

# **Audit: Burden of Eczema**

*The burden of disease of atopic dermatitis*

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Prepared for the National Eczema Association

December 28, 2015

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## I. Introduction

Atopic dermatitis (AD), also known as eczema, is a chronically relapsing skin disease with no known cure. It affects approximately 10.7% and 7.2% of American children and adults, respectively.<sup>1,2</sup> The onset of AD is usually in early childhood, and can have an impact on the entire family unit. Additionally, AD is increasingly recognized as a disease that often persists into or begins in adulthood. Thus, AD can have a detrimental effect on the lives of eczema sufferers and their partners and families throughout their lifespan. This includes major impacts on the quality of life (QoL) of patients and their families as well as social, academic and occupational impacts. AD places a tremendous financial burden on patients, their families, and society as a whole through the costs of healthcare practitioner visits, medications, and over-the-counter (OTC) products, and decreased productivity of patients or their caregivers. All of these aspects together – QoL, social, academic and occupational impacts along with direct and indirect costs – encompass the burden of disease of AD.

The purpose of this report, *Audit: burden of eczema*, is to comprehensively document the evidence to date on the burden of AD. The report focuses on the burden of disease in the US, but includes information on the burden of AD in other countries as well, particularly with regards to impacts on QoL. This report highlights the tremendous burden of AD in our society and makes suggestions for future research efforts where data is missing or insufficient.

### *References*

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## II. Methods

Sections III and IV of this report are comprehensive literature reviews on QoL and the economic, academic and occupational impact of AD, respectively. For each section and subsection, literature searches of the Pubmed database were designed in conjunction with a medical librarian (ES). Specific searches were done on the following topics (each sub-heading represents a separate search):

1. Quality of life
  - a) Impact of quality of life on patients with AD
  - b) Impact of itch on patients with AD
  - c) Pain in patients with AD
  - d) Impact of AD on sleep and further consequences
  - e) Impact of AD on patients' self-esteem
  - f) Impact of AD on marital status and stability
  - g) Impact of AD on patients' social life
  - h) Impact of AD on the QoL of patients' families or partners
  - i) The impact of AD on patients seeking counseling or mental health care
  - j) Time spent managing AD
2. Economic, academic and occupational impact
  - a) Costs associated with AD (direct and indirect)
  - b) Health care resource utilization among patients with AD
  - c) Academic and occupational impact of AD
  - d) Impact of AD on socioeconomic status

All searches were performed between September and December 2015. The search strategies used, including specific search terms and limits, and the date each individual search was conducted can be found in the appendices, which are available upon request.

Two reviewers (AMD and ARW) performed title and abstract screening for every search, using specific PICOTS queries for each topic. Inclusion and exclusion criteria for each search can be found in the appendices. In brief, inclusion criteria were original articles relating to the impact of AD on various facets of patients' and families' lives and on society. Exclusion criteria included studies on other types of eczema (eg. chronic hand eczema), validation studies of outcome measures, interventional studies and review articles. Following title and abstract screening, one reviewer per search (either AMD or ARW) extracted information from the relevant articles and recorded them in the tables found in the appendices. Some articles were excluded at that stage if, upon full-text review, they were not found to be relevant to the audit. Additional articles were found through bibliography reviews or other incidental searches, or

were brought to the authors' attention through other means, such as staff at the National Eczema Association or members of its Scientific Advisory Board. Flow diagrams for each search are available in the appendices.

From the data in these tables, narrative reviews were constructed for each topic. Not all relevant articles were included in the narrative review – only those most relevant with high-quality data were included. The tables containing the original information extracted for all articles are available in the appendices for the reference of any interested parties. Some articles and other resources that did not meet inclusion criteria, and thus were excluded from the tables, were included in the narrative reviews if they were important from an advocacy standpoint.

Section V of this report provides preliminary results of a pilot study using social media monitoring to determine what is being discussed about eczema on social media. The methods for this study are reported in Section V.

### III. Quality of life in atopic dermatitis

AD has a major impact on the quality of life (QoL) of patients and their families. In this section we will examine the impact of AD on the QoL of patients in different age groups followed by the impact of AD on the QoL of families of eczema sufferers. QoL can be studied in many different ways, including qualitative interviews and through the use of validated tools designed to measure the impact of diseases on QoL. While numerous studies have been published that study QoL in AD, this section focuses on studies that describe the impact on QoL qualitatively or compare QoL in AD to other conditions using quantitative methods. Other articles not highlighted here can be found in appendices, which will be made available upon request.

#### *QoL in children with AD*

In a study published in *Pediatrics* in 2003, Chamlin et al. interviewed the parents of 26 children with AD (mean age 23 months) to determine how AD impacts the QoL of these young patients.<sup>1</sup> They divided their findings into 4 domains: physical health, emotional health, physical functioning and social functioning. In that paper they list the impacts of AD mentioned by at least 20% of participating families. Impacts on physical health include itching and scratching, sleep, pain, bleeding and dietary limitations. Emotional impacts included behavioral problems, irritability, crying and problems with treatments. Physical functioning was impaired via clothing restrictions, interference with activities such as bathing, playing (especially outdoors) and swimming and having to hold children's hands to prevent scratching. One parent said, "I have to hold him all of the time. I can't drive because I have to hold his hands to keep him from scratching."<sup>1</sup> Social functioning was impaired as parents noted that both adults and children avoided interacting with children with AD. One parent was quoted as saying "Everyone wants to play with our other child. They stay away from this infant. Parents tell their kids to stay away."<sup>1</sup>

In other studies, consequences of AD that have been found to be most impactful on QoL in childhood are itching and scratching, impacts on sleep, treatment, sports and embarrassment related to the condition.<sup>2-6</sup> A Swedish birth cohort study assessed overall health-related QoL using the EQ-5D questionnaire and compared participants with eczema (n=508) to participants without (n=2648) at age 8.<sup>7</sup> Overall health

### Quality of life

- The impact of AD on QoL in childhood is comparable to other chronic diseases such as renal disease, cystic fibrosis and asthma
- The impact of AD on QoL in adulthood is similar to that of psoriasis
- AD impacts the QoL of patients' families, including impacts on parental sleep and emotional distress

state scores (out of 100) were lower for those with eczema than those without (mean 92.2 vs. 95.4,  $p < 0.01$ ). Specific areas impacted by AD more than controls were interference with usual activities (3.1% vs. 1.4%,  $p < 0.01$ ), pain or discomfort (16.0% vs. 4.5%,  $p < 0.01$ ) and anxiety or depression (11.0% vs. 5.8%,  $p < 0.01$ ). There was no significant difference between those with eczema and controls with regards to mobility or self-care. Decreased QoL has also been associated with increased depressive and anxious symptoms in children in other studies as well.<sup>8</sup>

QoL does not necessarily correlate with disease severity for all patients, but many studies have found that, in general, as AD severity increases in children, so does the detriment to QoL.<sup>2,5,9-14</sup> Specifically, QoL has been correlated with itch intensity.<sup>15</sup> Interestingly, decreasing QoL also correlates with fear of corticosteroids,<sup>10</sup> which can have a major impact on the effectiveness of AD treatment. Studies have compared QoL in boys and girls with AD, with some reporting more of an impact in girls compared to boys<sup>16,17</sup> and others finding no difference.<sup>14,18</sup>

It can be difficult to compare QoL across different diseases, as generic QoL tools often fail to capture the impact specific diseases have. However, Beattie et al. performed a study using the Children's Dermatology Life Quality Index (CDLQI), a skin specific instrument, and the Children's Life Quality Index (CLQI), a generic instrument, to compare QoL among children aged 5-16 years old with chronic skin diseases and other chronic diseases.<sup>19</sup> In that study there were 106 patients with generalized eczema, with a mean age of 7.75 years. Other chronic diseases included in the study were cerebral palsy, renal disease, cystic fibrosis, urticaria, asthma, psoriasis, epilepsy, enuresis, diabetes, alopecia, localized eczema, acne and nevi. Using the CDLQI, psoriasis and generalized eczema had the most impact on QoL among chronic skin diseases (mean scores 9.17 and 9.14, respectively). Using the CLQI, generalized eczema had the 2<sup>nd</sup> largest impact on QoL (mean score 11.9), following only cerebral palsy (13.8), among all chronic diseases. Scores were similar in patients with renal disease (11.75), cystic fibrosis (11.4), urticaria (10.0), asthma (10.0) and psoriasis (9.6). Studies comparing CDLQI scores in AD and vitiligo have had conflicting results, with one study finding QoL to be worse in vitiligo<sup>20</sup> and another finding it worse in AD.<sup>21</sup> Children with AD have been found to have worse skin-specific QoL than controls with morphea (median CDLQI score 4 vs. 2,  $p = 0.045$ ), but the two diseases had comparable overall health-related QoL.<sup>22</sup> In a recently published meta-analysis of QoL in skin diseases measured with the CDLQI, mean CDLQI scores were 8.5, higher than those for other chronic skin diseases psoriasis (8.0) and vitiligo (6.5).<sup>23</sup>

### *QoL in adults with AD*

AD can impact the lives of adult patients in many ways. Aspects of QoL reported to be most affected by AD are symptoms and emotional impact, with less of an impact on social functioning.<sup>24</sup> However, social functioning can be impacted as well – in a survey of college students (n=336), 25.5% of participants with eczema felt that it impaired their social life.<sup>25</sup> AD can also limit simple every day activities. One community-based survey of 559 AD patients in the US found AD to impact choice of clothing in 35% and limited shaving or wearing makeup in 32%.<sup>26</sup> Impaired QoL in adults with AD is associated with depressive and anxious symptoms, as well as increased body consciousness.<sup>27,28</sup> Additionally, decreased QoL in AD is associated with decreased work productivity.<sup>29</sup>

Impaired QoL in AD is correlated with disease severity, increased itch and sleep disturbance.<sup>11,15,24,28,30-32</sup> However, the association of QoL with objective disease severity has not been consistent in the literature. In a study of 54 patients with AD in the Netherlands, DLQI (Dermatology Life Quality Index – a common tool for measuring QoL in skin diseases) was not correlated with the objective SCORAD (a tool used to measure AD severity) or the SASSAD (Six area, six sign atopic dermatitis severity score).<sup>33</sup> While that study found a correlation between DLQI and SCORAD after 6 weeks of treatment ( $r=0.34$ ,  $p=0.02$ ), changes in severity scores were associated with only small changes in DLQI scores. Another study found that DLQI scores correlated with severity in women but not in men.<sup>34</sup> Involvement of body areas visible to the public, such as the face, and genital involvement have been found to be predictors of impaired QoL in AD.<sup>30,32,34</sup> These above findings suggest that in adults with AD, factors outside of the severity of the disease itself have a significant impact on QoL.

As in children, QoL of adults with AD has been compared to the impact on QoL of other diseases. Kiebert et al. used the Short Form (36) Health Survey (SF-36), a generic health status measure, to assess QoL among 107 AD patients at a tertiary care center in Detroit, and compared their results with previously published SF-36 scores in the literature.<sup>17</sup> While their patients may have been skewed to the moderate to severe end of the AD spectrum, their results are still informative. While physical component scores of the SF-36 were higher (indicating better QoL) in AD compared with patients with clinical depression, type 2 diabetes and hypertension, mental component scores were lower in AD compared to type 2 diabetes and hypertension (all  $p<0.0001$ ). Only clinical depression had a lower mental component score than AD ( $p<0.0001$ ). There was no statistically significant difference between DLQI scores ( $p=0.48$ ) and SF-36 physical component scores ( $p=0.60$ ) in AD and psoriasis, but SF-36 mental component scores were significantly lower in AD (46.2 vs. 50.9,  $p<0.0001$ ).



A large community-based German study used the DLQI to assess QoL in adult patients with AD (n=1678), and were able to compare their results with a study that used similar methodology in adults with psoriasis (n=2009).<sup>35</sup> The mean DLQI score in patients with AD was 8.5, compared with 7.5 in psoriasis (p<0.0001), and the proportion of AD patients with DLQI >10 was higher in AD (32.1%) than psoriasis (28.2%, p=0.012) (higher DLQI scores indicate worse QoL).

A German population-based study examined QoL in AD, psoriasis, hidradenitis suppurativa, acne, “hand rash” and controls without skin disease.<sup>36</sup> In this study, skin-specific QoL was impacted less in AD compared to other skin diseases. However, all skin diseases in this study did not appear to have a large impact on QoL. For example the mean DLQI score in AD was 2.4 and the mean DLQI score in hidradenitis suppurativa, a severe skin disease with a major QoL burden, was just 3.7. The significantly lower DLQI scores in this study compared to others is likely due to this study’s use of the general population as its source of patients, rather than patients at physicians’ offices, potentially leading to a higher proportion of cases with mild disease.

Evers et al. used the Impact of Rheumatic Disease on General Health and Lifestyle (IRGL) tool to assess psychological distress and QoL in 120 patients with AD and 128 with psoriasis.<sup>37</sup> While psychological distress and social functioning did not differ between the two diseases, AD had significantly higher impacts on daily life (p<0.01). A French study compared QoL in AD (n=386) with psoriasis (n=408) and chronic urticaria (CU; n=367) using the VQ-Dermato questionnaire.<sup>38</sup> Overall QoL scores were significantly worse in AD (P<0.0001) than in both psoriasis and CU. After adjusting for age, sex and disease severity, AD had better self-perception scores than psoriasis but worse than CU (P<0.001 and P<0.01, respectively) and had slightly better daily living scores than CU but worse than psoriasis (P<0.01 and P<0.0001, respectively). Notably, AD had significantly worse scores in the physical discomfort domain than both psoriasis and CU (P<0.01 and P<0.001, respectively).

