BJD
British Journal of Dermatology

Symptoms and diagnosis of anxiety and depression in atopic dermatitis in U.S. adults*

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Linked Comment: Nicholas and Drucker. Br J Dermatol 2019; **181**:442–443.

Summary

Background The relationship between atopic dermatitis (AD), anxiety and depression in the U.S. adult population is not well established.
Objectives To determine the relationship of AD and its severity with symptoms and diagnosis of anxiety and depression in U.S. adults.
Methods A cross-sectional, population-based study of 2893 adults was performed. AD was determined using modified U.K. Diagnostic Criteria.
Results Adults with AD vs. those without AD had higher mean Hospital Anxiety and Depression Scale anxiety (HADS-A) (7·7 vs. 5·6) and depression (HADS-D) (6·0 vs. 4·3) scores and higher prevalences of abnormal (≥ 11) HADS-A (28·6% vs. 15·5%) and HADS-D (13·5% vs. 9·0%) scores. In multivariable linear and logistic regression models controlling for sociodemographics, AD was associated with significantly higher mean HADS-A and HADS-D scores (7·7 and 6·0) and higher odds of abnormal HADS-A [odds ratio (OR) 2·19, 95% confidence interval (CI) 1·65–2·91] and HADS-D scores (OR 1·50, 95% CI 1·04–2·17) ($P \leq 0·03$ for all). Mean and abnormal HADS-A and HADS-D scores were increased in moderate and severe/very severe self-reported global AD severity, Patient-Oriented Eczema Measure (POEM), Patient-Oriented Scoring AD (PO-SCORAD), PO-SCORAD itch and sleep ($P < 0·0001$ for all). All respondents with severe PO-SCORAD, POEM and PO-SCORAD itch had borderline or abnormal HADS-A and HADS-D scores. Adults with AD vs. those without AD had higher prevalence of self-reported healthcare-diagnosed anxiety or depression in the past year (40·0% vs. 17·5%). Many adults with AD who had borderline and/or abnormal HADS-A or HADS-D scores reported no diagnosis of anxiety or depression.
Conclusions AD is associated with significantly increased anxiety and depression, which may go undiagnosed.

What's already known about this topic?

- Previous studies found higher rates of anxiety and depression in clinical cohorts of patients with atopic dermatitis.

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Accepted for publication
21 January 2019

Funding sources
The Atopic Dermatitis in America Study is an independent research project of the Asthma and Allergy Foundation of America in partnership with the National Eczema Association and sponsored by Sanofi Genzyme and Regeneron.

Conflicts of interest
See Appendix.

*Plain language summary available online

DOI 10.1111/bjd.17683

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What does this study add?

- This study found dramatically higher rates of anxiety and depression among adults with atopic dermatitis in the U.S. population, which was primarily driven by atopic dermatitis severity.
- Anxiety and depression often go undiagnosed in adults with atopic dermatitis.

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by itch, skin pain, sleep disturbances and multiple comorbidities, all of which can lead to significant psychosocial distress and mental health burden.[1–6] However, previous studies found conflicting results regarding whether AD is associated with increased mental health disorders, e.g. depression or anxiety.[7–9] We hypothesized that AD is associated with higher likelihood of anxiety and/or depression.

In addition, there are a number of outstanding questions about the relationship between AD, anxiety and depression. Firstly, the prevalence and severity of anxiety and depression in the U.S. adult population with AD are not well established. Secondly, the relationship of different aspects of AD severity with anxiety and depression requires elucidation. We hypothesized that symptoms of anxiety and depression are very common in AD, especially in moderate-to-severe AD. Finally, anxiety and depression may go undiagnosed in all age groups.[10,11] We hypothesized that a large proportion of adults with AD have undiagnosed anxiety and/or depression. In the present study, we sought to determine the relationship of AD and its severity with symptoms and diagnosis of anxiety and depression in U.S. adults.

Materials and methods

Data source

Data were obtained from the Atopic Dermatitis in America survey for which the population was sampled from the long-standing Growth from Knowledge (GfK) Knowledge Panel. The GfK Knowledge Panel is the largest and oldest probability-based web panel in the U.S.A. and contains between 40 000 and 50 000 adult panel members at any given time. The GfK web panel was initially constructed from a national address-based sample of households in the U.S.A. who are recruited to participate and receive small incentives for completing web surveys on a regular basis. This approach uses a single sampling frame via the Delivery Sequence File of the U.S. Postal Service to provide a statistically valid representation of the U.S. population in addition to many difficult-to-survey populations. The GfK web panel also provides internet access to households without existing internet access. This web-based panel has been previously used in other large epidemiological studies and has been shown to be representative of the U.S. population.[12–14] The survey questionnaire and protocol were approved by the ICF Institutional Review Board.

Study design

This was a cross-sectional study involving a two-stage sampling process. Stage 1 was designed to determine the prevalence of AD in U.S. adults. In this stage, an initial cross-sectional sample of 2137 adults from the existing GfK Knowledge Panel was invited to participate in the survey. The focus of the survey was not disclosed in the invitation to members of the web panel in order to avoid biasing participation based on respondent interest or disinterest in the subject. A total of 1286 adults completed the survey (response rate 59·80%), of which 1278 qualified for the study (qualification rate 99·4%). Although this sample provided a precise estimate of the prevalence of AD among the adult population, it did not yield a large enough sample of patients with AD and control participants to investigate differences between different levels of disease severity. In stage 2, an additional sample of 13 713 adults from the GfK Knowledge Panel 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 U.K. Working Party (UKWP) definition of AD and 2291 controls without AD (Fig. S1; see Supporting Information). Using data from the U.S. Census Bureau, sample weights were created that 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 U.S. population.

Based on an expected lifetime prevalence of AD of 20%,[15] it was determined that a sample size of 500 would provide an adequate estimate with a maximum expected sampling error of ± 4·4% at the 95% confidence level.

