Published in final edited form as:

Lupus. 2018 August ; 27(9): 1524–1531. doi:10.1177/0961203318778368.

Less than Seven Hours of Sleep per Night is Associated with Transitioning to Systemic Lupus Erythematosus

Kendra A. Young¹, Melissa E. Munroe², John B. Harley^{3,4}, Joel M. Guthridge², Diane L. Kamen⁵, Gary S. Gilkensen⁵, Michael H. Weisman⁶, David R. Karp⁷, Daniel J. Wallace⁶, Judith A. James^{2,8}, and Jill M. Norris¹

¹Department of Epidemiology, University of Colorado Anschutz Medical Campus, Aurora, CO

²Arthritis and Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK

³Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Children's Hospital Medical Center, Cincinnati, OH

⁴US Department of Veterans Affairs Medical Center, Cincinnati, OH

⁵Division of Rheumatology, Medical University of South Carolina, Charleston, SC

⁶Division of Rheumatology, Cedars Sinai Medical Center, Los Angeles, CA

⁷Division of Rheumatic Diseases, University of Texas Southwestern Dallas, TX

⁸Departments of Medicine and Pathology, Oklahoma University Health Sciences Center, Oklahoma City, OK

Abstract

Background—The role of sleep in the etiology of systemic lupus erythematosus (SLE) has not been well studied. We examined whether sleep duration was associated with subsequent transitioning to SLE in individuals at risk for SLE.

Methods—436 relatives of SLE patients who did not have SLE themselves at baseline were evaluated again an average of 6.3 ($\pm$ 3.9) years later. Fifty-six individuals transitioned to SLE (4 cumulative ACR criteria). Sleep duration, medication use, and medical history were assessed by questionnaire; ACR criteria were confirmed by medical record review. Vitamin D was measured by ELISA. Generalized estimating equations, accounting for correlation within families, assessed associations between baseline sleep and the outcome of transitioning to SLE.

Results—Reporting sleeping less than seven hours per night at baseline was more common in those who subsequently transitioned than those who did not transition to SLE (55% versus 32%, $p=0.0005$; OR: 2.8, 95% 1.6–4.9). Those who transitioned to SLE were more likely to sleep less than seven hours per night than those who did not transition to SLE adjusting for age, sex and race

Corresponding Author: Kendra Young, MSPH, PhD, Department of Epidemiology, Colorado School of Public Health, 13001 East 17th Place, Box B119, Aurora, Colorado 80045 USA, kendra.young@ucdenver.edu.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

(OR: 2.8, 95% CI 1.6–5.1). This association remained after individual adjustment for conditions and early symptoms that could affect sleep, including prednisone use, vitamin D deficiency, and number of ACR criteria (OR: 2.0, 95% CI 1.1–4.2).

Conclusion—Lack of sleep may be associated with transitioning to SLE, independent of early clinical manifestations of SLE that may influence sleep duration. Further evaluation of sleeping patterns and biomarkers in at-risk individuals is warranted.

Keywords

SLE; sleep; preclinical disease; environmental factors; depression

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by autoantibody production, acute and chronic inflammation of various tissues, and fluctuating manifestations such as fever, rash and nephritis. The etiology and pathogenesis of SLE remains largely unidentified, but is most likely a combination of genetic and environmental risk factors.

Both quality and quantity of sleep have been shown to have significant impacts on health, including increased risk of metabolic diseases, hypertension, and mortality^{1, 2}. Both acute and chronic sleep disturbances and deprivation have reported associations with increased inflammatory markers^{3, 4}. Approximately one-third of adults in the United States sleep less than seven hours a night⁵, a threshold below which health impacts are manifested^{6, 7}. Sleep disturbances are commonly reported in SLE patients^{8–14}. Poor sleep quality in SLE has been correlated with fatigue^{11, 15, 16}, depression¹³, and anxiety¹³. Prednisone use, commonly prescribed in SLE for other rheumatic disease symptoms, may have deleterious effects on sleep^{17, 18}. In addition, we have previously shown that vitamin D deficiency is associated with transitioning to SLE¹⁹, and lower vitamin D levels may be related to decreased sleep duration and quality^{20–22}, including in women with SLE²³.

While sleep disturbances have been associated with disease activity⁸ and quality of life measures²⁴ in patients with SLE, whether the duration of sleep is related to risk of developing SLE has not been clearly established. A small case-control study of Japanese patients found that while self-reporting “sufficient sleep” was protective for SLE, no association was found for those reporting >7 hours of sleep per night²⁵. Two recent Taiwan population studies indicated that individuals, particularly females, diagnosed with a sleep disorder had an increased risk of SLE than those without a sleep disorder^{26, 27}. To further explore the association between sleep quantity and transitioning to SLE, we studied a cohort of individuals who reported having a family member with SLE, putting them at increased genetic risk for SLE^{28, 29}, but who did not meet SLE disease classification³⁰ at their baseline visit. We examined whether self-reported sleep duration at baseline was prospectively associated with transitioning to SLE at follow-up, independent of self-reported associated manifestations of SLE such as depression, fatigue, anxiety, or prednisone use.

