

Cutaneous Comorbidities Associated With Atopic Dermatitis in Israel: A Retrospective Real-World Data Analysis

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Background: Patients with atopic dermatitis (AD) are susceptible to infectious and inflammatory cutaneous comorbidities.

Objective: The aim of the study was to describe the prevalence of cutaneous comorbidities associated with AD, including their relationship with AD severity.

Methods: A retrospective cross-sectional analysis was performed using the Israeli Maccabi Healthcare Services database. Prevalent AD cases on December 31, 2017, were diagnosed with AD at any time since 1998 and had 1 or more recent (2013–2017) AD diagnoses. Dispensed AD treatments within 5 or fewer years served as a surrogate for AD severity. Cutaneous comorbidities in AD cases were compared with non-AD controls matched 1:1 on age, sex, and residential area. Among adults, comorbidities were compared across AD severity using multinomial logistic regression.

Results: The eligible population included 94,483 patients with mild (57.7%), moderate (36.2%), or severe (6.1%) AD, and 94,483 matched non-AD controls. Skin infections, inflammatory skin conditions, cutaneous manifestations of AD, and sweat gland disorders were more prevalent ($P < 0.001$) in patients with AD than in controls. Most cutaneous comorbidities that were more prevalent in adult patients with AD were also significantly ($P < 0.001$) associated with AD severity.

Conclusions: This study suggests that AD is associated with many infectious and inflammatory cutaneous comorbidities and highlights the relationship between AD severity and comorbidity prevalence.

Atopic dermatitis (AD) is a common, chronic inflammatory disease associated with significant physical, psychological, and economic burden.^{1–3} In Israel, an AD incidence of 7.0 per 1000 person-years and prevalence of 4.4% has been reported.⁴ Patients with AD have reduced health-related quality of life associated with AD symptoms and disease activity,^{2,5,6} with approximately one-third of patients estimated to have moderate to severe disease.

Real-world data from the United States⁷ and Israel⁴ suggest that patients with AD, particularly those with severe AD, have significantly higher health care use and costs than non-AD controls, further emphasizing the multidimensional burden of AD.

Additional burden in patients with AD is attributed to an increased risk for comorbidities, primarily atopic diseases. Cutaneous comorbidities are also reported in patients with AD including cutaneous

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infections (eg, *Staphylococcus aureus*, viral infections)^{8,9} and autoimmune diseases (eg, alopecia areata, vitiligo).^{10–12} Other studies have described seborrheic dermatitis and contact dermatitis (CD) associated with AD, although no consistent signal has emerged.^{13–15}

Real-world evidence on the burden of cutaneous comorbidities in AD and their association with disease severity remains scarce. Identification of cutaneous comorbidities, which can be challenging in patients with active dermatitis, is key to disease management and improving patient outcomes.¹⁶ This study aimed to evaluate the cutaneous comorbidities associated with AD in Israel, including their relationship with AD severity.

MATERIALS AND METHODS

Data Source

This is a retrospective cross-sectional analysis of electronic health care data routinely collected by Maccabi Healthcare Services (MHS), a nationwide health payor/provider with more than 2.3 million members in 2017, representing approximately 25% of the Israeli population. Routinely collected diagnoses (inpatient and outpatient), procedures, and pharmacy data (dispensed medications) were integrated with demographic data from a stable population (annual turnover rate, <1%).

Diagnoses are coded according to the *International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM)* and MHS-developed codes. Medications coded using the Israeli system are translated to the Anatomical Therapeutic Chemical coding system where available. Procedures are coded using the Current Procedural Terminology codes.

Study Populations

The study population included MHS members alive on December 31, 2017, with 12 or more months of prior enrollment or younger than 1 year. Within this population, eligible patients with AD were identified according to the case definition described hereinafter and were matched to non-AD controls. Eligible patients with AD were identified by inpatient and outpatient diagnoses of AD (*ICD-9-CM* code, 691.8). Patients were required to have 1 or more recently documented AD diagnosis codes (in the past 5 years, 2013–2017) and meet 1 or more of the following criteria in 1998–2017: (i) 1 or more diagnoses from a relevant specialist (dermatology or allergy/immunology), (ii) 1 or more diagnoses from a hospital or MHS medication approval center, (iii) 2 or more separate diagnoses from a primary care physician (including pediatricians and general practitioners), and (iv) 1 or more diagnoses from a primary care physician or related specialist combined with a dispensed prescription of a topical calcineurin inhibitor (TCI). Eligible non-AD controls (without prior AD diagnosis in 1998–2017) were selected by matching 1:1 with AD patients according to year of birth, sex, and residential area. Patients younger than 12 months were age matched in 2 groups, younger than 6 months and 6 to younger than 12 months.

