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Association of itch triggers with atopic dermatitis severity and course in adults

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ABSTRACT

Background: Atopic dermatitis (AD) is associated with heterogeneous triggers of itch, which may affect AD course and severity.
Objective: To characterize the triggers of itch in adult AD.
Methods: This was a prospective dermatology practice–based study using questionnaires and evaluation by a dermatologist (n = 587). Thirteen itch triggers were assessed using the patient-reported outcomes measurement information system Itch-Triggers.
Results: Overall, 381 (64.9%) patients reported greater than or equal to 1 itch trigger in the past week and 212 (36.1%) reported greater than or equal to 3 itch triggers. The most commonly reported triggers were stress (35.4%), sweat (30.5%), weather change (24.7%), dry air (24.4%), and heat (24.0%). In multivariable Poisson regression models, the number of itch triggers was associated with more severe patient-reported global AD severity, Numeric Rating Scale worst itch, Patient-Oriented Eczema Measure, Scoring Atopic Dermatitis sleep, Numeric Rating Scale skin pain, Eczema Area and Severity Index, and objective Scoring Atopic Dermatitis. The seasonality of AD was associated with distinct itch triggers. In multivariable logistic regression models, the number of itch triggers was associated with less than or equal to 3 months of AD remission during the year, greater than or equal to 2 AD flares, and AD being worse during some seasons. Four patterns of itch triggers were identified using latent class analysis, each associated with different clinical characteristics.
Conclusion: Itch triggers are common and affect the course of AD. Itch triggers are an important end point to assess in patients with AD.

Introduction

Atopic dermatitis (AD) is associated with substantial variability of itch, skin pain,[1,2] sleep disturbance and fatigue,[3,4] variable lesional morphology[5] and distribution,[6] and comorbid health disorders.[7-13] Although AD has heterogeneity of triggers for itch, including heat, sweat, dryness, clothing, and stress,[14,15] none of

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these triggers universally affect all patients with AD. Yet, little is known about which triggers of itch are most common in adults with AD and their predictors. In addition, little is known about the relationship of having multiple potential itch triggers and specific patterns of triggers with AD severity and clinical course. We sought to determine the most common triggers of itch in adults with AD and ascertain which patients with AD have many itch triggers and what are the specific patterns of itch triggers. Furthermore, we examined whether itch triggers affected the course of AD. Finally, we sought to determine the feasibility of assessing itch triggers in clinical practice of adults with AD.

Methods

Study Design

A cross-sectional, dermatology practice–based study of adults (≥18 years) was performed with AD as defined by the Hanifin-Rajka diagnostic criteria.[16] Exclusion criteria included those without a definite diagnosis of AD (based on Hanifin-Rajka criteria), with an alternative diagnosis (based on skin biopsy results and epicutaneous patch testing where indicated), or being unwilling or unable to complete assessments. Almost all patients (>99%) who were invited agreed to participate. Patients received appropriate standard-of-care follow-up and treatment, including emollients, prescription topical, systemic, and/or phototherapy. Outcome measures assessed in the study are presented in the eMethods.

Surveys were administered electronically between January 2017 and September 2019. The study was approved by the institutional review boards of Northwestern University. Informed consent was obtained electronically.

Statistical Analysis

Summary statistics were estimated for baseline population characteristics. The number of itch triggers selected from PROMIS Itch-Triggers was calculated. Bivariable associations of number of itch triggers with personal demographics and medical history were tested using nonparametric Mann-Whitney *U* test and Kruskal-Wallis test.

Poisson regression models were used to evaluate the association of disease severity (independent variable [IV]) with number of itch triggers (dependent variable [DV]). Logistic regression models were used to evaluate the association of disease severity (IV) with individual itch triggers (binary DV). AD severity was evaluated using patient-reported global AD severity, Numeric Rating Scale (NRS) worst itch, Patient-Oriented Eczema Measure (POEM), Scoring Atopic Dermatitis (SCORAD) sleep, NRS skin pain, Eczema Area and Severity Index (EASI), and objective SCORAD (oSCORAD), which were classified using available severity strata.[17-20] Covariables included current age (years, continuous), age at AD diagnosis (years, continuous), race and ethnicity (white, non-Hispanic/black/Hispanic/Asian/multiracial, other), and history of asthma, hay fever, or food allergy (yes/no).

Logistic regression models examined the association of multiple itch triggers (≥3 vs 0-2; IV) with patient-reported period of AD remission during the year (≤3 vs >3 months), number of AD flares (≥2 vs 0-1), and AD being worse during some seasons (yes vs no) (DV). Logistic regression models examined the association of individual triggers (yes/no; IV) with patient-reported season(s) of worsening AD in winter, spring, summer, or autumn (yes/no; DV). Models included the abovementioned covariables, POEM (continuous), self-reported global AD severity (clear-mild/moderate/severe), and NRS worst itch (continuous).

Latent class analysis (LCA) was used to evaluate phenotypical patterns of the 13 itch triggers (eMethods). χ^2 tests were used to test the associations of age, race/ethnicity, sex, current alcohol use or smoking, history of asthma, hay fever, or food allergy, self-reported global AD severity, POEM, NRS worst itch, NRS skin pain, EASI, or oSCORAD with membership in the latent classes.

Feasibility of assessing PROMIS Itch Questionnaire (PIQ) Itch-Triggers was examined by survey completion rates and time to completion.

