



# Major Comorbidities of Atopic Dermatitis: Beyond Allergic Disorders

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## Abstract

The consequences of atopic dermatitis reach beyond the skin and past childhood. Patients with atopic dermatitis are at risk of developing allergic comorbidities, but less is known about the associations between atopic dermatitis and non-allergic conditions. Understanding these non-allergic comorbidities has the potential to improve patient outcomes and to help mitigate the cost and burdens associated with these conditions. Atopic dermatitis is associated with cutaneous bacterial infections, more severe forms/courses of cutaneous viral infections, and extra-cutaneous infections. Atopic dermatitis is also associated with several mental health comorbidities particularly attention-deficit hyperactivity disorder, anxiety, and depression. Data are largely inconsistent for specific cancers, but atopic dermatitis appears to protect against malignancy overall; severe long-term atopic dermatitis is associated with adult lymphomas. Atopic dermatitis may also be associated with obesity, cardiovascular disease, and autoimmune disease, particularly alopecia areata and gastrointestinal immune-mediated disorders. Although the causative mechanisms underlying these associations are poorly understood, treating physicians should be aware of associations in seeking to alleviate the burden for patients with atopic dermatitis.

## Key Points

Numerous non-allergic comorbidities have been associated with atopic dermatitis, suggesting that it may be more of a systemic disorder than previously recognized.

Among these are extra-cutaneous infections, neuropsychiatric conditions, and emerging comorbidities, obesity, autoimmune disease, and lymphoma.

Managing physicians should consider these potential associations in their holistic approach to treating atopic dermatitis.

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## 1 Introduction

Atopic dermatitis (AD), a common chronic inflammatory skin disease in children and adolescents, impacts the quality of life of patients and their families, and has become a global health issue [1]. Patients with AD are at a slightly, but significantly, increased risk of all-cause mortality compared with the general population [2, 3]. The association between AD and food allergy, asthma, and allergic rhinitis as part of the so-called ‘atopic march’ has been the subject of several

recent reviews [4, 5]. It has been well established that AD is also associated with an increased risk of allergic contact dermatitis, hand dermatitis, and irritant contact dermatitis [6–8]. Much less attention, however, has been given to the risk of non-allergic comorbidities of AD, which include cutaneous and extra-cutaneous infections, neuropsychiatric conditions, and emerging comorbidities, such as obesity, cardiovascular disease, and some cancers. Most of these comorbidities affect children, while others occur during adulthood in patients with long-standing disease, supporting the systemic nature of AD [9, 10] and suggesting that measures during childhood to reduce disease severity could protect against the development of these comorbidities.

## 2 Materials and Methods

This project was intended to generate a narrative review describing the associations between AD and non-allergic comorbidities that have evidence of a positive association, as well as the current concepts for the mechanisms underlying their association. During the initial roundtable meeting of experts in the management of AD, the authors determined the main categories of comorbidities to be included in the review. In the initial phase, one of the authors (JCJ) performed a comprehensive search using PubMed for literature supporting these associations using the following terms: (atopic dermatitis OR eczema) AND (herpes OR herpeticum OR coxsackium OR molluscum OR infection); (atopic dermatitis OR eczema) AND (attention deficit OR autism OR depression OR anxiety OR mental health OR epilepsy); (atopic dermatitis OR eczema) AND (obesity OR overweight OR underweight); (atopic dermatitis OR eczema) AND cardiovascular disease; (atopic dermatitis OR eczema) AND type 2 diabetes; (atopic dermatitis OR eczema) AND (inflammatory bowel disease OR alopecia OR autoimmune); (atopic dermatitis OR eczema) AND malignancy. Literature published between January 2000 and December 2017 (the date of the final search) was included. Altogether, 261 articles were evaluated for inclusion. Three of the authors (ELS, ST, SRF) reviewed the search results to exclude references that only evaluated symptoms, surrogate markers of disease (e.g., skin sensitivity), or precursors for disease (e.g., studies of bacterial colonization). The remaining 181 articles were reviewed for inclusion by a subset of the authors (AP, MB, JJR, LFE), who each also further reviewed the literature, filling in gaps and prioritizing articles based on higher levels of clinical evidence and inclusion of most recent data. In this final round of review, 30 articles were excluded and 20 articles were added, leaving a total of 171 articles to be included in this narrative review (Fig. 1). The odds ratios of evidence related to each comorbidity was organized by three of the authors (AP, JCJ, GS). Conclusions based on

systematic reviews were given greater weight than data from individual papers. No case reports or case series were included. The ages of patients included in each selected reference are listed in the data tables; no age-related search term limits were used.

## 3 Infections

Patients with AD are often colonized with *Staphylococcus aureus* and are more susceptible to bacterial skin infections than the general population [11–13] (Table 1). Among allergic disorders, the increased risk of infection is AD specific; no association with impetigo has been observed for asthma or allergic rhinitis. Despite the frequency of antibiotic use to treat these infections, methicillin-resistant *S. aureus* appears to be no more common (and perhaps even less common) among patients with AD than the general population [14–17]. However, data from a large national database found the prevalence of serious infections including cutaneous, respiratory, multi-organ, and systemic infections to be higher in hospitalized adults with AD than in those without AD [18].

Patients with AD are also more susceptible to certain viral skin infections (Table 1). Although there is no apparent increased risk for common herpes simplex infection, [11] patients with AD have a greater risk of developing eczema herpeticum (a potentially life-threatening, disseminated herpes simplex virus infection), [19–22] especially patients with more severe AD, [19] a history of cutaneous *S. aureus* infection, [19, 20] a history of food allergy or asthma, [19–21] or with early-onset AD [20, 22]. Patients with AD and coxsackie infection, especially coxsackie A6, may develop “eczema coxsackium,” with extensive cutaneous involvement that can resemble that of eczema herpeticum [23]. Whether patients with AD have increased susceptibility to molluscum contagiosum infection remains controversial, [11, 24–26] but molluscum dermatitis and more severe courses of molluscum contagiosum infection (including accentuation of AD lesional sites) occur more commonly [11, 27–29]. Susceptibility to human papillomavirus-related cervical cancer [30] and chickenpox [31, 32] also appears to be greater in patients with AD. In addition, patients with AD are at increased risk for extra-cutaneous infections, including those of the respiratory, [12, 13, 31–37] gastrointestinal, [13, 31, 38] and urinary [32] tracts (Table 1); this risk increases as the number of allergic diseases increases [13].

The increased susceptibility to bacterial and disseminated viral skin infections observed in AD is thought to be owing, at least in part, to epidermal barrier defects. However, because patients with psoriasis, which is associated with a similar degree of epidermal barrier dysfunction (based on transepidermal water loss), [39, 40] do not demonstrate a similar propensity for skin infection, other factors likely

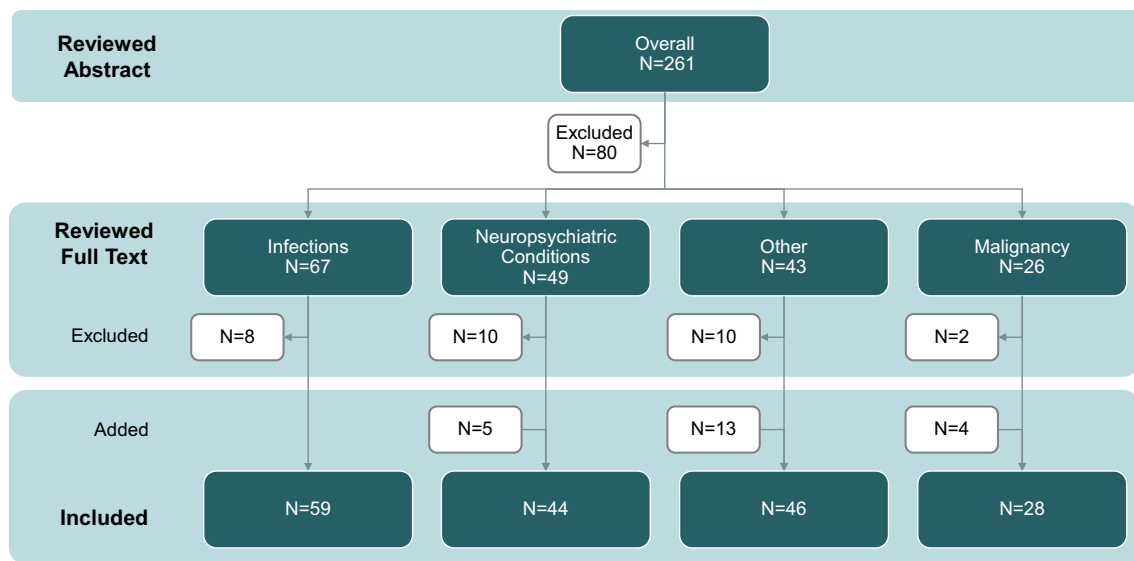


**Fig. 1** Search strategy schematic. References are accounted for in each applicable section (i.e., values in this figure are greater than the totals listed in the text)

