Sleep Disturbances in Atopic Dermatitis in US Adults

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Background: **The relationship between atopic dermatitis (AD) severity, sleep disturbance (SD), and health-related outcomes is not fully elucidated.**

Objective: **The aim of the study was to determine the prevalence of SD in adult AD and its relationship with AD severity and health outcomes among the US population.**

Methods: **A cross-sectional, US population–based survey study of 2893 adults was performed.**

Results: **Among adults meeting the UK Diagnostic Criteria for AD, 255 (40.7%) reported 1 or more, 67 (11.1%) reported 3 to 4, and 57 (9.5%) reported 5 to 7 nights of SD in the past week; 475 (79.7%) reported at least some trouble sleeping in the past 3 days. Moderate and severe Patient-Oriented Scoring AD, Patient-Oriented Eczema Measure, and Numeric Rating Scale–itch and Numeric Rating Scale–skin pain scores were associated with more severe SD compared with those without AD. More frequent and severe SDs were associated with higher Dermatology Life Quality Index, lower 12-item Short-Form Health Survey, and higher Hospital Anxiety and Depression Scale (HADS) scores. Significant mediation by SD severity was observed between Patient-Oriented Eczema Measure and Numeric Rating Scale–itch with Dermatology Life Quality Index, 12-item Short-Form Health Survey physical and mental component scores, HADS-anxiety and HADS-depression scores, diagnosed anxiety, and heart disease.**

Conclusions: **Atopic dermatitis and AD severity are associated with SDs, which considerably impact quality of life and other health outcomes in adults with AD.**

Abbreviations: AD = atopic dermatitis, aOR = adjusted odds ratio, CI = confidence interval, DLQI = Dermatology Life Quality Index, HADS-A = Hospital Anxiety and Depression Scale–anxiety, HADS-D = Hospital Anxiety and Depression Scale–depression, HRQoL = health-related quality of life, HS = high school, MCS = mental component score, NRS = Numerical Rating Scale, PCS = physical component score, POEM = Patient-Oriented Eczema Measure, PO-SCORAD = Patient-Oriented Scoring Atopic Dermatitis, SD = sleep disturbance, SE = standard error, SF-12 = 12-item Short-Form Health Survey, UKWP = UK Working Party

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by itch, which can lead to increased scratching, and skin pain, all of which can result in significant sleep disturbances

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(SDs).[1–4] Previous studies found that AD, particularly moderate and severe AD, is associated with poor health-related quality of life (HRQoL),[5] depression and anxiety,[6–9] and cardiovascular risk and disease.[10–13] In turn, SDs also have a profound impact on HRQoL, increased mental health burden, and increased risk of other systemic conditions, such as cardiovascular disease and other health outcomes.[3,13–19] However, the impact of SD and its relationship with AD severity have not been fully elucidated. In the present study, we sought to determine the relationship of AD severity, SDs, and health outcomes in US adults. We hypothesized that SDs are increased in adults with increasing AD severity. We further hypothesized that SDs in adults with AD contribute to poor HRQoL, depression and anxiety, and increased cardiovascular comorbidity, aside from AD severity.

METHODS

Study Design

The Atopic Dermatitis in America study was cross-sectional and involved a 2-stage sampling process from the long-standing GfK Knowledge Panel as previously described.[20] This web-based panel was previously used in other large, epidemiological studies and shown to be representative of the US population.[21–23] The survey questionnaire and protocol were approved by the ICF Institutional Review Board.

Stage 1 was designed to determine the prevalence of AD in US adults. An initial cross-sectional sample of 2137 adults was invited to participate in the survey; 1286 adults completed the survey (response rate = 59.80%), and 1278 were qualified for the study (qualification rate = 99.4%). In stage 2, an additional sample of 13,713 adults completed screening to identify and interview an additional group of adults with AD and controls. The final cohort consisted of 602 adults who met an adapted UK Working Party (UKWP) definition of AD and 2291 controls without AD. Using the data from the US Census Bureau, sample weights were created that were adjusted for age, sex, race, ethnicity, education level, census region, household income, home ownership status, and metropolitan area using an iterative proportional fitting procedure. Sample weights were included in all analyses to allow for representative estimates of the US population.

Assessment of AD and SD

An adaptation of the UKWP criteria was selected by the *AD in America* advisory committee as the screening tool for patient eligibility.[24] This included all aspects of the UKWP criteria (having an itchy skin condition during the past 12 months and 3 or more of the following: [1] a history of skin crease involvement, [2] a personal history of asthma or hay fever, [3] a history of general dry skin during the past year, and [4] onset at younger than 2 years). Assessment of visible flexural eczema by a clinician was not included as it was not performed.

