American Academy of Dermatology Guidelines: Awareness of comorbidities associated with atopic dermatitis in adults

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Key words: alcohol; allergies; atopic dermatitis; cardiovascular disease; comorbidities; dermatology; diabetes; guidelines; mental health; metabolic syndrome; obesity; osteoporosis; skin infection.

SUMMARY

AD is a burdensome condition with significant effects on quality of life and overall health. The patient- and population-level burden of AD is increased by associated comorbidities. Associations between AD and other atopic conditions have been recognized for decades and even contribute to diagnostic criteria for AD. More recently, studies examined links between AD and autoimmune, metabolic, cardiovascular, and mental health comorbidities.

We created the American Academy of Dermatology's guidelines on comorbidities associated with AD in adults to provide an evidence-based synthesis of the literature to date to educate clinicians, patients, and other stakeholders on important comorbidities associated with AD. We used best practice for guideline development, including systematic reviews with meta-analyses, and applied the Grading of Recommendations, Assessment, Development, and Evaluation for prognosis approach for assessing the certainty of the evidence. We used that evidence to formulate statements on the association between AD and selected comorbidities. Our multidisciplinary team used a consensus approach to finalize and approve 32 evidence-based statements.

There is clear evidence of an association between AD in adults and atopic and immune-mediated conditions. The presence of atopic comorbidities can help establish the diagnosis of AD. While the guideline does not make specific recommendations for the management of AD, we recognize that comorbid inflammatory conditions may be considered when selecting AD treatments for individual patients. As biologics and other targeted agents continue to be evaluated, approved, and prescribed across different inflammatory conditions, medications with multiple indications have the potential to simultaneously treat 2 or more diseases for individual patients.

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Funding sources: This study was funded in total by internal funds from the American Academy of Dermatology.

IRB approval status: Not applicable.

Conflicts of Interest: Listed in text.

Accepted for publication January 11, 2022.

Reprints not available from the authors.

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Published online January 24, 2022.

J Am Acad Dermatol 2022;86:1335-6.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2022.01.009

There is ample evidence supporting the association between AD and mental health conditions, such as depression and anxiety. For many patients, low mood may be driven by the symptoms of AD, including chronic itch and poor sleep. Successfully treating AD may alleviate depressive symptoms for some patients; for others, assessment and treatment specific to their mental health may be needed.

There is limited but consistent evidence supporting a link between AD and adverse bone health, including osteoporosis and fractures. Although the mechanism of this association is unclear, it is possible that systemic corticosteroids, which are known to increase fracture risk and are sometimes prescribed to treat AD and comorbid asthma, may play a role.

Associations between AD and cardiovascular risk factors and comorbidities, including hypertension, myocardial infarction, and stroke, are more controversial. A few studies have found that increasing AD severity is associated with a corresponding increase in cardiovascular risk, but still the absolute risk attributable to AD is small. Some mechanistic work has been done to show that the inflammation of AD is associated with cardiovascular markers in the blood and vasculature, but there is no evidence to date suggesting that treating AD affects cardiovascular risk.

In summary, AD has been associated with several comorbidities, ranging from inflammatory to mental health to cardiovascular conditions. Evidence for these associations is summarized in the complete guideline online. Further research is needed to determine whether screening for or management of comorbidities is beneficial for adults with AD.

Key points

- American Academy of Dermatology guidelines on comorbidities associated with atopic dermatitis (AD) in adults is an evidence-based synthesis of the literature to date
- There is ample evidence supporting associations between AD and atopic comorbidities, such as asthma and other immune-mediated conditions
- AD is associated with mental health conditions, such as depression and anxiety
- Associations between AD and cardiovascular conditions are more controversial

Click here to read the full article: American Academy of Dermatology Guidelines: Awareness of comorbidities associated with atopic dermatitis in adults (https://www.jaad.org/article/S0190-9622(22)00080-9/fulltext).

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Rochester, Minnesota; Toronto, Ontario, Canada; Sacramento and San Diego, California; Providence, Rhode Island; New York, New York; Denver, Colorado; Rosemont and Chicago, Illinois; Washington, DC; Madison, Wisconsin; and Seattle, Washington

Background: Studies found associations between atopic dermatitis (AD) and various 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 Grading of Recommendations, Assessment, Development, and Evaluation 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 and bone health conditions and skin infections was identified. There is some evidence supporting an association between AD and substance use, attention deficit hyperactivity disorder, 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 inconclusive.

