Association of atopic dermatitis severity with cognitive function in adults

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Background: Atopic dermatitis (AD) is associated with itch, pain, and sleep disturbance, all of which may contribute toward cognitive dysfunction.

Objective: To determine the relationship of AD severity and cognitive function in adults.

Methods: We performed a prospective dermatology practice-based study using questionnaires and evaluation by a dermatologist (n = 386). Cognitive function was assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Cognitive Function 8-item Short-Form.

Results: At baseline, 118 patients (58.1%) reported ≥1 symptoms of cognitive dysfunction in the past 4 weeks, with 29 (14.3%) having mild, 11 (5.4%) moderate, and 4 (2.0%) severe PROMIS Cognitive Function T-scores. In propensity score-weighted regression models, PROMIS Cognitive Function T-scores were inversely associated with patient-reported global AD severity, Patient Oriented Eczema Measure (POEM), Numeric Rating Scale worst itch and skin pain, SCORing Atopic Dermatitis (SCORAD)-sleep, POEM-sleep, Eczema Area and Severity Index, and SCORAD, with stepwise decreases of cognitive function with worsening AD severity. At all AD severity levels, cognitive dysfunction was associated with increased Dermatology Life Quality Index and ItchyQoL scores. Changes from baseline in PROMIS Cognitive Function T-scores were weakly to moderately inversely correlated with changes from baseline in multiple AD outcomes.

Limitations: Single-center study without non-AD controls.

Conclusion: Cognitive dysfunction is associated with AD severity. Cognitive function may be an important end point for monitoring treatment response in AD. (J Am Acad Dermatol 2020;83:1349-59.)

Key words: atopic dermatitis; burden; cognition; concentration; eczema; executive function; itch; memory; patient-reported outcomes; pruritus; quality of life; severity.

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Atopic dermatitis (AD) is a heterogenous disorder associated with itch, skin pain,[1,2] sleep disturbance and fatigue,[3,4] variable signs, lesional morphology[5] and distribution,[6] and atopic and mental health comorbidities.[7-13] All of these symptoms and signs may negatively affect health-related quality of life (HRQOL).[14-17] In addition, they may negatively affect aspects of cognitive function, including concentration, thinking, memory, and executive functioning. For example, chronic itch, skin pain, and scratching may lead to distraction.[18] Sleep disturbance and fatigue may contribute to slowed thinking and other cognitive dysfunction. Some medications used to treat AD, including sedating antihistamines and neuroleptics, may lead to drowsiness, concentration problems, memory loss, and confusion.[19]

CAPSULE SUMMARY

- More severe atopic dermatitis was associated with lower cognitive function scores. Cognitive dysfunction was associated with worse quality of life.
- These data demonstrate that cognitive dysfunction is a novel, common, and burdensome symptom in atopic dermatitis. Cognitive function may be an important end point for monitoring treatment response in atopic dermatitis.

To our knowledge, previous studies have not examined the impact of AD severity on cognitive function in adults. We sought to determine whether AD severity is associated with increased cognitive dysfunction. Moreover, we examined the predictors of cognitive dysfunction and its impact on HRQOL. Finally, we sought to determine the feasibility of assessing cognitive function using the Patient-Reported Outcomes Measurement Information System (PROMIS) Cognitive Function 8-item Short Form (SF) in clinical practice of adults with AD.

METHODS

Study design

A prospective, dermatology practice-based study of adults (aged ≥18 years) was performed with AD as defined by the Hanifin-Rajka diagnostic criteria.[20] Exclusion criteria included those without a definite diagnosis of AD or being unwilling or unable to complete assessments. Of the patients who were invited, >99% agreed to participate. Patients received standard of care follow-up and treatment, including any or all of emollients, prescription topical therapy, systemic therapy, or phototherapy, where appropriate.

Outcome measures

Self-administered questionnaires were completed by patients of the eczema clinic at an academic medical center before their encounter. Questionnaires included the following in order: self-reported severity of AD,[21,22] Numeric Rating Scale (NRS) and Verbal Rating Scale for worst itch and average itch, frequency of itch, and NRS skin pain, Patient Oriented Eczema Measure (POEM),[23,24] PROMIS Cognitive Function 8-item SF (available at http://www.healthmeasures.net/)[25,26] (lower scores indicate poorer cognitive function), Dermatology Life Quality Index (DLQI),[27,28] and ItchyQoL.[28-30]

Patients were assessed with a full-body skin examination by one of the authors, a dermatologist (J.S.). Eczema Area and Severity Index (EASI)[31] and SCORing AD (SCORAD)[32] were the clinically reported outcomes examined. Surveys were administered between January 2017 and February 2019. The Northwestern University Institutional Review Boards approved the study, and informed consent was obtained electronically.

