4).
- All the predictors listed in univariate analysis were included in the multivariate analysis.

Table 6. Mixed Models Analysis predicting Sleep Related Impairment – Longitudinal

Predictors	Univariate Regression			Multivariate Regression		
	Estimate	95% CI	P-value	Estimate	95% CI	P-value
Active SLE baseline	1.25	-1.9-4.4	0.44	-2.2	-4.3 to -0.19	0.03
Active SLE	0.27	-3.1-3.6	0.87	1.2	-0.83-3.3	0.24
Depression baseline	-7.5	-11 to -4.1	<.00	-2.2	-4.8-0.36	0.09
Depression	-7.8	-12 to -4.0	<.00	0.24	-2.7-3.2	0.87
Fatigue baseline	0.43	0.28-0.58	<.00	0.26	0.066-0.45	0.01
Fatigue	0.47	0.33-0.60	<.00	0.67	0.47-0.86	<.00
Anxiety baseline	-0.031	-0.23-0.17	0.76			
Anxiety	0.50	0.29-0.70	<.00	0.077	-0.095-0.25	0.38
Prednisone baseline	4.4	-0.002-8.9	0.0501			
Prednisone	0.71	-3.8-5.2	0.75			

- Depression at baseline and at subsequent visits predict better sleep (lower SRI/SD), which is the opposite direction as demonstrated in cross-sectional analyses.
- Fatigue and Anxiety significantly predict worse sleep (higher SRI/SD) in longitudinal studies. Fatigue remains significant in multivariate analyses.
- When accounting for other variables in the multivariate analysis, active SLE at baseline predicts worse sleep. This was not seen in PROMIS-SD

Figure 3. Revised model based on statistically observed relationships – longitudinal