contribute. This difference in susceptibility may be a reflection of the nature of skin inflammation in AD vs. psoriasis, i.e., increased type 2 helper T cell (Th2; also called type 2) cytokines (interleukin-4 and interleukin-13) and a decreased Th1/Th2 ratio in AD, but not in psoriasis [41–43]. Furthermore, the risk of infection/*S. aureus* colonization correlates with markers of systemic Th2 predominance [19, 22, 32, 44–49]. Th2-mediated inflammation is thought to suppress inducible antimicrobial peptide expression and/or secretion (including  $\beta$ -defensins and cathelicidin) in symptomatic/lesional and asymptomatic skin of patients with AD relative to that seen in patients with psoriasis and healthy controls [41, 50–52]. However, antimicrobial peptide expression in healthy control skin in young children is much greater than in healthy control adult skin, and cutaneous antimicrobial responses in early AD (within the first 6 months in children under 5 years of age) are not reduced relative to age-matched controls, [53] suggesting the need for further investigation.

Th2 cytokine expression also reduces the expression of the constitutive antimicrobial peptide dermcidin in sweat [54]. Among subgroups of patients with AD, dermcidin [54] and cathelicidin [55] expression is lower for those with a history of bacterial superinfection and/or eczema herpeticum, demonstrating a potential causal link between Th2 inflammation and susceptibility to infection. The risk for eczema herpeticum in patients with AD may be the result of distinct genetic abnormalities, as filaggrin mutations that confer risk of AD also confer greater risk for eczema herpeticum [56]. In addition, patients with eczema herpeticum appear to have unique abnormalities in interferon- $\gamma$  response and genetic variants in interferon regulatory factor 2 have been reported to be associated with eczema herpeticum [57].

Th2-mediated alterations in antimicrobial peptide expression have also been implicated in the microbiome shifts observed with flares, [58–60] including a reduction in commensal organisms that may produce anti-*S. aureus* factors. Topical application of non-pathogenic organisms that produce anti-*S. aureus* factors is being considered as potential therapy [61]. Th2 inflammation also increases fibronectin and/or fibrinogen expression on the skin surface, [62] leading to greater attachment of *S. aureus* in AD than in patients with psoriasis or healthy controls [58]. Scratching may also contribute by exposing laminin and fibronectin on the skin surface, [63] while loss-of-function filaggrin mutations contribute via reduced amounts of filaggrin breakdown products, which have been shown to inhibit *S. aureus* colonization [64]. *Staphylococcus aureus*-derived staphylococcal enterotoxin can also trigger skin inflammation directly, [65] perpetuating inflammation and further increasing susceptibility to infection. Shared risk factors such as low vitamin D levels, [66, 67] or exposure to cigarette smoke and other air pollutants, [68, 69] may also contribute to the increase in susceptibility to infection observed in AD.

## 4 Neuropsychiatric Conditions

Patients with AD appear to have a greater likelihood of conduct problems/disorder, [70–72] attention-deficit hyperactivity disorder, [70–81] emotional problems, [70] anxiety, [2, 3, 71–73] depression, [2, 3, 71–75, 82, 83] and suicidal ideation/self-harm [84, 85] (Table 2). Additional allergic comorbidities [76, 77, 86, 87] and AD severity, [2, 3, 72, 73, 76] persistence, [70] and symptoms [84] increase these

**Table 1** Studies investigating an association between atopic dermatitis (AD) and infections listed in order of strength of evidence

| Comorbidity                                                                | Direction of association | Supporting studies                                                                                                                                                 | AD vs. control      |                |             |
|----------------------------------------------------------------------------|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|----------------|-------------|
|                                                                            |                          |                                                                                                                                                                    | Odds ratio (95% CI) | Prevalence (%) | P value     |
| Impetigo                                                                   | Positive                 | Population-based cohort study ( $N=448,311$ cases, 3,112,617 controls; AD diagnosis age < 18 years) [12]                                                           | 1.6 (1.5–1.6)       |                | NA          |
|                                                                            |                          | Community-based cross-sectional study ( $N=1117$ ; age $\leq 6$ years) [11]                                                                                        | 1.8 (1.2–2.8)       |                | <0.01       |
|                                                                            |                          | Community-based cross-sectional survey ( $N=8754$ ; age 10–18 years) [13]                                                                                          | 8.7 (4.4–17.4)      |                | <0.05       |
| Herpes simplex                                                             | No association           | Community-based cross-sectional study ( $N=1117$ ; age $\leq 6$ years) [11]                                                                                        |                     | 23 vs. 15      | NS (0.211)  |
| Eczema herpeticum                                                          | Positive                 | Population-based cross-sectional survey ( $N=976$ cases, 4655 weighted cases; age < 18 years) [21]                                                                 | 11.7 (9.5–14.5)     |                | <0.0001     |
| Eczema coxsackium                                                          | Positive                 | Retrospective case series ( $N=80$ ; age 4 months to 16 years) [23]                                                                                                |                     | 81 vs. 24      | <0.0001     |
| Molluscum contagiosum                                                      | Positive                 | Systematic review ( $N=3$ studies, 1060 patients; age 1–14 years) [24]                                                                                             |                     | 18–43 vs. 5    | NA          |
|                                                                            |                          | Population-based case–control study ( $N=259$ cases, 109 controls; age $\leq 4$ years) [25]                                                                        | 2.5 (1.1–6.0)       |                | 0.029       |
|                                                                            |                          | Community-based cross-sectional study ( $N=1117$ ; age $\leq 6$ years) [11]                                                                                        | 1.6 (1.0–2.7)       |                | NA          |
| Molluscum dermatitis/more severe course of molluscum contagiosum infection | Positive                 | Prospective epidemiologic studies ( $N=650$ ; age < 15 years) [27]                                                                                                 |                     |                |             |
|                                                                            |                          | Number of lesions ( $N=284$ ; age 6 months to 15 years) [28]                                                                                                       |                     | No difference  | NS (0.18)   |
|                                                                            |                          | Molluscum dermatitis > 20 lesions                                                                                                                                  |                     | 68 vs. 36      | 0.001       |
|                                                                            |                          | Number of body regions affected                                                                                                                                    |                     | Trended higher | NS (0.223)  |
|                                                                            |                          | Community-based cross-sectional study ( $N=1117$ ; age $\leq 6$ years) [11]                                                                                        | 1.6 (1.0–2.7)       | Trended higher | 0.045       |
|                                                                            |                          | Retrospective chart/medical record review ( $N=696$ ; age 7 months to $\leq 17$ years) [29]                                                                        |                     |                | NS          |
|                                                                            |                          | Molluscum dermatitis                                                                                                                                               |                     | 51 vs. 32      | <0.001      |
|                                                                            |                          | Inflamed lesions                                                                                                                                                   |                     | 22 vs. 22      | NS (0.93)   |
|                                                                            |                          | Gianotti–Crosti syndrome-like reaction                                                                                                                             |                     | 5 vs. 5        | NS (> 0.99) |
|                                                                            |                          | > 50 lesions                                                                                                                                                       |                     | 20 vs. 5       | <0.001      |
| Chickenpox                                                                 | Positive                 | Population-based case–control study ( $N=2488$ cases, 32,100 controls; age $\geq 18$ years) [31]                                                                   | 1.6 (1.4–1.9)       |                | <0.001      |
|                                                                            |                          | Population-based cross-sectional survey ( $N=9417$ ; age $\leq 17$ years) [32]                                                                                     | 1.2 (1.2–1.2)       |                | <0.0001     |
| Cervical cancer                                                            | Positive                 | Population-based birth cohort survey ( $N=87$ ; AD presence evaluated at age 11 or 16 years, followed until age 30 or 42 years for cervical cancer diagnosis) [30] | 3.3 (2.0–5.5)       |                | <0.0001     |

