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Comorbidities and the impact of atopic dermatitis

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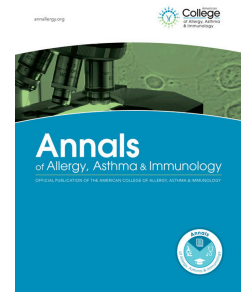
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Title: Comorbidities and the impact of atopic dermatitis

Running title: Comorbidities and impact of AD

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Introduction

Atopic dermatitis (AD) is a common, chronic inflammatory skin disease that affects children and adults. Several international studies examined the incidence of AD and found a broad range across different countries and periods of observation (from 2,150 per 100,000 person-years in Denmark 1997-2011¹ to 17,600 per 100,000 person-years in Germany 1997². While no studies examined the incidence of AD in the United States (US), several studies explored AD prevalence. The US prevalence of AD was 12% (2012 National Health Interview Survey [NHIS]) to 13% (2007-2008 National Survey of Children's Health [NSCH]) in children (age <18 years) and 7% [2012 NHIS³ and AD in America study^{4, 5}] in adults (age ≥18 years) in the US.

AD has been found to be associated with substantial patient-burden and numerous atopic comorbidities, including asthma, hay fever, food allergy and eosinophilic esophagitis (EOE), as well as non-atopic comorbidities, including allergic contact dermatitis (ACD), anxiety, depression, suicidality, infections and cardiovascular disease. The relationship between AD and comorbidities is likely bidirectional and multifactorial. Some comorbidities may be secondary to the effects of the burden of chronic AD and/or distinct pathomechanisms that are shared with or triggered by AD. Patient-burden and comorbidities should be incorporated into the evaluation and management of AD patients and may improve therapeutic decision-making and patient outcomes. This review will summarize recent developments in the understanding of the burden and comorbidities of AD.

Burden of AD

AD is a heterogeneous disorder with variable lesional morphology (e.g. erythema, lichenification, erosions, scaling, oozing/weeping, prurigo nodules)⁶, distribution (e.g. extent, head and neck, hands and feet⁷), age of onset^{8,9}, persistence¹⁰, symptoms (e.g. itch, skin pain¹¹, sleep disturbance¹²⁻¹⁴). A recent global systematic review and meta-analysis of AD characteristics identified 78 different signs and symptoms of AD, with significant variability by global region and patient-age⁶. These factors can contribute toward psychosocial distress, stigma¹⁵, functional disturbances and limited activities of daily living.

Overall, the most burdensome symptoms reported by adults with AD were itch (approximately 1 in 2 adults), dryness or scaling, and red or inflamed skin⁵. Approximately 1 in 10 adults reported that skin pain and sleep disturbance were their second most burdensome symptoms⁵. However, adults with moderate and severe AD were more likely to report blisters or bumps, red or inflamed skin, sleep disturbance, pain, and open sores or oozing as their most burdensome symptoms⁵. Itch is a burdensome symptom with complex interactions between disease-specific and environmental factors and baseline characteristics¹⁶.

Many adults with AD reported that AD limited their lifestyle (51.3%), caused them to avoid social interaction (39.1%) and impacted their activities (43.3%); they had only fair or poor overall health (25.8%) and were somewhat or very dissatisfied with life (16.7%)⁵. These effects occurred even in mild AD, but even more so in moderate and severe AD.

AD was found to be associated with significantly poorer dermatology-related QOL (higher Dermatology Life Quality Index [DLQI]⁵, Children's DLQI [CDLQI]¹⁷, and Skindex¹⁸), itch-related QOL (ItchyQOL¹⁹, 5-dimensions of itch¹⁹), and generic health-related QOL (Short form-12 [SF-12]⁵ and EuroQOL 5-D [EQ5D]²⁰). These effects were even more pronounced with

increasing severity of AD signs and symptoms^{21, 22}. Together, the results demonstrate that even mild AD, but especially moderate-severe AD, profoundly impacts patients' QOL. In addition, AD was associated with more quality adjusted life year loss in the US than self-reported autoimmune disorders, diabetes, food allergy, and heart disease, owing to a combination of high prevalence and major QOL impact²³.

