DRAFT

Guidelines on comorbidities associated with atopic dermatitis

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- service as a member of a speaker bureau, consultant, advisory board, for pharmaceutical companies on atopic dermatitis or atopic dermatitis drugs in development or FDA-approved.
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Disclaimer

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care or be deemed inclusive of all proper methods of care, nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biologic behavior of the disease. This guideline reflects the best available data at the time the guideline

was prepared. The results of future studies may require revisions to the recommendations in this guideline to reflect new data.

Abstract

Background: Studies found associations between atopic dermatitis (AD) and many comorbidities.

Objective: To appraise evidence of the association between AD and comorbidities among adults.

Methods: Our multidisciplinary work group conducted a systematic review of the association between AD and selected comorbidities. We applied the GRADE for prognosis approach for assessing the certainty of the evidence, providing statements of association based on the available evidence.

Results: Analysis of the evidence resulted in 32 statements. Clear evidence of the association of AD in adults and select allergic, atopic, immune-mediated, mental health, bone health, and skin infections was identified. There is some evidence supporting an association between AD and substance use, ADHD, and elements of metabolic syndrome. Evidence suggests a small association with various cardiovascular conditions. The association between AD in adults and autism spectrum disorders, myocardial infarction, stroke, and metabolic syndrome is uncertain.

Limitations: This analysis is based on the best available evidence at the time it was conducted. This guideline does not make recommendations for screening or management of comorbidities in adults with AD.

Conclusions: Clinicians should be aware of comorbidities associated with AD. Further research is needed to determine whether screening or management of comorbidities is beneficial for adults with AD.

Abbreviations Used

AAD: American Academy of Dermatology
AD: atopic dermatitis
ADHD: attention deficit hyperactivity disorder
CI: confidence interval
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
HR: hazard ratio
OR: odds ratio
RR: risk ratio

Scope and objectives

This guideline addresses the association between atopic dermatitis (AD) and other medical conditions (comorbidities) among adults. Reported comorbidities include other atopic or allergic conditions, infections, autoimmune diseases, mental health disorders, metabolic conditions, and cardiovascular disease. The objective of this guideline is to appraise the evidence for the association between AD and comorbid conditions, with the aim of improving awareness and understanding among dermatologists and other clinicians. Importantly, this guideline does not make recommendations for screening or management of comorbidities in adults with AD.

The target population of this guideline includes adults aged 18 years and older with AD of any severity in any healthcare setting or context. The exposure of interest is AD and, when possible, we compare the incidence or prevalence of comorbidities with the general population or other relevant populations. Outcomes are the incidence and prevalence of select comorbid conditions (**Table I**).

Methods

Our multidisciplinary work group conducted a systematic review of the evidence of the association between AD and selected comorbid conditions (**Table 1**), and employed the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) for prognosis approach for assessing the certainty of the evidence.[1-4] The Work Group drafted statements regarding the association between AD and comorbid conditions based on the evidence and by considering the following: the strength of the estimated association between AD and a selected comorbid condition and the overall quality of the evidence of association. The implications of the wording of statements of association as a reflection of the strength of association and quality of evidence are summarized in **Table II**.

For detailed methodology, see **Appendix 1**.

Definition

AD (also known as atopic eczema) is a chronic, pruritic inflammatory skin disease that occurs most frequently in children, but also affects many adults. It follows a relapsing course. AD is often associated with a personal or family history of allergic rhinitis and asthma.

Introduction

AD is a burdensome condition with significant impacts on quality of life, overall health, and health system utilization.[5, 6] In addition to AD itself, the patient- and population-level burden of disease is increased by associated comorbidities. Associations between AD and other atopic and allergic conditions have been recognized for decades and even contribute to diagnostic criteria for AD.[7, 8] More recently studies examined links between AD and autoimmune,[9] metabolic,[10, 11] cardiovascular[12] and mental health comorbidities.[13] This section of the guidelines reviews the evidence for potential comorbidities of AD in adults (**Table III**). For select comorbidities with supporting evidence, we evaluate whether the association is modified by the severity of AD.

Atopic and allergic conditions

Asthma

The association of AD and asthma is well established. While not proven, the atopic march theory has biologic plausibility and may partly explain the association.[14] This theory posits that epidermal barrier disruption associated with AD leads to epicutaneous allergen sensitization and inflammation with consequent immune response at other epithelial surfaces, including the gastrointestinal tract (food allergy), upper respiratory tract (allergic rhinitis), and lower respiratory tract (asthma).[14] Longitudinal studies have found that among patients with atopic multimorbidity, AD does not usually precede other atopic comorbidities, suggesting that shared genetic factors and environmental exposures beyond barrier disruption are important.[15, 16]

