Sleep Disturbance and Sleep-Related Impairment in Adults With Atopic Dermatitis: A Cross-sectional Study

Jennifer C. Li, BS,* Anna Fishbein, MD,†‡ Vivek Singam, BLA,* Kevin R. Patel, BS,* Phyllis C. Zee, MD, PhD,‡§ Hrayr Attarian, MD,‡§ David Cella, PhD,|| and Jonathan I. Silverberg, MD, PhD, MPH*||¶#

Background: **Little is known about the impact of sleep disturbances (SD) or sleep-related impairment (SRI) in adults with AD or their relationship with severity of AD and itch and other predictors.**

Objective: **The aim of this study was to determine the relationship between AD severity, SD, and SRI.**

Methods: **We conducted a prospective online questionnaire-based study of 287 adults with AD, including assessment of AD severity by Patient-Oriented Eczema Measure, self-reported global AD severity, Self-Assessed Eczema Area and Severity Index and visual analog scale–itch, Patient-Reported Outcome Measurement Information System SD and SRI individual items, and *T* scores.**

Results: **Adults with AD commonly endorsed all SD and SRI symptoms examined; only 58 (21.8%) reported having good or very good sleep quality in the past week. However, only a minority of adults with AD endorsed a more profound impact from these individual aspects of SD and SRI in the past week or Patient-Reported Outcome Measurement Information System *T* scores greater than 55. In particular, SD and SRI were associated with severe or very severe AD (Patient-Oriented Eczema Measure, self-reported severity, visual analog scale–itch, and/or Self-Assessed Eczema Area and Severity Index). Sleep-related impairment was also associated with comorbid hay fever and/or anxiety.**

Conclusions: **This study suggests that SD and SRI are common in adults with AD, particularly those with severe diseases. Sleep disturbances and SRI should be considered when assessing burden of AD and therapeutic decisions.**

Atopic dermatitis (AD) is a highly symptomatic, inflammatory skin condition that is associated with intense itch and skin pain.[1] A previous study found that fatigue, regular insomnia, and regular daytime sleepiness were reported by 26% to 34% of US adults with AD and associated with poorer quality of life.[2] Another study found that US adults with AD have significantly impaired sleep and fatigue affecting instrumental activities of daily living.[3] Although sleep disturbances (SDs) are a well-established concern in the management of AD, little is known about the relationship of the severity of AD and itch with SDs and sleep-related impacts (SRIs). We hypothesized that most patients with AD have at least some symptoms of SD and SRI, but only a small subset has profound SD and SRI. However, little is known about other predictors of profound SD and SRI among adults with AD. We hypothesized that SD and SRI have a complex relationship with severity of AD and itch. In the present study, we studied the impact of SD and SRI in adults with AD.

*From the Departments of *Dermatology and †Allergy and Immunology, ‡Center for Circadian and Sleep Medicine, and Departments of §Neurology, ||Medical Social Sciences, and ¶Preventive Medicine, Feinberg School of Medicine at Northwestern University; and #Northwestern Medicine Multidisciplinary Eczema Center, Chicago, IL.*

Address reprint requests to Jonathan I. Silverberg, MD, PhD, MPH, Department of Dermatology, Northwestern University Feinberg School of Medicine, Suite 1600, 676 N St Clair St, Chicago, IL 60611. E-mail: JonathanISilverberg@gmail.com.

This publication was made possible with support from the Agency for Healthcare Research and Quality (grant K12HS023011) and the Dermatology Foundation.

The authors have no conflicts of interest to declare.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.dermatitisjournal.com).

DOI: 10.1097/DER.0000000000000401

METHODS

Subjects

This questionnaire-based study was approved by the institutional review board at Northwestern University for adults (aged ≥18 years, male or female) with AD. The questionnaire was uploaded to Research Data Capture Software, and members of nonprofit support groups (National Eczema Association and National Eczema Society) for AD were invited to participate by responding to the survey. All patients provided electronic informed consent. Neither the initial invitation to participate in the study nor the informed consent statement explicitly mentioned that the study was about SDs.

Responses from initiation of the study in June 2014 to January 2015 were reviewed. The completion rate for the survey was 95.1% among those who began the survey; partial responses were excluded. The questionnaire took an average of 18 minutes (range, 15–23 minutes) to complete. Data were deidentified and confidential and posed a minimal risk to participants.