Comorbidities of AD

Atopic comorbidities

The presence of atopic comorbidities, including asthma, hay fever and food allergy, is one of the diagnostic criterion for AD according to Hanifin and Rajka²⁴ and the United Kingdom Working Party²⁵. However, there remains some controversy over the mechanism(s) and epidemiology of comorbid atopic disease in AD (Figure 1).

Mechanism

Impaired skin-barrier function in AD patients may allow for transcutaneous penetration of allergens, thereby leading to activation of the sensitization and development of atopic disease²⁶. A study of an English birth cohort found that Filaggrin (FLG) gene null mutations were associated with higher risk of AD, particularly early-onset and more persistent AD²⁷. Further, FLG mutations were associated with higher population-based risk of asthma, and even higher risk of asthma in children with AD; sensitization to grass, house dust mite, and cat dander²⁷. A study of exclusively-breastfed infants at 3 months of age demonstrated that children with AD, particularly severe AD, had higher rates of food sensitization overall, and particularly

to eggs, cow's milk and peanuts²⁸. Since the children studied had no dietary exposure to food, the authors suggested the relationship between AD and food sensitization was mediated by transcutaneous penetration of food allergens and sensitization via cutaneous antigen-presenting cells²⁸.

A recent study using a minimally invasive skin tape strip sampling method found that children with AD and food allergy have stratum corneum abnormalities that distinguish them from those who had AD without FA or nonatopic controls. Children with AD and food allergy had highest levels of transepidermal water loss, greatest abundance of *Staphylococcus aureus* in non-lesional skin, and lowest expression of filaggrin and ceramides in nonlesional skin²⁹. Activation of T helper 2 (Th2) inflammatory pathways plays a primary role in both AD and asthma, irrespective of IgE status³⁰.

Epidemiology

Several US population-based studies examined the prevalence of atopic comorbidities in AD. In children, the lifetime and 1-year prevalences of self-reported asthma were 25.1% and 19.8%; 1-year prevalence of hay fever was 34.4%; and 1-year history of food allergy was 15.1% from the 2007-2008 NSCH³¹. Remarkably, the prevalences of these disorders were very similar in adults from the 2012 NHIS (25.5%, 18.7%, 28.4% and 13.2%, respectively)³. While the 1-year prevalence of food allergy was similar at 14.6%, the lifetime prevalence of asthma was considerably higher at 49.8% in the AD in America study; and the lifetime prevalence of hay fever was 87.0%³². Different prevalences of asthma and hay fever across studies may be attributable to differences of AD severity and/or other characteristics. Regardless, all three of

these studies found that AD was associated with statistically significantly higher prevalences of these atopic comorbidities compared to population-based controls without AD^{3, 31, 32}.

The prevalence and severity of self-reported asthma, hay fever and/or food allergy were increased in children with more severe AD³¹. Severe vs. mild-moderate AD was associated with: a higher lifetime prevalence of asthma (36.9% vs. 24.3%), 1-year prevalence of asthma (32.2% vs. 19.0%); prevalence of severe asthma (36.1% vs. 5.5%); prevalence of severe hay fever (29.1% vs. 4.6%); 1-year prevalence of food allergy (27.0% vs. 14.1%); and prevalence of severe food allergy (48.6% vs. 23.3%)³¹.

Similarly, the lifetime prevalences of asthma and hay fever and 1-year prevalence of food allergy were increased in adults with more severe AD³². Asthma prevalence increased with more severe scores for multiple validated AD severity measures, including Patient-Oriented Scoring AD (PO-SCORAD), Patient-Oriented Eczema Measure (POEM), and self-reported global AD severity²¹; 63.5-73.8% of adults with severe AD reported ever having asthma³². Similarly, there were stepwise increases in the 1-year prevalence of food allergy by more severe AD; 17.4-42.9% of adults with severe AD reported having food allergy³². In contrast, hay fever prevalence was similarly increased across all different severities of AD; 82.2-89.2% of adults with AD reported ever having hay fever³².

While AD severity was the strongest predictor, several other characteristics were found to be associated with atopic comorbidities in adult AD patients³². Asthma was associated with significantly younger age, lower level of education, lower household income, and larger household size³². These are consistent with previous studies showing that asthma is increased in

persons with lower socio-economic status³². Whereas, hay fever was associated with older age, lower level of education and higher household income³².