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. (J Am Acad Dermatol 2022;86:1336.e1-18.)

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Accepted for publication January 11, 2022.

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Published online May 12, 2022.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2022.01.009

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CONFLICT OF INTEREST STATEMENT

The American Academy of Dermatology (AAD) strives to produce clinical guidelines that reflect the best available evidence supplemented with the judgment of expert clinicians. Significant efforts are taken to minimize the potential for conflicts of interest to influence guideline content. The management of conflict of interest for this guideline complies with the Council of Medical Specialty Societies' Code of Interactions with Companies. Funding of guideline production by medical or pharmaceutical entities is prohibited, full disclosure is obtained and evaluated for all guideline contributors throughout the guideline development process, and recusal is used to manage identified relationships. The AAD conflict of interest policy summary may be viewed at www.aad.org.

The information below represents the authors' disclosed relationship with industry during guideline development. Authors (listed alphabetically) with relevant conflicts with respect to this guideline are noted with an asterisk*. In accordance with AAD policy, a minimum 51% of work group members did not have any relevant conflicts of interest.

Participation in one or more of the listed activities below constitutes a relevant conflict:

- service as a member of a speaker bureau, consultant, advisory board, for pharmaceutical companies on atopic dermatitis or atopic dermatitis drugs in development or approved by the US Food and Drug Administration
- sponsored research funding or investigator-initiated studies with partial/full funding from pharmaceutical companies on atopic dermatitis or atopic dermatitis drugs in development or approved by the US Food and Drug Administration

If a potential conflict was noted, the work group member recused themselves from the discussion and drafting of recommendations pertinent to the topic area of interest. Complete group consensus was obtained for draft recommendations. Areas where complete consensus was not achieved are shown transparently in the guideline.

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.

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 health care setting or context. The exposure of interest is AD and, when possible, we compare the incidence or prevalence of comorbidities with those of 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 I) and employed the Grading of Recommendations, Assessment, Development, and Evaluation for prognosis approach to assessing the certainty of the evidence.[1-4] The work group drafted statements regarding the association between AD and comorbidities based on the evidence and by considering the following: the strength of

Abbreviations used:

AA: alopecia areata
AD: atopic dermatitis
HR: hazard ratio
OR: odds ratio
RR: risk ratio

the estimated association between AD and a selected comorbid condition and the overall certainty of the evidence of association. The implications of the wording of statements of association as a reflection of the strength of association and certainty of evidence are summarized in Table II. A detailed methodology is described in 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 that significantly impacts quality of life, overall health, and health system utilization.[5,6] In addition to AD itself, the patient- and population-level burdens of disease are 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 conditions.[13] This section of the guidelines reviews the evidence for potential comorbidities of AD in adults (Table III).[14-168] For select comorbidities with supporting evidence, we evaluate whether the association is modified by the severity of AD.

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
AA
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

AA, Alopecia areata; *AD,* atopic dermatitis; *ADHD,* attention deficit hyperactivity disorder.

ATOPIC AND ALLERGIC CONDITIONS

Asthma

The association between AD and asthma is well established. In our meta-analysis, we found the pooled prevalence of asthma in adults with AD to be 24.8% (95% 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 (Supplementary Table I; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1). 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], 1.94; 95% CI, 1.66-2.21) and mild AD (RR, 1.34; 95% CI, 1.12-1.56).[112]

The concept of the "atopic march" as an explanation for these associations is unproven.[113] This theory posits that epidermal barrier disruption associated with AD leads to epicutaneous allergen sensitization and inflammation with a consequent immune response at other epithelial surfaces, including the gastrointestinal tract (food allergy), upper respiratory tract (allergic rhinitis), and lower

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

Statement wording	Overall certainty of supporting evidence	Implication
Is associated	High or moderate	Clear evidence of an important large effect
Is not associated	High or moderate	Clear evidence of no association
Probably associated	High or moderate	Evidence of a moderate effect
Probably not associated	High or moderate	Evidence of small or unimportant effect
May be associated	Low	Evidence of a large, moderate, or small effect based on low quality evidence
May not be associated	Low	Evidence of no association based on low certainty evidence
Uncertain association	Any quality	Evidence of any magnitude of effect from very low certainty evidence or imprecise or inconsistent effect estimates from evidence of any certainty

