



Global Patient Initiative  
TO IMPROVE **ECZEMA CARE**


# High Burden and Unmet Medical Needs Among Patients with Eczema and Their Caregivers in 8 Developed Countries: FINDINGS FROM A COMPREHENSIVE LITERATURE REVIEW

The literature scan reviews burden and satisfaction with healthcare and treatments across eight countries representing a cross-section of developed nations with disparate health care systems.

This project is supported  
with funding from:



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# EXECUTIVE SUMMARY

## Objective

The objective of this report is to characterize the disease burden, unmet needs, and satisfaction with care among patients with atopic dermatitis (AD) and their caregivers in the United Kingdom (UK), United States (US), Germany, Denmark, France, Italy, Canada, and Australia. A comparison of findings from each country of interest (COI) will guide future research.

## Introduction

AD is a chronic, relapsing and remitting inflammatory skin condition characterized by itchy and inflamed patches of skin.<sup>1</sup> In each COI evaluated in this report, AD affected 7.0%–17.1% of children and 2%–14.3% of adults. In children, the prevalence of AD was well-studied globally in the ISAAC studies;<sup>2</sup> in adults, AD prevalence studies have varied in their methodology across countries, likely contributing to differences in prevalence statistics both within and between the COI. The burden attributable to AD symptoms is likely similar across the patients surveyed in this report; however, some of the COI have healthcare systems and intervention methods that are more effective at recognizing AD, intervening, and mitigating the disease burden for patients and their caregivers.

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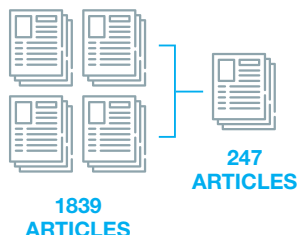
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<sup>1</sup>Eichenfield, L. F. et al. GUIDELINES OF CARE FOR THE MANAGEMENT OF ATOPIC DERMATITIS. *J Am Acad Dermatol* 71, 116–132 (2014).

<sup>2</sup>Odhiambo, J. A., Williams, H. C., Clayton, T. O., Robertson, C. F. & Asher, M. I. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *Journal of Allergy and Clinical Immunology* 124, 1251–1258.e23 (2009).

## Methods

A PubMed literature review of articles published in COI regarding the AD burden, unmet needs, and/or patient satisfaction with care was conducted between October 26th and November 15th, 2020. Searches for the eight COI yielded a total of 1839 articles, of which 247 described the disease burden, unmet needs, and satisfaction with care of patients with AD and their caregivers. Abstracts of published articles were reviewed to assess the relevance to this report; if relevant, the full-text articles were reviewed.



## Results

Variations in methodology made cross-country comparisons difficult. However, the prevalence of pediatric and adult AD seems to be relatively consistent across developed nations<sup>2</sup>, including the COI. AD tends to affect children at higher rates than adults.<sup>2-3</sup> Within the UK, US, and Canada, outcomes varied between racial and ethnic groups, indicating an unmet need for equitable care in these populations. The ISAAC studies are a promising model for AD prevalence studies; a similar global effort would offer a valuable comparison of the burden of adult AD across the COI.

In all eight COI, greater AD severity is associated with a worse burden and greater unmet need for both patients and their caregivers. The Atopic Dermatitis in America (ADIA) study found that for patients, itch, dryness, scaling, and red or inflamed skin are the most burdensome components of AD<sup>4</sup>; Silverberg et al. demonstrated the important role of skin pain in overall AD disease burden.<sup>5</sup> Patients with AD may be at higher risk than the general population for certain comorbidities, and providers should be aware of these risks when evaluating overall health. COI such as the US and Denmark have robust literature on comorbid conditions, such as autoimmune disorders, infections, and cardiovascular disease (specifically in the US), while the literature on comorbid conditions in the UK, Italy, and Canada is relatively sparse.

The QoL burden experienced by AD patients has been studied in each COI and is documented most extensively in the UK, US, Germany, and Denmark. Comorbid mental health symptoms such as anxiety, depression, and suicidal ideation are common in all COI. QoL is most commonly assessed with the Dermatology Life Quality Index and EuroQoL-5D instruments; the latter is also used to calculate a health utility score (scaled 0-1 from death to perfect health). Other determinants of the AD burden as assessed in the COI include work absenteeism, which also contributes to the financial burden.

The burden experienced by caregivers of AD patients is considerable and has been best documented in the UK, US, and Germany. Caregiver burden often manifests as mental health symptoms, sleep disturbances, and financial strain, especially among those who care for children with severe AD. Wider use of standard measures for assessing caregiver burden would be useful for enabling comparisons between the COI.

Of all the aspects of the AD burden, financial burden varies the most between the COI in this report. There is an important distinction between direct costs, indirect costs, and out-of-pocket (OOP) expenses. While direct and indirect costs are important determinants of the overall economic

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<sup>2</sup>Odhiambo, J. A., Williams, H. C., Clayton, T. O., Robertson, C. F. & Asher, M. I. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *Journal of Allergy and Clinical Immunology* 124, 1251-1258.e23 (2009).

<sup>3</sup>Vinding, G. R. et al. Is adult atopic eczema more common than we think? - A population-based study in Danish adults. *Acta Derm Venereol* 94, 480-482 (2014).

<sup>4</sup>Chiesa Fuxench, Z. C. et al. Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. *J Invest Dermatol* 139, 583-590 (2019).

<sup>5</sup>Silverberg, J. I. et al. Pain Is a Common and Burdensome Symptom of Atopic Dermatitis in United States Adults. *J Allergy Clin Immunol Pract* 7, 2699-2706.e7 (2019).

burden, they do not necessarily reflect the personal financial burden experienced by the patient or their caregiver. To that end, OOP expenses are a more useful metric. Of the COI, the US has the highest OOP associated with AD: the median annual OOP expenses among patients with moderate and severe AD exceed \$1000 and \$5000, respectively.<sup>6</sup> By contrast, annual OOP expenses in the European COI are estimated to be €927 with no significant increase for more severe disease.<sup>7</sup>

## The median annual OOP expenses among patients in the US with moderate and severe AD exceed \$1000 and \$5000

The burden faced by patients and their caregivers stems partly from significant unmet needs. Most notably, there is a lack of effective treatments especially for patients with moderate-to-severe AD, though dupilumab has improved the landscape of AD care by balancing efficacy with increased safety/tolerability. Even though research suggests systemic corticosteroids should not be routinely used to managed AD, they are still commonly prescribed, even in children.<sup>8–10</sup> Another unmet need is adequate access to dermatologists, especially in the UK, Canada, and Denmark; this obstacle may reduce satisfaction with care.

Data is most lacking in the realm of patient and caregiver satisfaction with both the treatments and providers. With regard to treatment, patients in the UK, US, France, and Italy cited concerns over the use and potential side effects of topical corticosteroid (TCS); caregivers in the UK, Denmark, France, and Italy also cited concerns about potential adverse effects related to TCS use, which seems to lead to decreased treatment adherence. With regard to providers, patients and caregivers commonly raised questions about finding a “cure” for AD and requested more information about diet interventions and allergy testing, while physicians focused more on managing AD as a chronic illness; patients found the psychosocial burden of disease to be at least as burdensome as physical manifestations of the disease, but physicians often focused narrowly on disease signs and symptoms.

In Germany and the UK, educational interventions were effective at reducing disease severity and the caregiver burden. Of note, German patients reported higher satisfaction with their care than patients in other countries surveyed in this report.

## Conclusions

The lack of common methodologies makes it difficult to draw direct comparisons between the COI regarding the disease burden, unmet needs, and satisfaction with care. Therefore, strong conclusions may be drawn within but not between the COI, though we can make some inferences about between-COI variations. For example, access to dermatologic care is an unmet need that impacts satisfaction with care in the UK, Canada, and Denmark; OOP expenses are especially burdensome for patients in the US; German patients seem the most satisfied with care overall; educational and nursing interventions can reduce disease severity and the caregiver burden in the UK, Germany, and Italy; and patients with moderate-to-severe AD have a high need for more efficacious treatments in all COI. This report highlights the countries with the most robust research in the areas of the patient and caregiver burden, unmet needs, and patient satisfaction with care. Observational studies that identify common problems and successful interventional studies in each COI may be used to guide future research with the goal of providing equitable care for AD patients and their caregivers around the globe.

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<sup>6</sup>Smith Begolka, W., Chovatiya, R., Thibau, I. J. & Silverberg, J. I. Financial Burden of Atopic Dermatitis Out-of-Pocket Health Care Expenses in the United States. *Dermatitis Publish Ahead of Print*, (2020).

<sup>7</sup>Zink, A. G. S. et al. Out-of-pocket Costs for Individuals with Atopic Eczema: A Cross-sectional Study in Nine European Countries. *Acta Derm Venereol* 99, 263–267 (2019).

<sup>8</sup>Alexander, T., Maxim, E., Cardwell, L. A., Chawla, A. & Feldman, S. R. Prescriptions for atopic dermatitis: oral corticosteroids remain commonplace. *J Dermatolog Treat* 29, 238–240 (2018).

<sup>9</sup>Bridgman, A. C., Eshtiaghi, P., Cresswell-Melville, A., Ramien, M. & Drucker, A. M. The Burden of Moderate to Severe Atopic Dermatitis in Canadian Children: A Cross-Sectional Survey. *J Cutan Med Surg* 22, 443–444 (2018).

<sup>10</sup>Schmitt, J., Schmitt, N. M., Kirch, W. & Meurer, M. Outpatient care and medical treatment of children and adults with atopic eczema. *J Dtsch Dermatol Ges* 7, 345–351 (2009).

# INTRODUCTION

Atopic Dermatitis (AD) is a chronic, relapsing and remitting inflammatory skin disease characterized by itchy, often painful patches of redness, swelling, oozing, crusting, and dryness. AD is classically described as a childhood disease that remits in adulthood. Often, AD presents in patients with a history of seasonal allergy, asthma, or hypersensitivity to food or other allergens.<sup>11</sup> AD may also be called “eczema,” “atopic eczema,” or “neurodermatitis.”

The clinical signs and symptoms of AD range from mild disease, which typically requires only moisturization or as-needed use of mild topical corticosteroids/calcineurin inhibitors for near or complete clearance, to severe disease, which can be unresponsive even to systemic immunosuppression. As such, the disease burden experienced by patients varies considerably, and AD can be truly debilitating for patients with moderate-to-severe disease. Lack of treatments that are both safe and efficacious is an especially devastating unmet need, particularly for those with moderate-to-severe AD. The quality of life (QoL) detriment is greatest for patients and caregivers who live with severe AD; as such, this report stratifies every component of the physical, psychosocial, caregiver, and financial disease burdens by disease severity.

Symptoms such as itch and skin pain are inversely correlated with QoL and impact many other domains such as sleep quality and health.<sup>1</sup> The QoL burden can be measured with instruments, such as the Dermatology Life Quality Index (DLQI), that encompass multiple QoL domains including sleep dysfunction, work or activity impairment, mental health symptoms, and sexual intimacy.<sup>12</sup> Although clinical trials conducted in each of the countries of interest (COI) report QoL using these and other metrics, many AD patients and their caregivers still struggle to obtain care that holistically addresses the impact of AD on their lives.

The caregiver burden is an under-recognized component of AD, especially in the moderate-to-severe context. Unfortunately, the caregiver burden associated with AD often is not considered by the general public or even physicians<sup>13,14</sup> even though the phenomenon is well-established in chronic diseases such as Alzheimer disease and multiple sclerosis<sup>15,16</sup> and even informs guidelines for multiple sclerosis.<sup>17</sup>

Considerable differences may exist between the COI in the management of the AD disease burden and patients' unmet needs. Studies of patient satisfaction with care are an important tool for identifying country-wide gaps in addressing the AD burden. Current research on novel or optimized treatment regimens often focuses on treating the clinically visible signs and symptoms of AD while neglecting the psychosocial burden faced by both the patients and their caregivers. Although these aspects of burden improve demonstrably with the treatment of disease signs and symptoms, many patients and caregivers report a desire for their physicians would acknowledge and address elements such as caregiver-reported mental illness, sleep dysfunction, and personal expenses. All eight COI in this report have strived to implement effective pharmaceutical interventions to treat the physical symptoms of AD, but some countries have also successfully implemented other types of interventions (mostly educational) to assist patients and caregivers with disease management and to mitigate the considerable psychosocial burden associated with AD.

This report identifies and summarizes the research that has been conducted in eight COI: the United Kingdom (UK), United States (US), Germany, Denmark, France, Italy, Canada, and Australia. Studies were included in the literature review if they pertained to the disease burden, unmet needs of patients and caregivers, and/or satisfaction with care. Findings from each COI may inform future research addressing each of these factors.

<sup>11</sup>Eichenfield, L. F. et al. *Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies.* *J. Am. Acad. Dermatol.* 71, 116–132 (2014).

<sup>12</sup>Finlay, A. Y. & Khan, G. K. *Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use.* *Clin Exp Dermatol* 19, 210–216 (1994).

<sup>13</sup>Capozza, K. et al. *Insights From Caregivers on the Impact of Pediatric Atopic Dermatitis on Families: “I’m Tired, Overwhelmed, and Feel Like I’m Failing as a Mother”.* *Dermatitis* 31, 223–227 (2020).

<sup>14</sup>Cowdell, F. *Knowledge mobilisation: an ethnographic study of the influence of lay mindlines on eczema self-management in primary care in the UK.* *BMJ Open* 8, (2018).

<sup>15</sup>Dunkin, J. J. & Anderson-Hanley, C. *Dementia caregiver burden: a review of the literature and guidelines for assessment and intervention.* *Neurology* 51, S53-60; discussion S65-67 (1998).

<sup>16</sup>Maguire, R. & Maguire, P. *Caregiver Burden in Multiple Sclerosis: Recent Trends and Future Directions.* *Curr Neurol Neurosci Rep* 20, (2020).

<sup>17</sup>Köpke, S. et al. *Patient and caregiver involvement in the formulation of guideline questions: findings from the European Academy of Neurology guideline on palliative care of people with severe multiple sclerosis.* *Eur J Neurol* 26, 41–50 (2019).

# METHODS

**A PubMed literature review was conducted between October 26th and November 15th, 2020.**

The time range was set from the year 2000 onward. MeSH search terms were included for the disease and each country; for example, (“United Kingdom”[Mesh]) AND (“Dermatitis, Atopic”[Mesh] OR (“Eczema”[Mesh])) returned 221 articles, 50 of which described the burden of AD in patients and caregivers of patients with AD in the UK. Searches for the eight COI yielded a total of 1839 articles, of which 247 described the disease burden, unmet needs, and satisfaction with care of patients with AD and their caregivers. Abstracts of published articles were reviewed to assess the relevance to this report; if relevant, the full-text articles were reviewed. Additional articles were included at the discretion of the authors in areas where MeSH searches did not return robust results. These articles were obtained through independent searches and communications between team members.

Information determined to be within the scope of this review was initially synthesized into sections on burden, unmet needs, and satisfaction with care. Later, the organization was revised to better reflect the topics that emerged in the studies and to reduce redundancy. The final section topics are the disease burden (including prevalence, diagnosis, and comorbidities; physical and psychosocial consequences; caregiver burden, and financial burden), treatment, and healthcare (including utilization, patient and caregiver satisfaction with care, and patient-centered interventions).

“ Abstracts of published articles were reviewed to assess the relevance to this report; if relevant, the full-text articles were reviewed.



# UNITED KINGDOM

## Disease Burden

### Prevalence, Diagnosis, and Comorbidities

The prevalence of AD in the UK has been increasing over the past fifty years; 11%–20% of children and 5%–10% of adults in the UK currently are diagnosed with AD.<sup>18,19</sup>

Not all UK children are equally likely to have AD. The Born in Bradford study showed that children of Pakistani descent were more likely than white British children to be diagnosed with rhinitis, eczema, or wheezing disorders, perhaps indicating an increased AD burden in the UK in this ethnic minority population.<sup>20</sup> Ben-Gashir et al. found that although London-born black Caribbean children seemed to have less severe AD than white children at first glance, they actually were almost 6 times more likely to experience severe AD after making necessary adjustments to erythema scores based on skin color.<sup>21</sup> This finding points to a larger problem: the assessment of disease severity, which is essential for adequate treatment, may be an unmet need that exists in populations with darker skin.

Beyond the considerable impact of AD disease symptoms themselves, the disease burden includes comorbid conditions for which patients with AD are at increased risk. It is well-described that patients with AD are at increased risk for allergic conditions.<sup>22–24</sup> More recent epidemiologic studies are exploring other comorbid associations; for instance, Arana et al. reported a higher incidence of cancer overall, as well as of certain subtypes such as lymphoma, in patients with AD compared to the general population in the UK.<sup>25</sup> Further research is required within the UK to determine the scope of comorbid conditions and to identify any unmet needs related to their management.

<sup>18</sup>Simpson, C. R., Newton, J., Hippisley-Cox, J. & Sheikh, A. Trends in the epidemiology and prescribing of medication for eczema in England. *J R Soc Med* 102, 108–117 (2009).

<sup>19</sup>Cork, M. J., Danby, S. G. & Ogg, G. S. Atopic dermatitis epidemiology and unmet need in the United Kingdom. *J Dermatolog Treat* 31, 801–809 (2019).

<sup>20</sup>Mebrahtu, T. F., Feltbower, R. G. & Parslow, R. C. Incidence and Burden of Wheezing Disorders, Eczema, and Rhinitis in Children: findings from the Born in Bradford Cohort. *Paediatric and Perinatal Epidemiology* 30, 594–602 (2016).

<sup>21</sup>Ben-Gashir, M. A. & Hay, R. J. Reliance on erythema scores may mask severe atopic dermatitis in black children compared with their white counterparts. *Br J Dermatol* 147, 920–925 (2002).

<sup>22</sup>Hua, T. & Silverberg, J. I. Atopic dermatitis in US adults: Epidemiology, association with marital status, and atopy. *Ann Allergy Asthma Immunol* 121, 622–624 (2018).

<sup>23</sup>Silverberg, J. I. & Simpson, E. L. Associations of childhood eczema severity: a US population-based study. *Dermatitis* 25, 107–114 (2014).

<sup>24</sup>Silverberg, J. I. et al. Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults. *Ann Allergy Asthma Immunol* 121, 604–612. e3 (2018).

<sup>25</sup>Arana, A. et al. Incidence of cancer in the general population and in patients with or without atopic dermatitis in the U.K. *British Journal of Dermatology* 163, 1036–1043 (2010).

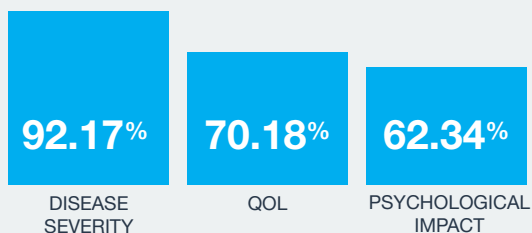
## Physical and Psychosocial Consequences

Health utility scores incorporate all aspects of an individual's health state, including physical, mental, and social determinants of health. Health utility scores for UK adults with mild, moderate, and severe AD were 0.985, 0.875, and 0.675, respectively; among UK children, the scores were 0.86, 0.69, and 0.59, respectively.<sup>26</sup> The calculated score ranges from 0 to 1, where 1 is a state of perfect health, and 0 is equivalent to death.<sup>27,28</sup>

Several studies in the UK context have examined psychosocial consequences of AD among both children and adults. In a study of UK children, Dennis et al. found that those with AD were more likely to have psychosocial difficulties compared to other peers of their age. The study also noted that parental psychological health and family functioning were important determinants of whether children coped with AD by internalized emotions, which can lead to anxiety, depression, and social withdrawal.<sup>29</sup> Ramirez et al. used the Avon Longitudinal Study of Parents and Children to examine sleep dysfunction among UK children with AD.<sup>30</sup> While the total sleep duration was not significantly different between children with and without AD, sleep quality was worse among children with AD across all severities; children with active AD of any severity had almost 50% greater odds of experiencing reduced sleep quality compared to children without AD. Sleep quality was worst among children with severe AD and comorbid asthma, which corresponded to almost 80% higher odds of reduced sleep quality.<sup>30</sup>

In a study of UK adults, Schonmann et al. used data from the UK Clinical Practice Research Datalink and found that AD was associated with an increased incidence of depression and anxiety. The strength of the association between incident depression and AD correlated positively with disease severity.<sup>31</sup> Hussain et al. analyzed the association of asthma, AD, and the combination with depression and anxiety symptoms (DAS) in UK adults aged 40–69 using data acquired from the UK Biobank.<sup>32</sup> The sample contained 502,641 patients, of whom 13,642 (2.7%) reported AD. PHQ-4 scores were used to evaluate DAS. AD patients on current therapy for their condition were found to have worse DAS than AD patients not on therapy, suggesting that patients with disease severe enough to require regular treatment experience worse QoL outcomes. Additionally, patients who were first diagnosed with AD between ages 40–59 had worse DAS than patients who were first diagnosed between ages 20–39 or 60–69.<sup>32</sup>

### Disease Severity Mentions in Documented Reports



Although AD clearly has profound impacts on both QoL and psychological well-being, dermatologists may neglect to address these components of disease burden. The British Association of Dermatologists (BAD) and the British Society for Pediatric Dermatology audited documentation from dermatology clinics and compared it to the standards for the management of AD established by the National Institute for Healthcare and Excellence (NICE). The audit found that QoL and psychologic well-being were documented less often than disease severity and treatment regimens.<sup>33</sup> Specifically, disease severity was mentioned at least once in 92.17% of documented reports; QoL was assessed at least once in only 70.18% of the reports, and psychological impact in only 62.34%. Furthermore, compared to 64.64% of reports which contained information about disease severity at every visit, only 29.34% of the reports contained information about QoL at every visit, and only 24.05% of reports contained information about psychological impact at every visit.<sup>33</sup>

*The study also noted that parental psychological health and family functioning were important determinants of whether children coped with AD by internalized emotions, which can lead to anxiety, depression, and social withdrawal.<sup>29</sup>*

<sup>26</sup>Stevens, K. J., Brazier, J. E., McKenna, S. P., Doward, L. C. & Cork, M. J. The development of a preference-based measure of health in children with atopic dermatitis. *Br J Dermatol* 153, 372–377 (2005).

<sup>27</sup>Zhang, P. et al. Health Utility Scores for People With Type 2 Diabetes in U.S. Managed Care Health Plans: Results from Translating Research Into Action for Diabetes (TRIAD). *Diabetes Care* 35, 2250–2256 (2012).

<sup>28</sup>Silverberg, J. I. et al. Health Utility Scores of Atopic Dermatitis in US Adults. *J Allergy Clin Immunol Pract* 7, 1246–1252.e1 (2019).

<sup>29</sup>Dennis, H., Rostill, H., Reed, J. & Gill, S. Factors promoting psychological adjustment to childhood atopic eczema. *J Child Health Care* 10, 126–139 (2006).

<sup>30</sup>Ramirez, F. D. et al. Association of Atopic Dermatitis With Sleep Quality in Children. *JAMA Pediatr* 173, (2019).

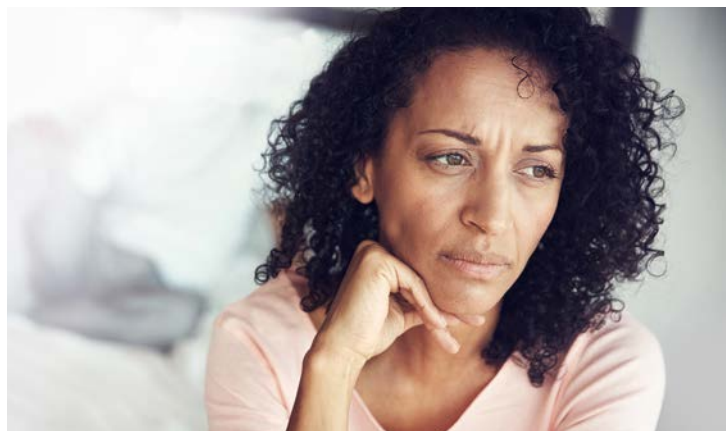
<sup>31</sup>Schonmann, Y. et al. Atopic Eczema in Adulthood and Risk of Depression and Anxiety: A Population-Based Cohort Study. *J Allergy Clin Immunol Pract* 8, 248–257.e16 (2020).

<sup>32</sup>Hussain, S. et al. Depressive and anxiety symptomatology among people with asthma or atopic dermatitis: A population-based investigation using the UK Biobank data. *Brain, Behavior, and Immunity* 90, 138–144 (2020).

<sup>33</sup>Alsharqi, A., Mustapa, M. F. M. & Berker, D. de. UK multicentre audit of the management of eczema in children. *Clinical and Experimental Dermatology* 43, 78–79 (2018).



