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## Mental health comorbidity in youth with atopic dermatitis: A narrative review of possible mechanisms

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### Abstract

The presence of atopic dermatitis (AD) in youth has been linked to a variety of mental health concerns including disruptive behavior, symptoms of anxiety and depression, and diagnoses of attention deficit/hyperactivity disorder and autism spectrum disorder. However, the factors accounting for these relationships are not well understood. The current review summarizes possible mechanisms identified in previous research and highlights areas for future investigation. Among the primary mechanisms studied to date, child sleep is the only factor that has been characterized in relative detail, with findings generally supporting the mediating role of sleep problems in the relationship between AD and psychological symptoms. There is substantial evidence suggesting a negative impact of child AD on parent mental health and the impact of parent mental health on child psychological functioning, although the latter has not been assessed specifically in populations of children with AD. There is also preliminary support for other mechanisms, including pruritus and pain, atopic comorbidities, social functioning, and systemic antihistamine use, in the development of mental health concerns in pediatric AD. Furthermore, research suggests the presence of bidirectional relationships between AD and psychological functioning via inflammatory responses to stress and impaired treatment adherence. Overall, significant additional research is needed to better characterize the nature and magnitude of the relationships among these multiple mechanisms and various psychosocial outcomes. Nevertheless, the findings to date support routine screening of psychological health in patients with AD as well as screening for potential risk factors, which may also serve as targets of therapeutic intervention.

### Keywords

adolescent; atopic dermatitis; child; comorbidity; eczema; mental health; psychological symptoms; psychosocial

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#### AUTHOR CONTRIBUTIONS

Sarah Radtke completed the literature review and all authors contributed to manuscript writing and editing.

## 1 | INTRODUCTION

Atopic dermatitis (AD) is an inflammatory skin disease that is highly prevalent during childhood and persists into adulthood for a subset of patients.<sup>1</sup> Its presence impairs quality of life for patients and their families across numerous domains, including patients' psychosocial functioning. In both cross-sectional and longitudinal studies, AD has been found to be associated with a variety of mental health concerns including internalizing<sup>2,3</sup> (e.g., anxiety, depression) and externalizing symptoms<sup>3,4</sup> (e.g., inattention, disruptive behavior), and neurodevelopmental disorders<sup>3,4</sup> (e.g., attention deficit/hyperactivity disorder [ADHD] and autism spectrum disorder). These associations are particularly strong for patients with severe AD.<sup>2,4</sup> However, a detailed characterization of the factors underlying these relationships is lacking, despite consistent evidence supporting their existence and frequent suggestions by researchers of potential mechanisms. In this narrative review, we thus sought to cohesively summarize the various mechanisms examined to date, beginning with the mechanisms with more empirical support. Areas where further research is needed will be highlighted throughout. To identify relevant publications, we conducted a search in PubMed for articles in English with titles or abstracts containing the keywords "atopic dermatitis" or "eczema"; "child" or "adolescent"; and "mental health," "psychosocial," or "psychological symptoms." We then manually searched the references of relevant articles for additional studies not identified by the electronic search.

## 2 | POTENTIAL MECHANISMS

### 2.1 | Child sleep

To date, sleep has been most thoroughly explored as a mechanism for poor psychosocial functioning in children with AD. Studies have primarily focused on the influence of sleep on externalizing symptoms (e.g., disruptive behavior, inattention, hyperactivity), with results largely supporting the mediating role of sleep problems. In a large sample of 6484 children between 3 and 11 years old, Romanos and colleagues<sup>5</sup> found a strong association between AD and ADHD in children with parent-reported sleep problems but not in children without sleep problems; and Dahl and colleagues<sup>6</sup> found difficulty falling asleep and night awakening due to itching were significantly correlated with having a parent-reported "major discipline problem" in their sample of 5- to 12-year-old children with AD. Furthermore, Schmitt and colleagues<sup>7</sup> found parent-reported sleep problems to occur at significantly higher rates in children with comorbid AD and ADHD compared to children with AD alone; however, child-reported sleep problems were not associated with having comorbid ADHD in this sample of children with AD. In the only study to explore these relationships in a sample that included adolescents, Camfferman and colleagues<sup>8</sup> demonstrated sleep problems partially mediated the relationship between AD and oppositional behavior, hyperactivity, and overall ADHD symptoms in 6- to 16-year-old youth. The overall model in Camfferman et al.'s study also included asthma and allergic rhinitis, and all three conditions significantly predicted sleep problems as reported by parents on the Sleep Disturbance Scale for Children.

