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REVIEW ARTICLE

# Comorbidities & burden of disease in atopic dermatitis

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## Abstract

**Background:** Atopic dermatitis is associated with an increased frequency of other atopic & allergic manifestations, including asthma in 10% to 30% of cases depending on age, allergic rhinitis, food allergies, eosinophilic diseases, and allergic conjunctivitis. The comorbidities outside the atopic march are overall less frequent than in psoriasis.

**Objective:** This review aims to demonstrate the intense, broad burden of this disease, comorbidities and its multidimensional involvement as a complex, heterogeneous disease.

**Methods:** The present narrative review summarizes the findings from the world's largest epidemiological studies and smaller, AD-specific studies on the comorbidities and burdens of this disease.

**Results:** The risk of asthma, specifically, and other atopic manifestations and skin infections, generally, is clearly increased among patients with AD. Of the other skin diseases, there is an undeniable risk of alopecia areata, vitiligo, and contact eczema and a lower risk of developing other autoimmune diseases. While comorbidities exist, their frequency seems to be modified by lifestyle, particularly by smoking. There is a link with overweight, obesity, and metabolic syndrome, especially in severe AD. This is also the case for cardiovascular diseases; however, with OR/HRs below 1.5. There is no link to type II diabetes but, rather, to type I in children. In all other areas, the data are often inconsistent, and any increase in risk is low. Eye diseases seem to be the only exception. AD also has psychiatric consequences, including attention-hyperactivity disorder, anxiety, depression, and sometimes suicidality, especially when severe.

**Conclusions:** The recently published work largely confirms our existing understanding of AD.

**Key words:** Atopic dermatitis, Comorbidity, Asthma, Allergic rhinitis, Vitiligo, Mental Health

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## Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease and can be severe and persistent.[1] Incidence and prevalence or AD have significantly increased. In the last 10 years we have understood much more the different phenotypes, as well as the genetic factors that contribute to the disease. Studies analyzing disease associations have exploded over the past 20 years with other diseases of inflammatory origin in the skin such as psoriasis, but despite being such a common disease, studies that bring together data from these epidemiological studies in AD, or on the contrary that show more clearly the multidimensional impact and comorbidity that may exist in the disease are scarce.

This narrative review covers the comorbidities and burdens of AD reported in the literature. In addition to well-known large epidemiological studies, namely the General Practitioners' from the UK, the American Nurses' Health Study, and the almost exhaustive data on the adult Danish and Taiwanese populations, cohorts have been intentionally constructed to answer specific questions about AD. As always, caution must be exercised when interpreting published associations, especially when hazard ratios (HRs) and odds ratios (ORs) dip below 2. Practicing clinical common sense when discussing the relevance and implication of the data is paramount.

## Atopic march

Associations between AD and asthma, allergic rhinitis (AR), allergic conjunctivitis, and food allergies are well-established and quantifiable. The relative prevalence of AR, eosinophilic esophagitis (EoE), urticaria, asthma, conjunctivitis, and chronic rhinosinusitis with nasal polyps is greater in children with AD.[1] The burden of type 2 inflammatory diseases increases in patients with more severe forms of AD, as proxied by treatment potency. Notably, patients with treatment severity level 3 were more than 4 times as likely to be diagnosed with asthma and twice as likely to be diagnosed with chronic rhinosinusitis with nasal polyps, AR, and EoE compared to patients with treatment severity levels 1–2.[1,2] Among infants, the risk of developing subsequent type 2 inflammatory diseases was 1.5 times higher in patients with AD than those without AD. The higher prevalence of type 2 inflammatory diseases among patients with more severe forms of AD is consistent with findings from recent epidemiological studies highlighting the role of AD disease severity among risk factors for developing other atopic diseases (i.e., asthma, EoE, AR), Similarly, it has been shown that patients who receive treatment earlier and who have better control, have less presence to manifestations of comorbidity of diseases of immunoallergic origin.[3-5]

## Cutaneous xerosis

In a German study of nearly 50,000 employees, the prevalence of cutaneous xerosis was 29.4%. Xerosis was significantly associated with AD [OR = 3.99 (3.42–4.65)], cracked eczema [OR = 2.96 (2.4–3.6)], and psoriasis [OR = 1.57 (1.38–1.78)].[1]