Atopic dermatitis and SD questions were assessed in all respondents who endorsed having an itchy skin condition and other screening questions, even if they did not meet the UKWP criteria. Self-assessments of AD severity and burden included the self-reported global AD severity question: "Would you describe your atopic dermatitis or eczema as mild, moderate, or severe?"[25,26] as well as patient-reported outcomes related to AD, including the Patient-Oriented Scoring Atopic Dermatitis (PO-SCORAD) index (range = 0–103), the Numeric Rating Scale (NRS)-itch score of PO-SCORAD (range = 0–10, 3-day recall period),[26–28] the Patient-Oriented Eczema Measure (POEM, 7 questions, range = 0–28, 7-day recall period),[26,28–30] and the NRS–skin pain (range = 0–10, 7-day recall period).[31] For all analyses of AD severity, scores were divided into 3 categories (clear/almost clear/mild, moderate, severe/very severe) using the respective previously reported severity strata.[30,32]

Health-related quality of life was assessed using the Dermatology Life Quality Index (DLQI, 10 questions, range = 0–30, 7-day recall period),[33] as well as the 12-item Short-Form Health Survey (SF-12) version 1.0 (12 items, 8 domains, 4-week recall period) mental component scores (MCSs) and physical component scores (PCSs).[34,35] Higher DLQI and lower PCS and MCS scores indicate poorer overall health. Mental health was assessed using the Hospital Anxiety and Depression Scale–anxiety (HADS-A) and HADS-depression (HADS-D) scores (7 items, range = 0–21 per score, 7-day recall period).[36–38] A self-reported 1-year history of diagnosis was assessed for the following comorbidities (yes/no): anxiety or depression, high blood pressure, and heart disease.

Sleep disturbance was assessed using an NRS-sleep score from the PO-SCORAD (range = 0–10, 3-day recall period)[27] and the frequency of SD from eczema in the past week from the POEM (1 question, 0/1–2/3–4/5–6/7 nights).[30]

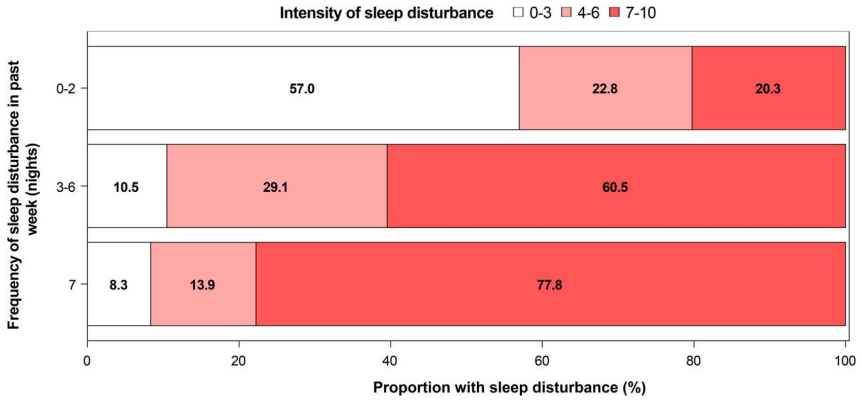

Figure 1. Overlap of proportion of different levels of SD (0–2, 3–6, 7 nights) with severity of SD (NRS = 0–3, 4–6, 7–10) among US adults with AD.

Statistical Analyses

All data analyses and statistical processes were performed using SAS version 9.4 (SAS Institute) and included representative sample weights. Baseline respondent characteristics were determined. Rao-Scott χ^2 tested the association between SD severity and frequency, as well as sociodemographic associations of SD severity and frequency. To determine the relationship between AD severity and SD, multivariable linear regression models were constructed with the PO-SCORAD (no AD/clear mild/moderate/severe), the POEM (no AD/clear mild/moderate/severe/very severe), the NRS-itch (no AD/clear mild/moderate/severe), or the NRS–skin pain (no AD/clear mild/moderate/severe) as the independent variables and severity of SD as the dependent variable. For these analyses, respondents who met some but not all the UKWP criteria were considered to have no AD and were considered as the reference group. Multivariable ordinal regression models tested the associations of the PO-SCORAD (clear mild/moderate/severe), the POEM (clear mild/moderate/severe/very severe), the NRS-itch (clear mild/moderate/severe), and the NRS–skin pain (clear mild/moderate/severe) with frequency of SD from AD (a dependent variable).