**Table 1** (continued)

| Comorbidity                      | Direction of association | Supporting studies                                                                                         | AD vs. control             |                |                    |
|----------------------------------|--------------------------|------------------------------------------------------------------------------------------------------------|----------------------------|----------------|--------------------|
|                                  |                          |                                                                                                            | Odds ratio (95% CI)        | Prevalence (%) | P value            |
| Respiratory tract infections     | Positive                 | <b>Influenza/pneumonia</b>                                                                                 |                            |                |                    |
|                                  |                          | Community-based birth cohort study ( $N=4098$ ; age $\leq 2$ years) [33]                                   | 1.0 (0.8–1.3) <sup>a</sup> |                | NA                 |
|                                  |                          | Population-based cohort study ( $N=448,311$ cases, 3,112,617 controls; AD diagnosis age $< 18$ years) [12] | 1.3 (1.2–1.3)              |                | NA                 |
|                                  |                          | Population-based case–control studies                                                                      |                            |                |                    |
|                                  |                          | ( $N=2488$ cases, 32,100 controls; age $\geq 18$ years)[31]                                                | 1.7 (1.3–2.1)              |                | $< 0.001$          |
|                                  |                          | ( $N=174$ cases, 348 controls; all ages) [34]                                                              | 2.5 (1.1–5.7)              |                | 0.04               |
|                                  |                          | Population-based cross-sectional survey ( $N=9417$ ; age $\leq 17$ years) [32]                             | 1.7 (1.7–1.7)              |                | $< 0.0001$         |
|                                  |                          | Community-based cross-sectional survey ( $N=8754$ ; age 10–18 years) [13]                                  | 2.1 (0.3–16.3)             |                | NS ( $\geq 0.05$ ) |
|                                  |                          | <b>Otitis media</b>                                                                                        |                            |                |                    |
|                                  |                          | Community-based birth cohort study ( $N=4098$ ; age $\leq 2$ years) [33]                                   | 1.1 (1.15–1.2)             |                | NA                 |
|                                  |                          | Population-based cohort study ( $N=448,311$ cases, 3,112,617 controls; AD diagnosis age $< 18$ years) [12] | 2.2 (2.2–2.3)              |                | NA                 |
|                                  |                          | Population-based cross-sectional study ( $N=3406$ ; age 10 years) [35]                                     | 1.5 (1.1–2.1)              |                | NA                 |
|                                  |                          | Population-based cross-sectional surveys                                                                   |                            |                |                    |
|                                  |                          | ( $N=79,667$ ; age $\leq 17$ years) [37]                                                                   |                            | 10 vs. 6       | $< 0.0001$         |
|                                  |                          | ( $N=9417$ ; age $\leq 17$ years) [32]                                                                     | 1.3 (1.3–1.3)              |                | $< 0.0001$         |
|                                  |                          | Community-based cross-sectional survey ( $N=8754$ ; age 10–18 years) [13]                                  | 1.6 (0.8–3.4)              |                | NS ( $\geq 0.05$ ) |
|                                  |                          | <b>Streptococcal throat infection/respiratory tract infection</b>                                          |                            |                |                    |
|                                  |                          | Population-based cohort study ( $N=448,311$ cases, 3,112,617 controls; AD diagnosis age $< 18$ years) [12] | 1.3 (1.3–1.4)              |                | NA                 |
|                                  |                          | Community-based cohort study ( $N=327$ ; age 5–13 years) [36]                                              | 1.3 (1.0–1.7) <sup>b</sup> |                | NS (0.06)          |
|                                  |                          | Population-based case–control study ( $N=2488$ cases, 32,100 controls; age $\geq 18$ years) [31]           | 1.7 (1.3–2.3)              |                | $< 0.001$          |
|                                  |                          | Population-based cross-sectional survey ( $N=9417$ ; age $\leq 17$ years) [32]                             | 1.6 (1.5–1.6)              |                | $< 0.0001$         |
| Other extra-cutaneous Infections | Positive                 | <b>Sinusitis</b>                                                                                           |                            |                |                    |
|                                  |                          | Population-based case–control study ( $N=2488$ cases, 32,100 controls; age $\geq 18$ years) [31]           | 1.5 (1.3–1.8)              |                | $< 0.001$          |
|                                  |                          | Population-based cross-sectional surveys ( $N=9417$ ; age $\leq 17$ years) [32]                            | 2.6 (2.6–2.6)              |                | $< 0.0001$         |
|                                  |                          | Community-based cross-sectional survey ( $N=8754$ ; age 10–18 years) [13]                                  | 0.6 (0.2–2.0)              |                | NS ( $\geq 0.05$ ) |
|                                  |                          | <b>Gastroenteritis</b>                                                                                     |                            |                |                    |
|                                  |                          | Population-based cross-sectional survey ( $N=2488$ cases, 32,100 controls; age $\geq 18$ years) [31]       | 1.6 (1.3–2.0)              |                | $< 0.001$          |
|                                  |                          | Community-based cross-sectional survey ( $N=8754$ ; age 10–18 years) [13]                                  | 2.0 (1.4–3.0)              |                | $< 0.05$           |
|                                  |                          | Practice-based retrospective chart/medical record review ( $N=365$ ; age $\leq 3$ years) [38]              |                            | 58 vs. 38      | $< 0.01$           |
|                                  |                          | <b>Urinary tract infection</b>                                                                             |                            |                |                    |
|                                  |                          | Population-based cross-sectional survey ( $N=9417$ ; age $\leq 17$ years) [32]                             | 3.1 (3.1–3.1)              |                | $< 0.0001$         |

CI confidence interval, NA not available, NS not significant

<sup>a</sup>Rate ratio<sup>b</sup>Risk ratio

risks, which are apparent for children [70–72, 74, 76–79] and adults [2, 3, 73, 75, 82, 83]. Longitudinal studies have demonstrated a temporal relationship between early AD and the subsequent risk for emotional problems and conduct disorder [70] as well as attention-deficit hyperactivity disorder [78, 86, 88]. The inverse also appears to be true—psychosocial issues/mental health problems in childhood appear to increase the risk of developing AD [89, 90]. A few studies have indicated that these associations may be specific to AD, [78, 80] while others have found them to apply to other allergic comorbidities in addition to or in lieu of AD [71, 87].

Mental health disorders are increased in chronic childhood illnesses in general [91]. The association between AD and various mental health problems is largely independent of environmental and lifestyle risk factors [80, 92] and a family history of AD or personal history of atopic airway disease [80]. Genetic factors may also play a role, but the magnitude of the effect remains to be determined [93–95]. Health anxiety and/or decreased quality of life [96, 97] as well as sleep disturbance [72, 76, 88, 96, 98] are likely to be significant factors in the relationship between AD and mental health concerns.

Allergic disease is linked to autism spectrum disorder [71, 72] (Table 2), Tourette's syndrome, [99] tic disorder, [100] learning delay, [71] and psychotic experiences [101]. The number [86] and severity [72, 102] of allergic diseases increases the risk of autism spectrum disorder and, likewise, the frequency of allergic symptoms increases autism spectrum disorder severity [103]. However, these results have not been uniformly reproduced. In one study, the relationship with autism spectrum disorder was AD specific, [71] while other studies have demonstrated a specific association with asthma [104, 105] and/or a weak-to-non-existent association with AD.

Recent database analyses have suggested an association between AD and epilepsy [106, 107] (Table 2) and that the risk of epilepsy is increased by the number of allergic disorders, as well as the severity of AD and allergic rhinitis. This effect is observed for children, [106, 107] but not adults, [106, 108] perhaps owing to the low incidence of adult-onset epilepsy. Unlike asthma, the relationship between AD and epilepsy does not appear to be mediated by obesity, and environmental factors do not appear to be a factor [107].

