BJD
British Journal of Dermatology

Pain severity and use of analgesic medication in adults with atopic dermatitis: a cross-sectional study

J.P. Thyssen,[1,2] A.-S. Halling-Sønderby,[1,2] J.J. Wu[3] and A. Egeberg[1,2]

[1]Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark
[2]Copenhagen Research Group for Inflammatory Skin (CORGIS), Herlev and Gentofte Hospital, Hellerup, Denmark
[3]Dermatology Research and Education Foundation, Irvine, CA, U.S.A.

Correspondence
Jacob P. Thyssen.
E-mail: jacob.pontoppidan.thyssen@regionh.dk

Accepted for publication
20 September 2019

Funding sources
The Danish Skin Cohort is supported by grants from the Danish National Psoriasis Foundation and the Kgl Hofbundtmager Aage Bang Foundation.

Conflicts of interest
A.E. has received research funding from Pfizer, Eli Lilly, the Danish National Psoriasis Foundation and the Kgl Hofbundtmager Aage Bang Foundation, and consultant and/or speaker honoraria from AbbVie, Almirall, Leo Pharma, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly and Company, Novartis, Galderma, Dermavant, Bristol-Myers Squibb and Janssen Pharmaceuticals. J.P.T. has attended advisory boards for Sanofi-Genzyme, AbbVie, Pfizer, Union Therapeutics and Eli Lilly & Co., has received speaker honoraria from LEO Pharma and Sanofi-Genzyme, and has been an investigator for Sanofi-Genzyme, Eli Lilly & Co., LEO Pharma, Pfizer and AbbVie. J.J.W. is an investigator for AbbVie, Amgen, Eli Lilly, Janssen, Novartis and Regeneron.

DOI 10.1111/bjd.18557

Summary

Background Adult patients with atopic dermatitis (AD) report skin pain, but the relationship with disease severity, anatomical location and use of pain medication is unclear.

Objectives To examine pain in adults with AD.

Methods We performed a cross-sectional study of nationwide healthcare data and survey data from the Danish Skin Cohort. In total, 3208 randomly selected adults from the general population and 3834 adults with a dermatologist-verified diagnosis of AD present in adulthood were included. Patient-Oriented SCORing Atopic Dermatitis determined AD severity, and numerical rating scales estimated the severity of pruritus and skin pain. Complete information on the use of analgesic medication was obtained from the Danish nationwide prescription registry.

Results Respectively, 6·8%, 55·5%, 34·0% and 3·7% of the AD cohort reported that they were asymptomatic, or had mild, moderate or severe disease at the time of assessment. Skin pain was positively associated with AD severity and itch. Higher skin pain scores were observed in plantar, chest and palmar areas. Use of pain medication was not increased in patients with AD.

Conclusions Patients with AD did not display increased use of pain medication, but few had severe disease. The close relationship observed between itch and pain highlights the potential benefits of established AD treatments to also reduce skin pain in AD.

What's already known about this topic?

- There is increased awareness about skin pain being a significant burden of atopic dermatitis (AD).

What does this study add?

- We found that skin pain is increased with AD severity and itch.
- The comparable use of pain medication in patients with AD and controls suggests that dermatological treatments reduce skin pain.

Atopic dermatitis (AD) is a common chronic inflammatory skin condition. Nearly all affected patients suffer from chronic and relentless itch, which may be located at both lesional and nonlesional skin. The partly neglected association between AD and skin pain has been highlighted in recent epidemiological studies, and the association is increasingly acknowledged.[1–3] Several explanations for the associated skin pain may be put forward, including a burning skin sensation from AD and topical medication, as well as painful fissured skin. To our knowledge, there is no mention of skin pain assessment or treatment in any current guidelines or consensus reports.

Previous studies on skin pain in AD have been relatively small, and it has therefore not been firmly established whether disease severity and itch are associated with skin pain, and

whether certain anatomical areas are particularly prone to skin pain. Importantly, it is currently unknown whether the increased occurrence of skin pain translates into increased consumption of pain medication.