A study by Girolomoni et al. sought to determine the economic and psychosocial burden in European patients (specifically from France, Germany, Italy, Spain, and the UK) with moderate-to-severe AD.<sup>34</sup> In the UK, 29.7% of patients with AD indicated that it affected their QoL – measured by Dermatology Life Quality Index (DLQI) – moderately (DLQI 6-10); 23.9% of patients reported a very large effect (DLQI 11-20); and 33.3% of patients reported an extremely large effect (DLQI 21-30).<sup>34</sup> Sleep disturbance, anxiety, and depression rates were also examined in patients with moderate-to-severe AD. In the UK, 30.0% and 8.5% of patients experienced either moderate or severe sleep difficulties, respectively. 61.5% of patients reported anxiety; mild, moderate, moderately severe, and severe depression was experienced by 25.1%, 19.1%, 16.6%, and 15.2% of patients, respectively, as measured by the PHQ-9.<sup>34</sup>



Howells et al. used the input of patients and caregivers to develop measures of AD “control.”<sup>35</sup> Patients and caregivers noted that symptoms of AD may change over time, so a reasonable measure of control involves the return to the patient or caregiver’s definition of “normal.” A common sentiment expressed by patients and caregivers was that self-reporting should be the primary method of assessing one’s control of AD, as each person’s perception of “control” was too unique and too variable to be solely determined by the healthcare provider.<sup>35</sup> A patient-centered definition of “control” may focus as much on the psychologic impact, itch/scratch burden, limitations in activities of daily living, and social impact as on the classic signs and symptoms. Ghio et al. considered both objective disease symptoms and the subjective QoL burden and identified three psychosocial needs: to feel understood, to feel “normal,” and for emotional support. The relative salience of these needs appeared to correlate with both the patient’s age and disease severity; university-aged individuals and those with severe disease expressed a greater desire to be understood, while younger individuals and those with mild disease expressed a greater desire to feel normal.<sup>36</sup>

**Sleep disturbance, anxiety, and depression rates were also examined in patients with moderate-to-severe A.D.**

## Caregiver Burden

An interview-based study by Santer et al. found that the primary source of caregiver burden was the implementation of treatment regimens; topical regimens in particular can take multiple hours to complete over the course of a day. Caregivers felt exhausted by the treatment requirements and guilty if they missed treatments.<sup>37</sup> While certainly not unique to the UK, the considerable variance in opinions about evidence-based treatment regimens may result in undertreatment of AD and additional uncertainty and stress for caregivers.<sup>38</sup>

In light of the difficulty and uncertainty associated with topical regimens, it is perhaps unsurprising that caregivers often search for causes and solutions—most often, diet. Chan et al. surveyed 211 caregivers and adults mostly in the UK and found that 68% of children and 46% of adults with AD were excluding at least one food from their diet; of those, 40% of the children and 52% of the adults were excluding foods specifically to reduce symptoms of AD.<sup>39</sup> Of course, diet modifications for children usually require substantial effort from caregivers, and unfortunately, the benefit is unclear—there are no robust data to support any particular dietary intervention for AD.<sup>40</sup> The lack of robust data leaves caregivers to browse online, where they often feel dissatisfied with the amount of information, quality of information, and uncertainty about financial interests underlying the promoted treatment options.<sup>41</sup>

The substantial caregiver burden may manifest in psychosocial symptoms. A longitudinal cohort study conducted in Avon, UK followed new mothers whose child was or was not diagnosed with AD; the study focused on maternal metrics related to sleep quality when the child was aged 6

<sup>34</sup>Girolomoni, G. et al. *The Economic and Psychosocial Comorbidity Burden Among Adults with Moderate-to-Severe Atopic Dermatitis in Europe: Analysis of a Cross-Sectional Survey*. *Dermatol Ther (Heidelb)* 11, 117–130 (2021).

<sup>35</sup>Howells, L. M. et al. ‘When it goes back to my normal I suppose’: a qualitative study using online focus groups to explore perceptions of ‘control’ among people with eczema and parents of children with eczema in the UK. *BMJ Open* 7, (2017).

<sup>36</sup>Ghio, D. et al. *Psychosocial needs of adolescents and young adults with eczema: A secondary analysis of qualitative data to inform a behaviour change intervention*. *British Journal of Health Psychology* n/a.

<sup>37</sup>Santer, M. et al. *Managing childhood eczema: qualitative study exploring carers’ experiences of barriers and facilitators to treatment adherence*. *Journal of Advanced Nursing* 69, 2493–2501 (2013).

<sup>38</sup>Santer, M. et al. *Experiences of carers managing childhood eczema and their views on its treatment: a qualitative study*. *Br J Gen Pract* 62, e261–e267 (2012).

<sup>39</sup>Chan, J. & Ridd, M. J. *Beliefs and practices among adults with eczema and carers of children with eczema regarding the role of food allergy*. *Clinical and Experimental Dermatology* 44, e235–e237 (2019).

<sup>40</sup>Wollenberg, A. et al. *Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I*. *Journal of the European Academy of Dermatology and Venereology* 32, 657–682 (2018).

<sup>41</sup>Santer, M. et al. ‘You don’t know which bits to believe’: qualitative study exploring carers’ experiences of seeking information on the internet about childhood eczema. *BMJ Open* 5, e006339 (2015).

months and then 11 years. Mothers of children with AD reported significantly greater difficulty falling asleep, subjectively insufficient sleep, and daytime exhaustion compared to mothers of children without AD; all these measures were worse in mothers of children with severe AD.<sup>42</sup> Moore et al. surveyed parents of children with either asthma or moderate-to-severe atopic eczema and found that mothers and fathers of children with moderate-to-severe atopic eczema lost a median of 39 and 45 minutes of sleep per night compared to 0 minutes of sleep lost per night in parents of children with asthma. Of note, sleep disturbance was significantly associated with anxiety and depression scores in mothers and with anxiety scores in fathers.<sup>43</sup>

Unfortunately, struggling caregivers can have unintentional detrimental effects on their children. In an analysis of 7,250 children from the Avon Longitudinal Study of Parents and Children, Teyhan et al. found that maternal anxiety and depression was associated with a stronger tendency for eight year old children to internalize their symptoms (a proxy for childhood anxiety and depression symptoms).<sup>44,45</sup>

## Financial Burden

The personal financial burden for patients and caregivers in the UK is smaller than in countries such as the US and Australia.<sup>45</sup> A 2001 study conducted by Emerson et al. found an estimated personal financial cost of £28.94 annually per child; the most common expenses were making changes in the home environment, transportation, over-the-counter (OTC) medications, and consultations with alternative healthcare providers. In one family, consultations with an alternative healthcare provider totaled £625 over a 12-month period.<sup>46</sup>

The Girolomoni et al study also evaluated the economic impact of moderate-to-severe AD. The economic impact was described in terms of work absenteeism %, work presenteeism %, and overall work impairment; all of which were assessed by the Work Productive and Activity Impairment: General Health (WPAI-GH) questionnaire.<sup>34</sup> In the UK, rates of absenteeism (absent from work in the past 7 days) ranged from 10.9% for those in the moderate effect DLQI group to 23.9% in the extremely large effect group; rates of presenteeism (AD impacted work performance within the past 7 days) ranged from 29.5% in the moderate effect group to 60.6% in the extremely large effect group; and overall work impairment rates (combining both absenteeism and presenteeism) ranged from 32.3% in the moderate effect group to 67.9% in the extremely large effect group.<sup>34</sup>

## Treatment

Current treatments are often inadequate for severe AD,<sup>19</sup> leading to decreased QoL and negative psychosocial impacts. In a retrospective study utilizing the UK Health Improvement Network, Eckert et al. noted that the unmet need for the treatment of AD manifests in high prevalence of comorbidities such as depression and contact dermatitis. Systemic treatments are available but are associated with potentially significant side effects, though the newer therapy dupilumab is a safer and effective option. Still, a recent study found that 6.6% of patients with AD were requiring systemic steroids or another immunosuppressive therapy and therefore exposed to the side effects that come with these treatment options.<sup>47</sup>

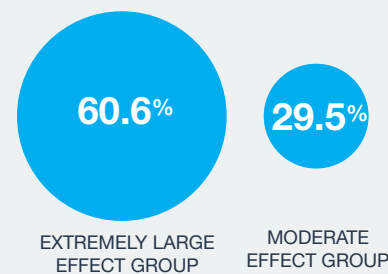
For less severe AD, both emollients and potent topical corticosteroids (TCS) can be highly effective but often are underutilized. Cork et al. found that 24% of children were not being treated with emollients, and 25% of children were not using TCS according to guidelines. Teasdale et al.'s analysis of UK social media platforms found that caregivers were concerned that TCS use might cause harms such as skin damage and withdrawal rash symptoms.<sup>48</sup> In a survey-based study of



The most common expenses were making changes in the home environment, transportation, over-the-counter (OTC) medications, and consultations with alternative healthcare providers.

### Rates of Presenteeism

(AD impacted work performance within the past 7 days)



<sup>42</sup>Ramirez, F. D. et al. Assessment of Sleep Disturbances and Exhaustion in Mothers of Children With Atopic Dermatitis. *JAMA Dermatol* 155, 556–563 (2019).

<sup>43</sup>Moore, K., David, T. J., Murray, C. S., Child, F. & Arkwright, P. D. Effect of childhood eczema and asthma on parental sleep and well-being: a prospective comparative study. *British Journal of Dermatology* 154, 514–518 (2006).

<sup>44</sup>Teyhan, A., Galobardes, B. & Henderson, J. Child Allergic Symptoms and Mental Well-Being: The Role of Maternal Anxiety and Depression. *J Pediatr* 165, 592–599.e5 (2014).

<sup>45</sup>Herd, R. M. The financial impact on families of children with atopic dermatitis. *Arch Dermatol* 138, 819–820 (2002).

<sup>46</sup>Emerson, R. M., Williams, H. C. & Allen, B. R. What is the cost of atopic dermatitis in preschool children? *Br J Dermatol* 144, 514–522 (2001).

<sup>47</sup>Eckert, L. et al. Treatment patterns in UK adult patients with atopic dermatitis treated with systemic immunosuppressants: data from The Health Improvement Network (THIN). *J Dermatolog Treat* 31, 815–820 (2020).

<sup>48</sup>Teasdale, E. J., Muller, I. & Santer, M. Carers' views of topical corticosteroid use in childhood eczema: a qualitative study of online discussion forums. *British Journal of Dermatology* 176, 1500–1507 (2017).

200 patients with AD, 24% reported non-compliance with TCS due to fears about potential side effects.<sup>49</sup> Patients may also be reluctant to step up therapy during exacerbations out of fear that the treatments might stop working and they would be left with no alternative.<sup>35</sup>

Beyond concerns about TCS use, uncertainty about treatment plans explains many instances of poor adherence. Cork et al. found that less than 5% of parents of children with AD remembered having discussions about the causes of AD or the proper treatments for AD. Batchelor et al. identified four treatment uncertainties most commonly shared by patients and healthcare providers: the optimal use of TCS, safety of TCS, food allergy testing, and emollient use in AD.<sup>50</sup> Meanwhile, patients and caregivers shared uncertainty about psychologic interventions for itching, bathing methods, natural products, irritant and allergen avoidance, diet, and supplements.<sup>50</sup> For parents caring for infants, Gore et al. identified nine areas in which parents requested more information, ranging from medication use and side effects to treatments and diet.<sup>51</sup>



Batchelor et al. identified four treatment uncertainties most commonly shared by patients and healthcare providers: [the optimal use of topical corticosteroids \(TCS\), safety of TCS, food allergy testing, and emollient use in AD.](#)<sup>50</sup>

Prescribing practices in AD may differ between primary care providers may differ from established guidelines.<sup>52</sup> Santer et al. examined prescriptions for children with AD over a 17-month period and found that less than half of the children received an emollient. 22.8% of patients were prescribed a TCS; 15.9% of these patients received a potent TCS, and 60.2% of patients prescribed TCS received a combination of TCS and antibiotics, suggesting that maintenance therapy could be improved and more judicious use of potent TCS/antimicrobial formulations may be indicated.<sup>52</sup> In the primary care setting specifically, 44% of patients with AD were not using any emollient, and providers rarely prescribed higher potency TCS for more severe disease.<sup>53</sup> De Lusignan et al. reported that potent and very potent TCS were less likely to be prescribed to non-white patients and patients with low socioeconomic status.<sup>54</sup>

## Healthcare

### Healthcare Utilization

Patients with AD in the UK may benefit from increased access to care from dermatologists and a reduced reliance on primary care providers. Baron et al. found that new adult patients referred from primary care to a dermatologist improved significantly in both the Severity Scoring of AD (SCORAD) and the Dermatology Life Quality Index (DLQI) over the course of three months.<sup>55</sup> In UK primary care practice settings, only 46% of patients diagnosed with AD actually met the UK criteria for diagnosis. Specifically, providers' assessments had 44% agreement with the Eczema Area and Severity Index (EASI) and 48% with the parent-assessed Patient Oriented Eczema Measure (POEM). Furthermore, primary care providers seem to underutilize both emollients and higher

<sup>49</sup>Charman, C. R., Morris, A. D. & Williams, H. C. Topical corticosteroid phobia in patients with atopic eczema. *British Journal of Dermatology* 142, 931–936 (2000).

<sup>50</sup>Batchelor, J. M. et al. The Eczema Priority Setting Partnership: a collaboration between patients, carers, clinicians and researchers to identify and prioritize important research questions for the treatment of eczema. *Br J Dermatol* 168, 577–582 (2013).

<sup>51</sup>Gore, C., Johnson, R. J., Caress, A. L., Woodcock, A. & Custovic, A. The information needs and preferred roles in treatment decision-making of parents caring for infants with atopic dermatitis: a qualitative study. *Allergy* 60, 938–943 (2005).

<sup>52</sup>Santer, M., Lewis-Jones, S. & Fahey, T. Appropriateness of prescribing for childhood eczema: evidence from a community-based study. *Clinical and Experimental Dermatology* 31, 671–673 (2006).

<sup>53</sup>Jacquet, L., Gaunt, D. M., Garfield, K. & Ridd, M. J. Diagnosis, assessment, and treatment of childhood eczema in primary care: cross-sectional study. *BJGP Open* 1, bigpopen17X1000821 (2017).

<sup>54</sup>de Lusignan, S. et al. Patterns and trends in eczema management in UK primary care (2009–2018): A population-based cohort study. *Clin Exp Allergy* (2020) doi:10.1111/cea.13783.

<sup>55</sup>Baron, S. E., Morris, P. K., Dye, L., Fielding, D. & Goulden, V. The effect of dermatology consultations in secondary care on treatment outcome and quality of life in new adult patients with atopic dermatitis. *British Journal of Dermatology* 154, 942–949 (2006).

potency TCS for more severe disease.<sup>53</sup> Primary care providers are less likely than specialists to view AD as a chronic condition and tend to assign it a less significant priority.<sup>14</sup> Notably, non-white patients and patients with low SES were less likely to be referred to a dermatologist.<sup>54</sup>

The Girolomoni et al study examined rates of healthcare provider visits, emergency department visits, and hospitalizations (all within the past 6 months) among patients with moderate-to-severe AD stratified by moderate, very large, and extremely large impact to DLQI.<sup>34</sup> Significant differences in the UK cohort were found in emergency department visit rates (0.25%, 0.47%, and 1.00% in the moderate, very large, and extremely large effect groups, respectively) and hospitalization rates (0.68%, 0.57%, and 1.52%, respectively).<sup>34</sup>

## Satisfaction with Care

Patients and their caregivers may be dissatisfied with care when there are misaligned conceptualizations of the disease, treatment goals, and priorities.

One difference in perspectives involves the nature of AD itself. A study involving 14 general practices across the UK found “several areas of dissonance,” including that parents often searched for an underlying cause, such as an allergen, while GPs sought to manage AD as a chronic condition.<sup>56</sup> Santer et al. affirmed that caregivers and healthcare providers disagreed about the chronic nature of AD; parents often expressed frustration that diet interventions and allergy testing were not pursued.<sup>37</sup> The Chan et al. questionnaire-based study found that 57% of respondents (adults with AD or caregivers of children with AD) had discussed the role of diet in AD with their provider, and 38% of respondents who did were dissatisfied with the conversation.<sup>39</sup>

Diverging conceptualizations of the disease translate into diverging perspectives on treatment strategies—caregivers focus on finding cures for their child’s AD, while the current treatment guidelines focus on disease control.<sup>38</sup> In the aforementioned study of 14 general practices, parents were more likely to view emollients as a passive method of treatment, while GPs viewed moisturization as an active form of treatment. GPs often attributed disease recurrence to poor adherence to topical treatment regimens, while parents doubted the efficacy of emollient therapy and voiced concerns about the side effects of long-term TCS use.<sup>56</sup> Santer et al. found that caregivers were generally dissatisfied with the information available about treatment options, but they were most dissatisfied with information about the efficacy of emollient therapy and TCS therapy.<sup>41</sup>

Despite these diverging views on treatment goals and measures of success, providers expected that patients would adhere to treatment regimens and yet did not prioritize patient education. These “mindlines,” or mental schemas, toward AD were held by experienced providers, indicating a need for further education about the disease burden and current guidelines for evidence-based treatment.<sup>14</sup> The same study investigated the mindlines of patients at a general practice in central England, and four common beliefs emerged: “the doctor knows best,” “it’s not worth bothering the doctor,” “I need to manage this myself,” and “now I know what to do.” The author argued that changing both the mindlines held by providers about AD and mindlines held by patients about doctors and their own AD may lead to improvements in care.<sup>14</sup>

Finally, a difference in priorities may lead to dissatisfaction during medical encounters. In the aforementioned study of 14 general practices, parents and GPs took different approaches to severity; parents focused on the psychosocial impact, while GPs focused on the severity of the signs and symptoms.<sup>56</sup> In an evaluation of the information needs and treatment decision-making roles of parents of children with AD, Gore et al. found that parents of infants with AD often felt their concerns were not taken seriously and had to invest extra effort to receive sufficient information regarding AD from their provider.<sup>51</sup> Santer et al. found that some parents felt that their child’s physician was not dedicating enough time or support to their child’s AD.<sup>41</sup>

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*Santer et al. found that caregivers were generally dissatisfied with the information available about treatment options, but they were most dissatisfied with information about the efficacy of emollient therapy and TCS therapy.<sup>4</sup>*

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<sup>56</sup>Powell, K., Le Roux, E., Banks, J. & Ridd, M. J. GP and parent dissonance about the assessment and treatment of childhood eczema in primary care: a qualitative study. *BMJ Open* 8, (2018).

## Patient-Centered Interventions

Powell et al. advocated for a Written Action Plan (WAP) as a method for clear communications with caregivers. The WAP was developed with the input of caregivers, who preferred plans that were individualized, concise, and clear about the criteria for stepping down and stepping up therapy.<sup>57</sup>

Several interventions have aimed to promote adequate emollient usage. An “educational support program” evaluated by Mason et al. significantly increased emollient use among children with AD and improved several measures of burden: the Patient Oriented Eczema Measure (POEM) scores, sleep disturbances, and parental feelings of control.<sup>20</sup> An educational intervention from a dermatologic nurse resulted in an increase in emollient therapy but no increase in TCS use; the intervention was successful at reducing the severity of AD by 89%.<sup>58</sup> Santer et al. interviewed parents and caregivers of children 5 years of age or younger about eczema therapies and used these responses to develop a web-based intervention. This intervention was then used in another cohort of parents of children 5 years of age or younger with eczema in order to judge the effectiveness of the intervention. Parents and caregivers in the initial cohort believed that emollient use improved AD to some extent but were unsure about long-term effectiveness; all parents surveyed after completing the web intervention believed emollients provided long-term benefit for eczema care.<sup>39</sup>

Effective education programs seem to be one viable method and may be especially valuable for their ability to ease the financial burden of the disease.

The modest success of these emollient-focused interventions reflects one of the previously discussed components of the caregiver burden: uncertainty about the most effective ways to manage their child’s AD. Effective education programs seem to be one viable method and may be especially valuable for their ability to ease the financial burden of the disease—patients who were prescribed emollients (relative to those who were not) incurred lower per-visit costs, had fewer primary care visits, and required fewer high-potency TCS and antibiotic prescriptions.<sup>59</sup> Multicenter randomized control trials are likely required to assess the effectiveness of these interventions.<sup>60</sup>

Other interventions have focused more broadly on nurse-led interventions to improve communication and dedicate adequate time to managing a complex disease. In one study, patients seen at a nurse-led clinic were more effective at acquiring prescriptions and finding avenues for additional support for AD, compared to patients seen at only a dermatology clinic.<sup>61</sup> De Vere Hunt et al. examined the impact of a dermatology clinic with dedicated dermatologic nursing and clinical psychologic support on teenage patients with skin disorders. All patients with skin disorders were “very satisfied” or “satisfied” with their care from the doctor or clinical psychologist, and the AD cohort experienced significantly improved Teenage Quality of Life scores (T-QoL) at a follow-up appointment with a consultant psychologist compared to their baseline T-QoL scores.<sup>62</sup> Finally, in the Eczema Education Programme (EEP) for parents of children with AD, a nurse-led intervention educated parents about disease processes, triggers, appropriate treatment, and strategies for reducing itch and sleep disturbances, all with the goal of improving treatment outcomes and QoL for both the children and caregivers.<sup>60</sup> Among caregivers who participated in at least two EEP sessions, 98% were satisfied with the EEP; of those, 90% were “very satisfied.”<sup>60</sup>

<sup>57</sup>Powell, K., Le Roux, E., Banks, J. P. & Ridd, M. J. Developing a written action plan for children with eczema: a qualitative study. *Br J Gen Pract* 68, e81–e89 (2018).

<sup>58</sup>Cork, M. J. et al. Comparison of parent knowledge, therapy utilization and severity of atopic eczema before and after explanation and demonstration of topical therapies by a specialist dermatology nurse. *Br J Dermatol* 149, 582–589 (2003).

<sup>59</sup>Moncrieff, G. et al. Cost and effectiveness of prescribing emollient therapy for atopic eczema in UK primary care in children and adults: a large retrospective analysis of the Clinical Practice Research Datalink. *BMC Dermatol* 18, (2018).

<sup>60</sup>Jackson, K., Ersser, S. J., Dennis, H., Farasat, H. & More, A. The Eczema Education Programme: intervention development and model feasibility. *J Eur Acad Dermatol Venereol* 28, 949–956 (2014).

<sup>61</sup>Gradwell, C., Thomas, K. S., English, J. S. C. & Williams, H. C. A randomized controlled trial of nurse follow-up clinics: do they help patients and do they free up consultants’ time? *Br J Dermatol* 147, 513–517 (2002).

<sup>62</sup>Hunt, I. D. V. et al. Establishing and developing a Teenage and Young Adult dermatology clinic with embedded specialist psychological support. *Clinical and Experimental Dermatology* 44, 893–896 (2019).

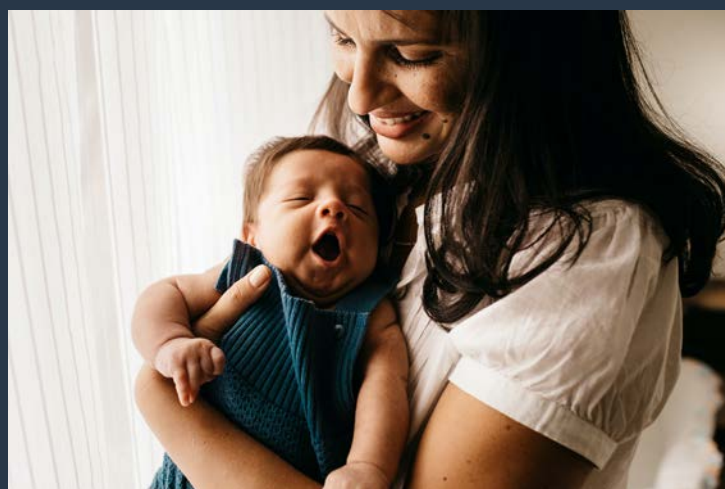
## KEY FINDINGS

Patients with AD and their caregivers in the UK experience significant burden due to disease symptoms and psychosocial consequences of AD. Several studies have characterized the QoL and psychosocial burdens, but relatively few studies assessed interventions to mitigate them. Different subsets of the increasingly diverse population in the UK have unique needs regarding AD, and future studies should better characterize these differences to reduce inequalities in diagnosis and treatment based on race and SES. Finally, few studies in the UK have mapped the comorbidities associated with AD; this topic is better studied in the US, Germany, and Denmark.

A misalignment in the conceptualization of AD and treatment goals causes patient and caregiver dissatisfaction with care and suboptimal treatment. Providers tend to focus on visible disease manifestations, but many patients care just as much about improving QoL, reducing itching and scratching, improving sleep, and alleviating mental health symptoms. Survey studies conducted in the UK noted that some patients and caregivers felt these concerns were not evaluated as thoroughly as those pertaining to physical disease symptoms. Furthermore, providers focus on managing the symptoms of AD while caregivers search for a treatable cause, often leading to the pursuit of burdensome dietary changes without demonstrated benefit.

Both parents and caregivers experience confusion regarding appropriate and effective treatment regimens, adding to the caregiver burden and reducing adherence to the evidence-based recommendations for emollient and TCS use. Critically, patients and caregivers have mixed feelings regarding the effectiveness of emollient therapy and the safety of TCS therapy. Educational interventions succeeded at increasing adherence to treatment regimens and improving outcomes. Although the personal financial burden is not as dramatic in the UK as in other countries, the cost of AD treatment still can be significant, and costly alternative therapies for AD may add to this measure of burden. Increasing adherence to emollient therapy as outlined in the study by Mason et al. was found to be both efficacious and cost neutral.<sup>63</sup>

Several additional interventions have had modest success in the UK by devoting sufficient time to patient education and clear communication, often with nurse-led programs. These preliminary findings suggest that the key to improving patient satisfaction may be thorough strategies like education with continuous reinforcement of key ideas. The ongoing development of additional treatment options for severe disease and more efficacious treatments may significantly reduce the burden, address unmet needs, and increase satisfaction with treatment options and healthcare delivery in the UK.



<sup>63</sup>Mason, J. M. et al. Improved emollient use reduces atopic eczema symptoms and is cost neutral in infants: before-and-after evaluation of a multifaceted educational support programme. *BMC Dermatol* 13, 7 (2013).



# UNITED STATES

## Disease Burden

### Prevalence, Diagnosis, and Comorbidities

The 2019 Atopic Dermatitis in America (ADIA) study found a prevalence of AD of 7.3% in a cohort of 1,278 US adults.<sup>4</sup> Of those with AD, 28.9% had moderate disease and 11% had severe disease.

Extrapolating to the entire US population, the authors estimated that 6.6 million US adults in the US met criteria for moderate-to-severe AD.<sup>4</sup> US children have an estimated AD prevalence between 6% and 12.98%<sup>64</sup>; a cross-sectional study of 10 primary care practices in 5 US states found a lifetime prevalence of AD of 24% of US children aged 0 to 5 years;<sup>65</sup> a different study estimated a lifetime prevalence of 15% among children under the age of 1 and 38% among children aged 4 to 5 years.<sup>44</sup>

Several studies have suggested that the prevalence of AD may vary across several demographic dimensions. The ADIA study found that the odds of receiving an AD diagnosis were higher for female patients (vs. male patients), for those with an annual household income of less than \$15,000 (vs. higher income categories), and for multiracial non-Hispanic patients (vs. white non-Hispanic patients).<sup>4</sup> Similarly, Silverberg et al. found that AD was more prevalent in multiracial patients (14.6%) than in white patients (10.5%) and Black patients (7.7%).<sup>80</sup>

Black patients may be at higher risk for undiagnosed AD because the morphology differs from the erythematous patches that physicians are trained to recognize in white patients.<sup>66</sup> Despite the possibility of underdiagnosis, some studies have found that AD is more prevalent and persistent in non-Hispanic Black children than in non-Hispanic white children.<sup>67,68</sup> Similarly, a prospective cohort study of 4,898 women and children residing in 20 urban environments found that Black children had increased odds of having persistent AD. Additionally, the prevalence of AD among urban children of all races in the US was estimated at 15%,<sup>69</sup> higher than overall national

<sup>64</sup>Silverberg, J. I. Public Health Burden and Epidemiology of Atopic Dermatitis. *Dermatol Clin* 35, 283–289 (2017).