Materials and methods

Participant information

All protocols were approved by the Institutional Review Boards at the University of Colorado Denver, the Oklahoma Medical Research Foundation (OMRF) and the University of Oklahoma Health Sciences Center. Study participants were enrolled in the Lupus Family Registry and Repository (LFRR)³¹ and provided informed consent prior to enrollment. Letters were sent to 3823 individuals with a family member with SLE, who did not meet 4 American College of Rheumatology (ACR)³⁰ criteria for SLE at their prior (baseline) visit. These individuals were invited to enroll in a follow-up study to gather information regarding interim development of symptoms consistent with or a diagnosis of SLE. Compared to those not enrolled, the 436 individuals who enrolled were younger (mean age at follow-up 53.5 years vs 59.1 years), more likely to be female (84% vs 69%), and more likely to be European American (73.9% vs 55.4%). Of the 436 individuals enrolled, 402 individuals were first degree relatives (FDRs) and 34 individuals were second degree or more distant relatives of an individual with SLE.

Identical questionnaires and laboratory tests were completed at the baseline and follow-up examinations (mean time between contact 6.3 ± 3.9 years). Participants completed the Connective Tissue Disease Screening Questionnaire (CSQ)³². The SLE portion of the CSQ (SLE-CSQ) was scored using an algorithm based on ACR classification criteria³². Twenty-eight questions were grouped into 12 categories. If < 3 SLE-CSQ categories were true, then a person was categorized as unlikely SLE. If 3 of the 12 categories were true, then a person was categorized as possible SLE. If 4 of the 12 categories were true, then a person was categorized as probable SLE. Detailed demographic, environmental, clinical, and therapeutic information was collected by validated questionnaire³¹. Body mass index (BMI) was calculated as reported weight (kg)/height (m²). Peripheral blood samples were obtained from all study participants and processed for serum, plasma and DNA. Antinuclear antibodies (ANA) were detected using a HEp-2 indirect immunofluorescent assay (positive titer 1:120) and anti-dsDNA was detected using *Crithidia luciliae* (positive titer 1:30) according to manufacturer instructions (INOVA Diagnostics, San Diego, California, USA) in the College of American Pathologists-certified OMRF Clinical Immunology Laboratory. Plasma levels of 25-hydroxyvitamin D 25[OH]D were determined in duplicate using a commercial enzyme immunoassay (Immunodiagnostic Systems, Inc., Scottsdale, AZ) according to manufacturer instructions. Vitamin D deficiency was defined as 25[OH]D <20 ng/ml. Medical records were obtained and reviewed by a rheumatology-trained physician, physician assistant, or nurse for ACR classification criteria for individuals who reported signs and symptoms of SLE. Individuals were classified as having transitioned to SLE by the time of follow-up if they met 4 cumulative ACR criteria, in which medical record verified ACR criteria could accumulate towards the total count of ACR, and did not need to be all present at the same time. Fifty-six individuals were identified who transitioned to SLE at follow-up.

Measurement of Sleep Duration, Fatigue, Anxiety and Medication Use

Sleep duration in hours was assessed by the question “How many hours do you sleep at night on average?” Based on the Institutes of Medicine recommendation of 7–8 hours of sleep a night³³ and the literature threshold for health impacts^{5–7}, we categorized our sleep outcome as <7 hours of sleep a night or ≥7 hours of sleep a night. Chronic fatigue, depression and anxiety were determined by whether the individual answered ‘yes’ when asked “whether you have had the condition or if a doctor has told you that you have the condition.” Prednisone use and sleep medication use within the last year were assessed by self-reported medication history.