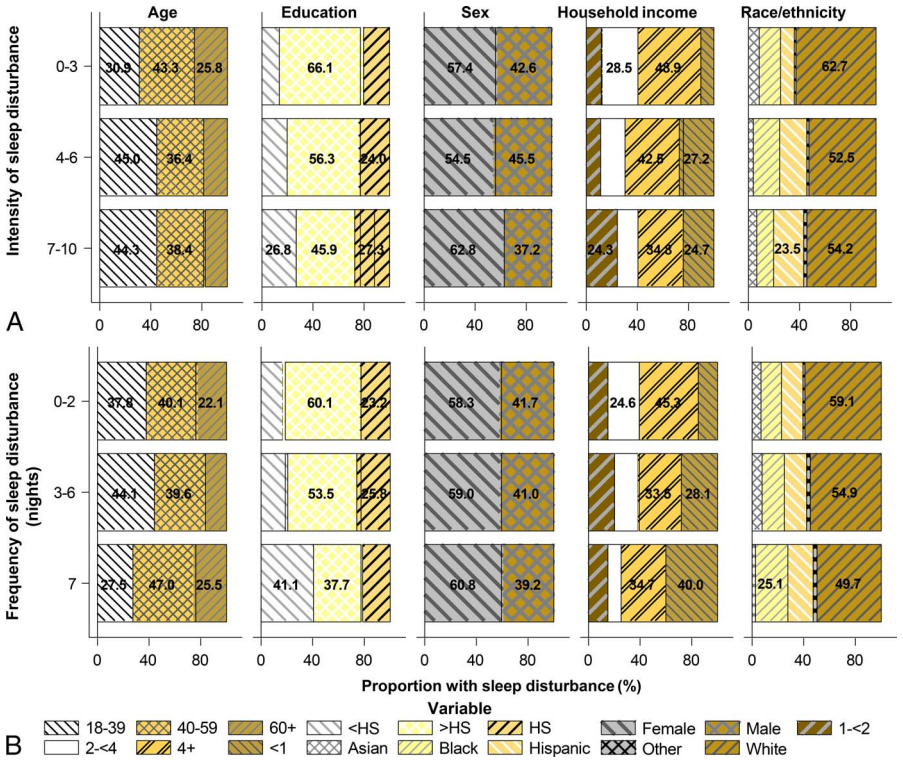

Figure 2. Relationship of sociodemographic variables with severity and frequency of SD among the US adults with AD. Proportion of different groups of age, education level, sex, household income, and race/ethnicity were stratified by (A) severity (NRS = 0–3, 4–6, 7–10) and (B) frequency (0–2, 3–6, 7 nights) of SD.

Models included age (continuous), sex (male/female), self-reported race/ethnicity (White, non-Hispanic/Black, non-Hispanic/Hispanic/multiracial other), level of education (less than high school [HS]/HS or equivalent/more than HS), poverty income ratio (continuous), history of asthma, and hay fever (yes/no) as covariables. Least squares mean SD severity, adjusted β, adjusted odds ratios (aORs), and 95% confidence intervals (CIs) were estimated.

To determine the relationship of SD with HRQoL impact and mental health symptoms, multivariable linear regression models were constructed with SD severity (0–3/4–6/7–10) and SD frequency (0–2/3–7 nights) as the independent variables and the DLQI, SF-12 PCS and MCS, as well as HADS-A and HADS-D scores as the continuous dependent variables. Models were adjusted for the PO-SCORAD (no AD/clear mild/moderate/severe), POEM (no AD/clear mild/moderate/severe/very severe), NRS-itch (no AD/clear mild/moderate/severe), NRS–skin pain (no AD/clear mild/moderate/severe), age (continuous), sex (male/female), race/ethnicity (White, non-Hispanic/Black, non-Hispanic/Hispanic/multiracial other), level of education (less than HS/HS or equivalent/more than HS), poverty income ratio (continuous), history of asthma, and hay fever (yes/no). Adjusted β and 95% CI were estimated.

To test whether the associations of AD severity with HRQoL, mental health, and comorbidities are mediated by SD, causal mediation analysis was conducted using a counterfactual framework in Proc Causalmed. The exposures were the POEM or NRS-itch. The outcomes were the DLQI, SF-12 PCS and MCS, HADS-A and HADS-D (all continuous), diagnosis of anxiety or depression, and heart disease or hypertension (all binary). The mediator was SD severity (continuous). Age (continuous), race/ethnicity (White, non-Hispanic/Black, non-Hispanic/Hispanic/multiracial other), and sex (male/female) were included as potential confounding variables. Mediator interactions were tested but not found to be significant in any models. Therefore, the final models did not include interaction terms. The total effect and decomposed effects for SD-independent and SD-mediated (adjusted β, standard error, *P* value) associations between the exposures and outcomes were estimated. The percentage of the total effect mediated by SD was also estimated.