Questionnaire

The questionnaire was developed to determine the burden of AD in adults (Supplemental Digital Content, http://links.lww.com/DER/A14). The questionnaire included questions about sociodemographics, health behaviors, employment, history of atopic and mental health disorders, and previously validated patient-reported outcome (PRO) assessments of eczema, including Patient-Oriented Eczema Measure (POEM),[4,5] self-reported global AD severity, Self-administered Eczema Area and Severity Index (SA-EASI) as a measure of lesional extent and severity,[6] and visual analog scale for itch (VAS-itch).[7]

Sleep was assessed using questions about self-reported sleep duration and the Patient-Reported Outcome Measurement Information System (PROMIS) questionnaires for SD and SRI.[8] Patient-Reported Outcome Measurement Information System was developed by a National Institutes of Health–funded consortium that aims to develop questionnaires that measure key health-outcome domains.[9] Patient-Reported Outcome Measurement Information System SD assesses perceptions of sleep quality, sleep depth, and restoration associated with sleep; perceived difficulties and concerns with getting to sleep or staying asleep; and perceptions of the adequacy of and satisfaction with sleep. Patient-Reported Outcome Measurement Information System SRI assesses perceptions of alertness, sleepiness, and tiredness during usual waking hours and the perceived functional impairments during wakefulness associated with sleep problems or impaired alertness. These instruments were previously validated and found to strongly correlate with both objective and other PRO measures of sleep quality.[8] Using lookup tables,[8] the total score was converted to a *T*-score that is referenced to the US general population.

Data Processing and Statistical Analysis

Patient-Oriented Eczema Measure, SA-EASI, VAS-itch, and PROMIS SD and SRI *T*-scores were analyzed as both interval and ordinal variables. None of the scores were normally distributed; therefore, nonparametric assessments were used. Patient-Oriented Eczema Measure was analyzed as an ordinal variable using previously developed bands (clear/almost clear, 0–2; mild, 3–7; moderate, 8–16; severe, 17–24; very severe, 25–28).[10] Visual analog scale for itch was analyzed using previously developed bands (none, 0; mild, >0 to <40; moderate, ≥40 to <70; severe, ≥70 to <90; very severe, ≥90).[11] Self-administered Eczema Area and Severity Index was analyzed as an ordinal variable by dividing into tertiles.

To determine the relationship of AD severity with sleep outcomes, ordinal logistic regression models were constructed with individual questions from PROMIS SD and SRI as the outcome variables. All questions used a 5-point Likert scale. This approach was used because it allowed for an estimation of a single odds ratio (OR) and 95% confidence interval (CI) across all levels of the dependent variable simultaneously, rather than arbitrarily setting a cutoff point and analyzing with binary logistic regression. The proportional odds assumption was met for all outcomes (score test, $P > 0.05$). Patient-Oriented Eczema Measure, self-reported global AD severity VAS-itch, and SA-EASI were the ordinal explanatory variables. Multivariable models included comorbid asthma, hay fever, depression and anxiety (binary), body mass index (continuous), insurance status (binary), alcohol consumption (binary), history of smoking cigarettes (binary) or using snuff (binary), race/ethnicity (white, black, Hispanic, Asian, multiracial/other), age (continuous), and sex (male, female). Adjusted OR and 95% CI were estimated.

To test the relationship of AD severity with PROMIS SD and SRI, 2 different approaches were used. First, linear regression models were constructed with PROMIS SD or SRI as the continuous dependent variable. The continuous independent variables were AD severity, that is, POEM, VAS-itch, or SA-EASI. Based on a visual inspection of scatterplots, a nonlinear relationship was examined. Linear and multiple orders of spline functions were tested and retained based on the best statistical fit. A penalized spline term with 1 knot was the best-fitting model. Inclusion of the penalized spline in the regression models allowed for a nonlinear relationship between variables. Second, the proportions of patients with no to slight (*T*-score < 55), mild (55–59), moderate (60–69), and severe (≥70) SD and SRI were determined across different strata for POEM, self-reported global AD severity, VAS-itch, and SA-EASI scores.

Because factors other than itch and AD severity impact sleep, we constructed multivariable logistic regression models with SD and SRI *T*-scores of 55 or greater as the binary outcome variables and stepwise selection from 20 independent covariates, including sociodemographics and comorbid allergic and mental health disorders ($\alpha = 0.15$).

All data analyses and statistical processes were performed using SAS version 9.4 (SAS Institute, Cary, NC). A 2-sided value of $P < 0.05$ was used to indicate significance for all estimates.

RESULTS

Participant Characteristics

Two hundred eighty-seven adults were enrolled in the study. Participants were distributed across ages 18 to 69 years and a range of household income levels; were predominantly female (79.1%), white (80.7%), and non-Hispanic (89.9%); and had post–high school education (83.3%) (Table 1).

Most subjects reported their AD to be moderate to very severe over the past week based on the POEM score (92.3%) and self-reported global AD severity (90.5%), with a median active itch of 65 on a 100-point scale (range, 5–100) and a median total SA-EASI score of 16.8 (range, 1.1–81).