Strength of evidence	Wording	Implication[1,2,4]
High	"High certainty evidence"	Very confident that the true magnitude of association lies close to that of the estimate
Moderate	"Moderate certainty evidence"	Moderately confident in the estimate of association, but there is a possibility that it is substantially different
Low	"Low certainty evidence"	Confidence in the estimate is limited; the true magnitude of association may be substantially different from the estimate
Very low	"Very low certainty evidence"	The estimate is very uncertain; the true magnitude of association may be substantially different from the estimate

respiratory tract (asthma).[113] 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.[114,115]

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.[116] 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, have the potential to benefit patients with both conditions.[117,118]

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 (Supplementary Table II; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1). The heterogeneity is likely related to different definitions of food allergy used in those studies, including different foods and the use of self-report, physician diagnosis, or administrative codes. As with asthma, there appears to be a relationship between the severity of AD and immunoglobulin-E–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.[112]

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.[119]

Allergic rhinitis, conjunctivitis, and eosinophilic esophagitis

Although not as extensively studied as the association with asthma, allergic rhinitis 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 (Supplementary Table III; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1). We found little evidence to support

Table III. AD comorbidity statements

No.	Statement	Evidence
Atopic and allergic conditions		
1.0	AD in adults **is associated** with asthma (**moderate** certainty evidence)	14-41,112,150,161
1.1	Greater AD severity **is associated** with increasing asthma prevalence (**moderate** certainty evidence)	112
1.2	AD in adults **is associated** with food allergies (**high** certainty evidence)	19,21,33,42-48,112
1.3	Greater AD severity **is associated** with increasing food allergy prevalence (**moderate** certainty evidence)	112
1.4	AD in adults **is associated** with allergic rhinitis (**moderate** certainty evidence)	15,38,39,49-54,138
1.5	The association between AD in adults and allergic conjunctivitis **is uncertain** (**low** certainty evidence)	38,138
1.6	AD in adults **may be associated** with eosinophilic esophagitis (**low** certainty evidence)	55-58
Immune-mediated conditions		
2.0	AD in adults **is associated** with AA (**moderate** certainty evidence)	9,59-61
2.1	AD in adults **is associated** with urticaria (**moderate** certainty evidence)	9,16,39,62,63,126
Mental health and substance use		
3.0	AD in adults **is associated** with clinician-diagnosed depression (**moderate** certainty evidence)	15,30,40,64-75,129,133,138
3.1	AD in adults **is associated** with clinician-diagnosed anxiety (**moderate** certainty evidence)	15,40,64-69,71,72,74,76,129,133,138
3.2	AD in adults **may be associated** with suicide (**low** certainty evidence)	66,67,70,72,74,77,130-133,138
3.3	AD in adults **may be associated** with alcohol abuse disorders (**low** certainty evidence)	68,78-81,136,150
3.4	AD in adults **may be associated** with cigarette smoking (**low** certainty evidence)	22,68,80,136,137,150
ADHD and autism spectrum disorders		
4.0	AD in adults **may be associated** with ADHD (**low** certainty evidence)	82,138
4.1	The association between AD in adults and autism spectrum disorders **is uncertain** (**very low** certainty evidence)	138
Cardiovascular diseases		
5.0	AD in adults **is probably associated** with hypertension (**moderate** certainty evidence) *Remark: The evidence suggests a small magnitude of association between AD and hypertension in adults.*	15,21,22,30,68,83-92,112,136,150,152
5.1	AD in adults **is probably associated** with coronary artery disease (**moderate** certainty evidence) *Remark: The evidence suggests a small magnitude of association between AD and coronary artery disease in adults.*	30,36,88,89,91-93,142
5.2	AD in adults **is probably associated** with peripheral artery disease (**moderate** certainty 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.*	89,91,93
5.3	The association between AD in adults and myocardial infarction **is uncertain** (**low** certainty evidence)	34,36,68,84,85,88,89,91,93-95,142
5.4	Severe AD in adults **may be associated** with myocardial infarction (**low** certainty evidence)	68,88,91,94,142
5.5	The association between AD in adults and stroke is uncertain (**very low** certainty evidence)	34,36,68,84,85,88,89,91-94,96,142,