Statistical analysis

Summary statistics were estimated for baseline population characteristics. PROMIS Cognitive Function T-scores were not normally distributed. Therefore, bivariable associations of PROMIS Cognitive Function T-scores with personal demographics, comorbidities, medical disorders, and patient-reported global AD severity were tested using nonparametric Mann-Whitney *U* and Kruskal-Wallis tests.

Propensity score-weighted linear regression models were used to examine the association of disease severity (independent variables) on PROMIS Cognitive Function T-scores (dependent variable) (Supplemental Methods, available via Mendeley at https://data.mendeley.com/datasets/publish-confirmation/44y6k59t79/1at).

Linear regression models were constructed with the PROMIS Cognitive Function T-scores as the dependent variable, the AD severity measures as the independent variables, and incorporating inverse probability propensity score weighting. Assumptions for linear regression modeling were met based on visual examination and the Kolmogorov-Smirnov test of residuals ($P > .05$). Similarly, ordinal logistic regression models were constructed with each individual PROMIS Cognitive Function item as the dependent variable and patient-reported global AD severity as the independent

Abbreviations used:

AD:	atopic dermatitis
DLQI:	Dermatology Life Quality Index
EASI:	Eczema Area and Severity Index
HRQOL:	health-related quality of life
NRS:	Numeric Rating Scale
POEM:	Patient Oriented Eczema Measure
PROMIS:	Patient-Reported Outcomes Measurement Information System
SCORAD:	SCORing Atopic Dermatitis
SF:	short form

variable. This approach was used because the data met the proportional odds assumption (score test, $P > .05$).

Kruskal-Wallis tests were used to examine the relation of DLQI or ItchyQoL scores (dependent variables) with cognitive dysfunction (PROMIS Cognitive Function T-score of ≤45% as the independent variable), stratified by AD severity (patient-reported global AD severity, NRS worst itch). Multivariable PS-weighted linear regression models were also constructed with cognitive dysfunction (defined as PROMIS Cognitive Function T-score of ≤45%[33]) as the independent variable and DLQI or ItchyQoL as the dependent variables. Models included patient-reported global AD severity, POEM, NRS worst itch, EASI, SCORAD, and SCORAD-sleep as covariables. Two-way statistical interactions were tested and included in final models if the P value was <.01 and there was modification of estimates by >20%.

Responsiveness of cognitive function was determined using Spearman correlations between the absolute change from baseline at the first follow-up visit for PROMIS Cognitive Function T-scores with change of other patient-reported outcomes (patient-reported global AD severity, POEM, NRS worst itch, NRS skin pain, and SCORAD-sleep) and clinically reported outcomes (EASI and SCORAD). Correlation coefficients (ρ) were interpreted as ≥0.70 or ≤−0.70, very strong; 0.50 to 0.69 or −0.69 to −0.50, strong; 0.30 to 0.49 or −0.49 to −0.30, moderate; and 0.10 to 0.29 or −0.29 to −0.10, weak.[34] We hypothesized that changes of cognitive function would correlate with changes in AD severity.

Internal consistency of PROMIS Cognitive Function 8-item SF was assessed using the Cronbach α and item-total correlations. Differential item functioning was analyzed by age (<50 vs ≥50 years), education (high school graduate or less, more than high school), sex, and race/ethnicity (white, nonwhite) (Supplemental Methods). Feasibility of assessing PROMIS Cognitive Function was examined by survey completion rates and time to completion.

The statistical analyses were performed in SAS 9.4.3 software (SAS Institute, Inc, Cary, NC). Missing values were encountered in ≤0.1% of respondents for all analyzed variables. Complete case analysis was performed. Correction for multiple dependent tests with the approach of Benjamini and Hochberg yielded a critical P value of .02.

RESULTS

Patient characteristics

Overall, 386 adults (age range, 18-88 years) were included in the study, of which 245 were evaluated at follow-up (the mean ± SD follow-up interval was 4.3 ± 4.6 months). The cohort included 162 women (42.0%) and 204 whites (52.9%). The age at enrollment was 43.1 ± 17.1 years. The body surface area of involvement was 25.2% ± 29.0%, NRS worst itch was 4.9 ± 3.2, objective-SCORAD was 23.2 ± 14.6, SCORAD was 32.0 ± 17.5, EASI was 9.5 ± 12.0, POEM was 12.0 ± 7.3, and DLQI was 8.3 ± 6.8.