Complete case analysis was performed. A 2-sided $P < 0.05$ was taken to indicate statistical significance for all estimates.

RESULTS

Respondent Characteristics

Overall, the prevalence (95% CI) of AD was 7.3% (5.9%–8.8%). Six hundred two subjects met the AD criteria, and 2291 controls without AD were included in the final cohort. Fifty-eight percent of the respondents with AD were female, and 65.8% were White, with a weighted mean (95% CI) age of 46.6 years (45.1–48.1 years). Sociodemographics of the cohort are presented in Supplemental Table 1 see Supplemental Digital Content 1, http://links.lww.com/DER/A56. The weighted mean (95% CI) duration of AD was 16.7 years (14.7–18.7 years), the PO-SCORAD was 27.5 (25.7–29.3), the POEM was 7.5 (6.8–8.1), and the DLQI was 4.9 (4.2–5.5).

Frequency and Severity of SD

Among the adults with AD, 255 (40.7%) reported at least 1 night of SD from AD in the past week, with 121 (20.1%) with 1 to 2 nights, 67 (11.1%) with 3 to 4 nights, 21 (3.5%) with 5 to 6 nights, and 36 (6.0%) with 7 nights of SD in the past week. Moreover, 475 (79.7%) reported at least some trouble sleeping in the past 3 days, with 138 (23.2%) with moderate trouble sleeping and 176 (29.5%)

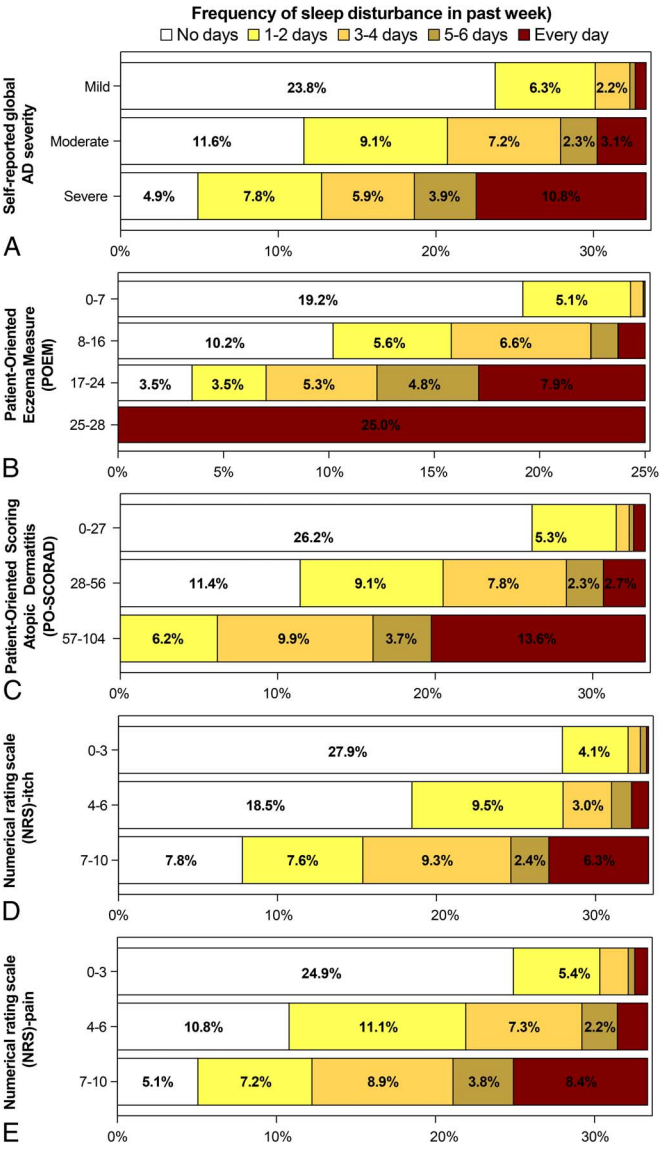

Figure 3. Relationship of AD severity with frequency of SD among the US adults with AD. Proportions of different frequencies of SD in the past week (0, 1–2, 3–4, 5–6, 7 nights) were stratified by different measures of AD severity, including (A) self-reported global AD severity (mild, moderate, severe), (B) Patient-Oriented Eczema Measure (0–7, 8–16, 17–24, 25–28), (C) Patient-Oriented Scoring Atopic Dermatitis (0–27, 28–56, 57–104), and NRS of (D) itch or (E) pain (0–3, 4–6, 7–10).

with severe trouble sleeping (median [interquartile range] = 4 [6]). Frequency of SD was associated with an increased severity of SD, with SD occurring on 3 to 7 versus 0 to 2 nights having higher proportions of moderate and/or severe SD (χ^2, $P < 0.0001$; Fig. 1).