In our meta-analysis, we found the pooled prevalence of asthma in adults with AD to be 24.8% (95% confidence interval [CI] 22.2%- 27.5%), but with substantial heterogeneity across studies. Additionally, adults with AD are 3 times as likely to have asthma compared with the general population (**e-Table 1**). More severe AD appears to have a stronger association with asthma than mild or moderate AD. In a cross-sectional population-based survey, having severe AD defined by Patient Oriented Eczema Measure scores had a relative risk of 2.38 (95% CI 1.91-2.85) for asthma compared to the participants without AD, with small relative risk seen with moderate (Risk ratio [RR] 1.04, 95% CI 1.66-2.21) and mild AD (RR 1.34, 95% CI 1.12-1.56).[17]

The association between AD and asthma may have implications for clinical practice. In the Avon Longitudinal Study of Parents and Children, having asthma by age 7 or 13 years was associated with a more persistent AD phenotype.[18] This may be helpful in counseling patients about the likelihood their AD will persist into adulthood. Targeted therapies that are effective for both severe AD and asthma, such as dupilumab, may be considered for patients with both conditions.[19, 20]

Food allergy

We found clear evidence that adult AD is associated with food allergy, but our estimate of the prevalence of food allergy among adults with AD (11%, 95% CI 6-16%) is limited by significant heterogeneity across studies (**e-Table 2**). The heterogeneity is likely related to different definitions of food allergy used in those studies, including different foods and use of self-report, physician diagnosis, or administrative codes. As with asthma, there appears to be a relationship between the severity of AD and IgE mediated food allergy, with the odds of having food allergy compared to the general population increasing from mild (RR 1.48, 95% CI 0.89 - 2.07), to moderate (RR 2.40, 95% CI 1.54 - 3.27), to severe (RR 8.49, 95% CI 5.44-11.54) AD.[17]

The clinical implications of the association between AD and food allergy are unclear. Anecdotally, patients often ask whether food allergies are a trigger for their AD and whether testing is indicated. A James Lind Priority Setting exercise identified "What role might food allergy tests play in treating eczema?" as a top-10 priority research question for AD.[21] At present, we are unaware of evidence to suggest the presence or severity of AD in adults is an indication for screening for food allergy without a history suggestive of an immediate hypersensitivity reaction to food. Additionally, there is no evidence that either screening for food allergy or avoidance of identified allergens impacts AD severity in adults.[22] There are plans to conduct a randomized controlled trial examining the impact of food allergy screening in children with AD,[23] but we are unaware of similar pending investigations in adults.

Allergic rhinitis, conjunctivitis, and eosinophilic esophagitis

Though not as extensively studied as the association with asthma, allergic rhinitis (sometimes referred to as hay fever) is a recognized common comorbidity of AD and is a component of some diagnostic criteria for AD.[7, 8] Our systematic review identified few studies that systematically report on the prevalence of allergic rhinitis in adults with AD. In studies comparing the prevalence or incidence of allergic rhinitis between AD and the general population or general clinic population controls, AD was consistently associated with allergic rhinitis, but the magnitude of the association varied widely across different study designs and populations (**e-Table 3**). While it is logical to assume that allergic conjunctivitis (which is often associated with rhinitis or "allergic rhinocunjunctivitis") and eosinophilic esophagitis would also be associated with AD, we found little evidence to support those associations (**e-Tables 4 & 5**). This does not imply that a relationship is unlikely (i.e., not evidence of absence), but rather points to a lack of existing studies (i.e., absence of evidence).

Immune-mediated conditions

The pathogenesis of AD is primarily rooted in a feedback loop of skin barrier dysfunction and an aberrant immune response leading to inflammation.[24] While a genetic predisposition to barrier dysfunction may be the inciting event for many people with AD, multiple immune-related genes have also been associated with AD.[25] This may, at least in part, explain the association between AD and various autoimmune conditions; in a Danish population-based study, AD was associated with 2.5 times the odds of having any autoimmune condition and 3.5 times the odds of having two or more autoimmune conditions compared to the general population.[26]

Alopecia areata

Epidemiologic studies consistently show an association between AD and alopecia areata.[27] In the Danish study mentioned above, the adjusted odds ratio (OR) for the association between AD and alopecia areata was 26.31 (95% CI 14.48-47.80) (**e-Table 6**).[26] While some of the strength of that association may be related to diagnostic bias (i.e., dermatologists treating patients for one of those diagnoses are more likely to make a formal, coded diagnosis of the other condition), the association is likely valid. There is also a widespread belief that AD portends a worse prognosis for alopecia areata in terms of the severity and response to treatment, but studies are limited. In an alopecia areata registry study, having atopic dermatitis was associated with a higher likelihood of having alopecia totalis or universalis (OR 1.24, 95% CI 0.95-1.61).[28] While there are currently no targeted systemic treatments approved for alopecia areata, dupilumab was posited as a potential treatment option.[29] Conversely, dupilumab was also reported to cause new-onset alopecia areata.[29] Janus Kinase (JAK) inhibitors show promise for both AD and alopecia areata but are not yet approved in North America for either indication.[30]