Assessment of atopic dermatitis and mental health

An adaptation of the UKWP criteria was selected by the AD in America advisory committee as the screening tool for patient eligibility.[16] This included all aspects of the UKWP criteria (having an itchy skin condition during the past 12 months and three or more of the following: (i) history of skin crease

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Table 1 Participant characteristics

Variable	Overall		Atopic dermatitis (AD)			
			No		Yes	
	Frequency (n = 2893)	Weighted percentage	Frequency (n = 2291)	Weighted percentage	Frequency (n = 602)	Weighted percentage
Age, years						
18–39	775	38·5%	602	38·6%	173	38·0%
40–59	1069	36·7%	833	35·8%	236	40·5%
60–100	1049	24·8%	856	25·6%	193	21·5%
Female sex	1551	52·5%	1202	52·5%	349	58·0%
Race/ethnicity						
White	2080	62·9%	1684	73·5%	396	65·8%
African-American/black	269	11·6%	195	8·5%	74	12·3%
Hispanic	341	17·6%	264	11·5%	77	12·8%
Multiracial/other	203	7·8%	148	6·5%	55	9·1%
Level of education						
Less than high school	188	16·0%	140	6·1%	48	8·0%
High school or equivalent	832	26·7%	668	29·2%	164	27·2%
Some college	889	30·2%	703	30·7%	186	30·9%
Bachelor's degree or higher	984	28·1%	780	34·1%	204	33·9%
Poverty Income Ratio						
< 1·00	366	13·8%	260	12·6%	106	18·6%
1·00–1·99	451	14·5%	349	14·1%	102	15·9%
2·00–3·99	796	25·8%	649	26·6%	147	22·7%
≥ 4·00	1280	46·0%	1033	46·7%	247	42·9%
Region						
Northeast	533	18·2%	422	18·1%	111	18·6%
Midwest	723	20·3%	571	20·1%	152	21·0%
South	956	36·4%	743	35·5%	213	40·4%
West	681	25·0%	555	26·3%	126	20·0%
Prescription AD treatment (ever)						
Topical therapy	–	–	–	–	410	70·7%
Systemic antihistamines	–	–	–	–	259	49·9%
Systemic corticosteroids	–	–	–	–	119	20·6%
Systemic immunosuppressants					47	10·6%
Self-reported AD severity						
Mild	–	–	–	–	289	59·4%
Moderate	–	–	–	–	172	34·8%
Severe	–	–	–	–	34	6·9%

involvement; (ii) a personal history of asthma or hay fever; (iii) a history of general dry skin during the past year and (iv) onset under the age of 2 years), except for an assessment of visible flexural eczema performed by a clinician.

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?',[17] in addition to patient-reported outcomes related to AD, including Patient-Oriented Scoring AD (PO-SCORAD) index (range 0–103) and numeric rating scale for itch and sleep scores of PO-SCORAD (range 0–10),[18] Patient-Oriented Eczema Measure (POEM) (seven questions; range 0–28)[19] and Dermatology Life Quality Index (DLQI) (10 questions; range 0–30).[20] For all analyses of AD severity, scores were divided into three categories (clear, almost clear, mild; moderate; severe, very severe) using the respective previously reported severity strata.[19,21]

Mental health was assessed using the Hospital Anxiety and Depression Scale anxiety (HADS-A) and depression (HADS-D) scores (seven items; range 0–21 per score).[22,23] Borderline and abnormal anxiety/depression scores were defined as ≥ 8 and ≥ 11, respectively. Self-reported 1-year history of anxiety or depression was assessed using the question 'Have you been diagnosed by a healthcare provider with any of the following in the past 12 months: Anxiety or depression?' (Yes/No).

Statistical analyses

All data analyses and statistical processes were performed using SAS version 9·4 (SAS Institute Inc., Cary, NC, U.S.A.) and included representative sample weights. Baseline respondent characteristics were determined. Rao-Scott χ^2-test was used to test the association between AD and responses to individual

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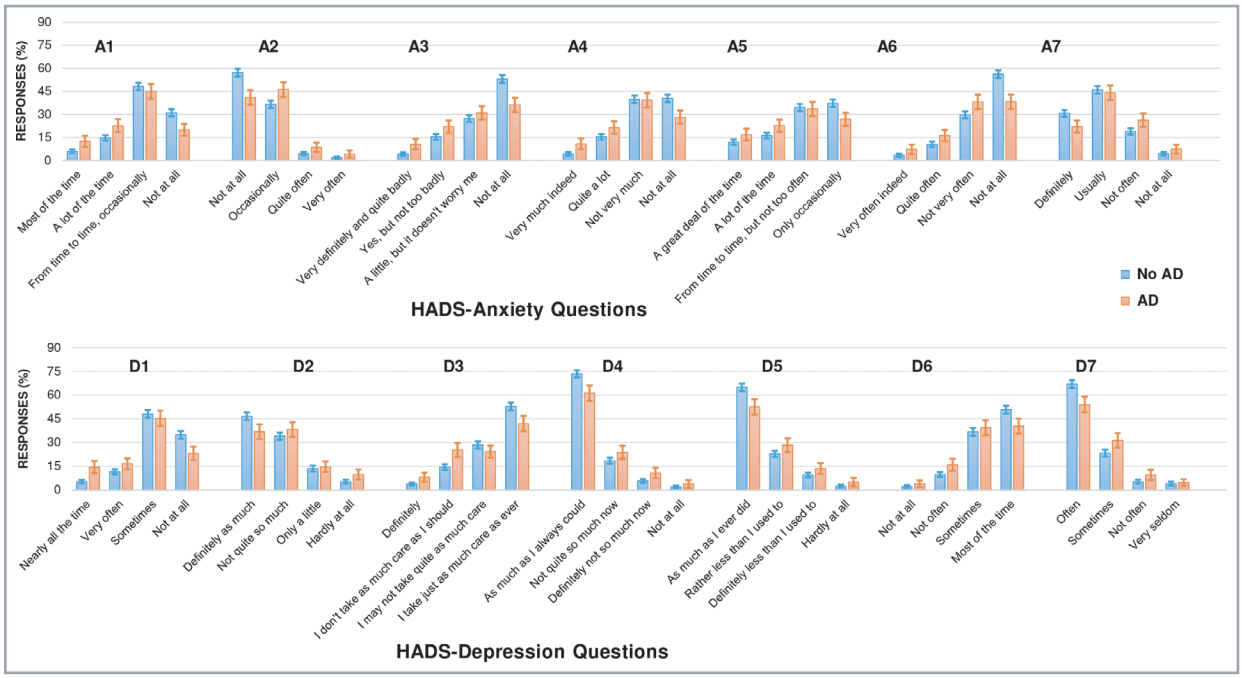

Fig 1. Proportions (95% confidence intervals) of responses to Hospital Anxiety and Depression Scale (HADS) questions among U.S. adults with and without atopic dermatitis. AD, atopic dermatitis. [Colour figure can be viewed at wileyonlinelibrary.com]

items from HADS. Bivariable linear regression models were used to test the associations of AD and AD severity with continuous HADS-A and HADS-D scores. Bivariable binary logistic regression models were used to test the associations of AD and AD severity with abnormal HADS-A and HADS-D scores (≥ 11). Multivariable models included age (continuous), sex (male/female), race/ethnicity (white, black, Hispanic, multiracial or other), level of education [less than high school (HS), HS or equivalent, more than HS], household size (continuous), and poverty income ratio (PIR) (< 1, 1–1·9, 2–3·9, ≥ 4). Crude and adjusted beta, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. A two-sided P-value < 0·05 was taken to indicate statistical significance for all estimates.