The abovementioned statistical analyses were performed in SAS version 9.4.3 (SAS Institute, Cary, Indiana). Complete case analysis was performed, that is missing values were excluded. The multiple dependent tests (k = 130) performed in this study increase the risk of falsely rejecting the null hypothesis. *P* values were corrected for the false discovery rate.[21] A 2-sided corrected *P* value less than .05 was taken to indicate statistical significance for all estimates.

Results

Patient Characteristics

Overall, 587 adults (aged 18-90; mean ± SD, 45.4 ± 17.1; median [interquartile range or IQR] 44.0 [28.9] years) were included in the study. The cohort included 364 women (62.2%) and 340 whites (57.9%) (Table 1). The mean ± SD (median [IQR]) body surface area of involvement was 21.1% ± 25.8% (9.5% [29.0]), NRS worst itch was 5.0 ± 3.1 (5.0 [6.0]), oSCORAD was 28.6 ± 15.0 (28.1 [20.1]), SCORAD was 36.5 ± 18.3 (34.4 [27.0]), EASI was 11.2 ± 12.7 (5.5 [14.8]), and POEM was 12.1 ± 7.9 (12.0 [12.0]). A total of 26 and/or 17 adults were excluded from the study for alternative diagnoses based on skin biopsy and/or patch testing result, respectively. Treatments included prescription topical therapy alone (n = 291, 49.6%), oral nonsedating antihistamines (n = 28, 4.8%), sedating antihistamines (n = 3, 0.5%), gabapentin (n = 88, 15.0%), cyclosporine A (n = 112, 19.1%), methotrexate (n = 77, 13.1%), mycophenolate (n = 5, 0.9%), systemic corticosteroids (n = 11, 1.9%), subcutaneous dupilumab (n = 176, 30.0%), and narrow-band ultraviolet B (n = 63, 10.7%).

A total of 381 (64.9%) patients reported at least 1 itch trigger in the past week. The most commonly reported triggers were stress (35.4%), sweat (30.5%), weather change (24.7%), dry air (24.4%), and heat (24.0%) (Fig 1A). The median (min-max, IQR) number of itch triggers was 1 (0-13, 4), with 169 (28.8%) having 1-2 and 212 (36.1%) having greater than or equal to 3 itch triggers.

Associations of Itch Triggers in Atopic Dermatitis

In bivariable analyses, the number of itch triggers was significantly higher in patients with AD of younger age, but higher in those with hay fever and food allergy and those of younger age of AD onset (Kruskal-Wallis test, $P \leq .01$) (eTable 1). There were no associations with sex, race/ethnicity, level of education, insurance status, current smoking, or alcohol use.

Atopic Dermatitis Severity and Number of Itch Triggers

In multivariable linear regression models, number of itch triggers was associated with patient-reported global AD severity, NRS worst itch, POEM, SCORAD sleep, NRS skin pain, EASI, and oSCORAD, with the highest number of triggers generally in those with severe AD (Table 2).

In addition, patient-reported moderate and/or severe AD were significantly associated with higher proportions of all 13 individual itch triggers, with the highest proportion of each trigger generally occurring in those with severe AD (Table 2).

Individual Triggers and Atopic Dermatitis Seasonality

Patient-reported worsening of AD in specific seasons was associated with distinct itch triggers (Table 3). Reported worsening of AD in winter was associated with cold temperature and weather

Table 1
Association of Atopic Dermatitis Severity With Number of Itch Triggers

Variable	Number of triggers			
Patient-reported outcomes	Overall, frequency (%)	Least squares means (95% CI)	Adjusted Poisson regression coefficient (95% CI)	*P* value
Patient-reported global AD severity (n = 581)				
Clear/almost clear/mild	233 (40.1)	1.5 (1.3, 1.7)	0.00 (ref)	–
Moderate	224 (38.6)	2.6 (2.4, 2.9)	0.59 (0.44, 0.74)	.001
Severe	124 (21.3)	3.0 (2.6, 3.4)	0.72 (0.56, 0.88)	<.001
NRS worst itch (n = 523)				
None (0)	50 (9.6)	0.7 (0.5, 0.9)	0.00 (ref)	–
Mild (1-3)	145 (27.7)	1.9 (1.7, 2.2)	1.07 (0.70, 1.44)	<.001
Moderate (4-6)	136 (26.0)	2.4 (2.1, 2.7)	1.28 (0.91, 1.64)	<.001
Severe (7-8)	120 (22.9)	3.0 (2.6, 3.4)	1.51 (1.14, 1.87)	<.001
Very severe (9-10)	72 (13.8)	4.5 (4.0, 5.1)	1.92 (1.55, 2.28)	<.001
POEM (n = 585)				
None/almost clear/mild (0-7)	191 (32.7)	1.5 (1.3, 1.7)	0.00 (ref)	–
Moderate (8-16)	211 (36.1)	2.1 (1.8, 2.3)	0.33 (0.17, 0.50)	<.001
Severe (17-24)	136 (23.3)	2.8 (2.4, 3.1)	0.63 (0.46, 0.80)	<.001
Very severe (25-28)	47 (8.0)	4.0 (3.5, 4.7)	1.01 (0.81, 1.20)	<.001
SCORAD sleep (n = 278)				
None (0)	76 (27.3)	1.9 (1.5, 2.3)	0.00 (ref)	–
Mild (1-3)	86 (30.9)	2.3 (1.9, 2.7)	0.19 (-0.04, 0.42)	.11
Moderate (4-6)	69 (24.8)	3.2 (2.7, 3.8)	0.53 (0.30, 0.76)	<.001
Severe (7-10)	47 (16.9)	3.6 (3.0, 4.4)	0.66 (0.41, 0.91)	<.001
NRS skin pain (n = 481)				
None (0)	371 (77.1)	1.7 (1.5, 1.9)	0.00 (ref)	–
Mild (1-3)	39 (8.1)	2.3 (1.9, 2.8)	0.31 (0.09, 0.52)	.005
Moderate (4-6)	30 (6.2)	3.3 (2.7, 4.0)	0.67 (0.47, 0.86)	<.001
Severe (7-10)	41 (8.5)	3.3 (2.7, 4.0)	0.66 (0.48, 0.85)	<.001
Clinical-reported outcomes				
EASI (n = 273)				
Clear/almost clear/mild (0-5.9)	140 (51.3)	2.0 (1.7, 2.4)	0.00 (ref)	–
Moderate (6.0-22.9)	90 (33.0)	3.0 (2.6, 3.5)	0.39 (0.21, 0.57)	<.001
Severe (23.0-72.0)	43 (15.8)	3.0 (2.5, 3.7)	0.40 (0.17, 0.63)	<.001
Objective SCORAD (n = 278)				
Mild (0-23.9)	118 (42.5)	1.9 (1.6, 2.3)	0.00 (ref)	–
Moderate (24.0-27.9)	90 (32.4)	2.7 (2.3, 3.2)	0.33 (0.13, 0.53)	.001
Severe (38.0-83.0)	70 (25.2)	3.3 (2.8, 3.9)	0.54 (0.33, 0.74)	<.001

Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis.
NOTE. Missing values were encountered in 6 (1.0%) patients for self-reported global AD severity, 4 (0.8%) for NRS worst itch, 2 (0.3%) for POEM, 9 (3.1%) for objective SCORAD and SCORAD sleep, 6 (1.2%) for NRS skin pain, and 14 (4.9%) for EASI. N.B. Some outcomes were implemented later in the study resulting in different total frequencies.

change as itch triggers. Worsening of AD in spring was associated with weather change and dry air as itch triggers. However, reported worsening of AD in summer was associated with hot temperature, heat, sweat, weather change, sunlight, and humid and dry air as itch triggers. Finally, worsening of AD in autumn was associated with weather change and humid air as itch triggers.

Itch Triggers and Atopic Dermatitis Course

Among patients with AD with greater than or equal to 3 itch triggers, 89.7% reported less than or equal to 3 months of AD remission per year, 78.3% reported greater than or equal to 2 AD flares per year, and 60.9% reported that AD is worse during some seasons (Table 4). In multivariable logistic regression models, the number of itch triggers was associated with less than or equal to 3 months of AD remission during the year (adjusted odds ratio [95% CI]: 2.41 [1.21-4.80]), greater than or equal to 2 AD flares (2.00 [1.20-3.34]), and AD being worse during some seasons (2.38 [1.42-3.99]).

Combinations and Associations of Itch Triggers in Atopic Dermatitis

LCA was used to identify patterns of itch triggers (n = 273). The best-fit model had 4 classes based on minimal adjusted Bayesian Information Criterion. Conditional probabilities of having different itch triggers in each class are plotted in Figure 1A. Class 1 had the highest membership probability (53.9%) and consisted of very low probabilities of any trigger. Class 3 had the next highest membership probability (22.3%) and consisted of higher probabilities of triggers from stress, dry air, weather change, and cold temperature. Class 2 (15.5%) consisted of higher probabilities of triggers from sweat, stress, heat, hot temperature, and weather change. Class 4 (8.3%) consisted of the highest probabilities of all triggers.

There were significant associations of latent class membership with age, history of asthma, hay fever, and food allergy (Fig 1B) and almost all AD severity assessments (Fig 1C). Class 1 was associated with highest proportion of ages 40-59 years, white non-Hispanics, with hay fever and mild AD. Class 2 was associated with higher proportions of ages 18-39 years, current alcohol use, hay fever, mild-moderate AD lesions (EASI, oSCORAD) but severe AD symptoms (patient global assessment, POEM, NRS worst itch). Class 3 was associated with a fairly even distribution across mild, moderate, and severe AD. Class 4 was associated with higher proportions of ages 18-39 years, asthma and food allergy, and moderate-severe AD (patient global assessment, POEM, NRS worst itch, NRS skin pain, EASI, oSCORAD), but lower proportions of hay fever.

Feasibility of Assessing PROMIS Itch Questionnaire Itch-Triggers

The mean ± SD time to completion of PIQ Itch-Triggers was 0.8 ± 1.0 minute, with a median (min, max) completion time of less than 1 (<1, 2) minute. There were no significant differences of completion time by age (Wilcoxon rank-sum test; $P = .31$), sex ($P = .54$), race/ethnicity ($P = .72$), level of education ($P = .82$), or patient-reported global AD severity ($P = .29$).