Eosinophilic esophagitis (EOE) has more recently been recognized as a comorbidity of AD and atopic disease. A recent systematic review and meta-analysis found that AD was associated with significantly higher prevalence of EOE in 2 of 11 studies, numerically higher EOE prevalence in another 7 of 11 studies, and significantly higher odds of EOE (odds ratio [95% confidence interval]: 2.85 [1.87-4.34]) compared to controls³³. While the extant data suggest that EOE occurs more often in AD, future studies are needed to confirm this association and determine the risk factors and pathomechanisms for this association.

The “atopic march” refers to the propensity for AD to begin early in life and be followed by the serial incidence of food allergy, asthma, and hay fever³⁴. Recently, EOE has been considered as a late manifestation of the atopic march in children³⁵. However, there are may be as many as 8 different sequences for the development of AD and allergic disease, including AD but no atopic comorbidities, the classic atopic march, persistent AD and wheeze, persistent AD with late-onset rhinitis, no AD but persistent wheeze and late-onset rhinitis, no AD but transient wheeze, no AD but rhinitis³⁴.

Clinical ramifications

The presence of atopic comorbidities may lead to worsening of the underlying AD in some patients. Comorbid hay fever may lead to eyelid edema and intense pruritus, with secondary lichenification and excoriations of the eyelids and face, loss of eyelashes and/or

eyebrows secondary to chronic rubbing and scratching (madarosis), and infraorbital allergic shiners. Eyelid and facial dermatitis secondary to hay fever may be recalcitrant to topical therapies. Adjunctive anti-histamine eye-drops and/or orally may be required to treat the underlying hay fever, thereby improving the eyelid dermatitis. Of note, this is a unique scenario where oral anti-histamines may be effective in AD, whereas they have not proven to be effective and are not recommended for treatment in AD³⁶.

Allergic contact dermatitis

Mechanism

Several reasons have been proposed for an association between AD and ACD. AD patients have increased transcutaneous absorption of irritants and contact allergens secondary to barrier disruption, leading to immune activation and ultimately contact sensitization³⁷⁻⁴⁰. AD patients frequently apply emollients and topical medications, including topical corticosteroids, many of which contain contact sensitizers, such as propylene glycol and sorbitans⁴¹⁻⁴⁴. There may also be shared immune pathways between AD and ACD, such as Th1, Th2, Th9 and/or Th17⁴⁵⁻⁵³.

Epidemiology

Two systematic reviews and meta-analyses recently examined the relationship between AD and ACD. The first included assessed 31 pediatric studies and found that one in three

children with AD who were patch-tested had at least one positive epicutaneous patch test⁵⁴. However, results were conflicting about whether children with AD have higher rates of ACD. In meta-analysis, children with AD actually had lower rates of positive epicutaneous patch tests compared to those without AD (41.7% and 46.6%). However, the authors noted major weaknesses of and variability between studies that limit conclusions⁵⁴. The second systematic review included 74 pediatric and/or adult studies and found that AD was associated with higher rates of positive epicutaneous patch tests compared to the general population, but lower rates compared to patch-test referral populations⁵⁵. The latter finding may be due to severe AD patients being patch tested as per consensus guidelines⁵⁶ even without a clear indication of ACD. Whereas, non-AD patients are referred for patch testing when there is a high suspicion for ACD and high pre-test probability of having a positive patch test. The results of this meta-analysis suggest that ACD may be more common in AD patients than the general population. However, more studies and higher quality studies are needed to confirm this association.

Even if AD is associated with higher likelihood of ACD than the general population, the effect-size of this association is relatively small. That is, only a small subset of AD patients appear to develop ACD. Thus, epicutaneous patch testing is not recommended in all AD patients. Expert consensus guidelines specifically recommend patch testing in adolescent- or adult-onset AD, pediatric and adult AD patients with worsening or more generalized dermatitis, localized or atypical lesional distribution, lesions recalcitrant to topical therapy, prior to initiation of systemic therapy, and if the AD worsens with therapy, or rebounds upon cessation of therapy⁵⁶. Some of the most common allergens encountered in AD patients are present in their emollients⁴², personal care products and topical medications, such as lanolin, methylisothiazolinone, neomycin, formaldehyde, sesquiterpine lactone mix, compositae mix, and fragrances^{42, 54, 55, 57-68}. An

expanded patch testing series is recommended in AD patients, which includes these common allergens⁵⁶.