Urticaria

As discussed above, AD is associated with food allergy, which commonly manifests as acute urticaria. AD is also associated with chronic idiopathic urticaria (**e-Table 7**). A Danish study on autoimmune conditions demonstrated a strong association between chronic urticaria and AD (OR 9.92, 95%CI 6.43- 15.32).[26] A cohort study, also from Denmark, found individuals diagnosed with chronic urticaria were more likely to have a subsequent diagnosis of AD (Hazard Ratio

(HR) 3.1, 95% CI 2.0-4.8).[31] This association has clinical relevance, as itch associated with chronic urticaria may potentiate the itch-scratch cycle of AD, leading to worsening of dermatitis. Omalizumab, an anti-IgE monoclonal antibody that is effective for chronic idiopathic urticaria, was studied in randomized controlled trials for the treatment of AD in children with mixed results.[32, 33]

Mental health and substance use

Depression, anxiety, and self-harm

Adults with AD are more likely to have symptoms of depression and anxiety and to be diagnosed with depressive or anxiety disorders.[13, 34] In our analysis pooling four studies, including 11,244 adults with AD and 149,713 controls, AD was associated with double the odds of self-reported or clinician-diagnosed depression (OR 1.99, 95% CI 1.53-2.59) (**e-Table 8**). The association with anxiety is similar; pooling four studies with 157,222 adults with AD and 300,719,113 controls, the OR was 1.40 (95% CI 1.12-1.75) (**e-Table 9**).

While we found high-certainty evidence that adults with AD are more likely to have suicidal ideation than adults without AD (OR 1.71, 95% CI 1.43-2.03), there is lower certainty and conflicting evidence supporting a potential association with death from suicide, with one case-control and one cohort study finding a modest increase in suicide among adults with AD,[35, 36] and other case-control and cohort studies finding non-significant decreases in suicide (**e-Table 10**).[37, 38]

The reasons for the association between AD, depression, and anxiety are unclear; one possible explanation is the psychosocial burden of AD. Itch, poor sleep, and decreased overall quality of life may lead to symptoms of depression and anxiety. The notion that uncontrolled symptoms of AD adversely impact mental health is supported by results from clinical trials in moderate-to-severe AD, which demonstrate substantial decreases in symptoms of depression and anxiety associated with improvement of skin disease.[39, 40]

Substance Use

There is limited evidence to support a potential association between AD and alcohol use disorders or cigarette smoking (**e-Tables 11 and 12**). A Danish population-based study found alcohol abuse was more common among adults with AD (OR 1.38, 95% CI 1.24-1.53), and a US population-based survey found adults with AD were more likely to have moderate (OR 1.33, 95% CI 1.09-1.62) and heavier (OR 1.58, 95% CI 1.23-2.03) alcohol intake than controls.[41, 42] In a US population-based survey, AD was associated with having smoked ≥100 cigarettes (OR 1.32, 95% CI 1.18-1.47) and being a current smoker (OR 1.28, 95% CI 1.12-1.45).[43]

Most studies of the association between alcohol use and smoking are cross-sectional, making causality difficult to determine. As with depression and anxiety, an association could be explained by the burden of AD increasing patients' likelihood of engaging in those harmful behaviors. Conversely, chemical irritants in cigarette smoke could increase the likelihood of developing AD in someone predisposed, similar to the association seen between environmental

pollutants and AD.[44, 45] In one cohort study that assessed preceding cigarette smoking and the development of AD among US nurses, no association was found.[46]

Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorders

Associations between AD and ADHD and autism spectrum disorders are better studied in children than adults, and the association in children will be covered in the forthcoming Pediatric Atopic Dermatitis Clinical Practice Guideline. We found only two studies examining the association with ADHD in adults, only one of which had controls from the general population (**e-Table 13**).[47, 48] That US population-based study found an association between AD and ADHD among adults (OR 1.61, 95% CI 1.25-2.06). The only study that compared the prevalence of autism spectrum disorders among adults with AD to adults with non-AD dermatologic conditions found a positive association; however, confidence intervals were very wide, preventing any definitive conclusions (**e-Table 14**).[47]

Cardiovascular diseases

Systemic inflammation is an established risk factor for cardiovascular disease and targeting inflammation can decrease the risk of cardiovascular events.[49] Therefore, inflammatory skin diseases may be potentially modifiable cardiovascular risk factors. Psoriasis is the best-studied inflammatory skin disease with regards to cardiovascular risk, with a large body of evidence supporting psoriasis as an independent cardiovascular risk factor.[50] Recent research has focused on a potential link between AD and cardiovascular disease. Vascular inflammation and markers of atherosclerosis were shown to correlate with markers of Th2 inflammation in the skin and blood of patients with AD, and AD patients have increased levels of proteins associated with cardiovascular risk.[51, 52]

Epidemiologic evidence is mounting for small associations between AD and hypertension, peripheral and coronary artery disease, congestive heart failure, and acute events such as myocardial infarction and cardiovascular death (**e-Tables 15 to 21**). In general, the associations are not as strong as those seen with psoriasis, which is why we have added qualifying remarks on the strength of association to some of our statements (**Table III**). For example, in our meta-analysis of the occurrence of hypertension in adults with AD compared with controls, the OR was 1.06 (95% CI 1.00-1.13). When pooling cohort studies for the association between AD and congestive heart failure, the HR was 1.25 (95% CI 1.03-1.53).