Results

Respondent characteristics

Overall, the prevalence of AD was 7·3% (95% CI 5·9–8·8). A total of 602 participants met AD criteria and 2291 controls without AD were included in the final cohort. In total 58·0% of respondents with AD were female and 65·8% were white, with a weighted mean age of 46·6 years (95% CI 45·1–48·1). Sociodemographics of the cohort and AD characteristics are presented in Table 1. The weighted mean duration of AD was 16·7 years (95% CI 14·7–18·7), PO-SCORAD was 27·5 (95% CI 25·7–29·3), POEM was 7·5 (95% CI 6·8–8·1) and DLQI was 4·9 (95% CI 4·2–5·5).

Hospital Anxiety and Depression Scale anxiety and depression scores

Significantly higher proportions of adults with AD endorsed being affected by all individual items from the HADS questionnaire (Rao-Scott χ^2-test, P < 0·001 for all) when compared with adults without AD (Fig. 1).

Adults with AD also had higher weighted mean HADS, HADS-A and HADS-D scores and higher weighted prevalences of borderline (8–10) and/or abnormal (≥ 11) HADS-A and HADS-D scores (Table 2) when compared with adults without AD. Borderline or abnormal HADS-A, HADS-D or both HADS-A and HADS-D scores were present in 48·4%, 34·5% and 26·6% of adults with AD, respectively; this included severe scores for 9·9% (HADS-A) and 4·1% (HADS-D).

In bivariable linear regression and multivariable models controlling for sociodemographics, AD was associated with significantly higher mean HADS-A and HADS-D scores (Table 3). There were stepwise and significantly increased HADS-A and HADS-D scores in patients with moderate and severe/very severe self-reported global AD severity, POEM, PO-SCORAD, PO-SCORAD itch and PO-SCORAD sleep (P < 0·0001 for all).

Similarly, in bivariable logistic regression and multivariable models controlling for sociodemographics, AD was associated with significantly higher odds of abnormal HADS-A or HADS-D scores (scores ≥ 11) (Table 4). In multivariable models, abnormal HADS-A scores were also associated with female sex (1·32, 95% CI 1·01–1·73), < HS education (1·60 95% CI

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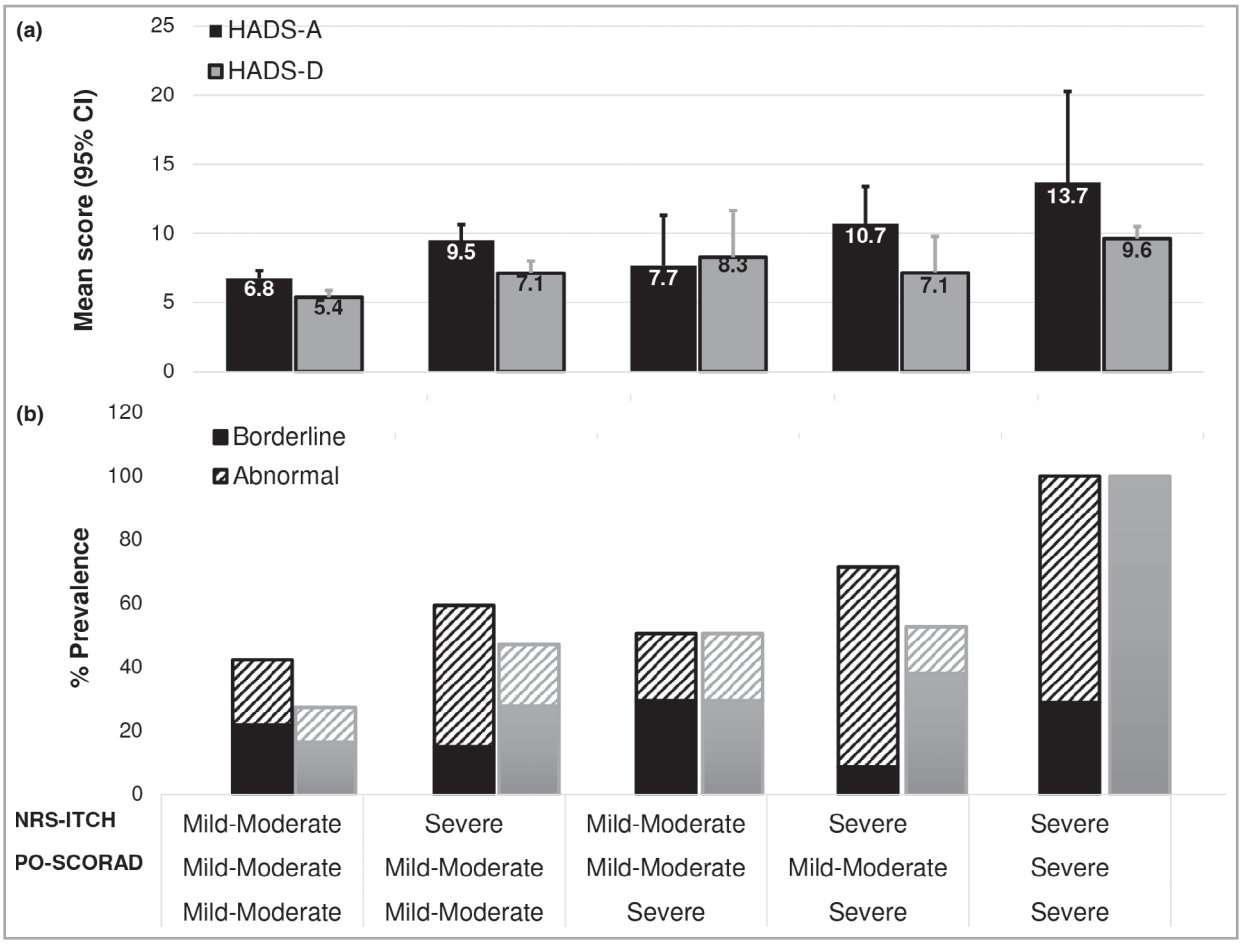

Fig 2. (a) Combined effects of mild-to-moderate and severe atopic dermatitis (AD) [Patient-Oriented Scoring Atopic Dermatitis (PO-SCORAD)], frequency of symptoms (Patient-Oriented Eczema Measure) and severity of pruritus (PO-SCORAD itch) on weighted mean [95% confidence interval (CI)] Hospital Anxiety and Depression Scale anxiety (HADS-A) and depression (HADS-D) scores and (b) the proportion of borderline and abnormal HADS-A and HADS-D scores. All subsets of combined AD severity had significantly higher HADS-A and HADS-D scores compared with patients with mild-to-moderate scores for all three assessments ($P < 0.001$). Overall, 100% of respondents with severe scores for all three assessments had borderline and/or abnormal HADS-A and HADS-D scores. NRS, numeric rating scale.