Statistical analyses

All analyses were performed in SAS 9.4 (Cary, NC). T-tests for continuous variables and chi-square tests for categorical variables were used to determine differences between individuals who transitioned to SLE (n=56) and individuals who did not transition to SLE (n=380). Associations between sleeping less than seven hours a night and sleeping medication use, prednisone use, reported depression, reported fatigue, reported anxiety, SLE-CSQ category and number of ACR criteria at baseline were assessed by chi-square tests. We did not see any associations between baseline sleep and specific ACR classification criteria (e.g. arthritis, mucocutaneous, serositis, renal disorder, etc.). Within this cohort, individuals within the same family could be enrolled; family size ranged from 1–6 family members, with 23% of our population with at least one other family member enrolled. We therefore accounted for the correlation among these family members using generalized estimating equations, when assessing associations between a categorical measure of sleeping <7 hours a night at baseline and transitioning to SLE. All multivariable models were adjusted for age, sex, and race. BMI at baseline did not add significantly to these models, and was not included as a covariate. In addition, to determine if the association between sleep duration and SLE was independent of early clinical manifestations of SLE, we additionally adjusted for other sleep associated variables at baseline, including depression, prednisone use, chronic fatigue, SLE-CSQ category, number of ACR criteria and vitamin D deficiency. Due to the co-linearity of several of these factors (prednisone use, depression and chronic fatigue; and number of ACR criteria and SLE-CSQ category), we initially adjusted for these variables one at a time. A model was also included adjusting for prednisone use, number of ACR criteria and vitamin D deficiency. Odds ratios and 95% confidence intervals were determined for all models.

Results

We compared individuals who transitioned to SLE at follow-up to those who did not transition with respect to demographics, number of ACR criteria, and measures of sleep duration (Table 1). Individuals who transitioned had a greater number of confirmed ACR criteria, were more likely to be classified as probable or possible SLE by SLE-CSQ, and were more likely to be ANA positive at baseline compared to those who did not transition. Reported sleep medication and prednisone use at baseline were higher in those who transitioned compared to those who did not transition. A higher proportion of relatives who transitioned reported depression, fatigue, and anxiety at baseline. Individuals who

transitioned to SLE reported fewer hours of sleep a night at baseline compared those who did not transition to SLE, and a higher proportion of individuals who transitioned to SLE reported sleeping less than seven hours a night (Table 1).

Because specific conditions and early pre-clinical manifestations of SLE may be associated with sleep duration and therefore may be potential confounders, we examined whether presence of these characteristics were associated with sleeping less than seven hours a night at baseline (Table 2). Prednisone use, depression, and chronic fatigue, were all associated with sleeping less than seven hours a night. In addition, those who were vitamin D deficient, those with possible or probable SLE by SLE-CSQ, and those with 2 or 3 confirmed ACR criteria reported sleeping less than seven hours a night.

Adjusting for age, gender, and race, those who slept less than 7 hours a night at baseline were more likely to transition to SLE than those who slept more (adjusted OR: 2.8, 95% CI 1.6–5.1). In order to examine whether this association is confounded by reported conditions and early pre-clinical features of SLE at baseline, we individually adjusted for baseline prednisone use, self-reported depression, self-reported chronic fatigue, vitamin D deficiency, SLE-CSQ category and number of ACR criteria (Table 3). The association between < 7 hours of sleep and transitioning to SLE remained significant in all models. In addition, we ran a final model adjusting for baseline prednisone use, number of ACR criteria, vitamin D deficiency. Sleeping < 7 hours per night was significantly associated with transitioning to SLE in this model as well, indicating there is an independent association between sleep duration and transitioning to SLE (Table 3). Sleep data was missing for 3 who transitioned and 20 who did not transition to SLE. Sensitivity analyses assuming those with missing sleep data had either all <7 hours of sleep per night or >7 hours of sleep per night did not significantly affect the magnitude of the association between sleep and transitioning to SLE. The final model adjusting for prednisone use, number of ACR criteria and vitamin D deficiency was also run excluding the second degree and more distantly related family members from the analysis. The magnitude of the association between sleeping < 7 hours per night and transitioning to SLE did not change (OR=2.1, 95% CI 0.9–4.6).

Of note, depression, and chronic fatigue were all significantly associated with transitioning to SLE, after adjusting for sleep. Interestingly, these associations with transitioning to SLE remained significant after additional adjusting for number of ACR classification criteria (chronic fatigue adjusted OR: 11.8, 95% CI 4.9–28.4; depression adjusted OR: 2.9, 95% CI 1.5–5.9).

Discussion

We found that sleep duration was associated with transitioning to SLE within a unique cohort of relatives of SLE patients without classified SLE at the baseline visit. This association was independent of several important variables which could indicate accompanying signs and symptoms of SLE, including: depression and prednisone use, both of which are increased in SLE and known to have an effect on sleep quality and architecture; and chronic fatigue, one of the most common and debilitating complaints in SLE and related to sleep. While we have shown that being vitamin D deficient is associated with

transitioning to SLE¹⁹, the association between sleep and transitioning to SLE was independent of vitamin D status. In addition, the association between sleep and transitioning to SLE was independent of SLE-CSQ category and the number of ACR criteria. In a full model adjusting for prednisone use, number of ACR criteria and vitamin D deficiency, sleep remained significantly associated with transitioning to SLE. This could indicate that while increasing signs and symptoms contribute to sleep disturbances, the contribution of sleep duration to transitioning to SLE may also be related to the deleterious health effects of disturbed and shortened sleep.