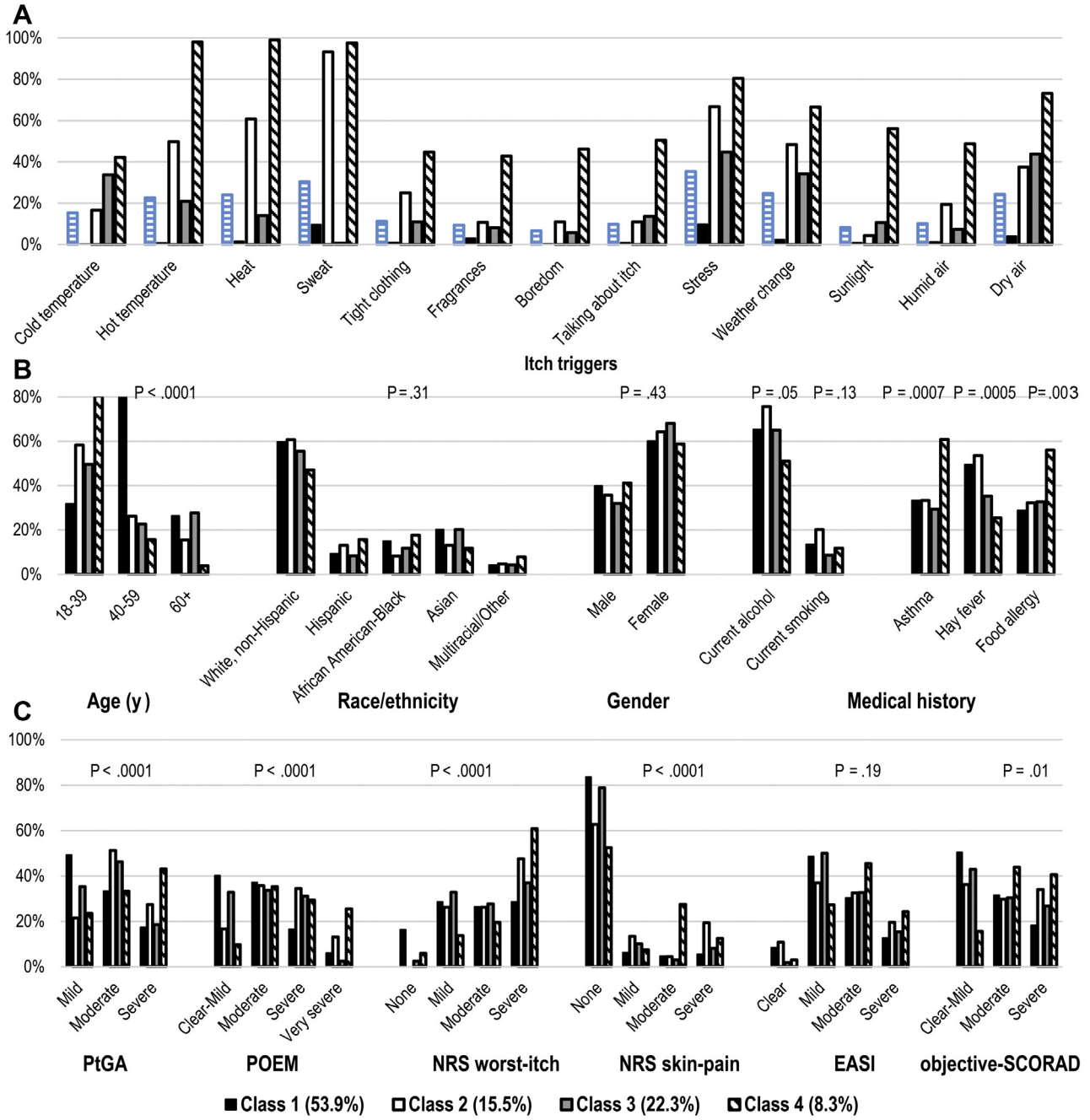

Figure 1. The LCA of patterns of itch triggers in adults with AD. LCA was used to evaluate patterns of binary variables of itch triggers in adults with AD. Observed binary data were used to identify homogeneous patterns, that is, n = 4 latent classes. Conditional probabilities were estimated using maximum likelihood to characterize the latent classes. (A) Conditional probability plots are presented, in which probabilities closer to 0 or 1 indicate lower or higher chances, respectively. ▨ indicates overall distribution of itch triggers. □ indicates class 1. ■ indicates class 2. ▩ indicates class 3. ▧ indicates class 4. The proportion of respondents who are members of these classes is presented. (B) χ^2 tests were performed comparing (B) clinical characteristics and (C) AD severity with class membership. AD, atopic dermatitis; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis. LCA, latent class analysis; PtGA, patient global assessment.

Discussion

This study found that adults with AD commonly reported having multiple itch triggers. The most commonly reported triggers were stress, sweat, dry air, and heat. More severe AD was associated with higher proportions of every trigger examined, including hot temperature, heat, stress, and humid air as triggers than mild AD. These results are consistent with those of previous studies that found sweating from exercise and hot weather were among the most common triggers of childhood AD.[14] Similarly, the severity of itch was most commonly worsened by sweat, dryness, and stress in a Chinese cohort of mostly adolescents and young adults with AD.[15] These results are important because they highlight which triggers require the greatest attention by clinicians. Furthermore, PIQ Itch-Triggers may be used to identify specific itch triggers that warrant educational and/or therapeutic intervention in clinical practice. PIQ Itch-Triggers was efficient and feasible for use in clinical practice.