A study of nurses in Taiwan compared QoL as measured by the SF-36 in 90 people with AD, 205 with non-atopic hand eczema and 837 controls.<sup>39</sup> While participants with AD had worse scores on social functioning, bodily pain, vitality, mental health and general health components of the SF-36 compared with controls, there were no differences between participants with AD and those with non-atopic hand eczema on any SF-36 component.

A Korean study compared QoL in patients with AD and patients with vitiligo using the DLQI. QoL was significantly worse in AD (DLQI: 12.8) compared to vitiligo (DLQI: 7.6, p<0.001).<sup>40</sup> While much of that

difference may be related to AD being a symptomatic skin condition and vitiligo being asymptomatic, AD patients also had worse scores on other indices in that study, including Beck's Depression Inventory ( $p<0.01$ ), Spielberger State-Trait Anxiety Inventory ( $p<0.05$ ) and the Interaction Anxiousness Scale ( $p<0.01$ ). There was no statistically significant difference between AD and vitiligo on a body consciousness questionnaire used in that study.

An alternative way to measure the impact a disease has on QoL is willingness to pay. That is, the amount of money a patient would pay to be disease-free. A study in Germany of patients enrolled in an AD patient support group investigated willingness to pay in adults with AD, and was able to compare their results to those for other skin diseases from previous studies.<sup>30</sup> In total, there were 384 participants with AD. On average, they were willing to pay €1,884 (range €0-1,000,000) for sustainable healing. This compared to an average of €2,879.8 for rosacea and €7,359.7 for vitiligo.

#### *QoL in families and partners of AD patients*

The impact of AD on QoL is not limited to patients themselves. In a large multinational study, 30% of patients and caregivers believe that AD impacts other members of their household.<sup>41</sup> Parents of young children with AD can be particularly burdened by a lack of sleep and by the emotional toll seeing their child suffer can take. In a German study of parents of children with AD, maternal mental health scores on the Short Form (12) Health Survey (SF-12), a generic measure of overall health, were significantly impaired on average compared to normative standards, indicating that AD may have a significant impact on the mental health of parents.<sup>42</sup> Lebovidge et al. presented data from their multidisciplinary eczema clinic which provides access to psychologists for patients with AD (generally moderate to severe) and their families.<sup>43</sup> Nearly 70% of patients and their families were seen by psychologists, 43.8% of whom went on to receive parental psychoeducation.

In their qualitative study of the impact of AD on young children and their families, Chamlin et al. listed specific impacts of AD reported by more than 20% of the parents they interviewed.<sup>1</sup> Their results demonstrate the pervasiveness of the impact of AD on the family unit. Reported impacts of AD on parents include exhaustion and sleep deprivation, embarrassment about their child's appearance, frustration, helplessness, sadness and depression and guilt. Parents also reported strain on their relationship with their spouse, something that was echoed in a vignette from Dr. Gil Yosipovitch's book on itch (see section III.i).<sup>44</sup> In addition to impacting marital relationships, participants in Chamlin's study reported that AD negatively affected their relationships with other friends and relatives.<sup>1</sup> Parents also reported worry about their children making friends and their self-esteem and costs of care. Parents conveyed that treatments

were time-consuming and that AD led to more housework and the family staying home more, and impacted parents' decision whether or not to work. It even led to families avoiding taking family photos. Another qualitative study in the UK found that parents of children with AD sometimes altered activities (such as swimming and going to the beach) because of their child's eczema, and some worried that their child's future might be impacted by AD (eg. bullying and development).<sup>45</sup>

In a study of 270 AD patients and their parents in Chicago and San Francisco, 61% of parents said that their own sleep was disturbed because of their child's AD.<sup>46</sup> A UK study of 26 families with a child with AD and 29 families with a child with asthma aimed to compare the two diseases in terms of their impact on parental sleep.<sup>47</sup> Mothers spent 78 minutes per night and fathers spent 90 minutes attending to children with AD, compared to no time for parents of children with asthma. Maternal sleep disruption was correlated with younger child age ( $\rho=0.42$ ,  $p=0.002$ ) but paternal sleep disruption was not ( $\rho=0.28$ ,  $p=0.09$ ). Maternal sleep disruption was associated with higher depressive and anxious symptoms as measured by the Hospital Anxiety and Depression Scale (HADS), and paternal sleep disruption was associated with higher anxious but not depressive symptoms.

The Dermatitis Family Impact questionnaire (DFI) was developed as an objective means to measure the impact of AD on families.<sup>48</sup> Using data from the DFI, researchers have found that impact of AD on family QoL increases with disease severity.<sup>4-6,12,49-51</sup> However, even mild AD can have an impact on family QoL.<sup>6,51</sup> The impact of patient age and gender on DFI scores has not been well-established, with conflicting reports.<sup>4,16,52</sup> Consistently high scoring items on the DFI (indicating larger impact) are costs, sleep, food preparation and parental emotional distress.<sup>4,5,49,50,53,54</sup> DFI scores are also correlated with poor maternal mental health, as measured by the SF-12.<sup>5</sup>

While the impact of AD on the families of children with AD has been relatively well-studied, data on the impact AD has on the families, and specifically on the partners, of adult patients with AD is scant. Misery et al. studied 156 partners of adult patients with AD in France.<sup>32</sup> In that study, 32% of partners of AD patients felt that their partner's AD interfered with their sex life at least sometimes, and the impact on sex life was correlated with AD severity ( $p=0.005$ ). Partners' QoL, as measured by the SF-12, and their sleep, as measured by the Epworth scale, were not correlated with AD severity.

#### *Summary and directions for future research*

Numerous studies have examined the impact of AD on QoL, and it is clear that AD is quite burdensome with regards to QoL. Areas where further research is needed include more studies examining the QoL of

partners and families of adults with AD. Additionally, further studies are needed to investigate the QoL of patients and their families outside of healthcare settings, particularly tertiary care centers. This could include population-based assessments of QoL across the AD severity spectrum in children, adults and their families.

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## I.i. Itch

Itch, or pruritus, is the primary symptom of AD, and one that drives much of the burden of disease. Underscoring its importance, itch is an essential feature in the UK Working Party diagnostic criteria for AD,<sup>1</sup> and is a major criterion for the diagnosis of AD in the Hanifin and Rajka criteria.<sup>2</sup> In the following sub-sections, we will discuss medical and non-medical literature related to itch in AD, with a focus on qualitative aspects of itch and the impact itch has on AD patients' lives.

### *Describing itch in AD*

A few researches have sought to characterize the subjective experience of itch in AD. A web-based questionnaire survey of 304 participants with AD recruited from the NEASE (now National Eczema Association; NEA) website found that 91% of participants reported experiencing itch at least once per day, and that 68% experienced it 5 times per day.<sup>3</sup> While itch is by definition an unpleasant sensation, this study described that unpleasantness further, with 98% of respondents described their itch as 'annoying', 'bothersome', 'unpleasant' or 'bothering'. In contrast to that unpleasant sensation, 63.4% of respondents described the act of scratching as pleasurable, partly explaining why eczema sufferers continue to scratch despite the knowledge that it can make their AD worse and potentially lead to complications such as infection. A German study of 1678 AD patients found that 35.8% of AD patients find themselves often or always scratching until they bleed.<sup>4</sup> In addition to the itch itself, participants in that study found that itch was often associated with pain (58.6%), sweating (25.3%), a heat sensation (53.3%) or a cold sensation (6.6%).

Using similar methodology to the web-based survey described above in a group of Chinese patients, Yosipovitch et al. found that 100 out of 100 participants were experiencing itch at the time of the survey, and that 87% had daily itch episodes.<sup>5</sup> In that survey, AD patients were asked to rate, using a visual analogue scale, how intense their itch was at its worst. They were asked to do the same for the itch they experience with a mosquito bite. Amazingly, the itch rating for AD was nearly double that for mosquito bites, helping to put the sensation of itch in AD in perspective for people without a chronic skin disease.

## Itch

- Itch is the most common symptom of AD
- The intensity of itch may be double that of the experience of itch from a mosquito bite
- Itch in AD has been shown to correlate with poor overall health related quality of life
- Itch in AD has been associated with mental health problems, including suicidal ideation



A French study compared the qualities of itch in AD with that of psoriasis, non-atopic eczema, scabies and urticaria.<sup>6</sup> Similar to the findings from Dawn et al.,<sup>3</sup> Brenaut et al found that itch in AD was associated with more sweating ( $p < 0.05$ ) and pain ( $p < 0.005$ ) compared to the other dermatoses.<sup>6</sup> It was also more associated with headache ( $p < 0.05$ ), stinging sensation ( $p < 0.05$ ), pinching sensation ( $p < 0.05$ ) and stabbing sensation ( $p < 0.05$ ). Factors that were found to exacerbate itch in AD in that study were sweating (80%), skin dryness (93%) and physical activity (71%). Not only did this study find that scratching was pleasurable in 69% of AD participants, but scratching was found to be more common in AD compared to the other diseases.

Another study that surveyed members of the NEASE and the National Psoriasis Foundation found that AD patients were more likely to experience itch compared with psoriasis patients (OR=9.3, 95% CI 3.4-25.6) and that itch episodes were more intense in AD (8.2/10 vs. 6.8/10,  $p < 0.001$ ).<sup>7</sup> Evers et al. also compared scores on an itch scale between 128 patients with psoriasis and 120 patients with AD and found that itch scores were higher in AD (10.2 vs. 8.2 out of 16,  $p < 0.0001$ ).<sup>8</sup>

#### *The specific impact of itch on QoL*

Itch is the predominant symptom in AD, and thus is a preeminent factor in tools used to assess symptoms in AD, such as the Patient Oriented Eczema Measure (POEM).<sup>9</sup> Additionally, itch is thought to be such an important factor in quality of life (QoL) in AD and other skin diseases that it is often assessed as part of commonly used QoL measurement tools such as the DLQI and Skindex.<sup>10,11</sup> As such, it can be difficult to separate out the impact itch has on other aspects of QoL. However, numerous studies have attempted to tease out that information and it will be presented here.

A German cross-sectional survey study of 384 AD patients looked at the relationship of itch, QoL, general state of health and willingness to pay for a cure for AD.<sup>12</sup> Itch was measured with a 4-point Likert scale, skin-specific QoL with the DLQI and overall health-related QoL with the EQ-5D. While itch in AD was not associated with a willingness to pay for a cure, it was predictive of adverse skin-specific (regression coefficient  $\beta = 0.269$ ,  $p < 0.001$ ) and general health-related quality of life ( $\beta = -0.334$ ,  $p < 0.001$ ).

A Danish study also examined the correlation between itch intensity and QoL.<sup>13</sup> In 101 participants with AD (66 adults and 35 children), itch was assessed using a visual analogue scale and QoL with the DLQI and SF-36 for adults and the Children's DLQI (CDLQI) for children. Not only was itch correlated with the skin-specific DLQI ( $r = 0.62$ ,  $p < 0.0001$ ) and CDLQI ( $r = 0.60$ ,  $p < 0.0001$ ), but it was also correlated with

the physical ( $r=-0.28$ ,  $p<0.05$ ) and mental ( $r=-0.27$ ,  $p<0.05$ ) components of the SF-36, suggesting that itch can have a profound impact on overall health-related quality of life and general health perception.

It is not surprising, then, that in a German study to assess treatment goals and satisfaction with treatment in 216 patients with AD, 35.5% of participants named treating itching and burning as the most important treatment goal, and 89.9% rated it as a top-5 treatment goal.<sup>14</sup>

#### *Psychological and social impact of itch*

A Norwegian study published in 2014 examined links between eczema, social function and mental health.<sup>15</sup> Using data from a cross-sectional survey with 3553 participants, 346 of whom had eczema, they found some staggering results. In participants with current eczema, 69% reported itch in the last week and 15.8% reported “very much” itchy skin in the last week. Participants with current eczema and itchy skin in the last week had a 23.8% prevalence of suicidal ideation in the last week, 22.1% prevalence of mental health problems on the Strength and Difficulties Questionnaire (SDQ) and 42.4% prevalence of mental distress on the Hopkins Symptoms Checklist (HSCL-10). When compared with controls without eczema, current eczema associated with itch in the last week had increased odds of suicidal ideation (OR=3.57, 95% CI 2.46–5.67), mental health problems (OR=2.57, 95% CI 1.59–4.15) and mental distress (OR=2.53, 95% CI 1.66–3.84). These associations were not significant in subjects who reported a current diagnosis with eczema but no itch in the last week, suggesting that itch plays a central role in psychological and mental distress in eczema patients. Interestingly, that study found no association between eczema with itch and social problems (attachment, thriving at school, bullying or romantic relationships) other than boys with eczema and itch having an increased risk of never having been in a romantic relationship.