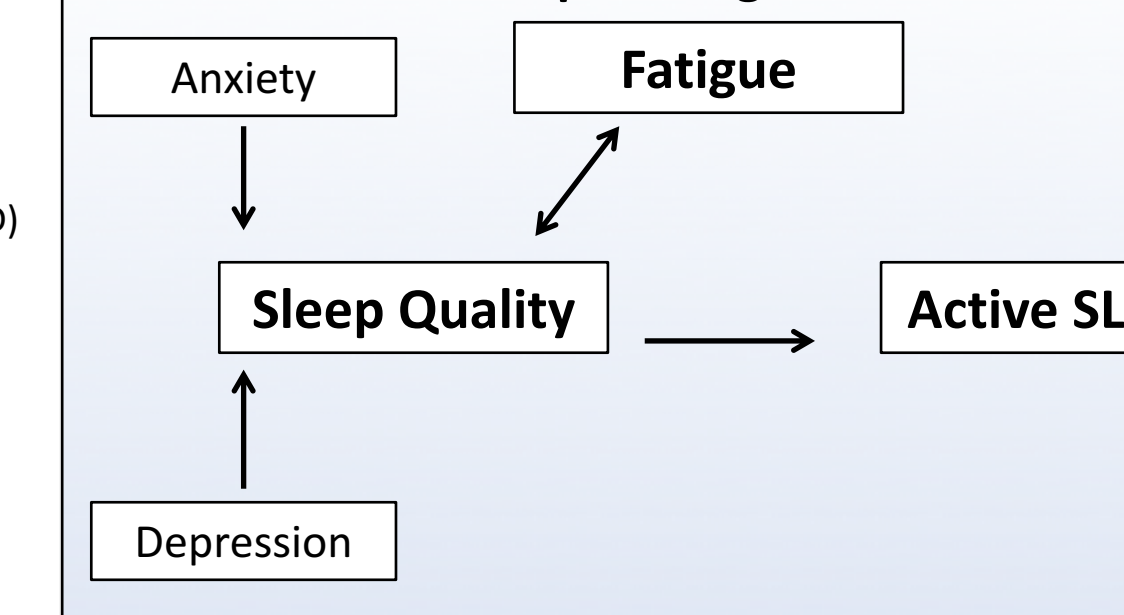


Figure 4. Sample Sleep Diary and Actigraphy Data

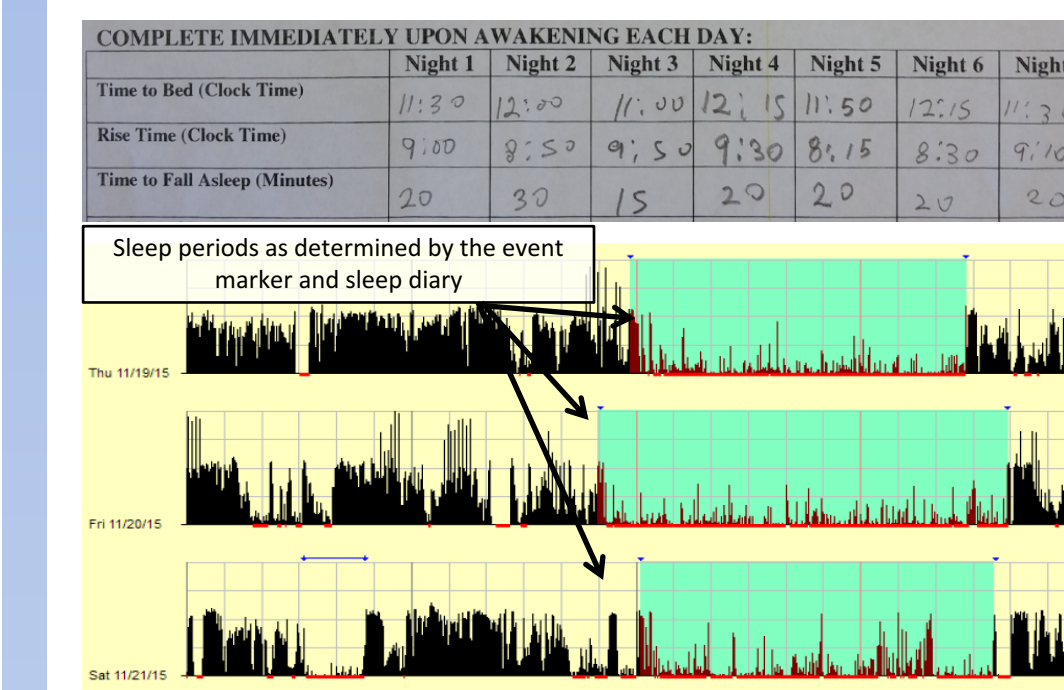


Table 7. Correlation of Sleep Efficiency by Actigraphy with Active SLE and Subjective Sleep Measures (N=51)

	Pearson Correlation	P-value
Active SLE	-0.22	0.12
SD	-0.17	0.24
SRI	-0.17	0.25
PSQI	-0.26	0.15
ESS	-0.091	0.53

- Objective Sleep Efficiency measured by actigraphy trends towards significance with active SLE as well as PSQI.

CONCLUSIONS

- Poor sleep was associated with active SLE in both cross-sectional and longitudinal analyses.
- Of the 4 sleep surveys, only PROMIS-SRI and PROMIS-SD correlated with active SLE, albeit the effect size is mild.

- The cross-sectional analysis suggested that fatigue best explained the relationship between subjective sleep quality and SLE disease activity. Interestingly, this relationship was not observed in the longitudinal analysis.
- Sleep efficiency objectively measured by actigraphy trended toward significance with active SLE, but was underpowered.
- These data suggest that there is a relationship between sleep quality and active SLE.

FUTURE DIRECTIONS

- The sleep efficiency data obtained through actigraphy are encouraging, and power calculations suggest that a sample size N=100 will be sufficient to accurately evaluate this relationship with active SLE.
- We have also implemented a pain survey to evaluate at the time of sleep survey collection this potential effect modifier in the relationship between sleep quality and SLE disease activity.

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- Study data were collected and managed using REDCap at Washington University, STL.

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