## Asthma and allergic rhinitis

In more than 1,000 patients treated with pimecrolimus (or an excipient) for an average of 7 years, after an average follow-up of 2.8 years, 37% had atopic comorbidity: AR (18.5%), food allergies (14.9%), allergic conjunctivitis (11.9%), and asthma (10.7%).[3] The prevalence of eczema among 80,000 American children was 12.8%, of whom 25.1% had asthma and 32.1% had AR, significantly higher than the 12.3% and 14.3% prevalence observed among controls.[1,4] Furthermore, eczema severity is significantly associated with the prevalence of asthma and AR.[1,4] From the American nurses' study, of the 8,000 atopic patients aged 55 and up, 33% had a family history of asthma; 32% patients had asthma, 49% had allergic rhinitis, and 20% had food allergies during the 20-year follow-up. This study revealed an association between high body mass index and AD.[6] Young Singaporean soldiers had asthma in 23.3% of AD cases, AR in 17.9%, and a food allergy in 1.8%.[7] The Danish population data enable comparing the prevalence of asthma in the adult population with AD and psoriasis: 18% in AD vs. 2.8% in psoriasis vs. 2% in the general population. There is thus a high risk of asthma in AD: Adjusted odds ratio (aOR) = 8.79 (8.08–9.56) vs. the general population. Comparing AD and psoriasis gives an aOR = 5.95 (5.38–6.59).[8] Thus, the older you get, the more the risk of asthma increases in the case of AD, 10% in young children, 20% in childhood, and up to 30% in adults.

## Cancer

A general review and meta-analysis of 32 studies (290,000 adults and 9,000 children) showed an inverse association between AD and brain tumors with OR = 0.77 (0.71–0.83). This is especially true for gliomas and and meningiomas in adults. When considering only children, the risk is not significant: OR = 0.85 (0.71–1.02). The authors could not show any significant association between AD and solid cancer.[9] In isolation, a Swedish cohort had shown a risk of lung cancer with a standardized incidence ratio (SIR) of 2 (1.3–2.8), and in Taiwan, an HR = 1.40 (1.05–1, 87). In Korea, there was a decrease in the incidence of thyroid cancer but of low significance with an OR = 0.38 (0.02–0.97), and in Sweden, an association with esophageal cancer [SIR = 3.5 (1.3–7.7)]. The literature does not show any association with breast, colon, stomach, or liver cancer.[9]

Immune stimulation may play a tumor suppressive role in tumor growth and thus seems to protect against brain tumors. These studies are very heterogeneous, making it difficult to give definitive results. However, overall, there are no major indications of an association between cancer and AD.

A moderate increase in the risk of lymphoma was supported by a meta-analysis that addressed controversies on the risk induced by local treatments for AD. It is likely that there is a confounding factor here, as mycosis fungoides can be confused with AD. Severe AD incurs a moderate risk: OR = 1.43 (1.12–1.81). However, in the case-control studies, there was an even lower OR of 1.18, which was not significant (0.94–1.47).[10,11]

## Morbidity

Danish authors conducted a 10-year mortality study in 576 patients hospitalized for AD and 951 for psoriasis.[11] The risk of death was reduced in AD vs. psoriasis with an HR = 0.75 (0.57–1) but was slightly higher than in the control population (10 per case) with an HR = 1.71 (1.2–2.44). The authors conclude that the patients hospitalized for AD died 8.3 years before the controls. This cannot be extrapolated to AD since these are the most severely affected patients. When restricted to AD in adults, the risk of death is lower

[HR = 1.27 (1.11–1.45)].[12] The only significant causes were cardiovascular diseases [HR = 1.45 (1.07–1.96)], infectious diseases [HR = 3.71 (1.43–9.6)], and urogenital diseases [HR = 5.5 (1.54–19.8)]. Taken together, the studies suggest that absolute risk is overall very low, with few fatalities.