In the present cross-sectional study, we examined the characteristics of skin pain in adult patients with AD and whether pain was associated with an increased number of dispensed prescriptions of pain medication.

Materials and methods

Approvals relevant for this study were obtained (ref. 2012-58-0004, j.no. VD-2018-286, I-Suite no.: 6528).

The Danish Skin Cohort provided data for this study.[4] Briefly, the Danish Skin Cohort is a prospective cohort with three independent samples of, respectively, adults from the Danish general population (without a recorded diagnosis of AD or psoriasis in the Danish registries); adult patients with a dermatologist-verified diagnosis of psoriasis; and adult patients with a clinical dermatologist-verified diagnosis of AD. In this study, data on adults from the general population and adult patients with AD were included. Initially, 10 000 randomly selected adults from the Danish general population and 10 000 adults with a dermatologist-verified diagnosis AD present in adulthood were invited by mail to participate in the Danish Skin Cohort between 15 May 2018 and 15 July 2018. All nonresponders were contacted a maximum of five times, by either mail or phone. A total of 3208 adults from the Danish general population and 3834 patients with AD accepted the invitation and were interviewed by a professional researcher over the telephone about subjective symptoms, including itch, skin and joint pain. If a participant preferred to answer the survey electronically, that was also an option.

AD severity at the time of questioning was defined according to the patients' current Patient-Oriented SCORing Atopic Dermatitis (PO-SCORAD). Patients were classified as being asymptomatic (PO-SCORAD of 0), having mild disease (PO-SCORAD 1–24), moderate disease (PO-SCORAD 25–50) or severe disease (PO-SCORAD > 50). Body surface area (BSA) currently affected by AD was also reported. A high correlation has previously been identified between patient- and physician-reported BSA.[5] Skin and joint pain were assessed using a numerical rating scale (NRS), where 0 indicated no symptoms (least affection) and 10 very strong symptoms (highest affection).[6–8] Participants were asked the following: 'In the past week, how much pain did you have in your skin on a scale from 0 to 10, with 10 being the worst?' For joint pain, participants were asked: 'In the past week, how much pain did you have in your joints on a scale from 0 to 10, with 10 being the worst?' (Both questions were asked in Danish.). We observed few missing data. For skin pain, data were missing for 10 (0·3%) reference individuals and 15 (0·4%) patients with AD. For joint pain, data were missing for 20 (0·6%) reference individuals and 14 (0·4%) patients with AD. Joint pain was used as a reference marker of pain outside the skin as we had included this variable for the psoriasis cohort where joint pain is common. The severity of pruritus (within the past 3 days) was also assessed using the NRS. Complete information on the number of dispensed prescriptions of analgesic medication {paracetamol [Anatomical Therapeutic Chemical (ATC) code N02BE01 and N02BE51]; nonsteroidal anti-inflammatory drugs [NSAIDs; ATC code M01A]; opioids [ATC code N02A] and gabapentin/pregabalin [ATC codes N03AX12 and N03AX16]} was obtained for all study participants through an individual-level linkage with the nationwide Register of Medicinal Products Statistics.[9,10]

Statistical analysis

We present frequencies with percentages for categorical variables and means ± SDs for continuous variables. Furthermore, we estimated the interquartile ranges (IQRs) for non-normally distributed continuous outcome variables. To estimate the strength and direction of association between itch and skin pain, we used Spearman's rank order correlation. Graphical distribution of joint pain was weighted by age to account for the increased pain seen in older people, as the reference individuals were older (mean age 55·5 ± 17·5 years) than the adults with AD (mean age 48·8 ± 14·5 years). In addition, skin pain was weighted by severity of AD in the analysis 'skin pain according different anatomical locations in adult patients with AD' to account for the association between more severe