At baseline, 258 patients (66.8%) reported at least 1 symptom of cognitive dysfunction in the past 4 weeks (Supplemental Fig 1). The most commonly reported symptom was slowed thinking, followed by difficulty concentrating. The median PROMIS Cognitive Function T-score was 53.4 (interquartile range, 17.3), with 48 (12.4%) having mild, 21 (5.4%) having moderate, and 20 (5.2%) having severe PROMIS Cognitive Function T-scores.

Associations of cognitive dysfunction in AD

In bivariable analyses, PROMIS Cognitive Function T-scores were lower (ie, poorer cognitive function) in patients with AD who had comorbid asthma (Mann-Whitney U Test, $P = .03$), depression ($P < .0001$), and anxiety ($P = .0004$), and use of dupilumab ($P = .04$) (Table I). However, there were no associations with age, sex, race/ethnicity, level of education, insurance status, current smoking or alcohol use, comorbid hay fever or food allergy, or any other medication use.

Association of AD severity with cognitive dysfunction

In propensity score-weighted regression models, PROMIS Cognitive Function T-scores were inversely associated with all severity measures of AD (patient-reported global AD severity, POEM, EASI, SCORAD), itch (NRS worst itch), sleep disturbance (SCORAD-sleep and POEM-sleep) and pain (NRS skin pain), with stepwise decreases of cognitive function with worsening severity (Table II).

Table I. Characteristics of participants and bivariable associations with Patient-Reported Outcomes Measurement Information System (*PROMIS*) Cognitive Function T-scores

Variable	Value, frequency (%) (N = 386)	PROMIS Cognitive Function T-score, median (min, max)	*P* value
Demographics			
Age, y			.63
18-39	185 (47.9)	53.4 (22.4, 63.5)	
40-59	128 (33.2)	55.4 (22.4, 63.5)	
60-79	67 (17.4)	53.4 (33.9, 63.5)	
≥80	6 (1.6)	56.7 (33.9, 63.5)	
Sex			.34
Female	162 (42.0)	53.4 (22.4, 63.5)	
Male	224 (58.0)	53.4 (22.4, 63.5)	
Race/ethnicity			.56
Caucasian/white	204 (52.9)	52.6 (25.7, 63.5)	
African American/black	46 (11.9)	55.4 (25.7, 63.5)	
Hispanic	44 (11.4)	58.1 (22.4, 63.5)	
Asian	80 (20.7)	54.4 (22.4, 63.5)	
Multiracial/other	12 (3.1)	47.2 (35.6, 63.5)	
Level of education			.35
High school or less	27 (7.0)	58.1 (35.6, 64.5)	
Greater than high school	359 (93.0)	53.4 (22.4, 63.5)	
Insurance coverage			.14
None	15 (3.9)	58.1 (33.9, 63.5)	
Public	58 (15.2)	50.5 (25.7, 63.5)	
Private	308 (80.4)	55.4 (22.4, 63.5)	
Social history			
Current smoker	338 (88.7)	55.4 (22.4, 63.5)	.07
No	43 (11.3)	52.6 (25.7, 63.5)	
Yes			
Current alcohol use			.33
No	148 (40.3)	53.4 (22.4, 63.5)	
Yes	219 (59.7)	51.8 (22.4, 63.5)	
Past medical history			
Asthma			.03
No	219 (57.5)	55.4 (22.4, 64.5)	
Yes	162 (42.5)	52.6 (22.4, 63.5)	
Hay fever			.08
No	133 (34.9)	55.4 (22.4, 63.5)	
Yes	248 (65.1)	53.4 (22.4, 63.5)	
Food allergy			.77
No	228 (60.3)	53.4 (22.4, 63.5)	
Yes	150 (39.7)	53.4 (22.4, 63.5)	
Depression			<.0001
No	324 (83.9)	55.4 (22.4, 63.5)	
Yes	62 (16.1)	44.4 (22.4, 63.5)	
Anxiety			.0004
No	315 (81.6)	55.4 (22.4, 63.5)	
Yes	71 (18.4)	47.2 (22.4, 63.5)	
Current treatments			
Topical therapy alone	191 (49.5)	52.6 (22.4, 63.5)	…
Nonsedating antihistamines	18 (4.7)	52.6 (41.1, 63.5)	.89
Sedating antihistamines	2 (0.5)	63.5 (43.6, 63.5)	.45
Gabapentin	58 (15.0)	55.4 (33.1, 63.5)	.53
Cyclosporine	71 (18.4)	51.8 (22.4, 63.5)	.73
Methotrexate	53 (13.7)	55.4 (33.1, 63.5)	.88
Mycophenolate	3 (0.8)	63.5 (55.4, 63.5)	.15