1·05–2·44), and were inversely associated with age (0·97, 95% CI 0·96–0·98) and PIR (0·91, 95% CI 0·86–0·97), but not with race/ethnicity (0·86, 95% CI 0·65–1·14) or household size (0·99, 95% CI 0·90–1·08). HADS-D was inversely associated with age (0·99, 0·98–0·99), nonwhite race/ethnicity (0·69, 0·48–0·99) and PIR (0·82, 0·75–0·90), but not with female sex (0·99, 0·71–1·37), < HS education (1·58, 0·99–2·53) or household size (1·03, 0·91–1·16).

In addition, there were stepwise and significantly increased HADS-A and HADS-D scores in patients with moderate and severe/very severe self-reported global AD severity, POEM, PO-SCORAD, PO-SCORAD itch and PO-SCORAD sleep ($P \leq 0·02$ for all). In multivariable models, HADS-A and HADS-D scores were not significantly associated with any covariables in the model other than AD severity assessments, except for inverse associations of HADS-A with age and HADS-D with nonwhite race/ethnicity.

As AD severity can be defined by different constructs, weighted mean HADS-A and HADS-D scores were stratified by the lesional severity and extent (PO-SCORAD), frequency of symptoms (POEM) and intensity of itch (PO-SCORAD itch) (Fig. 2). When compared with mild-to-moderate POEM and PO-SCORAD itch scores alone, as judged by existing interpretability bands, severe scores on these assessments were associated with significantly higher mean HADS-A and HADS-D scores, and higher prevalence of borderline and abnormal HADS-A and HADS-D scores($P < 0·0001$). Concurrent severe PO-SCORAD, POEM and/or PO-SCORAD itch were associated with even higher HADS-A and HADS-D scores compared with severe scores for only one of these assessments ($P < 0·0001$). Overall, 100% (100·0–100·0) of respondents with severe PO-SCORAD, POEM and PO-SCORAD itch had borderline or abnormal HADS-A and HADS-D scores.

Diagnosis of anxiety or depression

Overall, adults with AD vs. those without AD had higher prevalence of self-reported healthcare-diagnosed anxiety or

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Table 2 Prevalence of borderline and/or abnormal Hospital Anxiety and Depression Scale (HADS) anxiety and/or depression scores and 1-year history of anxiety or depression

	Atopic dermatitis					
	No (n = 2291)		Yes (n = 602)		1-year diagnosis of anxiety or depression	
Variable	Frequency, n	Prevalence, % (95% CI)	Frequency	Prevalence, % (95% CI)	Frequency	Prevalence, % (95% CI)
HADS anxiety						
Borderline	308	13·9 (12·1–15·7)	112	19·8 (15·9–23·7)	51	45·6 (34·4–56·8)
Abnormal	303	15·5 (13·6–17·5)	150	28·6 (24·0–33·2)	104	70·6 (61·8–79·3)
Moderate	216	10·8 (9·2–12·5)	102	18·7 (14·7–22·7)	63	61·5 (50·0–73·0)
Severe	87	4·7 (3·6–5·8)	48	9·9 (6·7–13·1)	41	87·8 (77·1–98·5)
Borderline or abnormal	611	29·4 (27·1–31·8)	262	48·4 (43·5–53·3)	155	60·4 (53·2–67·5)
HADS depression						
Borderline	236	10·5 (8·9–12·0)	115	21·0 (16·8–25·2)	73	66·6 (56·0–77·2)
Abnormal	185	9·0 (7·5–10·6)	79	13·5 (10·0–17·0)	52	71·9 (60·3–83·4)
Moderate	138	7·0 (5·6–8·3)	54	9·4 (6·3–12·4)	34	73·2 (60·4–86·0)
Severe	47	2·1 (1·4–2·8)	25	4·1 (2·1–6·2)	18	68·8 (45·2–92·5)
Borderline or abnormal	421	19·5 (17·5–21·6)	194	34·5 (29·7–39·3)	125	68·7 (60·7–76·6)
HADS anxiety and depression						
Borderline						
One	414	18·7 (16·7–20·7)	163	30·6 (25·9–35·2)	84	52·5 (43·1–61·9)
Both	65	2·9 (2·0–3·6)	32	5·1 (3·0–7·2)	20	67·9 (48·4–87·4)
Abnormal						
One	258	12·6 (10·9–14·4)	135	24·5 (20·2–28·8)	82	64·9 (55·4–74·4)
Both	115	6·0 (4·7–7·3)	47	8·8 (5·7–11·8)	37	79·5 (65·4–93·7)
Borderline or abnormal						
One	462	20·8 (18·7–22·9)	162	29·6 (25·0–34·1)	70	45·4 (36·0–54·7)
Both	285	14·1 (12·3–15·9)	147	26·6 (22·1–31·2)	105	74·0 (65·4–82·7)
1-year history of anxiety or depression	412	17·5 (15·7–19·4)	222	40·0 (35·1–44·8)		

CI, confidence interval.

depression in the past year (40·0% vs. 17·5%) (Table 2). In combination, 50·3% (45·5–55·2) of adults with AD and 27·3% (25·1–29·6) of adults without AD had abnormal HADS-A or HADS-D scores or reported a healthcare diagnosis of anxiety or depression.

However, substantial proportions of adults with AD who had borderline and/or abnormal HADS-A or HADS-D scores reported no diagnosis of anxiety or depression (Table 2). Adults with both abnormal HADS-A and HADS-D scores were more likely to be diagnosed with anxiety or depression compared with those with either score being abnormal, or those who had a borderline score for either or both.