The number of itch triggers appears to be clinically important. Approximately 1 in 3 adults with AD reported having greater than or equal to 3 itch triggers. Patients with many itch triggers likely find it more challenging to avoid all triggers compared with those with fewer triggers. This is clinically important because trigger

Table 2
Association of Atopic Dermatitis Severity With Individual Itch Triggers (n = 581)

Patient-reported global AD severity	Frequency (%)		Adjusted OR (95% CI)	*P* value
	No	Yes		
	Cold temperature			
Clear/almost clear/mild	207 (88.8)	26 (11.2)	1.00 (ref)	–
Moderate	179 (79.9)	45 (20.1)	**2.11 (1.20, 3.73)**	**.01**
Severe	105 (84.7)	19 (15.3)	1.32 (0.66, 2.65)	.43
	Hot temperature			
Clear/almost clear/mild	202 (86.7)	31 (13.3)	1.00 (ref)	–
Moderate	170 (75.9)	54 (24.1)	**2.39 (1.40, 4.09)**	**.001**
Severe	76 (61.3)	48 (38.7)	**3.91 (2.20, 6.96)**	**<.001**
	Heat			
Clear/almost clear/mild	202 (86.7)	31 (13.3)	1.00 (ref)	–
Moderate	160 (71.4)	64 (28.6)	**2.75 (1.61, 4.71)**	**<.001**
Severe	78 (62.9)	46 (37.1)	**3.76 (2.10, 6.75)**	**<.001**
	Sweat			
Clear/almost clear/mild	184 (79.0)	49 (21.0)	1.00 (ref)	–
Moderate	147 (65.6)	77 (34.4)	**2.08 (1.30, 3.34)**	**.002**
Severe	71 (57.3)	53 (42.6)	**2.79 (1.64, 4.76)**	**<.001**
	Tight clothing			
Clear/almost clear/mild	219 (94.0)	14 (6.0)	1.00 (ref)	–
Moderate	193 (86.2)	31 (13.8)	**2.44 (1.19, 5.02)**	**.01**
Severe	103 (83.1)	21 (16.9)	**2.86 (1.30, 6.25)**	**.009**
	Fragrances			
Clear/almost clear/mild	219 (94.0)	14 (6.0)	1.00 (ref)	–
Moderate	199 (88.8)	25 (11.2)	**2.55 (1.20, 5.41)**	**.01**
Severe	108 (87.1)	16 (12.9)	2.13 (0.91, 4.99)	.08
	Boredom			
Clear/almost clear/mild	222 (95.3)	11 (4.7)	1.00 (ref)	–
Moderate	212 (94.6)	12 (5.4)	1.09 (0.44, 2.68)	.85
Severe	108 (87.1)	16 (12.9)	**2.65 (1.10, 6.37)**	**.03**
	Talking about itch			
Clear/almost clear/mild	219 (94.05)	14 (6.0)	1.00 (ref)	–
Moderate	207 (92.4)	17 (7.6)	1.24 (0.58, 2.61)	.58
Severe	97 (78.2)	27 (21.8)	**3.23 (1.56, 6.72)**	**.002**
	Stress			
Clear/almost clear/mild	178 (76.4)	55 (23.6)	1.00 (ref)	–
Moderate	126 (56.3)	98 (43.8)	**2.90 (1.83, 4.59)**	**<.001**
Severe	69 (55.7)	55 (44.4)	**2.50 (1.48, 4.24)**	**<.001**
	Weather change			
Clear/almost clear/mild	191 (82.0)	42 (18.0)	1.00 (ref)	–
Moderate	162 (72.3)	62 (27.7)	**2.16 (1.31, 3.57)**	**.003**
Severe	83 (66.9)	41 (33.1)	**2.28 (1.30, 4.01)**	**.004**
	Sunlight			
Clear/almost clear/mild	224 (96.1)	9 (3.9)	1.00 (ref)	–
Moderate	199 (88.8)	25 (11.2)	**3.43 (1.48, 7.96)**	**.004**
Severe	110 (88.7)	14 (11.3)	**2.83 (1.11, 7.16)**	**.02**
	Humid air			
Clear/almost clear/mild	219 (94.0)	14 (6.0)	1.00 (ref)	–
Moderate	202 (90.2)	22 (9.8)	1.51 (0.69, 3.28)	.30
Severe	100 (80.7)	24 (19.4)	**3.74 (1.76, 7.96)**	**<.001**
	Dry air			
Clear/almost clear/mild	194 (83.3)	39 (16.7)	1.00 (ref)	–
Moderate	160 (71.4)	64 (28.6)	**2.00 (1.23, 3.23)**	**.005**
Severe	84 (67.7)	40 (32.3)	**2.09 (1.20, 3.62)**	**.009**

Abbreviations: AD, atopic dermatitis; OR, odds ratio.
NOTE. Missing values were encountered in 6 (1.0%) patients for self-reported global AD severity.
Bold indicate statistical significance.