Continued

Table III. Cont'd

No.	Statement	Evidence
5.6	AD in adults **is probably associated** with congestive heart failure (**moderate** certainty 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.*	34,89,93,97,112,142
5.7	AD in adults **is probably associated** with thromboembolic diseases (**moderate** certainty evidence) *Remark: The evidence suggests a small magnitude of association between AD and thromboembolic diseases in adults.*	98
5.8	AD in adults **may be associated** with cardiovascular death (**low** certainty evidence) *Remark: The evidence suggests a small magnitude of association between AD and cardiovascular death in adults.*	88,94,99,142
Metabolic disorders		
6.0	AD in adults **is probably associated** with obesity (**moderate** certainty evidence)	22,30,89,90,100-103,112,136,150,152
6.1	AD in adults **is probably associated** with dyslipidemia (**moderate** certainty evidence)	15,21,30,68,84,86-88,90,92,136,150,152,153
6.2	AD in adults may **not be associated** with diabetes (**low** certainty evidence)	15,21,22,30,68,83-90,92,97,104,112,136,150,152,153
6.3	The association between AD in adults and metabolic syndrome **is uncertain** (**very low** certainty evidence)	51,152,153
Bone health		
7.0	AD in adults **is associated** with osteoporosis (**high** certainty evidence)	15,105,154
7.1	AD in adults **is associated** with bone fractures (**moderate** certainty evidence)	106,155
Skin infection		
8.0	AD in adults **is associated** with skin infection (**moderate** certainty evidence)	107-111,168

Bold is used to highlight the strength of the association statement and the certainty of the evidence.
AA, Alopecia areata; *AD*, atopic dermatitis; *ADHD*, attention deficit hyperactivity disorder.

the associations between AD and allergic conjunctivitis and eosinophilic esophagitis (Supplementary Tables IV and V; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1).

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.[120] 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.[121] 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 2 or more autoimmune conditions compared to the general population.[9]

Alopecia areata

Epidemiologic studies consistently show an association between AD and alopecia areata (AA).[122] In the Danish study mentioned above, the adjusted odds ratio (OR) for the association between AD and AA was 26.31 (95% CI, 14.48-47.80) (Supplementary Table VI; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1).[9] While some of the strength of that association may be related to diagnostic bias (ie, dermatologists treating patients for 1 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 AA in terms of the severity and response to treatment, but studies are limited. In an AA registry study, having AD was associated with a higher likelihood of having alopecia totalis or universalis, but the association was not statistically significant (OR 1.24; 95% CI, 0.95-1.61).[123] While there are

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.

currently no targeted systemic treatments approved for AA, dupilumab was posited as a potential treatment option.[124] Conversely, dupilumab was also reported to cause new-onset AA.[124] Janus kinase inhibitors show promise for both AD and AA but are not yet approved in the United States for either indication.[125]

Urticaria

As discussed above, AD is associated with food allergy, which commonly manifests as acute urticaria. AD is also associated with chronic idiopathic urticaria (Supplementary Table VII; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1). A Danish study on autoimmune conditions demonstrated a strong association between chronic urticaria and AD (OR, 9.92; 95%CI, 6.43-15.32).[9] 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).[126] 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−immunoglobulin-E 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.[127,128]

MENTAL HEALTH AND SUBSTANCE USE

Depression, anxiety, and self-harm

Adults with AD are reported to be more likely to have symptoms of depression and anxiety and to be diagnosed with depressive or anxiety disorders.[13,129] In our analysis pooling 4 studies, including 11,244 adults with AD and 149,713 controls, AD was associated with double the odds of self-reported clinical depression or clinician-diagnosed depression (OR, 1.99; 95% CI, 1.53-2.59) (Supplementary Table VIII; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1). The association with anxiety is similar; pooling 4 studies with 157,222 adults with AD and 300,719,113 controls, the OR was 1.40 (95% CI, 1.12-1.75) (Supplementary Table IX; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1).