## Comorbidities: Charlson Comorbidity Index

The Charlson Comorbidity Index (CCI) is a scale used to assess comorbidities (relative weight of 1 to 6) based on disease diagnoses classified by the ICD (International Statistical Classification of Diseases and Related Health Problems) code. A study in Denmark compared 10,700 adults with AD to 43,000 controls and found the CCI score increased in smokers with AD compared to controls: 0.41 vs. 0.13, $p < 0.001$.[13] On the other hand, in atopic patients who do not smoke, the ICCs were identical to the controls: 0.09 vs. 0.08, $p = 0.12$. When restricted to patients with severe AD vs. non-severe, the scores were markedly higher in smokers (0.48 vs. 0.14, $p < 0.001$) than in non-smokers (0.10 vs. 0.08, $p = 0.01$). Using the CCI places comorbidities into perspective, revealing that tobacco use is an essential factor, suggesting morbidity risk is not related to AD directly but to lifestyle. These findings suggest that AD could be a systemic disease based on comorbidities and atopic progression.[14]

## Cardiovascular diseases

### *Obesity and metabolic syndrome*

A meta-analysis of 30 studies, most of which were cross-sectional, including 900,000 patients, mostly children (878,000), revealed associations with being overweight [OR = 1.27 (1.19–1.36)] and obese [OR = 1.69 (1.54–1.84)] and a slightly higher risk of AD. After sensitivity analysis, the figures remained significant, but the ORs fell below 1.5 in children.[15] An Israeli study of 116,000 adults with AD found an increase in dyslipidemia and a decrease in diabetes and metabolic syndrome.[16] In moderate to severe AD, there was more metabolic syndrome (17% vs. 9.4%), obesity (22.2% vs. 18.6%), diabetes (15.9% vs. 9.2%), hypertension (27.9% vs. 15.3%), and dyslipidemia (47.1% vs. 28.5%), all of which were statistically significant with $p < 0.001$. Finally, cardiovascular mortality increased. In multivariate analysis, there is more metabolic syndrome in moderate to severe AD ($p = 0.04$). This study shows a link between AD severity and cardiovascular risk as somewhat increased.

In Korea, among 5,000 adults aged 19 to 40, after adjustment, there was an increased risk of metabolic syndrome (OR = 2.92), central obesity (OR = 1.73), and hypertriglyceridemia (OR = 2.20).[17] An American study on 132 children with moderate to severe AD and 143 controls found a positive association with body mass index, obesity, and waist circumference. However, the relationship between obesity and adiponectin remains unclear, as indicated by other studies on type 2 inflammation, and as is also the case for asthma.[18] In moderate to severe AD in children, there is, therefore, an increase in central obesity and blood pressure.[19] Korean authors showed that childhood obesity increases disease severity in a rat model of AD. This increase in weight could lead to a decrease in immunological tolerance and, therefore, worsen dermatosis.[20]

### *Infarction and stroke*

In a cohort of English general practitioners, 385,000 atopic patients with a median age of 43 years were matched with 1,500,000 controls. After a median follow-up of five years, there was a 20% increase in the risk of stroke in severe AD [HR = 1.22 (1.01–1.48)] and more than 40% risk of infarction, unstable angina, atrial fibrillation, and death from cardiovascular causes, as well as a 70% increase in the risk of heart failure [HR = 1.69 (1.38–2.06)]. This study shows a link between the most severe forms of AD and all cardiovascular diseases with an increased yet moderate remaining risk.[21]

In Sweden, in 100,000 cases of AD and 10 controls per case, there was a small increase in angina [aOR = 1.13 (1.08–1.19)]; in the event of severe AD in men, the was no association, but in the event of non-severe AD, an increased risk of heart attack [OR = 1.15 (1.07–1.23)] and stroke [aOR = 1.19 (1.07–1.33)] was found. Subgroup analyses show that smoking is a risk factor, particularly for severe AD.[22] The risk of stroke was analyzed in Denmark (7,000 moderate AD and 2,500 severe AD vs. 125,000 controls). The average age for infarction was 62.2 years in controls, 61.7 years in the non-severe AD, and 58.7 years in the severe AD. The mean age for strokes was 58.3 years in controls, 60.6 years for those with moderate AD, and 62.8 years for severe AD. In the adjusted model, infarction and stroke figures were significant. Ultimately, these authors show a decrease in cardiovascular risk in patients with moderate AD. The risk of severe AD is explained by comorbidities and factors related to lifestyle, particularly diet and smoking.[23] In the Nurses' Health Study, there was a non-significant increased risk of stroke [OR = 1.38 (1.03–1.85)], in the multivariate model matched on hypertension, hypercholesterolemia, and diabetes and no increased risk of a heart attack. Once again, the authors state that associated factors, and not AD, are related to comorbidities implicate the associated factors.[24]