Association of SD Severity in Adults With AD

Among the adults with AD, more severe SD was associated with a younger age ($P = 0.009$), a lower level of education (χ^2, $P = 0.0003$), Hispanic ethnicity ($P = 0.005$), and a lower household income ($P < 0.0001$), but not sex ($P = 0.26$; Fig. 2). Similarly, more frequent SD was associated with a lower level of education ($P = 0.0003$) and a lower household income ($P < 0.0001$), but not age ($P = 0.38$), sex ($P = 0.95$), or race/ethnicity ($P = 0.72$).

Association of SD With AD Severity

Sleep disturbances were increased with more severe AD, as judged by lesional severity and extent (PO-SCORAD), frequency of symptoms (POEM), and NRS-itch and NRS–skin pain (Fig. 3). In multivariable linear regression models, moderate and severe PO-SCORAD scores; moderate, severe, and very severe POEM scores; moderate and severe NRS-itch scores; and moderate and severe NRS–skin pain scores were associated with more severe SD in the past 3 days compared with those without AD (Table 1). However, mild AD was not associated with significant differences in SD severity compared with those without AD.

Similarly, in multivariable ordinal logistic regression models, moderate (aOR [95% CI] = 8.93 [5.76 to 13.85]) and severe (56.87 [21.38–151.28]) versus clear-mild PO-SCORAD scores; moderate (6.96 [4.51–10.74]), severe (44.70 [19.01–105.10]), and very severe (>999.99 [>999.99]) versus clear-mild POEM scores; moderate (3.73 [2.27–6.12]) and severe (20.12 [11.28–35.89]) versus clear-mild NRS-itch scores; and moderate (5.30 [3.21–8.74]) and severe (21.08 [10.81–41.09]) versus clear-mild skin NRS–pain scores were associated with more frequent SD in the past week secondary to eczema.

Association of SD on HRQoL and Mental Health

Adults with AD who had either more intense or frequent SD had increased DLQI scores, marked as HRQoL impact. Those who had both more intense and frequent SD had even higher DLQI scores (Fig. 4). In multivariable linear regression models adjusted for the total of POEM and NRS-itch scores, as well as sociodemographics, the DLQI scores were significantly increased with severe SD (7–10 vs 0–3, adjusted β [95% CI] = 1.77 [0.72–2.81]) and frequent SD (3–7 vs 0–2 nights, 6.68 [5.56–7.81]), but not moderate SD (0.54 [−0.49 to 1.58]). Meanwhile, the SF-12 MCSs and PCSs were both associated with moderate SD (MCS, −5.41 [−7.21 to −3.62]; PCS, −0.44 [−0.95 to 0.06]) and severe SD (MCS, −7.73 [−9.53 to −5.93]; PCS, −1.00 [−1.50 to −0.49]), but not frequency of itch (MCS, 0.59 [−1.65 to 2.84]; PCS, −0.42 [−1.05 to 0.21]).

TABLE 1. Association Between AD Severity and Severity of SD in US Adults

	Intensity of SD				
Variable	**Least Squares Mean**	**Adjusted β**	**95% CI**		***P***
PO-SCORAD					
No AD	3.2685	0.0000	–	–	–
Mild	2.9291	−0.3394	−0.7257	0.04683	0.085
Moderate	5.8328	2.5643	2.0943	3.0342	<0.0001
Severe	8.1743	4.9058	3.9799	5.8317	<0.0001
POEM					
No AD	3.2823	0.0000	–	–	–
Mild	3.5569	0.2746	−0.1474	0.6966	0.2021
Moderate	5.7844	2.5021	1.5922	3.412	<0.0001
Severe	9.0376	5.7553	4.6418	6.8689	<0.0001
Very severe	4.8889	1.6066	1.0486	2.1646	<0.0001
NRS-itch					
No AD	3.2884	0.0000	–	–	–
Mild	2.8991	−0.3893	−0.8271	0.04857	0.0814
Moderate	4.7131	1.4247	0.9045	1.945	<0.0001
Severe	5.9191	2.6307	2.0132	3.2483	<0.0001
NRS−skin pain					
No AD	3.2728	0.0000	–	–	–
Mild	3.3862	0.1134	−0.2758	0.5025	0.5678
Moderate	5.2337	1.9608	1.3122	2.6095	<0.0001
Severe	6.8707	3.5979	2.9069	4.2888	<0.0001