Other studies have examined links between itch, stress and psychological morbidity. Stress, as measured by both the Holmes and Rahe Social Readjustment Rating Scale (SRRS) and Stress Self-assessment verbal rating Scale, and depressive symptoms, as measured by the Beck Depression Inventory (BDI) are associated with itch visual analogue scale scores in AD.<sup>16</sup> In a separate study itch was correlated with psychological distress ( $r=0.23$ ,  $P<0.05$ ), fatigue ( $r=0.54$ ,  $P<0.001$ ) and helplessness ( $r=0.31$ ,  $P<0.001$ ), although in multiple regression analyses itch did not predict psychological distress in AD.<sup>8</sup> A Korean study found that state ( $r=0.573$ ,  $p<0.05$ ) and trait ( $r=0.525$ ,  $p<0.05$ ) anxiety scores on the Spielberger State-Trait Anxiety Index (SSTAI) were increased in AD patients with higher scores on an itch visual analogue scale.<sup>17</sup>

Itch has been shown to interfere with AD patients' sex life as well. Among 172 Spanish adults with AD, itch was found to interfere with sexual desire in 23.5% and sexual function in 18.1%.<sup>18</sup>

While thus far we have suggested that itch in AD may be a causal factor for psychological morbidity, psychological distress has also been shown to trigger itching. Langenbruch et al. found that emotional factors or stress caused increased itching in 73.1% of adults with AD.<sup>4</sup>

#### *Itch and sleep*

The topic of sleep in AD will be covered in further detail in section III.iii. Briefly, though, we will discuss the specific impact of itch on sleep here. Using an Itch Severity Scale, a cross-sectional study in Spain examined links between itch and sleep in childhood and adult AD. Itching was found to frequently or nearly always wake up children (63%) and adults (73.5%) in the majority of cases with AD.<sup>18</sup> A Taiwanese study that looked at sleep in children with AD using questionnaires, actigraphy and polysomnography found that itch, as measured by the visual analogue scale component of the SCORAD was correlated with lower sleep efficiency ( $r=-0.54$ ,  $p<0.001$ ) and increased sleep fragmentation ( $r=0.5$ ,  $p<0.001$ ).<sup>19</sup> Another study in children with AD found that scores on an itch scale were significantly correlated with difficulty sleeping ( $r=0.44$ ,  $p<0.05$ ). In a large cross-sectional study of 1678 German adults with AD, sleeplessness often or every night due to itch occurred in 26.6% of participants.<sup>4</sup>

#### *The individual impact of itch*

While the data described above provides some context for the impact itch has on patients with AD on an aggregate level, it does not tell the whole story of what it means to live with itch. As a supplemental resource, we recommend the book *Living with Itch: a patient's guide*.<sup>20</sup> Therein, patients tell stories in the first person about how itch from various diseases, including AD, have impacted their lives. This includes the story of a father, to the detriment of his marriage, bringing his young son with severe AD into bed with him to prevent him from scratching. Another man, an AD patient himself, tells of the embarrassment of living with visible scratch marks from his uncontrollable scratching. He describes binding his hands when he slept to prevent himself from scratching in the night and of the stress of travelling without access to his usual means of controlling his AD.

#### *Limitations and suggestions for future work*

The essential nature of itch in AD has limited the investigation of itch as an independent driver of decreased QoL and psychological morbidity. Therapeutics in development for AD may target itch specifically, rather than inflammation, and, as such, understanding the direct impact itch has on QoL in

AD, independent of other measures of disease severity, will be important. Further studies examining links between the frequency and intensity of itch and QoL, psychological morbidity and sleep are warranted. Specifically, studies in the North American patient population would be welcome, as the majority of the literature cited in this report is derived from European and Asian studies. Additionally, while *Living with Itch: a patient's guide* is an excellent resource,<sup>20</sup> formal qualitative studies on the impact of itch in AD, particularly in adult patients, would be beneficial for clinicians, researchers and policy-makers to better understand the impact this symptom has on patients.

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### III.ii. Pain

#### *Overview of currently available literature*

While itch is the predominant symptom of AD, patients experience other symptoms as well. In their development of the Patient Oriented Eczema Measure (POEM), a tool to assess patient-reported symptoms in AD, Charman et al. interviewed 35 AD patients who were asked to identify the symptoms of their disease. In addition to itch, patients reported soreness or pain, sleep disturbance, redness of the skin, bleeding, weeping/oozing, dryness/roughness, flaking and cracking and tightness of the skin.<sup>1</sup> In a subsequent survey of 200 hospital- and community-based patients, including children, soreness was “never” experienced by only 7.9% of participants, and was experienced “most days” or “every day” 26.7%.<sup>1</sup> Among those who experienced soreness most days or every day, 84.1% were bothered by it “much” or “very much”.

In 2002, Yosipovitch et al. published findings of a survey regarding the characteristics of itch among 100 adolescent and adult Chinese patients with AD.<sup>2</sup> They found that 45% of participants reported pain in the pruritic areas of their eczema. Women were more likely than men to experience pain. Using similar methodology, pain was found to be associated with AD in 58.6% of 304 participants from the NEASE.<sup>3</sup> In that study, pain was significantly correlated with itch intensity. In another survey (n=284), pain was the 3<sup>rd</sup> most commonly reported symptom in AD (58% of participants), after only itch and sleep disturbance.<sup>4</sup> Finally, an Estonian study found that patients with AD had worse scores on the pain subcomponent of the RAND-36, a generic quality of life instrument.<sup>5</sup> However, it was not clear if the pain for those participants was directly related to their eczema or if it was a different pain they were experiencing.

#### *Limitations of currently available data*

Data on the impact of pain on patients with atopic dermatitis is sparse, with only 4 relevant references found in our search. None of the cited studies directly examined the impact of pain on eczema sufferers' QoL.

## Pain

- AD is painful in many patients with AD and is very troubling for them
- The impact pain has on QoL has not been adequately assessed

### *Suggestions for future work*

While itch is the predominant symptom of AD and is known to have a major impact on QoL, pain occurs in many patients with AD. Despite this, little is known about the impact pain and other less-studied symptoms have on AD patients. Future research should focus on:

- the prevalence of pain as a symptom in children with AD;
- the impact pain has on QoL in AD; and
- whether or not the impact of pain is captured by currently available tools for the measurement of patient-reported diseases severity and QoL in AD.

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### III.iii. Sleep

Sleep disturbance is a well-documented consequence of AD and has been reported in various forms in all ages. In open-ended interviews with parents of children with AD in San Francisco, sleep disturbance was mentioned as a problem by 22 of 23 parents.<sup>1</sup> Similarly, in a survey of adult members of an AD patient advocacy group in the UK, sleep difficulties were the 2<sup>nd</sup> most commonly cited symptom (66%), after itching.<sup>2</sup> In a population-based survey of 116,202 Americans, Hanifin and Reed found that 66% of participants with AD experienced sleep disturbance, and that it was frequent in 10%.<sup>3</sup>

In the following subsections, we will discuss observational studies that have linked AD with sleep disturbance in infants and children, followed by adults. Then we will examine some of the downstream consequences of sleep disturbance for eczema sufferers.

#### *Children*

A large population-based survey of American children found children with eczema had a higher prevalence of impaired sleep occurring  $\geq 4$  nights per week compared to children without eczema (10.8% vs. 7.6%,  $P < 0.0001$ ).<sup>4</sup> That same study found a gradient of sleep disturbance with severity, with 22.2% of subjects with self-reported severe AD having  $\geq 4$  nights/week of impaired sleep compared to 10.0% in subjects with mild-moderate disease ( $P = 0.003$ ). In a large multinational survey of patients with moderate to severe AD, children aged 2-13 and 14-17 had, on average, 5.0 and 11.7 nights, respectively, disturbed by a given eczema flare.<sup>5</sup> With an average of 8.7 and 7.5 flares per year, that amounts to 43.5 and 87.75 nights of disturbed sleep per year due to eczema flares in those age groups.

AD can have its onset in early infancy, and sleep disturbances secondary to AD have been documented very early on in life. In a study of infants aged 0-6 years-old in Chicago and San Francisco, Chamlin et al. reported that 68% of parents reported some sleep disturbance in their children with AD.<sup>6</sup> They also found that as AD severity increased, as defined by increasing SCORAD scores, child and parental sleep disturbance increased ( $p < 0.001$ ). The relationship between disease severity and childhood sleep

## Sleep

- Sleep disruption is common in children and adults with AD and has been documented by patient- and parent-report and objective measures such as actigraphy and polysomnography
- Sleep disturbances can have a major impact on the lives of eczema sufferers, including associations with cognitive and behavioral difficulties, including ADHD, and physical health comorbidities including fracture risk



disturbance was not significant when multivariate logistic regression was applied, but it approached significance (OR=3.9, 95% CI 0.99-15.4).

In a small Italian study, parents reported that 38% of young children with AD stayed awake for between 15 minutes and 1 hour per night, 20% between 1 and 2 hours per night and 11% stayed awake for more than 2 hours per night.<sup>7</sup> In comparison, 95% of children without AD stayed awake for only about 15 minutes per night. In a Japanese cross-sectional study, young children aged 3-41 months old with a history of sleep-related night-time crying were more than 2.5 times more likely to have chronic eczema than children without a history of sleep-related night-time crying (12.4% vs. 4.7%,  $p < 0.05$ ).<sup>8</sup>

AD can impact many components of sleep and fatigue in children. A cross-sectional survey based out of a tertiary care center in Australia found that children with AD had disordered initiation and maintenance of sleep as well as increased rates of daytime sleepiness.<sup>9</sup> An Israeli cross-sectional study found increased bedtime resistance, sleep duration, parasomnias and daytime sleepiness in AD patients.<sup>10</sup> All of these negative elements of sleep in AD can lead parents to co-sleep with their children, which has been reported with 30-70% of children with AD.<sup>1,6</sup>

In addition to self- or parent-report of sleep patterns and disruption, researchers have used objective tools such as polysomnography and actigraphy to assess the sleep patterns of children with AD. These objective measures have found increased sleep fragmentation in children with AD.<sup>11,12</sup> In a comprehensive sleep study comparing children with AD to controls, actigraphy demonstrated that patients with AD had longer sleep latency, time in bed, time to wake after falling asleep and poorer sleep efficiency.<sup>12</sup> In that same study polysomnography revealed decreased non-REM sleep, sleep efficiency and increased limb movements in subjects with AD. They also found that increasing AD severity, measured by the SCORAD, was correlated with lower sleep efficiency ( $r = -0.55$ ,  $p < 0.001$ ), shorter total sleep time ( $r = -0.29$ ,  $p = 0.017$ ), longer time to wake after sleep onset ( $r = 0.62$ ,  $p < 0.001$ ) and increased sleep fragmentation ( $r = 0.70$ ,  $p < 0.001$ ).

Sleep-disordered breathing has been investigated with AD with more mixed results. In a survey of parents of preschoolers in Singapore, subjects with AD were more likely to snore  $\geq 3$  times per week (9.7% vs. 5.6%,  $p < 0.0001$ , OR= 1.80, 95% CI 1.28–2.54) than participants without AD.<sup>13</sup> In an Australian cohort of children 3-84 months old with a history of allergic rhinitis, having current eczema was associated with increased snoring (OR=2.29, 95% CI 1.02–5.13), but not with snoring  $\geq 3$  nights per week.<sup>14</sup> A Japanese survey found parent-reported AD was associated with mouth breathing during the daytime (OR=2.19,

95% CI 1.15–4.15) and during sleep (OR=2.71, 95% CI 1.40–5.25).<sup>15</sup> A large Taiwanese study using a medical claims database found that patients with obstructive sleep apnea (OSA) were more likely to develop AD than controls (adjusted hazard ratio (aHR)=1.50, 95% CI 1.15–1.95), with the effect being most significant in children 0-18 years old (aHR=4.01, 95% CI 1.57–10.26).<sup>16</sup> However, a contrasting study from a single tertiary care center in Greece found no association between AD and OSA (OR = 0.89, 95% CI 0.62–1.30) or adenotonsillar hypertrophy (OR = 1.00, 95% CI 0.67–1.50) in children.<sup>17</sup> Another small study found no differences in AD patients compared to controls with regards to sleep-disordered breathing in general.<sup>10</sup>

### *Adults*

Data from a large US population-based survey found that adults with eczema had increased odds of having short (OR=1.35, 95% CI 1.20–1.51) and long sleep duration (OR= 1.44, 95% CI 1.19-1.74), fatigue (OR=2.97, 95% CI 2.65–3.34) and insomnia (OR=2.36, 95% CI 2.11–2.64) compared to the general population.<sup>18</sup> Another survey of 559 subjects with self-reported AD based on the National Family Opinion household panel in the US found that 27% of participants had sleep disturbance secondary to their skin more than 7 times in the past month.<sup>19</sup> A large international survey of patients with moderate to severe AD found that adults had, on average, 80.4 nights of disturbed sleep due to eczema flares.<sup>5</sup> AD has also been associated with restless leg syndrome, a specific sleep disorder, in adults.<sup>20</sup>

In a German study that examined QoL as a function of willingness to pay for a complete cure from AD, poor sleep was correlated with adverse QoL ( $\beta=0.123$ ,  $p=0.016$ ) and lower state of health ( $\beta=-0.180$ ,  $p=0.001$ ) but, of note, was not correlated with willingness to pay for a complete cure.<sup>21</sup>

As in children, sleep in adults with AD has been investigated with objective measures. Bender et al. administered the Pittsburgh Sleep Quality Index (PSQI) twice, 1 week apart, with actigraphy performed in between to 14 adults with AD and 14 controls.<sup>22</sup> Actigraphy demonstrated lower overall sleep efficiency ( $p=0.03$ ) in AD patients, corresponding to overall lower PSQI scores ( $P=0.0044$ ), with significantly worse scores in awakenings, sleep quality and daytime dysfunction. PSQI scores for sleep latency, duration, efficiency or sleep disturbance were not impaired, though. In another study using actigraphy and polysomnography in adults with AD, sleep efficiency was correlated with scratching and Rajka and Langeland skin scores, but not with an itching visual analogue scale.<sup>23</sup> DLQI scores did not correlate with sleep efficiency in that study.

While one French study using the Epworth scoring system for daytime sleepiness did not find adults with AD or their partners to have impaired daytime sleepiness,<sup>24</sup> the vast majority of evidence points towards AD having a major impact on sleep in adults and children with AD.

### *Consequences of poor sleep*

While the above sub-sections demonstrate the scope of the problem of sleep in AD with regards to prevalence and types of sleep disturbance, they do not speak to the impact sleep impairment can have on the lives and health of eczema sufferers.