<sup>65</sup>Al-Naqeeb, J. et al. The Burden of Childhood Atopic Dermatitis in the Primary Care Setting: A Report from the Meta-LARC Consortium. *J Am Board Fam Med* 32, 191–200 (2019).

<sup>66</sup>Vachiramon, V., Tey, H. L., Thompson, A. E. & Yosipovitch, G. Atopic Dermatitis in African American Children: Addressing Unmet Needs of a Common Disease. *Pediatric Dermatology* 29, 395–402 (2012).

<sup>67</sup>Abuabara, K. et al. Genetic ancestry does not explain increased atopic dermatitis susceptibility or worse disease control among African American subjects in 2 large US cohorts. *J Allergy Clin Immunol* 145, 192–198.e11 (2020).

<sup>68</sup>Kim, Y. et al. Racial/ethnic differences in incidence and persistence of childhood atopic dermatitis. *J Invest Dermatol* 139, 827–834 (2019).

<sup>69</sup>McKenzie, C. & Silverberg, J. I. The prevalence and persistence of atopic dermatitis in urban United States children. *Ann Allergy Asthma Immunol* 123, 173–178.e1 (2019).



Evidence suggests multiracial patients, urban patients and Black patients experience the highest burden of disease and thus the highest concentration of unmet needs.

estimates.<sup>70</sup> In short, the evidence suggests multiracial patients, urban patients and Black patients experience the highest burden of disease and thus the highest concentration of unmet needs.

A wealth of US-based studies investigated comorbid conditions. Patients with AD have a heightened risk of autoimmune disorders,<sup>71</sup> ocular disease,<sup>72</sup> infections (including serious, extracutaneous, and systemic infections)<sup>73</sup>, decreased physical activity,<sup>74</sup> headaches,<sup>75</sup> cardiovascular disease,<sup>76</sup> central obesity and high blood pressure (specifically in children with moderate-to-severe AD),<sup>77</sup> osteoporosis and osteopenia,<sup>78</sup> reduced bone mineral density (BMD) in children (particularly in malnourished children and Hispanic children),<sup>79</sup> and fractures and joint injury.<sup>80</sup> In general, disease severity is correlated with the likelihood of experiencing comorbidities.<sup>81,82</sup>

## Physical and Psychosocial Consequences

The burden inflicted directly by physical symptoms has been well described by several studies. The ADIA study found that AD patients were most bothered by itch, dryness and scaling, and red or inflamed skin.<sup>4</sup> Skin pain has been identified as a separate, distinct symptom from itch and inflammation; skin pain was present in 61% of adults surveyed in the ADIA study and was reported to be caused most commonly by scratching, followed by fissures in the skin, skin inflammation, and to a lesser extent by burning/stinging from topicals.<sup>83</sup>

The severity and persistence of physical symptoms translates into poorer quality of life in many domains. In the ADIA study, patients with AD and especially those with severe disease involvement had higher scores (denoting poorer outcomes) on the DLQI than control patients;<sup>4</sup> among those with severe AD, 68.8% of patients reported a moderate to large effect on their quality of life.<sup>4</sup>

The QoL burden of AD can be compared quantitatively with other disease burdens via health utility metrics; in the US, these studies have focused on adults. In a cross-sectional study of 3,495 US adults with AD, Silverberg et al. used the SF-6D to determine health utilities scores. US adults with AD averaged an SF-6D score of 0.69, significantly lower than the 0.79 averaged by adults without AD. An even lower score was associated with severe AD (0.59). Interestingly, when AD disease onset was within 2 years of the survey, lower SF-6D scores than other chronic conditions such as autoimmune disorders, diabetes, food allergy, and heart disease were observed.<sup>28</sup> The

<sup>70</sup>Hua, T. & Silverberg, J. I. Atopic dermatitis is associated with increased hospitalization in US children. *Journal of the American Academy of Dermatology* 81, 862–865 (2019).

<sup>71</sup>Narla, S. & Silverberg, J. I. Association between atopic dermatitis and autoimmune disorders in US adults and children: A cross-sectional study. *J Am Acad Dermatol* 80, 382–389 (2019).

<sup>72</sup>Govind, K., Whang, K., Khanna, R., Scott, A. W. & Kwatra, S. G. Atopic dermatitis is associated with increased prevalence of multiple ocular comorbidities. *J Allergy Clin Immunol Pract* 7, 298–299 (2019).

<sup>73</sup>Narla, S. & Silverberg, J. I. Association between atopic dermatitis and serious cutaneous, multiorgan and systemic infections in US adults. *Ann Allergy Asthma Immunol* 120, 66–72.e11 (2018).

<sup>74</sup>Silverberg, J. I. et al. Atopic Dermatitis Is Associated with Less Physical Activity in US Adults. *J Invest Dermatol* 136, 1714–1716 (2016).

<sup>75</sup>Silverberg, J. I. Association between childhood eczema and headaches: An analysis of 19 US population-based studies. *J Allergy Clin Immunol* 137, 492–499.e5 (2016).

<sup>76</sup>Silverberg, J. I. Association between adult atopic dermatitis, cardiovascular disease, and increased heart attacks in three population-based studies. *Allergy* 70, 1300–1308 (2015).

<sup>77</sup>Silverberg, J. I. et al. Central obesity and high blood pressure in pediatric patients with atopic dermatitis. *JAMA Dermatol* 151, 144–152 (2015).

<sup>78</sup>Shahen, M. S. & Silverberg, J. I. Atopic dermatitis is associated with osteoporosis and osteopenia in older adults. *Journal of the American Academy of Dermatology* 80, 550–551 (2019).

<sup>79</sup>Silverberg, J. I. Association between childhood atopic dermatitis, malnutrition, and low bone mineral density: a US population-based study. *Pediatr Allergy Immunol* 26, 54–61 (2015).

<sup>80</sup>Garg, N. & Silverberg, J. I. Association between eczema and increased fracture and bone or joint injury in adults: a US population-based study. *JAMA Dermatol* 151, 33–41 (2015).

<sup>81</sup>Eckert, L. et al. The burden of atopic dermatitis in US adults: Health care resource utilization data from the 2013 National Health and Wellness Survey. *J Am Acad Dermatol* 78, 54–61.e1 (2018).

<sup>82</sup>Shrestha, S. et al. Burden of Atopic Dermatitis in the United States: Analysis of Healthcare Claims Data in the Commercial, Medicare, and Medi-Cal Databases. *Adv Ther* 34, 1989–2006 (2017).

<sup>83</sup>Silverberg, J. I. et al. Pain Is a Common and Burdensome Symptom of Atopic Dermatitis in United States Adults. *J Allergy Clin Immunol Pract* 7, 2699–2706.e7 (2019).



Medical Expenditure Survey (MEPS) also used the SF-6D and found significantly lower SF-6D scores in adults with versus without AD (0.69 vs. 0.76;  $p = 0.04$ ). The SF-6D decreased further in AD patients with comorbid anxiety, depression, or lower SES.<sup>84</sup>

Zimmerman et al. used a similar quality of life survey, the EQ-5D, as part of dermatology clinical trials of dupilumab. Among US adults who were unresponsive to topical therapy, those with moderate disease scored an average of 0.684, while those with severe AD scored 0.535 prior to treatment with dupilumab. Interestingly, these scores are lower than in European studies that used the EQ-5D; the European Tacrolimus Ointment Study found average scores of 0.770 and 0.665 among adults with moderate and severe AD, respectively.<sup>85</sup>

# 24.73%

of adults with AD reported clinically significant anxiety and

# 13.98%

 met clinical criteria for depression

Other studies have examined the impact of AD on specific QoL dimensions—sleep, anxiety, and depression—and again, studies in the US context have focused predominantly on adults. Regarding sleep, the National Health and Nutrition Examination Survey (NHANES) found that patients with AD were more likely than controls to have sleep disturbances, a short sleep duration, difficulty falling asleep, early morning awakenings, feeling unrested, and feeling too fatigued to perform Instrumental Activities of Daily Living (IADLs).<sup>86</sup> Utilizing the 2012 National Health Interview Survey (NHIS), Silverberg et al. found that adults with AD were at higher odds of experiencing fatigue, daytime sleepiness, and insomnia after controlling for sleep duration, allergies, demographic factors, and body mass index (BMI). Adults with AD and either fatigue, sleepiness, or insomnia were at increased risk for poorer health status, absenteeism from work, and increased healthcare utilization.<sup>87</sup>

Regarding psychiatric consequences, in an analysis of the 2013 US National Health and Wellness Survey, Eckert et al. compared patients with AD to non-AD controls and found significantly more anxiety (29.8% vs. 16.1%), depression (31.2% vs. 17.3%), and sleep disorders (33.2% vs. 9.2%).<sup>81</sup> An analysis of the 2004–2015 Medical Expenditure Surveys (MEPS) found that adults with (vs. without) AD were more likely to screen positive for depression via the PHQ-2 assessment and severe psychologic distress via the Kessler-6 (K-6) index; patients with AD and low SES had even more severe K-6 scores.<sup>88</sup> An analysis of the 2005–2006 NHANES and 2012 NHIS databases found that adults with (vs. without) AD had a higher likelihood of depression as measured by the PHQ-9 survey; they also were more likely to have moderate or severe depression, to have had depression within the past year, and to have had depression ever in their lives.<sup>89</sup> Depression in AD has been associated with pruritus, sleep loss, unhappiness with the appearance of skin lesions, and personal financial costs.<sup>89</sup>

The ADIA study also examined associations between AD and both anxiety and depression. 24.73% of adults with AD reported clinically significant anxiety and 13.98% met clinical criteria for depression;<sup>4</sup> suggesting the presence of clinically significant, untreated mental health conditions in this population. Adults with (vs. without) AD also scored higher on the surveys for Hospital Anxiety and Depression Scale-Anxiety (HADS-A) and HADS-Depression (HADS-D).<sup>90</sup> Higher HADS-A and

<sup>84</sup> Cheng, B. T. & Silverberg, J. I. Association between atopic dermatitis and lower health utility scores in US adults. *Ann Allergy Asthma Immunol* 124, 88–89 (2020).

<sup>85</sup> Poole, C. D., Chambers, C., Allsopp, R. & Currie, C. J. Quality of life and health-related utility analysis of adults with moderate and severe atopic dermatitis treated with tacrolimus ointment vs. topical corticosteroids. *Journal of the European Academy of Dermatology and Venereology* 24, 674–678 (2010).

<sup>86</sup> Yu, S. H., Attarian, H., Zee, P. & Silverberg, J. I. Burden of Sleep and Fatigue in US Adults With Atopic Dermatitis. *Dermatitis* 27, 50–58 (2016).

<sup>87</sup> Silverberg, J. I., Garg, N. K., Paller, A. S., Fishbein, A. B. & Zee, P. C. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. *J Invest Dermatol* 135, 56–66 (2015).

<sup>88</sup> Cheng, B. T. & Silverberg, J. I. Depression and psychological distress in US adults with atopic dermatitis. *Ann Allergy Asthma Immunol* 123, 179–185 (2019).

<sup>89</sup> Yu, S. H. & Silverberg, J. I. Association between Atopic Dermatitis and Depression in US Adults. *J Invest Dermatol* 135, 3183–3186 (2015).

<sup>90</sup> Silverberg, J. I. et al. Symptoms and diagnosis of anxiety and depression in atopic dermatitis in U.S. adults. *Br J Dermatol* 181, 554–565 (2019).

HADS-D scores reflected higher odds of self-reporting moderate, severe, or very severe disease (based on PO-SCORAD, PO-SCORAD itch, and POEM scores). Hsu et al.'s analysis of the National Inpatient Survey (NIS) revealed that a diagnosis of AD was associated with increased rates of hospitalization for all mental health disorders.<sup>91</sup>

Only a couple of studies have focused on mental health outcomes in children, specifically. An analysis of the 2007 National Survey of Children's Health found that children with vs. without AD were at higher risk for also having comorbid ADHD, depression, anxiety, conduct disorder, and autism; the association between each of these comorbidities increased in a dose-dependent fashion with the severity of AD.<sup>92</sup> An analysis of the 2012 NHIS found that children with AD raised in family structures that differed from two married biological parents were more likely to have only good, fair or poor health (vs. very good or excellent overall health) and had a higher odds of depression, anxiety, or stress.<sup>93</sup>



## Caregiver Burden

A social media survey developed by Capozza et al. and posted on social media platforms measured the severity of the child's disease via POEM and asked caregivers about 8 domains of the impact of pediatric AD on caregivers: sleep, social isolation, time requirements, life decisions, family relationship dynamics, energy/fatigue, mental health impacts, and unmet treatment needs. Capozza et al. found that the child's disease severity correlated with increased sleep disturbances, low energy/fatigue, and an increased time burden among the caregivers. Further, caregivers reported significant mental health burden associated with caring for a child with AD, including anxiety, isolation, and depression.<sup>13</sup>

Balkrishnan et al. surveyed the parents/caregivers of children with AD before and after physician intervention. The parent/caregiver's perception of AD disease severity had the strongest correlation with the impact of the child's AD on the family.<sup>94</sup> An additional survey-based study by Balkrishnan et al. identified three factors that most strongly predicted an increased family impact score: the perception that the child's AD was severe (as in the previous study), the frequent use of nonmedical services for the care of AD, and the personal financial burden associated with the child's AD.<sup>95</sup>

A study analyzing the impact of childhood disease on caregiver sleep patterns found that the caregivers of children with AD (vs. healthy children) were more likely to experience poor sleep quality, clinically significant insomnia, an average total sleep time of less than 6 hours, and waking at least once per week to care for their child's AD.<sup>96</sup>

## Financial Burden

US patients with AD face a heavier personal financial burden than in any other COI. The National Eczema Association (NEA)<sup>6</sup> surveyed 1,118 US respondents with a median income between \$50,000-\$74,999; disease severity was minimal in 23.2%, somewhat controlled in 40.1%, moderate in 47.5%, and severe in 26.5%. The median annual OOP cost was \$600; 42% of respondents paid more than \$1000 annually, and 8.5% paid more than \$5000 annually. Another study compared the OOP costs in adult patients with AD versus adult patients without AD. Those with AD paid \$371-\$489 more OOP per person-year.<sup>63</sup> Also, individuals with both AD and an allergic condition (a common comorbidity) had a financial burden 1.5 times greater than individuals with AD alone.<sup>97</sup>

***An analysis of the 2007 National Survey of Children's Health found that children with vs. without AD were at higher risk for also having comorbid ADHD, depression, anxiety, conduct disorder, and autism; the association between each of these comorbidities increased in a dose-dependent fashion with the severity of AD.<sup>92</sup>***

<sup>91</sup>Hsu, D. Y., Smith, B. & Silverberg, J. I. Association between atopic dermatitis and hospitalization for mental health disorders in the United States. *Dermatitis* 30, 54–61 (2019).

<sup>92</sup>Yaghmaie, P., Koudelka, C. W. & Simpson, E. L. Mental Health Comorbidity in Atopic Dermatitis. *J Allergy Clin Immunol* 131, 428–433 (2013).

<sup>93</sup>McKenzie, C. & Silverberg, J. I. Association of family structure with atopic dermatitis in US children. *J Am Acad Dermatol* 79, 638–644.e4 (2018).

<sup>94</sup>Balkrishnan, R., Housman, T., Carroll, C., Feldman, S. & Fleischer, A. Disease severity and associated family impact in childhood atopic dermatitis. *Arch Dis Child* 88, 423–427 (2003).

<sup>95</sup>Balkrishnan, R. et al. The family impact of atopic dermatitis in children: the role of the parent caregiver. *Pediatr Dermatol* 20, 5–10 (2003).

<sup>96</sup>Meltzer, L. J. & Booster, G. D. Sleep Disturbance in Caregivers of Children With Respiratory and Atopic Disease. *J Pediatr Psychol* 41, 643–650 (2016).

<sup>97</sup>Suh, D.-C. et al. Economic burden of atopic manifestations in patients with atopic dermatitis--analysis of administrative claims. *J Manag Care Pharm* 13, 778–789 (2007).

Several studies have identified the primary sources of OOP expenses. As a chronic condition, AD requires ongoing healthcare utilization, so patients with AD have more copays than patients without AD.<sup>64</sup> In the NEA survey, the three most common domains of OOP expenses were medical appointments, deductibles, and prescriptions (including some not covered by insurance); nonprescription healthcare products; and complementary, alternative, and cleaning products.<sup>6</sup> Another study of OTC treatment costs found that US AD patients paid an average of \$9.94 monthly for moisturizers and \$7.88 monthly for OTC medications, resulting in an annual average of \$213 for non-prescription topical maintenance therapy.<sup>98</sup>

Other studies have focused on expenses paid by the caregivers. In a study of caregivers of children with moderate-to-severe AD, Filanovsky et al. found that caregivers incurred an average of \$274 in monthly direct costs (e.g., healthcare, treatment) and \$199 in monthly indirect costs (e.g., absenteeism, childcare).<sup>99</sup> On average, 34.8% of the caregivers' monthly budget was spent on costs related to AD management, and this resulted in an additional emotional burden in lower income families.<sup>99</sup>

Indirect costs affect adults with AD as well. Silverberg et al. found that AD was associated with lifestyle limitations, social interaction avoidance, and activity impairment.<sup>100</sup> An analysis of the 2013 US National Health and Wellness Survey found that adults with (vs. without) AD had higher rates of work absenteeism (9.9% vs. 3.6%) and activity impairment (33.6% vs. 25.2%).<sup>81</sup> Whiteley et al. analyzed the same data and found that 30% of employed AD patients reported lost work productivity (vs. 16.3% of non-AD patients); furthermore, AD severity had a negative relationship with work productivity and a positive relationship with difficulty with daily activities.<sup>101</sup> In a separate study, adult patients with (vs. without) AD were more likely to have lost workdays because of illness and to have paid for urgent care, emergency care, and hospitalizations.<sup>102</sup>

## Treatment

The high cost of medical care in the US heightens the need for effective therapies that reduce healthcare utilization, improve QoL, and minimize the side-effect profiles associated with current systemic therapies. In a study about the adequacy of existing systemic treatments for adults with moderate-to-severe AD, 38.3% reported no relief from oral corticosteroids, systemic immunosuppressant therapy (e.g., cyclosporine, azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide), or phototherapy in the preceding 12 months.<sup>103</sup> Armstrong et al. found that patients treated (vs. not treated) with immunosuppressant therapy required additional monitoring and were more likely to require systemic corticosteroids.<sup>104</sup> Dupilumab is a promising new therapy that has been estimated to add 1.9 Quality-Adjusted Life Years (QALYs), but it is currently expensive. At willingness-to-pay (WTP) thresholds of \$50,000, \$100,000, and \$150,000, the probability of dupilumab being cost-effective compared to usual therapy was determined to be 2%, 59%, and 88%, respectively.<sup>105</sup> At the other end of the severity spectrum, it is possible that improved emollient adherence may reduce the cost of AD treatment; a study has investigated this possibility in the UK<sup>59</sup> but not yet in the US.

There is much variation in the type of systemic therapy used to treat severe AD in US and Canadian children, suggesting an unmet need for optimal management in this patient population. Among children in the US and Canada, cyclosporine (CSA; 45.2%) and methotrexate (MTX; 29.6%) were the most common first-line systemic agents; MTX (31.3%) and mycophenolate mofetil (MMF; 30.4%) were the most common second-line agents; and azathioprine (AZA; 33.0%) and MMF (24.3%) were the most common third-line agents. The fact that no single agent comprises a majority of prescriptions at any level of treatment indicates substantial heterogeneity in prescribing practices. A larger issue may be parent and caregiver concern with such



On average, 34.8% of the caregivers' monthly budget was spent on costs related to AD management, and this resulted in an additional emotional burden in lower income families.<sup>99</sup>

<sup>98</sup>Anderson, R. T. & Rajagopalan, R. Effects of allergic dermatitis on health-related quality of life. *Curr Allergy Asthma Rep* 1, 309–315 (2001).

<sup>99</sup>Filanovsky, M. G. et al. The Financial and Emotional Impact of Atopic Dermatitis on Children and Their Families. *J Pediatr* 169, 284–290.e5 (2016).

<sup>100</sup>Silverberg, J. I. et al. Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. *Ann Allergy Asthma Immunol* 121, 340–347 (2018).

<sup>101</sup>Whiteley, J., Emir, B., Seitzman, R. & Makinson, G. The burden of atopic dermatitis in US adults: results from the 2013 National Health and Wellness Survey. *Current Medical Research and Opinion* 32, 1645–1651 (2016).

<sup>102</sup>Silverberg, J. I. Health Care Utilization, Patient Costs, and Access to Care in US Adults With Eczema: A Population-Based Study. *JAMA Dermatol* 151, 743–752 (2015).

<sup>103</sup>Wei, W. et al. A real-world study evaluating adequacy of Existing Systemic Treatments for patients with moderate-to-severe Atopic Dermatitis (QUEST-AD): Baseline treatment patterns and unmet needs assessment. *Ann Allergy Asthma Immunol* 123, 381–388.e2 (2019).

<sup>104</sup>Armstrong, A. W. et al. Real-world utilization patterns of systemic immunosuppressants among US adult patients with atopic dermatitis. *PLoS One* 14, (2019).

<sup>105</sup>Zimmermann, M. et al. Economic Evaluation of Dupilumab for Moderate-to-Severe Atopic Dermatitis: A Cost-Utility Analysis. *J Drugs Dermatol* 17, 750–756 (2018).

treatments: 65.2% of pediatric dermatologists who responded to the survey said they did not prescribe systemic agents at all due to concerns held by parents and caregivers.<sup>106</sup>

A systematic review found a lack of studies that examine the efficacy of systemic AD therapies in racial and ethnic minorities.<sup>107</sup> Unfortunately, the lack of research in this area may be contributing to poorer outcomes—Black children with AD tend to have worse disease control than non-Hispanic white children.<sup>67</sup> After investigating poorer treatment outcomes in minority patient populations, Vachiramon et al. recommended that providers emphasize emollient use and make dose adjustments for cyclosporine and phototherapy relative to the standard treatment courses for white patients.<sup>66</sup>

The inadequacy of existing therapies translates into poor satisfaction among patients and caregivers. Paller et al.'s study of caregivers of children with AD found that 69% were “not at all satisfied” and 82% were at most “fairly satisfied” with current treatment options. Reasons for dissatisfaction included the messiness of topicals, ineffectiveness, cost, and side effects.<sup>108</sup> Patient and caregiver dissatisfaction with current treatments may drive the use of complementary and alternative medicine (CAM); an analysis of the 2007 NHIS found that 46.9% of children in the US used at least one CAM.<sup>109</sup> Unfortunately, certain common home-care practices may be detrimental to AD, suggesting a need for education on proper treatment guidelines in patients with AD and their caregivers.<sup>65</sup>

## The inadequacy of existing therapies translates into poor satisfaction among patients and caregivers.

Interestingly, physicians view the existing prescription treatment options more favorably than patients—in a national survey, 91% responded that prescription treatment options for AD were “moderately” or “very” effective, while only 46% of patients reported the same.<sup>110</sup> This overall satisfaction does not mean, however, that all physicians follow the same treatment strategies. A review of the NAMCS and National Hospital Ambulatory Care Survey (NHAMCS) databases revealed that dermatologists were more likely than non-dermatologists to prescribe higher potency TCS in accordance with evidence-based guidelines.<sup>111</sup>

As in other countries, the effectiveness of existing topical regimens is often limited by patient and caregiver fears regarding TCS. In an interview-based study conducted with mothers of children with AD, treatment use was most affected by the ease of use, concerns about adverse effects of TCS, the physician-patient relationship, and education efforts.<sup>112</sup> Another study evaluated different education strategies and found, disappointingly, that patients' willingness to apply TCS was not affected by the type of explanation provided (namely, an explanation of the risks of not applying treatment versus the benefits of applying treatment).<sup>113</sup> Among caregivers of children with AD, Curry et al. found that anchoring methods (e.g., proposing four-times-daily TCS therapy with the goal of improving adherence to a once-daily regimen) increased caregivers' willingness to treat children at least once daily with TCS.<sup>114</sup>

Finally, treatment effectiveness may be limited by the ability of patients and caregivers to understand the instructions for complicated regimens. Stringer et al. conducted a readability, suitability, and content analysis of eczema action plans (EAPs) submitted by the Society for Pediatric Dermatology and found that only one in five EAPs were written at or below the recommended 6th grade reading level.<sup>115</sup> This shortcoming may be especially detrimental given that AD may be more prevalent among patients of lower SES,<sup>4</sup> as discussed in the section on prevalence.

<sup>106</sup>Totri, C. R. et al. Prescribing practices for systemic agents in the treatment of severe pediatric atopic dermatitis in the US and Canada: The PeDRA TREAT survey. *J Am Acad Dermatol* 76, 281–285 (2017).

<sup>107</sup>Bhattacharya, T. & Silverberg, J. I. Efficacy of systemic treatments for atopic dermatitis in racial and ethnic minorities in the United States. *JAMA Dermatol* 150, 1232–1234 (2014).

<sup>108</sup>Paller, A. S., McAlister, R. O., Doyle, J. J. & Jackson, A. Perceptions of physicians and pediatric patients about atopic dermatitis, its impact, and its treatment. *Clin Pediatr (Phila)* 41, 323–332 (2002).

<sup>109</sup>Silverberg, J. I., Lee-Wong, M. & Silverberg, N. B. Complementary and alternative medicines and childhood eczema: a US population-based study. *Dermatitis* 25, 246–254 (2014).

<sup>110</sup>McAlister, R. O., Tofte, S. J., Doyle, J. J., Jackson, A. & Hanifin, J. M. Patient and physician perspectives vary on atopic dermatitis. *Cutis* 69, 461–466 (2002).

<sup>111</sup>McGregor, S. P., Farhangian, M. E., Huang, K. E. & Feldman, S. R. Treatment of Atopic Dermatitis in the United States: Analysis of Data from the National Ambulatory Medical Care Survey. *J Drugs Dermatol* 16, 250–255 (2017).

<sup>112</sup>Fenerty, S. D., O'Neill, J. L., Gustafson, C. J. & Feldman, S. R. Maternal adherence factors in the treatment of pediatric atopic dermatitis. *JAMA Dermatol* 149, 229–231 (2013).

<sup>113</sup>Maghen, P. et al. Regardless of how risks are framed, patients seem hesitant to use topical steroids for atopic dermatitis. *British Journal of Dermatology* 181, 842–844 (2019).