AD, atopic dermatitis, CI, confidence interval; NRS, Numeric Rating Scale; PO-SCORAD, Patient-Oriented Scoring Atopic Dermatitis; POEM, Patient-Oriented Eczema Measure; SD, sleep disturbance.

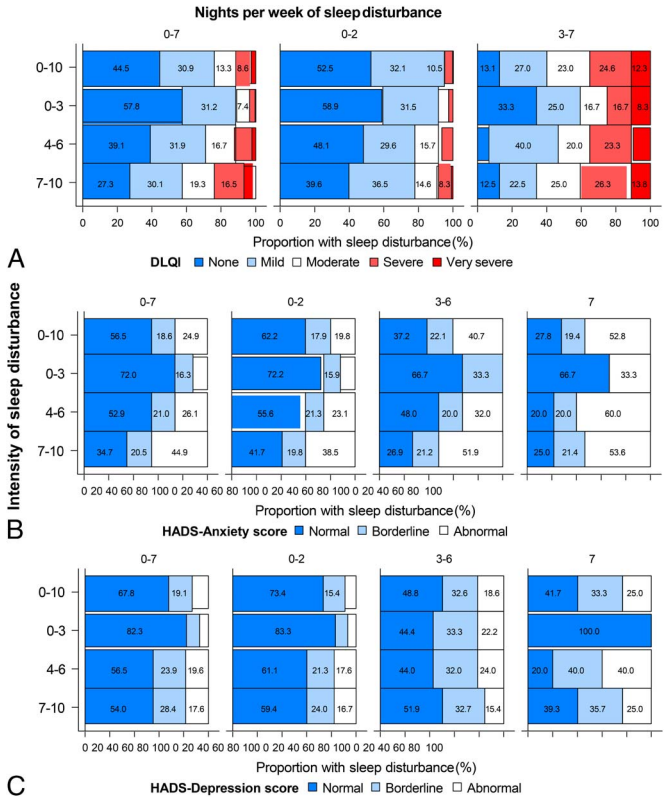

Figure 4. Relationship of SD and frequency with quality of life and mental health. Proportion of different frequencies of SD (0–2, 3–6, 7 nights) and intensities of SD (NRS: 0–3, 4–6, 7–10) with (A) DLQI (none, mild, moderate, severe, very severe) and HADS scores for (B) anxiety or (C) depression (normal, borderline, abnormal).

The HADS-A and HADS-D scores were both associated with moderate SD (HADS-A, 1.96 [1.12 to 2.80]; HADS-D, 3.60 [2.76 to 4.45]) and severe SD (HADS-A, 2.80 [2.00 to 3.60]; HADS-D, 2.76 [1.96 to 3.57]), but not frequency of SD (HADS-A, 0.04 [−1.02 to 1.10]; HADS-D, −0.69 [−1.69 to 0.31]). Similarly, being diagnosed with depression or anxiety was associated with moderate SD (aOR [95% CI] = 2.42 [1.34 to 4.37]) and severe SD (2.84 [1.63 to 4.96]), but not frequency of SD (0.72 [0.35 to 1.46]).

Direct and Indirect Effects of SD on HRQoL, Mental Health, and Cardiovascular Comorbidities

To determine how much of the previously established associations of AD severity with HRQoL, mental health, and comorbid hypertension and heart disease are mediated by SD. Significant mediation by SD severity was observed between the POEM and the NRS-itch with the DLQI, SF-12 PCS and MCS, HADS-A and HADS-D scores, and diagnosed anxiety and heart disease, whereas marginally significant mediation by SD was observed for hypertension (Table 2). There was no significant effect modification in any models.