Discussion

Using a U.S. population-based sample, we found that adults with AD had significantly higher mean HADS-A and HADS-D scores, and that among adults with AD there were higher proportions of respondents with borderline and/or abnormal HADS-A and HADS-D scores, and higher proportions of self-reported healthcare-diagnosed anxiety or depression in the past year; all of which indicate a significant mental health burden of AD. All of these outcomes were associated with AD severity, such that those with moderate and severe AD had significantly worse mental health than those with mild AD. Importantly, 100% of respondents with severe POEM, PO-SCORAD and PO-SCORAD-itch scores vs. those with mild/moderate scores were found to have borderline and/or abnormal HADS-A and HADS-D scores. Of note, HADS-A scores were consistently higher than HADS-D scores across all analyses in respondents with AD. These associations remained significant even after extensively controlling for sociodemographics. Moreover, in multivariable models, abnormal HADS-A and HADS-D scores were associated only with AD severity, but not with any other sociodemographic covariables. This finding suggests that AD severity is the major driver of anxiety and depression in adults with AD. Taken together, it appears that AD, particularly moderate-to-severe AD, is associated with profound symptoms of anxiety and depression.

The HADS is a multidimensional mental health assessment that is not specific to skin disease, and has been studied extensively in many medical disorders. The mean HADS, HADS-A and HADS-D scores for AD (13·6, 7·7 and 6·0, respectively), are similar to previous observational clinical studies in Germany (HADS-A 8·2, HADS-D 4·9)[24] and Singapore (HADS-A 7·2, HADS-D 5·0).[25]

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Table 3 Association of atopic dermatitis and atopic dermatitis severity with Hospital Anxiety and Depression Scale (HADS) scores, and anxiety and depression subscores

Variable	Weighted mean (95% CI)[a]	Crude beta (95% CI)	P-value[b]	Adjusted beta (95% CI)	P-value[b]
HADS score					
Atopic dermatitis					
No	9·9 (9·5–10·3)	0·00 (ref)	–	0·00 (ref)	–
Yes	13·6 (12·8–14·5)	3·72 (2·81–4·63)	**< 0·0001**	3·47 (2·60–4·34)	**< 0·0001**
Self-reported global atopic dermatitis severity					
Mild	10·7 (9·8–11·7)	0·00 (ref)	–	0·00 (ref)	–
Moderate	16·6 (15·0–18·2)	5·84 (3·98–7·70)	**< 0·0001**	4·89 (3·08–6·72)	**< 0·0001**
Severe	20·3 (17·3–23·3)	9·54 (6·53–12·56)	**< 0·0001**	8·63 (5·38–11·89)	**< 0·0001**
Patient-Oriented Eczema Measure (POEM)					
Clear/almost clear/mild	11·4 (10·5–12·3)	0·00 (ref)	–	0·00 (ref)	–
Moderate	16·0 (14·5–17·5)	4·60 (2·85–6·36)	**< 0·0001**	4·10 (2·56–5·65)	**< 0·0001**
Severe/very severe	18·5 (15·6–21·4)	7·12 (4·14–10·09)	**< 0·0001**	6·44 (3·63–9·24)	**< 0·0001**
Patient-Oriented Scoring Atopic Dermatitis (PO-SCORAD)					
Mild	10·4 (9·5–11·3)	0·00 (ref)	–	0·00 (ref)	–
Moderate	15·5 (14·2–16·8)	5·09 (3·49–6·68)	**< 0·0001**	4·21 (2·72–5·69)	**< 0·0001**
Severe	22·2 (20·5–23·9)	11·78 (9·90–13·66)	**< 0·0001**	10·31 (8·01–12·61)	**< 0·0001**
PO-SCORAD itch					
Clear/almost clear/mild	10·5 (9·4–11·6)	0·00 (ref)	–	0·00 (ref)	–
Moderate	14·6 (13·1–16·1)	4·11 (2·27–5·94)	**< 0·0001**	3·98 (2·30–5·67)	**< 0·0001**
Severe/very severe	17·3 (15·7–18·9)	6·79 (4·85–8·73)	**< 0·0001**	6·18 (4·35–8·02)	**< 0·0001**
PO-SCORAD sleep					
Clear/almost clear/mild	9·6 (8·7–10·6)	0·00 (ref)	–	0·00 (ref)	–
Moderate	15·6 (14·3–16·8)	5·92 (4·36–7·49)	**< 0·0001**	5·48 (3·90–7·06)	**< 0·0001**
Severe/very severe	18·2 (16·6–19·8)	8·58 (6·77–10·40)	**< 0·0001**	7·81 (6·1–9·5)	**< 0·0001**
HADS anxiety score					
Atopic dermatitis					
No	5·6 (5·4–5·8)	0·00 (ref)	–	0·00 (ref)	–
Yes	7·7 (7·2–8·2)	2·05 (1·51–2·59)	**< 0·0001**	1·92 (1·41–2·43)	**< 0·0001**
Self-reported global atopic dermatitis severity					
Mild	6·1 (5·5–6·7)	0·00 (ref)	–	0·00 (ref)	–
Moderate	9·2 (8·2–10·2)	3·10 (1·96–4·25)	**< 0·0001**	2·64 (1·52–3·75)	**< 0·0001**
Severe	11·2 (9·2–13·1)	5·07 (3·11–7·02)	**< 0·0001**	4·67 (2·57–6·76)	**< 0·0001**
Patient-Oriented Eczema Measure (POEM)					
Clear/almost clear/mild	6·4 (5·9–6·9)	0·00 (ref)	–	0·00 (ref)	–
Moderate	8·9 (8·0–9·8)	2·49 (1·43–3·54)	**< 0·0001**	2·29 (1·37–3·20)	**< 0·0001**
Severe/very severe	10·6 (8·8–12·3)	4·16 (2·37–5·96)	**< 0·0001**	3·90 (2·19–5·61)	**< 0·0001**
Patient-Oriented Scoring Atopic Dermatitis (PO-SCORAD)					
Mild	5·9 (5·3–6·4)	0·00 (ref)	–	0·00 (ref)	–
Moderate	8·7 (7·9–9·4)	2·78 (1·83–3·73)	**< 0·0001**	2·23 (1·35–3·12)	**< 0·0001**
Severe	12·5 (11·0–14·0)	6·61 (5·09–8·14)	**< 0·0001**	5·88 (4·23–7·53)	**< 0·0001**
PO-SCORAD itch					
Clear/almost clear/mild	6·0 (5·4–6·7)	0·00 (ref)	–	0·00 (ref)	–
Moderate	7·8 (7·0–8·7)	1·78 (0·70–2·86)	**0·001**	1·75 (0·75–2·75)	**0·0006**
Severe/very severe	9·9 (8·9–10·9)	3·88 (2·70–5·07)	**< 0·0001**	3·57 (2·43–4·70)	**< 0·0001**
PO-SCORAD sleep					
Clear/almost clear/mild	5·5 (4·9–6·1)	0·00 (ref)	–	0·00 (ref)	–
Moderate	8·2 (7·4–9·0)	2·69 (1·71–3·66)	**< 0·0001**	2·47 (1·49–3·44)	**< 0·0001**
Severe/very severe	10·5 (9·6–11·4)	5·02 (3·94–6·10)	**< 0·0001**	4·57 (3·54–5·59)	**< 0·0001**
HADS depression score					
Atopic dermatitis					
No	4·3 (4·1–4·5)	0·00 (ref)	–	0·00 (ref)	–
Yes	6·0 (5·6–6·4)	1·67 (1·20–2·13)	**< 0·0001**	1·55 (1·10–2·00)	**< 0·0001**
Self-reported global atopic dermatitis severity					
Mild	4·6 (4·1–5·2)	0·00 (ref)	–	0·00 (ref)	–
Moderate	7·4 (6·6–8·2)	2·74 (1·79–3·69)	**< 0·0001**	2·26 (1·33–3·19)	**< 0·0001**
Severe	9·1 (7·8–10·5)	4·48 (3·09–5·86)	**< 0·0001**	3·97 (2·50–5·43)	**< 0·0001**