Depression, suicidality and anxiety

Mechanism

Intense pruritus, high rates of sleep disturbance, stigma, social isolation, poor quality of life and neuro-inflammation have been postulated to contribute towards increased anxiety, depression and/or suicidality in AD. Sleep disturbances in AD were shown to be associated with a number of poor outcomes in AD patients, including headaches⁶⁹, shorter stature in children⁷⁰, poor QOL in children and adults^{5, 13, 14, 71}, increased fractures and other injuries⁷² and even cardiovascular risk factors and/or disease in adults⁷³. Fatigue and sleep disturbances may increase the risk of, or share a common mechanism with, anxiety and/or depression. Sleep disturbance in AD might be related to chronic itch, inflammation^{74, 75} and degree of atopy⁷⁶. AD might also upregulate neuroimmune factors, e.g. neuropeptide-induced sensitivity⁷⁷ and inflammatory cytokines, and the subsequent development of mental health disorders^{78, 79}. Future studies are needed to elucidate the precise mechanisms of association between AD, anxiety, depression and their optimal treatments.

Epidemiology

Two systematic reviews and meta-analyses recently examined the relationship of AD with depression, suicidality and/or anxiety. The first included 23, 13 and 6 studies in meta-analyses of depression, anxiety and suicidality, respectively, and found significant higher odds of

AD with depression and anxiety in adults, depression in children suicidality in adults and adolescents⁸⁰. The second included 36 studies with sufficient data for meta-analysis and found that 1 in 5 persons (20.1%) with AD had depression compared to only 14.8% in non-AD controls⁸¹. In the US particularly, two studies found that approximately 1 in 5 adults with AD either met the SIGECAPS criteria for major depressive disorder or reported a healthcare diagnosis of depression in the previous year⁸². AD patients had significantly higher rates of clinical depression (14.9% vs. 12.6%), numerically higher rates of antidepressant use (29.3% vs. 20.3%), and significantly higher rates of suicidality in adults (12.2% vs. 6.4%)⁸¹. Depression occurred particularly in moderate-severe AD⁸¹. Depression and anti-depressant use particularly occurred in adults⁸¹. Children with vs. without AD also had higher prevalence of parental depression (29.3% vs. 20.3%)⁸¹.

Four studies found that different topical, oral systemic or biologic treatment regimen for AD improved depression and/or depressive symptoms⁸³⁻⁸⁶. The results of these studies suggest that depressive symptoms occurring in AD may be directly related to disease severity and modifiable with improved AD treatments.

AD was also associated with higher rates of depressive symptoms overall (22.2% vs. 14.5%)⁸¹, including little interest in doing things, feeling down, depressed or hopeless, feeling tired or having little energy, having a poor appetite, feeling bad themselves, having trouble concentrating, moving or speaking slowly or too fast and having thoughts of being better off dead⁸². A subsequent US population-based study of 2893 adults with vs. without AD found higher prevalences of abnormal (≥ 11) Hospital Anxiety and Depression (HADS) - anxiety (28.6% vs. 15.5%) and depression (13.5% vs. 9.0%) subscores⁸⁷. Mean and abnormal anxiety and depression scores were increased in moderate and severe self-reported global AD severity,

POEM, PO-SCORAD, PO-SCORAD itch and sleep. One hundred percent of respondents with severe PO-SCORAD, POEM and PO-SCORAD-itch had borderline or abnormal anxiety and depression scores. However, 13-55% of adults with AD that had borderline and/or abnormal anxiety or depression scores reported not being diagnosis of anxiety or depression. Together, these studies suggest that anxiety and depression are symptoms of AD that correlate with disease severity, may be modifiable with treatment, and unfortunately often go undiagnosed by clinicians.

There are a number of different measures that could potentially be used to screen for depression and/or anxiety in AD patients. AD was found in some studies to be associated with higher mean scores for Hamilton Depression Scale, Beck's Depression Inventory⁸¹ and Patient Health Questionnaire-9⁸². While these may be reasonable options for use in clinical practice, their measurement properties and validity in AD have not been examined. A recent study examined the measurement properties of the HADS and showed that it had good discriminant and convergent construct validity, and no observed floor or ceiling effects for total scores in AD, suggesting it is sufficiently valid⁸⁸.