Importantly, the aforementioned studies are all cross-sectional, limiting their ability to demonstrate causation. However, a prospective birth cohort study followed 1578 infants with AD until they were 10-years-old and found the co-occurrence of infant AD and

sleep problems significantly predicted conduct problems and emotional problems at age 10.<sup>9</sup> However, in contrast to the cross-sectional studies reported above, this longitudinal study found the presence of AD, not co-occurring AD and sleep problems, independently predicted hyperactivity/inattention. Only one other study was identified that explored the relationship between AD, sleep, and internalizing symptoms. Results indicated parent-reported sleep quality partially mediated 11%–15% of the association between AD and mother-reported emotional symptoms on the Strengths and Difficulties Questionnaire when the children were 4 and 7 years old.<sup>2</sup>

Although compelling, these findings regarding the role of child sleep are preliminary due to significant methodological weaknesses. Most critical is the dearth of longitudinal studies examining the intersection of AD, sleep, and mental health outcomes, and the conflicting findings regarding ADHD symptoms in the one known longitudinal study. In addition, the methods used to measure ADHD and other mental health symptoms vary widely across studies, and AD severity is not accounted for in many studies. Potential differences between parent and child report of sleep difficulties should also be explored given most research to date has been limited to parent report, and Schmitt and colleagues<sup>7</sup> found discrepant outcomes when child report was included. Polysomnography and other objective measures of sleep could be used to better understand whether specific sleep disturbances (e.g., sleep onset latency, limb movement, nighttime awakenings) are more prevalent than others in youth with AD or are more correlated with patient mental health. More research is also needed on the role of child sleep on internalizing symptoms and the effect of sleep on mental health in adolescents. This is important given the higher rates of internalizing symptoms during adolescence and the fact impaired sleep is a symptom of major depressive episodes and generalized anxiety disorder,<sup>10</sup> common internalizing conditions.

## 2.2 | Parent mental health

Another likely mechanism contributing to the increased mental health concerns in children with AD is parent mental health. Mothers of infants with AD describe themselves as more depressive/hopeless and anxious/overprotective than mothers of children without AD.<sup>11</sup> In addition, mothers of children with AD from 7 months to 7 years old rated the quality of their mental health as lower than that of the normative sample.<sup>12</sup> In two separate interview studies, mothers of children with AD from 18 to 48 months endorsed higher levels of psychosocial stress than mothers of children without AD<sup>13</sup> and 71% of interviewed parents of children with AD reported experiencing feelings of frustration, guilt, helplessness, exhaustion, and resentment.<sup>14</sup> The prevalence of impaired parental mental health in this population is likely influenced by many factors, including parental sleep. Research demonstrates sleep disruption is common in parents of youth with AD and other chronic illnesses.<sup>15</sup> For parents of children with AD, disrupted sleep is significantly correlated with parental anxiety and depression.<sup>16</sup>

It is clear parenting a child with AD contributes to poor parental mental health, and there is also substantial evidence demonstrating parent mental health significantly impacts socioemotional development across childhood.<sup>17–19</sup> However, no studies were identified that explored the effect of parent mental health on child psychological outcomes, specifically, in

samples of youth with AD. While it is likely the same relationships exist in this population, future research is needed to provide evidence for this conclusion.

### 2.3 | Pruritus and pain

In addition to the notable effects of sleep and parent mental health, there are several other mechanisms that could play a role in the relationship between AD and child mental health, which warrant further research. Skin symptoms, such as pruritus, have long been thought to have negative effects on sleep and attention. The presence of pruritus is a cardinal feature of AD and other dermatologic conditions and is associated with decreased quality of life.<sup>20</sup> Furthermore, the presence and intensity of pruritus is positively correlated with symptoms of depressed mood, anxiety, and stress across the lifespan.<sup>21–23</sup> However, the mechanisms that underpin the association of pruritus and psychological symptoms are not well understood, and no longitudinal studies were identified, which examined the relationships among these variables. A commonly proposed explanation is that pruritus leads to impairment in sleep, which then subsequently influences mental health, as summarized above.<sup>22</sup> Although not yet explored in patients with AD, Zachariae et al.<sup>24</sup> found impaired sleep quality partially mediated the association between pruritus severity and psychological symptoms in adults with psoriasis.

Skin pain is also a component of AD, and over recent years, efforts have been made to better characterize this experience.<sup>25</sup> Skin pain predicts elevated depression symptoms in adults with AD<sup>26</sup> and poorer quality of life in children with AD.<sup>27</sup> The presence of other types of acute and chronic pain is consistently found to predict increased mental health symptoms in youth.<sup>28,29</sup> These findings highlight the need for further exploration of the relationship between skin pain and mental health in children with AD.