<sup>114</sup>Curry, Z. A., Johnson, M. C., Unrue, E. L. & Feldman, S. R. Caregiver willingness to treat atopic dermatitis is not much improved by anchoring. *J Dermatol Treat* 30, 471–474 (2019).

<sup>115</sup>Stringer, T. et al. The readability, suitability, and content features of eczema action plans in the United States. *Pediatr Dermatol* 35, 800–807 (2018).

## Healthcare

### Utilization

A survey by Silverberg et al. found that one in ten adults with AD required an urgent care, ED, or hospital visit during the preceding year. Other risk factors for increased ED and urgent care visits included Black or Hispanic race, lower SES, and the insurance denial of AD prescriptions.<sup>116</sup>

Other studies have confirmed racial discrepancies in healthcare utilization for AD. Children with AD who indicated that their race was Black or “other” had higher odds of overnight hospitalization.<sup>70</sup> Black (vs. white) children with poorly controlled AD were less likely to be seen by a dermatologist.<sup>117</sup> An analysis of 1990–1998 NAMCS data found that Black patients and Asian/Pacific islander patients were more likely than white patients to seek care for AD; the authors posit that unmet needs for treatment education and guidance may have driven this observation.<sup>118</sup> A study by Fischer et al. found that after having at least one ambulatory care visit, non-Hispanic Black (vs. white) patients had higher healthcare utilization.<sup>119</sup>

### Satisfaction with Care

An analysis of the Consumer Assessment of Healthcare Providers and Systems (CAHPS) data within the 2000–2015 MEPS survey data found that patients with (vs. without) AD were generally less satisfied with their healthcare; patients with AD also had lower odds of reporting the highest satisfaction in every category of CAHPS (listened carefully, explained in a way that was easy to understand, spent enough time, and showed respect). Other associations with lower patient satisfaction scores included low/middle income, non-white race/ethnicity, public/no insurance, and multimorbidity.<sup>120</sup> The suboptimal satisfaction of patients with AD has been replicated by other studies; Paller et al. found that only 44% of respondents were “a lot” or “very much” satisfied with the care provided by their physician; 50% were “somewhat” satisfied, and 6% were “not at all” satisfied.<sup>108</sup>

Dissatisfaction may be rooted in different perceptions of disease severity and treatment options. Nearly one-third of patients with moderate-to-severe AD (based on DLQI scores) rated their disease as more severe than their physicians did.<sup>121</sup> A survey study of parent-caregiver perceptions of pediatric AD found that although caregivers generally agreed with the physician’s assessment, those who disagreed tended to perceive their child’s AD as more severe than the physician.<sup>108</sup> Paller et al. found that patients preferred cream-based treatments while physicians preferred ointment-based treatments. Parents also expressed a desire for more educational content, including videos and access to support groups.<sup>108</sup>

### Patient-Centered Interventions

The literature search did not yield any additional intervention studies beyond those mentioned briefly in the Treatment section regarding TCS adherence.



**Dissatisfaction may be rooted in different perceptions of disease severity and treatment options. Nearly one-third of patients with moderate-to-severe AD (based on DLQI scores) rated their disease as more severe than their physicians did.<sup>121</sup>**

<sup>116</sup>Silverberg, J. I. et al. Atopic Dermatitis in US Adults: From Population to Health Care Utilization. *J Allergy Clin Immunol Pract* 7, 1524–1532.e2 (2019).

<sup>117</sup>Wan, J. et al. Racial/Ethnic Variation in Use of Ambulatory and Emergency Care for Atopic Dermatitis among US Children. *J Invest Dermatol* 139, 1906–1913.e1 (2019).

<sup>118</sup>Janumpally, S. R., Feldman, S. R., Gupta, A. K. & Fleischer, A. B. In the United States, blacks and Asian/Pacific Islanders are more likely than whites to seek medical care for atopic dermatitis. *Arch Dermatol* 138, 634–637 (2002).

<sup>119</sup>Fischer, A. H., Shin, D. B., Margolis, D. J. & Takeshita, J. Racial and ethnic differences in healthcare utilization for childhood eczema: an analysis of the 2001–2013 Medical Expenditure Panel Surveys. *J Am Acad Dermatol* 77, 1060–1067 (2017).

<sup>120</sup>Cheng, B. T. & Silverberg, J. I. Atopic Dermatitis Is Associated With Lower Patient Satisfaction in US Adults. *Dermatitis* (2021) doi:10.1097/DER.0000000000000733.

<sup>121</sup>Wei, W. et al. Discordance Between Physician- and Patient-Reported Disease Severity in Adults with Atopic Dermatitis: A US Cross-Sectional Survey. *Am J Clin Dermatol* 18, 825–835 (2017).

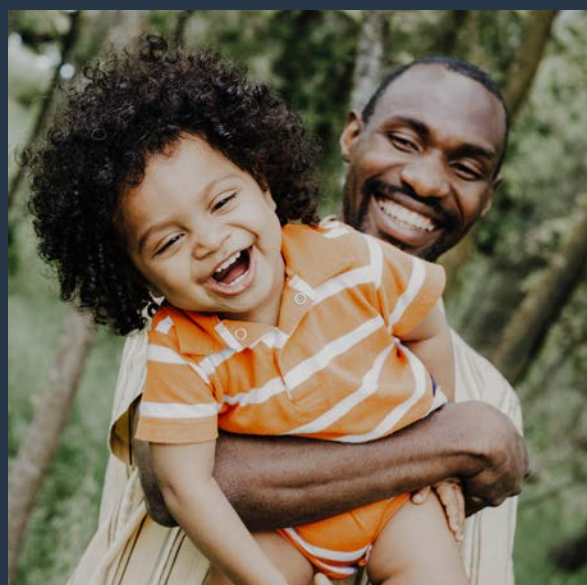
## KEY FINDINGS

A review in 2001 by Lapidus outlined three key areas for improvement: an accurate evaluation of the prevalence of AD; national programs to increase awareness of AD in healthcare systems, families, and schools with concurrent psychosocial intervention; and further research into treatment delivery methods, particularly for low-income patients.<sup>122</sup> Much progress has been made toward the first goal—the factors associated with a higher odds of AD diagnosis, disease severity, QoL burden, and comorbidities are now so well described that the US appears to set a global standard in this regard. However, few studies have developed and tested patient-centered interventions (e.g., nurse-led education programs) that might alleviate the physical, psychosocial, and financial burdens of AD. Such studies exist in many other COI in this report, and US-specific studies should be conducted in light of important differences between the US and western European countries (namely, the diversity of the patient population and cost of healthcare).

An AD diagnosis confers a much greater financial burden on US patients than on patients in other COI. It is worth repeating that 42.6% of patients with moderate-to-severe disease paid \$1000 or more in annual OOP expenses, and 8.5% paid \$5000 or more.<sup>6</sup> After considering indirect expenses such as work absenteeism, Filanovsky et al. found that the families of children with moderate-to-severe AD spent 34.8% of their monthly budget on expenses related to their child's AD.<sup>99</sup> Unsurprisingly, the personal financial burden is one of the main determinants of family impact. Especially in light of the cost of US healthcare and treatment, it may be worth investigating the possibility of reducing costs through interventions that promote regular moisturization even in the absence of a flare, as has been investigated in the UK and Denmark.

The physical and psychosocial consequences of AD are well characterized among US adults but not well studied in the pediatric population and only moderately well understood in caregivers. The existing evidence regarding caregivers' financial and sleep burdens suggest that pediatric dermatology clinical trials should include caregiver burden metrics as secondary endpoints. Otherwise, future US-based research should prioritize understanding the individual burden experienced across a diverse pediatric patient population, perhaps using the type of interview-based studies that have been insightful in Germany and the UK.

Finally, as in other COI, the current dissatisfaction of US patients and caregivers with both the available treatments and medical care lead to decreased adherence, and sometimes an increase in (costly) healthcare utilization. Studies in Germany and the UK show that educational interventions can be effective at increasing adherence to treatment regimens and improving QoL for patients and caregivers; perhaps similar initiatives should be pursued in the US as initially recommended by Lapidus.



<sup>122</sup>Lapidus, C. S. Role of social factors in atopic dermatitis: The US perspective. *Journal of the American Academy of Dermatology* 45, S41–S43 (2001).

# GERMANY

## Disease Burden

### Prevalence, Diagnosis, and Comorbidities

The prevalence of AD in German children was estimated at 15.6% in a nationally representative sample of patients; AD was most prevalent in children less than one year of age (22%), followed by adolescents (8%) and then adults (2–4%).<sup>123</sup>

Other studies have found similar results: a lifetime prevalence of 13.2% in German children and adolescents<sup>124</sup> and a lifetime prevalence of 4.3% in German adults aged 50–75, much lower than the estimates in younger individuals.<sup>125</sup> A survey-based study found that the prevalence of AD in German school-aged children increased during a 5-year period between 1994/1995 and 1999/2000, a trend that was observed in other developed nations around the same time.<sup>126,2</sup>

Recent epidemiologic studies have captured disease associations with AD in the German population. A study analyzing data from the German National Health Insurance beneficiaries found that patients with (vs. without) AD were at increased risk for incident rheumatoid arthritis and inflammatory bowel disease.<sup>127</sup> In a cohort of German adults sampled from the LIFE-Adult-Study, AD was significantly associated with autoimmune disease.<sup>128</sup> Children with AD had an increased relative risk of impetigo and vitiligo.<sup>129</sup>

### Physical and Psychosocial Consequences

The Atopic Health study, a nationally representative sample of 1,678 AD patients with a mean SCORAD of 42.3 (indicating moderate disease), reported a mean DLQI of 8.5 (indicating a moderate effect on the patient's QoL),<sup>130</sup> and up to a third of patients felt that their quality of life could be improved.<sup>131</sup> By contrast, the ADIA study of US patients found a much lower (better

<sup>123</sup>Schmitt, J., Schmitt, N. M., Kirch, W. & Meurer, M. [Significance of atopic dermatitis in outpatient medical care. Analysis of health care data from Saxony]. *Hautarzt* 60, 320–327 (2009).

<sup>124</sup>Schmitz, R., Atzpodien, K. & Schlaud, M. Prevalence and risk factors of atopic diseases in German children and adolescents. *Pediatr Allergy Immunol* 23, 716–723 (2012).

<sup>125</sup>Wolkewitz, M. et al. Lifetime prevalence of self-reported atopic diseases in a population-based sample of elderly subjects: results of the ESTHER study. *Br J Dermatol* 156, 693–697 (2007).

<sup>126</sup>Maziak, W. et al. Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and phase III surveys in Münster, Germany. *Allergy* 58, 572–579 (2003).

<sup>127</sup>Schmitt, J. et al. Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes. *J Allergy Clin Immunol* 137, 130–136 (2016).

<sup>128</sup>Treudler, R., Zeynalova, S., Walther, F., Engel, C. & Simon, J. C. Atopic dermatitis is associated with autoimmune but not with cardiovascular comorbidities in a random sample of the general population in Leipzig, Germany. *Journal of the European Academy of Dermatology and Venereology* 32, e44–e46 (2018).

<sup>129</sup>Augustin, M. et al. Epidemiology and Comorbidity in Children with Psoriasis and Atopic Eczema. *DRM* 231, 35–40 (2015).

<sup>130</sup>Langenbruch, A. et al. Quality of health care of atopic eczema in Germany: results of the national health care study AtopicHealth. *J Eur Acad Dermatol Venereol* 28, 719–726 (2014).

<sup>131</sup>Steinke, S., Langenbruch, A., Ständer, S., Franke, N. & Augustin, M. Therapeutic benefits in atopic dermatitis care from the patients' perspective: results of the German national health care study 'Atopic Health'. *Dermatology* 228, 350–359 (2014).

DLQI of 4.71, though a majority of those patients (60.1%) had mild disease as classified by POEM; only 28.9% had moderate disease.<sup>4</sup> This discrepancy highlights the importance of accounting for disease severity. Comorbidities matter as well; AD and hay fever were found to contribute to worse health-related quality of life (HRQoL) in German adolescents.<sup>132</sup> As these data were collected at intervals of four weeks and 12 months, the authors posit that it is important to consider more immediate relief for symptoms of AD and hay fever when considering treatment for this population.<sup>133</sup>

Several studies have focused on the burden associated with pruritus (itch), specifically. In the German Atopic Dermatitis Intervention Study (GADIS), itch and sleeplessness were found to be significantly correlated;<sup>134</sup> another study found that 26.6% of patients reported suffering “often” or “every night” as a result of pruritus.<sup>130</sup> As pruritus worsened, QoL worsened in both German children and adolescents.<sup>134</sup> 24.3% of German-language google searches on the topic of pruritus included AD, indicating that there may be an unmet need for patients specifically with symptoms of pruritus.<sup>135</sup> A nationwide survey of patients’ needs revealed that a top priority was “to be free of itching” (96.0% rated this as “quite important” or “very important”), followed by “to get better skin quickly” (87.7%) and “to be healed of all skin defects” (85.7%).<sup>136</sup>

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*This discrepancy highlights the importance of accounting for disease severity.*

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**24.3%** of German-language google searches on the topic of pruritus included AD, indicating that there may be an unmet need for patients specifically with symptoms of pruritus.<sup>135</sup>

German children who were diagnosed with AD at infancy and followed until age 10 were found to be at significantly increased risk for mental health problems and emotional symptoms at age 10; the association between these variables strengthened if AD was persistent the entire time.<sup>137</sup> An additional study found that infants with AD were at increased risk for developing hyperactivity/inattention at 10 years; the odds of developing emotional and/or behavioral problems were the highest with an infant diagnosis of AD,<sup>138</sup> onset before age four,<sup>139</sup> and comorbid sleep problems.<sup>138</sup> Romanos et al. found that AD and ADHD were independently associated with sleep difficulties but not with each other, and the authors posited that the observed association between AD and ADHD could be influenced by a lack of sleep.<sup>140</sup> A study that analyzed the effect of chronic conditions (of which AD made up a significant portion) on school performance in German first-graders found that children with chronic conditions and special healthcare needs performed worse than both healthy children and children with chronic conditions but no special healthcare needs.<sup>141</sup>

The Girolomoni et al study analyzing the psychosocial and economic burden attributable to moderate-to-severe AD examined a cohort of German patients as well. 16.4%, 19.5%, and 24.6% of patients had a moderate effect, very large effect, and extremely large effect of AD on reported DLQI, respectively.<sup>34</sup> 29.0%, 30.1%, and 9.8% of patients reported mild, moderate, and severe sleep difficulties, respectively. 29.5% of German patients reported anxiety, which was lower than other countries surveyed in the report including France (57.4%), Italy (51.3%), and the UK (61.5%), as well as across the EU5 (52.7%).<sup>34</sup> As measured by the PHQ-9, mild, moderate, moderately severe, and severe depression was experienced by 31.7%, 26.2%, 14.8%, and 8.2% of German patients, similar to other countries surveyed in the report.<sup>34</sup>

<sup>132</sup>Beikert, F. C. et al. Willingness to pay and quality of life in patients with atopic dermatitis. *Arch Dermatol Res* 306, 279–286 (2014).

<sup>133</sup>Matterne, U., Schmitt, J., Diepgen, T. L. & Apfelbacher, C. Children and adolescents’ health-related quality of life in relation to eczema, asthma and hay fever: results from a population-based cross-sectional study. *Qual Life Res* 20, 1295–1305 (2011).

<sup>134</sup>Weisshaar, E. et al. Itch intensity evaluated in the German Atopic Dermatitis Intervention Study (GADIS): correlations with quality of life, coping behaviour and SCORAD severity in 823 children. *Acta Derm Venereol* 88, 234–239 (2008).

<sup>135</sup>Zink, A. et al. Medical needs and major complaints related to pruritus in Germany: a 4-year retrospective analysis using Google AdWords Keyword Planner. *J Eur Acad Dermatol Venereol* 33, 151–156 (2019).

<sup>136</sup>Augustin, M. et al. Characterizing treatment-related patient needs in atopic eczema: insights for personalized goal orientation. *J Eur Acad Dermatol Venereol* 34, 142–152 (2020).

<sup>137</sup>Schmitt, J. et al. Infant-onset eczema in relation to mental health problems at age 10 years: results from a prospective birth cohort study (German Infant Nutrition Intervention plus). *J Allergy Clin Immunol* 125, 404–410 (2010).

<sup>138</sup>Schmitt, J. et al. Infant eczema, infant sleeping problems, and mental health at 10 years of age: the prospective birth cohort study LISApplus. *Allergy* 66, 404–411 (2011).

<sup>139</sup>Genuneit, J. et al. Infant atopic eczema and subsequent attention-deficit/hyperactivity disorder—a prospective birth cohort study. *Pediatr Allergy Immunol* 25, 51–56 (2014).

<sup>140</sup>Romanos, M., Gerlach, M., Warnke, A. & Schmitt, J. Association of attention-deficit/hyperactivity disorder and atopic eczema modified by sleep disturbance in a large population-based sample. *J Epidemiol Community Health* 64, 269–273 (2010).

<sup>141</sup>Hoffmann, I. et al. Chronic health conditions and school performance in first graders: A prospective cohort study. *PLOS ONE* 13, e0194846 (2018).



In adults, Schmitt et al. found that the risk for developing psychiatric comorbidities increased with AD severity.<sup>142</sup> Compared to German adults without AD, German adults with AD were at increased risk for suicidal ideation, anxiety, and depression; the odds of experiencing suicidal ideation were 11 times higher in adults with AD compared to adults without.<sup>143</sup> Another study estimated the prevalence of suicidal ideation in German adults with AD to be 21.3%, with 3.9% of patients above the cutoff for acute suicidality. Again, severe AD was positively associated with suicidality in this population, indicating a possible unmet need for psychiatric screening.<sup>144</sup> A study comparing the happiness of patients with various chronic diseases found that patients with AD experienced significantly lower heuristic happiness and positive affect than the healthy control group, greater positive affect than patients with chronic IBD, and lower positive affect than patients with HIV.<sup>145</sup>

An association was observed between German mothers with asthma, AD, or hay fever and a reduced numbers of children independent of reproductive ability; this may be because mothers with atopy, including AD, are reluctant to pass their condition on to their children.<sup>146</sup>

The profound impacts of AD may be best illustrated by two studies that posed hypothetical scenarios in which patients could be cured of their AD for a price. In one study, patients with uncontrolled AD were willing to accept a 40% shorter life expectancy as a hypothetical tradeoff for curing their AD, on par with conditions such as severe angina pectoris, rheumatoid arthritis, multiple sclerosis, chronic anxiety, regional esophageal cancer, and interferon therapy for melanoma.<sup>147</sup> In contrast, a study examining willingness to pay (WTP) in German adults with AD found that patients would be willing to pay a median of €1,000 to cure their AD.<sup>132</sup>

## Caregiver Burden

Among mothers of children with AD, single mothers (vs. mothers living with a partner) scored higher on measures of helplessness, aggression, and experiencing stress within the family; they scored lower on general life satisfaction.<sup>148</sup> This highlights a particularly vulnerable caregiver population that may benefit from targeted intervention. An analysis by Schut et al. found a significant association between parent-caregiver interest in educational interventions and dissatisfaction with medical care, low social support, and high active problem-solving behavior. I.e. parents and caregivers who scored highly in these areas were more likely to be interested in education interventions. The authors suggest that additional educational interventions may be more successful in this population.<sup>149</sup> Indeed, several interventions have focused on the German caregiver population and are discussed in the Interventions section.

## Financial Burden

The financial burden for German patients with AD is comparable to other developed countries except for the US (which has higher costs). German patients had average annual costs ranging from €956 for mild AD to €1425 for severe AD; the direct cost of one flare was an average of €123.<sup>150</sup>

The Girolomoni et al study examined work absenteeism, presenteeism, and overall work impairment in a German cohort of patients as well. Work absenteeism rates ranged from 22.4% to 38.3% in patients with moderate and extremely large effect to DLQI, respectively; work presenteeism rates ranged from 34.8% to 41.0%; and overall work impairment rates ranged from 40.4% to 64.4%.<sup>34</sup>



**An analysis by Schut et al. found a significant association between parent-caregiver interest in educational interventions and dissatisfaction with medical care, low social support, and high active problem-solving behavior.**

<sup>142</sup>Schmitt, J., Romanos, M., Pfennig, A., Leopold, K. & Meurer, M. Psychiatric comorbidity in adult eczema. *Br J Dermatol* 161, 878–883 (2009).

<sup>143</sup>Dieris-Hirche, J., Gieler, U., Kupfer, J. P. & Milch, W. E. [Suicidal ideation, anxiety and depression in adult patients with atopic dermatitis]. *Hautarzt* 60, 641–646 (2009).

<sup>144</sup>Dieris-Hirche, J. et al. Suicidal Ideation in Adult Patients with Atopic Dermatitis: A German Cross-sectional Study. *Acta Derm Venereol* 97, 1189–1195 (2017).

<sup>145</sup>Schuster, B. et al. Happiness in dermatology: a holistic evaluation of the mental burden of skin diseases. *Journal of the European Academy of Dermatology and Venereology* 34, 1331–1339 (2020).

<sup>146</sup>Karmaus, W. & Eneli, I. Maternal atopy and the number of offspring: is there an association? *Pediatr Allergy Immunol* 14, 470–474 (2003).

<sup>147</sup>Schmitt, J., Meurer, M., Klon, M. & Frick, K. D. Assessment of health state utilities of controlled and uncontrolled psoriasis and atopic eczema: a population-based study. *British Journal of Dermatology* 158, 351–359 (2008).

<sup>148</sup>Gieler, U. et al. Atopic Eczema and Stress among Single Parents and Families: An Empirical Study of 96 Mothers. *Acta Derm Venereol* 97, 42–46 (2017).

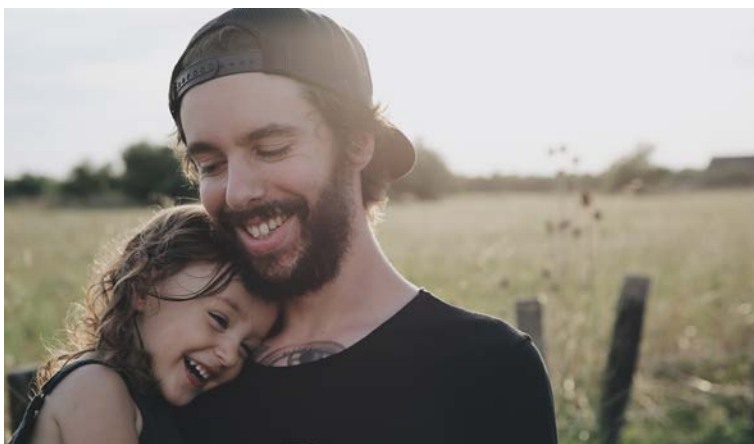
<sup>149</sup>Schut, C., Mahmutovic, V., Gieler, U. & Kupfer, J. Patient education programs for childhood atopic dermatitis: who is interested? *J Dtsch Dermatol Ges* 10, 657–661 (2012).

<sup>150</sup>Ehlsen, B. et al. [Cost-of-illness study in patients suffering from atopic eczema in Germany]. *Hautarzt* 56, 1144–1151 (2005).

Interestingly, there are published inpatient rehabilitation guidelines for patients whose AD severely limits their capacity to work and/or impairs everyday life. These comprehensive guidelines cover areas such as the need for and suitability of rehabilitation, prognosis, diagnosis, therapy goals and elements, and objective symptom evaluation.<sup>151</sup>

## Treatment

Schmitt et al. found that AD patients were much more likely to be prescribed high-potency TCS than TCI and systemic corticosteroids than other systemic immunosuppressants. Systemic corticosteroids were prescribed at higher rates than cyclosporine (over 10% and less than 0.1%, respectively, in a sample of 11,555 patients with AD) despite the more favorable tolerability profile of cyclosporine compared to systemic corticosteroids.<sup>10</sup> AD patients with concomitant atopic comorbidities were found to be prescribed TCS and systemic corticosteroids more often than AD patients without other atopic comorbidities; this may suggest that the AD phenotype may be more severe in patients with atopic comorbidities, or that the comorbid conditions themselves warranted additional steroid therapy. In either case, patients with AD and atopic comorbidities incur a greater treatment burden and potential side effects associated with systemic therapy.<sup>152</sup>



Patients with AD and atopic comorbidities incur a greater treatment burden and potential side effects associated with systemic therapy.<sup>152</sup>

Concerns about the overuse of corticosteroids notwithstanding, several studies have found German AD patients to be relatively satisfied with their treatments—unlike in most other COI. In the Atopic Health study, 82.1% of patients reported high satisfaction with treatment, and 88.4% of patients reported a therapeutic benefit.<sup>131</sup> Also, 75.8% of patients in the Atopic Health study felt as though their treatment regimens were not bothersome or were only moderately so.<sup>130</sup> Topical TCIs were well-liked by patients; 76.5% of patients rated the efficacy as “good,” and 83.1% of patients rated the tolerability as “good.”<sup>153</sup> Topical therapy was associated with a significant improvement in QoL scores in both adults and children with AD.<sup>153</sup>

As in other COI, some caregivers choose to pursue homeopathic/CAM therapies, but this approach is usually not supported by empirical evidence. Parents of children with mild-to-moderate AD did not find any therapeutic benefit to homeopathic therapy relative to conventional therapy. Furthermore, adjusted costs in the homeopathic group were €935.02 at 6 months and €1524.23 at 12 months compared to €514.44 at 6 months and €721.21 at 12 months in the control group.<sup>154</sup> A study of the long-term outcomes of homeopathic therapy vs. conventional therapy found once again that homeopathic therapy did not outperform conventional therapy in the long-term and was associated with increased costs.<sup>155</sup>

<sup>151</sup>Buhles, N., Wehrmann, J., Hinsch, K.-D. & Nürnberg, W. S1 Guideline: Dermatological inpatient rehabilitation in adult atopic dermatitis\*. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft* 9, 558–561 (2011).

<sup>152</sup>Werner-Busse, A., Kostev, K., Heine, G. & Worm, M. Impact of comorbidities on the treatment of atopic dermatitis in clinical practice. *Int J Clin Pharmacol Ther* 52, 726–731 (2014).

<sup>153</sup>Sunderkötter, C., Weiss, J. M., Bextermöller, R., Löffler, H. & Schneider, D. [Post-marketing surveillance on treatment of 5,665 patients with atopic dermatitis using the calcineurin inhibitor pimecrolimus: positive effects on major symptoms of atopic dermatitis and on quality of life]. *J Dtsch Dermatol Ges* 4, 301–306 (2006).

<sup>154</sup>Witt, C. M. et al. Homeopathic versus conventional therapy for atopic eczema in children: medical and economic results. *Dermatology* 219, 329–340 (2009).