TABLE 1. Baseline Demographics and Clinical Parameters of Study Cohort (N = 287)

Parameter	n (%)
Age, y	
18–29	111 (39.0)
30–39	71 (24.9)
40–49	48 (16.8)
50–59	39 (13.7)
60–69	16 (5.6)
Sex	
Female	220 (79.1)
Male	58 (20.9)
Race	
White	218 (80.7)
African American	8 (3.0)
Asian/Pacific Islander	24 (8.9)
Other/multiracial	20 (7.4)
Hispanic origin	
Yes	26 (10.1)
No	231 (89.9)
Household income	
<$25,000	66 (25.9)
$25,000–$74,999	102 (40.0)
$75,000–$199,999	70 (27.5)
≥$200,000	17 (6.7)
Highest level of household education	
Less than high school	2 (0.7)
High school or GED	43 (15.9)
Greater than high school	225 (83.3)
Health insurance coverage	
No insurance	47 (17.9)
Government insurance	90 (34.2)
Private insurance	126 (47.9)
History of asthma	
No	136 (49.3)
Yes	140 (50.7)
History of hay fever	
No	97 (35.3)
Yes	178 (64.7)
History of depression	
No	179 (66.1)
Yes	92 (34.0)
History of anxiety	
No	197 (73.8)
Yes	70 (26.2)
Body mass index, median (interquartile range), kg/m^2	24.6 (8.7)
Alcohol consumption, mean ± standard deviation	
No. days per week	1.4 ± 1.5
No. drinks per day	1.8 ± 2.2
Current smoking history	
No	177 (65.1)
Yes	95 (34.9)
Current snuff/tobacco chewing history	
No	269 (99.3)
Yes	2 (0.7)

Sleep Disturbance and SRI

Most patients reported 1 or more nights of SD in the past week due to their eczema (224 [79.1%]). One hundred thirty-four subjects (47.3%) reported an average of 6 or fewer hours of sleep (short duration), whereas 130 (45.9%) and 19 (6.7%) reported 7 to 8 (normal duration) or 9 to 10 (prolonged duration) hours of sleep.

Only 58 adults with AD (21.8%) endorsed having good or very good sleep quality in the past week. In particular, adults with AD commonly endorsed having restless sleep (41.1% reporting quite a bit or very much); were not satisfied with their sleep (54.8% reporting not at all or a little bit); did not have refreshing sleep (58.5% reporting not at all or a little bit); had difficulty sleeping (36.4% reporting often or always), including falling asleep (31.4% reporting often or always) and staying asleep (31.4% reporting often or always); and did not get enough sleep (24.7% reporting often or always) (Table 2). In addition, most adults with AD reported some SRI, including difficulty getting things done because of being sleepy, not feeling alert when waking up, feeling tired, having problems during the day because of poor sleep, having a hard time concentrating because of poor sleep, being irritable because of poor sleep, feeling sleepy during daytime, and having trouble staying awake during the day.

However, a subset of subjects with AD endorsed a more profound impact from SD than SRI, with fewer than half of the subjects having a profound impact from SRI in the past week (quite a bit/very much or often/always) (Table 2). Moreover, most adults with AD had no to slight (PROMIS *T*-scores < 55) SD (208 [74.8%]) or SRI (148 [53.2%]) in the past week compared with the general population. Sixty-five (23.4%) and 5 (1.8%) subjects reported mild and moderate to severe SD, whereas 49 (17.6%) and 81 (29.1%) reported mild and moderate to severe SRI.

Similarly, a subset of adults with AD reported unintentionally falling asleep during daytime 3 times or more a month (121 [42.1%]), having some or very much difficulty at school or work because of sleepiness (124 [44.6%] and 32 [11.9%], respectively), and falling asleep while driving (22 [7.8%]).

AD Severity, SD, and SRI

Multivariable ordinal logistic regression models were constructed to determine the relationship between AD severity and individual aspects of SD and SRI. Increasing AD severity was associated with numerically higher odds for all of the aforementioned individual symptoms of SD and SRI. However, only a subset of subjects with severe or very severe POEM, moderate and severe self-reported global assessment of AD, severe or very severe VAS-itch, and highest tertile SA-EASI scores had significantly higher odds for all aspects of SD and SRI (Fig. 1).

Patient-Reported Outcome Measurement Information System SD and SRI *T*-scores rescale the raw composite SD and SRI scores into standardized scores with a mean of 50 and a standard deviation of 10, where a score of 50 is the average score for people in the US general population. Patient-Oriented Eczema Measure, VAS-itch, and SA-EASI were all only weakly or moderately correlated with