Table 1 Characteristics of the study population

Characteristics	Patients with AD (n = 3834)	Reference individuals (n = 3208)
Mean ± SD age (years)	48·8 ± 14·5	55·5 ± 17·5
Sex		
Female	2644 (69·0)	1731 (54·0)
Male	1190 (31·0)	1477 (46·0)
Median (IQR) age of AD onset (years)	3 (1–11)	–
Median (IQR) affected BSA[a]	3 (1–10)	–
Severity of AD[b]		
Asymptomatic	261 (6·8)	–
Mild	2126 (55·5)	–
Moderate	1304 (34·0)	–
Severe	143 (3·7)	–
Atopic comorbidities		
Asthma	1464 (38·2)	303 (9·5)
Hayfever	1873 (48·9)	419 (13·1)
Current medication		
Azathioprine	76 (2·0)	< 3 (not shown)
Ciclosporin	6 (0·2)	0 (0·0)
Methotrexate	103 (2·7)	25 (0·8)
Mycophenolate	12 (0·3)	3 (0·1)

AD, atopic dermatitis; IQR, interquartile range; BSA, body surface area. [a]Affected BSA at the time of assessment; [b]severity of AD according to Patient-Oriented SCORing Atopic Dermatitis at the time of assessment.

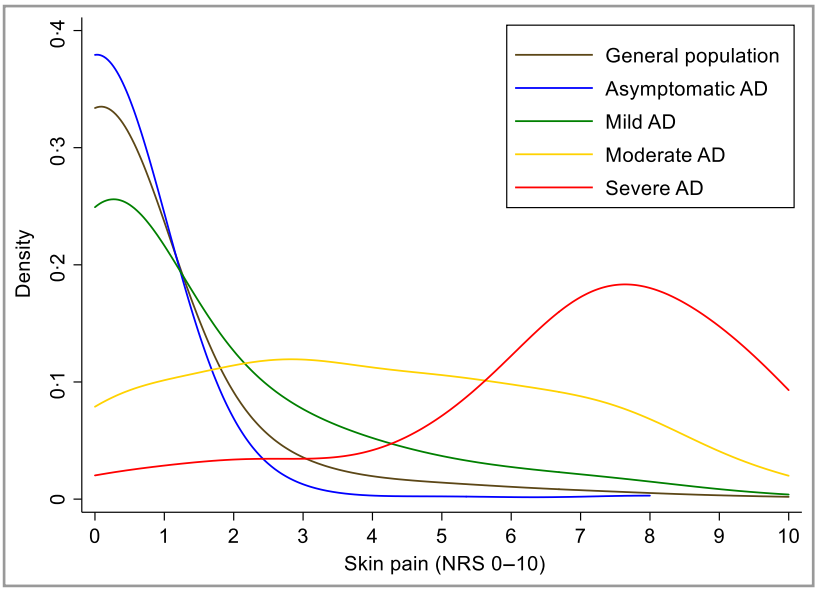

Fig 1. Skin pain in the adult general population and in adult patients with atopic dermatitis (AD). NRS, numerical rating scale.

AD and specific anatomical locations of the lesions. Analyses were performed using SAS statistical software version 9·4 (SAS Institute, Cary, NC, U.S.A.) and Stata software version 13·0 (StataCorp, College Station, TX, U.S.A.).

Results

The mean age of study participants was 55·5 ± 17·5 years (3208 reference individuals) and 48·8 ± 14·5 years (3834 patients with AD) (Table 1). Fifty-four per cent of reference individuals and 69% of patients with AD were women. Of those with AD, 261 (6·8%) were asymptomatic, and 2126 (55·5%), 1304 (34·0%) and 143 (3·7%) reported that they had mild, moderate and severe AD, respectively, according to the PO-SCORAD at the time of assessment. Median BSA was 3 (IQR 1–10). A total of 973 (25·4%) patients with AD reported eczema located to the face. Moreover, 867 (22·6%) had periorbital eczema, 1018 (26·6%) neck eczema, 418 (10·9%) chest eczema, 605 (15·8%) palmar eczema and 186 (4·9%) plantar eczema. Nearly all reported childhood onset of AD; median age of onset of AD was 3 years (IQR 1–11).