Continued

Table I. Cont'd

Variable	Value, frequency (%) (N = 386)	PROMIS Cognitive Function T-score, median (min, max)	*P* value
Systemic corticosteroids	7 (1.8)	47.2 (41.9, 63.5)	.41
Dupilumab	112 (29.0)	52.6 (28.9, 63.5)	.04
Narrow-band ultraviolet B	35 (9.1)	52.6 (39.5, 63.5)	.71
Patient-reported global AD severity			.01
Clear/almost clear	22 (6.2)	63.5 (33.9, 63.5)	
Mild	136 (38.4)	55.4 (31.2, 63.5)	
Moderate	111 (31.4)	51.8 (22.4, 63.5)	
Severe	85 (24.0)	51.8 (22.4, 63.5)	

AD, Atopic dermatitis; *max*, maximum; *min*, minimum.

In addition, patient-reported global AD was associated with more severe responses for all 8 items from PROMIS Cognitive Function, with similar or even poorer cognitive function in severe AD than moderate AD (Table III).

Impact of cognitive dysfunction on HRQOL

The impact of cognitive dysfunction (PROMIS Cognitive Function T-score ≤45%) on HRQOL was examined in bivariable models stratified by mild, moderate, or severe AD (Patient's Global Assessment). There were generally stepwise increases in DLQI and ItchyQoL scores between mild, moderate, and severe AD (Fig 1). At all AD severity levels, cognitive dysfunction was associated with even higher DLQI or ItchyQoL scores compared with those without cognitive dysfunction.

In multivariable propensity score-weighted regression models controlling for patient-reported global AD severity, POEM, NRS worst itch, EASI, SCORAD and SCORAD-sleep, and PROMIS Cognitive Function T-scores were inversely associated with higher DLQI (adjusted $\beta = -0.07$; 95% confidence interval, −0.11 to −0.03; $P = .002$) and ItchyQoL ($\beta = -0.03$; 95% confidence interval, −0.04 to −0.02; $P < .0001$) scores. There were no statistically significant 2-way interactions between AD severity scores and PROMIS Cognitive Function T-scores as predictors of DLQI or ItchyQoL.

Improvement of cognitive function with reduced AD severity

Changes from baseline in PROMIS Cognitive Function T-scores were weakly inversely correlated with changes from baseline in the patient-reported outcome measures POEM ($\rho = -0.19$, $P = .002$), NRS worst itch ($\rho = -0.36$, $P = .004$), SCORAD-itch ($\rho = -0.24$, $P = .02$), and NRS skin pain ($\rho = -0.21$, $P = .005$), DLQI ($\rho = -0.22$, $P = .0003$), and the clinically reported outcome measures of EASI ($\rho = -0.29$, $P = .004$) and SCORAD ($\rho = -0.31$, $P = .002$). That is, the cognitive function score got better over time as AD severity decreased.

Other measurement properties of PROMIS Cognitive Function

PROMIS Cognitive Function showed good internal consistency, no differential item functioning, and good feasibility (Supplemental Results).

DISCUSSION

This study found high rates of cognitive dysfunction in a cohort of adult patients with AD. Cognitive function was lower with increased severity of AD, itch, skin pain, and sleep disturbance, even after controlling for numerous potential confounders in propensity score-weighted regression models. PROMIS Cognitive Function is scored using a standardized T-score with a mean of 50 and a SD of 10, which is centered around the United States population mean. A person with a T-score of 40 is 1 SD below the national mean. We observed a 10-20 point (ie, 1-2 SD) difference of least squares mean T-scores for PROMIS Cognitive Function between patients in the highest and lowest AD severity groups, which are substantial differences.

Cognitive dysfunction was associated with worse HRQOL across all levels of AD severity but had the greatest effect on HRQOL in patients with mild AD. Cognitive dysfunction was an independent predictor of poor HRQOL, even after controlling for multiple AD severity measures and comorbid health disorders such as depression and anxiety. Cognitive function was responsive to changes of AD severity over time; that is, cognitive function improved as AD severity decreased. Together, cognitive dysfunction is a symptom of AD that considerably affects HRQOL.