TABLE 2. Sleep Disturbance and SRI

Variable	Not at All	A Little Bit	Somewhat	Quite a Bit	Very Much
SD					
Restless sleep	20 (7.2%)	73 (26.3%)	71 (25.5%)	51 (18.4%)	63 (22.7%)
Satisfied with sleep	89 (32.3%)	62 (22.5%)	77 (27.9%)	36 (13.0%)	12 (4.4%)
Refreshing sleep	90 (32.7%)	71 (25.8%)	74 (26.9%)	33 (12.0%)	7 (2.6%)
Difficulty falling asleep	54 (19.4%)	62 (22.3%)	51 (18.4%)	56 (20.1%)	55 (19.8%)
	Never	**Rarely**	**Sometimes**	**Often**	**Always**
Trouble staying asleep	28 (10.1%)	65 (23.5%)	97 (35.0%)	49 (17.7%)	38 (13.7%)
Trouble sleeping	22 (8.0%)	61 (22.2%)	92 (33.5%)	63 (22.9%)	37 (13.5%)
Got enough sleep	37 (13.4%)	76 (27.5%)	95 (34.4%)	57 (20.7%)	11 (4.0%)
	Very Poor	**Poor**	**Fair**	**Good**	**Very Good**
Sleep quality	22 (8.2%)	65 (24.3%)	122 (45.7%)	53 (19.9%)	5 (1.9%)
SRI	Not at All	A Little Bit	Somewhat	Quite a Bit	Very Much
Hard to get things done because sleepy	66 (23.8%)	89 (32.1%)	59 (21.3%)	38 (13.7%)	25 (9.0%)
Felt alert when woke up	110 (39.6%)	79 (28.4%)	53 (19.1%)	25 (9.0%)	11 (4.0%)
Felt tired	14 (5.1%)	64 (23.2%)	64 (23.2%)	77 (27.9%)	57 (20.7%)
Problems during the day because of poor sleep	88 (31.7%)	73 (26.3%)	62 (22.3%)	28 (10.1%)	27 (9.7%)
Hard time concentrating because of poor sleep	73 (26.4%)	91 (32.9%)	38 (17.3%)	35 (12.6%)	30 (10.8%)
Irritable because of poor sleep	59 (21.2%)	81 (29.1%)	56 (20.1%)	43 (15.5%)	39 (14.0%)
Sleepy during daytime	42 (15.2%)	93 (33.7%)	57 (20.7%)	48 (17.4%)	36 (13.0%)
Trouble staying awake during the day	96 (34.8%)	84 (30.4%)	47 (17.0%)	22 (8.0%)	27 (9.8%)

PROMIS SD (Spearman correlation; $\rho_{POEM} = 0.18$, $\rho_{VAS\text{-}itch} = 0.13$, $\rho_{SA\text{-}EASI} = 0.22$) and SRI ($\rho_{POEM} = 0.34$, $\rho_{VAS\text{-}itch} = 0.24$, $\rho_{SA\text{-}EASI} = 0.28$) *T*-scores. There were nonlinear relationships of PROMIS SD and SRI *T*-scores with POEM, VAS-itch, and SA-EASI, which were significantly better depicted using higher-order polynomial functions ($P < 0.001$) and improvement of model fit (Fig. 2). That is, SD and SRI occurred particularly among a subset of adults with severe or very severe POEM, VAS-itch, and SA-EASI scores.

In order to interpret PROMIS SD and SRI *T*-scores, the proportions of subjects falling within previously established severity strata (none, mild, moderate, and severe) were determined across different AD severities (Fig. 3). Virtually no subjects with AD had moderate or severe SD compared with the US population. In contrast, substantial proportions of subjects with AD had moderate and severe SRIs. The proportion of patients with mild, moderate, and severe SDs and SRIs generally increased with more severe POEM, self-reported global AD severity, VAS-itch, and SA-EASI scores, although there was poor concordance between severity of AD, and SD and SRI. Even among patients with severe or very severe AD, the majority did not perceive SD. In addition, there were substantial proportions of patients with clear or mild AD who perceived SRI and patients with severe or very severe AD who did not perceive SRI.

Other Predictors of SDs and SRI

To identify other predictors of SD and SRI, multivariate logistic regression models with stepwise selection from 20 covariates, including sociodemographics and comorbid allergic and mental health disorders were created. Sleep disturbance *T*-scores greater than 55 were significantly associated with VAS-itch scores (OR, 1.025 [95% CI, 1.002–1.049]). In contrast, an SRI was associated with self-reported severe AD (adjusted OR, 13.198 [95% CI, 2.041–85.344]), history of hay fever (adjusted OR, 2.983 [95% CI, 1.148–7.747], and anxiety (adjusted OR, 7.926 [95% CI, 2.602–24.146]).