Table 3
Association of Individual Itch Triggers With Patient-Reported Seasonal Worsening of AD (n = 377)

Season	Adjusted OR (95% CI)	*P* value
	Cold temperature	
Winter	**2.45 (1.33, 4.50)**	**.004**
Spring	1.28 (0.57, 2.88)	.54
Summer	0.96 (0.44, 2.11)	.92
Autumn	1.53 (0.68, 3.43)	.31
	Hot temperature	
Winter	1.45 (0.84, 2.50)	.18
Spring	0.73 (0.34, 1.56)	.42
Summer	**3.77 (1.89, 7.52)**	**<.001**
Autumn	1.33 (0.63, 2.81)	.46
	Heat	
Winter	1.46 (0.82, 2.60)	.19
Spring	1.61 (0.75, 3.49)	.22
Summer	**3.75 (1.83, 7.67)**	**<.001**
Autumn	1.83 (0.83, 4.03)	.14
	Sweat	
Winter	0.88 (0.51, 1.51)	.65
Spring	1.10 (0.52, 2.31)	.80
Summer	**3.01 (1.51, 5.99)**	**.002**
Autumn	1.41 (0.67, 2.98)	.36
	Tight clothing	
Winter	0.97 (0.46, 2.02)	.93
Spring	0.78 (0.29, 2.11)	.62
Summer	1.66 (0.68, 4.02)	.27
Autumn	2.012 (0.84, 4.83)	.12
	Fragrances	
Winter	1.55 (0.75, 3.20)	.24
Spring	1.67 (0.67, 4.17)	.27
Summer	1.30 (0.52, 3.23)	.58
Autumn	1.18 (0.45, 3.10)	.74
	Boredom	
Winter	1.39 (0.60, 3.24)	.44
Spring	0.77 (0.25, 2.35)	.64
Summer	2.95 (1.08, 7.52)	.035
Autumn	0.96 (0.32, 2.91)	.94
	Talking about itch	
Winter	1.47 (0.72, 3.00)	.29
Spring	1.48 (0.62, 3.54)	.38
Summer	1.85 (0.82, 4.21)	.14
Autumn	2.07 (0.86, 4.99)	.10
	Stress	
Winter	1.32 (0.77, 2.25)	.31
Spring	1.35 (0.65, 2.79)	.42
Summer	1.10 (0.54, 2.22)	.80
Autumn	1.61 (0.76, 3.44)	.22
	Weather change	
Winter	**2.01 (1.15, 3.53)**	**.01**
Spring	**4.58 (2.17, 9.69)**	**<.001**
Summer	**2.20 (1.10, 4.38)**	**.025**
Autumn	**3.52 (1.65, 7.55)**	**.001**
	Sunlight	
Winter	2.08 (0.97, 4.46)	.06
Spring	0.93 (0.34, 2.58)	.89
Summer	**5.36 (2.35, 12.22)**	**<.001**
Autumn	0.95 (0.32, 2.80)	.92
	Humid air	
Winter	0.96 (0.45, 2.04)	.92
Spring	1.76 (0.72, 4.33)	.22
Summer	**3.31 (1.44, 7.58)**	**.005**
Autumn	**4.12 (1.70, 9.96)**	**.002**

	Dry air	
Winter	1.55 (0.91, 2.64)	.11
Spring	**2.11 (1.04, 4.27)**	**.038**
Summer	**2.24 (1.15, 4.35)**	**.017**
Autumn	1.78 (0.87, 3.66)	.11

Abbreviations: AD, atopic dermatitis; OR, odds ratio.

avoidance and other nonmedicated treatment approaches are considered the first step for all patients in the "step-up" approach used in various AD guidelines.[22,23] It may not be feasible for patients to successfully avoid numerous common triggers. As such, patients with multiple itch triggers may benefit from stepping up therapy earlier than those with fewer and/or more manageable itch triggers.

Specific itch triggers were also associated with different seasons of worsening AD. For example, those who reported cold temperature as an itch trigger also reported more worsening of AD in winter. However, hot temperature, heat, sweat, and sunlight as itch triggers were associated with summer worsening of AD. Thus, PIQ Itch-Triggers may be useful for clinicians to predict the longitudinal course of AD and therapeutic needs. These can be used to guide proper patient education. Patients should be counseled on which triggers to avoid. For example, patients with hot temperature or cold as triggers should be advised to avoid extremes within those temperature ranges. Patients with tight clothing as a trigger should consider wearing looser fitting clothing with a light, breathable cotton fiber. Patients with fragrances as triggers should minimize fragrance exposures in personal care products. Humidifiers can be recommended to patients with dry air as a trigger. Understandably, it is not always feasible to avoid these triggers. When exposure is unavoidable, patients can consider a short-term increase in therapy before or after exposure to reduce the risk of a flare.

This study found that a higher number of itch triggers was associated with more severe AD signs and symptoms even after controlling for multiple confounders. This relationship is likely bidirectional. Having more itch triggers likely results in more exogenous insults to the skin, ultimately leading to more frequent and severe exacerbations. Indeed, this study found that having greater than or equal to 3 itch triggers was associated with more chronic AD, AD flares, and seasonal worsening of AD. On the other hand, more severe AD is associated with greater skin barrier defects and immune dysregulation, which likely predisposes toward a greater number of exogenous insults. Moreover, patients with more severe AD may develop neural sensitization to chemical and mechanical stimuli.[24] Thus, a higher number of itch triggers may be a manifestation of more chronic, unstable, and/or severe AD. As such, PIQ Itch-Triggers may be used to calculate the number of itch triggers as a proxy measure of AD severity in clinical practice.

