# Prevalence of asthma in patients with atopic dermatitis: A systematic review and meta-analysis

Nanna Ravnborg, MS,[a,b] Danni Ambikaibalan, MD,[a,b] Gaurav Agnihotri, MD,[c] Shmuel Price, MD,[d] Supriya Rastogi, MD,[e] Kevin R. Patel, MD,[f] Vivek Singam, MD,[g] Yuki Andersen, MD, PhD,[a,b] Anne-Sofie Halling, MD,[a,b] Jonathan I. Silverberg, MD, PhD, MPH,[e,h] Alexander Egeberg, MD, PhD,[a,b] and Jacob P. Thyssen, MD, PhD, DMSc[i]

*Hellerup, Denmark; Chicago and North Chicago, Illinois; and Kansas City, Missouri*

***Background:*** It is well established that asthma is common in patients with atopic dermatitis (AD).

***Objectives:*** We performed a systematic review and meta-analysis to determine the prevalence of asthma and respiratory symptoms in individuals with AD as well as the association between AD and asthma.

***Methods:*** At least 2 authors independently searched the medical databases PubMed, EMBASE, LILACS, and SCOPUS for all English-language studies with data on asthma prevalence among patients with AD or the association between AD and asthma. Pooled odds ratios with 95% confidence intervals (CIs) and pooled proportions were estimated with random-effects models. The Newcastle-Ottawa scale was used to assess study quality.

***Results:*** The search yielded 39,503 articles. Of these, 213 studies were included in a quantitative analysis. The overall pooled prevalence of asthma was 25.7% (95% CI, 23.7-27.7) in patients with AD and 8.1% (95% CI, 7.0-9.4) among reference individuals. There was a significant association between AD and asthma when compared with reference individuals (odds ratio, 3.03; 95% CI, 2.64-3.47).

***Limitations:*** The definitions of AD and asthma differed across the included studies and varied from self-report to physician diagnosed.

***Conclusions:*** Asthma is a common comorbidity of AD. Physicians should be cognizant of this relationship and address asthma symptoms in their patients. ( J Am Acad Dermatol 2021;84:471-8.)

***Key words:*** association; atopic dermatitis; asthma; eczema; meta-analysis; prevalence; systematic review.

From the Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark[a]; Copenhagen Research Group for Inflammatory Skin (CORGIS), Hellerup, Denmark[b]; University of Illinois at Chicago College of Medicine[c]; Midwestern University Chicago College of Osteopathic Medicine, Illinois[d]; Northwestern University Feinberg School of Medicine, Chicago, Illinois[e]; Rosalind Franklin University of Medicine and Science, North Chicago, Illinois[f]; University of Missouri—Kansas City School of Medicine.[g]; Northwestern Medicine Multidisciplinary Eczema Center, Chicago, Illinois[h]; and Department of Dermatology and Venereology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark.[i]

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Reprint requests: Jacob P. Thyssen, MD, PhD, DMSc, Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Gentofte Hospitalsvej 1, 2900 Hellerup, Denmark. E-mail: Jacob.p.thyssen@regionh.dk.

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Atopic dermatitis (AD) is a chronic inflammatory skin disease that may be lifelong.[1,2] It is well documented that pediatric and adult patients with AD have an increased occurrence of asthma,[3] in part due to an overlap in genetic risk variants and environmental triggers.[4,5] A subgroup of patients with AD may become sensitized to allergens through an impaired skin barrier with filaggrin deficiency; this subgroup may then develop asthma after subsequent exposure to the same allergens in the airways.[3,5]

In both AD and asthma, an adaptive immune response is observed where T helper (Th) type 2 cells,[6-8] through secretion of interleukin (IL) 4, IL-5, IL-10, and IL-13, can further drive type 2 immune reactivity and enable eosinophilic recruitment as well as production of immunoglobulin (Ig) E.[3,6] Interestingly, patients with both AD and asthma seem to have an increased risk of systemic and cutaneous infections compared to those with AD alone.[9]

The exact prevalence of asthma among individuals with AD remains unknown. Previous systematic reviews and meta-analyses examined restricted populations or specific pathophysiologic profiles.[2,10,11] This systematic review and meta-analysis determined (1) the prevalence of asthma in individuals with AD compared with control individuals and (2) the association between AD and asthma.

**CAPSULE SUMMARY**

- Patients with atopic dermatitis have an elevated risk of developing asthma compared with healthy control individuals, but the extent of this association is unknown.
- The mean prevalence of asthma among patients with atopic dermatitis was 25.7%. Physicians should be aware of this and address asthma symptoms in their patients with atopic dermatitis.

## MATERIALS AND METHODS

### Literature search

A study protocol was developed before the start of the study and registered online at PROSPERO (ID CRD42019133923). We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. The medical databases PubMed, EMBASE, LILACS, and SCOPUS were searched from June through October 2018 by using the search terms listed in Supplementary Table I (available via Mendeley at https://data.mendeley.com/datasets/vwhb8vhp4c/2). The search included all English language articles from database inception until search end (October 5, 2018).

### Inclusion and exclusion criteria

All studies that contained data on (1) the prevalence of asthma in patients with AD or (2) the association between AD and asthma were included. Data were reconstructed through information on sample size, binary data, and related confidence intervals (CI)[12] in studies without absolute data. Studies examining the association between AD and asthma, but without providing primary epidemiologic data for the meta-analysis, were included only in the qualitative analysis. A priori, all studies with fewer than 50 patients with AD were excluded because a population of this size was deemed too small to provide adequate data. No limitation was set regarding age, study type, or year of publication.