Although 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 1 case-control study and 1 cohort study finding a modest increase in suicide among adults with AD[130,131] and other case-control and cohort studies finding nonsignificant decreases in suicide (Supplementary Table X; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1).[132,133]

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.[134,135]

Substance use

There is limited evidence to support a potential association between AD and alcohol use or cigarette smoking (Supplementary Tables XI and XII; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1). 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.[68,136] 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).[136]

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. In 1 cohort study that assessed preceding cigarette smoking and the development of AD among nurses in the United States, no association was found.[137]

Attention deficit hyperactivity disorder and autism spectrum disorders

Associations between AD and attention deficit hyperactivity disorder 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 2 studies examining the association with attention deficit hyperactivity disorder in adults, only 1 of which had controls from the general population (Supplementary Table XIII; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1), which was a[82,138] population-based study in the United States that found an association between AD and attention deficit hyperactivity disorder 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, CIs were very wide, preventing any definitive conclusions (Supplementary Table XIV; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1).[138]

CARDIOVASCULAR DISEASES

Systemic inflammation is an established risk factor for cardiovascular disease and targeting inflammation can decrease the risk of cardiovascular events.[139] Therefore, inflammatory skin diseases may be potentially modifiable cardiovascular risk factors. 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.[140,141]

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 (Supplementary Tables XV to XXI; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1). 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: 1) 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); 2) 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); 3) congestive heart failure (mild AD: HR, 1.12; 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 4) 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).[142] It should be noted that treatment is frequently used as a proxy to define AD severity in epidemiologic studies, including in the aforementioned study in the United Kingdom.

The clinical implications of these associations are unclear. At this point, there is no evidence that increased cardiovascular screening or treatment is needed 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 Janus kinase inhibitors, which have black box warnings from the Food and Drug Administration for thrombosis based on their use in other conditions. To date, trials in AD did not demonstrate an increased risk of venous thromboembolism.[143-149]

METABOLIC DISORDERS

Current evidence points to a small association between adult AD and obesity and dyslipidemia. Pooling data from 8 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 (Supplementary Tables XXII and XXIII; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1). 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.[150] 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).[151] 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 (Supplementary Table SXXIV; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1). 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 2 studies compared the prevalence of metabolic syndrome as a whole in people with and without AD (Supplementary Table XXV; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1). A cross-sectional study[152] 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.[153]

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) (Supplementary Table XXVI; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1).[154] In a UK cohort study, the risk of 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) (Supplementary Table XXVII; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1).[155] Furthermore, the risk was much higher for fractures related to osteoporosis, with severe AD associated with 200%, 66%, and 50% increased rates of spinal, pelvic, and hip fractures, respectively.[155]

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.[156-158] On average, patients with AD are more likely to be deficient in vitamin D.[159] Sleep disturbance may interact with AD to increase the risk of traumatic injury in general.[106] Oral corticosteroids are a risk factor for fractures and are commonly used to treat severe AD flares.[160-162] Whether topical corticosteroids increase fracture risk is unclear, although a recent study from Denmark found increased fracture risk associated with high cumulative use of potent topical corticosteroids.[163]

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 fracture prevention therapy if they meet established risk thresholds (eg, oral corticosteroid use with a cumulative dose equivalent to ≥3 months of ≥5-7.5 mg daily of prednisone).[164-166]

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[167] and a cohort study in the United Kingdome found HSV infections to be more than twice as common among people with AD compared to general population controls.[168] Based on hospitalization data in the United States, 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) (Supplementary Table XXVIII; available via Mendeley at https://data.mendeley.com/datasets/cm9h5g2m63/1). Bacterial skin infections and eczema herpeticum are more likely to occur with poorly controlled dermatitis and successful treatment may decrease the incidence of these infections.[169]

PATIENT EDUCATION

Individualized management of and shared decision-making for AD should incorporate 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 in 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 AD, but we are not aware of any similar studies planned in adults.[170] Systematic investigations to understand the mechanisms underlying comorbidities and whether screening or treatment for depression, cardiovascular disease, or fracture risk, are needed.

SUMMARY

Key points

- American Academy of Dermatology guidelines on comorbidities associated with atopic dermatitis (AD) in adults is an evidence-based synthesis of the literature to date
- There is ample evidence supporting associations between AD and atopic comorbidities, such as asthma and other immune-mediated conditions
- AD is associated with mental health conditions, such as depression and anxiety
- Associations between AD and cardiovascular conditions are more controversial

AD is a burdensome condition with significant effects on quality of life and overall health. The patient- and population-level burden of AD is increased by associated comorbidities. Associations between AD and other atopic conditions have been recognized for decades and even contribute to diagnostic criteria for AD. More recently, studies examined links between AD and autoimmune, metabolic, cardiovascular, and mental health comorbidities.