AD Severity Estimation

Disease severity was estimated on December 31, 2017, based on dispensed AD medication within the previous 5 years,¹⁷ including topical corticosteroids (TCSs), TCIs, systemic corticosteroids, systemic immunomodulators (methotrexate, azathioprine, cyclosporine, mycophenolate mofetil), and phototherapy; biologic therapy for AD was not available in Israel during the study period. Topical corticosteroid potency was defined according to the World Health Organization classification, adapted to Israeli guidelines. Moderate AD was defined as 2 or more dispensed TCIs or TCSs of mid/high potency or 1 or more phototherapy. Severe AD was defined as 2 or more dispensed systemic corticosteroids combined with moderate AD criteria or 1 or more dispensed systemic immunomodulators. Patients not meeting these criteria were defined as having mild AD.

Cutaneous Comorbidities

Cutaneous comorbidity burden was evaluated using data on cutaneous comorbidities within 5 years before December 31, 2017. These comorbidities included cutaneous infections and inflammatory conditions, cutaneous malignancies, and premalignant lesions (specifically basal cell carcinoma, squamous cell carcinoma, melanoma, and actinic keratosis), and disorders of sweat glands. Atopic dermatitis–related cutaneous manifestations were separately defined as cutaneous conditions that can be clinical manifestations of AD and included pityriasis alba, keratosis pilaris, nummular eczema, hand eczema (HE), papular dermatitis, prurigo nodularis, lichen simplex chronicus, eczema/dermatitis unspecified, and facial dermatitis unspecified.

Among adults, conditions that were significantly associated with AD (vs non-AD controls) were further investigated to better understand their relationship with AD severity. The adult population was selected for this analysis as moderate to severe AD was well represented in this population.

Covariates

The AD study population was characterized according to age on December 31, 2017, sex, and residential area. Socioeconomic status (SES) was derived by the Points Location Intelligence score integrating expenditure data, which correlates highly with SES measured by the Israeli Central Bureau of Statistics¹⁸ and categorized as low (1–4), medium (5–6), or high (7–10).

Statistical Analysis

Descriptive statistics were presented as number (percent), mean $\pm$ SD, or median (interquartile range). For univariate comparisons across groups, χ^2 tests were performed and effect size was reported as the standardized mean difference based on Cohen's *d* for the 2 groups and its extension to more than 2 groups based on the Mahalanobis distance.¹⁹ A *P* value less than 0.05 was considered statistically significant. Standardized mean difference of 0.1 or greater was defined as a notable difference in this analysis; this cutoff was used to select

variables for investigation in further analyses. Conditional logistic regression was used to calculate adjusted odds ratios (ORs) and 95% confidence intervals, adjusting for age and SES to assess the association between cutaneous conditions and AD (vs matched non-AD controls). Multinomial logistic regression was used to compute adjusted ORs for moderate versus mild AD and severe versus mild AD, adjusting for differences in age, sex, and residential area. Analyses were performed using SPSS Statistics v.2.5. (IBM, Armonk, NY) and R statistical software v.3.5 (The R Foundation for Statistical Computing, Vienna, Austria).

Ethical Approval

This study was approved by the Maccabi Research Committee and institutional review board of the Bait Ba-Lev Medical Center, Israel.

RESULTS

Study Population

A total of 94,483 patients with AD (December 31, 2017) were included in the study, with 94,483 matched non-AD controls.⁴ Median (interquartile range) age was 11.2 years (5.7–28.4 years) and 52.3% were female. Patients younger than 6 months, 6 months to younger than 12 years, 12 to younger than 18 years, and 18 years or older accounted for 0.2%, 52.5%, 13.7%, and 33.6% of AD cases, respectively. Using dispensed treatment data as a surrogate for AD severity, 43.8%, 46.3%, and 9.9% of adult patients had mild, moderate, and severe AD, respectively.

Cutaneous Comorbidities and Manifestations in Patients With AD

With respect to infectious cutaneous comorbidities, cellulitis/abscess, impetigo, and dermatophytosis were more common in AD patients than in controls across all age groups, except for infants younger than 6 months (Table 1). Other associated cutaneous infections by age group are presented in Table 1.