Sleep can mediate a number of psychological, behavioral and cognitive effects in patients with AD. At a multidisciplinary pediatric eczema clinic in Boston, difficulty sleeping was associated with an increased risk of requesting to meet with a psychologist.<sup>25</sup> In a group of 21 AD patients and 20 controls without AD in Australia, AD patients were found to have lower IQ scores (91.6) compared to controls (108.6, F test statistic=16.6,  $p<0.001$ ).<sup>11</sup> While there was no significant correlation between polysomnography results and neurocognitive scores in that study, overall Sleep Disturbance Scale for Children (SDSC) scores as well as parental report of excessive somnolence, sleep disordered breathing were correlated with lower IQ scores. In a separate study, Camfferman et al. used structural equation modeling analysis to demonstrate that sleep mediated the effect of AD on the risk for hyperactivity and attention deficit hyperactivity disorder (ADHD) as well as oppositional behavior, but did not impact cognitive problems.<sup>9</sup> The link between AD and ADHD has been supported by a large nationwide German study that found increased odds of ADHD in children with AD with sleeping problems (OR=2.67, 95% CI 1.51-4.71,  $p<0.001$ ), but not in children with AD without sleeping problems (OR=1.24, 95% CI 0.83-1.84;  $p=0.30$ ).<sup>26</sup> Further, in a German prospective birth cohort, infantile eczema with associated sleep problems was associated with a future risk (at age 10) of emotional problems (OR=2.63, 95% CI 1.20-5.76) and conduct problems (OR=3.03, 95% CI 1.01-9.12) as assessed by the German Strength and Difficulties Questionnaire.<sup>27</sup>

Large US population-based surveys have linked poor sleep in subjects with eczema to a number of adverse health consequences. Children with eczema and insomnia had roughly 6 times the odds of having headaches compared to children with neither eczema nor headaches.<sup>28</sup> They were roughly 3 times more likely to have headaches when compared with children with eczema but without insomnia. Children with eczema and poor sleep are also at increased risk for short stature, a finding seen in American and Korean studies.<sup>29,30</sup>

Eczema in combination with fatigue (OR=2.61, 95% CI: 1.91-3.55, P<0.001), sleepiness (OR=2.31, 95% CI: 1.69-3.16) or insomnia (OR=2.62, 95% CI: 1.94-3.55) is associated with increased skeletal fractures or other bone or joint injuries in adults.<sup>31</sup> Interactions have also been found between eczema, fatigue and various cardiovascular risk factors, including hypertension, diabetes and hypercholesterolemia.<sup>32</sup> Finally, when asked about their overall health status, adults in a large survey were significantly more likely to rate their overall health as only poor or fair (OR=8.63, 95% CI: 7.15-10.43) if they had a history of eczema and fatigue compared to respondents with neither.<sup>18</sup> Those odds were also significantly higher compared to participants with only one of either eczema or fatigue.

#### *Limitations and suggestions for future research*

The majority of the research to date on the impact of sleep in AD is cross-sectional, limiting our ability to understand the problem over time. While various studies have demonstrated that AD severity is associated with worse sleep within a population, it would be informative to know whether sleep patterns of individual patients change through cycles of relatively quiescent and flaring skin disease. We also cannot draw any conclusions about how sleep disorders in childhood impact comorbidities in the future.

Longitudinal cohort studies examining how AD patients' sleep patterns and the impact they have on QoL and overall health change over time would be welcome. While the impact of various AD management strategies on sleep is beyond the scope of this report, researchers should continue to use sleep as an important outcome in clinical trials for AD.

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### III.iv. Self-esteem

The impact AD has on self-esteem or self-worth have not been widely studied in the medical literature. This may be because this is a difficult concept to measure or because it is difficult to separate out from the broader concept of QoL. However, one large study did delve into the issue of self-esteem in some detail, in addition to a number of smaller studies.

The International Study on Life with Atopic Eczema (ISOLATE) is a cross-sectional survey study of patients with moderate to severe AD from 8 countries (US, France, Germany, Spain, UK, Netherlands, Mexico and Poland).<sup>1</sup> In that study, 2002 AD patients of all ages or their caregivers completed comprehensive questionnaires about the impact of AD on their lives. ISOLATE found major impacts of AD on self-esteem - 27% of those surveyed had been teased or bullied because of AD, 36% said AD affects their self-confidence and 43% were fairly or very concerned about being seen in public because of their AD. Among adults with moderate-severe AD, 47% reported embarrassment when they are with people they don't know very well and 44% reported embarrassment about their appearance.

An Australian research group conducted an extensive qualitative study on many aspects of the patient perspective in skin disease, including AD, psoriasis and acne.<sup>2-4</sup> These have been published as various themed journal articles, and while most of the data they present cannot be separated out based on specific diagnosis, some features linked directly with AD can be extracted. One article examines the effects on bullying and teasing in skin disease.<sup>2</sup> Thankfully, the majority of skin disease patients did not experience impactful teasing, taunting or bullying, but it did make an impact in a "significant minority" of participants. In these participants, those experiences were connected with self-esteem and self-image. One 21 year-old woman with AD was quoted as saying, "Like high school students can be a bit nasty, I just felt like a bit of a freak, one kid told me once I was a leper, that wasn't very nice [and I felt] disgusting, like as if I didn't already feel like a total freak anyway."<sup>2</sup> The authors noted that among their participants, teasing was more disquieting for AD and acne sufferers than for psoriasis sufferers.

A separate article by Magin et al. examined how the media's portrayal of perfect skin can impact skin disease patients.<sup>3</sup> While they do not give specific details for AD patients, the authors state that a common theme in the study population was that participants felt they could not live up to the ideals portrayed in

## Self-esteem

- AD can have a major impact on self-esteem, which can be related to teasing or bullying
- Future research is necessary to further characterize the impact AD has on self-esteem

the media, and felt stigmatized as a result. In a third publication, Magin et al. examined themes related to sexual functioning in skin disease.<sup>4</sup> They found that both psoriasis and eczema were associated with sexual self-consciousness, poor self-confidence and poor self-image. Nakedness was specifically reported as being “stress-inducing and shaming.”<sup>4</sup>

The following are 2 revealing quotations from AD patients related to their disease’s interference in their sexual life:

“I felt like my femininity was compromised because of it.” (from a 33 year-old woman with AD).<sup>4</sup>

“I was a bride covered in eczema. [It] made me feel really undesirable, very unsexy...I’m sure (my husband) wondered what sort of package he had.” (from a 58 year-old woman with AD).<sup>4</sup>

A UK study of 125 adult members of an AD patient support group examined various psychological, clinical and QoL factors.<sup>5</sup> One scale that they used with their participants was the Rosenberg Self-Esteem Scale, on which higher scores indicate worse self-esteem. Participants in this study had higher mean self-esteem scores compared to previously published controls, indicating lower self-esteem among AD patients. Self-esteem scores were correlated with DLQI scores ( $r=0.38$ ), perceived stigma ( $r=-0.67$ ), anxiety ( $r=0.69$ ), depression ( $r=0.68$ ) and social anxiety ( $r=0.64$ ) (all  $p<0.01$ ). Interestingly, self-esteem was not correlated with disease severity based on self-reported body surface area involvement, age, age at onset of AD or duration of AD.

In a study on QoL in 559 people in the US with AD aged 16 and older, Anderson and Rajagopalan used the Dermatology Specific Life Quality (DSQL) questionnaire which has a self-perception sub-scale.<sup>6</sup> They found that scores on that sub-scale worsened as patient-reported AD disease severity worsened ( $p=0.001$ ). Self-perception scores were weakly correlated with various other potential surrogates of disease severity, including out of pocket non-prescription medication costs ( $r=0.15$ ,  $p=0.0005$ ), sleep disturbance ( $r=0.33$ ,  $p=0.0001$ ) and the number of days the AD sufferer was symptomatic in the last month ( $r=0.23$ ,  $p=0.0001$ ). Thirty-one percent of respondents with severe disease reported often or always experiencing frustration, anger and embarrassment due to AD.



While AD has been consistently associated with increased rates of overweight and obesity, the reason for these associations are poorly understood.<sup>7</sup> We hypothesized that, given the impact AD has on self-esteem, overeating might be a further consequence of AD that contributes to weight gain in AD patients and conducted a literature search on the subject. However, no relevant studies were found in that search.

#### *Limitations and directions for future research*

Our review of the medical literature did not reveal many studies that directly examined self-esteem in AD. However, ISOLATE provides very important insights into the scope of the impact AD has on self-esteem, particularly in patients with moderate to severe disease.<sup>1</sup> However, as with itch, further qualitative studies would be welcome, particularly in North American AD patients of varying severities, to determine in more detail the impact AD has on self-esteem. Additionally, studies that examine a potential association between AD and overeating would be welcome. Finally, of the studies in this subsection, only ISOLATE involved participants younger than 16 years-old.<sup>1</sup> The pediatric age group may be particularly vulnerable to problems with self-esteem and so characterization of any self-esteem issues in that population will be important.

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### III.v. Marital status and stability

As was discussed in section III.i, AD is known to have a significant impact on the families of patients. Anecdotally, this can include impacts on intimate relationship or marital stability for partners or caregivers of patients with AD. In previous sections of this report, we referenced the book *Living with itch: a patient's guide*.<sup>1</sup> One patient testimonial in that book details how the day-to-day management of a young boy's severe AD played a role in the separation of his parents.

However, there is virtually no attention paid to this important area in the medical literature. Our search revealed 2 references that examined the impact of marriage on AD. One showed that married AD patients had better disease-related knowledge in some areas compared to non-married patients.<sup>2</sup> Another showed that married people had a higher probability of having high levels of compliance with oral medication for AD compared to non-married patients (there was no difference in level of compliance with topical therapies).<sup>3</sup> No references examined the impact of AD on marital stability.

#### *Suggestions for future research*

Research is needed to clarify whether a relationship exists between marital status or stability and AD.

There are 3 general study types that would be helpful:

1. Qualitative studies. It would be helpful to interview patients or their caregivers and their partners to learn what impact AD has on marital or relationship stability and if any themes emerge.
2. Survey studies. Surveys among larger numbers of patients with AD or their caregivers and their partners to determine quantitatively what impact AD has on intimate relationships.
3. Large studies in the general population to determine if patients with AD or their caregivers have increased rates of marital instability.

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## Marital stability

- We are not aware of any studies that have examined the impact AD has on marital stability or marital status

### III.vi. Social Life

Social life is a very important aspect of QoL and is accounted for in various QoL measures such as the DLQI.<sup>1</sup> The International Study on Life With Atopic Eczema (ISOLATE), a cross-sectional survey study of patients with moderate to severe AD from 8 countries including the US, highlighted the magnitude of the social problems caused by AD.<sup>2</sup> Of the 2002 participants (which included parents of children with AD and adults with AD), 33% felt AD had an effect on their home and social life. In this sub-section we will discuss medical literature related to social life in AD specifically, first in the pediatric age group and then in adults.

#### *Children*

In open-ended interviews with parents of young children (3-69 months old) with AD in San Francisco, social isolation had already been noted at that very young age.<sup>3</sup> Over half of those interviewed stated that adults and other children avoided interacting with their child with AD. Compounding that, parents of children with AD also reported that they themselves limited interactions between their child and family and friends so that they wouldn't have to engage in discussions about the child's skin. Semi-structured interviews with parents of children with AD (5 months- to 12 years-old) in South Africa also revealed that AD leads to social isolation.<sup>4</sup> This was sometimes caused by parents purposefully isolating their children, but parents also noted that their children avoided school because of AD-related teasing.

The impact of AD on the social lives of children has been described in quantitative studies as well. Brenninkmeijer performed a cross-sectional survey of young adults (18-30 years old) who had moderate to severe AD in childhood and compared them with controls of the same age.<sup>5</sup> Using a course of life questionnaire, subjects were asked questions pertaining to social development and social behaviors during their school years. Severity of AD was based on self-report. Severe childhood AD was associated with delayed social development compared to controls without AD ( $p < 0.05$ ) and patients with moderate AD ( $p < 0.001$ ). Severe childhood AD was associated with spending less time with friends and more time with family in primary ( $p < 0.01$ ) and secondary school ( $p < 0.05$ ) and was associated with decreased membership in sports clubs in primary ( $p < 0.01$ ) and secondary school ( $p < 0.001$ ) compared to controls. There was no association between severe AD and number of childhood friends, having a best friend, or

## Social life

- Particularly in patients with more severe disease, AD can have a major impact on patients' social lives
- Parents of children with AD note social isolation in their children very early in life
- In adults, AD can lead to difficulty forming romantic relationships

belonging to a group of friends compared to controls. AD was reported to impact feeling shame among peers (63.6% primary school and 70.0% secondary school), avoiding intimacy (39.1% primary school, 49.1% secondary school), social activities (31.5% primary school, 35.1% secondary school), and sports activities (34.5% primary school, 43.2% secondary school) and led to doing things alone (24.3% secondary school).

Using the Child Behavior Checklist, Park et al. found that scores on the Social Problems subscale were worse in elementary school children with AD compared to elementary school children without AD.<sup>6</sup> Scores on the personal relationships subscale of the Children's DLQI have been shown to correlate with disease severity ( $r=0.65$ ,  $p<0.01$ ).<sup>7</sup> Hon et al. found that very few 5-16 year-old children with AD reported "very much" or "a lot" of impact of AD on their friendships (9%) or teasing and bullying (5%).<sup>8</sup>

However, not all studies have found that AD impacts social life. In a group of Norwegian final year high school students, current eczema was not associated with low attachment to friends, thriving at school, experiencing bullying or never having a romantic relationship.<sup>9</sup> In a sub-group analysis, boys with eczema did have higher odds of never having a romantic relationship (OR=1.93, 95% CI 1.21–3.08). However, there was no stratification by disease severity in this study and it is likely that the impact of AD on the social lives of patients is mostly felt by those on the moderate to severe end of the disease spectrum.