### 2.4 | Atopic comorbidities

AD commonly co-occurs with asthma, food allergy, and allergic rhinitis in pediatric populations, and the risk of allergic comorbidity is higher in patients with severe AD.<sup>30</sup> Each of these comorbid conditions has also been shown to independently predict increased mental health symptoms.<sup>31–33</sup> It is possible the elevated occurrence of mental health symptoms in children with AD is partially a result of the presence of these other conditions. Hou and Silverberg<sup>3</sup> analyzed data from over 200,000 children ages 2 to 17 years and found the presence of comorbid atopic disorders was associated with higher rates of various psychological symptoms or conditions (e.g., autism, ADHD, worry, depression/sadness), and the presence of two or more comorbid disorders further increased the occurrence of psychological conditions when compared to the presence of one atopic disorder. However, the same study demonstrated that presence of AD remains linked to psychological symptoms when asthma, hay fever, and food allergy are controlled for, and other studies have reached similar conclusions.<sup>5,9</sup> More research is needed to identify the independent effects, as well as any additive effects, of each of these atopic conditions when they co-exist and to better understand the common factors that may contribute to increased psychological symptoms across various health concerns.

## 2.5 | Social functioning

Another factor that may contribute to the association between AD and mental health is impaired social functioning and bullying, which children with AD experience at higher rates than their peers.<sup>34,35</sup> For example, in a retrospective study asking young adults to reflect on their experiences growing up with AD, participants reported experiencing high rates of shame in peer situations, and frequent avoidance of social activities, sports, and intimacy.<sup>34</sup> The same study found patients with severe AD reported having fewer friends during primary and secondary school and spending less of their leisure time with friends than patients with moderate AD. Another qualitative study involving 8- to 12-year-old children with AD noted high rates of bullying, victimization, avoidance by peers, and negative attitudes from teachers.<sup>35</sup> While participants in these studies reported experiencing self-consciousness, poor self-esteem and self-image, and unhappiness and anger as result of their impaired social interactions, to our knowledge, no studies have assessed whether children with AD who experience impaired social interactions and bullying are more likely to develop psychological impairment. Nonetheless, this is likely given the effect peer victimization is known to have on children both with and without other chronic illnesses.<sup>36,37</sup>

## 2.6 | Systemic antihistamines

The impact of systemic antihistamine use early in life on children's psychological and behavioral development has also been explored. Studies have found higher rates of ADHD symptoms<sup>7,38</sup> as well as tic disorders, anxiety, and behavioral problems<sup>39</sup> in youth who were prescribed systemic antihistamines during early childhood. Fuhrmann and colleagues<sup>38</sup> found while children without AD who were exposed to systemic antihistamines had a 35% increased risk of developing ADHD symptoms compared to children without AD or systemic antihistamine exposure, the risk among children with AD and antihistamine exposure was 47%, indicating both antihistamine use and other factors likely contribute to the development of ADHD symptoms among children with AD. However, findings regarding antihistamine use are not consistent and discrepancies may be partly due to differences between first- and second-generation antihistamines. While the aforementioned studies either focused on first-generation antihistamines (e.g., hydroxyzine) or a composite of both first- and second-generation antihistamines, two studies have found no clinically significant differences on behavioral and developmental assessments between children prescribed cetirizine, a second-generation antihistamine, versus children who received a placebo.<sup>40,41</sup>

## 3 | BIDIRECTIONAL RELATIONSHIPS

There is also evidence to support the bidirectional relationship between AD and psychiatric symptoms in children and their parents. For example, Chan and colleagues<sup>42</sup> reviewed 11 studies, 9 of which were longitudinal in design, and concluded maternal prepartum and postpartum stress, anxiety, and depression increase the likelihood of childhood AD. However, there are no known studies that have explored whether maternal or paternal mental health later during a child's development also influences child AD presence or severity. In addition to parent mental health, patients' own psychosocial stress is consistently found to increase AD severity in individuals with AD of all ages. We refer the reader to Suárez

et al.<sup>19</sup> for a review of inflammatory and immune responses to psychological stress and their impacts on skin health. In adult patients, symptoms of AD are commonly found to worsen after the experience of stressful life events,<sup>43</sup>; this warrants further study in pediatric populations.