With respect to inflammatory cutaneous comorbidities, seborrheic dermatitis and CD were more common in AD patients than in controls across all age groups. Lichen planus (LP) was more common in AD patients than in controls among adults and adolescents (Table 1). Seborrheic dermatitis had the highest prevalence in infants with AD (14.5%), whereas CD prevalence increased with age, reaching 50% (compared with 15.5% in controls) in adults (Table 1). Disorders of sweat glands were also more common in AD patients than in controls for all age groups 6 months or older (Table 1).

With respect to AD-related cutaneous manifestations, nummular eczema was more common in AD patients than in controls across all age groups except for infants younger than 6 months. Other conditions showed an age-dependent association. Dermatographism, lichen simplex chronicus, and HE were more common in adults with AD than in controls. Hand eczema was also more common in adolescents with AD versus controls, whereas keratosis pilaris and pityriasis

alba were more common in AD patients versus controls in those aged 6 months to younger than 18 years (Table 1). None of the assessed malignant and premalignant skin conditions were found to be associated with AD overall or in any age group. For the comorbidities that were more prevalent in AD patients overall (all ages) than in controls, adjusted ORs are reported in Table 2.

Most of the cutaneous comorbidities that were more prevalent in adult AD patients were also associated with AD severity, except for impetigo, viral warts, and dermatographism (Table 3). All associations remained after adjustment in a multivariable model (Fig. 1). The conditions most strongly associated with AD severity in adults (ORs > 2 for moderate or severe vs mild AD) included scabies, CD, LP, sweat gland disorders, and several cutaneous manifestations of AD.

DISCUSSION

The current study provides real-world evidence of an increased burden of several infectious and inflammatory skin conditions in patients with AD compared with non-AD controls in a population where AD prevalence and severity distribution have been shown to be comparable with other real-world studies.⁴ In adults, this burden was observed to increase with severity.

Our findings suggest an association of AD with various bacterial and viral cutaneous infections,^{8,9,12,20–24} starting at 6 months of age. Impetigo and cellulitis are associated with AD across all age groups, highlighting the significance of bacterial infection, mainly with *Staphylococcus aureus*, in patients with AD.²³ The current study also identified an increased prevalence of dermatophytosis across all age groups. Data on the association of AD with dermatophyte infections are conflicting^{22,25,26}; however, a recent cohort study supports an association of AD with dermatophyte infection.²² In congruence with previous studies,²⁷ cutaneous viral infections (eg, herpes simplex virus, viral warts, molluscum contagiosum) were also shown to be more prevalent in AD patients than in controls. The profile of associated viral infections differed by age, with increased herpes simplex virus and viral warts associated with older patients (adolescents and adults), and increased molluscum contagiosum in children and adolescents. In adults, the prevalence of most cutaneous infections investigated in this study increased significantly with disease severity. In the current study, the association of some cutaneous infections with AD severity may be confounded by use of systemic immunosuppressive therapy in patients with severe AD. However, patients with moderate AD were more likely than those with mild AD to have a concurrent diagnosis of several cutaneous infections. These patients received minimal systemic immunosuppressants, suggesting that these associations may be due to AD itself.

Seborrheic dermatitis and CD were more prevalent in AD patients across all age groups compared with controls, and their prevalence increased with AD severity in adults. Atopic dermatitis and seborrheic dermatitis are frequently difficult to distinguish, especially in young children, and a diagnosis of seborrheic dermatitis may later be revised to AD.²⁸ A predisposition to allergic AD

TABLE 1. Prevalence of Cutaneous Comorbidities and Manifestations in Patients With AD and Non-AD Controls by Age Group