The mechanism of neurologic and psychiatric associations is poorly understood. Increases in systemic Th2 cytokine levels have recently been linked to central nervous system disease, suggesting early exposure may be causative. The increased risk of head injury with AD may also contribute [71, 108, 109]. Hypothalamic–pituitary–adrenal axis dysregulation as a result of chronic inflammation in early life or systemic exposure to corticosteroids has been hypothesized to contribute. Patients with AD demonstrate greater sympathetic excitability (higher heart rate, lower

vagal activity, and higher anxiety, depression, and emotional excitability) in response to stress than control patients [110]. Even during intervals without stress, patients with AD have higher heart rate and sympathetic overactivity that may contribute to sleep disturbance, which also is linked to neuropsychiatric disease exacerbation [111]. Although meningitis/encephalitis, cerebrovascular diseases, head/brain injury, and concussion are each increased in AD, the risk of epilepsy is still increased after adjustment for these disorders [106, 107].

## 5 Obesity

The relationship between obesity and allergic disease varies by specific allergic comorbidity. Associations have been observed for AD [74, 75, 112–117] (Table 3), asthma, and food allergy, but not for allergic rhinitis or allergic conjunctivitis. Obesity is associated with AD in childhood [74, 113–117] and adulthood [75, 114]. In a meta-analysis conducted by Zhang and Silverberg, [114] this association was only observed for studies conducted in North America or Asia, not in Europe; however, later studies conducted by Augustin et al. [74] and Radtke et al. [75] have found positive associations in population-based case–control studies in Germany. This inconsistency could be related to differences in definitions of obesity and/or AD prevalence across these regions. Obesity is associated with greater severity of AD in children; [112, 114–116] however, the reverse does not appear to be true [117]. The association may extend to being overweight, [113–116] but this has not been confirmed by all studies [66, 117]. Data have inconsistently shown an association with being underweight [66, 116]. The relationship between birth weight and AD risk is unclear [117–119]. It should be noted, however, that the obesity risk with AD is less than with psoriasis in children [rate ratio (95% confidence interval): 1.3 (1.3–1.4) vs. 1.9 (1.5–2.3)] [74] and adults [rate ratio (95% confidence interval): 1.2 (1.1–1.2) vs. 1.7 (1.7–1.8)] [75].

The association observed between obesity and atopy may be linked to genetics, [93] or shared risk factors for obesity and AD such as altered gut microbiome [120–122]. Differences in exposure to indoor allergens owing to a more sedentary lifestyle or a reduced dietary intake of certain nutrients (especially vitamin D) because of a poor diet or less time outdoors may play a role in allergic sensitization [123]. Impaired quality of life, sleep problems, and/or chronic inflammation associated with obesity may also predispose patients toward AD, or vice versa [112, 124]. Obesity itself reduces epidermal barrier function, [125, 126] perhaps as a result of increased sweating or increased blood pressure. Obesity may also be related to the more sedentary lifestyle [124] and the use of potent topical and/or systemic

**Table 2** Studies investigating an association between atopic dermatitis (AD) and neuropsychiatric conditions listed in order of strength of evidence

| Comorbidity               | Direction of association | Supporting studies                                                                                          | AD vs. control                  |                |           |
|---------------------------|--------------------------|-------------------------------------------------------------------------------------------------------------|---------------------------------|----------------|-----------|
|                           |                          |                                                                                                             | Odds ratio (95% CI)             | Prevalence (%) | P value   |
| Conduct problems/disorder | Positive                 | Population-based birth cohort<br>( <i>N</i> = 2916; age ≤ 10 years) [70]                                    | 1.3 (1.0–1.7)                   |                | 0.04      |
|                           |                          | Population-based cross-sectional surveys<br>( <i>N</i> = 79,667; age < 18 years) [72]                       | 2.0 (1.6–2.5)                   |                | < 0.0001  |
|                           |                          | ( <i>N</i> = 27,556; age < 18 years) [71]                                                                   | 2.3 (1.2–4.3)                   |                | NA        |
| ADHD                      | Positive                 | Systematic review of epidemiologic studies<br>( <i>N</i> = 20 studies, 170,175 patients; all ages) [80]     | 1.2 (0.9–1.6) to 7.8 (1.7–40.5) |                | NA        |
|                           |                          | Population-based birth cohort studies<br>( <i>N</i> = 2916; age ≤ 10 years) [70]                            | 1.3 (1.0–1.6)                   |                | NS (0.08) |
|                           |                          | ( <i>N</i> = 770; age ≤ 11 years) [78]                                                                      |                                 |                |           |
|                           |                          | Early ADHD (age 0–4 years)                                                                                  | 1.9 (1.0–3.6) <sup>a</sup>      |                | NA        |
|                           |                          | Late ADHD (age 5–8 years)                                                                                   | 1.2 (0.3–4.9) <sup>a</sup>      |                | NA        |
|                           |                          | Population-based case–control studies<br>( <i>N</i> = 35,865 cases, 316,456 controls; “children”) [76]      | 1.1 (1.0–1.3)                   |                | NA        |
|                           |                          | ( <i>N</i> = 30,354 cases, 261,514 controls; age < 18 years) [74]                                           | 1.4 (1.3–1.4) <sup>b</sup>      |                | < 0.05    |
|                           |                          | ( <i>N</i> = 4692 cases, 18,768 controls; age < 18 years) [77]                                              | 1.4 (1.2–1.6)                   |                | < 0.001   |
|                           |                          | ( <i>N</i> = 1436 cases, 1436 controls; age 6–17 years) [79]                                                |                                 | 5 vs. 3        | 0.02      |
|                           |                          | ( <i>N</i> = 48,140 cases, 1,257,075 controls; age ≥ 18 years) [75]                                         | 2.0 (1.7–2.2) <sup>b</sup>      |                | NA        |
|                           |                          | ( <i>N</i> = 2483 cases, 32,072 controls; age ≥ 18 years) [76]                                              | 1.6 (1.3–2.1)                   |                | NA        |
|                           |                          | ( <i>N</i> = 428 cases, 74,572 controls; age ≥ 18 years) [73]                                               |                                 | 5 vs. 1        | < 0.0001  |
|                           |                          | ( <i>N</i> = 8201 cases, 32,804 controls; all ages) [81]                                                    | 1.5 (1.4–1.6)                   |                | < 0.05    |
|                           |                          | Population-based cross-sectional surveys<br>( <i>N</i> = 79,667; age < 18 years) [72]                       | 1.6 (1.4–1.9)                   |                | < 0.0001  |
|                           |                          | ( <i>N</i> = 27,556; age < 18 years) [71]                                                                   | 3.9 (1.9–7.6)                   |                | NA        |
| Emotional problems        | Positive                 | Population-based birth cohort<br>( <i>N</i> = 2916; age ≤ 10 years) [70]                                    | 1.7 (1.4–2.1)                   |                | < 0.001   |
| Anxiety                   | Positive                 | Population-based case–control studies<br>( <i>N</i> = 10,038 cases, 4,259,457 controls; age ≥ 18 years) [2] |                                 | 0–1 vs. 0      | NA        |
|                           |                          | ( <i>N</i> = 7937 cases, 79,370 controls; age ≥ 18 years) [3]                                               | 1.4 (1.1–1.8)                   |                | < 0.0001  |
|                           |                          | ( <i>N</i> = 1044 cases, 8612 controls; age ≥ 18 years) [2]                                                 |                                 | 8 vs. 4        | NA        |
|                           |                          | ( <i>N</i> = 428 cases, 74,572 controls; age ≥ 18 years) [73]                                               |                                 | 43 vs. 21      | < 0.0001  |
|                           |                          | Population-based cross-sectional surveys<br>( <i>N</i> = 79,667; age < 18 years) [72]                       | 1.8 (1.4–2.3)                   |                | < 0.0001  |
|                           |                          | ( <i>N</i> = 27,556; age < 18 years) [71]                                                                   | 8.8 (3.8–20.6)                  |                | NA        |
| Depression                | Positive                 | Population-based case–control studies<br>( <i>N</i> = 30,354 cases, 261,514 controls; age < 18 years) [74]  | 1.2 (1.1–1.4) <sup>b</sup>      |                | < 0.05    |
|                           |                          | ( <i>N</i> = 48,140 cases, 1,257,075 controls; age ≥ 18 years) [75]                                         | 1.4 (1.4–1.5) <sup>b</sup>      |                | NA        |
|                           |                          | ( <i>N</i> = 7937 cases, 79,370 controls; age ≥ 18 years) [3]                                               | 1.6 (1.4–1.8)                   |                | < 0.0001  |
|                           |                          | ( <i>N</i> = 10,038 cases, 4,259,457 controls; age ≥ 18 years) [2]                                          |                                 | 0–1 vs. 0      | NA        |
|                           |                          | ( <i>N</i> = 1044 cases, 8612 controls; ‘adults’) [2]                                                       |                                 | 20 vs. 11      | NA        |
|                           |                          | ( <i>N</i> = 428 cases, 74,572 controls; age ≥ 18 years) [73]                                               |                                 | 37 vs. 21      | < 0.0001  |
|                           |                          | Population-based cross-sectional surveys<br>( <i>N</i> = 79,667; age < 18 years) [72]                       | 2.0 (1.5–2.7)                   |                | < 0.0001  |
|                           |                          | ( <i>N</i> = 27,556; age < 18 years) [71]                                                                   | 9.9 (2.9–33.4)                  |                | NA        |
|                           |                          | ( <i>N</i> = 34,163; age ≥ 18 years) [82]                                                                   | 2.3 (2.0–2.6)                   |                | < 0.0001  |
|                           |                          | ( <i>N</i> = 4052; age ≥ 20 years) [83]                                                                     | 2.1 (1.1–3.8)                   |                | NA        |