In the case of myocardial infarction, stroke, congestive heart failure and cardiovascular death, there may be a severity gradient, with uncertain risk for adults with mild AD but potentially an increased risk in adults with severe AD. In a UK cohort study, AD severity gradients were seen for: i) myocardial infarction (mild AD, HR 1.00, 95% CI 0.91-1.10; moderate AD, HR 1.07, 95% CI 0.97-1.18; severe AD, HR 1.37, 95% CI 1.12-1.68); ii) stroke (mild AD, HR 1.06, 95% CI 0.97-1.15; moderate AD, HR 1.09, 95% CI 1.00-1.20; severe AD, HR 1.20, 95% CI 0.99 - 1.46); iii) congestive heart failure (mild AD, HR1.12, 95%CI 1.02-1.24; moderate AD, HR 1.20, 95% CI 1.09- 1.33; severe AD, HR 1.67, 95% CI 1.36-2.05) and iv) cardiovascular death (mild AD, HR 0.90, 95% CI 0.89-0.98; moderate AD, HR 1.01, 95% CI 0.93-1.10; severe AD, HR

1.30, 95% CI 1.10-1.53).[53] It should be noted that treatment is frequently used as a proxy to define AD severity in epidemiologic studies, including in the aforementioned UK study. The clinical implications of these associations are unclear. At this point, there is no evidence for increased cardiovascular screening or treatment for people with AD beyond what is recommended for the general population. The modestly increased risk of deep vein thrombosis (OR 1.22, 95% CI 1.17-1.27) and pulmonary embolism (OR 1.08, 95% CI 1.02-1.15) associated with AD may have implications for interpreting pharmacovigilance studies for JAK inhibitors, which have black box warnings from the FDA for thrombosis based on their use in other conditions. To date, trials in AD did not demonstrate an increased risk for venous thromboembolism.[54-60]

Metabolic disorders

As with cardiovascular risk, current evidence points to a small association between adult AD and obesity and dyslipidemia. Pooling data from eight cross-sectional studies, we found AD was associated with 36% increased odds of obesity (OR 1.36, 95% CI 1.01-1.83) and 13% increased odds of hypercholesterolemia (OR 1.13, 95% CI 1.09-1.18), compared to the general population (**e-Tables 22 and 23**). It is unclear whether the association with obesity is accentuated in adults with more severe AD. In a Spanish study, the prevalence of obesity ranged from 13.6% in people with mild AD to 32.9% in people with severe AD.[61] Conversely, a study using data from the UK found small associations between AD severity and obesity in those with mild (OR 1.06, 95% CI 1.05-1.07) and moderate (OR 1.14, 95% CI 1.13-1.16) AD but not with severe AD (OR 1.00, 95% CI 0.96-1.03).[62] The association may vary by geography; a meta-analysis found significant associations between AD and obesity in studies conducted in North America and Asia, but not in Europe.[10]

Interestingly, AD may have an inverse association with diabetes (**e-Table 24**). We found AD was associated with a lower risk of diabetes overall (OR 0.89, 95% CI 0.80-0.99) and type 2 diabetes specifically (OR 0.83, 95% CI 0.76-0.90). Only two studies compared the prevalence of metabolic syndrome as a whole in people with and without AD (**e-Table 25**). A cross-sectional study[63] from Israel found metabolic syndrome to be less prevalent in people with AD, while a study from Korea found an increased risk of metabolic syndrome in women with AD but not men.[64]

Bone health

In a Taiwanese study, AD was associated with an increased risk of developing osteoporosis (HR 4.72, 95% CI 3.68-6.05) (**e-Table 26**).[65] In a UK cohort study, the risk for fracture associated with AD was modestly elevated overall (HR 1.07, 99% CI 1.05-1.09) and somewhat higher for patients with more severe AD (HR 1.22, 99% CI 1.14 -1.30) (**e-Table 27**).[66] Furthermore, the risk was much higher for fractures related to osteoporosis, with severe AD associated with a 200%, 66%, and 50% increased rates of spinal, pelvic, and hip fractures, respectively.[66]