Sleep disturbances have been reported in SLE patients^{8–14}; however, none of these studies have examined the effect sleep has on risk of disease. One small case-control study found that while reporting >7 hours of sleep a day was not associated with SLE, reporting the relatively subjective outcome of getting “sufficient sleep” prior to SLE classification was inversely associated with SLE risk²⁵. However, given that cases in that study had been treated for SLE for up to 10 years, the data regarding sleep habits prior to SLE diagnosis may have been inaccurate or biased. Two Taiwanese population studies indicated that individuals, diagnosed with a sleep disorder had an increased risk of SLE than those without a sleep disorder^{26, 27}. However, these studies did not account for medication use nor clinical manifestations of SLE, and their use of an insurance database may not adequately reflect individuals who do not seek medical care for their sleep disturbances.

The link between sleep duration and SLE etiology is feasible. Two studies utilizing the spontaneous (NZB/NZW) F₁ model of SLE revealed associations between sleep disturbances and disease. Sleep deprived mice demonstrated accelerated onset of lupus³⁴ through increased autoantibody production. Relatives of SLE patients are enriched in autoantibodies compared to controls^{35, 36}. Given the SLE-related autoantibodies progressively accumulate³⁷, less sleep could accelerate the production of autoantibodies. In addition, altered sleep architecture was present both during progression to this form of murine lupus and during periods of increased disease activity³⁸. Sleep loss may deregulate immune responses^{39–42}, leading to increased inflammatory cytokines and increased white blood cell and natural killer cell counts. It could also lead to a break in self-tolerance through impaired regulatory T cells⁴³. This pathophysiology is plausible, as obstructive sleep apnea has been associated with increased risk of autoimmune disease, including SLE and RA⁴⁴, as well as with increased biomarkers of immune function⁴⁵. Indeed, in this cohort of family members at increased genetic risk of SLE, SCF and TGFβ were shown to be independent predictors of transitioning to SLE⁴⁶.

Increasing evidence supports a reciprocal relationship between sleep and immunity^{47, 48}. An activated immune system alters sleep duration and quality, and sleep disturbances affect immune function. We saw a persistent magnitude of association when adjusting for accompanying signs and symptoms of SLE. This may indicate that less sleep duration is not merely an early symptom of SLE but may be involved in the pathogenesis of the disease prior to and during early SLE.

We also found that the associations between depression, anxiety, and chronic fatigue and transitioning to SLE remained significant independent of sleep. While poor sleep quality and

architecture in SLE patients has been correlated with fatigue^{11, 15, 16}, depression¹³, and anxiety¹³, this is one of the first studies to indicate that these symptoms occur prior to SLE classification. Interestingly, these associations with transitioning to SLE remained significant after additional adjusting for number of ACR classification criteria. Further study may explain whether anxiety, depression and chronic fatigue may also confer some independent risk other than as a symptom of early clinical manifestations of SLE.

One strength of the study is that the data are prospective. Consistent criteria were used at both visits using a validated questionnaire and examining medical records, making comparisons valid across time. However, one limitation to our study is the use of a self-reported measure of sleep, which is reported to have low correlation (0.43–0.45) with objective sleep measures such as actigraphy^{49, 50}. Self-reported sleep has been shown to over-report amount of sleep, possibly due to night-to-night variability and report of time spent in bed rather than actual sleep^{49, 50}. One study also found that people who report fair or poor health had no significant correlation between measured and reported sleep and report shorter hours of sleep on average⁵⁰. Therefore, it is possible that those reporting < 7 hours of sleep per night in this cohort are those who are experiencing poorer health. However, we did find that the association between sleep and transitioning to SLE was independent of number of ACR criteria and prednisone use, indicating that this may not be true in this population. In addition, we relied on self-reported measures of depression, sleep medication use, prednisone use, chronic fatigue and anxiety. Each of these measures were assessed by a single question, and more in-depth examination of effect of the quality of these measures could not be conducted. Family members who enrolled in this follow-up study were more likely to have a higher number of ACR criteria than those who did not enroll; therefore, they may be further along in the disease process and experiencing loss of sleep due to early signs/symptoms of SLE. However, we did see an association after adjusting for a greater number of ACR criteria, which could indicate that sleep may be a risk factor for transitioning to SLE independent of increasing number of signs or symptoms of disease. Further examination of the association between real-time, real-world monitoring of sleep and SLE using more objective measurements is warranted.

In summary, this is one of the first studies to determine that sleeping less than seven hours per night may be prospectively associated with transitioning to SLE, independent of several factors that may indicate early pre-clinical signs and symptoms of SLE, including prednisone use, the number of confirmed ACR criteria, and vitamin D deficiency. While increasing signs and symptoms may contribute to sleep disturbances, there may also be a contribution of the deleterious health effects of disturbed sleep on transitioning to SLE.