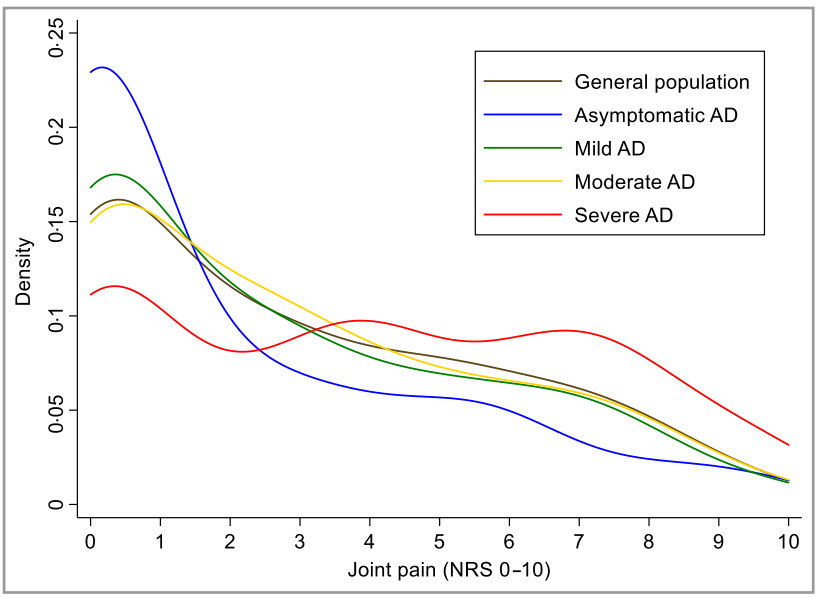

Fig 2. Joint pain in the general population and in adult patients with atopic dermatitis (AD). Estimates are weighted by age. NRS, numerical rating scale.

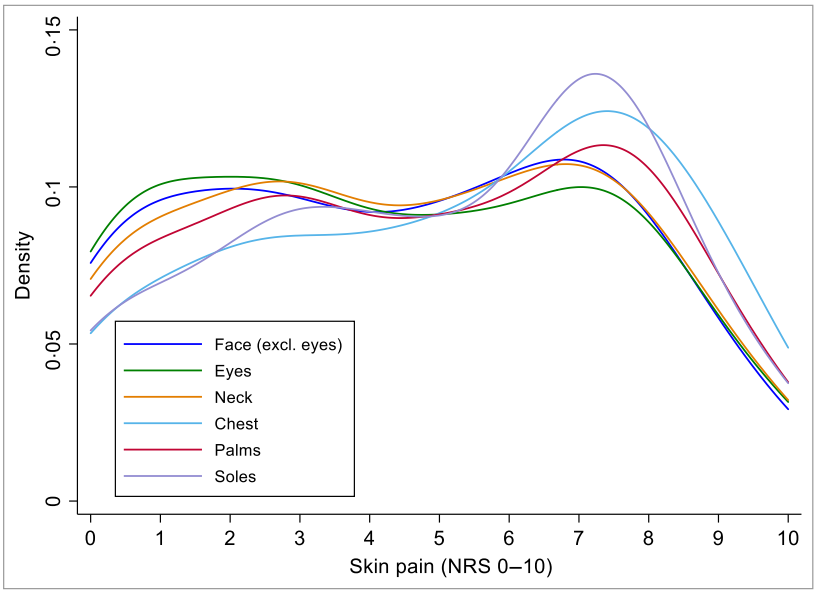

Fig 3. Skin pain according to different anatomical locations in adult patients with atopic dermatitis (AD). Estimates are weighted by severity of AD. NRS, numerical rating scale.

Median self-reported skin and joint pain in the general population was 0 (IQR 0–0) and 2 (IQR 0–5), respectively. In patients with AD, median skin pain was 0 (IQR 0–0) in patients with asymptomatic AD, 0 (IQR 0–2) in those with mild AD, 4 (IQR 2–6) in those with moderate AD and 7 (IQR 6–8) in those with severe AD (Fig. 1). For joint pain, the corresponding median values were 0 (IQR 0–3), 2 (IQR 0–4), 2 (IQR 0–5) and 4 (IQR 1–7), respectively. Figure 2 shows that apart from the higher joint pain scores in patients with severe AD, lower joint pain scores were observed for those with asymptomatic AD vs. general population controls. Higher skin pain scores were seen in individuals with eczema in the plantar, chest and palmar areas (Fig. 3). Overall, higher skin pain scores were seen in individuals with high itch scores resulting in a Spearman's correlation coefficient of 0·73 (Fig. 4). No difference in skin pain was observed between men and women with AD.