A meta-analysis of 19 studies reported a moderate increase in the risk of heart attack, [RR = 1.12 (1–1.25)], stroke [RR = 1.10 (1.03–1.17)], and angina [RR = 1.18 (1.13–1.24)] with AD. The cardiovascular risk appears to be increased in severe AD, but authors emphasize the heterogeneity of the studies and the low risk.[24,25] German authors have studied associations with heart disease in numerous cohorts, including one with a search for genes associated with cardiovascular risk. In the longitudinal study, the risk of angina was slightly increased [aRR = 1.17 (1.12–1.23)], as was hypertension [aRR = 1.04 (1.02–1.06)], and peripheral arterial disease [aRR = 1.15 (1.11–1.19)], with no increased risk of heart attack or stroke. No genetic factors common to AD and cardiovascular disease have been identified.[26]

***Diabetes***

A meta-analysis and systematic review pooled 16 publications and found no association between AD and type II diabetes [OR = 1.11 (0.87–1.42)], hypertension [OR = 1.16 (0.98–1.37)], stroke [OR = 1.15 (0.95–1.39)], or infarction [OR = 1.14 (0.83–1.56)] but there was an association with angina [OR = 1.73 (1.27–2.37)]. Authors concluded that the risk is linked primarily to obesity and tobacco use, without AD representing an independent risk factor.[27] Instead, type I diabetes in children could increase the risk of AD, as shown in a Taiwanese population stud in nearly 3,400 children with type I diabetes [HR = 1.76 (1.29–2.39)].[28] In atopic Danish adults, there is a reduced risk of type II diabetes [HR = 0.76 (0.68–0.83)].[29] It is important to consider patients' corticosteroid intake, as was done in the Danish but not in the American study.[29,30]

## Digestive diseases

In Denmark, researchers assessed the association of AD with inflammatory bowel disease (IBD): in 7,000 adults with AD, the prevalence of Crohn's disease was 0.3% vs. 0.5% in controls after 20 years of follow-up,[31] for rectocolitis, they reported 0.8% vs. 1.4%. These data yielded non-significant HRs = 0.69 (0.34–1.30) for Crohn's disease, 0.94 (0.61–1.41) for ulcerative colitis (UCH), and 1.13 (0.35–3.6) for unspecified IBD. A slight increase in risk was observed in a German cohort with a 5-year follow-up. Among these 50,000 atopic patients, the risk increased for rheumatoid arthritis [RR = 1.72 (1.25–2.37)], Crohn's disease [RR = 1.34 (1.11–1.61)], and rectocolitis [RR = 1.25 (1.03–1.53)].[32] Authors also found a reduction in the risk of type I diabetes with [RR = 0.72 (0.53–0.99)]. The risk of cholelithiasis has been analyzed in the Danish population: 3.8% in the general population, 3.5% in AD, and 5% in psoriasis.[33] There is thus less risk in AD [aOR = 0.81 (0.71–0.92)] than in psoriasis [aOR = 1.18 (1.14–1.23)]. These elements involve a patient´s lifestyle and genetics (i.e., obesity). There is a possible common genetic susceptibility that may explain the association between IBD and AD. For the moment, however, we can leave aside digestive diseases: the risks are very low, negative, or insignificant.

## Infection

It is widely accepted that AD increases the risk of staphylococcal and herpetic infections, yet its effect on the general risk of infection is less clear. Among nearly 105,000 Danish patients, there was an increased risk of infection in the event of asthma, with and without smoking, but not in AD nor allergic rhinitis.[33] In a database of general practitioners in England that includes more than 3.1 million adults followed for 14 years, there was a prevalence for AD of 14.4%. Logically, the authors found an increased risk of skin infections, including warts, [OR = 1.98 (1.96–2]], dermatophytosis, [OR = 2.54 (2.47–2.61]], herpes simplex [OR = 2.08 (2.04 – 2.12]], impetigo [OR = 1.55 (1.47–1.64)], and molluscum contagiosum [OR = 3.11 (3.07–3.14)]. For non-cutaneous infections, there was an increased risk of otitis [OR = 2.24 (2.22–2.25)], pneumonia [OR = 1.27 (1.23–1.31)], and streptococcal angina [OR = 1.34 (1.26–1.41)].[34,35] The OR for infections, mental health and cardiovascular diseases are summarized in **Figure 1**.