Acknowledgments

The authors would like to thank Lupus Family Registry and Repository and Systemic Lupus Erythematosus in Gullah Health personnel, participants, and the referring physicians for making this study possible.

Funding

Research reported in this publication was supported by the National Institute of Arthritis, Musculoskeletal and Skin Diseases, National Institute of Allergy, Immunology and Infectious Diseases, the National Human Genome Research Institute, and the National Institute of General Medical Sciences under award numbers under award

numbers P30 AR053483, P30 GM103510, U54 GM104938, U01 AI101934, U19 AI082714, R01 AI024717, U01 HG008666, R01 AI130830, and from the Kirkland Foundation and US Department of Veterans Affairs.

References

1. Alvarez GG, Ayas NT. The impact of daily sleep duration on health: a review of the literature. *Progress in cardiovascular nursing*. 2004; 19:56–9. [PubMed: 15133379]
2. Gallicchio L, Kalesan B. Sleep duration and mortality: a systematic review and meta-analysis. *Journal of sleep research*. 2009; 18:148–58. [PubMed: 19645960]
3. Irwin MR, Olmstead R, Carroll JE. Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biological psychiatry*. 2016; 80:40–52. [PubMed: 26140821]
4. Mullington JM, Simpson NS, Meier-Ewert HK, Haack M. Sleep loss and inflammation. *Best practice & research Clinical endocrinology & metabolism*. 2010; 24:775–84. [PubMed: 21112025]
5. Effect of short sleep duration on daily activities—United States, 2005–2008. *MMWR Morbidity and mortality weekly report*. 2011; 60:239–42. [PubMed: 21368739]
6. Belenky G, Wesensten NJ, Thorne DR, et al. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *Journal of sleep research*. 2003; 12:1–12. [PubMed: 12603781]
7. Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep*. 2003; 26:117–26. [PubMed: 12683469]
8. Chandrasekhara PK, Jayachandran NV, Rajasekhar L, Thomas J, Narsimulu G. The prevalence and associations of sleep disturbances in patients with systemic lupus erythematosus. *Modern rheumatology/the Japan Rheumatism Association*. 2009; 19:407–15.
9. Costa DD, Bernatsky S, Dritsa M, et al. Determinants of sleep quality in women with systemic lupus erythematosus. *Arthritis and rheumatism*. 2005; 53:272–8. [PubMed: 15818653]
10. Greenwood KM, Lederman L, Lindner HD. Self-reported sleep in systemic lupus erythematosus. *Clinical rheumatology*. 2008; 27:1147–51. [PubMed: 18408880]
11. Tench CM, McCurdie I, White PD, D'Cruz DP. The prevalence and associations of fatigue in systemic lupus erythematosus. *Rheumatology (Oxford, England)*. 2000; 39:1249–54.
12. Kasitanon N, Achavalertsak U, Maneeton B, et al. Associated factors and psychotherapy on sleep disturbances in systemic lupus erythematosus. *Lupus*. 2013; 22:1353–60. [PubMed: 24080701]
13. Vina ER, Green SL, Trivedi T, Kwok CK, Utset TO. Correlates of sleep abnormalities in systemic lupus: a cross-sectional survey in an urban, academic center. *Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases*. 2013; 19:7–13. [PubMed: 23319017]
14. Valencia-Flores M, Resendiz M, Castano VA, et al. Objective and subjective sleep disturbances in patients with systemic lupus erythematosus. *Arthritis and rheumatism*. 1999; 42:2189–93. [PubMed: 10524692]
15. Gudbjornsson B, Hetta J. Sleep disturbances in patients with systemic lupus erythematosus: a questionnaire-based study. *Clinical and experimental rheumatology*. 2001; 19:509–14. [PubMed: 11579709]
16. McKinley PS, Ouellette SC, Winkel GH. The contributions of disease activity, sleep patterns, and depression to fatigue in systemic lupus erythematosus. A proposed model. *Arthritis and rheumatism*. 1995; 38:826–34. [PubMed: 7779127]
17. Da Costa D, Dritsa M, Bernatsky S, et al. Dimensions of fatigue in systemic lupus erythematosus: relationship to disease status and behavioral and psychosocial factors. *The Journal of rheumatology*. 2006; 33:1282–8. [PubMed: 16758508]
18. Vgontzas AN, Chrousos GP. Sleep, the hypothalamic-pituitary-adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. *Endocrinology and metabolism clinics of North America*. 2002; 31:15–36. [PubMed: 12055986]
19. Young KA, Munroe ME, Guthridge JM, et al. Combined role of vitamin D status and CYP24A1 in the transition to systemic lupus erythematosus. *Annals of the rheumatic diseases*. 2017; 76:153–8. [PubMed: 27283331]