**Table 2** (continued)

| Comorbidity                 | Direction of association | Supporting studies                                                                      | AD vs. control             |                |                |
|-----------------------------|--------------------------|-----------------------------------------------------------------------------------------|----------------------------|----------------|----------------|
|                             |                          |                                                                                         | Odds ratio (95% CI)        | Prevalence (%) | P value        |
| Suicidal ideation/self-harm | Positive                 | Population-based cohort study<br>( <i>N</i> = 267,788; age ≥ 10 years) [85]             | 1.4 (1.3–1.5) <sup>b</sup> |                | NA             |
|                             |                          | Population-based cross-sectional survey ( <i>N</i> = 3775; age 18 years) [84]           | 1.9 (1.3–2.7)              |                | NA             |
| Autism spectrum disorders   | Inconsistent             | Population-based cross-sectional surveys<br>( <i>N</i> = 79,667; age < 18 years) [72]   | 2.7 (1.9–3.8)              |                | < 0.0001       |
|                             |                          | ( <i>N</i> = 27,556; age < 18 years) [71]                                               | 7.2 (2.6–20.0)             |                | NA             |
| Epilepsy                    | Children: positive       | Case-cohort study ( <i>N</i> = 35,312 cases, 35,312 controls; age < 18 years) [106]     | 3.3 (2.4–4.5) <sup>a</sup> |                | < 0.05         |
|                             |                          | Population-based cross-sectional survey<br>( <i>N</i> = 91,642; age < 18 years) [107]   | 1.6 (1.1–2.4)              |                | 0.01           |
|                             | Adults: no association   | Case-cohort study<br>( <i>N</i> = 35,312 cases, 35,312 controls; age 16–84 years) [106] | 1.8 (0.9–3.7) <sup>a</sup> |                | NS<br>(≥ 0.05) |
|                             |                          | Population-based cross-sectional study<br>( <i>N</i> = 5834; age ≥ 16 years) [108]      | 0.9 (0.5–1.7) <sup>c</sup> |                | NA             |

ADHD attention-deficit hyperactivity disorder, CI confidence interval, NA not available, NS not significant

<sup>a</sup>Relative risk

<sup>b</sup>Rate ratio

<sup>c</sup>Hazard ratio

corticosteroids, which can increase appetite and metabolic risk [127].

## 6 Metabolic Disease: Cardiovascular Disease, Stroke, and Type 2 Diabetes Mellitus

Cardiovascular disease and AD share several risk factors, including obesity and mental health comorbidity. There is emerging evidence that adults with AD also have a greater risk for congestive heart failure [128] and coronary artery disease (CAD) [128, 129] (Table 3). Atopic dermatitis is associated with CAD (most often mild single-vessel CAD), and the risk of CAD appears greatest for patients with severe long-term AD [129]. Data supporting a link with myocardial infarction [128, 130–134] and stroke [128, 131–135] in adults, however, are mixed (Table 3). While the risk of obesity is increased in pediatric AD, [113–117] the associations in children between AD and cardiovascular disease risk factors such as hypertension are less clear [113, 136]. These associations may be owing to genetic linkage, [136] circulating cytokines/systemic inflammation, [137] lifestyle factors (i.e., smoking, drinking, and/or sedentary lifestyle), [124, 129] or shared risk factors (i.e., impaired sleep) [124]. Overall, the prevalence of cardiovascular disease risk factors (hypertension, obesity,

hyperlipidemia) is lower for AD compared with psoriasis [74, 75].

Recent papers have suggested a positive association with type 2 diabetes, [138] while others have found an association with diabetes without specifying type 1 or 2 [74] and/or have not found an association [75, 113, 127, 131] (Table 3). The positive association observed in some studies may relate to the use of topical and systemic corticosteroids [127].

## 7 Autoimmune Disease

Regardless of age, sex, or disease duration, evidence of autoreactivity has been observed in 23–91% of patients with AD [139]. Allergic disease and/or AD increase the risk for several autoimmune diseases including Crohn's disease, [3, 74, 75, 140–144] ulcerative colitis, [3, 74, 75, 140–142] celiac disease, [140, 145] and alopecia areata [74, 75, 140, 146] (Table 3). The reverse may also be true; alopecia areata increases the risk of AD, and this risk is greatest for those with early-onset alopecia (before 10–13 years of age) [147–149] and/or alopecia totalis or universalis [146]. Greater risk with severe forms of alopecia areata is specific to AD, and the risk is also greater with filaggrin mutations, [150, 151] suggesting genetic linkage. Inflammatory bowel disease shares 39 genetic risk loci with AD, also suggesting a genetic cause [152].

**Table 3** Studies investigating an association between atopic dermatitis (AD) and other non-allergic comorbidities listed in order of strength of evidence