## Neurology and eye diseases

***Epilepsy and migraines***

Using the Taiwanese national bank (35,000 AD and 35,000 controls followed for more than 10 years), an increased risk of epilepsy was found, 0.94 vs. 0.27 per 1,000 person/year, or $p < 0.001$ and HR of 2.91 (2.23–3.82) after adjustment, sensitivity tests where still showing a significant risk.[36] This also seems true in asthma and rhinitis [HR = 1.34 (1.04–1.72) for both groups]. Like AD, epilepsy is considered a chronic inflammatory disease involving mast cells.

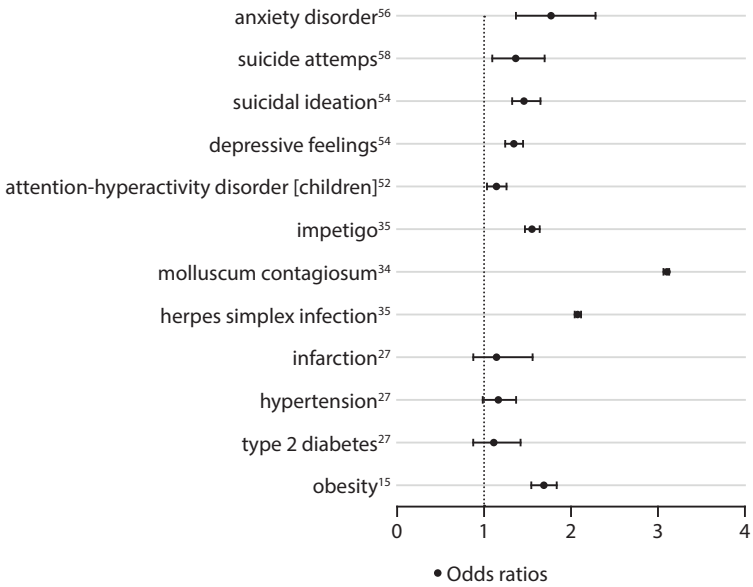


**Figure 1. Cardiovascular, mental health & infectious diseases OR: The chronic diseases reported in the literature with the greatest impact on the quality of life of AD patients are summarized.**

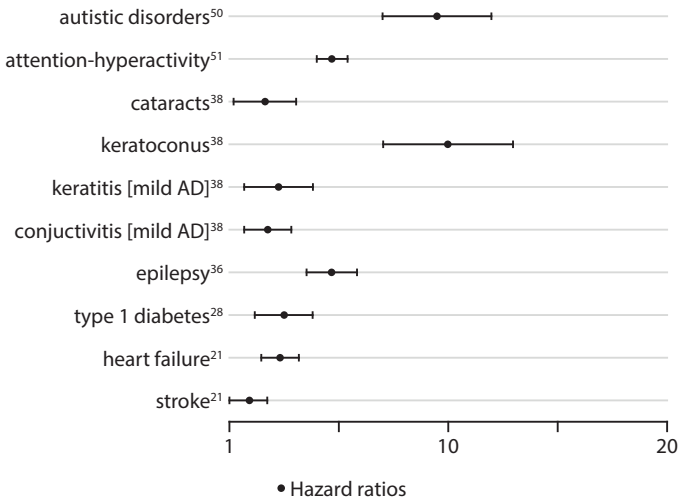


**Figure 2. Mental health, eye diseases and cardiovascular HR: Diseases reported in the literature with the greatest risk in AD patients are summarized.**

In Israel, a prospective study of 1,200,000 adolescents showed a prevalence of AD of 0.64% in boys and 0.9% in girls[37] with a higher prevalence of migrane in patients with AD: OR = 1.35 (1.18–1.54) in men and 1.51 (1.3–1.74) in women. A few small studies have also shown an increase in migraines in the context of atopic disease. Conversely, cases of migraine have a greater risk of AD. The reasons for this association are barely discussed by the authors. The relevant HR ratios are compiled in **Figure 2**.