There are several potential explanations for an association between AD, osteoporosis, and fractures. Chronic systemic inflammation can lead to aberrant bone metabolism and increased bone loss.[67-69] On average, patients with AD are more likely to be deficient in vitamin D.[70] Sleep disturbance may interact with AD to increase the risk of traumatic injury in general.[71] Oral

corticosteroids are a risk factor for fractures, and are commonly used to treat severe AD flares.[72-74] Whether topical corticosteroids increase fracture risk is unclear, though a recent study from Denmark found increased fracture risk associated with high cumulative use of potent topical corticosteroids.[75]

To inform potential preventative strategies for fractures in people with AD, further research is required to elucidate the true mechanism of the association, particularly the role of oral corticosteroids. Patients prescribed oral corticosteroids for AD may be candidates for concomitant bisphosphonate therapy if they meet established risk thresholds (e.g., oral corticosteroid use with a cumulative dose equivalent to ≥3 months of ≥5-7.5 mg daily of prednisone).[76-78]

Skin infection

The association of AD with staphylococcal skin infections is well known and included in some AD diagnostic criteria.[7] Herpes superinfection (eczema herpeticum) is a more severe complication of AD[79] and a UK cohort study found HSV infections to be more than twice as common among people with AD compared to general population controls.[80] Based on US hospitalization data, AD is also associated with serious cutaneous infections (defined as leading to hospitalization), requiring treatment in an inpatient setting, or is life-threatening) (OR 4.62, 95% CI 4.51-4.74) (**e-Table 28**). Bacterial skin infections and eczema herpeticum are more likely to occur with poorly controlled dermatitis and a meta-analysis found that targeted treatment with dupilumab may decrease the incidence of these infections in patients with moderate-to-severe disease.[81]

Associations with other cutaneous infections are less well-described, but AD is also associated with increased prevalence of verrucae and dermatophyte infections compared to the general population.[80]

Patient education

Individualized management of and shared decision making for AD should incorporate an awareness and consideration of comorbidities. Discussing the relationship of various comorbidities with AD can empower patients to better understand their skin condition and overall health and enable them to make treatment decisions that are best for them. Dermatologists can play an active role improving the overall health and health-related quality of life of people with AD, and patients should also be encouraged to consult with primary care practitioners to address comorbidities beyond the scope of dermatologic practice.

Pediatric considerations

Children with AD can also be affected by its comorbidities. Considerations specific to the pediatric AD population will be addressed in the pediatric section of these guidelines.

Gaps in research

To date, research on AD-associated comorbidities has focused on identifying potential associations in epidemiologic studies. There is currently no conclusive evidence demonstrating that screening for comorbid conditions associated with AD improves patient outcomes. For the evidence of AD associations to be put into action, research is required on whether screening or

management of these comorbidities among adults with AD beyond what is recommended for the general population is beneficial. Research is underway to understand the role of food allergy screening in children with atopic dermatitis.[23] Systematic investigations to understand the mechanisms underlying comorbidities and whether screening or treatment for depression, cardiovascular disease, or fracture risk, are needed.

501 **Table I. Clinical questions.**

Among adults, what is the association between AD and…
Atopic and allergic conditions
Asthma
Food allergy
Allergic rhinitis
Allergic conjunctivitis
Eosinophilic esophagitis
Immune-mediated conditions
Alopecia areata
Urticaria
Mental health and substance use
Depression
Anxiety
Suicide
Alcohol use disorders
Cigarette smoking
ADHD
Autism spectrum disorders
Cardiovascular disease
Coronary artery disease
Congestive heart failure
Peripheral artery disease
Thromboembolic disease
Myocardial infarction
Stroke
Cardiovascular death
Hypertension
Metabolic disorders
Diabetes
Dyslipidemia
Obesity
Metabolic syndrome
Bone health
Osteoporosis
Bone fractures
Skin infection

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503 **Table II. Strength of statements and supporting evidence: Wording and implications.**

Statement Wording	Overall Quality of Supporting Evidence	Implication
Is associated…Is not associated	High or Moderate	Important large effect or clear evidence of no association.

Probably associated…Probably not associated	High or Moderate	Moderate effect or unimportant small effect.
May be associated…may not be associated	Low	Large, moderate, or small effect based on low quality evidence.
Uncertain association	Any Quality	Any magnitude of effect from very low quality evidence or imprecise or inconsistent effect estimates from evidence of any quality.
Strength of Evidence	**Wording**	**Implication[1, 2, 4]**
High	"high quality evidence"	Very confident that the true magnitude of association lies close to that of the estimate.
Moderate	"moderate quality evidence"	Moderately confident in the estimate of association, but there is a possibility that it is substantially different.
Low	"low quality evidence"	Confidence in the estimate is limited; the true magnitude of association may be substantially different from the estimate.
Very Low	"very low quality evidence"	The estimate is very uncertain; the true magnitude of association may be substantially different from the estimate.