| Comorbidity | Direction of association                                   | Supporting studies                                                                                                                                                                    | AD vs. control                 |                |            |
|-------------|------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|----------------|------------|
|             |                                                            |                                                                                                                                                                                       | Odds ratio (95% CI)            | Prevalence (%) | P value    |
| Obesity     | Positive                                                   | Systematic review and meta-analysis of epidemiologic studies<br>( <i>N</i> = 30 studies, 900,358 patients; all ages) [114]                                                            | 1.3 (1.1–1.4)                  |                | NA         |
|             |                                                            | Systematic review of epidemiologic studies<br>( <i>N</i> = 3 studies; all ages) [115]                                                                                                 | 1.1 (0.9–1.3) to 2.0 (1.2–3.2) |                | NA         |
|             |                                                            | Population-based case–control studies<br>( <i>N</i> = 30,354 cases, 261,514 controls; age < 18 years) [74]                                                                            | 1.3 (1.3–1.4) <sup>a</sup>     |                | < 0.05     |
|             |                                                            | ( <i>N</i> = 48,140 cases, 1,257,075 controls; age ≥ 18 years) [75]                                                                                                                   | 1.2 (1.2–1.2) <sup>a</sup>     |                | NA         |
|             |                                                            | Practice-based case–control study<br>( <i>N</i> = 414 cases, 828 controls; age 1–21 years) [117]                                                                                      | 2.0 (1.2–3.2) to 0.8 (0.5–1.1) |                | < 0.05     |
|             |                                                            | International cross-sectional survey [ISAAC]<br>( <i>N</i> = 76,164, age 6–7 years, <i>N</i> = 201,370, age 13–14 years) [116]                                                        | 1.2 (1.1–1.4) to 1.4 (1.2–1.6) |                | < 0.05     |
|             |                                                            | Population-based cross-sectional survey<br>( <i>N</i> = 13,275; age ≤ 17 years) [113]                                                                                                 | 1.2 (1.2–1.7)                  |                | < 0.0001   |
|             |                                                            | <b>Myocardial infarction</b>                                                                                                                                                          |                                |                |            |
|             |                                                            | Population-based case-cohort study<br>( <i>N</i> = 20,323 cases, 20,323 controls; ‘adults’) [135]                                                                                     | 1.3 (0.9–2.0) <sup>b</sup>     |                | NS (0.180) |
|             |                                                            | Population-based case–control studies<br>(age ≥ 15 years) [133]                                                                                                                       |                                |                |            |
|             |                                                            | Mild AD ( <i>N</i> = 25,898 cases, 145,373 controls)                                                                                                                                  | 0.7 (0.6–0.9) <sup>a</sup>     |                | < 0.05     |
|             |                                                            | Severe AD ( <i>N</i> = 2527 cases, 145,373 controls)                                                                                                                                  | 1.1 (0.7–1.6) <sup>a</sup>     |                | 0.761      |
|             |                                                            | ( <i>N</i> = 7937 cases, 79,370 controls; age ≥ 18 years) [3]                                                                                                                         | 1.1 (0.9–1.3)                  |                | NS (0.298) |
|             |                                                            | ( <i>N</i> = 372 cases, 9109 controls; age 18–79 years) [132]                                                                                                                         |                                | 1 vs. 3        | NS (0.076) |
| CVD         | Myocardial infarction: inconsistent<br>Other CVD: positive | ( <i>N</i> = 4814 cases, 48,396 controls; age 30–55 years) [130]                                                                                                                      | 1.7 (1.2–2.5) <sup>b</sup>     |                | NA         |
|             |                                                            | Population-based cohort study [ <i>N</i> = 1,18,678; with 2 adult data-bases ( <i>n</i> = 1.2 million and <i>n</i> = 2990) and a birth-to-adolescent cohort ( <i>n</i> = 2286)] [134] | 1.1 (1.0–1.1) <sup>c</sup>     |                | NS (0.127) |
|             |                                                            | Population-based cross-sectional surveys [128]                                                                                                                                        |                                |                |            |
|             |                                                            | ( <i>N</i> = 34,525; age ≥ 18 years)                                                                                                                                                  | 1.3 (1.0–1.6)                  |                | 0.10       |
|             |                                                            | ( <i>N</i> = 27,157; age ≥ 18 years)                                                                                                                                                  | 1.5 (1.2–1.9)                  |                | 0.002      |
|             |                                                            | ( <i>N</i> = 4970; age ≥ 20 years)                                                                                                                                                    | 2.0 (1.0–4.1)                  |                | 0.07       |
|             |                                                            | Population-based cross-sectional survey<br>( <i>N</i> = 259,119; age 30–74 years) [131]                                                                                               | 0.9 (0.8–1.0)                  |                | NA         |
|             |                                                            | <b>Congestive heart failure</b>                                                                                                                                                       |                                |                |            |
|             |                                                            | Population-based case-cohort study<br>( <i>N</i> = 20,323 cases, 20,323 controls; ‘adults’) [135]                                                                                     | 1.5 (1.1–1.9) <sup>b</sup>     |                | 0.009      |
|             |                                                            | Population-based cross-sectional surveys [128]                                                                                                                                        |                                |                |            |
|             |                                                            | ( <i>N</i> = 34,525; age ≥ 18 years)                                                                                                                                                  | 1.9 (1.6–2.2)                  |                | < 0.0001   |
|             |                                                            | ( <i>N</i> = 27,157; age ≥ 18 years)                                                                                                                                                  | 1.9 (1.6–2.2)                  |                | < 0.0001   |
|             |                                                            | ( <i>N</i> = 4970; age ≥ 20 years)                                                                                                                                                    | 1.0 (0.4–2.6)                  |                | 0.99       |
|             |                                                            | <b>Coronary artery disease</b>                                                                                                                                                        |                                |                |            |
|             |                                                            | Population-based case–control study<br>( <i>N</i> = 372 cases, 9109 controls; age 18–79 years) [132]                                                                                  |                                | 3 vs. 4        | NS (0.850) |
|             |                                                            | Population-based cross-sectional surveys [128]                                                                                                                                        |                                |                |            |
|             |                                                            | ( <i>N</i> = 34,525; age ≥ 18 years)                                                                                                                                                  | 1.3 (1.0–1.7)                  |                | 0.02       |
|             |                                                            | ( <i>N</i> = 27,157; age ≥ 18 years)                                                                                                                                                  | 1.4 (1.1–1.7)                  |                | 0.003      |
|             |                                                            | ( <i>N</i> = 4970; age ≥ 20 years)                                                                                                                                                    | 2.0 (1.0–3.8)                  |                | 0.04       |