The results build on a case-control study of 41 children that found AD was associated with neurocognitive deficits, particularly verbal comprehension, perceptual reasoning, and working memory, and also a lower intelligence quotient that

Table II. Association of atopic dermatitis severity with Patient-Reported Outcomes Measurement Information System (*PROMIS*) Cognitive Function T-scores

		PROMIS Cognitive Function T-score		
Variable	**Overall, frequency (%)**	**LS means (95% CI)**	**Adjusted β (95% CI)**	***P* value**
Patient-reported outcomes				
Patient-reported global AD severity				
Clear/almost clear/mild	22 (6.2)	57.2 (54.9-59.6)	0.00 [Reference]	…
Mild	136 (38.4)	54.0 (53.0-55.0)	−3.23 (−5.76 to −0.71)	.01
Moderate	111 (31.4)	51.7 (50.6-52.8)	−5.49 (−8.06 to −2.91)	<.0001
Severe	85 (24.0)	51.3 (50.0-52.5)	−5.95 (−8.58 to −3.32)	<.0001
NRS worst itch				
None (0)	37 (10.6)	60.1 (59.3-61.0)	0.00 [Reference]	…
Mild (1-3)	113 (32.4)	59.9 (59.4-60.4)	−0.27 (−1.25 to 0.72)	<.0001
Moderate (4-6)	86 (24.6)	56.4 (55.8-57.0)	−3.74 (−4.82 to −2.67)	<.0001
Severe (7-8)	64 (18.3)	53.4 (52.5-54.4)	−6.72 (−7.99 to −5.45)	<.0001
Very severe (9-10)	49 (14.0)	47.8 (46.4-49.1)	−12.40 (−14.02 to −10.77)	<.0001
POEM				
Clear (0)	16 (4.2)	61.4 (60.5-62.3)	0.00 [Reference]	…
Almost clear/mild (1-7)	95 (25.1)	59.6 (59.2-60.0)	−1.77 (−2.78 to −0.76)	.0006
Moderate (8-16)	156 (41.2)	53.8 (53.1-54.4)	−7.62 (−8.75 to −6.49)	<.0001
Severe (17-24)	90 (23.8)	55.8 (55.0-56.5)	−5.64 (−6.83 to −4.44)	<.0001
Very severe (25-28)	22 (5.8)	43.0 (41.4-44.6)	−18.38 (−20.25 to −16.51)	<.0001
SCORAD-sleep				
None (0)	60 (19.6)	55.6 (54.3-56.9)	0.00 [Reference]	…
Mild (1-3)	127 (41.5)	56.4 (55.6-57.3)	0.82 (−0.74 to 2.38)	.90
Moderate (4-6)	71 (23.2)	51.6 (50.4-52.8)	−4.00 (−5.77 to −2.23)	<.0001
Severe (7-10)	48 (15.7)	48.7 (47.2-50.3)	−6.87 (−8.90 to −4.85)	<.0001
POEM-sleep				
0	131 (34.7)	55.0 (54.2-55.9)	0.00 [Reference]	…
1-2	99 (26.2)	54.5 (53.5-55.5)	−0.57 (−1.87 to 0.73)	.39
3-4	44 (11.6)	48.9 (47.4-50.5)	−6.10 (−7.90 to −4.31)	<.0001
5-6	28 (7.4)	51.2 (49.4-53.0)	−3.87 (−5.88 to −1.86)	.0002
7	76 (20.1)	49.5 (48.3-50.7)	−5.57 (−7.05 to −4.09)	<.0001
NRS skin pain				
None (0)	330 (90.9)	56.6 (55.5-57.7)	0.00 [Reference]	…
Mild (1-3)	10 (2.8)	50.2 (48.5-52.8)	−5.58 (−7.58 to −3.58)	<.0001
Moderate (4-6)	17 (4.7)	46.1 (43.8-48.4)	−10.52 (−13.07 to −7.97)	<.0001
Severe (7-10)	6 (1.7)	39.8 (36.7-42.9)	−16.81 (−20.07 to −13.55)	<.0001
Clinician-reported outcomes				
EASI				
Clear/almost clear (0-1.0)	66 (21.9)	54.7 (53.4-56.0)	0.00 [Reference]	…
Mild (1.1-7.0)	139 (46.2)	53.0 (52.1-53.8)	−1.70 (−3.25 to −0.19)	.03
Moderate (7.1-21.0)	64 (21.3)	53.6 (52.3-54.9)	−1.08 (−2.90 to 0.74)	.25
Severe (21.1-50.0)	27 (9.0)	53.5 (51.8-55.3)	−1.17 (−3.33 to 0.99)	.29
Very severe (50.1-72.0)	5 (1.7)	49.1 (44.7-53.6)	−5.57 (−10.20 to −0.94)	.01
SCORAD				
Mild (0-23.9)	137 (36.4)	59.8 (58.2-61.4)	0.00 [Reference]	…
Moderate (24.0-37.9)	123 (32.7)	55.7 (53.5-58.0)	−4.08 (−6.86 to −1.13)	.004
Severe (38.0-103.0)	116 (30.9)	48.3 (46.0-50.7)	−11.49 (−14.31 to −8.67)	<.0001

AD, Atopic dermatitis; *CI*, confidence interval; *EASI*, Eczema Area and Severity Index; *LS*, least squares; *NRS*, Numeric Rating Scale; *POEM*, Patient Oriented Eczema Measure, *SCORAD*, SCORing Atopic Dermatitis.

was 16 points lower than controls.[35] Those findings may be related to cognitive dysfunction. The results differ from a study of Swedish men aged 17 to 20 years who underwent a military conscription examination between 1969 and 1976. After adjusting for socioeconomic characteristics, AD was not associated with cognitive function or the highest level of education.[36] That study only selected young adult men, did not distinguish a history of AD from active AD, and did not assess AD severity.

