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Burden and characteristics of skin pain among children with atopic dermatitis

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**Title: Burden and characteristics of skin pain among children with atopic dermatitis**

**Short Title: Skin pain in childhood atopic dermatitis**

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**Clinical Implications Statement:**

Skin pain is a distinct, burdensome symptom of childhood atopic dermatitis (AD), with heterogeneous presentation and multiple AD phenotypes. Moreover, skin pain intensity is associated with significant decrements in quality of life, independent of AD severity.

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Atopic dermatitis (AD) is heterogeneous in clinical presentation, including variable itch severity, sleep disturbance, and mental health symptoms.<sup>1</sup> Skin pain is another reported symptom, but has not been well-characterized in children. We aimed to determine clinical features and quality-of-life burden associated with AD-induced skin pain.

We conducted a cross-sectional, national survey of child-parent dyads (ages 1-17 years) with AD, with planned oversampling for moderate and severe disease (n =200 out of 240) on Patient Oriented Eczema Measure (POEM) and 30% Black race. Details of the stratified sampling strategy have been described previously.<sup>1</sup> Inclusion criteria were parent-proxy-report of provider diagnosis of AD and scratching  $\geq 1$  night in the past week. Respondents who endorsed sleep disturbance due to comorbidities (e.g. allergic rhinitis, obstructive sleep apnea) were excluded. Questions were administered to parent-proxy for all participants; children  $\geq 8$  years completed a similar questionnaire adapted for self-report. Informed consent was obtained electronically after Institutional Review Board approval.

Pain was assessed by “Over the past week, did you/your child have any pain of their skin?” Pain intensity was assessed by “How severe was the pain on a scale of 0-10?” Frequency, proportion, and 95% confidence interval (CI95) were estimated for socio-demographics.

Median parent-rated skin pain intensity and interquartile range (IQR) were calculated. Bivariable and multivariable linear regression models were constructed to examine associations of skin pain intensity (dependent variable [DV]). Covariates included socio-demographic characteristics (gender [male/female], race [White/Black/other-multiracial], current age [1-4/5-7/8-12/13-17 years]), and (Model-1) total scores for POEM [almost clear-mild/moderate-very severe]) or (Model-2) individual POEM items (itch, bleeding, weeping/oozing, skin cracked, flaking off, dry/rough in past week).

We then examined associations of skin pain intensity (independent variable) with QOL measures (DV) using linear regression models adjusted for POEM severity. QOL metrics evaluated were Infants' Dermatitis Quality of Life (IDQOL, age <5 years), and Children's Dermatology Quality of Life Index (CDLQI, age  $\geq 5$  year). Higher IDQOL and CDLQI scores indicate worse QOL. CDLQI were severity stratified consistent with previous studies.<sup>2</sup> Models were constructed separately based on parent-proxy-report (5-17 years) and self-report (8-17 years). Statistical analyses were performed in SAS v9.4. A two-sided  $P \leq 0.05$  was considered statistically significant.

We surveyed 240 children with AD and parent dyads, including 60 infants (1-4 years) and 180 children (5-17 years). This cohort included 107 females (45%[CI95: 38,51%]), 77 Black (32%[26,38%]), 86 White (36%[30,42%]), and 200 (83%[79,88%]) with moderate-very severe disease (Table E1).

Overall, 111/240 participants (46%[40,53%]) had parent-proxy-reported skin pain, and 59/133 children (44%[36,53%]) 8-17 years self-reported skin pain. Children self-reported slightly greater pain intensity than did their parents (median[IQR]: 6.05[3.05] vs 5.81[2.56], paired t-test,  $P=0.02$ ). On sensitivity analysis, children 8-12 years and their parents reported similar skin pain intensity ( $P=0.22$ ), whereas adolescents 13-17 years reported greater pain intensity than their parents did ( $P=0.02$ ). Yet, there was strong correlation in parent-proxy- and self-reported skin pain intensity ( $n=47$ , Fisher z-transformation=0.87,  $P<.0001$ ).

Median parent-proxy-reported skin pain intensity of infants and children was 5.50[IQR:3.41]. In Model-1, of socio-demographic characteristics, pain intensity was associated with Black race (adjusted  $\beta$ [CI95]: 1.28[0.53,2.03]) and moderate-very severe AD (1.89[1.00,2.78]), and inversely associated with age 5-7 years (-1.25[-2.18,-0.32]) (Table 1).

Adjusting for socio-demographics and severity (Model-2), pain intensity was associated with clinical skin features of bleeding (1.47[0.61,2.33]), weeping/oozing (1.18[0.47,1.90]), cracking (1.00[0.27,1.73]), itch frequency (1.47[0.68,2.27]) and itch severity (0.69[0.53,0.85]).