(continued)

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Table 3 (continued)

Variable	Weighted mean (95% CI)[a]	Crude beta (95% CI)	P-value[b]	Adjusted beta (95% CI)	P-value[b]
Patient-Oriented Eczema Measure (POEM)					
Clear/almost clear/mild	5·0 (4·5–5·5)	0·00 (ref)	–	0·00 (ref)	–
Moderate	7·1 (6·3–7·9)	2·12 (1·19–3·05)	**< 0·0001**	1,82 (0·96–2·68)	**< 0·0001**
Severe/very severe	7·9 (6·6–9·3)	2·95 (1·58–4·33)	**< 0·0001**	2·54 (1·26–3·82)	**< 0·0001**
Patient-Oriented Scoring Atopic Dermatitis (PO-SCORAD)					
Mild	4·5 (4·0–5·0)	0·00 (ref)	–	0·00 (ref)	–
Moderate	6·8 (6·2–7·5)	2·31 (1·48–3·15)	**< 0·0001**	1·97 (1·19–2·76)	**< 0·0001**
Severe	9·7 (8·7–10·6)	5·17 (4·13–6·20)	**< 0·0001**	4·44 (3·25–5·62)	**< 0·0001**
PO-SCORAD itch					
Clear/almost clear/mild	4·5 (3·9–5·0)	0·00 (ref)	–	0·00 (ref)	–
Moderate	6·8 (6·0–7·6)	2·33 (1·36–3·30)	**< 0·0001**	2·24 (1·33–3·14)	**< 0·0001**
Severe/very severe	7·4 (6·6–8·2)	2·91 (1·94–3·88)	**< 0·0001**	2·61 (1·70–3·53)	**< 0·0001**
PO-SCORAD sleep					
Clear/almost clear/mild	4·1 (3·6–4·6)	0·00 (ref)	–	0·00 (ref)	–
Moderate	7·4 (6·6–8·1)	3·24 (2·35–4·11)	**< 0·0001**	3·02 (2·13–3·90)	**< 0·0001**
Severe/very severe	7·7 (6·9–8·5)	3·56 (1·63–4·50)	**< 0·0001**	3·24 (2·38–4·10)	**< 0·0001**

[a]Weighted mean [95% confidence interval (CI)] are presented including sample weights. [b]Bold indicates P-values with statistical significance. Linear regression models were created with short form-12 mental or physical health scores or Dermatology Life Quality Index as the dependent variables. The independent variable was having atopic dermatitis as defined by modified U.K. Working Party criteria or atopic dermatitis severity using self-reported global atopic dermatitis severity, POEM, PO-SCORAD, PO-SCORAD itch and PO-SCORAD sleep scores. Crude beta and 95% CI were estimated. Multivariable models included age (continuous), sex (male/female), race/ethnicity (white/other), level of education (less than high school/high school or greater), household size and poverty income ratio (continuous). Adjusted beta and 95% CI were estimated.

The observed mean HADS, HADS-A and HADS-D scores in adults with moderate AD (14·6–16·6, 7·8–9·2 and 6·8–7·4, respectively) and severe AD (17·3–22·2, 9·9–12·5 and 7·4–9·7, respectively) were slightly higher than scores observed at baseline in a clinical trial of adults with moderate-to-severe AD (HADS 12·2, HADS-A 7·0, HADS-D 5·2).[2] The HADS-A and HADS-D scores were also higher than previously reported in other chronic skin disorders, e.g. patients enrolled in clinical trials of biologics for moderate-to-severe psoriasis (6·8–7·2 and 5·3–5·7, respectively),[26,27] and other medical disorders such as diabetes (5·7 and 5·0, respectively) and HIV (6·5 and 5·5, respectively).[28] A cross-sectional study that used HADS scores of 1519 adults with AD from six U.S. medical centres found that approximately one-quarter of patients with mild AD and one-half of patients with moderate-to-severe AD had symptoms of anxiety or depression, with even more severe HADS scores among those with uncontrolled AD.[29] These results suggest that moderate-to-severe AD has an equal or even greater mental health burden than many other health disorders. The mental health burden of AD should be an important consideration in disease awareness, prioritizing appropriate resource allocation and clinical decision making.

The present study is consistent with a previous study that found higher rates of depression among U.S. adults with AD vs. those without AD.[30] However, there are some notable differences. We found that 40% of adults with AD reported being diagnosed with depression and/or anxiety, which is higher than the 19·9% of adults with AD who had depression in the past year according to the National Health Interview Survey.[30] The differences are likely related to the question used in our study that included both anxiety and depression. In addition, we found that 21·0% of adults with AD had borderline HADS-D scores and 13·5% had abnormal HADS-D scores, including 9·4% with moderate and 4·1% with severe HADS-D scores, which differs from the 17·5% of adults with AD who met SIGECAPS (Sleep, Interest, Guilt, Energy, Concentration, Appetite, Psychomotor function, Suicidal ideation) criteria for major depressive disorder and those with moderate (5·4%) and severe (5·8%) Patient Health Questionnaire-9 scores in the National Health and Nutrition Examination Survey.[30] These differences are likely attributable to different definitions of depression and its severity. Regardless of the differences, these studies and others demonstrate markedly increased symptoms of anxiety and depression in adult AD. Of note, the prevalences of borderline and abnormal HADS-A and HADS-D scores were consistently higher than prevalences of self-reported diagnosed anxiety or depression. Furthermore, a substantial proportion of respondents with AD who had marked elevations of their HADS-A and HADS-D scores were not diagnosed with anxiety or depression. This suggests that the mental health burden of AD is underappreciated, and that patients with AD would benefit from routine screening for symptoms of anxiety and depression.