DISCUSSION

The present study found that symptoms of SD and SRI were common among adults with AD, including multiple nights of disturbed sleep, difficulty falling asleep, short sleep duration, poor sleep quality, impaired alertness, increased sleepiness, and impaired function secondary to poor sleep, for example, having difficulty at school or work and falling asleep while driving. However, elevated PROMIS SD and SRI *T*-scores were observed in only a minority of patients with AD, particularly those with severe or very severe AD, indicating that most patients with AD do not have more profound SD and SRI than the rest of the US population. Nevertheless, SD and SRI are clinically relevant in a subset of patients with AD and may indirectly impact the health of adults with AD. Previous studies found that insomnia, daytime sleepiness, and fatigue in US adults with AD were associated with poor overall health, increased health care utilization and sick days,[2] and increased fractures and other injuries,[12,13] headaches,[14] and cardiovascular diseases.[15] Given the potential impact of SD and SRI on overall health and their poor correlation with AD severity, it seems that SD and SRI should specifically be assessed in patients with AD aside from AD severity. Furthermore, SD and SRI

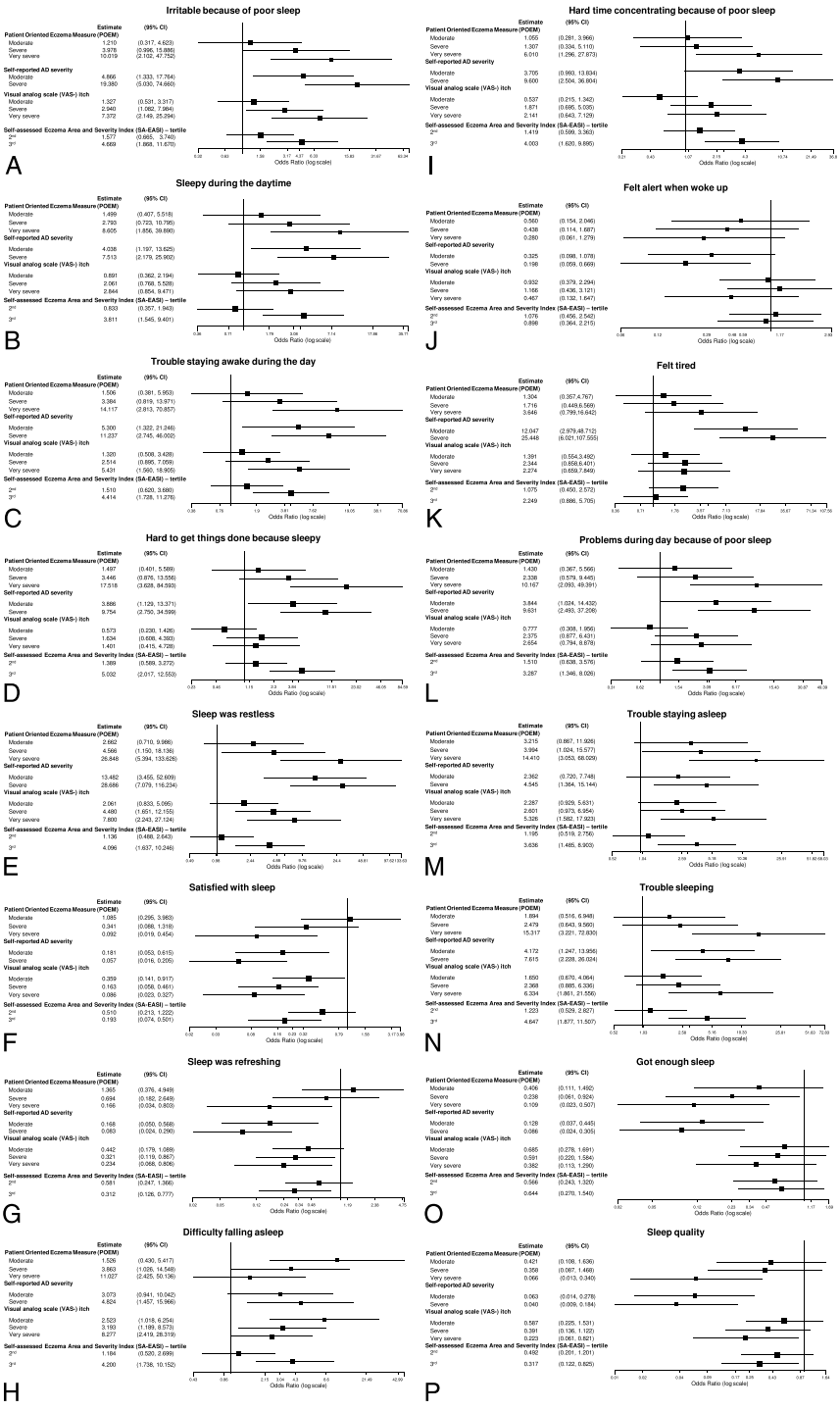

Figure 1. Forest plots of adjusted ORs and 95% CIs for the associations between AD severity and individual aspects from the PROMIS SD and SRI questionnaires.

should be considered together with other AD severity assessments when assessing the burden of and making therapeutic decisions in AD.[16]

Multiple previous studies using objective measures, such as actigraphy and polysomnography, demonstrated poor sleep outcomes in children with AD.[17,18] However, few studies have evaluated the impact of AD on sleep in adults. A case-control study of 14 adults with moderate to severe AD and 14 control subjects found significantly worse sleep outcomes, including lower sleep efficiency and more awakenings, using actigraphy and self-reported measures.[19]