<sup>155</sup>Roll, S. et al. Comparative effectiveness of homeopathic vs. conventional therapy in usual care of atopic eczema in children: long-term medical and economic outcomes. *PLoS One* 8, e54973 (2013).

## Healthcare

### Utilization

The Girolomoni et al study analyzing the psychosocial and economic burden experienced by patients with moderate-to-severe AD examined healthcare provider visit rates, emergency room visit rates, and hospitalization rates within a 6-month period preceding the survey in a German cohort of patients as well. These rates were reported among patients with moderate, very large, and extremely large effects to DLQI; statistically significant differences were observed among the DLQI groups within emergency room visit rates (0.28%, 0.34%, and 0.88% of patients, respectively) and hospitalization rates (0.28%, 0.34%, and 1.12%, respectively).<sup>34</sup> Additionally, a study by Schmitt et al found that adult AD patients accounted for 60% of all outpatient visits for AD.<sup>123</sup>

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*A study by Schmitt et al found that adult AD patients accounted for 60% of all outpatient visits for AD.<sup>123</sup>*

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### Satisfaction with Care

In the Atopic Health survey, 49.4% of patients reported their health care as either “good” or “very good,” 37.3% of patients assessed their healthcare as “moderate,” and 13.3% of patients felt that the care they received was either “bad” or “deficient.”<sup>131</sup> A cross-sectional study performed on two years of survey data from an AD outpatient unit in Dresden found that important determinants of treatment satisfaction included the professional competence of the physician (most important), the physician’s sensitivity, disease severity, education about the condition, and the patient’s ability to adjust treatment with disease activity.<sup>156</sup>

A large majority of physicians agreed that  
a treatment priority was the reduction of  
itch and burning (93.9%).<sup>158</sup>

Two studies have characterized the treatment goals of AD patients. In the first study, important treatment goals included complete skin clearing and minimizing itch and burning; a reduction in disease severity accounted for only 20% of the entirety of treatment satisfaction.<sup>157</sup> Similarly, in the second study, patients cared most about the healing of all skin changes (88.3%), decreasing itch and burning (73.3%), reducing healthcare visits, avoiding severe side effects, improving psychological well-being, and reducing the time spent administering treatment. Interestingly, a large majority of physicians agreed that a treatment priority was the reduction of itch and burning (93.9%).<sup>158</sup>

### Patient-Centered Interventions

The German Atopic Dermatitis Intervention Study (GADIS) sought to determine whether educational interventions could improve QoL parameters in caregivers.<sup>159</sup> In parents of children aged 3 months to 7 years, the intervention (relative to an untreated control group) significantly increased caregivers’ psychosomatic wellbeing, confidence in medical treatment, emotional coping, and acceptance of disease, and the intervention significantly decreased the effects of the child’s AD on the caregiver’s social life. Parents of children aged 8–12 years experienced significant improvements in their confidence in medical treatment, emotional coping, and acceptance of disease.<sup>159</sup>

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<sup>156</sup>Schmitt, J., Csötönyi, F., Bauer, A. & Meurer, M. Determinants of treatment goals and satisfaction of patients with atopic eczema. *J Dtsch Dermatol Ges* 6, 458–465 (2008).

<sup>157</sup>Breuer, K. et al. Predictors of benefit from an atopic dermatitis education programme. *Pediatric Allergy and Immunology* 25, 489–495 (2014).

<sup>158</sup>Zschocke, I., Hammelmann, U. & Augustin, M. [Therapeutic benefits in dermatological therapy. Evaluation of therapy from the physician’s and patient’s perspective in psoriasis and atopic dermatitis]. *Hautarzt* 56, 839–842, 844–846 (2005).

<sup>159</sup>Staab, D. et al. Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomised controlled trial. *BMJ* 332, 933–938 (2006).

Caregivers have been the primary focus of two other interventional studies. In an evaluation of individually tailored nursing consultations for the caregivers of children with AD, 90% of caregivers found the intervention to be highly supportive 14 days after the original consultation. Areas of significant improvement included increased self-efficacy regarding treatment recommendations, the frequency of moderate and severe symptoms, and scores for sleep disruption and pruritus.<sup>160</sup> Breuer et al. sought to determine factors that predict the long-term success of parent-oriented educational interventions; “success” was defined by improvements in the parent’s QoL, the child’s SCORAD, TCS use, and knowledge of AD. Parents with poor past treatment experiences who scored worse on measures of coping skills benefited most from the intervention; the association was even stronger for these parameters than for the child’s SCORAD at baseline.<sup>157</sup>

Kupfer et al. expanded on these findings to determine if educational interventions could bolster the psychological coping abilities of both caregivers *and* the children themselves.<sup>161</sup> Children in the intervention group scored significantly better on both measures: anxious or depressive mood and itching/scratching behavior. Parents in the intervention group improved in three out of the four domains: anger toward the child’s scratching, seeking to control their child’s scratching, and poor experience with treatment; they did not significantly improve on overprotective behavior. The authors also sought to determine whether the improvements were attributable to or independent from a reduction in disease severity (quantified via SCORAD); interestingly, the children’s improvement was independent of the change in disease severity, while the parents’ improvement was not.<sup>161</sup>



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In an evaluation of individually tailored nursing consultations for the caregivers of children with AD,

**90%** of caregivers found the intervention to be highly supportive 14 days after the original consultation.

<sup>160</sup>Rolinck-Werninghaus, C., Trentmann, M., Reich, A., Lehmann, C. & Staab, D. Improved management of childhood atopic dermatitis after individually tailored nurse consultations: A pilot study. *Pediatr Allergy Immunol* 26, 805–810 (2015).

<sup>161</sup>Kupfer, J. et al. Structured education program improves the coping with atopic dermatitis in children and their parents—a multicenter, randomized controlled trial. *Journal of Psychosomatic Research* 68, 353–358 (2010).

## KEY FINDINGS

While studies in the US have identified a wide range of comorbid associations, comorbidity studies in Germany have focused on inflammatory disorders, indicating a potential need for broader population-wide studies. However, the German literature comprehensively describes comorbid mental health associations in children with AD. The in-depth investigations into sleep and ADHD are particularly interesting, especially the finding that sleep disturbances may confound the observed association between AD and ADHD.<sup>140</sup>

Although German AD patients appeared to have worse DLQI scores than US AD patients, the difference seems attributable to the focus on moderate disease severity in the Germany study.<sup>4,130</sup> Studies with comparable patient populations would be more useful for drawing country-wide comparisons. In lieu of studies with common, reproducible methodologies, it may be possible to draw comparisons with hypothetical negotiations for disease clearance (e.g., adults with uncontrolled AD would be willing to accept a 40% shorter life expectancy<sup>147</sup> and to pay €1,000,132 in exchange for disease clearance).

Compared to patients in other COI, German patients seem more satisfied with their care, more satisfied with treatment options, and more amenable to using TCS, though it is hard to draw robust cross-national comparisons in the absence of standardized satisfaction measures. A major development in Germany has been the successful implementation of educational interventions, with improvements in the QoL parameters of both children with AD and their caregivers as well as a reduction in disease severity. The GADIS trial and subsequent studies of the effectiveness of educational interventions make Germany a leader in this regard and may provide a model with which other countries may begin to address unmet needs.





# DENMARK

## Disease Burden

### Prevalence, Diagnosis, and Comorbidities

In Danish adults, the one-year prevalence of AD decreased with age: 19.2% in adults aged 30–40 versus 14.3% in adults aged 30–89.<sup>3</sup> More recent estimates suggest overall prevalence among adults to be considerably lower, closer to 4–5%.\* While the prevalence of childhood AD seems to be increasing in the UK and Germany, temporal trends are less clear in Denmark.

One study found an increase in AD prevalence among urban children in Copenhagen, from 17.3% in 1986 to 27.3% in 2001.<sup>162</sup> However, two studies found a stable prevalence of AD in Danish children overall between 1993 and 1998<sup>143</sup> and between 1997 and 2011.<sup>163,164</sup> The prevalence of AD in Denmark is comparable to other COI reviewed. An unmet need may exist for children in Danish families of lower (vs. higher) SES and families with one or both parents from non-European countries (vs. with two European parents); the prevalence of AD was higher in both groups.<sup>165</sup>

Several studies have attempted to understand the reasons for persistent disease in older children. In a longitudinal study of children aged 0–16, 67% still showed disease activity 10 years after the study began. The strongest predictors for persistent AD were high-potency TCS/TCI prescriptions, use of antibiotics, and use of antihistamines.<sup>166</sup> Genetic risk seems to play a role. A birth cohort born to mothers with asthma were followed up at age 13; the lifetime prevalence of AD was 45.3%, of whom 24.1% had developed persistent AD.<sup>155</sup> Another study affirmed that parental AD and asthma increase the risk of persistent AD; other risk factors included known genetic markers, higher SES, specific Hanifin and Rajka minor criteria (i.e. the presence of specific clinical signs or comorbidities), and disease severity at onset. The authors posit that identifying children at increased risk for persistent disease may help improve management.<sup>167</sup>

<sup>3</sup>Vastrup, Anne, *Atopisk Eksem Forening*. Personal interview. 7 September 2021.

<sup>162</sup>Stensen, L., Thomsen, S. F. & Backer, V. Change in prevalence of atopic dermatitis between 1986 and 2001 among children. *Allergy Asthma Proc* 29, 392–396 (2008).

<sup>163</sup>Henriksen, L. et al. Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. *J Allergy Clin Immunol* 136, 360–366. e2 (2015).

<sup>164</sup>Olesen, A. B., Bang, K., Juul, S. & Thestrup-Pedersen, K. Stable incidence of atopic dermatitis among children in Denmark during the 1990s. *Acta Derm Venereol* 85, 244–247 (2005).

<sup>165</sup>Andersen, Y. M. F., Egeberg, A., Skov, L. & Thyssen, J. P. Demographics, healthcare utilization and drug use in children and adults with atopic dermatitis in Denmark: a population-based cross-sectional study. *J Eur Acad Dermatol Venereol* 33, 1133–1142 (2019).

<sup>166</sup>Thyssen, J. P., Corn, G., Wohlfahrt, J., Melbye, M. & Bager, P. Retrospective markers of paediatric atopic dermatitis persistence after hospital diagnosis: A nationwide cohort study. *Clinical & Experimental Allergy* 49, 1455–1463 (2019).

<sup>167</sup>Thorsteinsdottir, S. et al. Genetic, Clinical, and Environmental Factors Associated With Persistent Atopic Dermatitis in Childhood. *JAMA Dermatol* 155, 50–57 (2019).

Numerous recent studies have identified comorbidities. AD is associated with an increased risk of conjunctivitis, keratitis, and keratoconus;<sup>168</sup> non-melanoma skin cancer (NMSC), keratinocyte carcinoma, and lymphoma;<sup>169–171</sup> tobacco use, alcohol use, and psychiatric comorbidities,<sup>172</sup> including ADHD;<sup>173</sup> and myocardial infarction (MI)<sup>174</sup> and adverse cardiovascular outcomes generally.<sup>175</sup> The risk for death due to any cause was significantly higher in Danish patients with (vs. without) AD, though the absolute risk was still quite low. Common causes of death in AD were cardiovascular, infectious, and urogenital.<sup>176</sup>

A population-based study found that Danish patients with severe AD had an increased risk of developing comorbidities related to smoking, including chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA), suggesting that it may be beneficial to prioritize smoking cessation counselling in this population.<sup>177</sup> The 10-year mortality after first hospitalization was increased in Danish patients with AD compared to the general population; this finding was most correlated with smoking but was also correlated with low SES and multimorbidity.<sup>178</sup>

As noted in several other COI, AD comes with a theoretical increased risk for contact dermatitis because AD is characterized by a defective skin barrier.<sup>179</sup> In a study of 100 children with a diagnosis of AD, patch testing with 31 allergens yielded at least one positive reaction in 30% of the children, and 17% were found to have a contact allergy that might be contributing to the observed AD symptoms.<sup>180</sup> This may reflect an unmet need for contact dermatitis screening in patients with AD.

## Physical and Psychosocial Consequences

As observed in other COI, there is a strong association between disease severity and the QoL burden in Danish individuals. Holm et al. assessed DLQI, SCORAD, and filaggrin gene (FLG) mutation status in a cohort of 250 outpatients aged >4. Significant correlations were found between SCORAD and DLQI (0.42,  $p < 0.001$ ). The mean DLQI in patients with mild AD was 5.30, and this increased (i.e., worsened) to 8.59 and 11.94 in patients with moderate and severe AD, respectively. Female gender and AD involvement of the face were associated with higher (worse) DLQI scores.<sup>181</sup>

A few studies have evaluated the psychosocial burden of children and adults with AD in Denmark. In children, severe AD was associated with a higher likelihood of staying home from school due to AD and higher risks of problems with falling asleep, waking up at night, and concentration.<sup>182</sup> A study using the Strengths and Difficulties Questionnaire found that AD in children was associated with emotional, conduct, and hyperactivity problems.<sup>183</sup> In adults, depression, anxiety, and suicidal ideation are more common in patients with AD, and patients with moderate-to-severe AD were more likely to be prescribed anti-depressants or anti-anxiolytics.<sup>184</sup>

## Caregiver Burden

The caregiver burden has not been well characterized in Denmark.

## Financial Burden

The direct OOP costs associated with AD care and treatment have not been studied in Denmark, but a questionnaire study conducted by the Danish Association of Atopic Eczema evaluated indirect costs related to disability and work absenteeism. Adults with AD missed an average of 5.8 days of work every six months, 148% higher than the national average.<sup>185</sup> AD deterred 38% of individuals from pursuing their desired line of work or education. The number of early retirement pensions granted due to AD increased in Denmark from 4.2 per year in 1970–1976 to 18.0 per year in 1999–2002.<sup>185</sup> Hand AD and AD associated with the filaggrin gene (FLG) mutation was associated with an increased disability pension and avoidance of careers that tend to trigger hand dermatitis.<sup>183,186</sup>

<sup>168</sup>Thyssen, J. P. et al. Incidence, prevalence, and risk of selected ocular disease in adults with atopic dermatitis. *J Am Acad Dermatol* 77, 280–286.e1 (2017).

<sup>169</sup>Ruff, S. et al. Prevalence of Cancer in Adult Patients with Atopic Dermatitis: A Nationwide Study. *Acta Derm Venereol* 97, 1127–1129 (2017).

<sup>170</sup>Olesen, A. B., Engholm, G., Storm, H. H. & Thestrup-Pedersen, K. The risk of cancer among patients previously hospitalized for atopic dermatitis. *J Invest Dermatol* 125, 445–449 (2005).

<sup>171</sup>Jensen, A. O. et al. Atopic dermatitis and risk of skin cancer: a Danish nationwide cohort study (1977–2006). *Am J Clin Dermatol* 13, 29–36 (2012).

<sup>172</sup>Egeberg, A., Andersen, Y. M. F., Gislason, G. H., Skov, L. & Thyssen, J. P. Prevalence of comorbidity and associated risk factors in adults with atopic dermatitis. *Allergy* 72, 783–791 (2017).

<sup>173</sup>Riis, J. L., Vestergaard, C., Deleuran, M. S. & Olsen, M. Childhood atopic dermatitis and risk of attention deficit/hyperactivity disorder: A cohort study. *Journal of Allergy and Clinical Immunology* 138, 608–610 (2016).

<sup>174</sup>Riis, J. L. et al. Hospital-diagnosed atopic dermatitis and long-term risk of myocardial infarction: a population-based follow-up study. *BMJ Open* 6, e011870 (2016).

<sup>175</sup>Andersen, Y. M. F. et al. Risk of myocardial infarction, ischemic stroke, and cardiovascular death in patients with atopic dermatitis. *Journal of Allergy and Clinical Immunology* 138, 310–312.e3 (2016).

<sup>176</sup>Thyssen, J. P., Skov, L. & Egeberg, A. Cause-specific mortality in adults with atopic dermatitis. *J Am Acad Dermatol* 78, 506–510 (2018).

<sup>177</sup>Andersen, Y. M. F., Egeberg, A., Gislason, G. H., Skov, L. & Thyssen, J. P. Burden of respiratory comorbidities in patients with atopic dermatitis and psoriasis. *British Journal of Dermatology* 177, e145–e146 (2017).

<sup>178</sup>Egeberg, A. et al. Ten-year mortality is increased after hospitalization for atopic dermatitis compared with the general population, but reduced compared with psoriasis. *Journal of the American Academy of Dermatology* 76, 98–105 (2017).

<sup>179</sup>Egawa, G. & Kabashima, K. Multifactorial skin barrier deficiency and atopic dermatitis: Essential topics to prevent the atopic march. *J Allergy Clin Immunol* 138, 350–358.e1 (2016).

<sup>180</sup>Simonsen, A. B. et al. Children with atopic dermatitis may have unacknowledged contact allergies contributing to their skin symptoms. *J Eur Acad Dermatol Venereol* 32, 428–436 (2018).

<sup>181</sup>Holm, J. G., Agner, T., Clausen, M.-L. & Thomsen, S. F. Quality of life and disease severity in patients with atopic dermatitis. *J Eur Acad Dermatol Venereol* 30, 1760–1767 (2016).

<sup>182</sup>Germer, T. et al. Disease severity and trigger factors in Danish children with atopic dermatitis: a nationwide study. *Journal of the European Academy of Dermatology and Venereology* n/a.

<sup>183</sup>Bandier, J. et al. Carriers of filaggrin gene (FLG) mutations avoid professional exposure to irritants in adulthood. *Contact Dermatitis* 69, 355–362 (2013).

<sup>184</sup>Thyssen, J. P. et al. Atopic dermatitis is associated with anxiety, depression, and suicidal ideation, but not with psychiatric hospitalization or suicide. *Allergy* 73, 214–220 (2018).

<sup>185</sup>Holm, E. A., Esmann, S. & Jemec, G. B. E. The handicap caused by atopic dermatitis—sick leave and job avoidance. *J Eur Acad Dermatol Venereol* 20, 255–259 (2006).

<sup>186</sup>Heede, N. G. et al. Hand eczema, atopic dermatitis and filaggrin mutations in adult Danes: a registry-based study assessing risk of disability pension. *Contact Dermatitis* 77, 95–105 (2017).

## Treatment

Achieving complete or almost complete disease clearance was an important metric of treatment satisfaction for adults with AD in the Danish Skin Cohort, especially among patients with severe disease, substantial itch or skin pain, and AD located on the face or neck.<sup>187</sup>

As in most other COI, the parents of children with AD have concerns about TCS therapy. A higher parental score on the Topical Corticosteroid Phobia (TOPICOP) measure is associated with a longer delay between the start of a flare and initiation of TCS as well as a lower score on the parents' subjective "feel" for AD management. Higher TOPICOP scores tend to be found among the parents of children with severe AD and parents with low levels of educational attainment,<sup>188</sup> so focusing on educational interventions in parents who are hesitant to use TCS may improve outcomes in children.

Comprehensive interviews with AD patients revealed that concerns about the side effects of prescribed medications often led to an interest in alternative therapies. In one nationwide survey, 65.4% of the parents of children with severe AD and 59.1% of parents whose child developed AD within the past six months reported using diet interventions to attempt to control AD; 54.2% of the parents with a child with severe AD reported no improvement. 20% of parents also reported attempting alternative therapies such as reflexology, homeopathy, cranio-sacral therapy, and acupuncture.<sup>182</sup> Although patients who turned to alternative therapies were reluctant to return to conventional medications for fear of side effects, they did so when symptoms recurred.<sup>189</sup>

Adequate moisturization has been shown to reduce disease flares and the increased costs associated with more severe disease. Results from a study conducted in Sweden found that in patients with moderate AD in remission, maintenance therapy with moisturizers was more efficacious and cost-effective than no moisturizer.<sup>190</sup> This study was extrapolated to Denmark and other Nordic countries because dermatologic care is similar in those countries.<sup>190</sup>

## Healthcare

### Utilization

Children with AD were observed to utilize healthcare resources and use prescribed medications more frequently than children without AD.<sup>191</sup> Patients treated in hospital outpatient environments were more likely than patients treated in private clinics to be of lower SES and have a higher disease burden, described in the study as a combination of multiple medical comorbidities and the treatment burden attributable to AD.<sup>192</sup> An interview-based study of Danish adults found that adult AD patients and the parents of children with AD regarded dermatologists as much more knowledgeable about AD than GPs; parents often sought referrals to dermatologists in pursuit of better care.<sup>193</sup>

### Patient and Caregiver Satisfaction

In the aforementioned interview-based study, adult AD patients and the parents of children with AD commented at length about the interpersonal skills (or lack thereof) of their providers; those willing to spend more time and give clear instructions received more positive responses from patients and parents.<sup>193</sup>

### Patient-Centered Interventions

The literature search did not yield any studies of relevant interventions in Denmark.



**Comprehensive interviews with AD patients revealed that concerns about the side effects of prescribed medications often led to an interest in alternative therapies.**

<sup>187</sup>Egeberg, A. & Thyssen, J. P. Factors associated with patient-reported importance of skin clearance among adults with psoriasis and atopic dermatitis. *J Am Acad Dermatol* 81, 943–949 (2019).

<sup>188</sup>Gerner, T. et al. Healthcare utilization in Danish children with atopic dermatitis and parental topical corticosteroid phobia. *Pediatric Allergy and Immunology* n/a.

<sup>189</sup>Nørreslet, M., Bissell, P. & Traulsen, J. M. From consumerism to active dependence: Patterns of medicines use and treatment decisions among patients with atopic dermatitis. *Health (London)* 14, 91–106 (2010).

<sup>190</sup>Hjalte, F., Asseburg, C. & Tennvall, G. R. Cost-effectiveness of a barrier-strengthening moisturizing cream as maintenance therapy vs. no treatment after an initial steroid course in patients with atopic dermatitis in Sweden – with model applications for Denmark, Norway and Finland. *Journal of the European Academy of Dermatology and Venereology* 24, 474–480 (2010).

<sup>191</sup>Hammer-Helmich, L., Linneberg, A., Thomsen, S. F., Tang, L. & Glümer, C. Health service use among children with and without eczema, asthma, and hay fever. *Clin Epidemiol* 8, 341–349 (2016).

<sup>192</sup>Egeberg, A., Andersen, Y. M. F., Gislason, G. H., Thyssen, J. P. & Skov, L. Differential disease burden and treatment patterns among adults with psoriasis and atopic dermatitis seen in hospital vs. private clinics. *Journal of the European Academy of Dermatology and Venereology* 32, e23–e25 (2018).

<sup>193</sup>Noerreslet, M., Jemec, G. B. E. & Traulsen, J. M. Involuntary autonomy: patients' perceptions of physicians, conventional medicines and risks in the management of atopic dermatitis. *Soc Sci Med* 69, 1409–1415 (2009).



## KEY FINDINGS

The prevalence of AD is similar in Denmark and other western European nations, though the prevalence of AD among children seems to have remained more stable over time. Much like in the US, multiple recent studies have evaluated comorbid associations, including those that may be consequences of AD therapy (e.g., melanoma and non-melanoma skin cancer as a consequence of phototherapy). The association between AD and cardiovascular risk factors appeared weaker in Denmark than in the US, likely due to differing lifestyles and comorbid factors. The negative impacts of smoking in patients with severe AD are described in the Danish literature; patients with severe AD are more likely both to smoke and to suffer from adverse consequences related to smoking (e.g., COPD).

Fears about TCS use in both patients and caregivers are well-characterized in the Danish literature. Much like in Canada, Danish parents of children with AD preferred to receive care from dermatologists rather than from GPs. The impacts of AD on missed work, the choice of work, and the timing of retirement were also well-represented in the Danish literature, and other countries may find it useful to conduct similar assessments of these impactful and yet often forgotten consequences of AD.





# FRANCE

## Disease Burden

### Prevalence, Diagnosis, and Comorbidities

The prevalence of AD was found to be 6–9% in children younger than 15 and 4.65% among French adults.<sup>194,195</sup> These rates appear to be lower than in the other COI, though variations in survey inclusion criteria and methodology make it difficult to draw robust cross-country comparisons.<sup>64</sup>

However, France fell in the middle of the COI in a 2016 international survey-based study of the point prevalence of AD; Barbarot et al. reported a point prevalence of 3.6% in France, higher than in the UK (2.5%), Germany (2.2%), and Canada (3.6%), but lower than in the US (4.9%) and Italy (8.1%).<sup>196</sup>

French infants diagnosed with AD before 1 year of age were followed for 9 years to identify comorbidities and predictors of treatments costs. Significant comorbidities included respiratory disease (namely, asthma), ophthalmologic comorbidities, and skin comorbidities.<sup>197</sup> In adult patients, known comorbidities include neuropsychiatric disorders; AD also confers an increased risk of skin infections, tobacco use, and other atopic conditions in a dose-dependent manner (i.e., the risk increases with AD severity).<sup>198</sup>

As discussed in Denmark, patients with AD may have a higher risk of contact dermatitis because a defective skin barrier theoretically may lead to sensitization. One study conducted patch tests of children with and without AD; 17% of children with AD had sensitivities on either the cosmetic series patch tests or standard series patch tests, compared to 0% of healthy controls. Nickel sulphate, methylchloroisothiazolinone (a preservative found in some cosmetic products), and cocamidopropylamine (used in cleaning products) were the most common allergens encountered.<sup>199</sup>

<sup>194</sup>Taieb, A. [Atopic dermatitis: definition, epidemiology, natural history, severity and scores]. *Ann Dermatol Venerol* 132 Spec No 1, 1S35–43 (2005).

<sup>195</sup>Richard, M.-A. et al. Sex- and age-adjusted prevalence estimates of five chronic inflammatory skin diseases in France: results of the « OBJECTIFS PEAU » study. *J Eur Acad Dermatol Venereol* 32, 1967–1971 (2018).

<sup>196</sup>Barbarot, S. et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. *Allergy* 73, 1284–1293 (2018).

<sup>197</sup>Misery, L., Ansolabehere, X., Grandfils, N., Georgescu, V. & Taieb, C. Nine-Year Follow-Up of Children with Atopic Dermatitis by General Practitioners. *DRM* 228, 344–349 (2014).