Depressive and anxiety disorders can be classified in several ways according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), including classification as Axis I disorders (primary disorders) or Axis III disorders (secondary to a medical condition). It is important to recognize that depression and anxiety are symptoms of the AD per se in many patients, i.e. DSM-IV Axis III disorders. In many patients, HADS-A and HADS-D scores significantly improve with

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Table 4 Association of atopic dermatitis and atopic dermatitis severity with definite anxiety and depression

Variable	Weighted prevalence, % (95% CI)[a]	Crude OR (95% CI)	P-value[b]	Adjusted OR (95% CI)	P-value[b]
HADS anxiety score ≥ 11					
Atopic dermatitis					
No	15·5 (13·6–17·5)	1·00 (ref)	–	1·00 (ref)	–
Yes	28·6 (24·0–33·2)	2·17 (1·66–2·85)	**<0·0001**	2·19 (1·65–2·91)	**0·01**
Self-reported global atopic dermatitis severity					
Mild	16·3 (10·8–21·8)	1·00 (ref)	–	1·00 (ref)	–
Moderate	39·1 (29·7–48·5)	3·30 (1·87–5·81)	**< 0·0001**	2·75 (1·52–4·95)	**0·0008**
Severe	62·7 (43·6–81·8)	8·62 (3·46–21·51)	**< 0·0001**	8·34 (3·01–23·12)	**< 0·0001**
Patient-Oriented Eczema Measure (POEM)					
Clear/almost clear/Mild	17·2 (12·3–22·0)	1·00 (ref)	–	1·00 (ref)	–
Moderate	38·9 (29·7–48·2)	3·07 (1·83–5·16)	**< 0·0001**	3·11 (1·80–5·39)	**< 0·0001**
Severe	56·3 (41·9–70·7)	6·21 (3·15–12·22)	**< 0·0001**	6·67 (3·27–13·60)	**< 0·0001**
Patient-Oriented Scoring Atopic Dermatitis (PO-SCORAD)					
Mild	12·9 (8·7–17·1)	1·00 (ref)	–	1·00 (ref)	–
Moderate	39·1 (31·1–47·2)	4·35 (2·63–7·20)	**< 0·0001**	3·56 (2·09–6·05)	**< 0·0001**
Severe	63·0 (45·9–80·1)	11·50 (5·04–26·26)	**< 0·0001**	9·75 (3·99–23·86)	**< 0·0001**
PO-SCORAD itch					
Mild	13·0 (7·7–18·3)	1·00 (ref)	–	1·00 (ref)	–
Moderate	31·0 (22·4–39·7)	3·01 (1·62–5·61)	**0·0005**	3·12 (1·63–5·97)	**0·0006**
Severe	49·3 (39·6–58·9)	6·50 (3·53–11·97)	**< 0·0001**	6·33 (3·35–11·99)	**< 0·0001**
PO-SCORAD sleep					
Mild	12·9 (8·0–17·9)	1·00 (ref)	–	1·00 (ref)	–
Moderate	30·0 (20·2–39·8)	2·89 (1·51–5·50)	**0·001**	2·57 (1·29–5·11)	**0·007**
Severe	50·9 (41·9–60·0)	6·99 (3·94–12·40)	**< 0·0001**	6·30 (3·46–11·46)	**< 0·0001**
HADS depression score ≥ 11					
Atopic dermatitis					
No	9·0 (7·5–10·6)	1·00 (ref)	–	1·00 (ref)	–
Yes	13·5 (10·0–17·0)	1·57 (1·10–2·24)	**0·01**	1·50 (1·04–2·17)	**0·03**
Self-reported global atopic dermatitis severity					
Mild	7·8 (4·0–11·7)	1·00 (ref)	–	1·00 (ref)	–
Moderate	18·0 (10·6–25·4)	2·58 (1·24–5·40)	**0·01**	2·26 (1·04–4·89)	**0·03**
Severe	29·5 (9·9–49·2)	4·92 (1·66–14·65)	**0·004**	4·33 (1·44–13·05)	**0·009**
Patient-Oriented Eczema Measure (POEM)					
Clear/almost clear/mild	8·3 (4·8–11·8)	1·00 (ref)	–	1·00 (ref)	–
Moderate	20·4 (12·6–28·2)	2·83 (1·46–5·48)	**0·002**	2·58 (1·32–5·01)	**0·005**
Severe	21·2 (8·4–34·0)	2·97 (1·21–7·25)	**0·02**	2·31 (0·96–5·54)	0·06
Patient-Oriented Scoring Atopic Dermatitis (PO-SCORAD)					
Mild	7·6 (4·3–11·0)	1·00 (ref)	–	1·00 (ref)	–
Moderate	15·3 (9·6–21·1)	2·19 (1·14–4·19)	**0·02**	1·82 (0·92–3·61)	0·08
Severe	35·7 (17·6–53·8)	6·71 (2·67–16·87)	**< 0·0001**	4·14 (1·60–10·67)	**0·003**
PO-SCORAD itch					
Mild	6·0 (2·7–9·2)	1·00 (ref)	–	1·00 (ref)	–
Moderate	18·1 (10·8–25·4)	3·49 (1·62–7·50)	**0·001**	3·53 (1·54–8·11)	**0·003**
Severe	19·9 (11·8–27·9)	3·91 (1·81–8·47)	**0·0006**	3·69 (1·61–8·47)	**0·002**
PO-SCORAD sleep					
Mild	6·0 (3·1–8·9)	1·00 (ref)	–	1·00 (ref)	–
Moderate	18·9 (10·7–27·1)	3·62 (1·72–7·62)	**0·0007**	3·41 (1·50–7·73)	**0·003**
Severe	20·7 (12·5–28·9)	4·05 (1·98–8·30)	**< 0·0001**	3·52 (1·72–7·19)	**0·0006**

[a]Weighted prevalence [95% confidence interval (CI)] are presented including sample weights. [b]P-values in bold indicate statistical significance. Logistic regression models were created with definite anxiety (HADS anxiety ≥ 11 vs. 0–10) and depression (HADs depression ≥ 11 vs. 0–10) as the dependent variables. The independent variable was having atopic dermatitis as defined by modified U.K. Working Party criteria or atopic dermatitis severity using self-reported global atopic dermatitis severity, POEM, PO-SCORAD, PO-SCORAD itch and PO-SCORAD sleep scores. Crude odds ratios (ORs) and 95% CI were estimated. Multivariable models included age (continuous), sex (male/female), race/ethnicity (white/other), level of education (less than high school/high school or greater), household size and poverty income ratio (continuous). Adjusted ORs and 95% CI were estimated. HADS, Hospital Anxiety and Depression Scale.