Apart from the number of itch triggers, there seem to be several different patterns of itch triggers using LCA, which are as follows: (1) few reported itch triggers, which was associated with mild AD, particularly in middle-aged white patients with hay fever; (2) triggers from sweat, stress, dry air, weather change, and cold temperature, which occurred in mild-moderate AD lesions and severe AD symptoms, particularly in younger patients with less food allergy; (3) triggers from stress, dry air, weather change, and cold temperature, which was distributed across all AD severities; and (4) virtually all itch triggers being reported, which was

Table 4
Association of Number of Itch Triggers With Course of Atopic Dermatitis, But Not Quality of Life Impact

Course of atopic dermatitis	Overall, frequency (%)	Number of triggers			
		0-2	≥3		
		Frequency (%)	Frequency (%)	Adjusted OR (95% CI)	*P* value
Period of AD remission during the year (n = 422)					
>3 mo	87 (20.6)	70 (27.2)	17 (10.3)	1.00 (ref)	–
≤3 mo	335 (79.4)	187 (72.8)	148 (89.7)	2.41 (1.21, 4.80)	.01
Number of AD flares (n = 461)					
0-1	165 (35.8)	126 (44.8)	39 (21.7)	1.00 (ref)	–
≥2	296 (64.2)	155 (55.2)	141 (78.3)	2.00 (1.20, 3.34)	.008
AD worse during some seasons (n = 377)					
No	200 (53.1)	146 (61.1)	54 (39.1)	1.00 (ref)	–
Yes	177 (47.0)	93 (38.9)	84 (60.9)	2.38 (1.42, 3.99)	.001
Quality of life					
Dermatology Life Quality Index (n = 582)					
0-10	392 (67.4)	270 (72.6)	122 (58.1)	1.00 (ref)	–
11-30	190 (32.7)	102 (27.4)	88 (41.9)	0.91 (0.55, 1.51)	.71
PIQ Itch Interference T score (n = 443)					
<50	341 (77.0)	233 (84.7)	108 (64.3)	1.00 (ref)	–
≥50	102 (23.0)	42 (15.3)	60 (35.7)	0.77 (0.41, 1.43)	.40
PIQ Mood and Sleep Interference T score (n = 443)					
<50	339 (76.5)	232 (84.1)	107 (64.1)	1.00 (ref)	–
≥50	104 (23.5)	44 (15.9)	60 (35.9)	0.73 (0.39, 1.37)	.33
PIQ Scratching Behavior T score (n = 444)					
<50	265 (59.7)	193 (69.9)	72 (42.9)	1.00 (ref)	–
≥50	179 (40.3)	83 (30.1)	96 (57.1)	0.78 (0.43, 1.43)	.43

Abbreviations: AD, atopic dermatitis; PIQ, PROMIS Itch Questionnaire; PROMIS, Patient-Reported Outcomes Measurement Information System; OR, odds ratio.
NOTE. Missing values were encountered in 12 (2.8%) for AD remissions, 10 (2.6%) worsening during specific seasons, 5 (0.9%) for dermatology life quality index, 1 (0.2%) patient for PIQ mood and sleep interference and scratching behavior T score. N.B. Some outcomes were implemented later in the study resulting in different total frequencies.

associated with moderate-severe AD and skin pain, particularly in younger adults with more asthma and food allergy.

The rationale of why specific exogenous exposures triggers itch in some but not all patients with AD is not fully elucidated. There may be mechanistic differences underlying these trigger profiles. For example, patients with AD have been found to have increased density[25,26] or length of dermal nerve fibers.[27] Such nerve changes may account for stress, sweat, heat, and hot temperature as triggers in patients with AD with severe itch. Previous studies have suggested that neuropeptides and inflammatory cytokines are up-regulated in AD[28] and may result in heightened sensitivity to exogenous stimuli.[29,30] There may also be differences of systemic inflammation and atopy, because some itch trigger profiles were associated with less food allergy whereas others with more allergy and/or less asthma. Future studies are needed to sort out the complexities and mechanistic differences of itch triggers, AD severity, and longitudinal course.

This study has several strengths, including being prospective and using multiple validated patient- and clinician-reported outcomes to assess AD. The cohort also had good representation across sex, race/ethnicity, and AD severity. However, the study has limitations. Itch triggers were assessed by self-report. It is possible that patients did not recognize all relevant triggers of their itch. PIQ Itch-Triggers included 13 different triggers that were identified as being key itch triggers from a comprehensive conceptual model that incorporated a systematic literature review and patient-centric qualitative interviews with 33 patients.[31] However, there may be other relevant itch triggers that are not included in PIQ Itch-Triggers. Nevertheless, both the individual triggers and total number of triggers from PIQ Itch-Triggers were found to be clinically meaningful. Identification of triggers may be limited by confounding from other factors that are simultaneously modified. For example, warmer weather is accompanied by increased ultraviolet exposure, pollen counts and small-particle air pollution, and more time spent outdoors. Any of these confounding factors associated with warm weather may lead to worse itch. This is a common limitation of studies examining the role of environmental factors on itch/AD. Atopic comorbidities were assessed by self-report and/or documented diagnosis by other clinicians. Objective testing to confirm the diagnoses was not routinely performed. Disease course was assessed using self-report, which may be subject to misclassification. We did not assess any serum or tissue biomarkers of AD or atopy or the impact of different therapeutics on itch triggers. Finally, the study was performed in a US urban, academic, dermatologic setting in the Midwestern United States and may not be generalizable to all patients with AD. Future, larger-scale multicenter longitudinal studies are needed to confirm the results of this study and determine the impact of treatment.

