

Sleep disturbance in adults with chronic pruritic dermatoses is associated with increased C-reactive protein levels



Sagar P. Patel, MD,^a Raveena Khanna, BA,^{a,b} Justin Choi, BA,^a Kyle A. Williams, BS,^a Youkyung S. Roh, BA,^a Michael S. Hong, BS,^a Nishadh H. Sutaria, BS,^a Thomas Pritchard, MPH,^a Madan M. Kwatra, PhD,^c and Shawn G. Kwatra, MD^a
Baltimore, Maryland; Omaha, Nebraska; and Durham, North Carolina

Background: Pruritus is a common symptom that can significantly reduce quality of life through sleep disruption.

Objective: To examine features of disturbed sleep in patients with chronic pruritic dermatoses and test the hypothesis that systemic inflammation may serve as a biomarker for impaired sleep in these patients.

Methods: Cross-sectional analysis of the National Health and Nutrition Examination Survey investigating systemic inflammation using C-reactive protein (CRP) levels. Logistic regression was used to compare patients with and without sleep disturbances, adjusting for demographics (model 1) and medical comorbidities (model 2).

Results: Chronic pruritic dermatoses were associated with multiple sleep disturbances, including nighttime awakenings (model 1: odds ratio [OR], 1.646; 95% confidence interval [CI], 1.031-2.627; model 2: OR, 1.329; 95% CI, 0.888-1.989) and early morning awakening (model 1: OR, 1.669, 95% CI, 1.118-2.493; model 2: OR, 1.582; 95% CI, 1.008-2.481). Mean CRP levels were 52.8% higher among patients with pruritic dermatoses reporting trouble sleeping compared with those who did not (0.663 vs 0.434 mg/dL; $P = .034$). Trouble sleeping was also positively correlated with CRP levels ($\beta = 0.142$, $P = .025$).

Limitations: Potential recall bias among participants.

Conclusions: In addition to confirming sleep disturbances with pruritic dermatoses, we found these disturbances are more likely to present with elevated CRP levels. Clinicians should consider the potential risk for sleep-related and cardiac comorbidities in patients diagnosed with itchy skin conditions. (*J Am Acad Dermatol* 2021;84:265-72.)

Key words: biomarkers; C-reactive protein; dermatoses; eczema; inflammation; inflammatory; itch; NHANES; pruritic dermatoses; pruritic; pruritus; sleep.

Pruritus (itch) is a devastating symptom that dramatically reduces quality of life.¹ In particular, itch has been associated with depression, anxiety, and sleep disruption. Previous

studies assessing the impact of inflammatory skin disorders, including psoriasis and eczema, revealed an increased likelihood to report fatigue or impaired sleep quality among these patients.^{2,3} Studies also

From the Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore^a; the Creighton University School of Medicine, Omaha^b; and the Department of Anesthesiology, Duke University Medical Center, Durham.^c

Funding sources: None.

Conflicts of interest: Dr Shawn G. Kwatra is on the advisory board for Pfizer Inc, Regeneron Pharmaceuticals, and Menlo Therapeutics, has received grant funding from Pfizer Inc and Kiniksa Pharmaceuticals, and also received a Dermatology Foundation Medical Dermatology Career Development Award. Authors Patel, Khanna, Choi, Williams, Roh, Hong, Sutaria, Pritchard, and Madan M. Kwatra have no conflicts of interest.

IRB approval status: IRB approval was waived, because only an anonymous aggregate-level data count was used, and patient consent was not required.

Accepted for publication August 7, 2020.

Reprints not available from the authors.

Correspondence to: Shawn G. Kwatra, MD, Cancer Research Building II, Johns Hopkins University School of Medicine, Ste 206, 1550 Orleans St, Baltimore, MD 21231. E-mail: skwatra1@jhmi.edu.

Published online August 19, 2020.

0190-9622/\$36.00

© 2020 by the American Academy of Dermatology, Inc.

<https://doi.org/10.1016/j.jaad.2020.08.059>

found a correlation between psoriasis severity and both sleep difficulty and low sleep quality.⁴ Adults with atopic dermatitis were also more likely to present with disturbed sleep and impaired activities of daily living secondary to fatigue.⁵ The present study further describes features of disturbed sleep in patients with chronic pruritic dermatoses. In addition, we test the hypothesis that increased systemic inflammation, as measured by elevated C-reactive protein (CRP) levels, may serve as a biomarker for impaired sleep in patients with pruritic dermatoses.

METHODS

We conducted a cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES) data from 2005 to 2006, the most recent data set with our study variables.⁶ The NHANES study was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention and approved by their institutional review board with written informed consent from all participants. A stratified, randomized, multistage, probability-cluster design was used to select households that were all visited by interviewers. Survey data included sociodemographic factors, medical history, and health behaviors. Mobile examination centers were used to conduct physical examinations and collect laboratory specimens, including blood and urine. Our study population was restricted to adults, defined as participants who were at least 18 years old at the time of data collection.