Table III. Association of self-reported global atopic dermatitis severity with individual aspects of cognitive function in the past 4 weeks*

Patient-reported global AD severity	Never	Rarely (once)	Sometimes (2 or 3 times)	Often (about once a day)	Very often (several times a day)	Adjusted OR (95% CI)	*P* value
	Frequency (%)						
My thinking has been slow							
Clear/almost clear	17 (77.3)	4 (18.2)	1 (4.6)	0 (0.0)	0 (0.0)	1.00 [Reference]	…
Mild	59 (43.4)	47 (34.6)	19 (14.0)	8 (5.9)	3 (2.2)	3.93 (2.49-6.19)	<.0001
Moderate	34 (40.0)	26 (30.6)	15 (17.7)	6 (7.1)	4 (4.7)	4.82 (3.10-7.49)	<.0001
Severe	45 (40.5)	32 (28.8)	19 (17.1)	7 (6.3)	8 (7.2)	7.59 (4.82-11.95)	<.0001
It has seemed like my brain was not working as well as usual							
Clear/almost clear	17 (77.3)	4 (18.2)	1 (4.6)	0 (0.0)	0 (0.0)	1.00 [Reference]	…
Mild	70 (51.5)	39 (28.7)	17 (12.5)	9 (6.6)	1 (0.7)	2.57 (1.62-4.09)	<.0001
Moderate	42 (49.4)	26 (30.6)	7 (8.2)	5 (5.9)	5 (5.9)	3.98 (2.56-6.20)	<.0001
Severe	54 (48.7)	25 (22.5)	20 (18.0)	7 (6.3)	5 (4.5)	5.39 (3.42-8.48)	<.0001
I have had to work harder than usual to keep track of what I was doing							
Clear/almost clear	18 (81.8)	2 (9.1)	1 (4.6)	1 (4.6)	0 (0.0)	1.00 [Reference]	…
Mild	82 (60.3)	28 (20.6)	14 (10.3)	9 (6.6)	3 (2.2)	2.22 (1.37-3.57)	.001
Moderate	45 (52.9)	18 (21.2)	13 (15.3)	6 (7.1)	3 (3.5)	3.26 (2.07-5.14)	<.0001
Severe	53 (47.8)	29 (26.1)	14 (12.6)	7 (6.3)	8 (7.2)	5.64 (3.55-8.95)	<.0001
I have had trouble shifting back and forth between different activities that require thinking							
Clear/almost clear	18 (81.8)	2 (9.1)	0 (0.0)	2 (9.1)	0 (0.0)	1.00 [Reference]	…
Mild	86 (63.7)	27 (20.0)	12 (8.9)	9 (6.7)	1 (0.7)	1.51 (0.92-2.47)	.10
Moderate	48 (57.1)	20 (23.8)	9 (10.7)	4 (4.8)	3 (3.6)	2.98 (1.89-4.70)	<.0001
Severe	64 (57.7)	25 (22.5)	10 (9.0)	6 (5.4)	6 (5.4)	3.98 (2.50-6.33)	<.0001
I have had trouble concentrating							
Clear/almost clear	16 (72.7)	2 (9.1)	2 (9.1)	1 (4.6)	1 (4.6)	1.00 [Reference]	…
Mild	72 (53.3)	36 (26.7)	17 (12.6)	8 (5.9)	2 (1.5)	1.82 (1.19-2.78)	.006
Moderate	36 (42.9)	21 (25.0)	15 (17.9)	6 (7.1)	6 (7.1)	2.44 (1.62-3.66)	<.0001
Severe	40 (36.0)	32 (28.8)	24 (21.6)	7 (6.3)	8 (7.2)	5.48 (3.61-8.31)	<.0001
I have had to work really hard to pay attention or I would make a mistake							
Clear/almost clear	16 (72.7)	2 (9.1)	2 (9.1)	2 (9.1)	0 (0.0)	1.00 [Reference]	…
Mild	84 (62.2)	27 (20.0)	14 (10.4)	8 (5.9)	2 (1.5)	1.28 (0.82-2.01)	.28
Moderate	38 (45.2)	20 (23.8)	16 (19.1)	6 (7.1)	4 (4.8)	2.30 (1.52-3.49)	<.0001
Severe	55 (49.6)	30 (27.0)	12 (10.8)	7 (6.3)	7 (6.3)	3.28 (2.15-5.02)	<.0001
I have had trouble forming thoughts							
Clear/almost clear	19 (86.4)	2 (9.1)	0 (0.0)	1 (4.6)	0 (0.0)	1.00 [Reference]	…
Mild	87 (64.4)	32 (23.7)	10 (7.4)	5 (3.7)	1 (0.7)	2.11 (1.24-3.60)	.006
Moderate	56 (66.7)	15 (17.9)	5 (6.0)	5 (6.0)	3 (3.6)	2.24 (1.34-3.75)	<.0001
Severe	72 (64.9)	24 (21.6)	6 (5.4)	5 (4.5)	4 (3.6)	3.92 (2.35-6.54)	<.0001
My problems with memory, concentration, or making mental mistakes have interfered with the quality of my life							