In conclusion, AD and particularly moderate-severe AD are associated with multiple itch triggers. PIQ Itch-Triggers was efficient and feasible for use in clinical practice. The individual triggers and total number of triggers from PIQ Itch-Triggers provided clinically relevant and important information. Specific triggers tracked together in patient subsets, including stress with dry air, weather change, and cold temperature; stress with sweat, heat, hot temperature, and weather change; and subsets had minimal triggers or almost triggers. Future studies are needed to determine the precise mechanisms and optimal interventions for different itch triggers in AD.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2020.06.014.

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eMethods

Outcome Measures

Self-administered questionnaires were completed by patients of the eczema clinic at an academic medical center before their encounter. Questionnaires included self-reported severity of atopic dermatitis (AD) ("Would you describe your atopic dermatitis or eczema as clear, almost clear, mild, moderate, or severe?"),[32] Numeric Rating Scale for worst itch (1 question, range 0-10), Numeric Rating Scale skin pain (1 question, range 0-10), Patient-Oriented Eczema Measure (7 questions, range: 0-28),[17] questions about the course of their AD ("How would you describe the course of your disease throughout the year? More than 3 months of remission during a year/less than 3 months remission during a year/continuous course"[33]), number of AD flares ("How many flares of your eczema have you had on average per month?"), if AD is worse in some seasons ("Is your atopic dermatitis/eczema worse in some seasons than others?" Winter/Spring/Summer/Autumn). The Patient-Oriented Eczema Measure measures the frequency of patient-reported signs and symptoms of AD and is the preferred assessment of AD symptoms in clinical trials.[34] Patient-Reported Outcome Measurement Information System Itch Questionnaire Itch-Triggers (1 question, 13 multi-select response options) was used to assess specific itch triggers. The Patient-Reported Outcome Measurement Information System Itch Questionnaire Itch-Triggers was previously developed based on a comprehensive conceptual model of itch based on a systematic literature review, panel experts, and semistructured interviews with 33 patients to characterize itch-relevant domains and develop items to measure these domains.[31]

Patients were assessed with full-body skin examination by a dermatologist (JS). Eczema Area and Severity Index (4 signs [erythema, excoriation, swelling, lichenification] on 4 body sites, range: 0-72)[35] and objective component of the Scoring Atopic Dermatitis (6 signs [erythema, excoriation, swelling, oozing/crusting, lichenification, dryness] on 8 body sites, range: 0-83) and total Scoring Atopic Dermatitis [additional visual analog scales for intensity of itch and sleep loss in the past 3 days; range: 0-103][36] were the clinician-reported outcomes examined.

Latent Class Analysis

Latent class analysis (LCA) was used to evaluate phenotypical patterns of the 13 itch triggers (eMethods). LCA uses observed categorical or binary data to identify patterns or latent classes. Conditional probabilities were estimated using maximum likelihood to characterize the latent classes by indicating the chance that a member would give a certain response (yes/no) for the specific item. Conditional probability plots are presented, in which probabilities closer to 0 or 1 indicate lower or higher chances, respectively. LCA regression models evaluate the differential effects of individual variables across unobserved classes. The ideal number of latent classes and best fitting models were selected by minimizing the adjusted Bayesian Information Criterion and interpretability.

eTable 1
Subject Characteristics and Bivariable Associations With Number of Itch Triggers (n = 587)

Variable	Value, n (%)	Number of itch triggers, median (minimum, maximum)	*P* value
Demographics			
Age (y)			<.001
18-39	255 (43.4)	2 (0, 13)	
40-59	196 (33.4)	1 (0, 10)	
60-79	128 (21.8)	1 (0, 8)	
≥80	8 (1.4)	0.5 (0, 5)	
Sex			.34
Male	221 (37.8)	1 (0, 13)	
Female	364 (62.2)	1 (0, 12)	
Race/ethnicity			.43
White	340 (57.9)	1 (0, 13)	
African American/black	80 (13.6)	1 (0, 13)	
Hispanic	60 (10.2)	1 (0, 10)	
Asian	84 (14.3)	2 (0, 12)	
Multiracial/other	23 (3.9)	2 (0, 11)	
Level of education			.10
High school or less	45 (7.8)	2 (0, 13)	
Greater than high school	535 (92.2)	1 (0, 13)	
Insurance coverage			.31
None	15 (2.6)	1 (0, 13)	
Public	94 (16.3)	1 (0, 12)	
Private	468 (81.1)	1 (0, 10)	
Social history			
Current smoker			.20
No	491 (86.8)	1 (0, 13)	
Yes	75 (13.3)	2 (0, 12)	
Current alcohol use			.24
No	370 (65.4)	1 (0, 13)	
Yes	196 (34.6)	1 (0, 12)	
Medical history			
Asthma			.06
No	382 (65.1)	1 (0, 13)	
Yes	205 (34.9)	2 (0, 12)	
Hay fever			<.001
No	265 (45.1)	1 (0, 13)	
Yes	322 (54.9)	2 (0, 13)	
Food allergy			.01
No	166 (28.3)	1 (0, 13)	
Yes	421 (71.7)	2 (0, 13)	
Any atopic disease			.01
No	219 (37.3)	1 (0, 13)	
Yes	368 (62.7)	2 (0, 13)	
Age of AD onset (y)			.001
<2	190 (32.4)	2 (0, 13)	
2-5	107 (18.2)	1 (0, 13)	
6-17	55 (9.4)	3 (0, 11)	
≥18	235 (40.0)	1 (0, 9)	

Abbreviation: AD, atopic dermatitis.