Questionnaire data

Presence of chronic pruritic dermatoses was assessed by participants answering affirmatively to having “an itchy rash which was coming and going for at least 6 months.” This cohort was compared with a healthy control group without pruritic dermatoses. Each of the sleep disturbances was assessed as an ordinal variable corresponding to the frequency of the respective disturbance reported in the NHANES Sleep Disorder data set (Table I). The impact of sleep disturbances was further explored through a set of questions from the Functional Outcomes of Sleep Questionnaire focused specifically on factors affecting general productivity.⁷ This self-reported data emphasized the impact

of feeling sleepy on activities of daily living. Each of these outcome variables was assessed as a binary variable corresponding to the questions reported in the NHANES Sleep Disorder dataset (Table II).

Laboratory data

Laboratory blood samples were collected by certified phlebotomists trained in standardized laboratory procedures. Prescreened polyethylene vials and vacutainers were required for the specimen, which was stored at -20°C . All samples underwent extensive quality control procedures ensuring no background contamination. Any variation in collection procedure, collection device, or sample handling during storage and transport resulted in specimen rejection by the laboratory. Unscheduled quality assurance site visits were

used to confirm that all protocols met the 1988 Clinical Laboratory Improvement Act requirements. Specific biomarkers that have been associated with sleep disorders (eg, sleep apnea) were included in our analysis, including CRP, total cholesterol, white blood cell count, eosinophils, mean cell volume, and platelet count.^{8,9}

Serum CRP was quantified with the fully-automated Dade Behring Nephelometer II Analyzer System (Siemens Healthcare Diagnostics, Deerfield, IL) using latex particles coated with mouse monoclonal anti-CRP antibodies to form an antigen-antibody complex. Nephelometric light scattering measurements were used to calculate the CRP concentration using a calibration curve standardized to the World Health Organization International Reference Preparation of CRP. CRP levels below 0.3 mg/dL were normal, levels between 0.3 and 1.0 mg/dL were considered mildly elevated, and levels above 1.0 mg/dL were categorized as elevated.¹⁰

Statistical analysis

Statistical analysis was conducted using Stata 15 software (StataCorp, College Station, TX). Survey results were weighted to reflect the United States population using data from the United States Bureau of the Census, accounting for survey design, nonresponse, and poststratification. The statistical analysis was prespecified to specifically investigate sleep disturbances and CRP levels among the study population in an effort to reduce the risk of spurious

CAPSULE SUMMARY

- Sleep disturbance in patients with chronic pruritic dermatoses is associated with increased systemic inflammation, including increased C-reactive protein levels.
- Clinicians should consider the potential for sleep-related and cardiac comorbidities among patients with chronic pruritic dermatoses to reduce the risk of further medical morbidity.

Abbreviations used:

CI:	confidence interval
CRP:	C-reactive protein
NHANES:	National Health and Nutrition Examination Survey
OR:	odds ratio

results. The Student *t* test and the χ^2 test were used to analyze continuous and categorical data, respectively. Multiple logistic regression analysis was used to calculate unadjusted and adjusted odds ratios (ORs). Two-sided *P* values <.05 indicate statistical significance. Post hoc multiple comparisons adjustment using the Benjamini-Hochberg method, a modified Bonferroni correction, to balance the risk of type I and type II error was used, so that adjusted *P* values were ultimately reported.¹¹

To evaluate sleep disturbances, 3 total logistic regression models were constructed for each sleep disturbance in which the respective sleep disturbance was the dependent variable. In addition to the unadjusted model, model 1 included age, sex, race, education, marital status, and income to account for sociodemographic factors, and model 2 included age, sex, allergy history, hay fever history, coronary artery disease, and body mass index to account for potential confounding medical comorbidities. There was not enough power in the data set to combine the adjusted models.

To evaluate the impact of sleep on activities of daily living, an unadjusted logistic regression model and a model adjusted for age, sex, race, education, income, allergy history, hay fever history, coronary artery disease, and body mass index were constructed. The association between biomarkers and sleep disturbances was evaluated by constructing an unadjusted linear regression model and a model adjusted for age, sex, allergy history, coronary artery disease, psoriasis, and body mass index.

RESULTS

The NHANES 2005 to 2006 data set included 10,348 participants (Fig 1). Of those, there were 5563 adults. We excluded 1 participant because of incomplete data on the presence of pruritic dermatoses and then excluded 2 additional participants who had no data regarding sleep behavior. Our final analysis included 5560 adults, of whom 498 (8.96%) reported pruritic dermatoses.