Comorbidity or Manifestation	<6 mo			6 mo–<12 y			12 y–<18 y			≥18 y			All	
	AD	Control	SMD	AD	Control	SMD	AD	Control	SMD	AD	Control	SMD	AD	Control
n	193	192	NA	49,652	49,653	NA	12,941	12,941	NA	31,697	31,697	NA	94,483	94,483
Infectious, %														
Cellulitis/abscess	1.0	0	0.145	13.9	10.6	0.101*	12.2	9.0	0.106*	16.1	11.8	0.122*	14.4	10.8
Impetigo	2.1	0	0.206	14.7	7.8	0.219*	9.1	4.0	0.209*	2.7	0.9	0.134*	9.9	5.0
Candidiasis	4.1	2.6	0.085	11.7	9.8	0.062*	2.5	1.5	0.072*	11.4	7.9	0.117*	10.3	8.0
Dermatophytosis	0	0	NA	10.4	5.9	0.162*	18.9	12.4	0.179*	34.1	23.5	0.237*	19.5	12.7
Herpes simplex virus	0	0	NA	4.6	3.4	0.063*	4.3	3.1	0.068*	7.9	4.9	0.123*	5.7	3.8
Molluscum contagiosum	0	0	NA	17.3	9.2	0.239*	9.5	5.6	0.146*	1.2	0.8	0.039*	10.8	5.9
Viral warts	0	0	NA	9.3	7.7	0.055*	26.6	22.1	0.105*	16.6	12.6	0.114*	14.1	11.3
Scabies	0	0	NA	1.0	0.3	0.084*	1.2	0.6	0.063*	2.1	0.6	0.128*	1.4	0.5
Inflammatory, %														
Acne	3.1	0	0.253†	1.3	0.7	0.059*	21.9	18.7	0.079*	14.7	12.3	0.070*	8.6	7.1
LP	0	0	NA	0.3	0.1	0.050*	1.5	0.4	0.112*	5.7	1.3	0.239*	2.3	0.5
Seborrheic dermatitis	14.5	1.6	0.490*	10.0	3.1	0.284*	5.7	2.0	0.190*	9.6	4.1	0.217*	9.3	3.3
Contact dermatitis	8.3	0.5	0.386‡	27.1	12	0.389*	29.1	10.5	0.481*	50.0	15.5	0.788*	35.0	12.9
AD cutaneous manifestations, %														
Keratosis pilaris	0	0	NA	2.1	0.8	0.109*	5.1	2.8	0.118*	1.5	0.9	0.049*	2.3	1.1
Pityriasis alba	0	0	NA	4.3	2.0	0.133*	7.1	2.6	0.209*	1.0	0.4	0.076*	3.6	1.5
Dermatographism	0	0	NA	0.2	0.1	0.032*	0.6	0.2	0.058*	1.4	0.4	0.106*	0.6	0.2
Lichen simplex chronicus	0	0	NA	0.2	0	0.041*	1.1	0.3	0.086*	3.9	1.0	0.186*	1.6	0.4
Hand eczema	0.5	0	0.102	0.5	0.1	0.062*	1.6	0.3	0.139*	5.4	0.9	0.265*	2.3	0.4
Nummular eczema	0	0	NA	2.1	0.6	0.128*	2.5	0.6	0.152*	4.7	0.9	0.237*	3.1	0.7
Sweat gland disorders, %	2.1	0.5	0.137	5.6	2.6	0.150*	4.8	1.8	0.168*	8.8	2.9	0.253*	6.6	2.6

Age was assessed on December 31, 2017. Numbers are the percentage of patients with AD or non-AD controls with the condition reported in the previous 5 years. Conditions shown were more prevalent in patients with AD than in controls, with an SMD ≥0.1 for ≥1 age group or overall (SMD values ≥0.1 with P < 0.05 are bolded). Controls are individuals without documented AD matched 1:1 for age, sex, and residential area. Comparisons across groups were performed using χ^2 tests.

*P < 0.001.

†P < 0.05.

‡P < 0.01.

AD, atopic dermatitis; LP, lichen planus; NA, not applicable; SMD, standardized mean difference.

TABLE 2. Adjusted ORs for Cutaneous Comorbidities and Manifestations Associated With AD (N = 94,483 Matched Pairs)

Comorbidity or Manifestation	Prevalence, %		Adjusted OR (95% CI)*
	AD	Control	
Infectious			
Impetigo	9.9	5.0	2.16 (2.08–2.24)†
Molluscum contagiosum	10.8	5.9	1.96 (1.89–2.03)†
Dermatophytosis	19.5	12.7	1.74 (1.69–1.78)†
Cellulitis/abscess	14.4	10.8	1.41 (1.37–1.45)†
Inflammatory			
LP	2.3	0.5	4.39 (3.97–4.84)†
Contact dermatitis	35.0	12.9	3.73 (3.63–3.82)†
Seborrheic dermatitis	9.3	3.3	3.01 (2.89–3.15)†
AD cutaneous manifestations			
Hand eczema	2.3	0.4	6.27 (5.60–7.03)†
Nummular eczema	3.1	0.7	4.42 (4.05–4.82)†
Lichen simplex chronicus	1.6	0.4	3.88 (3.46–4.34)†
Pityriasis alba	3.6	1.5	2.37 (2.22–2.52)†
Sweat gland disorders	6.6	2.6	2.62 (2.50–2.75)†

*OR, adjusted for age and SES.