Clinical ramifications

Anxiety and depression are important considerations in the management of AD. First, it is important to recognize that anxiety and depression are symptoms of the AD per se, i.e. DSM-IV Axis III disorders (secondary to a medical condition). In many (if not most) instances, these symptoms resolve with improved control of AD signs and symptoms. Patients experiencing anxiety and depressive symptoms secondary to AD may warrant more aggressive AD treatment,

such as use of a systemic agent. However, symptoms of anxiety and depression may be indicators of standalone DSM-IV Axis I diagnoses, e.g. major depressive disorder or generalized anxiety disorder. AD patients experiencing anxiety and/or depressive symptoms may benefit from referral to a mental health specialist. It is important that clinicians managing patients with AD screen for anxiety and/or depression and treat or refer appropriately.

Infections

Mechanism

AD patients also have risk factors for increased cutaneous and extra-cutaneous infections, including skin-barrier dysfunction, immune dysregulation, lower anti-microbial peptides, increased bacterial colonization and infection of skin and use of immunosuppressive agents⁸⁹.

Epidemiology

Cutaneous infections

It is well established that cutaneous infections are increased in AD patients; this is one of the minor diagnostic criterion for AD according to Hanifin and Rajka²⁴.

A systemic review and meta-analysis found that 70% of AD patients were colonized with *Staphylococcus aureus* on lesional skin (n=81 studies), 39% on the non-lesional skin (n=30 studies), and 62% in the nose (n=43 studies)⁹⁰. In pooled analysis of studies with sufficient data, AD patients were found to have dramatically increased odds of being colonized with

Staphylococcus aureus than controls on lesional skin (odds ratio [95% confidence interval]: 19.74 [10.88–35.81], n=16 studies), non-lesional skin (7.77 [3.82–15.82], n=12 studies), and in the nose (4.50 [3.00–6.75], n=19 studies)⁹⁰.

Another systematic review of 32 studies examined the role of skin microbiome in AD⁹¹. AD skin was found in at least one study to have low bacterial diversity especially on lesional skin, depletion of *Malassezia* species, high non-*Malassezia* fungal diversity, increased *Staphylococcus aureus* and *Staphylococcus epidermidis*, decreased *Propionibacterium* and other genera⁹¹.

Yet another systematic review and meta-analysis of 10 controlled studies found that AD patients had high pooled prevalences of Immunoglobulin E against *Staphylococcal* enterotoxins A (33%, n=19 studies), B (35%, n=23 studies), C (14%, n=7 studies), and D (5%, n=3 studies), and toxic shock syndrome toxin 1 (16%, n=10 studies)⁹². AD was associated with increased odds of Immunoglobulin E against *Staphylococcal* enterotoxin A (8.37 [2.93-23.92]) and B (9.34 [3.54-24.93]) in 10 controlled studies⁹². Few studies examined IgG or IgM against *Staphylococcal* enterotoxins; those that did found high rates of positivity (34.6-87.0%). No studies examined IgA against *Staphylococcal* enterotoxins⁹².

Previous studies found conflicting results whether AD is associated with increased cutaneous warts or not⁹³⁻⁹⁵. A British birth cohort study found a lower prevalence of warts in children with vs. without visible AD at ages 11 and 16 years⁹⁶. A Swedish cohort found that teenagers with vs. without active AD aged 12 to 16 years had a lower prevalence of warts⁹⁴. However, analysis of the 2007 NHIS found that AD without atopic disease was associated

slightly lower odds of warts compared to those without AD. Whereas, AD with other atopic disease was associated with higher odds of warts⁹⁵.

Previous studies found strong associations between AD and eczema herpeticum (EH). Analysis of the 2008-2012 National Inpatient Sample (NIS), a representative cohort of hospitalized adults in the US, found that the mean annual incidence of hospitalization for EH per million children ranged from 4.03-7.30 and increased over time. The strongest observed association with EH was AD (odds ratio [95% confidence interval]: 11.72 [9.48-14.49]). While AD is the strongest risk factor for EH, most AD patients do not develop EH; approximately 3% of AD patients develop EH⁹⁷. EH occurs in a specific subset of AD patients characterized by more severe disease, early age of AD, comorbid atopic disorders, greater T-helper 2 polarity, allergen sensitization and other skin infections^{97, 98}.