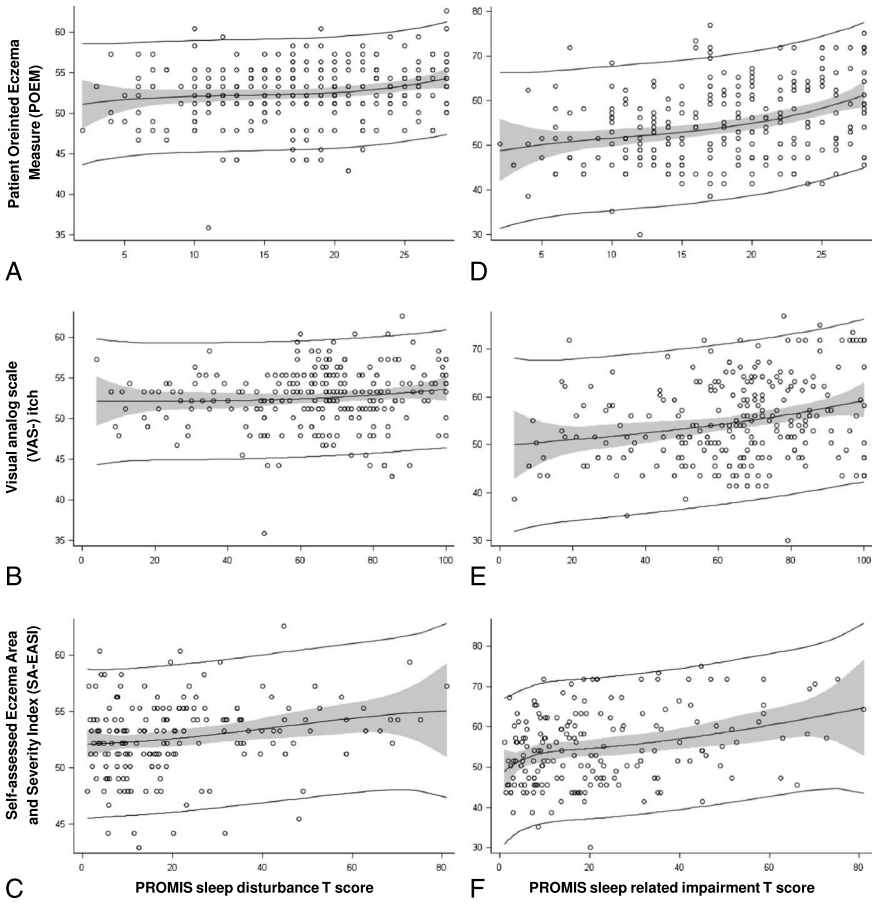

Figure 2. Relationship of POEM, VAS-itch, and SA-EASI with PROMIS SD and SRI *T*-scores. Scatterplots and penalized splines are plotted for PROMIS SD *T*-scores versus (A) POEM, (B) VAS-itch, and (C) SA-EASI, as well as PROMIS SRI *T*-scores versus (D) POEM, (E) VAS-itch, and (F) SA-EASI.

However, that study neither examined mild AD nor stratified SDs by AD severity. A previous study of 112 Japanese adults with AD found weak to moderate correlations between self-reported sleep outcomes using the Japanese version of the Pittsburgh Sleep Quality Index and AD severity as judged by scoring AD.[20] The present study demonstrated considerable SDs and SRIs using the respective PROMIS SD and SRI short forms, which were previously validated and found to strongly correlate with actigraphy.[8] Together, these studies indicate that severe to very severe AD is particularly associated with poor sleep outcomes.

A substantial proportion of subjects with milder AD still reported SD and SRI. These results are consistent with a previous study in which 14 children with AD in remission who had a significantly higher number of arousals and awakenings than non-AD control subjects, most of which were not related to itching or scratching.[21] To address this, we constructed regression models with stepwise selection to identify additional associations with poor sleep outcomes in AD. Comorbid hay fever and anxiety were associated with an increased SRI; these were previously found to be associated with poor sleep outcomes.[22,23] Future studies are needed to identify the ideal interventions to improve SD and SRI in adult AD.