### *Adults*

Adults in the ISOLATE study reported a number of social difficulties associated with AD.<sup>2</sup> Difficulty forming relationships with a partner was reported in 21%, and 12% reported experiencing relationship problems with a partner as a result of their AD. AD caused problems with intimacy, with 42% of adults always or sometimes feeling awkward about a partner touching or seeing their body during an eczema flare.

A survey of college students in California ( $n=336$ ) revealed that a quarter (25.5%) of participants with eczema felt that their skin disease affected their social life.<sup>10</sup> Specifically, they felt they were bullied/teased (21.8%), discriminated against at school/work (3.6%), stared at by others (29.1%), thought of as contagious by others (23.6%), prevented from making friends (12.7%) and had a hard finding a romantic partner (21.8%) because of their eczema. Echoing these sentiments, a qualitative study in Australia found that a "significant minority" of eczema patients, along with psoriasis and acne patients, had negative experiences with bullying, taunting and teasing.<sup>11</sup>

A study from a single institution in Detroit used the SF-36 and DLQI to measure QoL in 107 AD patients over the age of 16.<sup>12</sup> SF-36 social functioning scores were correlated with both severity ( $r=-0.32$ ,  $p<0.001$ ) and total DLQI scores ( $r=-0.44$ ,  $p<0.001$ ). The authors compared the SF-36 social functioning scores from their study to controls from previously published work with different diseases. Social functioning scores were worse in AD than the general population ( $p<0.05$ ) and patients with psoriasis ( $p<0.0001$ ) and hypertension ( $p<0.05$ ), were comparable to patients with type-2 diabetes but were better than for patients with depression ( $p<0.0001$ ).

Evers et al. examined levels of social support and social networks in AD and psoriasis patients using the Impact of Rheumatic Diseases on General Health and Lifestyle (IRGL) questionnaires.<sup>13</sup> AD and psoriasis patients were comparable in their social support and network scores, without significant differences between the two diseases. Within the AD group, perceived social support was negatively correlated with psychological distress ( $r=-0.30$ ,  $p<0.01$ ) and helplessness ( $r=-0.22$ ,  $p<0.05$ ). Perceived social support in AD was not correlated with skin disease severity, itching, fatigue, impact of skin on daily life or social network. Social network scores in AD was not correlated with any of the above parameters.

Wittkowski et al. surveyed 125 members of an AD patient support group in the UK and found that social anxiety, as measured by the Fear of Negative Evaluation scale, was not higher compared to previously published controls without AD and was not correlated with self-report disease severity by body surface area.<sup>14</sup> However, they did find that social anxiety was correlated with poorer QoL as measured by the DLQI ( $r=0.27$ ) as well as reports of stigmatization ( $r=-0.48$ ) and depressive ( $r=0.41$ ) and anxious ( $r=0.66$ ) symptoms (all  $p<0.01$ ). Social anxiety was also associated with decreased self esteem ( $r=0.64$ ,  $p<0.01$ ). Another study examined social anxiety using a different scale, the Interaction Anxiousness Scale (IAS).<sup>15</sup> In that study, which compared 60 AD patients and 60 vitiligo patients to 60 controls, AD was associated with higher IAS scores, while vitiligo was not.

#### *Limitations/future directions*

Several qualitative and quantitative studies on the social impact of AD have been performed, mostly on a cross-sectional basis. Longitudinal studies of the impact of AD over the course of life would be informative.

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### III.vii. Time spent managing atopic dermatitis

In Chamlin et al.'s qualitative study of the impact of AD on children and their families, time-consuming treatments and increased housework were among the important issues identified by parents that impact their QoL (mentioned by  $\geq 20\%$  of parents).<sup>1</sup> In a UK qualitative study of 28 parents of children with eczema, the time required to manage AD was brought up by many parents.<sup>2,3</sup> Parents in that study identified this as a cause of jealousy among siblings of patients with AD.

However, few studies have quantified the amount of time patients and families actually spend managing AD. Below we will discuss two studies that have examined time spent on treatment in AD.

A Danish study at a tertiary care center used parent reports of time spent performing various tasks related to AD management over the week preceding their visit to the clinic.<sup>4</sup> They also reported the time spent in the last 3 months on visits to various healthcare practitioners and the pharmacy, which was converted into time per day. There were 42 children with AD (age range 1-15 years, mean 7.1) included in the study over 65 visits. The total time (mean  $\pm$ SD) spent per day on AD was just over an hour (62.7  $\pm$ 83.2 min). The breakdown of the time per day was as follows: applying topical medications (29.0  $\pm$ 36.2 min); extra laundry (8.8  $\pm$ 17.6 min); avoiding irritants (6.2  $\pm$ 16.3 min); time spent awake at night (15.7  $\pm$ 15.48 min); visiting the pharmacy (1.6  $\pm$ 1.9 min), visiting their general practitioner (0.2  $\pm$ 0.5 min); visiting specialists (0.1  $\pm$ 0.4 min); and visiting the hospital (0.8  $\pm$ 1.1 min). Although the study population included patients of varying severity (as assessed by the objective SCORAD), the average disease severity was skewed to the more severe end of the spectrum. They found that time spent correlated with disease severity, and as such these results are likely an overestimate of the average time spent on managing eczema.

Another study by the same research group examined time spent on treatment in a different setting – an eczema education school (82 participants, mean age 13 years old).<sup>5</sup> No validated severity measure was used in this case, and only a patient-reported non-validated visual analogue scale was used to assess overall disease severity, making it difficult to interpret the relative severity of the AD in this group. The average time spent on treatment per day in this study (17 min/day, 95% CI 1.3-20) was much lower than

## Time managing AD

- Parents of children with AD report that the time required to manage their child's AD is burdensome
- In 2 studies, the average times spent managing childhood AD were 63 and 17 minutes per day
- To our knowledge, there are no studies on time spent managing AD in adult patients

the previously described study. Time spent on treatment was inversely correlated with age ( $\tau=-0.22$ ,  $p=0.007$ ) and positively correlated with parent-report severity ( $\tau=0.21$ ,  $p=0.009$ ) and QoL ( $\tau=0.31$ ,  $p=0.0003$ ).

#### *Current limitations and directions for future research*

Time spent managing AD is understudied. Current estimates of the time required to manage AD are only from 1 country, with significant variability between the results of the two studies to date. One study is biased by its inclusion of more severe patients. Additionally, to our knowledge there are no studies examining time spent on managing AD in adult patients. Future studies should examine time spent on treatment in different settings and in adults.

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## IV. Economic, academic and occupational impact of atopic dermatitis

### IV.i. Economic burden

AD is a costly disease. Management of AD with prescription, over-the-counter (OTC) and alternative treatments as well as visits to physicians, hospitals and other healthcare practitioners costs insurers, governments, patients and families. Lost productivity from AD due to sick days and doctors' visits (absenteeism) and decreased productivity while at work and school (presenteeism) take a financial toll on employers, society, patients and their families. Among skin conditions, eczema has the highest impact on disability-associated life-years worldwide<sup>1</sup> and in the US, eczema ranks 25<sup>th</sup> among all medical conditions in terms of years lived with disability.<sup>2</sup>

The most comprehensive investigation of the economic burden of AD in the US so far came from a special joint report of the American Academy of Dermatology and Society for Investigative Dermatology published in 2006.<sup>3</sup>

That study examined the financial impact of skin disease overall in the US using data from multiple sources, including national surveys and databases as well as published literature. They were able to estimate the costs of individual diseases in the following areas: direct medical costs (including medical visits and medication use), indirect costs (including lost productivity of patients and caregivers and lost productivity due to early mortality) and indirect costs due to impacts on QoL (using a willingness-to-pay model based on previously published DLQI data). All costs were converted to 2004 US dollars.

Based on a prevalence of 15.2 million, the total annual burden of AD in that study was \$4.228 Billion.<sup>3</sup> Direct costs were \$1.009 Billion (inpatient costs: \$6 million; hospital outpatient costs: \$108 million; ED visits: \$105 million; office visits: \$636 million; prescription costs: \$154 million). Lost productivity costs were \$619 million (lost workdays: \$182.6 million; restricted activity days: \$188.1 million; caregiver lost workdays: \$248.5 million). Costs due to a decrement in QoL were \$2.6 Billion. Of note, AD had the 4<sup>th</sup> highest overall QoL-related costs among skin diseases.

### Economic burden

- \$5.3 billion: conservative estimate of the annual cost of AD in the US in 2015
- Patients with AD spend more money out-of-pocket on healthcare and have increased physician visits and hospitalizations compared with the general population
- 14.5% of US adults with eczema miss at least 1 day of work per year because of their eczema

That same study also examined the costs of psoriasis, another chronic inflammatory skin disease, and found them to be lower than AD, despite the inclusion of OTC product costs for psoriasis and not for AD and of

	<b>Atopic dermatitis</b>	<b>Psoriasis</b>
<i>Direct costs</i>	\$1.009 Billion	\$1.244 Billion
<i>Indirect costs</i>	\$3.219 Billion	\$2.414 Billion
<i>Total</i>	\$4.228 Billion	\$3.658 Billion
Annual costs of AD and psoriasis in 2004 from Bickers et al. <sup>3</sup>		

lost productivity due to early mortality for psoriasis and not for AD.<sup>3</sup> Overall costs for psoriasis, based on a prevalence of 3.1 million, were \$3.658 Billion. Direct costs were \$1.244 Billion (inpatient costs: \$5 million; hospital outpatient costs: \$15 million; ED visit costs: \$3 million; office visit costs: \$169 million; prescription costs: \$555 million; OTC costs: \$498 million). Indirect costs due to lost productivity were \$114 million (lost workdays: \$50.8 million; restricted activity days: \$32.2 million; caregiver lost workdays: \$21.8 million; lost earnings due to premature death: \$9.6 million). Costs related to decreased QoL were \$2.3 Billion.

Based on data in the AAD/SID report,<sup>3</sup> an estimate of the 2015 financial burden of AD can be made using the Consumer Price Index (CPI) provided by the US Bureau and Labor Statistics.<sup>4</sup> Using the September 2004 and September 2015 CPIs, the total costs of AD in the US in 2015 is estimated to be \$5.297 Billion.\*

This is likely an underestimate of the true costs of AD in the US. Firstly, the AD prevalence estimate of 15.2 million, roughly 5% of the US population in 2004, is lower than other population-based estimates of the prevalence of AD in children (10.7% in 2003)<sup>5</sup> and adults (7.2% in 2012).<sup>6</sup> Secondly, the estimate does not include the costs of OTC products which, as demonstrated below, make up a substantial proportion of out-of-pocket costs of AD. Finally, productivity loss accounted for in this study include only time away from work or activities due to medical visits, and not missed days not associated with medical visits or lost productivity due to presenteeism.

In the following subsections, we will provide an overview of other data available on the diverse costs associated with AD in the US, followed by a summary of important international data.

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\* September 2004 CPI: 189.9  
 September 2015 CPI: 237.945  
 Costs in 2015 = 4.228 Billion X (237.945/189.9) = 5.297 Billion

### *Direct medical costs - Out of pocket costs*

The 2010 and 2012 National Health and Interview Surveys (NHIS) are population-based national surveys of non-institutionalized US adults.<sup>7</sup> These surveys provide valuable information on health and health service use for the American population. Data from these surveys demonstrate some of the impact AD has on medical costs. In 2010 and 2012, the NHIS asked participants how much money they spent out of pocket on healthcare, specifically asking them whether they spent within given ranges of money.<sup>7</sup> Survey participants with eczema had increased risk of spending across all levels of expenditures in both 2010 and 2012. Participants with eczema had roughly twice the risk of spending in the highest category ( $\geq$ \$5,000/year) in 2010 (adjusted OR=2.18, 95% CI 1.68-2.83) and 2012 (adjusted OR=1.74, 95% CI 1.34-2.27). While those costs are not specifically related to eczema, they speak to the overall medical cost burden eczema sufferers and their families bear, whether it be for eczema or its comorbidities.

Filanovsky et al. recently published the results of a study that surveyed caregivers of children with moderate to severe AD, aged 0.5-12 years old, from university-affiliated clinics in Cleveland, OH between 2011-2013 (n=79).<sup>8</sup> Caregiver-reported out-of-pocket costs for AD were \$75 per month (median \$45, IQR \$20-110). This included visit and medication copayments and OTC products, which themselves cost an average of \$35.30 per month. Combined with indirect costs (time off work and extra child care; did not include presenteeism), the total personal costs for AD were \$274 per month (median \$114, IQR \$29-276). This represented 34.8% of the average family's income. The percent of the family's income spent was correlated with the emotional impact of the disease as measured by the CADIS score ( $r=0.439$ ,  $P<0.001$ ), but not with caregiver-reported severity. Costs were higher in those with private insurance than those with Medicaid.

A study at a single tertiary care center in North Carolina published in 2003 that surveyed the parents of 1-12 year-old children with AD found that 12% of parents spent over \$200 in the past month on OTC products and household expenses such as air filters for AD.<sup>9</sup> Another single center study, from Detroit in 1997, examined costs associated with AD in children and adults from the patient or parents perspective.<sup>10</sup> They extracted costs based on claims and payments made and from a survey of patients and parents. They found total out-of-pocket annual costs related to AD of \$147 per patient. This included \$12 for practitioner visits, \$8 for visit copays, \$60 for medication costs and an additional \$7 for medication copays, \$54 for other household items and \$6 related to child care. While the article does not test for statistical significance, there appeared to be a relationship between disease severity and increasing costs.