**Table 3** (continued)

| Comorbidity              | Direction of association | Supporting studies                                                                                                                                                                                                                     | AD vs. control              |                |            |
|--------------------------|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|----------------|------------|
|                          |                          |                                                                                                                                                                                                                                        | Odds ratio (95% CI)         | Prevalence (%) | P value    |
| Stroke                   | Inconsistent             | Population-based case-cohort study ( $N=20,323$ cases, 20,323 controls; 'adults') [135]                                                                                                                                                | 1.3 (1.1–1.6) <sup>b</sup>  |                | 0.005      |
|                          |                          | Population-based case-control studies (age $\geq 15$ years) [133]                                                                                                                                                                      |                             |                |            |
|                          |                          | Mild AD ( $N=25,898$ cases, 145,373 controls)                                                                                                                                                                                          | 0.8 (0.7–1.0) <sup>a</sup>  |                | <0.05      |
|                          |                          | Severe AD ( $N=2527$ cases, 145,373 controls)                                                                                                                                                                                          | 1.2 (0.9–1.7) <sup>a</sup>  |                | 0.317      |
|                          |                          | ( $N=7937$ cases, 79,370 controls; age $\geq 18$ years) [3]                                                                                                                                                                            | 1.5 (1.3–1.7)               |                | <0.0001    |
|                          |                          | ( $N=372$ cases, 9109 controls; age 18–79 years)[132]                                                                                                                                                                                  |                             | 2 vs. 2        | NS (0.707) |
|                          |                          | Population-based cohort study [ $N=1,18,678$ ; with 2 adult data-bases ( $n=1.2$ million and $n=2990$ ) and a birth-to-adolescent cohort ( $n=2286$ )] [134]                                                                           | 1.0 (1.0–1.1) <sup>c</sup>  |                | NS (0.346) |
|                          |                          | Population-based cross-sectional surveys [128]                                                                                                                                                                                         |                             |                |            |
|                          |                          | ( $N=34,525$ ; age $\geq 18$ years)                                                                                                                                                                                                    | 0.7 (1.3–2.3)               |                | <0.0001    |
|                          |                          | ( $N=27,157$ ; age $\geq 18$ years)                                                                                                                                                                                                    | 1.4 (1.1–1.8)               |                | 0.02       |
|                          |                          | ( $N=4970$ ; age $\geq 20$ years)                                                                                                                                                                                                      | 0.6 (0.2–1.8)               |                | 0.37       |
| Type 2 diabetes mellitus | Inconsistent             | Population-based cross-sectional survey ( $N=259,119$ ; age 30–74 years) [131]                                                                                                                                                         | 0.8 (0.7–1.0)               |                | NA         |
|                          |                          | Population-based case-control study ( $N=30,079$ cases, 148,428 controls; age $\geq 18$ years) [127]                                                                                                                                   | 0.8 (0.7–0.8) <sup>b</sup>  |                | <0.001     |
|                          |                          | Population-based cross-sectional survey ( $N=259,119$ ; age 30–74 years) [131]                                                                                                                                                         | 0.8 (0.7–0.8)               |                | NA         |
|                          |                          | Random sample of patients with type 2 diabetes mellitus age $65.2 \pm 11.4$ years from a single center (cases) and random sample of patients age 18–69 years from a national registry (controls) [ $N=744$ cases, 7931 controls] [138] | 1.7 (1.0–2.9)               |                | 0.045      |
| Autoimmune disease       | Positive                 | <b>Crohn's disease</b>                                                                                                                                                                                                                 |                             |                |            |
|                          |                          | Population-based case-control studies                                                                                                                                                                                                  |                             |                |            |
|                          |                          | ( $N=30,354$ cases, 261,514 controls; age < 18 years) [74]                                                                                                                                                                             | 1.3 (0.9–2.0)               |                | NS         |
|                          |                          | ( $N=282$ cases, 282 controls; age < 17 years) [144]                                                                                                                                                                                   | 2.1 (1.0–4.5)               |                | 0.04       |
|                          |                          | ( $N=48,140$ cases, 1,257,075 controls; age $\geq 18$ years) [75]                                                                                                                                                                      | 1.7 (1.5–1.9)               |                | NA         |
|                          |                          | ( $N=8112$ cases, 40,560 controls; age $\geq 18$ years)[140]                                                                                                                                                                           | 2.1 (1.5–2.9)               |                | <0.001     |
|                          |                          | ( $N=7937$ cases, 79,370 controls; age $\geq 18$ years) [3]                                                                                                                                                                            | 1.7 (1.2–2.3)               |                | 0.0020     |
|                          |                          | Administrative database-based case-control study ( $N=737$ cases, 1997 controls; age < 20 years)[141]                                                                                                                                  | 1.3 (0.8–2.0)               |                | NA         |
|                          |                          | Single-center case-control study ( $N=276$ cases, 276 controls; age 16–45 years) [143]                                                                                                                                                 | 2.8 (1.2–6.4)               |                | 0.014      |
|                          |                          | Population-based cohort study ( $N=49,847$ ; age $\leq 40$ years) [142]                                                                                                                                                                | 1.3 (1.1–1.6) <sup>d</sup>  |                | NA         |
|                          |                          | <b>Ulcerative colitis</b>                                                                                                                                                                                                              |                             |                |            |
|                          |                          | Population-based case-control studies                                                                                                                                                                                                  |                             |                |            |
|                          |                          | ( $N=30,354$ cases, 261,514 controls; age < 18 years) [74]                                                                                                                                                                             | 1.8 (1.1–2.8) <sup>d</sup>  |                | <0.05      |
|                          |                          | ( $N=48,140$ cases, 1,257,075 controls; age $\geq 18$ years) [75]                                                                                                                                                                      | 1.7 (1.50–1.8) <sup>d</sup> |                | NA         |
|                          |                          | ( $N=8112$ cases, 40,560 controls; age $\geq 18$ years)[140]                                                                                                                                                                           | 1.6 (1.3–2.1)               |                | <0.001     |
|                          |                          | ( $N=7937$ cases, 79,370 controls; age $\geq 18$ years) [3]                                                                                                                                                                            | 1.9 (1.5–2.3)               |                | <0.0001    |
|                          |                          | Administrative database-based case-control study ( $N=488$ cases, 1310 controls; age < 20 years) [141]                                                                                                                                 | 1.4 (0.8–2.5)               |                | NA         |
|                          |                          | Population-based cohort study ( $N=49,847$ ; age $\leq 40$ years) [142]                                                                                                                                                                | 1.3 (1.0–1.5) <sup>d</sup>  |                | NA         |
|                          |                          | <b>Celiac disease</b>                                                                                                                                                                                                                  |                             |                |            |
|                          |                          | Prospective descriptive epidemiology study ( $N=351$ ; 'children') [145]                                                                                                                                                               | 4.2 (1.1–15.6)              |                | NA         |

**Table 3** (continued)

| Comorbidity | Direction of association | Supporting studies                                                                                        | AD vs. control             |                |         |
|-------------|--------------------------|-----------------------------------------------------------------------------------------------------------|----------------------------|----------------|---------|
|             |                          |                                                                                                           | Odds ratio (95% CI)        | Prevalence (%) | P value |
|             |                          | Population-based case-control study<br>( <i>N</i> =8112 cases, 40,560 controls; age ≥ 18 years) [140]     | 5.2 (2.9–9.2)              |                | <0.001  |
|             |                          | <b>Alopecia areata</b>                                                                                    |                            |                |         |
|             |                          | Meta-analysis of observational studies ( <i>N</i> =17 studies; all ages) [146]                            | 2.6 (2.3–2.9)              |                | <0.001  |
|             |                          | Population-based case-control studies<br>( <i>N</i> =30,354 cases, 261,514 controls; age < 18 years) [74] | 2.3 (1.8–3.1) <sup>a</sup> |                | <0.05   |
|             |                          | ( <i>N</i> =48,140 cases, 1,257,075 controls; age ≥ 18 years) [75]                                        | 3.3 (3.0–3.7) <sup>a</sup> |                | NA      |
|             |                          | ( <i>N</i> =8112 cases, 40,560 controls; age ≥ 18 years)[140]                                             | 26.3 (14.5–47.8)           |                | <0.001  |

CVD cardiovascular disease, NA not available, NS not significant

<sup>a</sup>Rate ratio

<sup>b</sup>Hazard ratio

<sup>c</sup>Relative risk

<sup>d</sup>Risk ratio

## 8 Malignancy

While some data suggest reduced rates of malignancy with allergic disorders, [153–155] the direction of the allergic disease–malignancy relationship, if any, varies for individual allergic disorders and specific cancer sites and types [153, 156–158]. Overall, AD appears to be protective for malignancy [3, 154, 159] (Table 4). The activated immune system of allergic disorders may be accompanied by enhanced immune surveillance, and thus a reduced risk of cancer; thymic stromal lymphopoietin, and other markers of Th2 inflammation has been suggested to play important inhibitory roles in a number of cancers, including breast, pancreatic, and melanoma [160]. In contrast, chronic Th2 inflammation associated with AD could be associated with an increased risk of cancer [161, 162].

Atopic dermatitis is associated with lymphoma overall [163–165] (Table 4), and the risk increases with AD severity [163, 164]. In cohort studies, the relative risk of lymphoma was increased with AD, while in case-control studies no significant risk of lymphoma is evident [163]. There may be a slight increase in lymphoma risk in patients with AD, with severity being a significant risk factor. Studies designed to assess the risk of non-Hodgkin lymphoma in AD have failed to yield consistent results [156, 166–169]. A history of AD has been associated with an increased risk of T-cell non-Hodgkin lymphoma, [166, 170, 171] primarily attributable to an increased incidence of cutaneous T-cell lymphoma (CTCL) and the peripheral T-cell lymphoma angioimmunoblastic subtype [166]. Wang et al. [170] and Aschebrook-Kilfoy et al. [171] found similarly increased risks for CTCL and peripheral T-cell lymphoma in their studies, respectively. The observed

association between AD and CTCL may be owing in part to the frequent misdiagnosis of CTCL as AD [164, 166].

Data for the risk of other skin cancers associated with AD are inconsistent. Wang and Diepgen [167] did not observe a consistent association between AD and non-melanoma skin cancer based on the only two studies available at the time of their study. Since then, four additional studies have demonstrated an association; [159, 165, 172, 173] however, this finding was not universal [174]. The risk of actinic keratosis, precursors to squamous cell carcinoma, has been found to be increased in AD, particularly in individuals with filaggrin mutations; [175] however, this is not a universal finding [176]. One study has found AD to be a risk factor for melanoma, [159] while others have found no association, [165, 172, 173, 177, 178] but meta-analyses have been hampered by the methodological differences among studies, particularly related to the inclusion of highly varied age groups. It is possible that increased AD/pruritus related to heat and sweating decreases sun exposure, nevus numbers, [172, 179] and skin cancer risk.