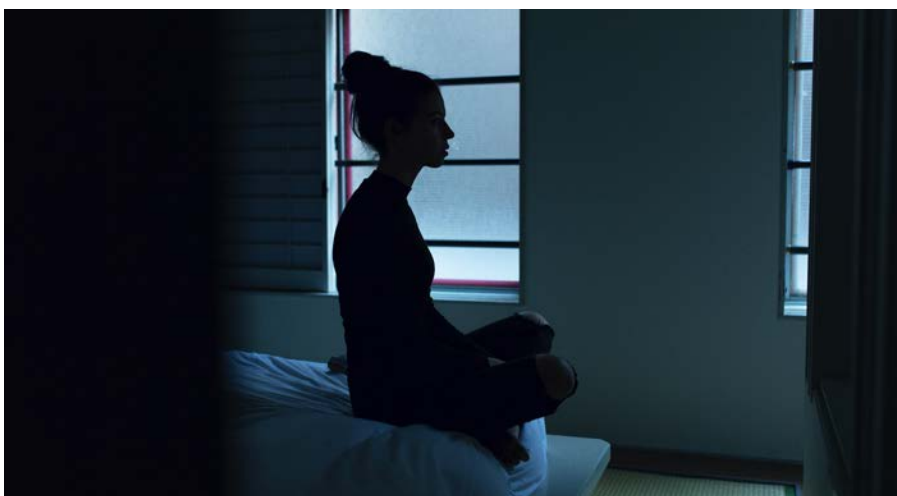
<sup>198</sup>Jachiet, M. et al. Low cardiovascular risk and poor quality of life associated with tobacco use and skin infections in adult atopic dermatitis: result of a French multicenter study. *J Eur Acad Dermatol Venereol* 33, e451–e453 (2019).

<sup>199</sup>Ozceker, D. et al. Contact sensitization in children with atopic dermatitis. *Allergol Immunopathol (Madr)* 47, 47–51 (2019).

## Physical and Psychosocial Consequences

The Eczema Cohorte Longitudinale Adultes (ECLA) study evaluated the QoL burden faced by patients with AD in France.<sup>200</sup> Patients with mild, moderate, and severe disease had health utility scores of 0.79, 0.68, and 0.60, respectively. Misery et al. evaluated a cohort of 266 French adults with a mean SCORAD of 44.6 (severe disease) and found a mean DLQI of 8.8 (indicating moderate impact to QoL), with higher (i.e., worse) scores in patients with visible lesions (i.e., hands and face).<sup>201</sup> Similarly, another survey study of French adults with AD found that visible and breast and/or genital disease involvement predicted worse scores on the DLQI, the mental component of the SF-12, the EQ-VAS (EuroQoL Visual Analog Scale), and the adult version of the ABS.<sup>200</sup>

Ezzedine et al. studied the QoL impact of AD among 399 French adolescents (ages 12–17). A majority of the cohort (57.6%) had mild disease as measured by POEM; 32.8% had moderate disease, and 9.5% had severe disease. Adolescents aged 12–14 completed the Children’s DLQI (CDLQI), where a score of 2–6 indicates a small effect on the child’s life, 7–12 indicates moderate impact, and 13–18 indicates very large impact.<sup>202,203</sup> The authors reported average scores of 5.6, 12.7, and 15.9 for mild, moderate, and severe disease, respectively. Adolescents aged 15–17 completed the standard DLQI and scored 6.7, 12.4, and 18.2 for mild, moderate, and severe disease, respectively. All participants also completed the EQ-VAS (a self-reported scale ranging from 0–100 with higher scores representing better health); the overall EQ-5D VAS across adolescents aged 12–17 was 72.7. When stratified by disease severity (measured by POEM), EQ-5D scores were 51.7 for severe disease, 68.8 for moderate disease, and 78.2 for mild disease.<sup>202</sup>



The Girolomoni et al study which analyzed the economic and psychosocial burden in EU5 patients (France, Germany, Italy, Spain, and the UK) with moderate-to-severe AD also examined sleep difficulty, anxiety, and depression in a French cohort of patients.<sup>34</sup> 64.8% reported mild, moderate, or severe sleep difficulty; 13.3% of whom indicated severe sleep difficulties. 57.4% of patients reported anxiety, and 73.0% of patients reported depression as measured by the PHQ-9. Of the patients who had a positive PHQ-9, 37.5% scored 10 or higher (at least moderate depression), and 7.0% scored 20–27 (severe depression).<sup>34</sup>

France is unique among the COI for its consideration of the effects of AD on sexual health. In the Misery et al. study of 266 French adults with moderate-to-severe AD, 57.5% reported at least an occasional decrease in sexual desire, 55.4% reported that the appearance of AD affected their sex life, and 46.8% reported that AD treatment impacted their sex life. Misery et al. also surveyed the patients’ partners; 32% overall (severe disease: 39.5%, moderate disease: 16.3%) reported at least an occasional decrease in their own sexual desire attributable to their partner’s AD.<sup>201</sup> In another survey study of French adults with AD, disease severity correlated with the likelihood of responding “always” or “often” to the question, “Has your AD had an impact on your sexual desire?” (severe disease: 9.5% “always,” 19.3% “often”; moderate disease: 4.4% and 10.9%; mild disease: 1.8% and 0.7%). Patients who responded “always” or “often” also reported worse scores on all measures of QoL. Disease severity also correlated with patients’ perceptions that their partners’ sexual desire was affected (severe disease: 2.6% “always,” 7.5% “often”; moderate disease: 4.3% and 10.7%; mild disease: 2.7% and 9%).<sup>200</sup>

**64.8%**  
reported mild,  
moderate, or  
severe sleep  
difficulty.

<sup>200</sup>Misery, L. et al. Patient Burden is Associated with Alterations in Quality of Life in Adult Patients with Atopic Dermatitis: Results from the ECLA Study. *Acta Derm Venereol* 98, 713–714 (2018).

<sup>201</sup>Misery, L. et al. Atopic dermatitis: impact on the quality of life of patients and their partners. *Dermatology* 215, 123–129 (2007).

<sup>202</sup>Ezzedine, K., Shourick, J., Merhand, S., Sampogna, F. & Taieb, C. Impact of Atopic Dermatitis in Adolescents and their Parents: A French Study. *Acta Derm Venereol* 100, adv00294 (2020).

<sup>203</sup>Children’s Dermatology Life Quality Index. Cardiff University <https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/childrens-dermatology-life-quality-index>.

## Caregiver Burden

The aforementioned Ezzedine et al. study evaluated the impacts of AD on the parents of adolescents. Disease severity correlated with parents' scores on the EQ-5D VAS (parents of adolescents with mild disease: 77.0; moderate disease: 72.3; severe disease: 59.1) and the family version of the ABS (mild: 8.6; moderate: 16.9; severe: 24.3).<sup>202</sup> Interestingly, those who attended a therapeutic patient education program scored worse on the QoL metrics, though this likely was due to self-selection bias.<sup>202</sup>

## Financial Burden

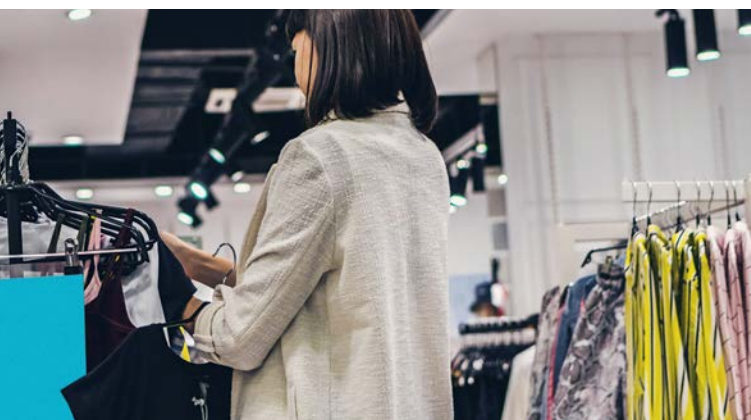
OOP costs among AD patients in France are lower than in Germany and significantly lower than in the US. Patients with moderate and severe AD had mean annual OOP costs of €247.4 and €462.1, respectively.<sup>204</sup> The largest proportion of OOP costs came from emollients (74.4% of the products purchased, for an annual OOP cost of €151.4). Clothing choice was also included in the OOP cost analysis; 27% of patients with severe AD made clothing purchases specifically to accommodate their skin changes, incurring an average annual cost of €162; 19% of patients with moderate AD did so and incurred an average annual cost of €91.<sup>204</sup>

Indirect costs were on par with those in other European COI. Girolomoni et al. estimated an annual indirect cost of €6490–13,315 based on work impairment and the median wage; this did not differ significantly from Germany, Italy, Spain, or the UK.<sup>34</sup> In the French cohort, overall work impairment ranged from 33.6% in the moderate DLQI impact group (DLQI 11–20) to 69.0% in the extremely large impact group (DLQI 21–30). As with most other components of the AD burden, indirect costs tend to increase with disease severity; work absenteeism due to AD was reported by 2.8% with mild disease, 15.3% with moderate disease, and 21.2% with severe disease. Furthermore, patients with severe AD took an average of 6.6 days off work in each period of sick leave.<sup>200</sup>

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*266 French adults with moderate-to-severe AD, 57.5% reported at least an occasional decrease in sexual desire, 55.4% reported that the appearance of AD affected their sex life, and 46.8% reported that AD treatment impacted their sex life.*

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**27%** of patients with severe AD made clothing purchases specifically to accommodate their skin changes, incurring an average annual cost of €162.

## Treatment

Studies regarding AD treatment in France have focused on TCS use. Patients and caregivers expressed concerns similar to those in other COI.<sup>179</sup> One questionnaire-based study found that 80.7% of parents/caregivers feared TCS and 36% avoided using them.<sup>205</sup> TCS concerns were predicted by beliefs about absorption into the bloodstream and prior adverse events related to AD treatment. Parents/caregivers with stronger TCS concerns needed more reassurance and were more likely to be inconsistent in their treatment adherence.<sup>205</sup>

<sup>204</sup>Launois, R. et al. Importance of out-of-pocket costs for adult patients with atopic dermatitis in France. *J Eur Acad Dermatol Venereol* 33, 1921–1927 (2019).

<sup>205</sup>Aubert-Wastiaux, H. et al. Topical corticosteroid phobia in atopic dermatitis: a study of its nature, origins and frequency. *Br J Dermatol* 165, 808–814 (2011).

Two studies quantified TCS concerns with the TOPICOP score. The Topical Corticosteroid Phobia (TOPICOP) score measures corticophobia, and can be completed by patients or their parents. The score is **based on 12 items assessing 3 different dimensions** of TCS phobia each scored on a 4-point Likert scale. The study found higher scores among parents of girls and parents with an observed lack of adherence to treatment regimens. Therapeutic patient education successfully decreased the mean TOPICOP score from 37% to 7.9%.<sup>206</sup> In a cross-sectional, multi-center study across 9 hospitals in France, the TOPICOP score correlated with whether the mother responded to questions and whether the patient was returning for a follow-up outpatient visit.<sup>207</sup>

Interestingly, French pharmacists expressed concerns about TCS therapy in AD. A national survey of French pharmacists found only moderate confidence (4.46/10) in TCS therapy.<sup>208</sup> Furthermore, 27.7% of pharmacists reported that TCS should be used only for severe AD, 24.5% of pharmacist stated that TCS are more dangerous than oral steroids for children younger than 2 years of age, 82.9% believed that TCS should not be applied to the face, and 82.3% believed that TCS should not be applied to the hands.<sup>208</sup>

## Healthcare

### Utilization

The Girolomoni et al. study examined rates of healthcare provider visits, emergency room visits, and hospitalizations within 6 months of survey administration in a French cohort of patients as well. Patients were grouped according to impact on DLQI (moderate effect, very large effect, or extremely large effect); statistically significant findings were reported for emergency room visit rates (0.50%, 0.73%, and 1.88%, respectively).



A national survey of French pharmacists found only moderate confidence (4.46/10) in TCS therapy.<sup>208</sup>

<sup>206</sup>Gonzales, F. et al. Monitoring of topical corticosteroid phobia in a population of parents with children with atopic dermatitis using the TOPICOP® scale: prevalence, risk factors and the impact of therapeutic patient education. *Journal of the European Academy of Dermatology and Venereology* 31, e172–e174 (2017).

<sup>207</sup>Moawad, S. et al. Topical Corticosteroid Concerns Among Parents of Children with Psoriasis versus Atopic Dermatitis: A French Multicenter Cross-Sectional Study. *Am J Clin Dermatol* 19, 261–265 (2018).

<sup>208</sup>Raffin, D. et al. Corticosteroid Phobia Among Pharmacists Regarding Atopic Dermatitis in Children: A National French Survey. *Acta Derm Venereol* 96, 177–180 (2016).

## KEY FINDINGS

The prevalence of AD in France appears to be lower than in other countries surveyed in this report, though (as mentioned previously) cross-country comparisons are difficult to make due to differing methodologies.

The French literature is notable for its nuanced analysis of the impacts of AD on the sexual health of both patients and their partners. In the other COI, considerations of sexual health have not extended beyond the one question in the DLQI. The French literature also includes studies of adolescents and their parents, which have been understudied in the other COI. There are also several studies which detail the mental health burden experienced by patients in France.

The Girolomoni et al study provides some context for healthcare utilization by patients with AD in France, but there is likely more research needed in this area. However, there is ample information regarding TCS phobia in both patients and healthcare providers. One study describes the success of a therapeutic patient education program at alleviating TCS phobia, supporting the notion that educational interventions may be an effective method for increasing adherence and generating downstream improvements in disease severity and QoL.





# ITALY

## Disease Burden

### Prevalence, Diagnosis, and Comorbidities

Several AD prevalence studies have been conducted for different age groups: preschool children (aged 3–5) had a one-year prevalence of 18.1%,<sup>209</sup> 9-year-old children had a point-prevalence of 5.8% (with a lifetime prevalence of 15.2%),<sup>210</sup> adolescents (aged 12–17) had a lifetime prevalence of 7.0%,<sup>211</sup> and 8.1% adults aged 20–44 years reported having current eczema.<sup>212</sup>

While AD remits in many cases, AD which persisted from childhood to adulthood (persistent AD) was found to affect 59.7% of adults with AD; 40.3% of adults developed AD in adulthood itself (adult-onset AD). Patients with persistent AD were more likely to have severe disease involvement as assessed by SCORAD.<sup>213</sup>

As in several other COI, the prevalence of AD in children seems to have increased in recent decades. Specifically, the prevalence of AD increased by 4.4% among Italian children and by 2.1% among Italian adolescents between 1994 and 2002.<sup>214</sup>

In adults, the prevalence of AD with asthma and/or hay fever (EAH) was 3.4%.<sup>212</sup> Adult patients with (vs. without) AD had a heightened prevalence of hypertension (7.1%) and thyroiditis (4.3%).<sup>213</sup>

### Physical and Psychosocial Consequences

As in other COI, disease severity correlates with the QoL burden. Children with SCORAD >40 were found to have significantly more impaired QoL.<sup>215</sup> Children and their families seem to be most impacted by itching, sleep problems, and mood problems.<sup>216</sup>

<sup>209</sup>Peroni, D. G. et al. Prevalence and risk factors for atopic dermatitis in preschool children. *Br J Dermatol* 158, 539–543 (2008).

<sup>210</sup>Girolomoni, G. et al. The epidemiology of atopic dermatitis in Italian schoolchildren. *Allergy* 58, 420–425 (2003).

<sup>211</sup>Naldi, L., Parazzini, F., Gallus, S., & GISED Study Centres. Prevalence of atopic dermatitis in Italian schoolchildren: factors affecting its variation. *Acta Derm Venereol* 89, 122–125 (2009).

<sup>212</sup>Pesce, G. et al. Adult eczema in Italy: prevalence and associations with environmental factors. *J Eur Acad Dermatol Venereol* 29, 1180–1187 (2015).

<sup>213</sup>Megna, M. et al. An Italian multicentre study on adult atopic dermatitis: persistent versus adult-onset disease. *Arch Dermatol Res* 309, 443–452 (2017).

<sup>214</sup>Galassi, C. et al. Changes in prevalence of asthma and allergies among children and adolescents in Italy: 1994–2002. *Pediatrics* 117, 34–42 (2006).

<sup>215</sup>Boccardi, D. et al. Disease severity and quality of life in children with atopic dermatitis: PO-SCORAD in clinical practice. *Minerva Pediatr* 69, 373–380 (2017).

<sup>216</sup>Ricci, G., Bendandi, B., Bellini, F., Patrizi, A. & Masi, M. Atopic dermatitis: quality of life of young Italian children and their families and correlation with severity score. *Pediatr Allergy Immunol* 18, 245–249 (2007).

The Girolomoni et al. study of moderate-to-severe AD in adults found sleep disturbances in 52.5% of Italian adults, with severe impairment in 5.0%. This was somewhat less than the rates of sleep disturbances observed in France (64.8% overall with 13.3% severe), Germany (68.9% overall with 9.8% severe), and the UK (57.6% overall with 8.5% severe). Anxiety was observed in 58.5% of Italian adults with AD, similar to in France (57.4%) and the UK (61.5%) but much higher than in Germany (29.5%). Moderate depression or worse was reported by 49.2% of Italian adults with AD; severe depression (PHQ-9 score between 20 and 27) occurred in 8.2%.<sup>34</sup>

## Caregiver Burden

The Caregiver Pictorial Representation of Illness and Self-Measure (Caregiver-PRISM) was created to explore factors associated with parents' suffering related to their child's AD.<sup>217</sup> Higher parent suffering on the Caregiver-PRISM was associated with a "less positive family affective climate," higher parent educational attainment, and having the child follow a specific diet due to AD. The Caregiver-PRISM results suggested that families and caregivers were on average moderately impacted by their child's AD, with the most profound impact on the domain of sleep.<sup>217</sup> Caregivers' well-being was also affected by fatigue/irritability and the costs associated with disease management.<sup>216</sup> Monti et al. found that a child's severe AD had a greater impact on the family's QoL than on the child's own QoL; the inadequacy of AD education seemed to contribute to the caregiver burden.<sup>195</sup>



On average, Italian adults with moderate-to-severe AD missed 9 days of work out of the year due to AD.

## Financial Burden

A study of the direct and indirect costs in patients with moderate-to-severe AD found an average annual burden per patient of €4,284. This figure was higher than in France, Germany, Canada, and Australia but lower than in the US, where OOP expenses alone may exceed \$5,000 for patients with severe AD.<sup>6,218</sup> For Italian patients, the total financial burden was attributable first and foremost to indirect costs (60.8%, namely, lost productivity) with the remaining burden split between direct medical costs (19.3%) and non-direct medical costs (19.9%).<sup>218</sup>

On average, Italian adults with moderate-to-severe AD missed 9 days of work out of the year due to AD and reported a loss of productivity while at work due to AD during 21 days.<sup>218</sup> The Girolomoni et al. study of moderate-to-severe AD found that 42.5% of Italian adults with a moderate QoL impact (DLQI 6–10) experienced work impairment; this increased to 74.0% of Italian adults with an extremely large QoL impact (DLQI 21–30).<sup>34</sup>

The caregivers of children with AD bear a significant financial burden, estimated at €1254 annually (and higher for more severe disease) and attributable primarily to moisturizers, detergents, and consultations with private specialists.<sup>219</sup> Caregivers also experience indirect costs; Sciattelli et al. found that caregivers lost an average of 2.5 days of work per year due to the patient's AD.<sup>218</sup>

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*Higher parent suffering on the Caregiver-PRISM was associated with a "less positive family affective climate," higher parent educational attainment, and having the child follow a specific diet due to AD.*

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<sup>217</sup>Marinello, E. et al. Assessing the Impact of Atopic Dermatitis on the Patients' Parents with the Visual Instrument 'Caregiver-PRISM'. *Dermatology* 232, 490–495 (2016).

<sup>218</sup>Sciattella, P. et al. The burden of atopic dermatitis in adults in Italy. *G Ital Dermatol Venereol* 155, 19–23 (2020).

<sup>219</sup>Ricci, G., Bendandi, B., Pagliara, L., Patrizi, A. & Masi, M. Atopic dermatitis in Italian children: evaluation of its economic impact. *J Pediatr Health Care* 20, 311–315 (2006).



## Treatment

We found sparse literature on the treatment burden attributable to AD in the Italian context, with the exception of one study on TCS fears among Italian parents of children with AD. Parents feared that TCS were dangerous, that they were applying too much cream, and that the risks outweighed the benefits of treatment.<sup>220</sup>

## Healthcare

### Utilization

AD can be severe enough to prompt visits to the emergency department. The Girolomoni et al. study of moderate-to-severe AD in adults found that patients with an extremely large QoL impact (DLQI 21–30) had an increased rate of ED visits (1.44% of patients with moderate-to-severe AD within 6 months of the survey) and hospitalizations (0.78%) compared to patients with a moderate QoL impact (DLQI 6–10; ED visits: 0.24%; hospitalizations: 0.08%).<sup>34</sup> Of the dermatologic conditions seen in Italian EDs from 2006–2011, 10.5% were classified as “eczematous conditions.”<sup>221</sup>

### Satisfaction with Care

Information regarding patient and caregiver satisfaction was absent in the Italian literature within the scope of this literature review.

### Patient-Centered Interventions

An educational intervention of 6 weekly meetings between parents and a pediatric allergist, dermatologist, and psychologist reduced caregiver anxiety and depression and increased relaxation and physical well-being (as measured at the conclusion of the intervention); overall, 85% were satisfied, and 81% felt calmer. Caregivers were most interested in learning about treatments, the typical disease course, allergies, psychological consequences, and alternative treatments options.<sup>219</sup>



**Caregivers were most interested in learning about treatments, the typical disease course, allergies, psychological consequences, and alternative treatments options.<sup>219</sup>**

<sup>220</sup>El Hachem, M. et al. Topical corticosteroid phobia in parents of pediatric patients with atopic dermatitis: a multicentre survey. *Ital J Pediatr* 43, 22 (2017).

<sup>221</sup>Rubegni, P. et al. Dermatological conditions presenting at the Emergency Department in Siena University Hospital from 2006 to 2011. *J Eur Acad Dermatol Venereol* 29, 164–168 (2015).

## KEY FINDINGS

The prevalence and persistence data in Italy are notable for the high rate at which childhood AD lasted into adulthood. The data on comorbidities are sparse, so future population-based studies are warranted.

Of the many dimensions of the psychosocial burden, sleep disturbances were common in both children with AD and their caregivers. As in most other COI, TCS phobia was a significant concern for parents, though this was characterized in only one study and was not explored among physicians or pharmacists. As in Germany and the UK, an educational program for Italian parents of children with AD was successful at improving the parents' psychological well-being. Future studies may apply similar educational approaches to improve treatment adherence and alleviate concerns about TCS use.





# CANADA

## Disease Burden

### Prevalence, Diagnosis, and Comorbidities

#### The International Study for Asthma and Allergies in Childhood (ISAAC)

revealed an increase in the prevalence of AD in Canadian children.

Specifically, the prevalence among children aged 6–7 increased from 8.7% in phase 1 of the study (1992–1998) to 12.0% in phase 3 (1999–2004).<sup>222</sup>

An analysis of the ISAAC phase 3 data by Wang et al. estimated a prevalence of 9.4% among 13–14 year-olds in 5 Canadian cities; the prevalence was higher among females (vs. males) and those who lived Winnipeg or Vancouver (vs. Saskatoon, Hamilton, or Halifax).<sup>223</sup> The prevalence of AD in Canadian adults was estimated to be 3.5% in an international web-based survey.<sup>196</sup>

Until recently, there was a lack of research regarding AD in the Canadian indigenous populations. A 2018 cross-sectional survey of first-grade students living in Iqaluit (approximately 50% Inuit<sup>224</sup>) found eczema prevalence to be 20.5%; eczema prevalence was even higher in the Inuit population specifically (25%).<sup>225</sup> Similarly, a survey of children aged 2–12 in Natuashish (a Mushuau Innu First Nations community<sup>226</sup>) found eczema prevalence to be 16.5%.<sup>227</sup> A cross-sectional survey of seventh-grade students in Iqaluit found a point prevalence of 27.6% and a lifetime prevalence 34.5%.<sup>228</sup> The estimates for AD prevalence in indigenous individuals are significantly higher than in the general Canada population as well as international estimates.<sup>225,227,228</sup> Notably, half of the children in Iqaluit who reported AD identified as mixed Inuit-Caucasian, and a quarter identified as Inuit.<sup>228</sup>

Drucker et al investigated cardiovascular and metabolic risk factors associated with AD; the authors did not find a significant association between AD and hypertension, MI, or stroke, much like in the European COI and unlike in the US.<sup>229</sup>

<sup>222</sup>Asher, M. I. et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *The Lancet* 368, 733–743 (2006).

<sup>223</sup>Wang, H.-Y. et al. Disparate geographic prevalences of asthma, allergic rhinoconjunctivitis and atopic eczema among adolescents in five Canadian cities. *Pediatric Allergy and Immunology* 21, 867–877 (2010).

<sup>224</sup>Demographics | City of Iqaluit. <https://www.iqaluit.ca/visitors/explore-iqaluit/demographics>.

<sup>225</sup>Ahmed, A., Hakim, A. & Becker, A. Evaluation of eczema, asthma, allergic rhinitis and allergies among the Grade-1 children of Iqaluit. *Allergy, Asthma & Clinical Immunology* 14, 9 (2018).

<sup>226</sup>Natuashish : Community of Utshimassit | Portrait of a Nation | Culture | Nametau innu: Memory and knowledge of Nitassinan. <http://www.nametauinnu.ca/en/culture/nation/detail/74>.

<sup>227</sup>Forsey, R. G. Prevalence of childhood eczema and food sensitization in the First Nations reserve of Natuashish, Labrador, Canada. *BMC Pediatr* 14, 76 (2014).

<sup>228</sup>Ahmed, A. & Becker, A. Evaluation of eczema, asthma, allergic rhinitis and allergies among the grade-7 children of Iqaluit. *Allergy Asthma Clin Immunol* 15, 1–10 (2019).

<sup>229</sup>Drucker, A. M., Qureshi, A. A., Dummer, T. J. B., Parker, L. & Li, W.-Q. Atopic dermatitis and risk of hypertension, type 2 diabetes, myocardial infarction and stroke in a cross-sectional analysis from the Canadian Partnership for Tomorrow Project. *Br J Dermatol* 177, 1043–1051 (2017).