Extracutaneous infections

The Swedish BAMSE birth cohort study found significantly higher proportions of parent-reported recurrent pneumonias, acute otitis media and higher usage of antibiotics in children aged 0-2 years with AD compared to healthy controls, even after stratifying by asthma history⁹⁹. Analysis of the 2007-2008 NSCH, a US population-based household survey, found higher odds of caregiver-reported serious recurrent ear infections in children with vs. without AD, and even higher odds in children with severe vs. mild-moderate AD⁷¹. Analysis of the 2007 NHIS found higher odds of caregiver-reported strep throat, influenza/pneumonia, sinus infections, recurrent ear infections, and urinary tract infections in children with AD and no atopic comorbidities compared to those without AD⁹⁵. Analysis of the 2012 NHIS demonstrated that adults with AD

and no atopic comorbidities had higher odds of self-reported influenza/pneumonia, strep throat, sinus infections, gastroenteritis, and infectious disease or immune problems compared to those without AD¹⁰⁰. In both studies, certain infections were even more common children or adults who had AD and other atopic disease compared to those with AD alone^{95, 100}.

These studies examined self-reported infections, which is vulnerable to potential misclassification. Recently, a study of the NIS found significantly higher prevalences of serious infections in adults with physician-diagnosed AD compared to those without AD (42.1% vs 25.4%)¹⁰¹. AD was associated with 32 of 38 infections examined, including erysipelas, cellulitis, tuberculosis, infectious arthropathy, endocarditis, encephalitis, and methicillin-resistant *Staphylococcus aureus* infections. A follow-up study in children from the same cohort found associations for 47 of 49 serious infections examined, including 8 cutaneous, 9 upper respiratory tract, 8 lower respiratory or lung, as well as cardiac, brain, gastrointestinal, and bone infections¹⁰².

A recent systematic review and meta-analysis found that AD compared to those without AD was associated with higher pooled prevalence of ear infection (26.6% vs. 21.9%), strep throat (8.4% vs. 3.1%) and UTI (8.4% vs. 3.1%), but not pneumonia (8.8% vs. 5.4%)¹⁰³. AD was associated with higher odds of infectious endocarditis and meningitis in two studies¹⁰³. Together, all these studies indicate that AD is associated with higher risk of both cutaneous and extra-cutaneous infections.

Cardio-metabolic comorbidities

Mechanism

AD patients have multiple potential risk factors for cardio-metabolic disease, including chronic sleep disturbance^{13, 14}, sedentary physical activity¹⁰⁴⁻¹⁰⁶, higher rates of cigarette smoking¹⁰⁷ and alcohol consumption⁷³, adverse effects from some systemic treatments (e.g. corticosteroids and cyclosporine A), etc.

Epidemiology

AD patients have been found to a number of cardiovascular risk factors, including smoking, and obesity. A systematic review and meta-analysis including 86 studies found that AD was associated with higher odds of active smoking and exposure to passive smoke, but not maternal smoking during pregnancy¹⁰⁷. A systematic review and meta-analysis including 30 studies found that AD was associated with higher odds of overweight and/or obese status, in both children and adults, and studies in North America and Asia but not Europe¹⁰⁸. A subsequent multi-center, pediatric dermatology practice-based case-control study of US children and adolescents found that active moderate-severe AD was associated with central obesity, elevated systolic and diastolic blood pressure¹⁰⁹.

Analysis of the 2010 and 2012 NHIS found that adults with self-reported AD had higher odds and earlier age of initiation of cigarette smoking, higher odds of consumption of alcoholic beverages, lower odds of daily vigorous physical activity and lower frequency of vigorous physical activity in the past week, and higher prevalences of class II/III obesity, hypertension, prediabetes, diabetes and high cholesterol⁷³. There were significant interactions between self-reported eczema and sleep disturbances, such that eczema associated with fatigue, daytime sleepiness, or insomnia was associated with even higher odds of obesity, hypertension, prediabetes, diabetes, and high cholesterol than AD alone. The particular impact of sleep on

cardiovascular risk is consistent with previous meta-analyses that showed difficulty of initiating or maintaining sleep or presence of restless, disturbed nights of sleep¹¹⁰, short (<7 hours per night) and long sleep duration (≥ 9 hours per night)¹¹¹ were all associated with increased cardiovascular disease and/or mortality.