## 9 Conclusions

Patients with AD appear to be at increased risk for certain infections and mental health conditions, with growing evidence of a relationship with obesity, several autoimmune diseases and, particularly in adults, cardiovascular disease and specific cancers. The causative mechanisms underlying these associations are largely unknown, and the absolute magnitude of the risks has not been well defined. Nevertheless, physicians should be aware of these potentially

**Table 4** Studies investigating an association between atopic dermatitis (AD) and malignancy listed in order of strength of evidence

| Comorbidity                 | Direction of association | Supporting studies                                                                                                                  | AD vs. controls                             |                            |         |
|-----------------------------|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|----------------------------|---------|
|                             |                          |                                                                                                                                     | Odds ratio (95% CI)                         | Incidence ratio (95% CI)   | P value |
| Overall malignancy          | Inverse/pro-<br>tective  | Population-based case-control study<br>( <i>N</i> = 7937 cases, 79,370 controls; age ≥ 18 years) [3]                                | 1.2 (1.1–1.3)                               |                            | 0.0002  |
|                             |                          | Population-based cohort studies<br>( <i>N</i> = 4,456,008; all ages) [159]                                                          |                                             | 0.8 (0.7–0.8) <sup>a</sup> | NA      |
|                             |                          | ( <i>N</i> = 34,263; all ages) [154]                                                                                                |                                             | 1.0 (0.9–1.1)              | NA      |
|                             |                          |                                                                                                                                     |                                             |                            |         |
| Lymphoma                    | Positive                 | Systematic review and meta-analysis of case-control and cohort studies<br>( <i>N</i> = 24 studies; all ages) [163]                  | 1.2 (0.9–1.5) to 1.4 (1.1–1.8) <sup>b</sup> |                            |         |
|                             |                          | Systematic review of case-control and cohort studies<br>( <i>N</i> = 19 studies; all ages) [164]                                    | 0.7 (0.5–1.0) to 1.8 (1.3–2.4) <sup>c</sup> |                            | NA      |
|                             |                          | Population-based case-control study<br>( <i>N</i> = 8112 cases, 40,560 controls; ‘adults’) [165]                                    | 1.9 (1.4–2.4)                               |                            | <0.0001 |
|                             |                          |                                                                                                                                     |                                             |                            |         |
| Non-Hodgkin lymphoma        | Inconsistent             | Systematic reviews<br>( <i>N</i> = 5 studies; all ages) [167]                                                                       | 0.5 (0.3–0.7) to 1.9 (0.6–5.8) <sup>b</sup> |                            | NA      |
|                             |                          | ( <i>N</i> = 8 studies; all ages) [168]                                                                                             | 0.5 (0.3–0.7) to 1.9 (0.6–5.8)              |                            | NA      |
|                             |                          | Population-based cohort study<br>( <i>N</i> = 16,539; ‘adults’) [169]                                                               | 1.3 (0.6–2.6) <sup>c</sup>                  |                            | NA      |
|                             |                          | Pooled analyses of case-control studies<br>( <i>N</i> = 20 studies; <i>N</i> = 17,471 cases, 23,096 controls; age ≥ 16 years) [156] | 1.0 (0.9–1.1)                               |                            | NA      |
| T-cell non-Hodgkin lymphoma | Positive                 | ( <i>N</i> = 13 studies, 13,535 cases, 16,388 controls; age ≥ 16 years) [166]                                                       | 1.0 (0.9–1.3)                               |                            | NA      |
|                             |                          | Pooled analyses of case-control studies<br>( <i>N</i> = 13 studies, 13,535 cases, 16,388 controls; age ≥ 16 years) [166]            | 1.9 (1.4–2.6)                               |                            | NA      |
|                             |                          | ( <i>N</i> = 15 studies, 584 cases, 15,912 controls; all ages) [170]                                                                | 1.4 (1.1–1.9)                               |                            | 0.02    |
|                             |                          | ( <i>N</i> = 14 studies, 324 cases, 17,217 controls; all ages) [171]                                                                | 2.4 (1.7–3.3)                               |                            | NA      |
| Non-melanoma skin cancer    | Inconsistent             | <b>Non-melanoma skin cancer overall</b>                                                                                             |                                             |                            |         |
|                             |                          | Systematic review<br>( <i>N</i> = 2 studies; all ages) [167]                                                                        | 0.8 (0.6–1.0) to 1.8 (0.8–3.9) <sup>b</sup> |                            | NA      |
|                             |                          | Population-based case-control study<br>( <i>N</i> = 8112 cases, 40,560 controls; ‘adults’) [165]                                    | 2.1 (1.7–2.6)                               |                            | <0.0001 |
|                             |                          | Population-based cohort study<br>( <i>N</i> = 4,456,008; all ages) [159]                                                            |                                             | 1.5 (1.3–1.7)              | NA      |
|                             |                          | <b>Basal cell carcinoma</b>                                                                                                         |                                             |                            |         |
|                             |                          | Systematic review and meta-analysis<br>( <i>N</i> = 9 studies; median age 6–72 years) [172]                                         | 3 (1.0–1.8) <sup>c</sup>                    |                            | NA      |

**Table 4** (continued)

| Comorbidity | Direction of association | Supporting studies                                                                                                           | AD vs. controls            |                          |                |
|-------------|--------------------------|------------------------------------------------------------------------------------------------------------------------------|----------------------------|--------------------------|----------------|
|             |                          |                                                                                                                              | Odds ratio (95% CI)        | Incidence ratio (95% CI) | P value        |
| Melanoma    | Inconsistent             | Population-based case-control study<br>( <i>N</i> = 375 cases, 251 controls; age 25–74 years at skin cancer diagnosis) [174] | 1.5 (0.8–3.0) <sup>d</sup> |                          | NS<br>(> 0.05) |
|             |                          | Population-based cohort study<br>( <i>N</i> = 31,330; all ages) [173]                                                        |                            | 1.4 (1.1–1.8)            | NA             |
|             |                          | <b>Squamous cell carcinoma</b>                                                                                               |                            |                          |                |
|             |                          | Systematic review and meta-analysis<br>( <i>N</i> = 9 studies; median age 6–72 years) [172]                                  | 1.9 (0.7–4.9) <sup>e</sup> |                          | NA             |
|             |                          | Population-based case-control study<br>( <i>N</i> = 254 cases, 432 controls; age 25–74 years at skin cancer diagnosis) [174] | 1.8 (1.0–3.5)              |                          | NS<br>(> 0.05) |
|             |                          | Population-based cohort study<br>( <i>N</i> = 31,330; all ages) [173]                                                        |                            | 2.5 (1.0–5.1)            | NA             |
|             |                          | Systematic review and meta-analysis<br>( <i>N</i> = 8 studies; median age 6–61 years) [172]                                  | 0.8 (0.4–1.4) <sup>e</sup> |                          | NA             |
|             |                          | Population-based case-control study<br>( <i>N</i> = 8112 cases, 40,560 controls; ‘adults’) [165]                             | 1.4 (1.0–1.9)              |                          | NS<br>(0.0791) |
|             |                          | Practice-based case-control study<br>( <i>N</i> = 184 cases, 169 controls; all ages) [177]                                   | 1.1 (0.5–2.2) (unadjusted) |                          | NA             |
|             |                          | Population-based cohort studies<br>( <i>N</i> = 4,456,008; all ages) [159]                                                   |                            | 1.7 (1.3–2.4)            | NA             |
|             |                          | ( <i>N</i> = 31,330; all ages) [173]                                                                                         |                            | 0.6 (0.3–1.0)            | NA             |
|             |                          | Practice-based cohort study<br>( <i>N</i> = 6280; all ages) [178]                                                            |                            | 0.5 (0.3–1.4)            | NS (0.08)      |

CI confidence interval, NA not available, NS not significant

<sup>a</sup>Excluding non-melanoma skin cancer

<sup>b</sup>Odds ratio or relative risk

<sup>c</sup>Relative risk

<sup>d</sup>Early onset (age < 50 years) basal cell carcinoma

<sup>e</sup>Rate ratio

under-recognized non-allergic comorbidities, proactively identify them, and address them. Effective AD management may mitigate the risk for these costly and burdensome comorbidities.

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each draft of the manuscript and approved the final version for submission. ST reviewed included articles for appropriateness, critically reviewed each draft of the manuscript, and approved the final version for submission. JDD critically reviewed each draft of the manuscript and approved the final version for submission. SRF reviewed included articles for appropriateness, critically reviewed each draft of the manuscript, and approved the final version for submission. ARC critically reviewed each draft of the manuscript and approved the final version for submission. GS reviewed the included literature for odds ratios, reviewed and edited the manuscript, and approved the final version for submission. LE reviewed the literature related to malignancy comorbidities, critically reviewed each draft, and approved the final version as submitted.

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