Children with moderate-to-severe AD reported **sleep disturbances (70%), anxiety symptoms due to AD (32%), and school absenteeism (20%, of which 23% missed 10 or more days of school due to their AD).**

## Physical and Psychosocial Consequences

An online cross-sectional survey of adult patients with moderate-to-severe AD, conducted by the Eczema Society of Canada (ESC), identified the most common QoL impairments. 87% reported some form of QoL impairment; the most common were sleep dysfunction (48%), anxiety (64%), and the avoidance of social activities (48%), physical activity (47%), and intimacy (40%).<sup>230</sup>

The ESC conducted another online cross-sectional survey study among children and their caregivers. Children with moderate-to-severe AD reported sleep disturbances (70%), anxiety symptoms due to AD (32%), and school absenteeism due to AD (20%, of which 23% missed 10 or more days of school due to their AD). Less prevalent concerns included depression, bullying from peers, avoidance of social activities, and difficulties performing physical activities due to AD.<sup>9</sup>

Among adolescents and adults, a case-control study by Drucker et al. found that individuals aged 15–55 with persistent AD (5 or more visits to the physician in the 5 years prior) were more likely to die by suicide than matched controls. Although this association is largely explained by the heightened risk of several neuropsychiatric illnesses (depression, anxiety, sleep disorders, and substance use), the finding nevertheless points to a significant mental health burden in adolescents and adults with persistent AD.<sup>231</sup> Another study of adults found a significant burden attributable to sleep disturbances.<sup>232</sup>

## Caregiver Burden

The literature search yielded only one study on the caregiver burden: the aforementioned ESC study involving children with moderate-to-severe AD. Caregivers reported impacts on the family's QoL, sleep loss, and mental health concerns such as anxiety and depression.<sup>9</sup>

## Financial Burden

Barbeau et al. found that Ontario adults with AD bore an average annual cost of \$282 for mild disease, \$454 for moderate disease, and \$1242 for severe disease in 2002 Canadian dollars (\$399, \$642 and \$1,758 respectively in 2021 CDN dollars). These sums included direct medical expenses (medical visits and prescriptions), indirect medical expenses (OTC medications and household items), and indirect costs (namely, work absenteeism). The authors note that the personal financial burden to patients in Canada is less than in the US.<sup>232</sup>

<sup>230</sup>Bobotsis, R., Fleming, P., Eshtiaghi, P., Cresswell-Melville, A. & Drucker, A. M. A Canadian Adult Cross-Sectional Survey of the Burden of Moderate to Severe Atopic Dermatitis. *J Cutan Med Surg* 22, 445–446 (2018).

<sup>231</sup>Drucker, A. M., Thiruchelvam, D. & Redelmeier, D. A. Eczema and subsequent suicide: a matched case-control study. *BMJ Open* 8, e023776 (2018).

<sup>232</sup>Barbeau, M. & Bpharm, H. L. Burden of Atopic dermatitis in Canada. *Int J Dermatol* 45, 31–36 (2006).

## Treatment

The Totri et al. study detailing prescribing patterns of US and Canadian clinicians for systemic medications in children with AD was previously discussed in the US section; 18 of the respondents were Canadian.<sup>106</sup> Briefly, there was observed to be great variation in choices for first-line (cyclosporine: 45.2%; methotrexate: 29.6%; mycophenolate mofetil: 13.0%), second-line (methotrexate: 31.3%; mycophenolate mofetil: 30.4%; azathioprine: 20.0%), and third-line (azathioprine: 33.0%; mycophenolate mofetil: 24.3%; methotrexate: 19.1%) agents among the combined US and Canadian respondents, suggesting that there may be improvements in the choice of systemic agents for Canadian children with severe AD.<sup>106</sup>



The ESC study on adult patients with moderate-to-severe AD found that 41% of respondents had unmet treatment needs.<sup>230</sup> Furthermore, only 9% of respondents reported feeling as though their AD was well-controlled, and 78% of respondents reported having lived at least one year without appropriate management of their AD.<sup>230</sup> Another study of Canadian adults found prevalent concerns regarding the use of TCS.<sup>232</sup>

The ESC study on children and caregivers found that many caregivers believed that their child's AD was not well controlled. 85% of respondents reported past use of at least 3 treatment modalities and 18% were using systemic corticosteroids. Furthermore, 80% of respondents noted difficulty with adhering to the prescribed treatment regimen due to time constraints and difficulties with topical applications.<sup>9</sup>

**The ESC study on adult patients with moderate-to-severe AD found that 41% of respondents had unmet treatment needs.<sup>230</sup>**

## Healthcare

### Utilization

The ESC study on adult patients with moderate-to-severe AD found that 32% perceived that it was difficult to access treatment. Only 42% of patients with severe AD had seen a dermatologist at all, and of those, 69% had waited 3 months or more for their first visit.<sup>230</sup> Canadian caregivers and their children with AD had similar difficulties: 27% of caregivers had trouble obtaining treatment for their child's AD, and of the 27% of children with AD who received care from a dermatologist, 46% waited 3 months or more for an appointment and 25% waited 6 months or more.<sup>9</sup>

### Satisfaction with Care

The literature search did not yield any studies on patient or caregiver satisfaction with care in Canada.

### Patient-Centered Interventions

The literature search did not yield any studies on educational interventions in Canada.

## KEY FINDINGS

The prevalence of AD in Canadian adults is lower than in other countries such as the US, but as in most other COI, the prevalence of AD in Canadian children has been increasing in recent years. Even more concerning, recent data suggests a substantially higher AD burden in Canada's indigenous population. Population-based studies of comorbidities associated with AD in Canadians are lacking, suggesting a potential area for further research.

A pair of cross-sectional surveys conducted by the ESC have done much to describe the burden of AD among both Canadian adults and children (and their caregivers) with moderate-to-severe AD. Sleep loss and mental health comorbidities were seen in adults, children, and caregivers. Finally, access to specialized dermatologic care is a widespread problem for both Canadian children and adults with AD.



# AUSTRALIA

## Disease Burden

### Prevalence, Diagnosis, and Comorbidities

Several studies have examined the prevalence of AD using the International Study of Allergy and Asthma in Childhood (ISAAC) protocol. A cross-sectional survey using the ISAAC protocol with Australian preschool-aged children found a 12-month AD prevalence of 18.8%.<sup>233</sup>

Another cross-sectional study performed using the ISAAC protocol with Australian children aged 4–6 found that the lifetime prevalence of AD increased each year between 2000 and 2005 (OR 1.05,  $p < 0.001$ ).<sup>234</sup> A questionnaire-based survey in Melbourne using the ISAAC protocol found that the 12-month prevalence of AD increased in children aged 6–7 from 11.1% in 1993 to 17.2% in 2002.<sup>235</sup> Interestingly, among children living in Australia, Australian-born children had a higher prevalence of AD compared to non-UK European-born children and Asian-born children.<sup>234</sup>

AD is less prevalent among Australian adults than children, with an estimated adult prevalence of 7%.<sup>236</sup> It is possible, however, that adults are underdiagnosed because of the perception that AD is a childhood disease. A cross-sectional study of 2.1 million patients attending 494 general practices in Australia found the lifetime (ever diagnosed) prevalence of AD in this general practice population was 16.4%.<sup>237</sup>

Correlations between AD, allergic rhinitis, and asthma are well-described. Burgess et al. found that AD in childhood was significantly associated with asthma initially presenting in preadolescence, adolescence, and adulthood. AD in childhood was also significantly associated with childhood asthma that persisted into adulthood.<sup>238</sup>

<sup>233</sup>Tai, A., Volkmer, R. & Burton, A. Prevalence of asthma symptoms and atopic disorders in preschool children and the trend over a decade. *J Asthma* 46, 343–346 (2009).

<sup>234</sup>Ponsonby, A.-L. et al. A temporal decline in asthma but not eczema prevalence from 2000 to 2005 at school entry in the Australian Capital Territory with further consideration of country of birth. *Int J Epidemiol* 37, 559–569 (2008).

<sup>235</sup>Robertson, C. F., Roberts, M. F. & Kappers, J. H. Asthma prevalence in Melbourne schoolchildren: have we reached the peak? *Med J Aust* 180, 273–276 (2004).

<sup>236</sup>Jenner, N., Campbell, J. & Marks, R. Morbidity and cost of atopic eczema in Australia. *Australasian Journal of Dermatology* 45, 16–22 (2004).

<sup>237</sup>Chidwick, K., et al. (2020). Prevalence, incidence and management of atopic dermatitis in Australian general practice using routinely collected data from MedicinesInsight. *Australas J Dermatol*, 61: e319–e327. <https://doi.org/10.1111/ajd.13268>

<sup>238</sup>Burgess, J. A. et al. Childhood eczema and asthma incidence and persistence: a cohort study from childhood to middle age. *J Allergy Clin Immunol* 122, 280–285 (2008).

\*Chidwick, K., Busingye, D., et al. (2020). Prevalence, incidence and management of atopic dermatitis in Australian general practice using routinely collected data from MedicinesInsight. *Australas J Dermatol*, 61: e319–e327. <https://doi.org/10.1111/ajd.13268>

## Physical and Psychosocial Consequences

In the Australia context, the consequences of AD are characterized better in adults than in children. Jenner et al. surveyed Australian adults aged 14–63 and found that over a 12-month period, 45% of patients responded either “a lot” or “very much” to questions asking whether their skin was itchy, sore, painful, or stinging; 77% of patients with severe AD answered “a lot” or “very much” to the same questions.<sup>236</sup> In the same study, DLQI data revealed that 36% of patients spent over 10 minutes applying treatments; 28% of patients considered their AD lesions when choosing which clothes to wear; and 21% experienced embarrassment.<sup>236</sup> In a smaller, interview-based study, female patients with AD were negatively impacted by societal depictions of “perfect skin”; this additional dimension of burden for female patients with AD may require further research and attention.<sup>239</sup>

## Caregiver Burden

Su et al. compared the caregiver burden for children with AD versus children with type 1 diabetes mellitus; the burden was significantly greater for AD with respect to the financial burden, social and family impact, personal burden, and disease management.<sup>240</sup> In a similar comparison, Faught et al. found that mothers of children aged 5 years or younger with AD experienced greater stress than both mothers of children with insulin-dependent diabetes and mothers of children with deafness. Parental stress scores were similar between parents of children with AD, parents of children who required enteral feeding, and parents of children with Rett syndrome.<sup>241</sup>

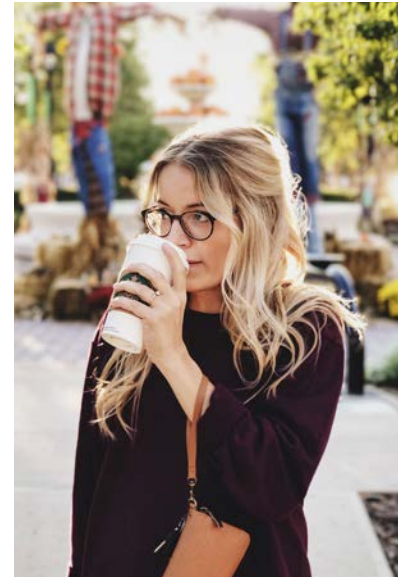
Mitchell et al. examined the relationship between parenting practices and child behavior in a cohort of children with AD. Increasing AD severity in children was associated with greater parental difficulty in managing behavioral problems. Additionally, decreased parental self-efficacy (i.e., the belief that parents could successfully manage their child’s AD) was significantly correlated with increased parental stress and depression, satisfaction with relationships, parenting conflicts, and the parent’s ability to manage their child’s behavior.<sup>242</sup> Taken together, these studies suggest that increasing the support of parents of children with AD may improve disease management and alleviate the parental burden.

## Financial Burden

Jenner et al. found an average annual out-of-pocket cost per patient of \$425 for treatment products and \$120 for consultations; unsurprisingly, costs increased with disease severity.<sup>236</sup> Su et al. found that when considering both direct and indirect costs, families spent an average of AUS \$480, \$1712, and \$2545 annually to care for children with mild, moderate, and severe AD, respectively.<sup>240</sup> Of note, no studies were found on this topic since 2004. New studies on the personal cost experienced by Australian patients and their caregivers are needed to more accurately determine current financial burden.

## Treatment

As in the other COI, the underutilization of TCS seems attributable to both inconsistent instructions from physicians and fears from patients and caregivers. On the physician side, a survey of 275 GPs in Australia found that 40.7% of GPs instructed patients to apply TCS for 2 weeks or less, 47.7% recommended applying TCS as little as possible, and 30.2% viewed skin thinning as the most common side effect of TCS use.<sup>243</sup> A separate study of Australian pharmacists found that only 27% instructed patients to use TCS until lesions cleared; meanwhile, 54% recommended the sparing use of TCS. These cautious recommendations were rooted in



**In a smaller, interview-based study, female patients with AD were negatively impacted by societal depictions of “perfect skin”; this additional dimension of burden for female patients with AD may require further research and attention.<sup>239</sup>**

<sup>239</sup>Magin, P., Adams, J., Heading, G. & Pond, D. ‘Perfect skin’, the media and patients with skin disease: a qualitative study of patients with acne, psoriasis and atopic eczema. *Aust. J. Prim. Health* 17, 181–185 (2011).

<sup>240</sup>Su, J. C., Kemp, A. S., Varigos, G. A. & Nolan, T. M. Atopic eczema: its impact on the family and financial cost. *Arch Dis Child* 76, 159–162 (1997).

<sup>241</sup>Faught, J., Bierl, C., Barton, B. & Kemp, A. Stress in mothers of young children with eczema. *Arch Dis Child* 92, 683–686 (2007).

<sup>242</sup>Mitchell, A. E., Fraser, J. A., Morawska, A., Ramsbotham, J. & Yates, P. Parenting and childhood atopic dermatitis: A cross-sectional study of relationships between parenting behaviour, skin care management, and disease severity in young children. *Int J Nurs Stud* 64, 72–85 (2016).

<sup>243</sup>Smith, S. D., Harris, V., Lee, A., Blaszczyński, A. & Fischer, G. General practitioners knowledge about use of topical corticosteroids in paediatric atopic dermatitis in Australia. *Aust Fam Physician* 46, 335–340 (2017).



pharmacists' wariness of the treatment: 46% believed that cutaneous atrophy was the most common side effect, and 56% believed that side effects would occur in spite of proper use.<sup>244</sup> An evidence-based information session proved effective; afterward, 92% of pharmacists recommended using TCS until the lesions cleared, only 8% recommended sparing use, 7% believed that cutaneous atrophy was the most common side effect, and 11% believed that side effects would occur in spite of proper use.<sup>244</sup> The authors concluded that education efforts for healthcare personnel may indirectly enable patients to make optimal use of the available therapies and reduce their disease burden.

On the patient and caregiver side, the risk-framing of TCS may influence parents to underuse TCS and subsequently lead to poor treatment adherence, worse disease burden, and increased QoL burden in children and caregivers.<sup>243</sup> A panel of Australian and New Zealand physicians agreed that TCS were underused in Australia and New Zealand due to fear of perceived side effects.<sup>245</sup> More generally, a survey by Jenner et al. found that 15% of patients with AD reported problems with their treatment as assessed by the DLQI, with 30.8% of patients with severe AD reporting that their treatment had been a “problem”.<sup>236</sup>

## Healthcare

### Healthcare Utilization

As observed in other countries, unmet treatment needs often drive patients with moderate-to-severe AD to higher levels of care. In a three-year study of patients who presented with a dermatologic problem to a tertiary-care emergency department in Melbourne, 27% of the 108 patients admitted to the inpatient dermatology unit were determined to have AD at time of discharge—a higher proportion than any other single diagnosis.<sup>246</sup> Similarly, in a year-long study at a tertiary care hospital in New South Wales, 37% of the 97 patients admitted for dermatologic conditions had AD.<sup>247</sup>

### Satisfaction with Care

A small, interview-based study of Australian patients with acne, psoriasis, and AD identified several common concerns regarding their GPs and dermatologists. Many patients felt that their providers did not understand the psychosocial effects of their disease, did not give enough emotional support, and did not take the condition seriously. Patients acknowledged the time restrictions faced by providers but felt that the limited time would be best spent addressing a balance of physical and psychological symptoms instead of the more typical narrow focus on physical manifestations of disease.<sup>239</sup>

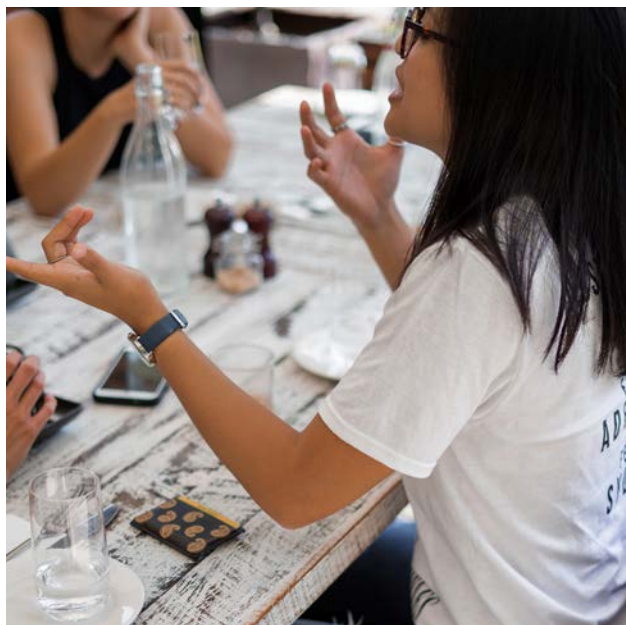
### Patient-Centered Interventions

Moore et al. evaluated a nurse-led workshop that promoted emollient use among caregivers and children with AD. In the workshop group, the mean weekly emollient use increased from 54.5g at baseline to 426g at week 4, and SCORAD values were better than among patients treated at a dermatologist-led clinic. Moore et al. concluded that interdisciplinary management strategies may increase patients' and caregivers' abilities to manage AD.<sup>248</sup> The literature search did not yield any other existing studies of interventions to improve patients' understanding of the disease, treatment adherence, or satisfaction.

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*Many patients felt that their providers did not understand the psychosocial effects of their disease, did not give enough emotional support, and did not take the condition seriously.*

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<sup>244</sup>Smith, S. D., Lee, A., Blaszczyński, A. & Fischer, G. Pharmacists' knowledge about use of topical corticosteroids in atopic dermatitis: Pre and post continuing professional development education. *Australas J Dermatol* 57, 199–204 (2016).

<sup>245</sup>Mooney, E. et al. Adverse effects of topical corticosteroids in paediatric eczema: Australasian consensus statement. *Australasian Journal of Dermatology* 56, 241–251 (2015).

<sup>246</sup>Lai-Kwon, J. E., Weiland, T. J., Jelinek, G. A. & Chong, A. H. Which patients with dermatological conditions are admitted via the emergency department? *Australasian Journal of Dermatology* 55, 255–259 (2014).

<sup>247</sup>Bale, J. & Chee, P. Inpatient dermatology: Pattern of admissions and patients' characteristics in an Australian hospital. *Australasian Journal of Dermatology* 55, 191–195 (2014).

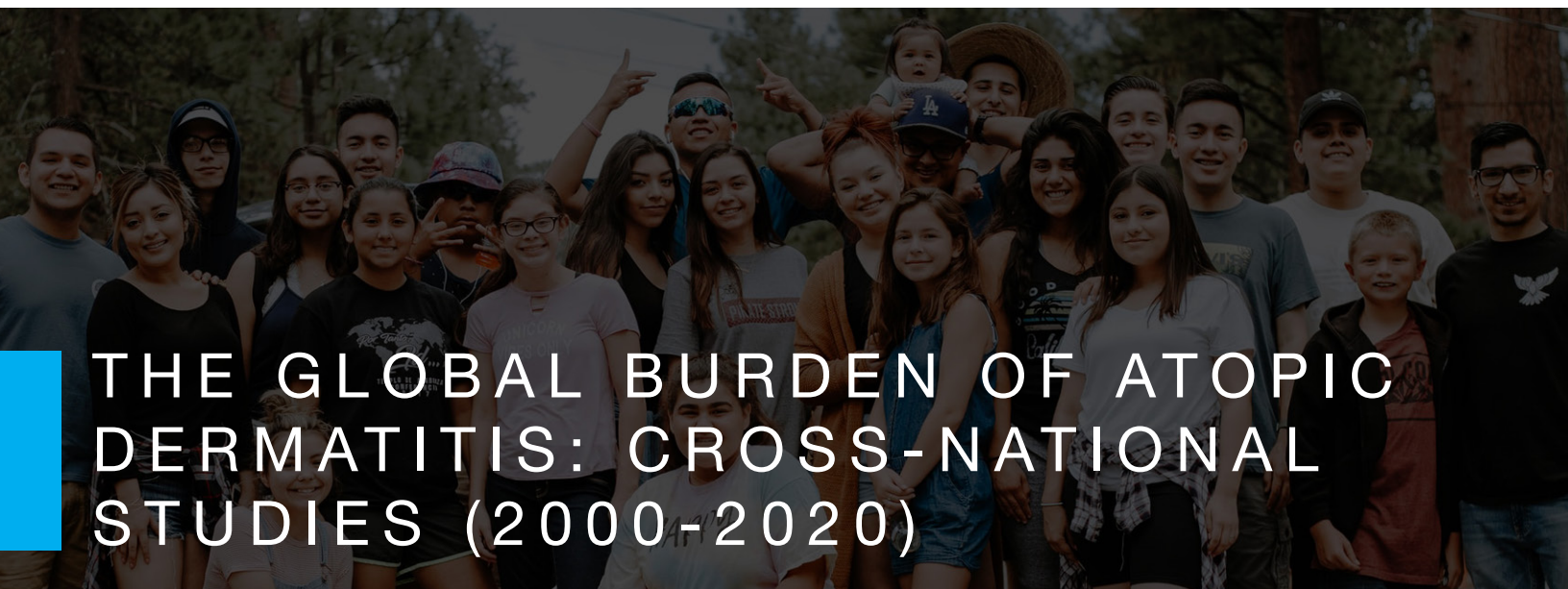
<sup>248</sup>Moore, E. J., Williams, A., Manias, E., Varigos, G. & Donath, S. Eczema workshops reduce severity of childhood atopic eczema. *Australasian Journal of Dermatology* 50, 100–106 (2009).

## KEY FINDINGS

Multiple studies noted that the prevalence of AD appears to be increasing in Australian children with AD, but trends among Australian adults are less studied. Additionally, there are few large-scale studies of comorbidities; the existing studies are smaller and interview-based. These findings provide a reasonable starting point, but population-wide studies may give a better picture of the scope of the burden of AD in Australia and may also reveal yet unknown associations.

Unmet treatment needs were most common among Australian patients with moderate-to-severe AD. As in other countries, part of the problem is rooted in the underutilization of TCS, which stems from both inconsistent prescribing practices and fears among patients and caregivers. Small interventions demonstrated preliminary success on both fronts, but much more work is needed in Australia to achieve a coherent approach to treatment.





# THE GLOBAL BURDEN OF ATOPIC DERMATITIS: CROSS-NATIONAL STUDIES (2000-2020)

## Disease Burden

### Prevalence, Diagnosis, and Comorbidities

The global prevalence of AD was within the top 50 disorders evaluated in a systematic review.<sup>249</sup> A lack of common diagnostic criteria for AD<sup>64</sup> and variations in naming (“eczema,” “atopic eczema,” “neurodermatitis,” and “atopic dermatitis” usually refer to the same entity) make it challenging to conduct international comparisons of AD epidemiology.<sup>250</sup>

Nevertheless, the ISAAC studies offer an example of a standardized analysis that applies common diagnostic criteria to evaluate AD epidemiology globally. Averaged across countries, the prevalence of AD in children increased between ISAAC phases 1 and 3. Prevalence may still be increasing in developing nations, but it appears to have plateaued in developed nations, especially in children aged 13–14.<sup>251</sup> In the COI studied in this report, ISAAC phase 3 reported an AD prevalence of 7.9%–17.1% in children aged 6–7 and of 7.0%–10.7% in children aged 13–14, with the highest prevalence in Australia and the UK.<sup>2</sup>

In global adult populations in the US and 25 European countries, Harrop et al. found an AD prevalence of 7.1% among adults aged 27–56. Barbarot et al. assessed the prevalence of AD in adults aged 18–65 in several countries (including the US, UK, Canada, France, Germany, Italy) using both the ISAAC criteria and self-reporting. The study found a point prevalence of AD of 4.9% in the US, 3.5% in Canada, and 4.4% in the European countries.<sup>196</sup> These rates are substantially lower than reported in any individual COI, and the discrepancy may be due to stricter definitions of AD diagnoses in the Barbarot et al. study.

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*The ISAAC studies offer an example of a standardized analysis that applies common diagnostic criteria to evaluate AD epidemiology globally.*

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<sup>249</sup>Hay, R. J. et al. *The Global Burden of Skin Disease in 2010: An Analysis of the Prevalence and Impact of Skin Conditions*. *Journal of Investigative Dermatology* 134, 1527–1534 (2014).

<sup>250</sup>Silverberg, J. I. *Public Health Burden and Epidemiology of Atopic Dermatitis*. *Dermatol Clin* 35, 283–289 (2017).

<sup>251</sup>Williams, H., Stewart, A., von Mutius, E., Cookson, W. & Anderson, H. R. *Is eczema really on the increase worldwide? Journal of Allergy and Clinical Immunology* 121, 947–954.e15 (2008).

Cross-national studies of comorbid associations with AD found an increased risk of other atopic comorbidities, mental health symptoms, sleep dysfunction, infection, and possibly an increased cardiovascular risk.<sup>252</sup> The variability in significant comorbid risks between the COI may be explained by prominent lifestyle differences. For instance, obesity is more prevalent in the US, and smoking is more prevalent in the European countries.<sup>253</sup>

## Physical and Psychosocial Consequences

Globally, skin disease was the 18th leading cause of health burden as measured by Disability Adjusted Life Years (DALYs).<sup>249</sup> One DALY is equivalent to one year of healthy life lost; DALYs are determined by both Years of Life Lost (YLL) and Years Lost due to Disability (YLD). When considering YLD in isolation, skin disease ranked 4th globally, ahead of COPD, anxiety disorders, migraine, diabetes mellitus, and drug use; nearly 40% of the total YLD from “skin disease” was attributed to pruritus and/or AD.<sup>249</sup> Similarly, Karimkhani et al. estimated that skin disease accounted for 1.79% of global DALYs. Within the overall category of skin disease, dermatitis (atopic, contact, or seborrheic) comprised 0.38% of the total, or 9.3 million DALYs.<sup>254</sup>

AD patients face a significant disease burden regardless of their country of residence. An international study (COI: the US, Canada, France, Germany, Italy, and the UK) assessed the perceptions of adult patients using natural language processing techniques. Itch, pain, and embarrassment were the most common complaints.<sup>255</sup> Adult patients with moderate-to-severe AD also suffered from sleep disturbances, fatigue, depression, anxiety, and hopelessness.<sup>255</sup> A global systematic review of studies associated with AD found pruritus to be the most common sign/symptom, followed by dry skin and skin thickening.<sup>256</sup> An international survey of 103 individuals with AD aged 5–74 found that 78% of individuals reported both skin pain and itch as components of their disease burden.<sup>257</sup>

## AD patients face a significant disease burden regardless of their country of residence.

Symptoms and the overall disease burden worsen with disease severity. In a study of Canadian and European adults aged 18–65, de Bruin-Weller et al. found that patients with severe (vs. mild or moderate) AD experienced worse overall QoL, itch, skin pain, sleep, anxiety, and depression. Interestingly, patients of all disease severities that were treated with cyclosporin or any systemic immunomodulatory agent had QoL measures that resembled those of patients with severe AD. The individuals receiving cyclosporin or other similar agents had an earlier age of diagnosis, so the authors hypothesized that their increased burden may be due to multiple failed treatment cycles and long-term inadequate control of AD.<sup>258</sup> An increase in AD severity was associated with a decrease in HRQoL (measured with the EQ-5D and DLQI) and POEM scores among patients in the US and Europe (COI: France, Germany, and the UK).<sup>253</sup> This corroborates data found in studies in each individual country.