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505 **Table III. AD comorbidity statements.**

No.	Statement	Evidence
Atopic & Allergic Conditions		
1.0	AD in adults is associated with asthma (moderate quality evidence)	17, 61, 73, 82-109
1.1	Greater AD severity is associated with increasing asthma prevalence (moderate quality evidence)	17
1.2	AD in adults is associated with food allergies (high quality evidence)	17, 87, 89, 101, 110-116
1.3	Greater AD severity is associated with increasing food allergy prevalence (moderate quality evidence)	17
1.4	AD in adults is associated with allergic rhinitis (moderate quality evidence)	47, 83, 106, 107, 117-122
1.5	The association between AD in adults and allergic conjunctivitis is uncertain (low quality evidence)	47, 106
1.6	AD in adults may be associated with eosinophilic esophagitis (low quality evidence)	123-126
Immune-mediated Conditions		
2.0	AD in adults is associated with alopecia areata (moderate quality evidence)	26, 127-129
2.1	AD in adults is associated with urticaria (moderate quality evidence)	26, 31, 84, 107, 130, 131

Mental Health & Substance Use		
3.0	AD in adults is associated with clinician-diagnosed depression (moderate quality evidence)	34, 38, 47, 83, 98, 108, 132-143
3.1	AD in adults is associated with clinician-diagnosed anxiety (moderate quality evidence)	34, 38, 47, 83, 108, 132-137, 139, 140, 142, 144
3.2	AD in adults may be associated with suicide (low quality evidence)	35-38, 47, 134, 135, 138, 140, 142, 145
3.3	AD in adults may be associated with alcohol abuse disorders (low quality evidence)	43, 61, 136, 146-149
3.4	AD in adults may be associated with cigarette smoking (low quality evidence)	43, 46, 61, 90, 136, 148
ADHD & Autism Spectrum Disorders		
4.0	AD in adults may be associated with ADHD (low quality evidence)	47, 150
4.1	The association between AD in adults and autism spectrum disorders is uncertain (very low certainty evidence)	47
Cardiovascular Diseases		
5.0	AD in adults is probably associated with hypertension (moderate quality evidence) *Remark*: The evidence suggests a small magnitude of association between AD and hypertension in adults.	17, 43, 61, 63, 83, 89, 90, 98, 136, 151-160
5.1	AD in adults is probably associated with coronary artery disease (moderate quality evidence) *Remark:* The evidence suggests a small magnitude of association between AD and CAD in adults.	53, 98, 104, 156, 157, 159-161
5.2	AD in adults is probably associated with peripheral artery disease (moderate quality evidence) *Remark:* The evidence suggests a small to moderate magnitude of association between AD and peripheral artery disease in adults, with greater AD severity associated with a greater magnitude of association.	157, 159, 161
5.3	The association between AD in adults and myocardial infarction is uncertain (low quality evidence)	53, 102, 104, 136, 152, 153, 156, 157, 159, 161-163
5.4	Severe AD in adults may be associated with myocardial infarction (low quality evidence)	53, 136, 156, 159, 162
5.5	The association between AD in adults and stroke is uncertain (very low quality evidence)	53, 102, 104, 136, 152, 153, 156, 157, 159-162, 164

5.6	AD in adults is probably associated with congestive heart failure (moderate quality evidence) *Remark:* The evidence suggests a small to moderate magnitude of association between AD and congestive heart failure in adults, with greater AD severity associated with a greater magnitude of association.	17, 53, 102, 157, 161, 165
5.7	AD in adults is probably associated with thromboembolic diseases (moderate quality evidence) *Remark*: The evidence suggests a small magnitude of association between AD and thromboembolic diseases in adults.	166
5.8	AD in adults may be associated with cardiovascular death (low quality evidence) *Remark:* The evidence suggests a small magnitude of association between AD and cardiovascular death in adults.	53, 156, 162, 167
Metabolic Disorders		
6.0	AD in adults is probably associated with obesity (moderate quality evidence)	17, 43, 61, 63, 90, 98, 157, 158, 168-171
6.1	AD in adults is probably associated with dyslipidemia (moderate quality evidence)	43, 61, 63, 64, 83, 89, 98, 136, 152, 154-156, 158, 160
6.2	AD in adults may not be associated with diabetes (low quality evidence)	17, 43, 61, 63, 64, 83, 89, 90, 98, 136, 151-158, 160, 165, 172
6.3	The association between AD in adults and metabolic syndrome is uncertain (very low quality evidence)	63, 64, 119
Bone Health		
7.0	AD in adults is associated with osteoporosis (high quality evidence)	65, 83, 173
7.1	AD in adults is associated with bone fractures (moderate quality evidence)	66, 174
Skin Infection		
8.0	AD in adults is associated with skin infection (moderate quality evidence)	80, 175-179

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Work Group Members' Disclosures

The following information represents the authors' disclosed relationships with industry during guideline development. Authors (listed alphabetically) with relevant conflicts of interest with respect to this guideline are noted with an asterisk (*).