Given their significant burden, routine screening for SDs seems warranted in adults with AD. However, the ideal screening instruments have yet to be established. An ideal screening instrument should be low cost, reliable, quickly and easily completed, and able to be incorporated in the busy clinical practice setting. Polysomnography is considered the criterion-standard objective measure of sleep but is fairly expensive and typically performed over an 8-hour period in an inpatient setting. Actigraphy can be used to record nighttime movement over a 7- to 30-day period and has been pilot and feasibility tested in the ambulatory clinical setting. However, actigraphy watches are expensive and can be easily lost by patients, especially because most are not waterproof and must be taken off before showering, swimming, and so on. We suggest using previously validated PRO assessments, such as the Pittsburgh Sleep Quality Index or PROMIS SD or SRI short forms. The Pittsburgh Sleep Quality Index is a validated, free, extensively used, self-reported instrument but can take 5 to 10 minutes to complete and has a complex scoring algorithm,[24] which may be a little cumbersome for incorporation into primary care, dermatology, and allergy settings. Patient-Reported Outcome Measurement Information System SD and SRI short forms can be completed within 2 to 3 minutes and

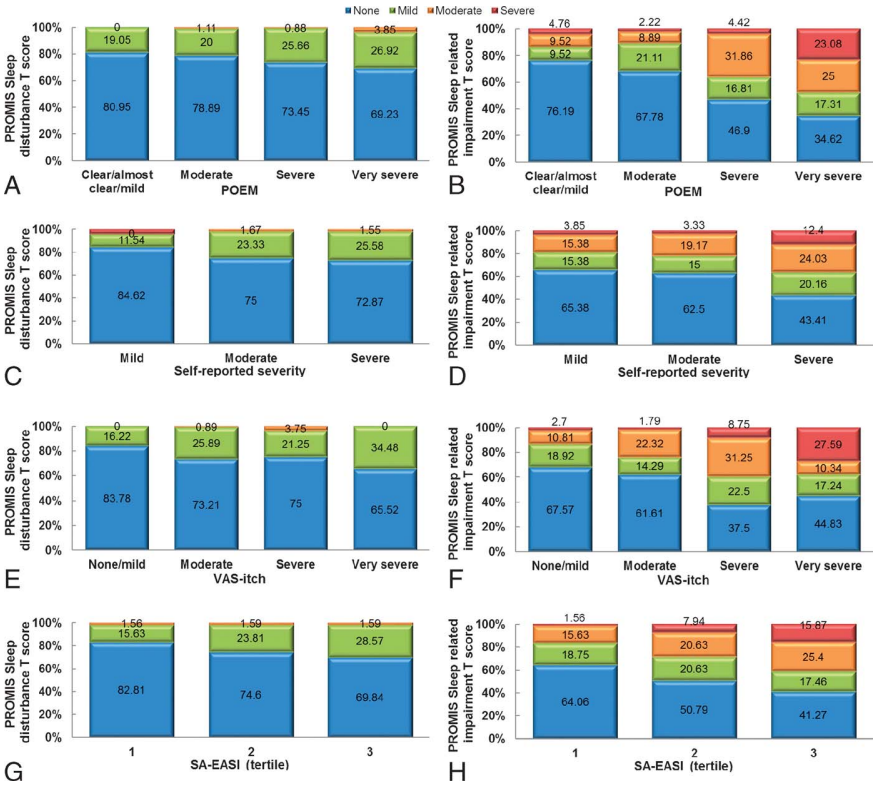

Figure 3. Proportions of patients with no to slight (*T*-score < 55 [blue]), mild (55–59 [green]), moderate (60–69 [orange]), and severe (≥70 [red]) PROMIS SD (A, C, E, and G) and SRI (B, D, F, and H) *T*-scores stratified by AD severity (POEM [A, B], self-reported global AD severity [C, D], VAS-itch [E, F], and SA-EASI [G, H]).

are easy to score, with lookup tables to convert to *T*-scores allowing for a comparison with the general population.[8] An alternative, perhaps enabled by further study, is the use of 1 to 2 highly predictive PROMIS sleep questions, response to which produces adequate sensitivity and specificity for clinical use. Clinical validation studies are underway to validate the use of these instruments in the clinical setting for AD.

This study has several strengths, including being prospective, inclusion of a large number of subjects at all levels of AD severity, and use of validated PRO assessments for AD severity (POEM,[4,5] self-reported AD severity,[25] SA-EASI,[6] and VAS-itch[7]) and SD and SRI (PROMIS). The PROMIS SD and SRI *T*-scores allowed for a comparison of adults with AD from this study with those of the general population. All of the analyses found highly consistent results across multiple measures of AD severity. However, this study has potential limitations. We were not able to determine the impact of sedating antihistamines and other medications on sleep. Although sedating antihistamines are commonly used to treat SDs in AD, they have been shown to cause residual daytime sedation and decreased vigilance and cognitive functioning.[26,27] The study was cross-sectional and was not able to capture the impact of waxing and waning AD on SDs. An objective assessment of AD extent and severity by a clinician was not performed. Future longitudinal, clinical studies would further address these points.

In conclusion, SD and SRI occurred even in mild AD but were most common in severe AD. We recommend routine screening of adults with AD for SDs in clinical practice. It may be that a multidisciplinary approach that aims to improve itch and AD severity, as well as symptoms of allergic diseases and mental health, is needed to achieve good sleep outcomes.