Among adults with chronic pruritic dermatoses, the mean age was 48.1 years vs 43.6 years in the control group (*P* = .0001; Table III). History of allergies was found in 39.6% of adults with pruritic

dermatoses vs 29.9% of the control group (*P* < .001). History of hay fever was found in 13.9% of participants with pruritic dermatoses vs 8.9% of the control group (*P* < .0001). History of coronary artery disease was found in 7.2% of participants with pruritic dermatoses vs 3.7% of the control group (*P* < .0001). The mean body mass index among those with pruritic dermatoses was 28.9 kg/m² vs 28.4 kg/m² in the control group (*P* = .163). There were no significant differences in the sex (*P* = .377), race (*P* = .098), and income (*P* = .156) between those with pruritic dermatoses and the control group.

Association between pruritic dermatoses and sleep disturbances

An association was found between having pruritic dermatoses compared with not having pruritic dermatoses and reporting trouble sleeping to a physician (30.2% vs 19.7%; OR, 1.436; 95% confidence interval [CI], 1.079-1.909; *P* = .029) (Table I). However, this association did not hold in the adjusted model 1 (OR, 1.377; 95% CI, 0.987-1.922; *P* = .105) or model 2 (OR, 1.329; [95% CI, 0.941-1.878; *P* = .220). Being diagnosed with a sleep disorder was associated with having pruritic dermatoses compared with not having pruritic dermatoses (11.5% vs 5.9%; OR, 1.889; 95% CI, 1.206-2.959; *P* = .016), which remained significant when adjusted for sociodemographic factors but not when adjusted for medical comorbidities in model 1 (OR, 1.715; 95% CI, 1.140-2.578; *P* = .023) and model 2 (OR, 1.581; 95% CI, 0.939-2.663; *P* = .180).

Pruritic dermatoses were associated with trouble falling asleep 1 to 5 times a month in all models (OR, 1.483 [95% CI, 1.111-1.979]; *P* = .020; model 1: OR, 1.490 [95% CI, 1.121-1.981]; *P* = .016; model 2: OR, 1.510 [95% CI, 1.102-2.069]; *P* = .031) but not with trouble falling asleep more than 5 times a month (OR, 1.419 [95% CI, 0.935-2.154]; *P* = .171; model 1: OR, 1.378 [95% CI, 0.830-2.289]; *P* = .358; model 2: OR, 1.009 [95% CI, 0.983-1.017]; *P* = .129).

Pruritic dermatoses were associated with waking up during the night (OR, 1.648 [95% CI, 1.077-2.521]; *P* = .044; model 1: OR, 1.646 [95% CI, 1.031-2.627]; *P* = .069; model 2: OR, 1.329 [95% CI, 0.888-1.989]; *P* = .073), waking up too early in the morning (OR, 1.616 [95% CI, 1.061-2.460]; *P* = .051; model 1: OR, 1.669 [95% CI, 1.118-2.493]; *P* = .029; model 2: OR, 1.582 [95% CI, 1.008-2.481]; *P* = .102), feeling overly sleepy during the day (OR, 1.732 [95% CI, 1.145-2.622]; *P* = .024; model 1: OR, 1.786 [95% CI, 1.144-2.789]; *P* = .025; model 2: OR, 1.664 [95% CI, 1.073-2.581]; *P* = .058), leg jerks while sleeping (OR, 1.860 [95% CI, 1.139-3.037]; *P* = .031; model 1: OR, 1.745 [95% CI, 1.058-2.878]; *P* = .056; model 2:

Table I. Association between pruritic dermatoses and sleep disturbances in adults