Subsequently, analysis of the 2005–2006 National Health and Nutrition Examination Survey, 2010 and 2012 NHIS found that AD was associated with higher odds of coronary artery disease, heart attack, and congestive heart failure, peripheral vascular diseases and/or stroke in at least one study, even after controlling for asthma, hay fever, BMI, history of smoking, alcohol consumption, and vigorous physical activity¹¹².

Analysis of the 2002–2012 NIS found that AD was associated with increased odds of cardiovascular risk and chronic sequela of cardiovascular disease similar to that observed in psoriasis, hidradenitis, pemphigus and pemphigoid¹¹³. AD was particularly associated with increased odds of hypertension, obesity, congestive heart failure, peripheral vascular disease, peripheral and vascular atherosclerosis, pulmonary circulation disorders, late effects of cerebrovascular disease and other cerebrovascular disease¹¹³. Of note, AD was not associated with acute cardiovascular and/or cerebrovascular events in this study, such as myocardial infarction and stroke. This is likely because patients with heart attacks and strokes have short hospitalizations that efficiently address these cardiovascular disorders, but not other chronic health issues. Thus, the lack of association between AD and acute cardiovascular events in this hospitalized cohort should be interpreted with caution.

A systematic review and meta-analysis including 19 studies were included and found significantly increased odds of angina in cross-sectional studies, increased risk of angina, heart

failure, ischemic stroke, myocardial infarction, and stroke in longitudinal studies¹¹⁴. Thus, the combined effects of available studies indicate modest but significant associations between AD and cardiovascular disease and/or events. Some of the associations were not significant when applying Bayesian prediction intervals, indicating that the associations may not always occur in individual settings. However, use of prediction intervals may not be entirely appropriate given the small number of studies and that some of the studies included have a high-risk of bias¹¹⁵. In addition, AD severity was significantly associated with increased risk of angina, cardiovascular death, heart failure, myocardial infarction, and marginally significant associations with ischemic stroke and stroke; however, there were only a few prospective studies available. Together, the results suggest there is an increased risk of cardiovascular disease and events in AD, particularly more severe AD.

A subsequent cross-sectional US population-based study found that adults with AD had higher odds of self-reported obesity (body mass index ≥ 30), diabetes, high blood pressure and heart disease compared to controls³². These associations were all significant in mild and/or moderate disease, with strongest effects in severe AD. Structural equation modeling revealed direct effects of moderate-to-severe AD on food allergy, anxiety/depression and diabetes, direct and indirect effects on obesity, and indirect effects on high blood pressure and heart disease. Thus, there appears to be a complex relationship between AD, comorbid atopic and mental health disorders, and cardiovascular disease.

Clinical ramifications

The association of AD with cardiovascular diseases is likely multifactorial, with contributions from chronic sleep disturbance, decreased physical activity, increased cigarette smoking and alcohol consumption, etc. However, it is unclear which of these risk factors play the most important in AD. Further, it remains unknown if excess cardiovascular risk in AD patients is modifiable.

Conclusions

AD is associated with multiple comorbid allergic, mental health, infectious and cardiovascular comorbidities, which should be accounted for in clinical decision-making. The occurrence of comorbid anxiety and depressive symptoms may warrant more aggressive treatment using systemic agents to achieve better long-term AD control. Treatment approaches should be used in AD that will not iatrogenically cause or worsen cutaneous or extracutaneous infections or cardiovascular risk. Finally, adequate screening and diagnosis of the comorbidities of AD is essential in order to improve the longevity and overall health of AD patients.

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These could be replaced with icons/images that reflect each concept
For the comorbidities with bullet points, there would need to be multiple icons that are clustered/arranged together but also show each comorbidity independently.



Key Messages

- Atopic dermatitis (AD) impacts all aspects of patients' quality of life and emotional well-being.
- AD has a complex relationship with atopic comorbidities, including asthma, food allergy and eosinophilic esophagitis.
- AD is associated with symptoms of anxiety and depression, which are highly correlated with severity of AD signs and symptoms.
- AD is associated with multiple cutaneous and extracutaneous infections of bacterial, mycobacterial, viral, and fungal etiologies.
- AD is associated with increased cardiovascular risk factors, and potentially cardiovascular disease and events.