Continued

Table III. Cont'd

Patient-reported global AD severity	Never	Rarely (once)	Sometimes (2 or 3 times)	Often (about once a day)	Very often (several times a day)	Adjusted OR (95% CI)	*P* value
	Frequency (%)						
Clear/almost clear	18 (81.8)	3 (13.6)	0 (0.0)	1 (4.6)	0 (0.0)	1.00 [Reference]	…
Mild	89 (65.9)	28 (20.7)	8 (5.9)	8 (5.9)	2 (1.5)	2.33 (1.37-3.97)	.002
Moderate	48 (57.1)	18 (21.4)	12 (14.3)	3 (3.6)	3 (3.6)	2.70 (1.62-4.50)	<.0001
Severe	69 (62.2)	22 (19.8)	9 (8.1)	6 (5.4)	5 (4.5)	3.71 (2.21-6.20)	<.0001

AD, Atopic dermatitis; *CI*, confidence interval; *OR*, odds ratio.
*Ordinal logistic regression was used because the data met the proportional odds assumption (Score test, $P > .05$).

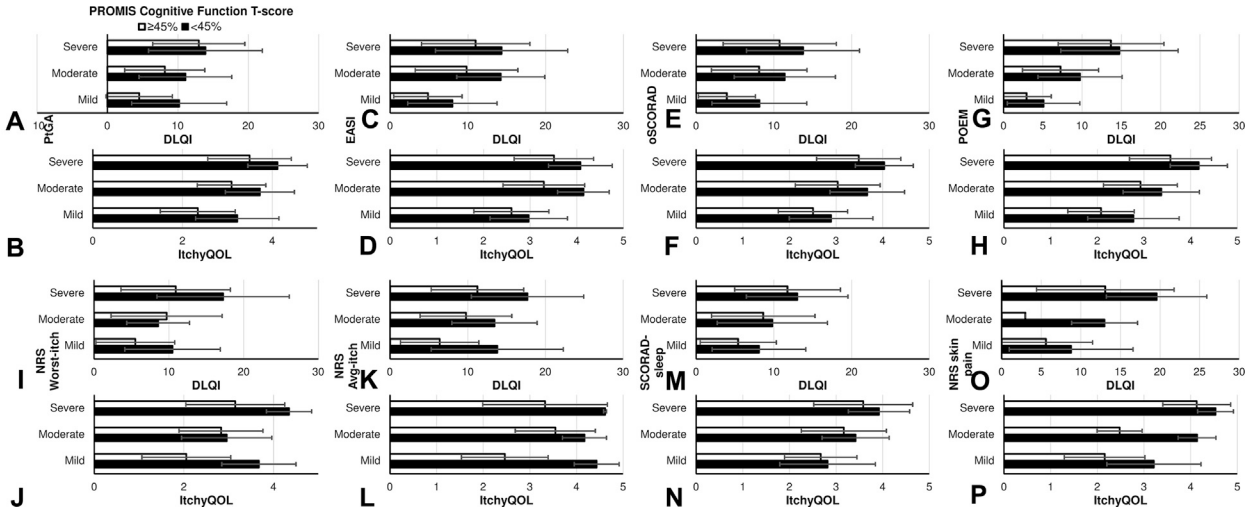

Fig 1. Relationship between atopic dermatitis severity, cognitive dysfunction, and health-related quality of life. Atopic dermatitis severity was divided into clear/almost clear/mild, moderate and severe/very severe using (**A, B**) patient-reported global atopic (*PtGA*) dermatitis severity, (**C, D**) eczema area and severity index (*EASI*), (**E, F**) objective-SCOring Atopic Dermatitis (*SCORAD*), (**G, H**) Patient-Oriented Eczema Measure (*POEM*), (**I, J**) Numeric Rating Scale (*NRS*) of worst itch, (**K, L**) NRS of average itch, (**M, N**) SCORAD-sleep, and (**O, P**) NRS skin pain. Health-related quality of life was assessed using (**A, C, E, G, I, K, M, O**) the Dermatology Life Quality Index (*DLQI*) and (**B, D, F, H, J, L, N, P**) ItchyQoL. DLQI and ItchyQoL scores are presented stratified by atopic dermatitis severity and Patient-Reported Outcomes Measurement Information System (PROMIS) Cognitive Function T-scores (≥50% and <50%). Lower PROMIS Cognitive Function T-scores indicate poorer cognitive function. Data are presented as the mean ± SD.

The present study found that more severe AD was associated with poorer cognitive function. Moreover, cognitive dysfunction was responsive to improvements of AD severity, highlighting the importance of achieving long-term disease control to mitigate potential long-term cognitive dysfunction.

Cognitive dysfunction is a clinically important symptom domain. First, cognitive dysfunction was an independent risk factor for poor HRQOL.

Second, we speculate that cognitive dysfunction may negatively affect school and workplace productivity, activities of daily living, and increase the risk of accidents and traumatic injuries. All of these were previously associated with AD,[37-41] but we were unable to examine whether cognitive function mediates those associations.

Third, given the impact of cognitive dysfunction on HRQOL, clinicians should consider assessing this symptom domain in clinical practice and incorporating it into therapeutic decision making. The PROMIS Cognitive Function SF was previously validated in multiple populations.[42,43] It can feasibly be incorporated into clinical practice, with good completion rates, short response times, and fairly simple scoring and interpretability. We found that the PROMIS Cognitive Function SF was valid to assess

cognitive function in clinical practice, with good known group validity, cross-cultural validity (no differential item functioning observed), internal consistency, and responsiveness.