†P < 0.001.

AD, atopic dermatitis; CI, confidence interval; LP, lichen planus; OR, odds ratio; SES, socioeconomic status.

(ACD) has been observed in patients with AD, particularly in those patients with a history of AD in childhood, although the true prevalence of ACD among patients with AD is unknown.^{29,30} The skin of patients with AD is more susceptible to colonization by commensal

organisms, including *Staphylococcus*, *Malassezia*, *Candida*, and *Alternaria*, than that of healthy individuals, and these patients frequently develop allergic reactions to weaker microbial protein antigens that would not elicit such a response in individuals with normal skin function.^{30–33} Allergic AD remains an important comorbidity and potential exacerbator of AD in clinical practice³⁴ and should be sought out when clinically suspected by a thorough history, physical examination, and patch testing when appropriate.^{29,35}

In the current study, patients with AD (≥12 years old) were more than 4 times more likely than non-AD controls to have a concurrent diagnosis of LP. In addition, LP prevalence increased with increasing AD severity. This was surprising, because LP is an interferon-driven, CD8⁺ T-cell disease,³⁶ whereas AD is primarily a T-helper type 2–driven disease.² Further studies are needed to validate this comorbidity and to characterize the clinical, immunohistochemical, and molecular patterns of coexistent disease.

Disorders of sweat glands were reported in all age groups older than 6 months, and prevalence increased significantly with AD severity. Disorders of sweat glands (ICD-9-CM group code 705.xx) are a broad diagnostic category, encompassing not only true sweat gland disorders, such as miliaria, but also dyshidrosis and hidradenitis, which were historically categorized in this group but are currently not considered to be sweat glands pathologies. Our database does not allow teasing out which diseases underlie the observed association of sweat gland disorders with AD. One possibility is that hidradenitis suppurativa, recently reported to have a bidirectional association with AD, is the cause of this finding.³⁷ It could also be that there is an association of AD with true sweat gland disorders, consistent with reports that patients with AD have a disturbed sweat

TABLE 3. Prevalence of Cutaneous Comorbidities and Manifestations in Adult Patients With AD by Severity

Comorbidity or Manifestation	Mild (n = 13,884)	Moderate (n = 14,680)	Severe (n = 3133)	SMD
Infectious, %				
Cellulitis/abscess	13.2	17.3	23.0	0.172*
Impetigo	1.8	3.3	4.2	0.093*
Candidiasis	9.1	12.6	15.6	0.132*
Dermatophytosis	28.9	37.6	41.0	0.169*
Herpes simplex virus	6.5	8.5	10.9	0.105*
Viral warts	15.1	17.7	17.8	0.048*
Scabies	1.4	2.4	4.1	0.113*
Inflammatory, %				
LP	3.0	7.3	10.4	0.202*
Seborrheic dermatitis	7.1	11.6	11.1	0.102*
Contact dermatitis	36.1	59.7	65.8	0.411*
AD cutaneous manifestations, %				
Dermatographism	1.2	1.3	2.3	0.057*
Lichen simplex chronicus	2.1	5.1	6.4	0.145*
Hand eczema	2.6	7.4	8.6	0.177*
Nummular eczema	2.5	6.2	8.0	0.168*
Sweat gland disorders	5.6	11.2	11.4	0.139*

Age was assessed on December 31, 2017. Numbers are the percentage of patients with AD with the condition reported in the previous 5 years. Conditions shown with bolded SMD values were more prevalent in more severe AD, with an SMD ≥ 0.1 and P < 0.05. Comparisons across groups were performed using χ^2 tests.

*P < 0.001

AD, atopic dermatitis; LP, lichen planus; SMD, standardized mean difference.