Ali Alikhan, MD, has no relationships to disclose. Lionel Bercovitch, MD, has no relationships to disclose. David E. Cohen*, MD, MPH, serves on the board of directors for Bickel Biotechnology, Dermira, and Kadmon Corporation receiving stock options and/or fees; as an advisory board member for Celgene, Cutanea Life Sciences, and Ferrer receiving honoraria; as a consultant for Ferndale Laboratories, Inc., Medimetriks Pharmaceuticals, Inc., Novartis, Facilitation of International Dermatology Education, Asana BioSciences, Dermavant Sciences, Leo Pharma, Inc., UCB, FIDE, and Cosmetic Ingredient Review receiving honoraria and/or stock options. Dawn M.R. Davis, MD, has no relationships to disclose. Lawrence F. Eichenfield*, MD, serves as an advisory board member for Forte Biosciences, Asana Biosciences, LLC., Glenmark Pharmaceuticals, Inc., and Verrica Pharmaceuticals, Inc., receiving honoraria and/or stock options; as an investigator for Leo Pharma, Inc., Galderma Laboratories, L.P., Regeneron, Pfizer, Inc., Valeant Pharmaceuticals North America, LLC., and AbbVie, receiving research grants, fees and/or honoraria; as a consultant for Leo Pharma, Inc., Wiley-Blackwell, Galderma Laboratories, L.P., TopMD, Regeneron, Lilly ICOS, LLC., Pfizer, Inc., Valent Pharmaceuticals International, Cutanea Life Sciences, Dr. Reddy's, DS Laboratories, Medimetriks Pharmaceuticals, Inc., Novan, Anacor Pharmaceuticals, Inc., Almirall, Dermira, Dermavant Sciences, Inc., and MatriSys Bioscience receiving honoraria; as an independent contractor for Elsevier, Inc. receiving royalties. Lindsy Frazer-Green, PhD, has no relationships to disclose. Jennifer Moyer Darr, LCSW, has no relationships to disclose. Amy S. Paller*, MD, serves as a consultant for Abbvie, Abeona, Almirall, Amagma, Anaptysbio, Arena, Bausch, Bristol Myer Squibb, Dermavant, Dermira, Eli Lilly, Exicure, Forte, Leo, Lifemax, Novartis, Phoenix, Pierre Fabre, Pfizer, Rapt, Regeneron, Sanofi, Sol-Gel, UCB, and Venthera receiving honoraria; as an investigator for Anaptysbio, Eli Lilly, Incyte, Janssen, Krystal Bio, Lenus, Regeneron, and UCB receiving no compensation. Robert Sidbury*, MD serves as an advisory board member for Pfizer, Inc. receiving honoraria; as a principal investigator for Regeneron

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Appendix 1. Detailed Methods

Expert Work Group Composition and Disclosures of Interest

The co-chairs of the Work Group (D.D. and R.S.) were reviewed for potential disclosures of interest (DOIs) and approved by the AAD's Clinical Guidelines Committee (CGC). Additional Work Group members were nominated by the co-chairs based on their expertise related to the research questions. All Work Group nominees were reviewed for potential DOIs by the CGC. The majority (at least 51%) of the Work Group was required to be free of financial DOIs relevant to the topic of the guideline. Nominees found to have no relevant financial DOIs were approved, whereas nominees found to have potentially relevant financial DOIs were approved with management. Work Group members approved with management were prohibited from discussions on recommendations in which they had relevant DOIs. Work Group members completed a DOI form that was periodically updated and reviewed for potential relevant DOIs throughout guideline development and used to ensure management terms were observed. The multidisciplinary Work Group consisted of the co-chairs, 7 members, an additional member serving as a methodologist, and a patient representative.

Formulation of Questions and Selection of Comorbid Conditions

The expert Work Group defined the objective of the systematic review to synthesize the evidence on associations between AD and comorbid conditions and established the outcomes of interest as incidence and prevalence of various comorbid conditions. After defining the research aims, the Work Group identified selected comorbid conditions considered critical or important to the clinical management of AD. Potential comorbid conditions were identified via a survey of AD literature, consultation with expert Work Group members, and review of conditions included in commonly used comorbidity indices.[180-182] The Work Group ranked the importance of each identified condition with respect to its relevance for clinical management of AD via anonymous online voting using a 9-point scale (a ranking of 7-9 was assigned to conditions considered critically relevant, 4-6 for conditions considered of important relevancy, and 1-3 for outcomes of limited relevancy). All conditions achieving a mean ranking of critical or important were included in the review of comorbidities of interest (**Table 1**).

Literature Searches

MEDLINE and the Cochrane Library were searched from November 01, 2012, through May 18, 2020, to update a search conducted to support a discussion of clinical associations with AD in previously published guidelines of care for the management of AD.[183] Studies included in the previous guideline discussion of clinical associations were hand-searched and included if compatible with the eligibility criteria of the current review. Bibliographic hand-searching was also performed. A combination of the National Library of Medicine's medical subject headings and other keywords specific to the exposure and comorbidities of interest were used to identify studies. A complete, representative MEDLINE (via PubMed) search strategy is available in **e-Appendix 1**. Searches were limited to English language results based on the authors' fluency.