Parent-proxy-reported pain intensity was associated with increased IDQOL at ages 1-4 years (adjusted  $\beta$ [CI95]: 1.16[0.18,2.14]) and CDLQI at ages 5-17 years (1.68[1.00,2.36]) (Table 2). Child-reported skin pain intensity was also associated with higher CDLQI scores (1.13[0.15,2.12]). In ordinal regression analysis, QOL impairment was associated with more intense skin pain reported by parents (adjusted OR[CI95]: 1.66[1.31,2.10]) and children (1.44[1.10,1.88]).

Nearly half (46.3%) of infants and children with AD had parent-proxy-reported skin pain, and 44.4% of children 8-17 years had self-reported skin pain in our study cohort oversampling for moderate-severe AD and Black race. Median skin pain intensity was 5.5 and was more intense in children with more severe disease. Moreover, skin pain intensity was associated with worse overall QOL in disease severity-adjusted models, similar to previous studies that found AD-induced pruritus is associated with worse QOL.<sup>3</sup> Yet, it is unclear if the differences in QOL are clinically significant. Previous studies found a 1-point difference in the Patient Global Impression of Disease scale was correlated with a change of 6 on CDLQI, whereas no threshold has been suggested for IDQOL.<sup>4</sup>

Interestingly, fewer Black children reported skin pain, yet those with skin pain had increased skin pain intensity. Racial/ethnic differences in presentation of AD have not been well-characterized. No evidence suggests a biologic difference, and variation in reporting and treatment access may explain differences in skin pain in our cohort.<sup>5</sup> Further research is necessary to elucidate these points.

Skin pain intensity was associated with multiple skin disease features including itch, bleeding, weeping/oozing, and skin cracking, suggesting skin pain has heterogeneous presentation and not limited to any particular AD phenotype.<sup>6</sup> The exact mechanism of skin pain is unclear. Decreased endogenous inhibition to repeated stimulation and abnormal receptor activation may contribute to skin pain.<sup>7</sup> Alternatively, pain may be secondary to aberrant nerve growth in skin damaged by inflammation or mechanical trauma. Previous research found children perceive severe itch as painful, whereas adults perceive itch and pain separately.<sup>8</sup> Activation of immune cells contributing to AD-induced skin pain also leads to increased pruritogenic signaling, suggesting a cyclical relationship.

Strengths of this study include stratified sampling and assessment of AD using multiple validated instruments. Limitations include small sample size from the US, limiting international generalizability. The study cohort oversampled for racial minority groups and severe disease and thus, is not generalizable to all childhood AD. AD severity was based on POEM responses, not objective measurements. Selection criteria included scratching  $\geq 1$  night in the past week, selecting for children with active AD. NRS skin pain is validated in adolescents  $\geq 12$  years but has not been investigated in younger children.<sup>9</sup> Data were unavailable on pain quality (e.g. burning, tingling). Future investigations of concurrent infections, triggers, quality, and other attributes of AD skin pain may elucidate underlying mechanisms.

Skin pain is a distinct, burdensome symptom of childhood AD with heterogeneous presentation and AD phenotypes. Moreover, skin pain intensity was associated with significant decrements on QOL, independent of disease severity. Given the link between skin pain and the severity of AD, skin pain may be an important endpoint for monitoring treatment response.

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**Table 1. Associations of parent-proxy-reported skin pain intensity in pediatric (ages 1-17) AD cohort (n=111).**