DISCUSSION

Studying a US population-based sample, we found that the adults with AD reported severe and frequent SD. We found that 40.7% of the adults with AD reported at least 1 night of SD from AD in the past week, and 79.7% had at least some trouble sleeping in the past 3 days. This study confirms and expands upon the results of a previous study that found higher rates of fatigue, regular daytime sleepiness, and insomnia among US adults with versus without AD.[3] However, that study did not examine the complex relationship of SD with AD severity, HRQoL, and AD-associated comorbidities. We found that SD was particularly associated with moderate and severe AD, but not clear/almost clear/mild AD based on the POEM, PO-SCORAD, NRS-itch, and NRS–skin pain. Of note, SDs were associated with worse HRQoL and increased symptoms of anxiety and depression, even after controlling for AD severity and sociodemographics. Moreover, much of the association of AD severity with HRQoL, mental health, and comorbid heart disease was mediated by SD. These findings suggest that SDs are very common and burdensome in AD and are a key driver of HRQoL impact, increased psychological burden, and cardiovascular comorbidity.

More severe and/or frequent SDs were associated with a younger age, Hispanic ethnicity, a lower household income, and/or a lower level of education. The associations of SD with a lower household income are consistent with previous studies in the United States[3,39] and Japan.[40] Hispanics and other racial/ethnic minority groups tend to underreport SD in general. Moreover, previous studies found that female sex and older age were associated with a higher prevalence of SD.[3,39,40] Our findings of more severe SD in adults with AD who were Hispanic, male, and younger are likely related to these subsets having more severe AD.

The associations of SD with multiple comorbid health disorders, including obesity, hypertension, diabetes, high cholesterol,[13] attention-deficit/hyperactivity disorder,[14] headaches,[15] decreased stature,[16] overall health,[3,17] fractures, bone and joint injuries,[18] and speech disorders.[19] In those studies, SD was used as a proxy measure of AD severity. Indeed, we found that SD was strongly associated with AD severity and partially mediated the associations of AD severity with HRQoL, mental health symptoms, and comorbid heart disease. Taken together, it seems that SD plays an important role in the overall health and comorbidities of persons with AD.

There are important clinical ramifications. First, SD should be assessed in clinical practice for all patients with AD and incorporated into therapeutic decision making. A subset of adults with moderate and severe did not report major SD, and some with moderate and severe SD did not report severe AD. Thus, assessing severity of AD, itch, and skin pain may be inadequate without also assessing SD. Second, interventions targeting SD are necessary and likely to improve the overall HRQoL and could potentially impact other health comorbidities in adults with AD. Profound SD is a potential indicator of poor AD control and should prompt consideration of stepping up to more potent or advanced anti-inflammatory agents. In addition, SD can be specifically targeted using sedating medications

TABLE 2. Direct and Indirect Effects of SD on Quality of Life, Symptoms of Anxiety and Depression, and Diagnosed Comorbid Health Conditions

	Total Effect			Decomposed Effect						
				SD Independent			SD Mediated			
Comorbidity	β	SE	*P*	β	SE	*P*	β	SE	*P*	%
Model 1 (POEM)										
DLQI	0.5179	0.0297	<0.0001	0.4531	0.0303	<0.0001	0.0648	0.0125	<0.0001	12.52
SF-12 PCS	−0.0565	0.015	0.0002	−0.0327	0.0155	0.0352	−0.0238	0.00581	<0.0001	42.06
SF-12 MCS	−0.4408	0.0579	<0.0001	−0.2485	0.0563	<0.0001	−0.1923	0.0293	<0.0001	43.62
HADS-A	0.2286	0.0268	<0.0001	0.1377	0.026	<0.0001	0.0909	0.0137	<0.0001	39.77
HADS-D	0.1795	0.0258	<0.0001	0.1026	0.0255	<0.0001	0.0768	0.0123	<0.0001	42.81
Anxiety or depression	0.0728	0.0155	<0.0001	0.0474	0.0156	0.0024	0.0254	0.0059	<0.0001	34.94
Heart disease	0.0740	0.0215	0.0006	0.0497	0.0222	0.025	0.0243	0.00849	0.0043	32.79
Hypertension	0.0511	0.0153	0.0008	0.0410	0.0159	0.0099	0.0101	0.00523	0.0533	19.77
Model-2 (NRS-itch)										
DLQI	0.9775	0.0776	<0.0001	0.7696	0.0813	<0.0001	0.2079	0.0375	<0.0001	21.27
SF-12 PCS	−0.1226	0.0358	0.0006	−0.0508	0.0381	0.1828	−0.0718	0.0164	<0.0001	58.56
SF-12 MCS	−1.1438	0.1373	<0.0001	−0.6076	0.1377	<0.0001	−0.5362	0.0748	<0.0001	46.88
HADS-A	0.5601	0.064	<0.0001	0.3043	0.0639	<0.0001	0.2558	0.0352	<0.0001	45.67
HADS-D	0.507	0.0607	<0.0001	0.3039	0.0622	<0.0001	0.2032	0.0312	<0.0001	40.07
Anxiety or depression	0.2629	0.0457	<0.0001	0.2023	0.0463	<0.0001	0.0606	0.0164	0.0002	23.06
Heart disease	0.1272	0.0592	0.0317	0.0501	0.0621	0.4198	0.0770	0.0253	0.0023	60.57
Hypertension	0.1425	0.0404	0.0004	0.1160	0.0426	0.0064	0.0265	0.0152	0.0827	18.57