*Direct costs - Costs to insurers and governments*

From 1997 to 2004, there were an estimated 7.4 million visits by children with AD to ambulatory medical clinics in the US.<sup>11</sup> Visits for AD were distributed among specialists (44%), hospital based clinics (13%) and generalists (43%). Over that time period, visits for AD increased from 620,000 per year in 1997 to 850,000 in 2004 (OR=1.10, 95% CI 1.02–1.18). Interestingly, the year 2003 saw the highest number of AD visits (1.7 million).

Based on data from the 2010 NHIS, it is estimated that 75% of people with eczema visited a doctor at least once in the last year specifically for their eczema.<sup>7</sup> In the 2010 and 2012 NHIS, eczema was associated with increased physician visits, ER visits and hospitalizations.<sup>7</sup> In 2010, eczema was also associated with increased utilization of homecare visits by nurses or other healthcare practitioners. A study from a pediatric dermatology inpatient service in Texas found that 86% of their admissions were for AD, indicating that AD is not just an ambulatory disease in the US.<sup>15</sup>

Fowler et al used an insurance claims database from 1998-2005 to examine costs related to AD from employees of 31 Fortune 500 companies and their families.<sup>12</sup> They compared enrollees with AD with at least 2 claims (based on diagnostic codes) to matched control without AD (who also had at least 2 non-AD claims) and calculated the direct incremental costs of AD in 2005 USD per patient month above those for controls. Total direct incremental costs for AD per patient month were \$88, including \$47 for medical services and \$42 for prescriptions. These differences were statistically significant, even in multivariate analyses accounting for atopic comorbidities. In the multivariate model, incremental direct costs due to AD were \$51.51 per patient month.

Ellis et al. published data from a large private managed care payer in the US in 1997-1998 and data from an Eastern state Medicaid program in 1997.<sup>13</sup> They estimated overall costs to insurers and the government for eczema patients 0-64 years-old by using data on the number of Americans enrolled in Medicaid and private insurance in the US. They included diagnostic codes for other forms of eczema, including contact dermatitis, in their study. For patients covered by private insurers they found per-patient annual costs directly related to eczema of \$240 for office visits, \$60 for hospital clinic visits, \$50 for inpatient hospital visits, \$10 for emergency department visits and other costs of \$70. In the Medicaid population, they found annual per-patient costs of \$60 for office visits, \$380 for outpatient hospital visits, \$480 for inpatient hospital visits, \$3 for ED visits and \$90 for other costs. For pharmacy costs, they divided prescriptions into those that were most likely or possibly related to treatment of eczema. When these two groups were

combined, per patient annual pharmacy costs were \$140 for private insurers and \$240 for Medicaid. Using this data, the overall annual costs of eczema in Americans younger than 65 was estimated to be between \$0.9 billion (using only claims directly linked to eczema and the incremental costs of claims most likely related to eczema) and \$3.8 billion (using total costs for all claims possibly related to eczema).

A study using data from 2 large group practices in the US from 2001-2003 found that 52% of pediatric patients with AD (age 2-12) had unscheduled office visits related to AD, resulting in an annual cost of \$93.54 per patient.<sup>14</sup> While no statistical significance was given, the number of unscheduled visits appeared to increase with disease severity, as assessed by AD Treatment Satisfaction Questionnaire (mild:  $1.7 \pm 1.0$  visits; severe:  $2.3 \pm 1.6$  visits).

Fivenson et al. found annual direct medical costs to insurers at a tertiary care center in Detroit in 1997 to be \$167.<sup>10</sup> This included inpatient costs (\$4), outpatient costs (\$105), medications (\$51), laboratory costs (\$2) and phototherapy (\$5).

#### *Indirect costs*

Indirect costs of disease are those that are not directly related to the management of the disease itself. This includes the impact of disease on quality of life, on absenteeism and presenteeism as well as unemployment. The impact of AD on QoL has been summarized in section III of this report. In this subsection, we will focus on the impact AD has on absenteeism and presenteeism from work and school. Unfortunately, our search did not reveal any data related to AD and unemployment.

The 2010 NHIS asked adults with eczema whether they had any lost work days specifically related to their skin condition.<sup>7</sup> While most participants with eczema did not report any lost work days due to their eczema, 12.2% did miss 1-2 days of work and 2.3% missed 3 or more days. In a claims database consisting of employees and their families from 31 Fortune 500 companies from 1998-2004 (with costs converted to 2005), AD conferred incremental indirect costs of \$64 per patient month, largely related to payments for disability (\$57), with a smaller proportion from sick leave (\$6).<sup>12</sup> In multivariate models controlling for covariates including atopic comorbidities, AD was still associated with incremental indirect costs of \$31.06 per patient month.

In a study of 2-12 year-old AD patients based on a survey from 2 large US group practices, about 8% of children had lost at least 1 day of school over the last 4 weeks due to AD and about 9% of caregivers had

lost at least 1 day of work over the last 4 weeks due to their child's AD.<sup>14</sup> In another study of parents of children with moderate to severe AD in Cleveland, OH (2011-2013), 40.5% of caregivers missed work at some point in the preceding month to care for their child's AD, with a mean of 20.5 hours of missed work.<sup>8</sup> Indirect costs per patient per month were \$199 per month (median: \$0; IQR \$0-208), although this did not include presenteeism.

Fivenson et al. found that among adult patients and parents of pediatric patients with AD at a single tertiary care center in Detroit, the mean annual cost of lost work productivity from absenteeism was \$295 in 1997.<sup>10</sup> The cost value was obtained by multiplying the number of days missed by the mean annual income where patients lived.

The ISOLATE study examined the burden of moderate-severe AD in 8 countries, including the US, in 2004.<sup>16</sup> Participants missed an average of 2.5 days from work or school due to their disease per year. For participants with severe disease, the average time missed from work or school per year was 5.3 days. In adults, the average number of days missed was 2.7. Additionally, adult patients spent 102 working days per year in an AD flare, with their productivity suffering 9.6% of that time (presenteeism). That study did not translate that lost productivity into American costs, but did calculate that in the European Union in 2004, lost productivity due to absenteeism and presenteeism was €2,281,453,279. Based on an exchange rate of 1.06 at the end of 2014, this translates to roughly \$2.5 billion US in 2004 for the 15 nations in the European Union. While ISOLATE does include US participants, there is currently no published US-specific data on presenteeism.

#### *Data from other countries*

In order to ascertain the burden of disease of AD in the US from an economic perspective, data from US studies is most valuable. Data from other countries is difficult to translate to the US, due to differences in healthcare payers across countries (ie. universal government payers vs. private insurers), disparities in the costs of medications and cultural differences related to sick leave, disability and other time off work. However, data from other countries can be instructive and as such we will summarize some of the available data here. Among skin conditions, AD has been cited among the most common reasons for healthcare visits in various countries around the world, including visits to general practitioners,<sup>17</sup> dermatology clinic visits in childhood,<sup>18</sup> dermatology inpatient consultations,<sup>19</sup> acute care dermatology clinic visits,<sup>20</sup> pediatric emergency visits,<sup>21,22</sup> and visits to homeopathic practitioners.<sup>23-25</sup>

A British survey of families of children 1-5 years old with AD in 1995-96 sought to comprehensively examine costs to the healthcare system and to families.<sup>26</sup> Total annual costs per child were £79.59 (\$46.49 USD at the end of 1996), which included £50.65 (\$29.59) in direct medical costs to the healthcare system. Among those with AD, 96% had seen a general practitioner, 4% had seen a dermatologist, 2% had seen a pediatrician and 2% had visited the accident and emergency department for their AD. Other costs included changes to the family home to accommodate the disease (bedding covers, clothing, vacuum cleaners, carpets, air treatment), OTC preparations (emollients, bath preparations), dietary products, transportation costs for healthcare and the costs of private specialist visits. The use of alternative medicine practitioners was rare, but was costly for some, including one family that spent £625 (\$365).

A Finnish birth cohort study followed participants to age 2 and monitored for development of allergic diseases.<sup>27</sup> In this cohort, 53 participants developed AD in their first 2 years of life. Because of the close follow-up of this study, the authors are able to provide very granular detail on costs for these participants. Mean total costs (including costs from payers, families and indirect costs) were higher in the AD group (€425±364; \$322 USD) compared to controls (€50±118; \$38 USD) but were lower than for those with asthma and food allergy (costs standardized to 2006 Euro, USD end of 2006).

A retrospective study that examined German children born in 1990 to the time they were 8 years old in 1998 looked at total direct costs in AD, asthma and rhinitis.<sup>28</sup> They calculated costs as an average of the cost per patient per year that they had active AD, and converted their costs to 1996 US dollars. Total costs per patient per year AD was active were \$219, lower than those for asthma (\$627 per year asthma was active) but higher than for seasonal rhinitis (\$57 per year rhinitis was active). Interestingly, they found that not only did costs increase as the severity of AD increased, but that 85% of the AD-related costs were associated with just 20% of AD patients.

A case control study in France sought to examine direct costs (physician visits, prescription costs) in patients with newly diagnosed AD being managed by general practitioners from 1 to 9 years old. The study, with its baseline in 2000-2003, found that costs in AD were 73% higher than controls in 1st year of life and 21% higher in the 9th year of life.<sup>29</sup>

A Canadian study based out of community pharmacies in Ontario in 2002 examined costs for people aged 0-84 diagnosed with AD who had been prescribed a topical anti-inflammatory medication in 2002.<sup>30</sup> Among the 74 participants, there was an average of 3.59 publicly funded healthcare visits per year, and participants missed on average 0.68 days of work per year. They estimated that total annual expenses in

Canada, taking into account direct costs and indirect costs, were \$1.4 Billion CAD (\$2.2 Billion USD end of 2002).

A survey of AD patients from a Danish patient support group examined the impact of AD on work life of patients. In 2002, participants self-reported absenteeism, and the mean number of days lost from work over the previous 6 months was found to be 5.8 (95% CI 0.36-11.30).<sup>31</sup> A 2012 Dutch study based out of a tertiary care center found similar results in their patients, with 42% of them having taken sick leave in the last year due to AD, with a mean of 7.1 days.<sup>32</sup> Interestingly, in multivariate analyses, sick leave was not associated with QoL or disease severity. However, in a Japanese study, decreased work productivity was associated with increasing severity as measured by the SCORAD.<sup>33</sup>

#### *Limitations and directions for future research*

There are still many gaps in the medical literature with regards to direct and indirect costs of AD. While the AAD/SID report, which found total annual costs of AD to be \$4.228 Billion in the US, is high quality, it is not fully comprehensive. It is missing data on OTC product costs as well as presenteeism. Out of pocket OTC costs are significant in AD, and their inclusion is essential in any comprehensive estimate of costs. Additionally, that study is over 10 years old, and while dollar figures can be converted to using the CPI to current estimates, more recent data would be preferred.

Studies specifically examining the following elements of costs of AD in the US would be beneficial:

- Updated direct costs of including those attributed to government and private insurance payers and patients and families themselves
- Estimates of the costs of presenteeism among adults with AD in the US
- Estimates of the impact of AD on unemployment (no studies to date)

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#### IV.ii. Academic and occupational impact

In the previous section, we outlined the direct and indirect costs of AD. Indirect costs included QoL, missed days at work due to the disease (absenteeism) as well as lost productivity at work (presenteeism). While absenteeism and presenteeism, in addition to unemployment, are the accepted measures of indirect costs, they do not fully capture the impact AD has on patients' academic and occupational lives. In a study of 2002 moderate to severe AD patients, 32% of participants felt their AD affected their school or work life, and 14% of the participating adults felt their career progression had been hindered by AD.<sup>1</sup> As a risk factor for occupational skin disease,<sup>2</sup> AD can affect patients' job choice, leading them to avoid occupations that may lead to occupational skin disease. In

this section we will describe the available evidence on these academic and occupational impacts that would not be captured by economic studies evaluating absenteeism and presenteeism.

### Academic and occupational impact

- People with AD avoid a wide variety of occupations, including jobs in healthcare, cooking and hairdressing
- Academic and occupational impacts of AD are most pronounced in people with moderate to severe disease

#### *AD and job choice and fulfillment*

A survey of the membership of the Danish Association of Atopic Eczema, a patient support group in Denmark, revealed that AD can have a major impact on the careers of eczema sufferers.<sup>3</sup> Among participants, 38% said they chose not to take a job or pursue some schooling due to their eczema. The mean severity score (as assessed by the patient) or QoL (as assessed by the DLQI) did not change the risk of job or school avoidance. Participants specifically cited the following jobs as being avoided because of AD:

- Nurse, nursing aid
- Physiotherapy (pool therapy)
- Surgery
- Veterinary medicine
- Catering, cooking
- Farming
- Automobile repair
- Hairdressing
- Cleaning

Reasons cited for avoiding various jobs included a fear of AD worsening due to the job, a fear of chronic hand eczema and a fear of infection.

A community-based study in Sweden used medical records to identify cases of childhood AD and non-AD controls, and then performed a cross-sectional survey of those cases and controls during adulthood (mean age 37 years) in order to obtain adult occupational history.<sup>4</sup> After dividing occupations into those that are high risk for skin disease and those that are not, they found no difference in job choice among cases with AD in childhood and those without. Similarly, a German study found no association between AD and choosing high risk jobs, and that job counseling associated with atopy had no impact on job choice.<sup>5</sup> However, in the Swedish study, 8.9% of those with AD reported changing their job due to eczema.<sup>4</sup> Among those who changed jobs (n=36), the jobs they switched away from were in healthcare, catering, industry, chemistry and journalism as well as jobs as shop assistants. While a number of these jobs are similar to those cited in the above-mentioned Danish study, it is interesting that other jobs that might not be considered high-risk, such as journalism and retail, were avoided as well.