The use of pain medication is shown in Figure 5. The proportions of individuals who had claimed prescriptions for paracetamol, NSAIDs and opioids within the past year was similar for general population reference individuals and patients with AD. The slightly (and nonsignificantly) higher

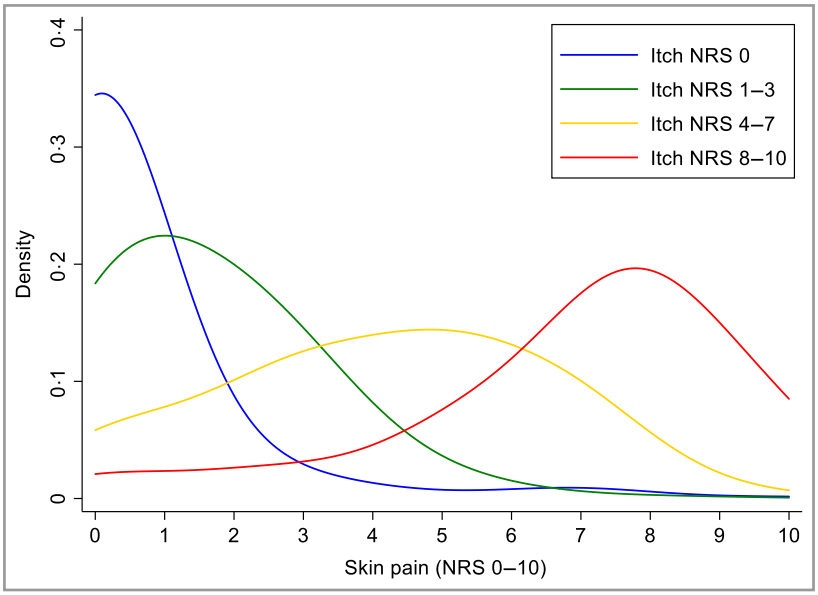

Fig 4. Skin pain according to severity of pruritus in adult patients with atopic dermatitis. NRS, numerical rating scale.