| Characteristic                     | Pain intensity | Bivariable model       |                  | Multivariable model*      |                  |
|------------------------------------|----------------|------------------------|------------------|---------------------------|------------------|
|                                    | Median [IQR]   | Crude $\beta$ [95% CI] | P-value          | Adjusted $\beta$ [95% CI] | P-value          |
| <b>Gender</b>                      |                |                        |                  |                           |                  |
| Male                               | 5.46 [3.35]    | 1.00 [ref]             | -                | 1.00 [ref]                | -                |
| Female                             | 5.55 [3.48]    | 0.24 [-0.56, 1.03]     | 0.56             | 0.20 [-0.52, 0.91]        | 0.58             |
| <b>Race/ethnicity</b>              |                |                        |                  |                           |                  |
| White                              | 5.04 [3.32]    | 1.00 [ref]             | -                | 1.00 [ref]                | -                |
| Black                              | 6.25 [2.21]    | 1.38 [0.50, 2.25]      | <b>0.002</b>     | 1.28 [0.53, 2.03]         | <b>0.001</b>     |
| Other/multiracial                  | 5.80 [3.43]    | 0.55 [-0.38, 1.49]     | 0.24             | 0.67 [-0.23, 1.56]        | 0.14             |
| <b>Current age</b>                 |                |                        |                  |                           |                  |
| 1-4 years                          | 6.06 [3.34]    | -0.24 [-1.37, 0.89]    | 0.68             | -0.23 [-1.26, 0.81]       | 0.67             |
| 5-7 years                          | 3.72 [2.22]    | -1.38 [-2.41, -0.34]   | 0.01             | -1.25 [-2.18, -0.32]      | <b>0.009</b>     |
| 8-12 years                         | 6.14 [2.03]    | 0.41 [-0.66, 1.47]     | 0.45             | 0.16 [-0.89, 1.22]        | 0.76             |
| 13-17 years                        | 5.50 [3.50]    | 1.00 [ref]             | -                | 1.00 [ref]                | -                |
| <b>Proxy POEM AD severity</b>      |                |                        |                  |                           |                  |
| Almost clear/Mild                  | 3.13 [1.86]    | 1.00 [ref]             | -                | 1.00 [ref]                | -                |
| Moderate-very severe               | 5.73 [3.17]    | 2.18 [1.26, 3.09]      | <b>&lt;.0001</b> | 1.89 [1.00, 2.78]         | <b>&lt;.0001</b> |
| <b>Treatment type</b>              |                |                        |                  |                           |                  |
| <b>Systemic therapy</b>            |                |                        |                  |                           |                  |
| No                                 | 6.00 [2.68]    | 1.00 [ref]             | -                | 1.00 [ref]                | -                |
| Yes                                | 5.48 [3.52]    | 0.89 [-0.26, 2.04]     | 0.13             | 0.94 [-0.18, 2.07]        | 0.10             |
| <b>Topical therapy</b>             |                |                        |                  |                           |                  |
| No                                 | 5.61 [3.51]    | 1.00 [ref]             | -                | 1.00 [ref]                | -                |
| Yes                                | 4.20 [2.42]    | 0.87 [-0.11, 1.85]     | 0.08             | 0.50 [-0.53, 1.52]        | 0.34             |
| <b>POEM weekly characteristics</b> |                |                        |                  |                           |                  |
| <b>Skin itchy</b>                  |                |                        |                  |                           |                  |
| 0-4 days                           | 3.88 [3.14]    | 1.00 [ref]             | -                | 1.00 [ref]                | -                |
| 5-7 days                           | 6.19 [2.26]    | 1.85 [1.12, 2.58]      | <b>&lt;.0001</b> | 1.47 [0.68, 2.27]         | <b>0.0004</b>    |
| <b>Bleeding</b>                    |                |                        |                  |                           |                  |
| 0-4 days                           | 5.15 [3.43]    | 1.00 [ref]             | -                | 1.00 [ref]                | -                |
| 5-7 days                           | 6.75 [2.17]    | 1.91 [1.14, 2.69]      | <b>&lt;.0001</b> | 1.47 [0.61, 2.33]         | <b>0.001</b>     |
| <b>Weeping or oozing</b>           |                |                        |                  |                           |                  |
| 0-4 days                           | 5.07 [3.53]    | 1.00 [ref]             | -                | 1.00 [ref]                | -                |
| 5-7 days                           | 6.38 [2.00]    | 1.69 [0.97, 2.40]      | <b>&lt;.0001</b> | 1.18 [0.47, 1.90]         | <b>0.001</b>     |
| <b>Skin cracked</b>                |                |                        |                  |                           |                  |
| 0-4 days                           | 5.04 [3.31]    | 1.00 [ref]             | -                | 1.00 [ref]                | -                |
| 5-7 days                           | 6.31 [2.26]    | 1.33 [0.58, 2.08]      | <b>0.0006</b>    | 1.00 [0.27, 1.73]         | <b>0.008</b>     |
| <b>Flaking off</b>                 |                |                        |                  |                           |                  |
| 0-4 days                           | 5.05 [3.51]    | 1.00 [ref]             | -                | 1.00 [ref]                | -                |
| 5-7 days                           | 5.92 [2.69]    | 1.14 [0.38, 1.90]      | <b>0.004</b>     | 0.66 [-0.15, 1.48]        | 0.11             |
| <b>Felt dry or rough</b>           |                |                        |                  |                           |                  |
| 0-4 days                           | 5.38 [3.34]    | 1.00 [ref]             | -                | 1.00 [ref]                | -                |
| 5-7 days                           | 5.53 [3.45]    | 0.12 [-0.72, 0.97]     | 0.77             | -0.48 [-1.42, 0.46]       | 0.32             |
| <b>Numeric Itch Rating</b>         | 5.50 [3.41]    | 0.79 [0.65, 0.93]      | <b>&lt;.0001</b> | 0.69 [0.53, 0.85]         | <b>&lt;.0001</b> |

Bold-face text indicates statistical significance.

\*Model 1 included gender, race/ethnicity, age, and POEM disease severity. Multivariable models were then constructed for each treatment type and POEM skin characteristic, adjusting for all covariates in Model 1.