A British birth cohort study of those born in 1958 examined participants' employment history at age 33, using data on the first 3 jobs a participant held in their life.<sup>6</sup> They divided jobs into those that were professional, clerical or administrative and those that were more high risk for occupational skin disease (eg. hairdressers, cleaners) and then a third group of other occupations. They found that a history of childhood AD (diagnosed before age 16) had no impact on the category of their first job choice (OR=1.12, 95% CI 0.89-1.41) in a multivariate model adjusting for age, sex, place of birth and father's socioeconomic status at birth.

With regards to satisfaction at work, a Spanish study of AD patients (many of whom had moderate to severe disease) found that 73% of adult participants felt their AD had limited their fulfilment at work.<sup>7</sup> Another single center study from the Netherlands of 253 adult AD patients found that 41% of participants expressed above average job dissatisfaction, with 5% reporting that their symptoms interfered at work.<sup>8</sup>

### *Impact on school*

Fortunately, for most AD patients, eczema does not negatively impact their academic achievement. A birth cohort in the Netherlands examined the impact various health conditions have on school performance.<sup>9</sup> The outcomes of the study were standardized test scores and teachers' assessment of the students, who, after being followed from birth, were 17 at the time of the study. No association was seen between either a diagnosis of AD or longer AD duration and scores on standardized tests or teachers' assessments. Similarly, Halvorsen et al. reported results of a large survey of adolescents in their last year of high school in Norway.<sup>10</sup> As a part of that survey, participants were asked whether they had eczema

and also whether they were thriving at school. Eczema was not associated with an increased risk of not thriving at school in crude (OR = 1.20, 95% CI 0.92-1.56) or multivariate-adjusted analyses (OR = 1.05, 95% CI 0.80-1.39).

However, for some eczema sufferers, their skin disease can have a major impact on their academic life. A Spanish study of AD patients, a large proportion of whom had moderate to severe disease, found that 48.1% of pediatric participants felt their AD limited their fulfilment at school.<sup>7</sup> AD led to missing school on average 2.53 days in the last year and missing extracurricular activities an average of 2.32 days in the last year.

#### *Limitations and directions for future research*

It is reassuring that on a population level, AD does not impact career choice or academic achievement. However, in studies among patients with more severe disease, AD appears to have a major impact. Studies examining the academic and occupational impact of AD on a population stratifying by disease severity may help to clarify these findings.

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## **V. Eczema in social media**

### Introduction

Healthcare practitioner (HCP) and researcher assessment of the burden of AD and the patient experience are not always correlated.<sup>1,2</sup> In an attempt to narrow that gap, crowdsourcing has been suggested as a method of data collection in AD,<sup>3</sup> and in a recent National Eczema Association report, Capozza et al. investigated online forums related to AD.<sup>4</sup> They compared the content of posts on those forums with Pubmed abstracts and found that 55% of patient-initiated posts were unique to the patient experience and were not mentioned in published peer-reviewed articles.

People are increasingly using real-time social media sites, such as Twitter and Facebook, as opposed to traditional online forums, to learn about, share and discuss diseases. To our knowledge, there are no publications in the scientific literature on the content or impact of AD-related activity on social media. We conducted a pilot study to determine the feasibility of using social media to study the burden of AD from the patient perspective. We aimed to examine data from this pilot to explore what patients and family members are discussing related to AD on social media.

### Methods

With the help of a social media intelligence company (Brandwatch - Brighton, UK), we searched posts and conversations related to AD and eczema on the internet, including content from Twitter, Facebook, Tumblr, forums and online blogs. Due to the availability of data and privacy settings of some social media sites, the posts available for analysis were predominantly from Twitter. Using the company's listening and analytics platform, a sophisticated query was created to search and track all English-language mentions of AD and eczema (specifically using the terms: eczema OR excema OR exzema OR exema OR atopic dermatitis) in January and July 2015 in the US. These months were selected to represent winter and summer, respectively.

The software attempted to categorize posts originating from patients (by searching key terms such as "I" or "me" or "I have" or "I have been suffering"), relatives and friends (eg. "mom", "dad", "son", "cousin, "daughter") or HCPs (eg. "I recommend"). Additional searches were done for posts related to itch, pain, hurt and sleep.

All posts identified by the platform as being patient-, relative-, friend- or HCP-made were manually screened by a reviewer (ARW) in an attempt to verify their source, and exclude advertisements or posts originating from fake accounts or “bots”. Posts were also excluded in which eczema was used as a comparator (eg. “I found out I have psoriasis not eczema”).

To identify phrases and words commonly associated with posts about AD and eczema, the Brandwatch platform generated word clouds to visually represent frequency of mention by size of the word or phrase. The words or topics included in the word cloud are generated based on a random sample of up to 600 mentions.

## Results

### *All posts related to AD and eczema*

In total, 79,029 posts were identified by the platform as being related to AD or eczema. Of these 57% (45,613 posts) were from January 2015 and 43% (33,669 posts) were from July 2015.

In January, 66% (30,282) of all posts analyzed were from Twitter, followed by Facebook (25%; 11,192) and blogs (3%; 1,447). The remaining posts were from forums (2%; 1017), news (2%; 783) and websites not otherwise categorized (1%; 655). In July, 83% of posts were from Twitter (27,985), followed by blogs (6%; 1890), Facebook (3%; 1073), forums (3%; 999), news (3%; 1000) and other websites (2%; 514).

Word clouds of words and phrases most commonly associated with AD and eczema on social media are presented in figure 1. Many posts were associated with skin signs and with treatments.





Figure 1. Word clouds associated with atopic dermatitis or eczema in social media posts in January (a) and July (b) 2015.

*Posts by patients, relative, friends or HCPs*

A total of 6,371 posts were identified by the platform as possibly originating from patients, relatives or friends or healthcare providers, 3,656 from January, and 2,715 from July. Of these, the majority of posts were from Twitter (76% in January, 81% in July), with others from Facebook (13%, 7%), blogs (5%, 4%), and forums (3%, 5%). Among posts where the gender of the author could be determined, the majority were posted by females (figure 2).

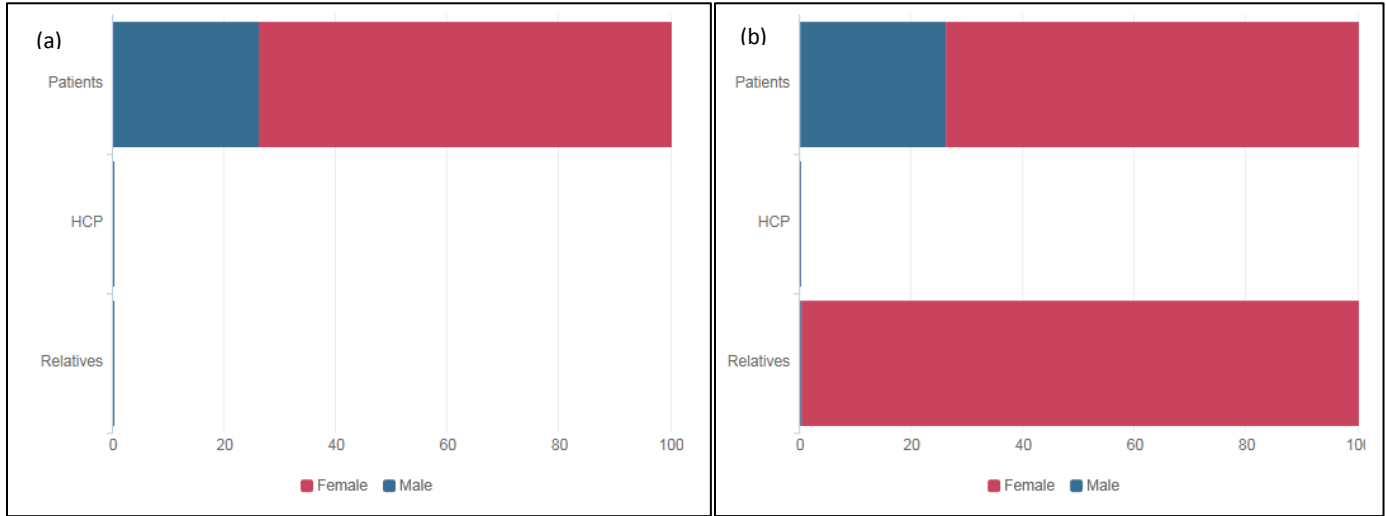
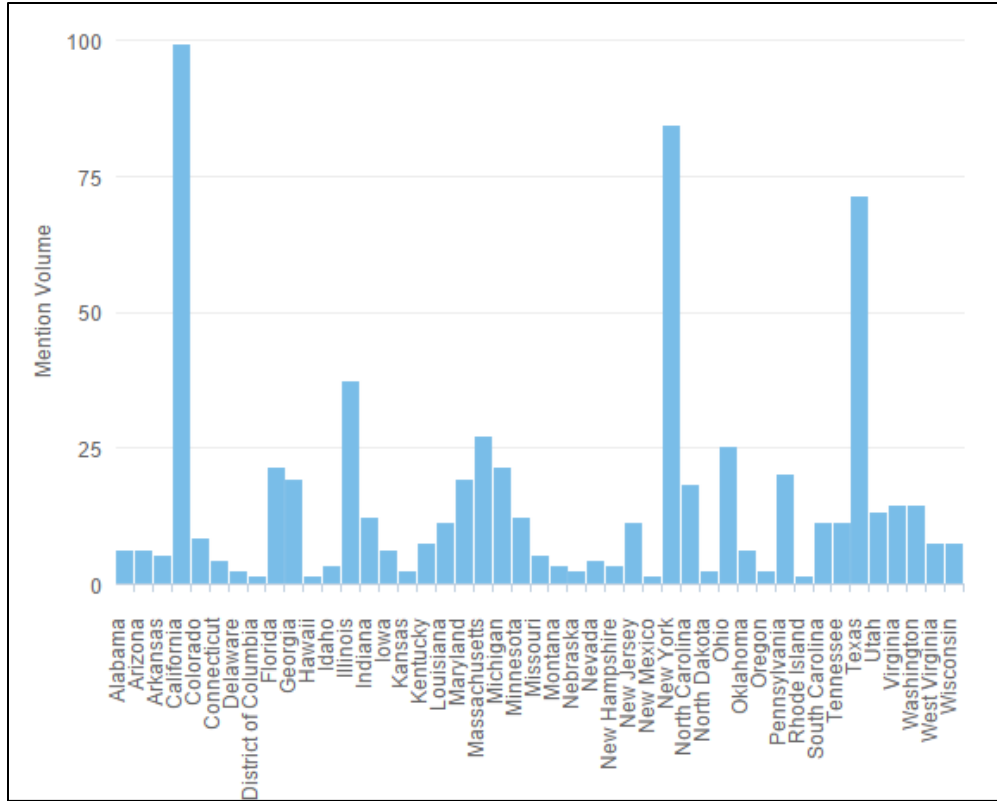


Figure 2. Gender of authors of posts by patients, relatives or friends (called “Relatives” in the chart) or HCPs, as identified by the platform, in January (a) and July (b), 2015.

In January there were 664 posts originating from a specified location; the 3 US states with the most posts were California (14.9%), New York (12.6%) and Texas (10.7%) (figure 3a). In July, of 530 posts with an associated location, California (17.3%), New York (10.6%) and Texas (9.2%) (figure 3b) were, again, the source of the most posts.

(a)



(b)

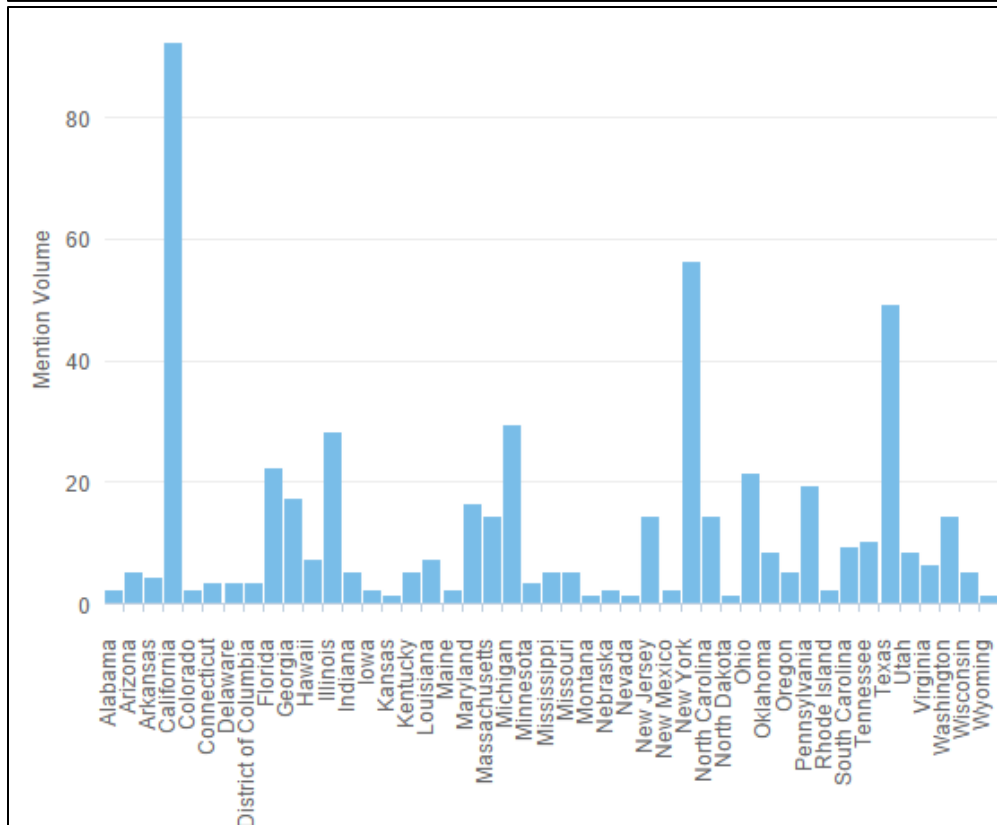
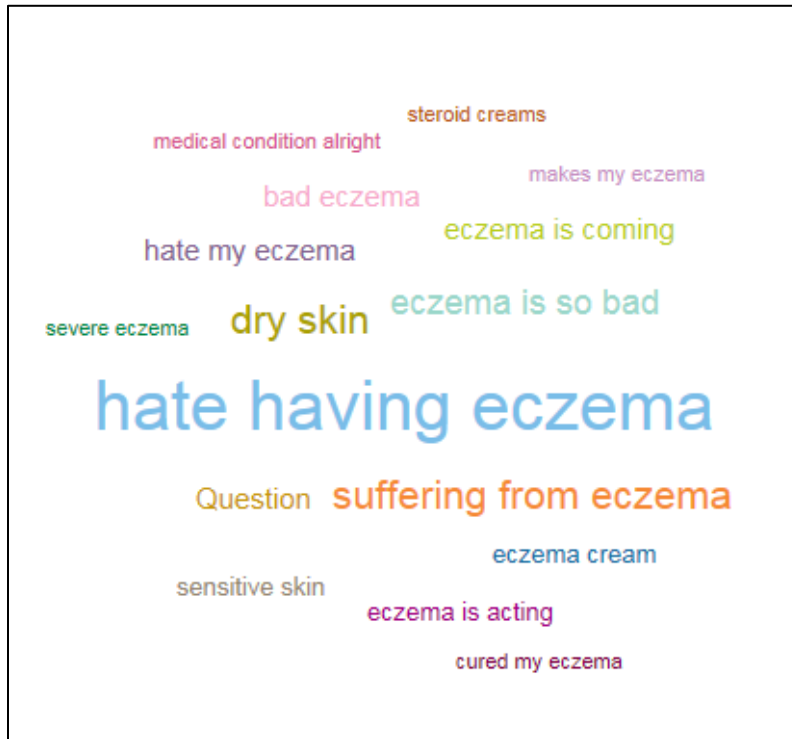