In the European Tacrolimus Ointment Study, adults from the UK, Italy, France, and Germany reported baseline EQ-5D index health utility scores of 0.770 for moderate disease and 0.665 for severe disease (the EQ-5D ranges from 0 = worst possible health to 1 = best possible health). This represents a substantial health burden on par with epilepsy (0.77) and rheumatoid arthritis (0.63).<sup>85</sup> A study of European patients found that 55% reported a moderate-to-extremely large impairment in DLQI.<sup>259</sup>



**Globally, skin disease was the 18th leading cause of health burden as measured by Disability Adjusted Life Years (DALYs).<sup>249</sup>**

<sup>252</sup>Silverberg, J. I. Comorbidities and the impact of atopic dermatitis. *Annals of Allergy, Asthma & Immunology* 123, 144–151 (2019).

<sup>253</sup>Andersen, L., Nyeland, M. E. & Nyberg, F. Higher self-reported severity of atopic dermatitis in adults is associated with poorer self-reported health-related quality of life in France, Germany, the U.K. and the U.S.A. *Br J Dermatol* 182, 1176–1183 (2020).

<sup>254</sup>Karimkhani, C. et al. Global Skin Disease Morbidity and Mortality. *JAMA Dermatol* 153, 406–412 (2017).

<sup>255</sup>Falissard, B. et al. Qualitative Assessment of Adult Patients' Perception of Atopic Dermatitis Using Natural Language Processing Analysis in a Cross-Sectional Study. *Dermatol Ther (Heidelb)* 10, 297–305 (2020).

<sup>256</sup>Yew, Y. W., Thyssen, J. P. & Silverberg, J. I. A systematic review and meta-analysis of the regional and age-related differences in atopic dermatitis clinical characteristics. *Journal of the American Academy of Dermatology* 80, 390–401 (2019).

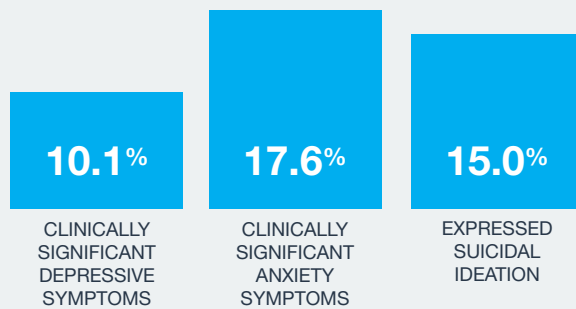
<sup>257</sup>Maarouf, M. et al. Pain and Itch Are Dual Burdens in Atopic Dermatitis. *Dermatitis* 29, 278–281 (2018).

<sup>258</sup>de Bruin-Weller, M. et al. The patient-reported disease burden in adults with atopic dermatitis: a cross-sectional study in Europe and Canada. *J Eur Acad Dermatol Venereol* 34, 1026–1036 (2020).

<sup>259</sup>Ring, J. et al. Atopic eczema: burden of disease and individual suffering – results from a large EU study in adults. *Journal of the European Academy of Dermatology and Venereology* 33, 1331–1340 (2019).

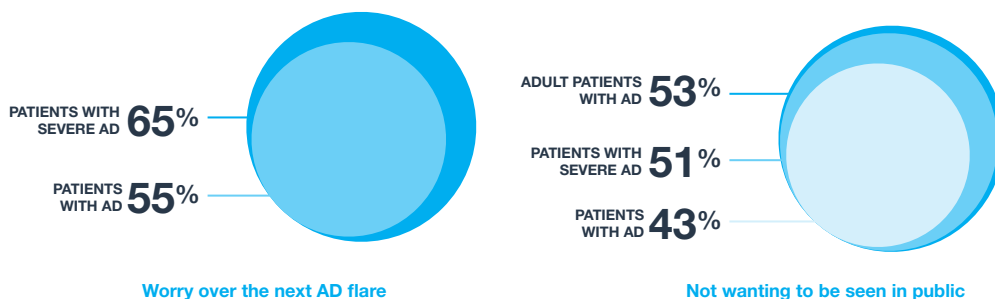
### A study of 13 European countries

(COI: Denmark, France, Germany, Italy, UK)



The mental health burden attributable to AD is relatively well-documented in each COI. A global systematic review and meta-analysis found several significant, positive associations between AD and anxiety in adults, AD and depression in both adults and children, and AD and suicidality in both adults and adolescents.<sup>260</sup> A study of 13 European countries (COI: Denmark, France, Germany, Italy, UK) found that 10.1% of patients with AD had clinically significant depressive symptoms (as measured by the HADS-D), 17.6% had clinically significant anxiety symptoms (HADS-A), and 15.0% expressed suicidal ideation.<sup>261</sup> In another study, 10% of European patients with AD scored above the 8-point threshold for depressive symptoms measured via HADS, and 57% reported experiencing various domains of emotional distress. 88% of patients with severe AD reported that AD made it challenging to face everyday life.<sup>259</sup> Girolomoni et al.'s cross-sectional survey of moderate-to-severe AD in 5 European countries (COI: France, Germany, the UK, and Italy) found that 61.6% of patients reported difficulty sleeping, 52.7% reported anxiety, and 75.8% reported depression.<sup>34</sup> In online focus groups, both patients and caregivers reported that an inability to achieve control of disease resulted in significant stress, embarrassment, and avoidance of social situations.<sup>262</sup>

The International Study of Life with Atopic Eczema (ISOLATE) sought to understand the impact of AD on patients' and caregivers' lives, methods of managing AD, and opinions on what constitutes disease "control." 2,002 patients (COI: the US, UK, France, and Germany) were randomly selected for telephone interviews. Patients reported sleep loss on 67 nights every year; the number rose to 162 nights every year in patients with severe AD. Worry over the next AD flare was reported in 55% of all patients with AD and 65% of patients with severe AD. Furthermore, 43% of all patients did not want to be seen in public; 53% of adult patients and 51% of patients with severe disease experienced similar embarrassment. 36% of all patients and 46% of patients with severe disease felt that AD impacted their self-confidence, and 51% of patients reported being "sometimes" or "always" unhappy and/or depressed. 39% of children aged 8–17 experienced bullying due to their AD; 11% of adults reported discrimination due to their AD, and 14% of adults felt that their careers had been negatively impacted by their AD. 30% acknowledged that AD had affected the family at large, and 21% of adult patients reported that AD negatively affected their ability to form relationships. Overall, adult patients were most impacted by embarrassment over AD in public situations, restrictions in clothing choices, and the chronic nature of the disease. 75% of respondents noted that being able to control their AD would be the most important factor in improving their overall QoL.<sup>263</sup>



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75% of respondents noted that being able to control their AD would be the most important factor in improving their overall QoL.<sup>263</sup>

<sup>260</sup>Rønnstad, A. T. M. et al. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: A systematic review and meta-analysis. *Journal of the American Academy of Dermatology* 79, 448–456. e30 (2018).

<sup>261</sup>Dalgaard, F. J. et al. The Psychological Burden of Skin Diseases: A Cross-Sectional Multicenter Study among Dermatological Out-Patients in 13 European Countries. *Journal of Investigative Dermatology* 135, 984–991 (2015).

<sup>262</sup>Howells, L. et al. Defining and measuring 'eczema control': an international qualitative study to explore the views of those living with and treating atopic eczema. *J Eur Acad Dermatol Venereol* 33, 1124–1132 (2019).

<sup>263</sup>Zuberbier, T. et al. Patient perspectives on the management of atopic dermatitis. *J Allergy Clin Immunol* 118, 226–232 (2006).

## Caregiver Burden

Parents and caregivers experienced similar burdens due to their child's AD in all of the individual COI, though differences in cost and educational intervention programs made a difference. Nearly all parents and caregivers of children with AD experienced sleep difficulty,<sup>9,44,45,96,216</sup> as well as increased anxiety and depression symptoms.<sup>9,44,45,96,216</sup> Other commonly reported domains of parent and caregiver burden included worry/anger over itching/scratching, adjusting life decisions due to AD, worry for the child's social well-being, caregiver fatigue, and mental health comorbidities.<sup>13,217</sup> The personal financial burden contributed to the caregiver burden in both the US and Italy.<sup>99,219</sup>

In the ISOLATE study, 62% of caregivers of young patients with AD reported worry over the next AD flare; 30% reported an impact of AD on the family at large. Caregivers reported that their biggest concerns were restrictions in clothing choices, their child's appearance, their lack of control, anxiety over the child's future, and side effects of treatment.<sup>263</sup>

## Financial Burden

AD confers both a direct financial burden (e.g., medications and visits) and an indirect burden (e.g., loss of work productivity). Both types of costs varied widely between the COI but increased with disease severity.<sup>264</sup> The Girolomoni et al. study of 5 European countries (COI: France, Germany, the UK, and Italy) stratified patients by the degree of QoL impairment. Annual per-patient direct costs averaged €2,242 among patients with a moderate impact (DLQI 6–10), €3,099 among patients with a large impact (DLQI 11–20), and €6,924 among patients with an extremely large impact (DLQI 21–30).<sup>34</sup>

Although both direct and indirect costs contribute to the economic burden of a country as a whole, OOP expenses are a better indication of the financial burden experienced by individual patients and caregivers. In a study of 1,189 patients who lived in one of nine European countries (COI: Denmark, France, Germany, Italy, Great Britain) and either took or were eligible for systemic medication, the average annual OOP expense was €927, with a direct relationship between OOP expenses and AD severity.<sup>7</sup>

Major areas of spending included emollients and moisturizers, non-reimbursed medications, and costs associated with physician and hospital visits; secondary areas of spending included personal hygiene products, laundry products, clothing, bedding, and food.<sup>7</sup>

Several cross-national studies have examined the indirect burden of lost work productivity. A study in European countries (France, Germany, UK) and the US found a significant negative association between all components of the Work Productivity and Activity Impairment scale and AD severity.<sup>265</sup> The authors found no significant differences between work productivity and daily activity impairment between the countries, but they noted that activity impairment was twice as high in European (vs. American) patients with severe AD after adjusting for confounding variables. The authors hypothesized that this finding may be due to fears among US patients about job loss, which may have motivated patients to continue working despite the significant disease burden.<sup>265</sup>

A study of European patients found that 57% missed at least 1 day of work in the preceding year due to AD.<sup>259</sup> In the ISOLATE study, patients reported an average of 2.5 days of missed school or work per year due to AD; the number increased to 5.3 days per year among patients with severe AD. A flare while at school or work affected concentration among 9% of all patients surveyed and 15% of patients with severe AD.<sup>263</sup> The Girolomoni et al. study found that difficulty sleeping, anxiety, and depression were associated with greater work impairment in adults with moderate-to-severe AD.<sup>34</sup>



**Major areas of spending included emollients and moisturizers, non-reimbursed medications, and costs associated with physician and hospital visits.**

<sup>264</sup>Hebert, A. A. et al. Patient impact and economic burden of mild-to-moderate atopic dermatitis. *Curr Med Res Opin* 34, 2177–2185 (2018).

<sup>265</sup>Andersen, L., Nyeland, M. E. & Nyberg, F. Increasing severity of atopic dermatitis is associated with a negative impact on work productivity among adults with atopic dermatitis in France, Germany, the U.K. and the U.S.A. *Br J Dermatol* 182, 1007–1016 (2020).

<sup>266</sup>Simpson, E. L. et al. Patient burden of moderate to severe atopic dermatitis (AD): Insights from a phase 2b clinical trial of dupilumab in adults. *Journal of the American Academy of Dermatology* 74, 491–498 (2016).

<sup>267</sup>Simpson, E. L. et al. Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): A phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD). *Journal of the American Academy of Dermatology* 75, 506–515 (2016).

## Treatment

There is a significant unmet need for effective therapies in all the COI reviewed in this report, but especially among patients with moderate-to-severe AD. A study of the disease burden due to AD in European countries (COI: France, Italy, the UK, Germany, and Denmark) found that 45% of patients reported experiencing moderate-to-very-severe AD in spite of being treated.<sup>259</sup>

New biologic therapies (namely, dupilumab) seem to be relatively effective at reducing AD severity and improving QoL measures. A phase 2b trial of dupilumab conducted with an international cohort of adult patients (COI included: Canada, US, Germany) found that at baseline, 85% of patients reported itch despite systemic therapy, and 41.5% itched for 18 or more hours per day;




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*Relative to baseline, dupilumab (vs. placebo) significantly improved pruritus, skin pain, sleep, POEM, anxiety and depression symptoms, EQ-5D and patients' perceptions of their disease.<sup>268</sup>*

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55% experienced sleep difficulties at least 5 days per week; and 21.8% had clinically significant anxiety or depression as measured by HADS scores.<sup>266</sup> After 16 weeks of treatment with dupilumab (vs. placebo), there were significant improvements in the POEM, itch, sleep, anxiety symptoms, depression symptoms, and EQ-5D.<sup>267</sup>

Phase 3 studies of dupilumab (LIBERTY AD SOLO 1 and SOLO 2 trials) were conducted with an international cohort of 1,379 adult patients (COI included: the US, Canada, UK, France, Germany, Denmark, and Italy) with moderate-to-severe AD. Again, relative to baseline, dupilumab (vs. placebo) significantly improved pruritus, skin pain, sleep, POEM, anxiety and depression symptoms, EQ-5D and patients' perceptions of their disease.<sup>268</sup> The data from this clinical trial were analyzed by de Bruin-Weller et al. to evaluate the impact of dupilumab on absenteeism from work and school. At 16 weeks, patients receiving dupilumab either every week or every 2 weeks (vs. placebo at the same frequencies) had a significant reduction in absenteeism; the improvement was most pronounced among patients with more severe disease or worse QoL at baseline.<sup>269</sup>

Silverberg et al. analyzed the effects of dupilumab on pain and discomfort using data collected from 5 trials in which adult patients with moderate-to-severe AD received dupilumab (or placebo) once every week or once every 2 weeks.<sup>270</sup> At baseline, 72.9%–83.1% of patients reported moderate-to-extreme pain or discomfort, and only 17.0%–24.1% of patients reported no pain or discomfort. After treatment with dupilumab, the proportions of patients reporting no pain or discomfort increased to 51.4%–70.1% for dupilumab dosed every other week, 48.3%–62.7% for dupilumab dosed every week, and 19.7%–37.0% for the placebo.<sup>270</sup>

A smaller body of research has investigated baricitinib, an oral Janus Kinase (JAK) 1 and 2 inhibitor. A 2020 phase 3 trial (baricitinib vs. placebo) found an improvement in DLQI and

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<sup>268</sup>Cork, M. J. et al. Dupilumab improves patient-reported symptoms of atopic dermatitis, symptoms of anxiety and depression, and health-related quality of life in moderate-to-severe atopic dermatitis: analysis of pooled data from the randomized trials SOLO 1 and SOLO 2. *Journal of Dermatological Treatment* 31, 606–614 (2020).

<sup>269</sup>de Bruin-Weller, M. et al. Dupilumab reduces absenteeism in patients with moderate to severe atopic dermatitis: Pooled results from the LIBERTY AD SOLO clinical trials. *Journal of the American Academy of Dermatology* 83, 1499–1501 (2020).

<sup>270</sup>Silverberg, J. I. et al. Dupilumab Significantly Modulates Pain and Discomfort in Patients With Atopic Dermatitis: A Post Hoc Analysis of 5 Randomized Clinical Trials. *Dermatitis Publish Ahead of Print*, (2020).

reductions in skin pain and nighttime awakenings in an international cohort of 1,239 patients (COI: Denmark, France, Germany, Italy, and Australia).<sup>271</sup>

For the individual COI, however, most literature focused on concerns about possible side effects of the current treatment options, specifically TCS (and especially in the UK, Denmark, and France).<sup>48,182,205</sup> In the ISOLATE study, 49% of all surveyed caregivers and 56% of caregivers of young children expressed concerns about TCS. Such concerns typically manifest in poorer treatment adherence; in the ISOLATE study, 39% of respondents used TCS less often than prescribed. Patients with moderate AD waited an average of 6.1 days into a flare to start treatment, and patients with severe AD waited for 7.7 days.<sup>263</sup>

## Healthcare

### Utilization

Although most COI had one or more studies on healthcare utilization, the literature search did not yield any cross-national studies. Given the variation in healthcare systems between countries, it may be best to study this topic at the country level.

### Patient and Caregiver Satisfaction

In the ISOLATE study, 75% of respondents felt that their physician was sympathetic to their AD or their child's AD, and 77% felt that the information provided by their physician was accurate. Respondents valued not only accuracy but also clear communication; 77% of patients and 74% of caregivers did not feel they would be able to manage AD without instructions from their physician.<sup>263</sup> However, 74% noted that their physician had not discussed the emotional burden of AD with them. For most participants, this shortcoming was not addressed with other types of care—84% did not know that support groups existed, and only 2% were actually in contact with a support group.<sup>263</sup>

Studies in several COI (the UK, Denmark, and Italy) found that patients, parents, and caregivers often experienced a disconnect with physicians regarding the chronic nature of AD, the value of searching for dietary and/or allergy triggers, and treatment priorities.<sup>39,40,182,217</sup> Howells et al. conducted online focus groups and sought to understand patients' and caregivers' conceptualizations of "long-term control." Participants came from an international cohort (COI included: the UK, US, and France); half of the groups comprised patients aged 16 or older, and the other half comprised children and their caregivers. Participants defined long-term control with several factors that went beyond disease severity; criteria included the ability to focus on activities and to have relief from itch, pain, and sleep difficulties.<sup>262</sup>

### Patient-Centered Interventions

Educational interventions seem to be a promising method for reducing the psychosocial burden and improving treatment adherence. In Germany, the GADIS study found that an educational intervention improved both disease severity and QoL measures among parents and caregivers.<sup>134</sup> Breuer et al. identified factors that improved QoL outcomes in parents, and Kupfer et al. showed that educational interventions improve coping in both children and caregivers.<sup>157,161</sup> Although there certainly is a need for more efficacious treatments for moderate-to-severe disease (as discussed in the Treatment section), educational interventions were also shown to be effective in Germany, the UK and Italy. More studies of educational interventions are warranted in the other COI studied in this report.



Participants defined long-term control with several factors that went beyond disease severity; criteria included the ability to focus on activities and to have relief from itch, pain, and sleep difficulties.<sup>262</sup>

<sup>271</sup>Simpson, E. L. et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. *British Journal of Dermatology* 183, 242–255 (2020).





# DISCUSSION

**This review of 247 studies of the AD disease burden and satisfaction with treatments and healthcare services found variation in the extent of research in the eight COI. The disease burden is well researched in all eight COI, with the most extensive coverage in the UK, US, and Germany.**

However, only 16 studies pertained to satisfaction with treatments and healthcare; several of the COI offer no research on satisfaction with healthcare services and patient-centered interventions. This gap is notable because, as shown in the UK and Germany, patient-centered interventions may improve many aspects of the patient experience, including disease severity, the QoL burden, and satisfaction with care.

Some of the national variation in the quantity of literature may be attributable to disparities in data availability. For example, in the US, large datasets (such as the Medical Expenditure Panel Survey (MEPS), the National Ambulatory Medical Care Survey (NAMCS), and the National Health Interview Survey (NHIS) allow for population-wide studies of prevalence and comorbidities; it is perhaps not surprising that these topics are well-represented in the US literature. Another explanatory factor may be the structure of the healthcare systems. For example, the notoriously high healthcare costs in the US<sup>272</sup> may have motivated more extensive research on the financial burden in the US than in the other COI.

Methodological differences make comparisons among countries difficult and establishing clear methodologic goals for assessing prevalence would enable comparisons between countries and within each country over time. The ISAAC methodology, which uses consistent age ranges and diagnostic criteria, may be a good candidate for a common approach and already has been conducted in many countries.

A robust characterization of the comorbid risks is important for both monitoring the holistic health of patients with AD and guiding therapy for AD. For example, given the prevalence of comorbid contact dermatitis, patients with AD may benefit from access to patch testing.

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*Methodological differences make comparisons among countries difficult and establishing clear methodologic goals for assessing prevalence would enable comparisons between countries and within each country over time.*

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<sup>272</sup>U.S. Health Care from a Global Perspective, 2019: Higher Spending, Worse Outcomes? <https://www.commonwealthfund.org/publications/issue-briefs/2020/jan/us-health-care-global-perspective-2019>  
doi:10.26099/7avy-1c29.

The caregiver burden has not been studied as extensively as the patient burden, but caregivers of AD patients clearly suffer from a large burden on their time, energy, mental health, and finances. The implementation of a standardized assessment tool in outpatient clinics would be a valuable step toward assessing, and later addressing caregiver burden. Such a tool could also be included as a secondary endpoint in pediatric clinical trials and intervention studies.

Several components of financial burden were studied in most of the COI. While OOP expenses were most burdensome in the US, patients and caregivers in all of the COI incurred an indirect financial burden in the form of work absenteeism.

For all types of burden discussed in this review, the burden worsens as disease severity increases. On the flip side, reductions in disease severity—perhaps through access to dermatologic care, a new treatment, or an educational intervention—are likely to improve all aspects of the disease burden.

Unfortunately, robust descriptions of the disease burden have not translated into an abundance of research on strategies for improving QoL and psychosocial outcomes. As previously noted in an audit of UK health records, physicians do not document the QoL burden as consistently as physical signs and symptoms.<sup>33</sup> Accordingly, patients and caregivers perceive that physicians do not spend enough time attending to their QoL and the psychosocial consequences of their disease.

It also is unclear why patient and caregiver satisfaction varies widely by country, and why satisfaction is poor overall. One clear priority for future research is to investigate factors that influence satisfaction with treatment and healthcare services. The current evidence suggests that satisfaction with treatment is most affected by the efficacy, short-term safety, and long-term risks of the treatment options. Patients with moderate-to-severe AD experience the highest burden and have the greatest need for more efficacious treatments across all COI. Patient and caregiver satisfaction is likely to improve with the approval of newer agents (such as dupilumab) that are more efficacious, have fewer immediate side effects, and confer fewer long-term risks.

In several countries, patient and caregiver dissatisfaction seems to be compounded by the inability to secure referrals to dermatologists or by the long wait times for outpatient dermatologic care. Additionally, a few studies indicated that the barriers may be higher for patients of racial and ethnic minorities, who are disproportionately underserved in outpatient dermatology clinics and then must use the emergency department and inpatient services for exacerbations of severe disease.

Notably, patient satisfaction seems to be higher in Germany than in the other COI. The reasons are unclear, but we posit that the success of the nationwide German Atopic Dermatitis Intervention Study (GADIS) program may have mitigated certain causes of dissatisfaction by teaching patients how to use treatments effectively and increasing face-to-face time with healthcare providers.<sup>159</sup> Rehabilitation guidelines also exist in Germany for patients with severe AD, providing an additional layer of support for patients for whom the available therapies are not effective.<sup>151</sup>

Educational interventions conducted in other countries, often led by nurses or multidisciplinary teams, also improved treatment adherence and reduced the disease severity and associated burden in both patients and their caregivers. This type of intervention may also be cost-effective—it does not require any additional medications to be prescribed, and it may not require additional physician hours. An educational intervention may even decrease OOP expenses if it



*The caregiver burden has not been studied as extensively as the patient burden, but caregivers of AD patients clearly suffer from a large burden on their time, energy, mental health, and finances.*




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*Future studies should further examine dimensions of patient and caregiver satisfaction and how it might be improved through policy changes, better treatments, and changes to care delivery.*

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enables patients to use treatments more effectively, and this may be especially useful in countries where patients have a high financial burden from AD such as the US. Focused educational interventions may also be helpful where appropriate patient education materials are lacking. (This may be discouragingly common—health literacy guidelines recommend that all materials be written at a sixth-grade reading level. In one study, only one-fifth of the materials assessed met this guideline.<sup>115</sup>) Observational studies that identify common problems and evaluate targeted interventions should guide future research to develop equitable care strategies for AD patients and their caregivers across the globe.

This review offers a valuable, up-to-date comparison of the AD disease burden and patient experience in eight developed COI. Although previous reviews have detailed the burden attributable to AD and areas for further research,<sup>259,273,274</sup> this review provides a more comprehensive view: multiple facets of the disease burden, satisfaction with both treatments and care, and the perspectives of both patients and caregivers. With a cross-national approach, this review may enable the international adaptation of promising approaches.

Future research should focus on ways to translate research on AD burden into interventions that reduce the burden. Importantly, studies should use common methodology to evaluate burden and satisfaction. A standardized approach would enable international comparisons and facilitate the adaptation of interventions from one country to another.

Literature is scarce regarding patient and caregiver satisfaction with treatments and care. The little available research paints a relatively bleak picture, save for German studies. Given the large global population impacted by AD and related high utilization of health care services and treatments associated with it, this gap in research is in need of urgent attention. More specifically, future studies should further examine dimensions of patient and caregiver satisfaction and how it might be improved through policy changes, better treatments, and changes to care delivery.

Future research should focus on ways to translate research on AD burden into interventions that reduce the burden. Importantly, studies should use common methodology to evaluate burden and satisfaction.

<sup>273</sup>Drucker, A. M. et al. *The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. J Invest Dermatol* 137, 26–30 (2017).

<sup>274</sup>Drucker, A. M., Wang, A. R. & Qureshi, A. A. *Research Gaps in Quality of Life and Economic Burden of Atopic Dermatitis: The National Eczema Association Burden of Disease Audit. JAMA Dermatol* 152, 873–874 (2016).



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