***Eye diseases***

Among 5,766 adults with mild AD and 4,272 with severe AD in Denmark, a prescription for an ocular anti-inflammatory agent was identified in 12% and 18.9% of cases, respectively.[38] After adjustment, we have a HR for conjunctivitis = 1.48 (1.15–1.9) for mild AD and 1.95 (1.51–2.51) for severe AD. The risk of keratitis was also increased with HRs = 1.66 (1.15–2.40) and 3.17 (2.31–4.35). In cases of severe AD, the risk of keratoconus is greatly increased with an HR = 10 (5.02–19.96). Finally, for cataracts, the risk was increased only in those under 50 with HRs = 1.44 (1.03–2.01) and 1.81 (1.29–2.54) for mild and severe AD, respectively. While not surprising, these figures still provide a thorough quantification of the risk. The relevant HR are compiled in **Figure 2**.

In Korea, a population study did not find the same risk, when analyzing longitudinal cohort comprising 34,375 patients with AD under 20 years of age, including 3,734 severe cases.[39] Comparing four controls per case, there was no increased risk of keratoconus, neither overall nor when limited to severe AD. In a nested case-control study of 229 patients with keratoconus aged under 30 and 10 controls per case, there was no difference in the prevalence of AD or severe AD in the 2 years before diagnosis. Study results must be carefully analized in order to state risk for any given AD patient. A US study compared 1,892 AD patients to a control population of 4.7 million (5-year retrospective study): the incidence of eye diseases was highly increased: blepharitis [OR = 11 (10–12]], conjunctivitis [OR = 12.8 (12–13.8]], keratoconjunctivitis [OR = 8.2 (6.9–9.7]], and dry eye [OR = 6.7 (5.8–7.7).[40] There was also an increase in keratoconus [OR = 5.40 (3.6–7.7]], uveitis [OR = 5.4 (4.3–6.7]], retinal detachment [OR = 3.2 (2.4–4.2]], glaucoma [OR = 4.1 (3.6–4.6)], and cataract [OR = 4.9 (4.5–5.2)]. As expected, ocular herpes was increased with an OR = 4.9 (2.2–9.4). No other associated factors were analyzed. This prevalence study involved comparison to the general population but did not include information on the severity of the disease or the general characteristics of the patients. However, overall, there are more eye-related diseases in the case of atopic dermatitis.

## Vitamin D and bone health

***Vitamin D***

In a series of 97 patients under 18 years of age, vitamin D deficiency was found in 39%, with no correlation with SCORAD.[41] There are lower Vitamin D serum levels after the age of 3, in patients with dark skin and during the winter season. A Korean study measured vitamin D levels in 15,000 individuals over the age of 19, showing a slightly lower level in AD (18.6 ± 0.3 U vs. 19.2 ± 0.15 in controls), i.e., a slightly increased risk of AD in the event of vitamin D deficiency.[42] In 1,500 adults with skin diseases, there was also a lower vitamin D level in psoriasis and AD compared to controls, but with no link between level and severity.[43] Of the five polynucleotide polymorphisms associated with low vitamin D levels in 40,000 people, none were associated with asthma, AD, or even high immunoglobulin E (IgE) levels.[44]

***Osteoporosis***

In Taiwan, 36,000 AD and matched controls were followed for 14 years, showing 1.02% osteoporosis in the AD group vs. 0.36 in the controls.[45] The incidence is 1.82 per 1,000 persons/year. Female sex, age, CCI, corticosteroid use, and depression are risk factors for osteoporosis in this study. The higher risk of osteoporosis in atopic adults has been confirmed in the United States: aOR = 1.31 (1.12–1.54) and 1.25 (1.24–1.26) in two samples, like that of osteopenia

in the first group, OR = 1.86 (1.36–2.55).[46] People over 70 are most at risk. The authors suggest screening for osteoporosis beyond the age of 50 and recommend physical activity, weight loss, and sufficient intake of calcium and vitamin D.