Figure 3. Number of posts by patients, relatives, friends or HCPs, as identified by the platform, per US state in January (a) and July (b), 2015.

Posts identified by the platform as authored by patients totaled 3,633 (median 121 posts/day) in January and 2,696 (median 83 posts/day) in July 2015. Word clouds for posts by patients (as identified by the platform) are presented in figure 4.

(a)



(b)

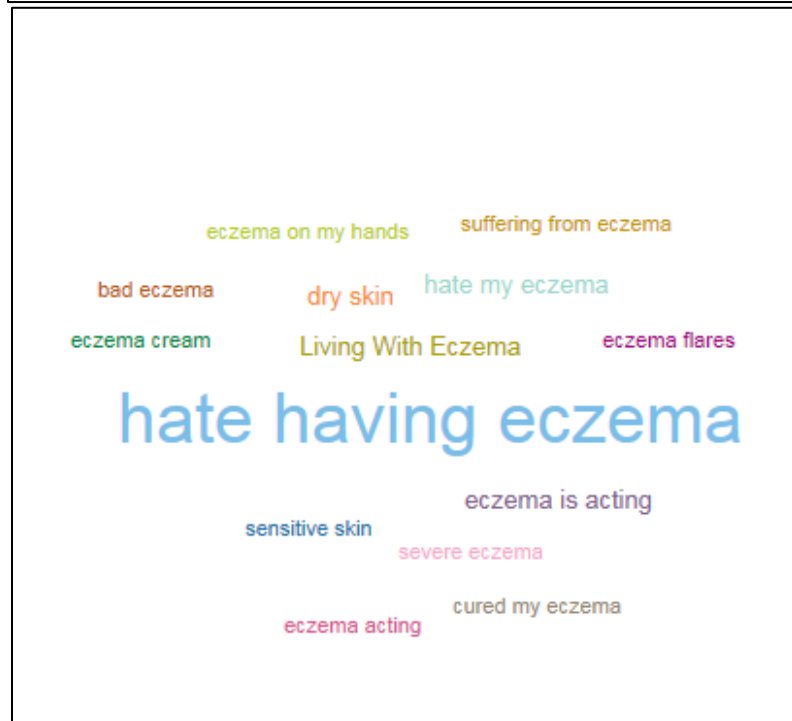
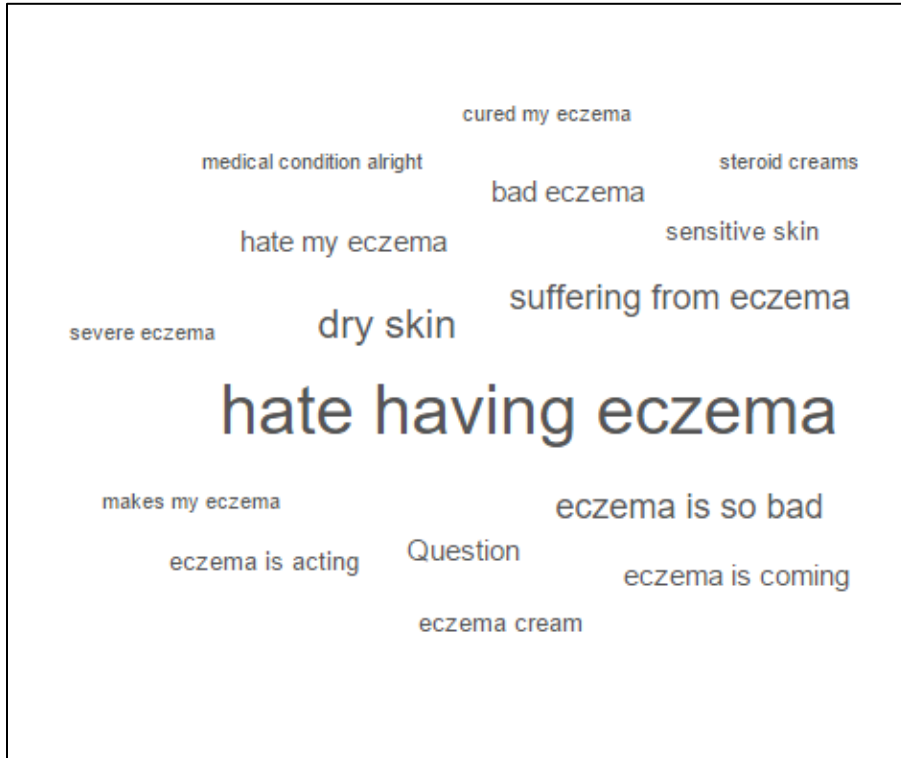


Figure 4. Word clouds generated from patient (as identified by the platform) posts in January (a) and July (b), 2015.

After manual review of the posts identified by the platform as being authored by patients, 2,513 of 3,633 (69.5%) in January and 1925 of 2696 (71.4%) in July 2015 were identified as likely authored by patients. Word clouds generated from these verified posts are presented in figure 5.

(a)



(b)

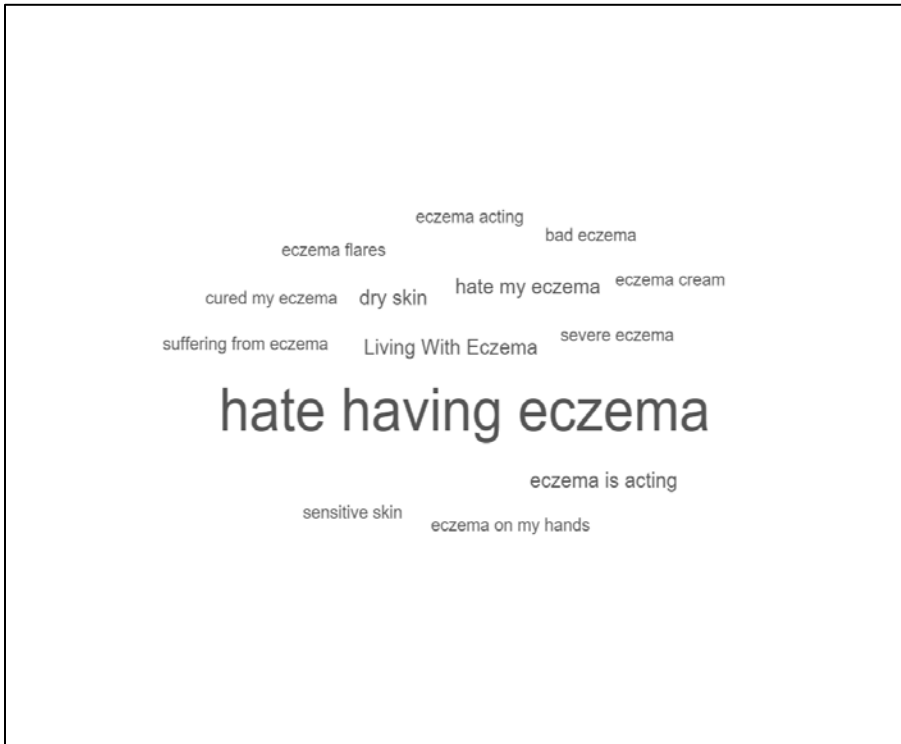


Figure 5. Word clouds generated from all manually verified patient-authored posts in January (a) and July (b), 2015.

Among the posts verified as likely authored by patients, 11 relevant posts discussed itch in January and 45 in July. Thirteen of the posts in July were retweets of a single tweet, suggesting agreement with a particular sentiment. Searches for pain-related posts resulted in 11 relevant posts in January and 26 in July. Ten of the 11 pain-related posts in January used the word “pain” figuratively and only one referred to physical pain. There were 39 and 7 relevant posts related to hurt in January and July, respectively. There were 15 and 11 relevant posts related to sleep in January and July, respectively.

The platform identified 11 posts in January and 3 in July as authored by HCPs. Of these, 10 were actually advertisements. There were 27 posts identified by the platform as being from relatives or friends of eczema patients, all of which were manually verified.

### Discussion

This study found that many patients use social media to discuss their disease, with 4,438 patient-authored posts in the US combined in January and July 2015. As demonstrated in the word clouds, most sentiment associated with eczema was negative. However, no specific themes emerged regarding the burden of disease as the words and phrases in the clouds were general in nature.

Much of the chatter related to eczema was commercial, with advertisements for various products being very common. Only 6% of posts were authored by patients. While social media may be a useful place for patients to discuss their disease, it is also fraught with advertisements, some of which may be misleading. Additionally, there were very few posts by healthcare practitioners. The lack of a strong presence of reputable dermatology professionals, organizations and journals on social media has been previously reported.<sup>5,6</sup>

Females made up the majority of authors of posts about eczema on social media. While women in general use social media more than men,<sup>7</sup> and more women in the US have eczema than men,<sup>8</sup> the difference in our study was quite pronounced. There were more posts in January compared to July, which may be a reflection of eczema worsening in the winter months.

This pilot study has a number of limitations. Our search to identify posts related to eczema was not specific to AD. As such, posts may have been related to other forms of eczema such as chronic hand eczema or allergic contact dermatitis, or to other skin diseases that have been misdiagnosed as eczema. The gender and location of the authors of posts could not always be identified, and the age of authors was not available. There are also several privacy restrictions on social media sites, particularly Facebook and

Instagram, which limited access to posts. As such, the majority of posts examined were from Twitter. Data on the total number of eligible social media posts in January and July were unavailable, limiting our ability to assess if the difference between the number of posts in July compared to January was related to a general trend (eg. less posts overall in July) or if it was specific to eczema. Additionally, we examined posts from only two sample months. It is possible that access to data from an entire year would improve the utility of social media for investigating burden of disease.

It was difficult for the platform to differentiate human posts from “.bots”, which are software applications that runs automated tasks over the internet. These bots typically perform repetitive tasks at a rapid rate, which can include retweeting mentions or posting hashtags or mentions under a fake username. While some bots and advertisements are easily identifiable (eg. “Try Product-X today!”), others are not. This necessitated manual review of the posts, which found that around 70% of posts identified by the platform as being authored by patients were in fact authored by patients. This makes reliance on software-based determination of post authorship in future studies dubious.

With increased use of social media by patients, crowdsourcing may be a viable and untapped source for insight into the patient experience. Several patient-authored posts offered genuine and illustrative insight into the experience of living with eczema. However, barriers exist to the utilization of social media as a means to study burden of disease on a large scale.

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## **VI. Conclusions**

It is clear that the burden of disease of AD nationally and globally is tremendous. The detriment in QoL of AD in children is comparable to that of debilitating diseases such as cystic fibrosis. While much of the detriment in QoL is driven by symptoms such as itch, pain and sleep loss, QoL in AD is complex with impacts on self-esteem and personal relationships. Those impairments are not limited to patients themselves, but is felt by the entire family unit with parents of children with AD experiencing sleep deprivation and emotional distress. AD is a costly disease, with a conservative estimate of its costs in the US of \$5.3 billion annually.

While we believe this report is comprehensive in its examination of the medical literature on burden of disease in the US, there are many areas that require further work, including the impact of AD on QoL at a population level and an updated, comprehensive determination of costs of AD.

## **VII. Acknowledgments**

We thank the National Eczema Association for the opportunity to write this report and their tremendous support during the process. Specifically, we thank Julie Block for her input as a patient advocate. We are also grateful to Dr. Eric Simpson and Dr. Robert Sidbury, members of the National Eczema Association Scientific Advisory Board, for their invaluable contributions. Finally, we thank Kimberly Marcolivio and Emily Coyne, Brown University Department of Dermatology, for their administrative support.