Variable	No rash, Freq (%)	Rash, Freq (%)	Unadjusted odds ratio (<i>P</i> value)	Adjusted model 1* (<i>P</i> value)	Adjusted model 2† (<i>P</i> value)
Ever told doctor had trouble sleeping?					
No	4058 (80.28)	346 (69.76)			
Yes	997 (19.72)	150 (30.24)	1.436 (.029)	1.377 (.105)	1.329 (.220)
Ever told by doctor have sleep disorder?					
No	4755 (94.03)	440 (88.53)			
Yes	302 (5.97)	57 (11.47)	1.889 (.016)	1.715 (.024)	1.581 (.180)
How often have trouble falling asleep?					
Never	2216 (43.79)	167 (33.60)			
1-5 times a month	2058 (40.66)	237 (47.69)	1.482 (.020)	1.490 (.016)	1.510 (.031)
6-30 times a month	787 (15.55)	93 (18.71)	1.42 (.171)	1.378 (.358)	1.553 (.129)
How often wake up during night?					
Never	1986 (39.27)	147 (29.64)			
1-5 times a month	2145 (42.42)	213 (42.94)	1.341 (.160)	1.467 (.076)	1.270 (.447)
6-30 times a month	926 (18.31)	136 (27.42)	1.648 (.044)	1.646 (.069)	1.629 (.073)
How often wake up too early in morning?					
Never	2313 (45.75)	192 (38.71)			
1-5 times a month	1917 (37.92)	189 (38.10)	1.13 (.876)	1.110 (.999)	1.119 (.999)
6-30 times a month	826 (16.34)	115 (23.19)	1.62 (.051)	1.669 (.029)	1.581 (.102)
How often feel unrested during the day?					
Never	1625 (32.16)	120 (24.14)			
1-5 times a month	2222 (43.97)	215 (43.26)	1.082 (.999)	1.167 (.627)	1.159 (.876)
6-30 times a month	1206 (23.87)	162 (32.60)	1.405 (.291)	1.552 (.176)	1.499 (.251)
How often feel overly sleepy during day?					
Never	1783 (35.27)	124 (25.05)			
1-5 times a month	2385 (47.18)	243 (49.09)	1.289 (.156)	1.306 (.171)	1.260 (.333)
6-30 times a month	887 (17.55)	128 (25.86)	1.732 (.024)	1.786 (.025)	1.664 (.058)
How often did you not get enough sleep?					
Never	1573 (31.19)	115 (23.19)			
1-5 times a month	2256 (44.74)	227 (45.77)	1.223 (.353)	1.319 (.204)	1.354 (.255)
6-30 times a month	1214 (24.07)	154 (31.05)	1.455 (.089)	1.603 (.056)	1.598 (.060)
How often take pills to help you sleep?					
Never	4252 (84.02)	401 (80.68)			
1-5 times a month	432 (8.54)	49 (9.86)	1.087 (.999)	0.990 (.999)	1.130 (.971)
6-30 times a month	377 (7.45)	47 (9.46)	0.941 (.999)	0.874 (.893)	0.840 (.853)
How often leg jerks while sleeping?					
Never	4038 (80.36)	350 (70.99)			
1-5 times a month	743 (14.79)	99 (20.08)	1.563 (.064)	1.589 (.045)	1.634 (.044)
6-30 times a month	244 (4.86)	44 (8.92)	1.860 (.031)	1.745 (.056)	1.825 (.076)
How often leg cramps while sleeping?					
Never	3552 (70.25)	280 (56.45)			
1-5 times a month	1220 (24.13)	161 (32.46)	1.789 (.002)	1.747 (.003)	1.759 (.004)
6-30 times a month	284 (5.62)	55 (11.09)	2.368 (.002)	2.460 (.002)	2.459 (.002)

Freq, Frequency.

*Model 1 has been adjusted for age, sex, race, education, marital status, and income.

†Model 2 has been adjusted for age, sex, allergy history, hay fever history, coronary artery disease, and body mass index.

OR, 1.825 [95% CI, 1.053-3.162]; *P* = .076), and leg cramps while sleeping (OR, 2.368 [95% CI, 1.540-3.640]; *P* = .002; model 1: OR, 2.460 [95% CI, 1.525-3.967]; *P* = .002; model 2: OR, 2.459 [95% CI, 1.574-3.840]; *P* = .002) more than 5 times a month in at least 1 of our models.

Pruritic dermatoses were not associated with feeling unrested during the day (OR, 1.404 [95% CI,

0.861-2.292]; *P* = .291; model 1: OR, 1.552 [95% CI, 0.914-2.636]; *P* = .176; model 2: OR, 1.499 [95% CI, 0.898-2.504]; *P* = .251), not getting enough sleep (OR, 1.455 [95% CI, 1.001-2.117]; *P* = .089; model 1: OR, 1.603 [95% CI, 1.049-2.450]; *P* = .056; model 2: OR, 1.598 [95% CI, 1.064-2.399]; *P* = .060), or taking sleeping pills (OR, 0.941 [95% CI, 0.628-1.409]; *P* = .999; model 1: OR, 0.875 [95% CI,

Table II. Association between pruritic dermatoses and difficulty with activities of daily living secondary to fatigue