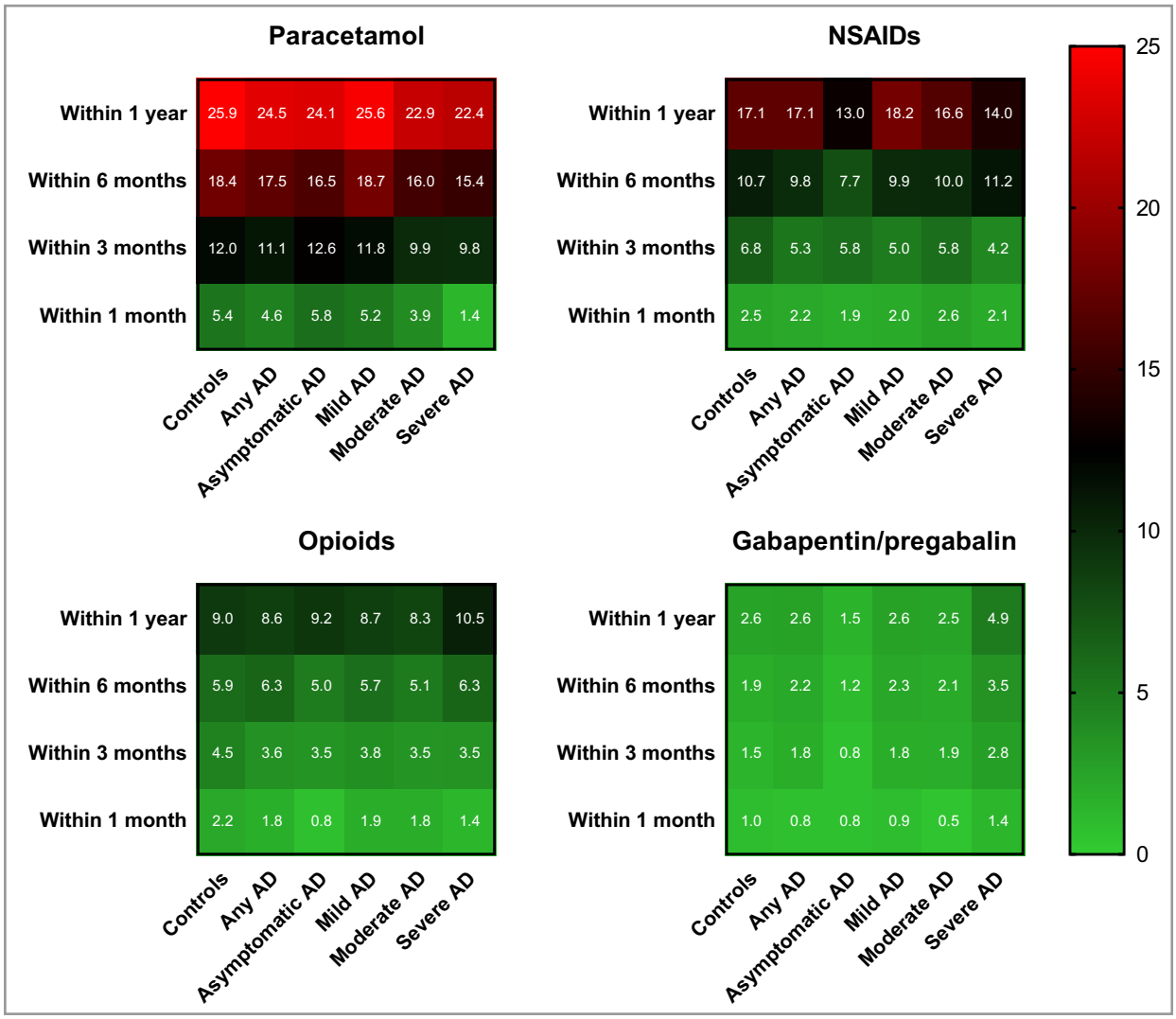

Fig 5. Use of analgesic medication in the general population and in adult patients with atopic dermatitis (AD). The numbers in the boxes show the percentages for each group. NSAIDs, nonsteroidal anti-inflammatory drugs.

use of gabapentin/pregabalin in patients with severe AD was driven by very few individuals (gabapentin/pregabalin use within 1 month, $n < 3$; within 3 months, $n = 4$; within 6 months, $n = 5$; within 1 year, $n = 7$) and no significant differences were observed across severities.

Discussion

This study showed that the intensity of skin pain is high in patients with moderate and severe AD, and, in particular, in patients with AD on the soles of the feet, the chest and the palms of the hands. Use of pain medication was similar in patients with AD and reference individuals without AD.

Our findings are in line with previous studies examining skin pain in patients with AD. A 2009 survey demonstrated that 59% reported skin pain associated with itch,[11] whereas a questionnaire and clinical study showed that 43% reported any skin pain in the past week and 14% severe or very severe skin pain.[1] In a recent international survey, 78% reported both itch and skin pain, 20% itch only and 1% skin pain only.[2] Respondents described the pain sensation as predominately being of a burning and stinging nature,[2] and aggravating factors included sweat, heat, emotional stress and warm water.

Despite the AD severity-dependent association between AD and skin pain observed in this and previous studies,[1,2] the pain experienced by patients with AD is likely multifaceted and very complex. Pain and pruritus are conveyed by the same cutaneous C nerve fibres and their density is increased in lesional vs. nonlesional AD skin.[12,13] However, little is known about central itch mechanisms in AD. Thus, it is possible that central pruriceptive disinhibition plays a role, which would cause analgesics to relieve pain while at the same time worsening the itch sensation.[14] While pain normally inhibits itch,[15,16] the co-occurrence of itch and pain in AD is notable. There is a need for better insight into the temporal relationship between itch and pain, as it possible that pain not only

replaces itch following scratching in some patients with AD, but also that they predominately co-occur.