## Respiratory diseases

Several studies show an association between sleep apnea and AD. The first comes from Taiwan, with 120,000 children with AD and as many controls: there is a higher prevalence of obstructive sleep apnea, HR = 1.86 (1.43–2.42).[47] This remained true regardless of comorbidities, habitat, age, or sex. Another team in Taiwan took a randomized sample study of one million people, 1,222 of whom had a diagnosis of obstructive sleep apnea, compared to 18,000 controls during a follow-up of 5.5 years.[48] These patients had a slightly higher risk of AD, OR = 1.5 (1.15–1.95). While researching asthma prevalence in Danish patients, 8,000 patients with AD and 24,000 with psoriasis and 80,000 controls from the general population, researchers found 18% of asthma in AD, 2.8% in psoriasis, and 2% in the general population.[8] Thereby, we have adjusted ORs of 5.95 (5.38–6.6) vs. psoriasis and 8.8 (8.08–9.5) vs. the general population. Chronic bronchitis was less common in AD than in psoriasis OR = 0.62 (0.53–0.72). However, in the case of severe AD, the risk of chronic bronchitis was increased vs. controls OR = 1.42 (1.17–1.73) it was decreased in AD vs. psoriasis, OR = 0.69 (0.56–0.86), but increased when compared vs. general population, OR = 1.24 (1–1.53). Also, there was less lung cancer in AD than in psoriasis, OR = 0.77 (0.59–0.99).

## Mental health

### *Hyperactivity and Autism Spectrum Disorders*

In Taiwan, 387,000 children with AD were compared to matched controls.[49] The prevalence of autism and attention disorders is 0.5 and 3.7% vs. 0.4 and 2.9% in controls, i.e., these diseases are increased in cases of very severe AD or very early onset. Also, in Taiwan, the authors included children born between 1998 and 2008 who were diagnosed with AD before the age of 3.[50,51] In this population, there were more attention-hyperactivity disorders HR = 2.92 (2.48–3.45) and autistic diseases HR = 8.9 (4.98–15.9). Children with all atopic diseases had the highest risk of attention-hyperactivity disorder [HR = 4.67 (3.8–5.4)] and autism spectrum disorder [HR = 16.6 (8.6–30.6)]. In the United States, based on 354,000 children and 34,000 adults, AD is associated with attention hyperactivity disorder, the risk being low in children [OR = 1.14 (1.03–1.26)] and a little higher in adults [OR = 1.61 (1.25–2.06)].[52] In the case of severe AD in children having less than three nights of normal sleep per week, the risk of attention disorders is much higher [OR = 16.8 (7–40)]. Some atopic children had severe attention problems. Similarly, when other atopic signs accompany AD, the risk is higher. In Saxony, 1,400 patients with AD and as many controls were studied and revealed that the prevalence of attention-hyperactivity disorder was increased, with an unadjusted OR of 1.5 (1.06–2.22); yet it was not associated with asthma or rhinitis.[53] In multivariate analysis, there remains a risk of attention disorders [OR = 1.47 (1.01–2.15)]. The significant HRs are summarized in **Figure 2**.

### *Depression and suicide*

For depression, a study of 72,000 Korean adolescents showed 6.8% AD, 31% depressive syndromes, 16% suicidal ideation, 5.8% suicide planning, and 4.2% suicide attempts.[54] The risks were higher in AD with OR = 1.27 (1.19–1.36) for depressive feelings, 1.34 (1.24–1.45) for suicidal ideation, 1.46 (1.32–1.65) for suicide planning, and 1.51 (1.33–1.7) for suicide attempts. In multivariate analysis, there was an association between suicidal ideation, suicide planning, and suicide attempts, yet with ORs less than 1.3. A twin study of Swedish children and adolescents found that the risk of depression and anxiety is somewhat higher in AD [OR = 1.22 (1.08–1.37)]. The numbers are identical in homozygotes and dizygotic twins, which indicates that there is no genetic link. When dealing with twins, the authors suggest always being interested in the second when one is atopic.[55] In an American study among children under 17, there was an increase in depression [OR = 1.81 (1.33–2.46)], anxiety [OR = 1.77 (1.36–2.29)], behavioral disorders [OR = 1.87 (1.46–2.39)], and autism [OR = 3 (2.13–4.34)]. There is a association between the risk of depression and suicide with the severity of AD.[56]

A meta-analysis of 36 articles showed a higher rate of depression in AD but no association with more severe depression, parental depression, use of antidepressants, or suicide.[57] The risk is increased for depression in general [OR = 1.71 (1.48–1.98)]. Another meta-analysis was done for "suicidality" on a total of 15 studies and 310,000 atopic, showing an increased risk of suicidal thoughts [OR = 1.44 (1.25–1.66)], and suicide attempts [OR = 1.36 (1.09–1.70)].[58] By contrast, Danish researchers found no increase in suicide risk, although they note an association with anxiety, depression, and suicidal ideation.[59]