Variable	No rash, Freq (%)	Rash, Freq (%)	Unadjusted odds ratio (P value)	Adjusted model* (P value)
Difficulty concentrating when tired?				
No	3827 (76.43)	324 (65.99)		
Yes	1180 (23.57)	167 (34.01)	1.564 (<.001)	1.412 (.008)
Difficulty remembering when tired?				
No	4095 (81.61)	346 (70.33)		
Yes	923 (18.39)	146 (29.67)	1.703 (.003)	1.524 (.032)
Difficulty eating when tired?				
No	4836 (96.01)	454 (91.90)		
Yes	201 (3.99)	40 (8.10)	2.409 (<.001)	2.400 (.003)
Difficulty with a hobby when tired?				
No	4247 (87.15)	355 (75.85)		
Yes	626 (12.85)	113 (24.15)	2.061 (<.001)	2.176 (.001)
Difficulty getting things done when tired?				
No	4223 (87.54)	372 (79.66)		
Yes	601 (12.46)	95 (20.34)	1.558 (.007)	1.492 (.035)
Difficulty with finance when tired?				
No	4225 (87.86)	367 (79.61)		
Yes	584 (12.14)	94 (20.39)	1.587 (.004)	1.514 (.040)
Difficulty at work because tired?				
No	4097 (90.28)	346 (83.57)		
Yes	441 (9.72)	68 (16.43)	1.925 (.002)	1.767 (.021)
Difficulty on phone when tired?				
No	4506 (90.43)	423 (85.63)		
Yes	477 (9.57)	71 (14.37)	1.489 (.022)	1.390 (.077)

Freq, Frequency.

*Adjusted model was adjusted for age, sex, race, education, income, allergy history, hay fever history, coronary artery disease, and body mass index.

0.585-1.309]; $P = .893$; model 2: OR, 0.841 [95% CI, 0.557-1.269]; $P = .853$).

Association between pruritic dermatoses and difficulty with activities of daily living secondary to fatigue

Participants with pruritic dermatoses were more likely to report difficulty with all activities of daily living secondary to fatigue compared with those without pruritic dermatoses in both the unadjusted and adjusted models (Table II). Specifically, they were more likely to report difficulty concentrating (OR, 1.564 [95% CI, 1.297-1.901]; $P < .001$; adjusted model: OR, 1.412 [95% CI, 1.145-1.740]; $P = .008$), difficulty remembering (OR, 1.703, 95% CI, 1.241-2.337]; $P = .003$; adjusted model: OR, 1.524 [95% CI, 1.114-2.085]; $P = .032$), difficulty eating (OR, 2.409 [95% CI, 1.612-3.601]; $P < .001$; adjusted model: OR, 2.400 [95% CI, 1.499-3.843]; $P = .003$), difficulty with a hobby (OR, 2.061 [95% CI, 1.572-2.701]; $P < .001$; adjusted model: OR, 2.176 [95% CI, 1.596-2.964]; $P = .001$), difficulty getting things done (OR, 1.558 [95% CI, 1.161-2.091]; $P = .007$; adjusted model: OR, 1.492 [95% CI, 1.104-2.017];

$P = .035$), difficulty with finance (OR, 1.587 [95% CI, 1.195-2.109]; $P = .004$; adjusted model: OR, 1.514 [95% CI, 1.097-2.088]; $P = .040$), difficulty at work (OR, 1.925 [95% CI, 1.341-2.762]; $P = .002$; adjusted model: OR, 1.767 [95% CI, 1.185-2.634]; $P = .021$), and difficulty on the phone (OR, 1.489 [95% CI, 1.078-2.055]; $P = .022$; adjusted model: OR, 1.390 [95% CI, 1.039-1.858]; $P = .077$) when tired (Fig 2).

Associations between sleep disturbances and biomarkers among those with pruritic dermatoses

Among patients with chronic pruritic dermatoses, mean CRP levels were 52.8% higher in those reporting trouble sleeping compared with those who did not (0.663 vs 0.434 mg/dL; $P = .034$). Furthermore, pruritic dermatoses were positively correlated with CRP levels in the unadjusted model with a β -coefficient of 0.155 (95% CI, 0.019-0.291; $P = .028$) and a β -coefficient of 0.142 (95% CI, 0.021-0.263; $P = .025$; $n = 454$) in the adjusted model, which included age, sex, allergy history, coronary artery disease, and body mass index (Supplemental