Skin pain in AD can represent a burning and stinging sensation associated with eczema flares, as well as exposure to heat and exercise.[2] However, it may also represent a more direct pain following use of hands or feet with cracked and atrophic skin. Notably, the hands and fingers may be particularly prone to skin cracks in filaggrin mutation carriers and following intense use of topical corticosteroids.[17,18] Moreover, the use of topical calcineurin and phosphodiesterase 4 inhibitors can cause a transient stinging pain and superimpose on the existing pain,[19,20] particularly when the skin is cracked.[21] Skin pain in AD has also been associated with excoriations following scratching, and it is therefore possible that the pain, to a high degree, is scratch-evoked. If so, antipruritic therapy should also lead to a reduction in or resolution of skin pain. Indeed, clinical trials in adults with AD have shown significant reductions in pain/discomfort following treatment with dupilumab, which has strong antipruritic effects.[22]

We identified the palms, soles and chest as locations of AD predominately associated with skin pain. A previous study identified the hands, toes and perioral region as eczema regions with increased pain, perhaps in part explained by the increased sensory nerve density in the areas.[2] However, a U.S. study found that periorbital eczema was associated with skin pain.[1] As the hands and feet have important daily functional tasks and may be prone to severe eczema in adult patients with AD with filaggrin deficiency, these may be frequently reported.[23] We have no explanation for the chest being associated with skin pain, but speculate that it might be explained by upper body involvement in young adults with AD or that exacerbation of AD may spread to this region and be associated with sensitization of pain.

The proven association between AD and skin pain emphasizes that, besides itch, patients with AD have another significant burden of their disease. Accordingly, skin pain has been associated with reduced quality of life,[1] and it is therefore important to examine whether this translates into increased consumption of pain medication. By using nationwide prescription data, we showed that similar proportions of reference individuals from the general population and patients with AD (independent of disease severity) used pain medication. While small packages (maximum 20 tablets and only one pack at a time) of paracetamol and NSAIDs can be purchased over the counter, all pharmacy-dispensed pain medication in Denmark is captured in national registries. Our observation – that pain medication use is not increased in patients with AD – indirectly supports the idea that skin pain is reduced following adequate AD therapy, as shown in one study to treatment with dupilumab.[22] However, it is also possible that patients neglect to report skin pain to their healthcare providers, and/or physicians chose not to treat pain specifically with pain medication. It should be emphasized that only a small proportion of our patients with AD had severe disease, which could have obscured increased consumption in this group. We also showed that joint pain was similar in patients with AD and reference individuals except from reports of slightly increased joint pain in those with severe AD. The reason for this observation is unclear, but it could be a result of systemic inflammation also affecting the joints. We included joint pain as we had access to this variable, originally intended for comparison with patients with psoriasis, but we acknowledge that other reference pain variables might have given different results.

This is by far the largest cross-sectional study that has examined skin pain in adults with AD, making it possible to distinguish clearly the intensity across different severity strata. However, a relatively small number of study participants suffered from severe AD, and the findings should therefore be interpreted with caution for the severe group. A particular study strength was the large reference population, along with joint pain as a reference marker of pain. The study could not identify the cause of pain and did not examine the temporal relationship with itch. This should be addressed in future studies, in order to affect treatment strategies. Moreover, it was not possible to identify if pain medication was prescribed for skin pain, or if there was another indication for the prescription. We chose to study pain medication use within the past 12 months, but potentially current use may be different.

This large study of adult patients with AD showed a clear severity-dependent association with skin pain, and the AD at specific body locations was associated with patient-reported skin pain. Regardless of severity, patients with AD did not show increased use of pain medication. The close observed relationship between itch and pain highlights the potential benefits of established AD treatments to reduce skin pain in AD.

Acknowledgments

J.P.T. and A.-S.H-S. are supported by an unrestricted grant from the Lundbeck Foundation.