Study Eligibility Criteria and Selection

Studies were eligible for inclusion if they were observational (including cohort, cross-sectional, and case-control studies) and provided data on the incidence or prevalence of the selected comorbid conditions in adults (≥ 18 years old) with AD of any severity.

The literature searches identified a total of 8,151 eligible studies across all comorbid conditions of interest. After two rounds of study screening, 117 unique studies were selected for the final evidence review. Study identification is detailed in **e-Appendix 2**. Studies retrieved by the literature searches were reviewed for relevance as defined by the predetermined eligibility criteria over two rounds of study selection. During the first round of study selection, title and abstract screening was performed by an independent methodologist (L.F.G) with subsequent quality control by independent reviewers. Discrepancies were resolved by discussion. The full text of studies appearing to meet inclusion criteria during the title and abstract screening were retrieved and then underwent a second round of study selection, during which a final inclusion

decision was made. Full-text screening inclusion decisions were made independently and in parallel by two Work Group members. Disagreements were resolved through independent review by a third Work Group member.

Data Extraction

Structured data tables were used to extract relevant data from all included studies. Data extraction was initially performed by an independent methodologist (L.F.G) with subsequent quality control performed by additional independent reviewers. Discrepancies were resolved through discussion by the original data extractor and the independent reviewer.

Risk of Bias Assessment and Evidence Synthesis

The risk of bias was assessed in all included studies using the Newcastle Ottawa Scale for assessing the quality of nonrandomized studies in meta-analyses[184] or a modified Newcastle Ottawa Scale for assessing the quality of cross-sectional studies[185]. The risk of bias assessment was completed by an independent methodologist (L.F.G) with subsequent quality control by independent reviewers.

Following risk of bias assessment, the Cochrane Collaboration Review Manager, version 5.4, or OpenMetaAnalyst meta-analysis software (Brown University, RI, USA) were used to conduct meta-analyses when data were homogenous and poolable. Crude prevalence data were pooled from studies that did not report estimates of association but listed the number of total patients with AD, patients with AD and a comorbid condition of interest, total reference individuals, and reference individuals with a comorbid condition of interest. Odds ratios with accompanying 95%CIs were estimated and reported for these analyses.

Association estimates from longitudinal cohort studies and cross-sectional studies were analyzed separately and meta-analysis was performed separately for unadjusted and adjusted association estimates. Unadjusted estimates were used only when adjusted data were unreported. For the meta-analysis of adjusted data, if multiple adjusted models were presented, only the association estimate from the most inclusive model was included. Estimates of association were pooled using the inverse variance method and summarized with point estimates with accompanying 95% CIs. Individual estimates were pooled using a random-effects model and the method of DerSimonian and Laird.[186, 187] Statistical heterogeneity was assessed using the Higgins I^2 value and the χ^2 test. A Higgins' I^2 value $\geq 50\%$ and P values $< .05$ were considered to represent significant heterogeneity.

Assessing the Overall Quality of the Body of Evidence

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) for prognosis approach was used to assess the overall certainty of the evidence for each outcome.[3, 4] The GRADEPro Guideline Development Tool was used to create evidence profiles that categorized the overall quality of the body of evidence for each outcome into one of four categories: high, moderate, low, or very low. Each category represents the confidence in the estimate of effect for an outcome (**Table IV**).

Table IV. *Levels of Evidence*

Level of Evidence	Confidence in the Estimate of Effect[4]
High	We are very confident that the association lies close to that of the estimate.
Moderate	We are moderately confident that the association is close to that of the estimate, but there is a possibility that it is substantially different.
Low	Our confidence in the estimate is limited; the true association may be substantially different from the estimate.
Very Low	We have very little confidence in the estimate; the true association is likely to be substantially different from the estimate.

Formulating Statements of Association

A Work Group member (J.I.S) drafted statements regarding the association between AD and comorbid conditions using the evidence profiles and considering the following: the strength of the estimated association between AD and a selected comorbid condition and the overall quality of the evidence of association. The drafted statements were then reviewed by additional Work Group members, including the patient advocate, and, for cardiovascular comorbidities, an independent subject matter expert. The implications of the wording of statements of association as a reflection of the strength of association and quality of evidence are summarized in **Table II**. Remarks were drafted to accompany selected statements when the Work Group considered the additional information essential to the interpretation of the statement.

Manuscript Review and Currency Statement

This guideline has been developed per the AAD/AAD Association Administrative Regulations for Evidence-Based Clinical Practice Guidelines (November 2019), which includes the opportunity for review and comment by the entire AAD membership and final review and comment by the AAD Board of Directors.[188] This guideline will be considered current for 5 years from the date of publication unless reaffirmed, updated, or retired before that time.