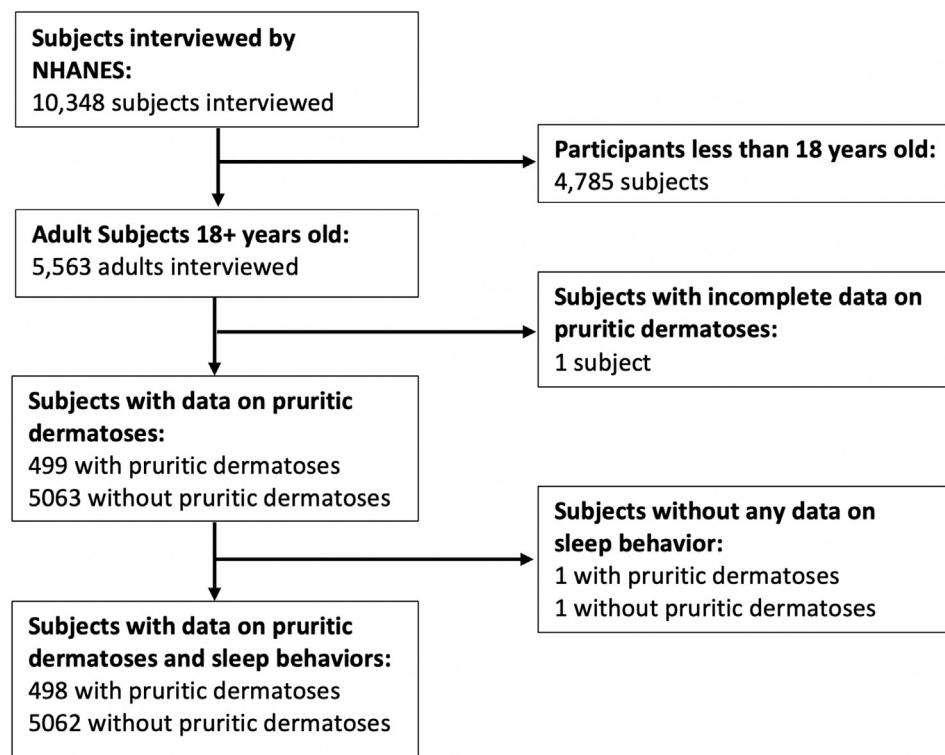


Fig 1. Summary of selection of study participants and the analytic population. *NHANES*, National Health and Nutrition Examination Survey.

Table III. Demographic characteristics of study population

Variable*	Pruritic dermatoses (n = 498)	No pruritic dermatoses (n = 5062)	P value
Age, mean (SE), y	48.1 (0.921)	43.607 (0.273)	.0001
Sex			.377
Female	249 (50.0)	2636 (52.07)	
Male	249 (50.0)	2426 (47.93)	
Race/ethnicity			.098
Hispanic	103 (20.68)	1253 (24.75)	
White	261 (52.41)	2370 (46.82)	
Black	111 (22.29)	1230 (24.30)	
Other	23 (4.62)	209 (4.13)	
Married	246 (49.40)	2462 (48.64)	.746
Income			.156
<\$35,000	221 (47.42)	2100 (44.01)	
≥\$35,000	245 (52.69)	2672 (55.99)	
Allergy history	197 (39.64)	1507 (29.85)	<.0001
Hay fever history	69 (13.94)	454 (8.99)	<.0001
Coronary artery disease	32 (7.17)	168 (3.73)	<.0001
BMI, mean (SE), kg/m ²	28.934 (0.319)	28.475 (0.098)	.163

BMI, Body mass index.

*Data are presented as number (%) unless indicated otherwise.

Table I, available via Mendeley at <https://data.mendeley.com/datasets/fm9xvwkfnr/2>.

Overall, 42.4% of patients with a rash had a mildly elevated/normal CRP vs 39.2% of patients without a rash ($P = .28$). Rates of elevated CRP were similarly

marginally higher among patients with a rash (12.9% vs 11.3%, $P = .43$). Among patients with pruritic dermatoses, mildly elevated/normal levels were observed in 50.6% of patients with sleep disturbances compared with 39.3% of patients without