Furthermore, although not yet directly studied in patients with AD, elevated psychological distress—particularly depression—in both adult patients and parents of children with chronic illness is known to impair treatment adherence.<sup>44,45</sup> Non-adherence is prevalent in families with children with chronic inflammatory skin diseases and is likely impacted by numerous factors.<sup>46,47</sup> It is important for providers to be aware that psychological distress within families is likely to further reduce treatment adherence and increase illness severity. At least two studies have found interventions designed to improve treatment adherence in adults with chronic illnesses (i.e., diabetes<sup>48</sup> and coronary artery disease<sup>49</sup>) improved both psychological functioning and patient adherence. However, neither study measured the outcome variables with sufficient frequency to dissect whether improvements in psychological functioning preceded improvements in adherence, improvements in adherence (and subsequent improvement in illness symptoms) preceded improvements in psychological functioning, or both occurred simultaneously. AD and mental health symptoms likely have reciprocal influences on each other over time and more research is needed to better understand these relationships so that interventions can be identified, which improve both AD control and patient mental health.

## 4 | DISCUSSION

Despite significant gaps in the literature, there is preliminary research supporting the influence of multiple factors in the relationship between AD and mental health in youth. Child sleep is the only factor whose effects have been characterized in greater detail, and evidence of both moderating and mediating effects have been identified. All other mechanisms reviewed have been shown to be present at higher rates in children with AD (e.g., poor parent mental health, pruritus, bullying) and separate studies have shown that these mechanisms negatively impact child mental health in control samples or samples of children with other chronic illnesses. However, no studies have directly assessed these mechanisms and patient mental health in pediatric populations with AD. Thus, the precise nuances of these relationships are unknown.

It is likely that all of the factors discussed in this review have at least some effect on the mental health of youth with AD. However, the magnitude of impact for each factor remains unclear. Better understanding of this is critically important in prioritizing future targets for intervention. It is also possible the magnitude of impact for each factor may vary among patients due to other characteristics (e.g., patient age, gender, AD severity, or co-occurring conditions). Longitudinal research will be particularly important in determining whether certain mechanisms have stronger effects at certain ages, or whether their effects are compounded over time. This longitudinal research will also be instrumental in identifying whether earlier or more aggressive treatment of AD can mitigate the development of psychological symptoms in some patients.

#### 4.1 | Clinical implications

While there is clearly more to understand about the interplay of AD, mental health, and their mediating or moderating factors, the findings to date provide sufficient evidence to inform patient care. Recommendations to screen for psychiatric impairment in children with AD abound. It may be equally as important to screen for the mechanisms summarized above and to intervene where possible. Understanding which factors are relevant for each patient will allow interventions to be tailored to each patient's individual needs and help determine whether the interventions can be provided by medical team members (e.g., for pruritus) or if engagement with a behavioral health provider may be indicated (e.g., in coping with bullying). Furthermore, identifying patients who may be at risk for the development of psychiatric problems due to their AD diagnosis and the presence of one or more additional risk factors (e.g., poor sleep, bullying, co-occurring inflammatory conditions) could facilitate access to preventative care that improves their psychological outcomes.

Regarding specific psychological interventions, there are evidence-based therapeutic and pharmacologic interventions for each of the most prevalent mental health disorders in youth (i.e., anxiety, depression, ADHD, disruptive behavior). However, little research has been performed on the effectiveness of such interventions for psychological conditions in youth with chronic illness in general, and the existing research provides only weak evidence.<sup>50,51</sup> Specifically, there are no studies to date that directly assess the acceptability and efficacy of evidence-based interventions for mental health impairments in children with AD. For example, selective serotonin reuptake inhibitors (SSRIs) are first-line treatments for depression and anxiety and may also reduce pruritus,<sup>52</sup> and trials to assess their effectiveness for mood symptoms in youth with AD should be considered. Thus, future research should focus not only on interrogating the mechanisms that drive mental health problems in children with AD but also on bolstering the evidence base for appropriate interventions in this population.

## 5 | CONCLUSION

A conceptual model of how AD influences mental health symptoms in children and adolescents is complex and includes characteristics of the child (e.g., AD severity, comorbid conditions), their parents (e.g., parent mental health), and their experiences (e.g., impaired sleep, bullying). Significant additional research is needed to understand the nature and magnitude of the interconnections among these mechanisms, various psychological outcomes (e.g., internalizing symptoms, externalizing symptoms, neurodevelopmental disorders), sociodemographic factors (e.g., age, sex), and time. Nevertheless, the clinical implications of the research to date include continued support for the routine screening of psychological health in patients with AD as well as the need to screen for potential risk factors in patients and their caregivers. Such screenings can help providers to identify patients at greater risk for mental health symptoms and to select intervention targets for those who present with mental health impairments.

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## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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