We created the American Academy of Dermatology's guidelines on comorbidities associated with AD in adults to provide an evidence-based synthesis of the literature to date to educate clinicians, patients, and other stakeholders on important comorbidities associated with AD. We used best practice for guideline development, including systematic reviews with meta-analyses, and applied the Grading of Recommendations, Assessment, Development, and Evaluation for prognosis approach for assessing the certainty of the evidence. We used that evidence to formulate statements on the association between AD and selected comorbidities. Our multidisciplinary team used a consensus approach to finalize and approve 32 evidence-based statements.

There is clear evidence of an association between AD in adults and atopic and immune-mediated conditions. The presence of atopic comorbidities can help establish the diagnosis of AD. While the guideline does not make specific recommendations for the management of AD, we recognize that comorbid inflammatory conditions may be considered when selecting AD treatments for individual patients. As biologics and other targeted agents continue to be evaluated, approved, and prescribed across different inflammatory conditions, medications with multiple indications have the potential to simultaneously treat 2 or more diseases for individual patients.

There is ample evidence supporting the association between AD and mental health conditions, such as depression and anxiety. For many patients, low mood may be driven by the symptoms of AD, including chronic itch and poor sleep. Successfully treating AD may alleviate depressive symptoms for some patients; for others, assessment and treatment specific to their mental health may be needed.

There is limited but consistent evidence supporting a link between AD and adverse bone health, including osteoporosis and fractures. Although the mechanism of this association is unclear, it is possible that systemic corticosteroids, which are known to increase fracture risk and are sometimes prescribed to treat AD and comorbid asthma, may play a role.

Associations between AD and cardiovascular risk factors and comorbidities, including hypertension, myocardial infarction, and stroke, are more controversial. A few studies have found that increasing AD severity is associated with a corresponding increase in cardiovascular risk, but still the absolute risk attributable to AD is small. Some mechanistic work has been done to show that the inflammation of AD is associated with cardiovascular markers in the blood and vasculature, but there is no evidence to date suggesting that treating AD affects cardiovascular risk.

In summary, AD has been associated with several comorbidities, ranging from inflammatory to mental health to cardiovascular conditions. Evidence for these associations is summarized in the complete guideline online. Further research is needed to determine whether screening for or management of comorbidities is beneficial for adults with AD.

The authors thank Oscar Colegio, MD for his contributions to establishing the scope of the AD guideline update and Philip Greenland, MD for serving as an independent reviewer of statements of association related to cardiovascular comorbidities.

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, LP, 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, LP, 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 receiving grants and research funding; as an investigator for Brickell Biotech, Inc, and Galderma USA receiving grants and research funding; as a consultant for Galderma Global and Microes receiving fees or no compensation. Jonathan I. Silverberg, MD, PhD, MPH,* serves as an advisory board member for BioMX, Boehringer Ingelheim, RAPT Therapeutics, Celgene, Ortho Dermatologics, TARGET Pharma, AFYX Therapeutics, Corrona, Inc, Dermira, Pfizer, Inc, Leo Pharma, Inc, and Menlo Therapeutics receiving honoraria and/or fees; as an investigator for DS Pharma, TARGET Pharma, Kiniksa Pharmaceuticals, Ltd, Menlo Therapeutics, GlaxoSmithKline, AbbVie, Leo Pharma, Inc, and Regeneron receiving research funding, honoraria, or no compensation; as a consultant for AOBiome, Bluefin Biomedicine, Bodewell, BiomX, Inc, Galderma Research & Development, LLC, Arena Pharmaceuticals, Dermavant Sciences, Incyte Corporation, DS Biopharma, Sun Pharmaceutical Industries, Ltd, AnaptysBio, Asana Biosciences, LLC, Pfizer, Inc, Glenmark Generics, Inc, Sanofi, Kiniksa Pharmaceuticals, Ltd, GlaxoSmithKlein, Eli Lilly and Company, AbbVie, Regeneron, and Medimmune receiving honoraria or fees; as a speaker for the Fall Clinical Dermatology Conference, Maui Derm, and Regeneron receiving honoraria or fees. Anne Marie Singh, MD, serves as a consultant for AbbVie.

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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.[171-173] 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 conditions 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.[174] 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[175] or a modified Newcastle Ottawa Scale for assessing the quality of cross-sectional studies.[176] 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.[177,178] 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 Certainty 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 certainty 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).

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 certainty 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 certainty 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.[179] This guideline will be considered current for 5 years from the date of publication unless reaffirmed, updated, or retired before that time.