The mechanisms of cognitive dysfunction in AD are not fully elucidated. Cognitive dysfunction may occur secondary to distraction from intense symptoms and behavioral responses to symptoms (eg, scratching, and sleep disturbances). However, a substantial proportion of patients with AD reporting cognitive dysfunction had only mild symptom scores. Sedating medications, such as antihistamines and neuroleptics, may alter cognitive function, although we did not find such associations. Although dupilumab was associated with lower cognitive function scores in bivariable analyses, this association was due to confounding by AD severity and did not remain significant in multivariable models (data not shown).

There may be underlying neuroinflammatory mechanisms of cognitive dysfunction in AD related to systemic inflammation or the degree of atopy, or both. Neuropeptides and inflammatory cytokines may be upregulated in AD,[44] resulting in heightened sensitivity to stimuli[45,46] and contributing to inattentiveness and attention deficit disorder.[12,38,47-49] Alternatively, patients with cognitive impairment may develop more severe AD owing to reduced avoidance of triggers or adherence to treatment, or both. Future studies are needed to better understand these mechanisms, which may lead to improved treatments of cognitive dysfunction in AD.

This study has several strengths, including being prospective and using multiple validated patient-reported outcomes and clinically reported outcomes to assess AD, and a validated patient-reported outcome to assess cognitive function. The cohort also had good representation across sex, race/ethnicity, and AD severity.

The study has some limitations. The study was limited to adults and performed in an urban, academic, dermatologic setting and may not be generalizable to the United States population. History of asthma, other atopic comorbidities, depression, anxiety, and sleep disturbances were assessed by self-report. No controls without AD were assessed, thereby precluding determination of whether AD is associated with lower cognitive function than controls who are healthy or who have other diseases. Whereas more severe AD was associated with cognitive function substantially poorer than the rest of the general population, it is possible that patients with mild AD are no different from healthy controls. Cognitive dysfunction may occur in other pruritic or debilitating skin diseases. Larger-scale multicenter studies including children and controls without AD are needed to confirm the results of this study and determine whether AD is associated with poorer cognitive function than controls without ADs.

CONCLUSION

AD severity is inversely associated with cognitive function in adults. For many patients, symptoms of itch, skin pain, and sleep disturbance are the major drivers of cognitive dysfunction. Cognitive dysfunction impacted patients' HRQOL. Cognitive function may be an important end point for monitoring burden of disease and clinical response to treatment. PROMIS Cognitive Function has sufficient validity and feasibility to assess cognitive function of patients with AD in clinical trials and in practice. Future studies are needed to determine the precise mechanisms and optimal treatment approaches for cognitive dysfunction in AD.

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