20. Bertisch SM, Sillau S, de Boer IH, Szklo M, Redline S. 25-Hydroxyvitamin D Concentration and Sleep Duration and Continuity: Multi-Ethnic Study of Atherosclerosis. *Sleep*. 2015; 38:1305–11. [PubMed: 25669179]
21. Kerley CP, Hutchinson K, Bolger K, McGowan A, Faul J, Cormican L. Serum Vitamin D Is Significantly Inversely Associated with Disease Severity in Caucasian Adults with Obstructive Sleep Apnea Syndrome. *Sleep*. 2016; 39:293–300. [PubMed: 26414899]
22. Massa J, Stone KL, Wei EK, et al. Vitamin D and actigraphic sleep outcomes in older community-dwelling men: the MrOS sleep study. *Sleep*. 2015; 38:251–7. [PubMed: 25581929]
23. Gholamrezaei A, Bonakdar ZS, Mirbagher L, Hosseini N. Sleep disorders in systemic lupus erythematosus. Does vitamin D play a role? *Lupus*. 2014
24. Mirbagher L, Gholamrezaei A, Hosseini N, Sayed Bonakdar Z. Sleep quality in women with systemic lupus erythematosus: contributing factors and effects on health-related quality of life. *International journal of rheumatic diseases*. 2014
25. Washio M, Horiuchi T, Kiyohara C, et al. Smoking, drinking, sleeping habits, and other lifestyle factors and the risk of systemic lupus erythematosus in Japanese females: findings from the KYSS study. *Modern rheumatology/the Japan Rheumatism Association*. 2006; 16:143–50.
26. Chung WS, Lin CL, Kao CH. Association of systemic lupus erythematosus and sleep disorders: a nationwide population-based cohort study. *Lupus*. 2016; 25:382–8. [PubMed: 26585071]
27. Hsiao YH, Chen YT, Tseng CM, et al. Sleep disorders and increased risk of autoimmune diseases in individuals without sleep apnea. *Sleep*. 2015; 38:581–6. [PubMed: 25669189]
28. Alarcon-Segovia D, Alarcon-Riquelme ME, Cardiel MH, et al. Familial aggregation of systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases in 1,177 lupus patients from the GLADEL cohort. *Arthritis and rheumatism*. 2005; 52:1138–47. [PubMed: 15818688]
29. Lawrence JS, Martins CL, Drake GL. A family survey of lupus erythematosus. 1. Heritability. *The Journal of rheumatology*. 1987; 14:913–21. [PubMed: 3430520]
30. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis and rheumatism*. 1997; 40:1725.
31. Rasmussen A, Sevier S, Kelly JA, et al. The lupus family registry and repository. *Rheumatology (Oxford, England)*. 2011; 50:47–59.
32. Karlson EW, Sanchez-Guerrero J, Wright EA, et al. A connective tissue disease screening questionnaire for population studies. *Annals of epidemiology*. 1995; 5:297–302. [PubMed: 8520712]
33. *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem* Washington DC: National Academy of Sciences; 2006
34. Palma BD, Gabriel A Jr, Colugnati FA, Tufik S. Effects of sleep deprivation on the development of autoimmune disease in an experimental model of systemic lupus erythematosus. *American journal of physiology Regulatory, integrative and comparative physiology*. 2006; 291:R1527–32.
35. Bruner BF, Guthridge JM, Lu R, et al. Comparison of autoantibody specificities between traditional and bead-based assays in a large, diverse collection of patients with systemic lupus erythematosus and family members. *Arthritis and rheumatism*. 2012; 64:3677–86. [PubMed: 23112091]
36. Ramos PS, Kelly JA, Gray-McGuire C, et al. Familial aggregation and linkage analysis of autoantibody traits in pedigrees multiplex for systemic lupus erythematosus. *Genes and immunity*. 2006; 7:417–32. [PubMed: 16775618]
37. Arbuckle MR, McClain MT, Rubertone MV, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *The New England journal of medicine*. 2003; 349:1526–33. [PubMed: 14561795]
38. Palma BD, Tufik S. Increased disease activity is associated with altered sleep architecture in an experimental model of systemic lupus erythematosus. *Sleep*. 2010; 33:1244–8. [PubMed: 20857872]
39. Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Archives of internal medicine*. 2006; 166:1756–62. [PubMed: 16983055]