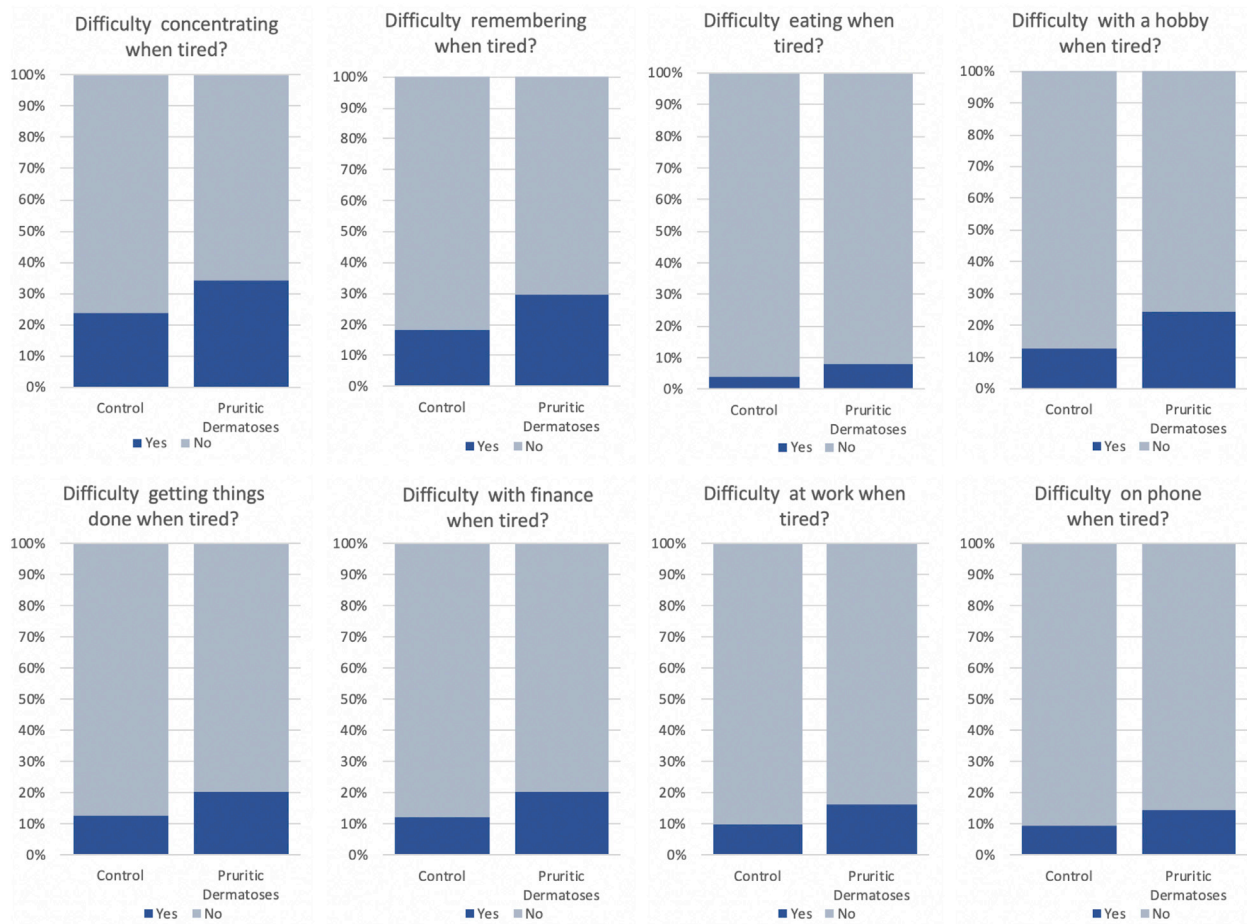


Fig 2. Reported difficulties with activities of daily living secondary to fatigue. Presence of pruritic dermatoses was associated with an increased odds of difficulty with each of these activities of daily living in both adjusted and unadjusted models. *P* value is <.05 unless otherwise noted.

sleep disturbances ($P = .083$). Among that same cohort, elevated CRP was observed in 17.7% of patients with sleep disturbances vs in 11.1% of patients without sleep disturbances ($P = .133$). Furthermore, trouble sleeping was associated with an increased likelihood of a mildly elevated CRP (OR, 1.701 [95% CI, 1.043-2.775]; $P = .035$; adjusted model: OR, 1.726 [95% CI, 1.039-2.864]; $P = .037$; $n = 454$) and elevated CRP (OR, 1.598 [95% CI, 1.004-2.642]; $P = .048$; adjusted model: OR, 1.712 [95% CI, 1.002-3.076]; $P = .046$; $n = 454$) when adjusted for age, sex, allergy history, coronary artery disease, and body mass index (Supplemental Table I).

No significant difference was found between those with and without sleep disturbances for total cholesterol (193 vs 198 mg/dL; $P = .364$), white blood cell count (7.64 vs 7.42 cells/ μ L; $P = .474$), eosinophils (3.2% vs 2.9%; $P = .439$), mean cell volume (90.0 vs 90.1 fL; $P = .936$), or platelet count (276.4 vs 269.7 $\times 10^3/\mu$ L; $P = .483$) (Supplemental Table II).

DISCUSSION

Our study demonstrates that adults with chronic pruritic dermatoses are more likely to experience fatigue and sleep disturbances, including trouble falling asleep, early morning awakenings, daytime sleepiness, lack of sleep, frequent nighttime awakening, and leg jerks and cramps while sleeping compared with adults without pruritic dermatoses. Those with itchy skin conditions are also more likely to report difficulty with all activities of daily living secondary to fatigue, even after controlling for comorbidities and sociodemographics. Despite these sleep disturbances and the effects of fatigue, adults with pruritic dermatoses were not more likely to report sleep difficulties to their physicians when we adjusted for comorbidities and sociodemographics. Furthermore, this study uncovers an association between elevated CRP levels in patients with pruritic dermatoses who have trouble sleeping compared with those with pruritic dermatoses and no trouble sleeping.