REFERENCES

1. Vakharia PP, Chopra R, Sacotte R, et al. Burden of skin pain in atopic dermatitis. *Ann Allergy Asthma Immunol* 2017;119(6):548.e3–552.e3.
2. Silverberg JI, Garg NK, Paller AS, et al. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. *J Invest Dermatol* 2015;135(1):56–66.
3. Yu SH, Attarian H, Zee P, et al. Burden of sleep and fatigue in US adults with atopic dermatitis. *Dermatitis* 2016;27(2):50–58.
4. Charman CR, Venn AJ, Williams H. Measuring atopic eczema severity visually: which variables are most important to patients? *Arch Dermatol* 2005;141(9):1146–1151; discussion 51.
5. Schram ME, Spuls PI, Leeflang MM, et al. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. *Allergy* 2012;67(1):99–106.
6. Housman TS, Patel MJ, Camacho F, et al. Use of the Self-Administered Eczema Area and Severity Index by parent caregivers: results of a validation study. *Br J Dermatol* 2002;147(6):1192–1198.

7. Phan NQ, Blome C, Fritz F, et al. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. *Acta Derm Venereol* 2012;92(5):502–507.
8. Yu L, Buysse DJ, Germain A, et al. Development of short forms from the PROMIS sleep disturbance and Sleep-Related Impairment item banks. *Behav Sleep Med* 2011;10(1):6–24.
9. Buysse DJ, Yu L, Moul DE, et al. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep* 2010;33(6):781–792.
10. Charman CR, Venn AJ, Ravenscroft JC, et al. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. *Br J Dermatol* 2013; 169(6):1326–1332.
11. Reich A, Heisig M, Phan NQ, et al. Visual analogue scale: evaluation of the instrument for the assessment of pruritus. *Acta Derm Venereol* 2012;92(5):497–501.
12. Garg N, Silverberg JI. Association between eczema and increased fracture and bone or joint injury in adults: a US population-based study. *JAMA Dermatol* 2015;151(1):33–41.
13. Garg NK, Silverberg JI. Eczema is associated with osteoporosis and fractures in adults: a US population-based study. *J Allergy Clin Immunol* 2015;135(4): 1085.e2–1087.e2.
14. Silverberg JI. Association between childhood eczema and headaches: an analysis of 19 US population-based studies. *J Allergy Clin Immunol* 2016;137(2): 492.e5–499.e5.
15. Silverberg JI, Greenland P. Eczema and cardiovascular risk factors in 2 US adult population studies. *J Allergy Clin Immunol* 2015;135(3): 721.e6–728.e6.
16. Simpson EL, Bruin-Weller M, Flohr C, et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. *J Am Acad Dermatol* 2017;77(4):623–633.
17. Stores G, Burrows A, Crawford C. Physiological sleep disturbance in children with atopic dermatitis: a case control study. *Pediatr Dermatol* 1998;15(4): 264–268.
18. Dahl RE, Bernhisel-Broadbent J, Scanlon-Holdford S, et al. Sleep disturbances in children with atopic dermatitis. *Arch Pediatr Adolesc Med* 1995; 149(8):856–860.
19. Bender BG, Leung SB, Leung DY. Actigraphy assessment of sleep disturbance in patients with atopic dermatitis: an objective life quality measure. *J Allergy Clin Immunol* 2003;111(3):598–602.
20. Yano C, Saeki H, Ishiji T, et al. Impact of disease severity on sleep quality in Japanese patients with atopic dermatitis. *J Dermatol Sci* 2013;72(2): 195–197.
21. Reuveni H, Chapnick G, Tal A, et al. Sleep fragmentation in children with atopic dermatitis. *Arch Pediatr Adolesc Med* 1999;153(3):249–253.
22. Pratt EL, Craig TJ. Assessing outcomes from the sleep disturbance associated with rhinitis. *Curr Opin Allergy Clin Immunol* 2007;7(3):249–256.
23. Pires GN, Bezerra AG, Tufik S, et al. Effects of acute sleep deprivation on state anxiety levels: a systematic review and meta-analysis. *Sleep Med* 2016;24:109–118.
24. Buysse DJ, Reynolds CF III, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193–213.
25. Vakharia PP, Chopra R, Sacotte R, et al. Validation of patient-reported global severity of atopic dermatitis in adults. *Allergy* 2018;73(2):451–458.
26. Zhang D, Tashiro M, Shibuya K, et al. Next-day residual sedative effect after nighttime administration of an over-the-counter antihistamine sleep aid, diphenhydramine, measured by positron emission tomography. *J Clin Psychopharmacol* 2010;30(6):694–701.
27. Wilken JA, Kane RL, Ellis AK, et al. A comparison of the effect of diphenhydramine and desloratadine on vigilance and cognitive function during treatment of ragweed-induced allergic rhinitis. *Ann Allergy Asthma Immunol* 2003;91(4):375–385.