40. Clinton JM, Davis CJ, Zielinski MR, Jewett KA, Krueger JM. Biochemical regulation of sleep and sleep biomarkers. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. 2011; 7:S38–42. [PubMed: 22003330]
41. Vgontzas AN, Zoumakis E, Bixler EO, et al. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *The Journal of clinical endocrinology and metabolism*. 2004; 89:2119–26. [PubMed: 15126529]
42. Wilder-Smith A, Mustafa FB, Earnest A, Gen L, Macary PA. Impact of partial sleep deprivation on immune markers. *Sleep medicine*. 2013; 14:1031–4. [PubMed: 23993876]
43. Bollinger T, Bollinger A, Skrum L, Dimitrov S, Lange T, Solbach W. Sleep-dependent activity of T cells and regulatory T cells. *Clinical and experimental immunology*. 2009; 155:231–8. [PubMed: 19040608]
44. Kang JH, Lin HC. Obstructive sleep apnea and the risk of autoimmune diseases: a longitudinal population-based study. *Sleep medicine*. 2012; 13:583–8. [PubMed: 22521311]
45. Anderson ME Jr, Buchwald ZS, Ko J, Aurora R, Sanford T. Patients with Pediatric Obstructive Sleep Apnea Show Altered T-Cell Populations with a Dominant TH17 Profile. *Otolaryngology–head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*. 2014; 150:880–6. [PubMed: 24486778]
46. Munroe ME, Young KA, Kamen DL, et al. Discerning Risk of Disease Transition in Relatives of Systemic Lupus Erythematosus Patients Utilizing Soluble Mediators and Clinical Features. *Arthritis & rheumatology (Hoboken, NJ)*. 2017; 69:630–42.
47. Lange T, Dimitrov S, Born J. Effects of sleep and circadian rhythm on the human immune system. *Annals of the New York Academy of Sciences*. 2010; 1193:48–59. [PubMed: 20398008]
48. Ranjbaran Z, Keefer L, Stepanski E, Farhadi A, Keshavarzian A. The relevance of sleep abnormalities to chronic inflammatory conditions. *Inflammation research : official journal of the European Histamine Research Society [et al]*. 2007; 56:51–7.
49. Cespedes EM, Hu FB, Redline S, et al. Comparison of Self-Reported Sleep Duration With Actigraphy: Results From the Hispanic Community Health Study/Study of Latinos Sueno Ancillary Study. *American journal of epidemiology*. 2016; 183:561–73. [PubMed: 26940117]
50. Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ. Self-reported and measured sleep duration: how similar are they? *Epidemiology (Cambridge, Mass)*. 2008; 19:838–45.

Table 1

Baseline Characteristics of the Study Participants by Transitioned Status.

Variable (n, %)	Transitioned to SLE N=56	Did Not Transition N=380	p-value
Age at baseline (years): mean (median) $\pm$ sd	47.4 (48.5) $\pm$ 12.1	47.2 (48.0) $\pm$ 15.8	0.93
Time between contact (years): mean (median) $\pm$ sd	5.9 (5.1) $\pm$ 3.5	6.3 (5.4) $\pm$ 3.9	0.50
Sex: Female	49 (87.5%)	316 (83.2%)	0.41
Race: European American	43 (76.8%)	279 (73.4%)	0.55
African American	9 (16.1%)	55 (14.5%)	
Other ^a	4 (7.1%)	46 (12.1%)	
BMI at baseline: mean (median) $\pm$ SD	28.5 (28.5) $\pm$ 7.4	28.1 (26.9) $\pm$ 6.8	0.71
ANA positive at baseline	43 (76.8%)	183 (48.2%)	<0.001
SLE-CSQ Categories Baseline ^b :			<0.0001
Unlikely SLE	5 (8.9%)	248 (65.3%)	
Possible SLE	5 (8.9%)	39 (10.3%)	
Probable SLE	46 (82.1%)	93 (24.4%)	
Number of ACR Criteria Baseline:			<0.0001
0–1 ^c	7 (12.5%)	291 (76.5%)	
2	23 (41.1%)	74 (19.5%)	
3	26 (46.4%)	15 (4.0%)	
Hours of Sleep Baseline ^d : mean (median) $\pm$ sd	6.5 (6.0) $\pm$ 1.7	6.9 (7.0) $\pm$ 1.4	0.03
Sleep <7 hours at Baseline ^d : Yes	31 (55.4%)	121 (31.8%)	0.0005
Sleep Medication Use at Baseline: Yes	15 (26.8%)	36 (9.5%)	0.0002
Prednisone Use at Baseline: Yes	33 (58.9%)	32 (8.4%)	<0.0001
Reported Depression at Baseline: Yes	36 (67.9%)	134 (37.1%)	<0.0001
Chronic Fatigue at Baseline: Yes	46 (86.8%)	103 (27.4%)	<0.0001
Anxiety Baseline: Yes	25 (49.0%)	89 (24.7%)	0.0003
Vitamin D Deficient: Yes	26 (46.4%)	126 (33.2%)	0.05

Significant differences are noted in bold. ANA, anti-nuclear antibodies. CSQ, Connective Tissue Disease Screening Questionnaire. ACR, American College of Rheumatology.