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adequate treatment of AD signs and symptoms.[31–34] However, some patients experiencing symptoms of anxiety and depression may have Axis I depressive or anxiety disorders and/or benefit from additional referral to a mental health specialist.

The strengths of this study include the following: it was a large-scale population-based study with a diverse sample and sample weights that adjusted for multiple sociodemographics and allowed for generalization of results that are representative of the U.S. population; it used multiple and well-validated assessments of AD severity and controlled for multiple confounding variables in multivariable models. POEM, PO-SCORAD and self-reported global AD severity have all been studied in patients with AD and are considered to have good overall face validity, construct validity, internal consistency, reliability and/or responsiveness; POEM is the preferred assessment of AD symptoms for clinical trials by the Harmonising Outcome Measures in Eczema group.[17,35–50] There is some debate regarding the optimal cut-off to use for a case definition of anxiety or depression. Initially, a cut-off of ≥ 11 was considered optimal for case definitions.[23] However, a recent review highlighted that in most studies an optimal balance between sensitivity and specificity was achieved when cases were defined by a score of ≥ 8 on both HADS-A and HADS-D.[51] Therefore, we analysed both cut-offs of ≥ 8 and ≥ 11.

This study has some limitations. We used an internet panel, which may be subject to false answers, answering too fast, giving the same answer repeatedly (also known as straight-lining), and receiving multiple surveys completed by the same respondent.[13] However, we do not believe these to be major concerns, given that there were < 0·05% missing values for AD and HADS questions, > 95% of surveys took 10 min or longer to complete, < 0·5% had the same responses for all HADS questions, and internet protocol and e-mail address verification was used for the panel. We used an adaptation of the extensively validated UKWP criteria[16] to establish the diagnosis of AD, which lacked one criterion based on physical examination. The validity of this case definition of AD has not yet been prospectively studied. However, the prevalence estimate for AD using this UKWP-like criteria (7·3%) is remarkably similar to the 2012 National Health Interview Survey that found the prevalence of adult AD to be 7·2%,[52] using a single self-reported question about eczema. These nearly identical estimates, despite using different cohorts and definitions of AD, support the validity of the definition used for AD. An international, cross-sectional, web-based survey found the U.S. prevalence of adult AD to be 4·9%.[53] AD was defined using UKWP-like criteria plus self-report of ever having an AD diagnosis by a physician. That definition was not validated and is likely excessively rigorous given numerous previous studies showing the validity of UKWP criteria alone for identifying AD. Requiring a diagnosis of AD is problematic given the lack of use of the terminology 'AD' by clinicians and patients during clinical encounters, health disparities and poor access to specialty care in the U.S.A. Had that study employed UKWP-like criteria alone, the prevalence would have likely been approximately 7%. The effects of past and present treatment were not examined. 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. Future studies are warranted to address these points.

In conclusion, AD is associated with increased symptoms of anxiety and depression, higher proportions of borderline and/or abnormal anxiety and depression scores, and higher proportions of diagnosed anxiety or depression in the U.S. population. Moderate and severe AD were particularly associated with markedly worse mental health. These data support the heavy mental health burden that AD places on patients. It is important for clinicians to recognize that virtually all patients with moderate-to-severe AD have symptoms of anxiety and depression. We recommend that clinicians incorporate assessment of mental health symptoms in clinical practice to determine disease burden and screen for patients with symptoms of anxiety and depression.

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Appendix

Conflicts of interest

J.I.S. served as a consultant and/or advisory board member for AbbVie, Asana, Eli Lilly, Galderma, GlaxoSmithKline, Glenmark, Kiniksa, Leo, Menlo, Pfizer, Regeneron-Sanofi, Realm and Roivant, receiving honoraria. He has been a speaker for Regeneron-Sanofi and received research grants from GlaxoSmithKline and Regeneron-Sanofi. J.I.S. is supported by the Dermatology Foundation. J.M.G. served as a consultant for BMS, Boehringer Ingelheim, GSK, Janssen Biologics, Menlo Therapeutics, Novartis Corp, Regeneron, Dr Reddy's Laboratories, UCB (DSMB), Sanofi and Pfizer Inc., receiving honoraria. J.M.G. receives research grants (to the Trustees of the University of Pennsylvania) from AbbVie, Janssen, Novartis Corp, Sanofi, Celgene, Ortho Dermatologics and Pfizer Inc. and received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly and Ortho Dermatologics. J.M.G. is a copatent holder of resiquimod for treatment of cutaneous T-cell lymphoma. J.M.G. is a Deputy Editor for the *Journal of Investigative Dermatology*, receiving honoraria from the Society for Investigative Dermatology. Z.C.C.F. has served as a consultant for the National Eczema Association and the Allergy and Asthma Foundation of America (AAFA), receiving honoraria, and receives or has received research grants (to the Trustees of the University of Pennsylvania) from Regeneron, Sanofi, Tioga and Vanda pharmaceuticals and Realm Therapeutics for work in atopic dermatitis. Z.C.C.F. has received payment for continuing medical education work related to atopic dermatitis, which was supported indirectly by Regeneron and/or Sanofi. D.J.M. is the chair of the data monitoring committee for many Sanofi clinical trials of dupilumab, and, with respect to atopic dermatitis, has received independent research funding to his institution from the National Institutes of Health and Valeant. M.B. has received research funding from Anacor and Regeneron and consulted for Regeneron, Sanofi Genzyme and Pfizer. L.F. has served as a consultant for Regeneron, receiving honoraria. L.F. has also been a speaker for Regeneron and has received research and educational grants from Genentech, Baxter and Pfizer. M.H.G. is a board member of the AAFA and chair for the AAFA Medical Scientific Council, and has served as a consultant for AstraZeneca. E.L.S. has served as a consultant and/or advisory board member for Regeneron-Sanofi. P.Y.O. is a coinvestigator of the Atopic Dermatitis Research Network. He has consulted for Pfizer and Theravance, and has received research funding from Regeneron.

Author contributions

J.I.S. had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. J.I.S. was responsible for the study concept and design. J.I.S., J.M.G., D.J.M., M.B., L.F, M.H.G., P.Y.O. and Z.C.C.F. were involved in the acquisition of data, analysis and interpretation of data and critical revision of the manuscript for important intellectual content. J.I.S carried out the statistical analysis and drafted the manuscript. The study was supervised by Allergy and Asthma Foundation of America.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Fig S1. Flowchart of study design.

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