Our results expand on previous studies assessing the burden of sleep and fatigue in patients with atopic dermatitis.^{5,12} We investigated pruritic dermatoses, assessing not only the impact of sleep disturbances and fatigue on patient activities of daily living and quality of life but also the systemic inflammatory response as measured by CRP. Various reports suggest the role of inflammatory mediators such as CRP as biomarkers for disease activity in conditions such as chronic spontaneous urticaria and sleep disorders such as obstructive sleep apnea.^{9,13,14} As a high-sensitivity marker of inflammation, CRP concentrations have also been shown to increase with shorter sleep duration and be a predictive measure of cardiovascular events and morbidity.^{13,15-18} As demonstrated in our study, systemic inflammation is linked to sleep disturbances associated with chronic pruritic skin disease as well.

The strengths of this study include use of a large-scale, nationally representative data set with more than 10,000 participants and a randomly sampled and diverse patient population. Given the range of conditions associated with pruritus, this is the first study, to our knowledge, to provide comprehensive epidemiologic data on the burden of disturbed sleep and fatigue in patients with pruritic skin conditions. Our results controlled for potentially confounding factors, including sociodemographic information and comorbidities.

Limitations of our study include lack of independent medical record review for itch severity and treatment. Our findings are also limited to self-reported results that were not verified clinically. Thus, there is significant risk for recall bias. Given the cross-sectional design of our investigation, our findings provide strong associations, but causality cannot be proven from our results. Future studies should further investigate the relationship between sleep disorders and the inflammatory cascade associated with pruritic dermatoses to explore causality.

CONCLUSION

Chronic pruritic dermatoses are associated with the diagnosis of a sleep disorder and increased sleep disturbances, which have a significant negative impact on patient activities of daily living secondary to fatigue. This study also reveals that among adults with pruritic dermatoses, those with sleep disturbances are more likely to present with elevated CRP levels. As such, clinicians should consider the potential risk for sleep-related and cardiac

comorbidities in patients diagnosed with itchy skin conditions.

REFERENCES

1. Boozalis E, Grossberg AL, Puttgen KB, Cohen BA, Kwatra SG. Itching at night: a review on reducing nocturnal pruritus in children. *Pediatr Dermatol*. 2018;35(5):560-565.
2. Mostaghimi L, Hetzel S. Insomnia and other sleep complaints in inflammatory versus noninflammatory skin disorders: an observational case-control study. *Int J Dermatol*. 2019;58(8):976-981.
3. Henry AL, Kyle SD, Chisholm A, Griffiths CEM, Bundy C. A cross-sectional survey of the nature and correlates of sleep disturbance in people with psoriasis. *Br J Dermatol*. 2017;177(4):1052-1059.
4. Smith MP, Ly K, Thibodeaux Q, et al. Factors influencing sleep difficulty and sleep quantity in the Citizen Scientist Psoriatic Cohort. *Dermatol Ther (Heidelb)*. 2019;9(3):511-523.
5. Yu SH, Attarian H, Zee P, Silverberg JI. Burden of sleep and fatigue in US adults with atopic dermatitis. *Dermatitis*. 2016;27(2):50-58.
6. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey Data. U.S. Department of Health & Human Services; 2006.
7. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep*. 1997;20(10):835-843.
8. Hirotsu C, Albuquerque RG, Nogueira H, et al. The relationship between sleep apnea, metabolic dysfunction and inflammation: the gender influence. *Brain Behav Immun*. 2017;59:211-218.
9. Li K, Wei P, Qin Y, Wei Y. Is C-reactive protein a marker of obstructive sleep apnea?: a meta-analysis. *Medicine (Baltimore)*. 2017;96(19):e6850.
10. Nehring SM, Patel BC. C reactive protein (CRP). StatPearls Publishing; 2019.
11. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B*. 1995;57(1):289-300.
12. Ramirez FD, Chen S, Langan SM, et al. Association of atopic dermatitis with sleep quality in children. *JAMA Pediatr*. 2019;173(5):e190025.
13. Liu R, Liu X, Zee PC, et al. Association between sleep quality and C-reactive protein: results from national health and nutrition examination survey, 2005-2008. *PLoS One*. 2014;9(3):e92607.
14. Deza G, Ricketti PA, Giménez-Arnau AM, Casale TB. Emerging biomarkers and therapeutic pipelines for chronic spontaneous urticaria. *J Allergy Clin Immunol Pract*. 2018;6(4):1108-1117.
15. Kushner I, Rzewnicki D, Samols D. What does minor elevation of C-reactive protein signify? *Am J Med*. 2006;119(2):166.e17-166.e28.
16. Van der Touw T, Andronicos NM, Smart N. Is C-reactive protein elevated in obstructive sleep apnea? A systematic review and meta-analysis. *Biomarkers*. 2019;24(5):429-435.
17. Richardson MR, Churilla JR. Sleep duration and C-reactive protein in US adults. *South Med J*. 2017;110(4):314-317.
18. Meier-Ewert HK, Ridker PM, Rifai N, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol*. 2004;43(4):678-683.