^a Other includes Native American (n=8), Asian (n=1) and Hispanic (n=2).

^b SLE-CSQ categories are based on responses to the SLE portion of the CSQ questionnaire. Twenty-eight questions were grouped into 12 categories. If the person indicated that < 3 categories were true, then a person was classified as unlikely SLE. If three of the 12 categories were

marked as true, then the person was classified as possible SLE. If the person indicated that at least four of the 12 categories were true, then the person was classified as probable SLE.

^cThe bottom two categories (0 and 1) for number of ACR criteria were combined as no individuals in the transitioned group had 0 ACR criteria at baseline.

^dSleep data are missing for 23 individuals-3 who transitioned and 20 who did not transition.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Reported Conditions and Associated Features of SLE by Sleep Status of the Study Participant at Baseline.

Variable (n, %)	Sleep <7 Hours N=152	Sleep ≥ 7 Hours N=261	p-value
Sleep Medication Use at Baseline: Yes	20 (13.2%)	30 (11.5%)	0.62
Prednisone Use at Baseline: Yes	34 (22.4%)	31 (11.8%)	0.005
Reported Depression at Baseline: Yes	73 (48.0%)	95 (36.3%)	0.02
Chronic Fatigue at Baseline: Yes	69 (45.4%)	76 (29.1%)	0.0008
Anxiety at Baseline: Yes	49 (32.2%)	64 (24.5%)	0.07
Number of ACR Criteria Baseline:			0.002
0–1	89 (58.6%)	191 (73.2%)	
2	40 (26.3%)	54 (20.7%)	
3	23 (15.1%)	16 (6.1%)	
SLE-CSQ Categories Baseline:			0.003
Unlikely SLE	74 (48.7%)	165 (63.2%)	
Possible SLE	13 (8.5%)	27 (10.3%)	
Probable SLE	65 (42.8%)	69 (26.4%)	
Vitamin D Deficient: Yes	73 (48.0%)	75 (28.7%)	<0.0001

Significant differences are noted in bold. CSQ, Connective Tissue Disease Screening Questionnaire. ACR, American College of Rheumatology

Less Than Seven Hours of Sleep a Night is Associated with Transitioning to SLE Independent of Associated Features of SLE.

Table 3

Baseline Characteristics	Base Model	Transitioned to SLE (Odds Ratio (95% CI))							
		Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Age	–	1.0 (0.98–1.01)	1.0 (0.96–1.01)	1.0 (0.98–1.01)	1.0 (0.98–1.03)	1.0 (0.98–1.02)	1.0 (0.98–1.02)	1.0 (0.98–1.02)	0.99 (0.97–1.02)
Sex	–	1.3 (0.6–3.0)	0.8 (0.3–1.0)	0.9 (0.4–2.3)	0.7 (0.3–1.8)	1.1 (0.4–3.1)	0.7 (0.3–1.7)	1.3 (0.6–2.9)	1.0 (0.4–2.8)
Race (Non EA)	–	0.9 (0.4–2.0)	1.1 (0.4–3.0)	0.7 (0.3–0.8)	1.1 (0.4–2.7)	1.1 (0.5–2.4)	1.4 (0.5–3.3)	0.7 (0.3–1.7)	0.9 (0.4–2.1)
Sleep <7 hours	2.8 (1.6–4.9)	2.9 (1.6–5.1)	2.1 (1.1–4.2)	2.5 (1.4–4.6)	2.1 (1.1–3.9)	2.3 (1.2–4.5)	2.0 (1.1–3.8)	2.7 (1.5–4.8)	2.0 (1.1–4.2)
Prednisone Use	–	–	15.5 (7.7–31.4)	–	–	–	–	–	7.9 (3.6–17.6)
Self-reported depression	–	–	–	3.6 (1.9–6.7)	–	–	–	–	–
Self-reported chronic fatigue	–	–	–	–	18.3 (7.7–43.1)	–	–	–	–
ACR criteria:	–	–	–	–	–	–	–	–	–
2						13.4 (5.3–34.3)			7.3 (2.9–18.3)
3						180.8 (27.8–1174.4)			52.7 (8.3–335.7)
SLE-CSQ Categories:	–	–	–	–	–	–	–	–	–
Possible SLE							5.3 (1.3–21.0)		
Probable SLE							28.1 (1.8–441.0)		
Vitamin D Deficient	–	–	–	–	–	–	–	2.6 (0.8–8.8)	1.5 (0.3–7.7)

CSQ, Connective Tissue Disease Screening Questionnaire, ACR, American College of Rheumatology.