**Table 2. Correlation of skin pain intensity and quality of life in children with AD reporting skin pain.**

| Quality of life scale                               | Crude $\beta$ [95% CI] | P-value          | POEM-adjusted $\beta$ [95% CI]* | P-value          |
|-----------------------------------------------------|------------------------|------------------|---------------------------------|------------------|
| <b>Parent-proxy response 1-17 years (n=111)</b>     |                        |                  |                                 |                  |
| Infant's Dermatitis Quality of Life (n=23)          | 1.65 [0.82, 2.48]      | <b>0.0005</b>    | 1.16 [0.18, 2.14]               | <b>0.02</b>      |
| Child Dermatology Quality of Life (n=88)            | 1.75 [1.14, 2.35]      | <b>&lt;.0001</b> | 1.68 [1.00, 2.36]               | <b>&lt;.0001</b> |
| Stratified Child Dermatology Quality of Life (n=88) | 1.71 [1.38, 2.11]      | <b>&lt;.0001</b> | 1.66 [1.31, 2.10]               | <b>&lt;.0001</b> |
| <b>Child self-report 8-17 years (n=59)</b>          |                        |                  |                                 |                  |
| Child Dermatology Quality of Life                   | 1.57 [0.71, 2.43]      | <b>0.0006</b>    | 1.13 [0.15, 2.12]               | <b>0.03</b>      |
| Stratified Child Dermatology Quality of Life        | 1.63 [1.26, 2.10]      | <b>0.0002</b>    | 1.44 [1.10, 1.88]               | <b>0.008</b>     |

192 \*Models adjusted for POEM disease severity.

193 Bold-face text indicates statistical significance.

194 Child Dermatology Quality of Life strata: no effect (0-1), small effect (2-6), moderate effect (7-12), very large effect (13-18),

195 extremely large effect (19-30).<sup>2</sup>

**Supplemental Table E1. Sociodemographic and clinical associations of skin pain among childhood AD**

| Characteristic                   | No skin pain (n=129)       | Parent-proxy-reported skin pain (n=111) |                            |
|----------------------------------|----------------------------|-----------------------------------------|----------------------------|
|                                  | Frequency (Prev. [95% CI]) | Frequency (Prev. [95% CI])              | Rao-Scott $\chi^2$ P-value |
| <b>Gender</b>                    |                            |                                         | 0.52                       |
| Male                             | 69 (51.9% [43.3-60.4%])    | 64 (48.1% [39.6-56.7%])                 |                            |
| Female                           | 60 (56.1% [46.6-65.5%])    | 47 (43.9% [34.5-53.4%])                 |                            |
| <b>Race/ethnicity</b>            |                            |                                         | <.0001                     |
| White                            | 29 (33.7% [23.7-43.8%])    | 57 (66.3% [56.2-76.3%])                 |                            |
| Black                            | 53 (68.8% [58.4-79.3%])    | 24 (31.2% [20.7-41.6%])                 |                            |
| Other/multiracial                | 47 (61.0% [50.1-72.0%])    | 30 (39.0% [28.0-49.9%])                 |                            |
| <b>Current age</b>               |                            |                                         | 0.42                       |
| 1-4 years                        | 37 (61.7% [49.3-74.1%])    | 23 (38.3% [25.9-50.7%])                 |                            |
| 5-7 years                        | 22 (46.8% [32.4-61.2%])    | 25 (53.2% [38.8-67.6%])                 |                            |
| 8-12 years                       | 41 (56.2% [44.7-67.6%])    | 32 (43.8% [32.4-55.3%])                 |                            |
| 13-17 years                      | 29 (48.3% [35.6-61.1%])    | 31 (51.7% [38.9-64.4%])                 |                            |
| <b>POEM AD severity</b>          |                            |                                         | 0.06                       |
| Almost clear/Mild                | 27 (67.5% [52.9-82.1%])    | 13 (32.5% [17.9-47.1%])                 |                            |
| Moderate-very severe             | 102 (51.0% [44.0-58.0%])   | 98 (49.0% [42.0-56.0%])                 |                            |
| <b>Treatment</b>                 |                            |                                         |                            |
| <b>Systemic therapy (n=238)</b>  |                            |                                         | <b>0.04</b>                |
| No                               | 123 (55.7% [49.1-62.3%])   | 98 (44.3% [37.7-50.9%])                 |                            |
| Yes                              | 5 (29.4% [7.6-51.2%])      | 12 (70.6% [48.8-92.4%])                 |                            |
| <b>Topical treatment (n=240)</b> |                            |                                         | 0.49                       |
| No                               | 19 (59.4% [42.2-76.5%])    | 13 (40.6% [23.5-57.8%])                 |                            |
| Yes                              | 110 (52.9% [46.1-59.7%])   | 98 (47.1% [40.3-53.9%])                 |                            |

Bold-face text indicates statistical significance.

Specific systemic therapies were prompted, including prednisone, dupilumab, cyclosporine, methotrexate, etc.