DLQI, Dermatology Life Quality Index; HADS-A, Hospital Anxiety and Depression Scale–anxiety; HADS-D, Hospital Anxiety and Depression Scale–depression; NRS, Numeric Rating Scale; MCS, mental component score; PCS, physical component score; PO-SCORAD, Patient-Oriented Scoring Atopic Dermatitis; POEM, Patient-Oriented Eczema Measure; SF-12, 12-item Short-Form Health Survey; SD, sleep disturbance; SE standard error.

(eg, first-generation antihistamines, oral melatonin, and gabapentin), improved sleep hygiene (eg, consistent bedtime, remove electronic devices, avoid caffeine), and behavioral health interventions aimed at reducing SD (eg, cognitive behavioral and relaxation therapy); sedating medications should be used with particular caution in elderly patients.[41] Third, future clinical trials should particularly examine the potential efficacy of therapeutics on SD, as SD may respond dissimilarly than itch and other aspects of AD severity.

Proposed mechanisms of association between AD and SD include the following: poor sleep hygiene, an itch-scratch cycle that interferes with initiation and maintenance of sleep,[42] circadian rhythm–induced modification of itch,[43] and upregulation of inflammatory cytokines implicated in sleep regulation.[44] Future studies are needed to determine why some patients with AD experience profound SD, whereas others do not.

Chronic SDs have detrimental effects on neurocognitive function[45] and are associated with increased psychological disorders,[46,47] hypertension,[48] type 2 diabetes mellitus,[49–51] obesity,[52–54] and cardiovascular disease.[55,56] All of these comorbidities were previously found to be increased in children and/or adults with AD, particularly those with more severe disease.[6–13,57–69] The results of this study were built upon those previous studies by showing that SD is an important mediating factor in the relationship between AD severity and these health comorbidities.

The strengths of this study include its large-scale and population-based approach with prospective data collection, a diverse sample, and sample weights that were adjusted for multiple sociodemographics and allowed for generalization of results that are representative of the US population, use of multiple and well-validated assessments of AD severity, and controlling for multiple confounding variables in multivariable models. The POEM, PO-SCORAD, NRS-itch and NRS–skin pain, self-reported global AD severity and SD severity (from the PO-SCORAD), and frequency (from the POEM) have all been studied in AD patients and found to have overall good face validity, construct validity, internal consistency, reliability, and/or responsiveness.[25,28,36,70–88] However, this study has limitations. Assessments of SD were performed using self-report, which may lead to underreporting of SD. We used an Internet panel, which may be subject to false answers, answering too fast, giving the same answer repeatedly (also known as straightlining), and getting multiple surveys completed by the same respondent.[22] However, we do not believe these to be major concerns, given that there were less than 0.05% missing values for AD and SD questions, more than 95% of surveys took 10 minutes or longer to complete, and Internet protocol and e-mail address verification was used for the panel. Given the cross-sectional design of the study, we are unable to ascertain the directionality of the associations observed, although we hypothesize that the relationships are bidirectional. Although the overall sample size was large, the frequencies were lower for some of the subset analyses resulting in a wider CI. We did not assess use of sleep medications or sedating antihistamines. Residual confounding may be present. Finally, the

cross-sectional nature of the study does not allow for determination of causality of association between AD and sleep. That is, AD may result in sleep impairment or perhaps underlying sleep disorders trigger AD in predisposed individuals. Future longitudinal studies with objective measures of SD are needed to verify these associations.

In conclusion, US adults with AD commonly report severe and frequent SD. Moderate AD and severe AD were particularly associated with SD. Sleep disturbance was a significant mediator of HRQoL, mental health, and comorbid health disorders in adults with AD. These data support the heavy burden that SDs place on AD patients. It is important for clinicians to recognize the impact of SD on the overall health of AD patients. We recommend that clinicians incorporate assessment of SD in clinical practice to better appreciate disease burden and screen for patients at high risk of mental health and cardiovascular comorbidities.

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