References

1 Vakharia PP, Chopra R, Sacotte R *et al.* Burden of skin pain in atopic dermatitis. *Ann Allergy Asthma Immunol* 2017; **119**:548–52.e3.
2 Maarouf M, Kromenacker B, Capozza KL *et al.* Pain and itch are dual burdens in atopic dermatitis. *Dermatitis* 2018; **29**:278–81.
3 Silverberg JI, Gelfand JM, Margolis DJ *et al.* Pain is a common and burdensome symptom of atopic dermatitis in United States adults. *J Allergy Clin Immunol Pract* 2019; **7**:2699–706.
4 Egeberg A, Andersen YMF, Thyssen JP. Prevalence and characteristics of psoriasis in Denmark: findings from the Danish skin cohort. *BMJ Open* 2019; **9**:e028116.
5 Housman TS, Patel MJ, Camacho F *et al.* Use of the Self-Administered Eczema Area and Severity Index by parent caregivers: results of a validation study. *Br J Dermatol* 2002; **147**:1192–8.
6 Humphrey L, Symonds T, Gable J *et al.* Mixed methods evaluation of an itch numeric rating scale among adult and adolescent patients with atopic dermatitis. *Value Health* 2017; **20**:A806.

7 Humphrey L, Symonds T, Gable J *et al*. Validity and interpretation of a skin pain numeric rating scale among adults and adolescents with atopic dermatitis. *Value Health* 2017; **20**:A806.

8 Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. *Pain* 2011; **152**:2399–404.

9 Schmidt M, Schmidt SA, Sandegaard JL *et al*. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015; **7**:449–90.

10 Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011; **39**:38–41.

11 Dawn A, Papoiu AD, Chan YH *et al*. Itch characteristics in atopic dermatitis: results of a web-based questionnaire. *Br J Dermatol* 2009; **160**:642–4.

12 Sugiura H, Omoto M, Hirota Y *et al*. Density and fine structure of peripheral nerves in various skin lesions of atopic dermatitis. *Arch Dermatol Res* 1997; **289**:125–31.

13 Urashima R, Mihara M. Cutaneous nerves in atopic dermatitis. A histological, immunohistochemical and electron microscopic study. *Virchows Archiv* 1998; **432**:363–70.

14 Andersen HH, Yosipovitch G, Arendt-Nielsen L. Pain inhibits itch, but not in atopic dermatitis? *Ann Allergy Asthma Immunol* 2018; **120**:548–9.

15 Brull SJ, Atanassoff PG, Silverman DG *et al*. Attenuation of experimental pruritus and mechanically evoked dysesthesiae in an area of cutaneous allodynia. *Somatosensory Motor Res* 1999; **16**:299–303.

16 Baron R, Schwarz K, Kleinert A *et al*. Histamine-induced itch converts into pain in neuropathic hyperalgesia. *Neuroreport* 2001; **12**:3475–8.

17 Thyssen JP, Ross-Hansen K, Johansen JD *et al*. Filaggrin loss-of-function mutation R501X and 2282del4 carrier status is associated with fissured skin on the hands: results from a cross-sectional population study. *Br J Dermatol* 2012; **166**:46–53.

18 Veien NK, Olholm Larsen P, Thestrup-Pedersen K *et al*. Long-term, intermittent treatment of chronic hand eczema with mometasone furoate. *Br J Dermatol* 1999; **140**:882–6.

19 Lin C, Gordon S, Her MJ *et al*. A retrospective study: application site pain with the use of crisaborole, a topical phosphodiesterase 4 inhibitor. *J Am Acad Dermatol* 2019; **80**:1451–3.

20 Draelos ZD, Feldman SR, Berman B *et al*. Tolerability of topical treatments for atopic dermatitis. *Dermatol Ther* 2019; **9**:71–102.

21 Seo SR, Lee SG, Lee HJ *et al*. Disrupted skin barrier is associated with burning sensation after topical tacrolimus application in atopic dermatitis. *Acta Dermatovenereol* 2017; **97**:957–8.

22 de Bruin-Weller M, Thaci D, Smith CH *et al*. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE). *Br J Dermatol* 2018; **178**:1083–101.

23 Heede NG, Thyssen JP, Thuesen BH *et al*. Anatomical patterns of dermatitis in adult filaggrin mutation carriers. *J Am Acad Dermatol* 2015; **72**:440–8.