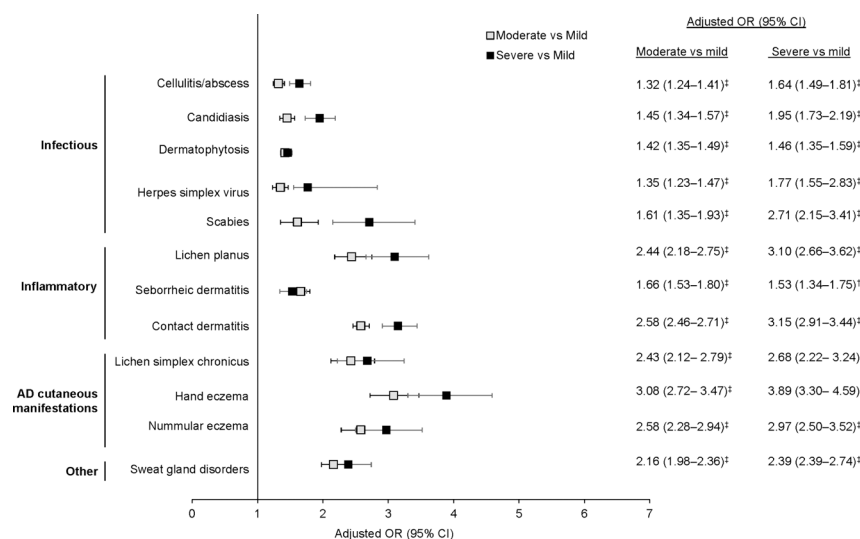


Figure 1. Cutaneous comorbidities and manifestations in adults by AD severity (n = 31,697). Moderate (n = 14,860) versus mild (n = 13,884) shown in gray squares; severe (n = 3133) versus mild (n = 13,884) shown in black squares. Odds ratios were calculated using multinomial logistic regression, adjusted for age, sex, and residential area. For each comparison, mild AD was used as the reference. Comorbidities were diagnosed in the previous 5 years (2013–2017). [†]P < 0.01; [‡]P < 0.001 for moderate or severe versus mild AD. AD, atopic dermatitis; CI, confidence interval; OR, odds ratio.

response, such as altered sweat content, sweat allergy, abnormal sweating dynamics, and altered sweat output.^{32,38–40} In contrast to earlier reports, the current study did not find an association of AD with cutaneous autoimmune diseases, such as alopecia areata and vitiligo.^{10–12,41}

As expected, we found an association with several cutaneous conditions, which are considered a manifestation or part of the clinical spectrum of AD.^{35,42–49} Pityriasis alba and keratosis pilaris were more prevalent in children and adolescents with AD compared with non-AD controls, but not in adults. Both conditions are generally asymptomatic, are associated with filaggrin mutations,^{50,51} and are markers of an atopic diathesis. In contrast, lichen simplex chronicus, HE, and nummular eczema are usually symptomatic and have a profound negative impact on the patient's quality of life.^{43,45,46,48,52} For all 3 conditions, prevalence increased with disease severity in adults.

Our analysis used a robust data source that included electronic health records and dispensed prescriptions for a previously defined AD patient population from a nationally representative database.⁴ In this real-world study of AD, prevalence and disease severity distribution were similar to those reported in other database studies.^{53–57}

As a health records database analysis, our study has some inherent potential limitations. The use of dispensed treatment as a surrogate for AD severity may result in the misclassification of severity. There was potential misdiagnosis of cutaneous comorbidities that resemble AD. These include scabies, which also presents with a highly pruritic papular rash,⁵⁸ and LP, which can be confused with an LP-like AD variant observed in heavily pigmented patients,⁵⁹ or with lichenified AD in the case of hypertrophic LP.^{60,61} Other limitations include detection of comorbidities that result from AD treatment (eg, TCS-induced acne from the treatment of infantile facial

AD or skin infections secondary to immunosuppressive treatment). Surveillance bias is another possible limitation, with enhanced detection of cutaneous comorbidities due to increased dermatologist examinations in AD patients than in controls. Because of the cross-sectional nature of the study, we are unable to comment on causality. A cohort study may provide further insights regarding the risk of comorbidities after a diagnosis of AD.

This study provides real-world evidence of many infectious and inflammatory cutaneous comorbidities that may arise in patients with AD and highlights the relationship between increasing AD severity and comorbidity prevalence. Cutaneous comorbidities are an important dimension of the burden of AD, especially in patients with severe disease. Recognizing and managing cutaneous comorbidities can be challenging on a background of dermatitis but are key to providing optimal patient care.

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