A Finnish study of 57,700 AD patients and 40,000 controls found at least one psychiatric diagnosis in 17.2% of AD cases vs. 13.1% for controls.[60] Finally, a systematic review and meta-analysis in adults and children in Denmark yielded ORs = 2.19 (1.87–2.57)] for depression and 2.19 (1.75–2.73) for anxiety. Depression was also increased, albeit slightly, in children [OR = 1.27 (1.12–1.45)]. In adults and adolescents with AD, suicidal ideation was more frequent [OR = 4.32 (1.93–9.66)] than controls.[61]

## Autoimmune and skin diseases

A study of the general population in Germany did not show an association with vascular comorbidities; however, autoimmune diseases occurred more frequently in adults with AD (5.4% aAD vs. 3.2% in controls, $p < 0.017$). There was also a slightly higher frequency of rheumatoid arthritis (7.8% vs. 5%, $p < 0.016$). Logistic regression analysis yielded a low OR of 1.6 (1–2.7, $p < 0.045$) in a relatively small group.[62]

A study from Denmark with 5 controls per case reported an increased incidence among AD adults for 11 of the 22 autoimmune diseases studied.[63] Among the most robust associations are alopecia areata [OR = 26.3 (14.5–47)], vitiligo [OR = 18 (7.7–42)], chronic urticaria [OR = 9.9 (6.4–15.3)], and celiac disease [OR = 5.2 (2.9–9.2)]. In contrast, there was no association with thyroid disease, multiple sclerosis, or type I diabetes.

From the 42,000 cases of AD and 167,000 matched controls included in the Taiwanese study, AD increased the risk of lupus erythematosus [OR = 1.94 (1.48–2.5)], especially in children under 18 [OR = 3.2 (1.30–7)]. There was also a risk of rheumatoid arthritis and some type I diabetes. However, in multivariate analysis, these risks were no longer significant.[64] The reverse study was carried out among patients with systemic lupus erythematosus, again in Taiwan, in 1,673 cases (mean age 40 years and 82% women) and 6,700 controls.[65] We found an incidence of AD twice as high with a risk of systemic lupus that increases along with clinical lupus signs. These data support a relationship between lupus erythematosus and AD, at least in adults.

Studies have been explicitly devoted to vitiligo and alopecia areata, including 87,000 cases and as many controls with a history of AD in 11% of patients with vitiligo or alopecia areata.[66] AD is associated with an increased risk of alopecia areata [OR = 1.80 (1.18–2.76)] and vitiligo [OR = 2.14 (1.29–3.5)] in multivariate analysis. Finally, a meta-analysis of 16 studies for vitiligo and 17 for alopecia areata concluded that vitiligo is associated with a high risk of AD [OR = 7.8 (3–20)] and alopecia areata [OR = 2.57 (2.25–2.94)].[67] Moreover, three studies focused on early onset vitiligo, showing a higher risk of AD [OR = 3.5 (2.2–5.3)]. For complete or universal alopecia, the risk is somewhat higher.[67-70]

## Conclusion

The recently published work largely confirms our current understanding of AD. The risk of asthma, specifically, and other atopic manifestations and skin infections, generally, is increased among patients with AD. Of the different skin diseases, there is an undeniable risk of alopecia areata, vitiligo, and contact eczema and a lower risk of developing other autoimmune diseases. While comorbidities exist, these tend to be related to lifestyle, particularly smoking. There is a link with overweight, obesity, and metabolic syndrome, especially in severe AD. This is also the case for cardiovascular diseases; however, with OR/HRs below 1.5. There is no link to type II diabetes but, rather, to type I in children. In all other areas, the data are often inconsistent, and any increase in risk is low. Eye diseases seem to be the only exception, as these are much more frequent in AD. AD also has psychiatric consequences, including attention-hyperactivity disorder, anxiety, depression, and sometimes suicidality, especially when severe. This clinical landscape stands in contrast to psoriasis, which carries a greater risk for comorbidities.

## Disclosure

The authors report no conflicts of interest in this work.

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