### Data extraction

At least 2 authors (NR, DA, GA, SP, SR, and KP) independently screened and reviewed titles and abstracts before retrieving full-text articles. Duplicates were removed, as were articles analyzing the same study population. If this occurred, the article presenting the most comprehensive data set was included. If studies had data on asthma prevalence at different ages, we identified and used the study with the highest number of patients with AD after the age of 6 years to obtain an asthma prevalence closest to a lifetime prevalence. After inclusion of all relevant studies, data extraction was carried out.

Study quality was assessed using the Newcastle-Ottawa Scale (NOS).[13] This scaling system is used to assess the quality of nonrandomized studies according to 3 variables: selection of study population, comparability, and ascertainment of exposure/outcome (depending on study design). Because the NOS was created for case-control and cohort studies, an adapted version of NOS was used for cross-sectional studies. Each study was awarded up to 9 points according to the original NOS and 10 points according to the adapted version.

### Statistical analysis

We performed a proportion meta-analysis to obtain a pooled effect estimate in the overall population and in prespecified subgroups. Odds ratios (ORs) with 95% confidence intervals (CIs) of asthma in individuals with AD compared with control individuals were estimated. Analysis was performed only if more than 5 articles had available data. Study heterogeneity was assessed by using Cochran $Q$ and the $I^2$ statistic, which portrays the

*Abbreviations used:*

AD: atopic dermatitis
CI: confidence interval
Ig: immunoglobulin
IL: interleukin
NOS: Newcastle-Ottawa Scale
OR: odds ratio
Th: T helper

percentage of variation across the included studies that is attributable to heterogeneity rather than chance. The pooled OR and pooled proportion with its 95% CI were calculated by using random-effects models according to the DerSimonian-Laird method for all investigated endpoints. The random-effects model was chosen because we observed significant between-study heterogeneity due to variable prevalence estimates and ORs. To further support this, we observed Cochrane $Q$ statistic $P$ values of less than .05 and $I^2$ values of greater than 75%. We assessed publication bias using funnel plots and the Egger test. We constructed forest plots to visually display the study results. All statistical tests were 2-sided, with a significance level of less than .05. Statistical analyses were performed with StatsDirect, version 3.0.22 (StatsDirect Ltd, Cheshire, UK).

## RESULTS

A total of 39,503 articles were identified (PubMed, n = 5762; EMBASE, n = 12,761; LILACS, n = 7507; SCOPUS, n = 13,473). After this, the literature search yielded a total of 37,767 nonduplicated articles. After screening titles and abstracts, we read 1189 articles in full. Of these, 970 articles were excluded for reasons listed in the PRISMA flow diagram (Fig 1). A total of 218 studies were included in the qualitative analysis, of which 213 contained data for the quantitative analysis. Detailed information on included studies is provided in Supplementary Tables II, III, and IV (available via Mendeley at https://data.mendeley.com/datasets/vwhb8vhp4c/2). An Egger's test for publication bias showed an asymmetric inverted funnel shape of the bias assessment plot in both meta-analyses. However, because the data set was large and data were scattered equally across the assessment plots, it did not indicate considerable publication bias. Heterogeneity was observed to be 99.7% in the proportion analysis. Heterogeneity ranged between 89.2% and 99.9% through all subanalyses.

### Quantitative analysis

**Asthma prevalence in patients with AD.** A total of 213 studies including 688,927 patients with AD and 2,223,921 reference individuals were analyzed. The overall pooled prevalence of asthma was 25.7% (95% CI, 23.7-27.7) in patients with AD and 8.1% (95% CI, 7.0-9.4) among reference individuals. When limiting analysis to 50 studies in which both AD and asthma were diagnosed by a physician, the pooled prevalence was 21.0% (95% CI, 17.9-24.3) among 428,037 patients with AD. A total of 33 studies comprising 60,582 individuals defined asthma as wheeze. When restricting analysis to these studies only, the prevalence was 28.8% (95% CI, 20.7-37.6). A total of 90 studies examined 468,096 children with AD and found a pooled asthma prevalence of 26.3% (95% CI, 23.5-29.1). In 31 studies examining 93,574 adults with AD, a pooled asthma prevalence of 21.8% (95% CI, 18.4-25.4) was observed. The prevalence of asthma was 24.1% (95% CI, 18.8-29.9) in female patients only (all ages), based on data from 14 studies and a total of 74,283 patients with AD. The prevalence of asthma among male patients (all ages) was 27.9% (95% CI, 20.5-36.0) based on data from 13 studies and 6380 patients with AD. When stratified by region, the highest prevalence of asthma was found in studies from Australia (34.1%; 95% CI, 26.1-42.6) and the lowest prevalence in studies from Asia (19.6%; 95% CI, 15.8-23.6). When stratifying according to age, sex, and region, no distinction was made regarding the assessment method of AD and asthma to ensure subcategories that were as large as possible. A total of 188 studies had a NOS score of 7 or higher, which indicated good study quality. Stratification by study quality did not alter asthma prevalence (Table I).

**Asthma prevalence by AD severity and disease activity.** Only a few studies reported data on the severity of AD. Based on data from 10 and 15 studies, the pooled prevalence of asthma was 21.8% (95% CI, 16.1-28.1) and 28.1% (95% CI, 22.7-33.8) in 14,005 patients with mild AD and 6453 patients with moderate to severe AD respectively; however, an overlap in CIs was seen. With data from 93 studies comprising 429,284 patients and 49 studies with 135,981 patients, no significant difference was found when patients were stratified by a diagnosis of ever having asthma and a diagnosis of current asthma, respectively (Table I). Similarly, no difference was observed when patients were stratified by ever AD or current AD based on 398,452 patients in 70 studies and 240,500 patients in 57 studies, respectively.

**Asthma prevalence by study design and study size.** Of the 213 included studies, 138 studies were cross sectional, 61 were cohort studies, 8 were case-control, and 6 were clinical trial studies. No

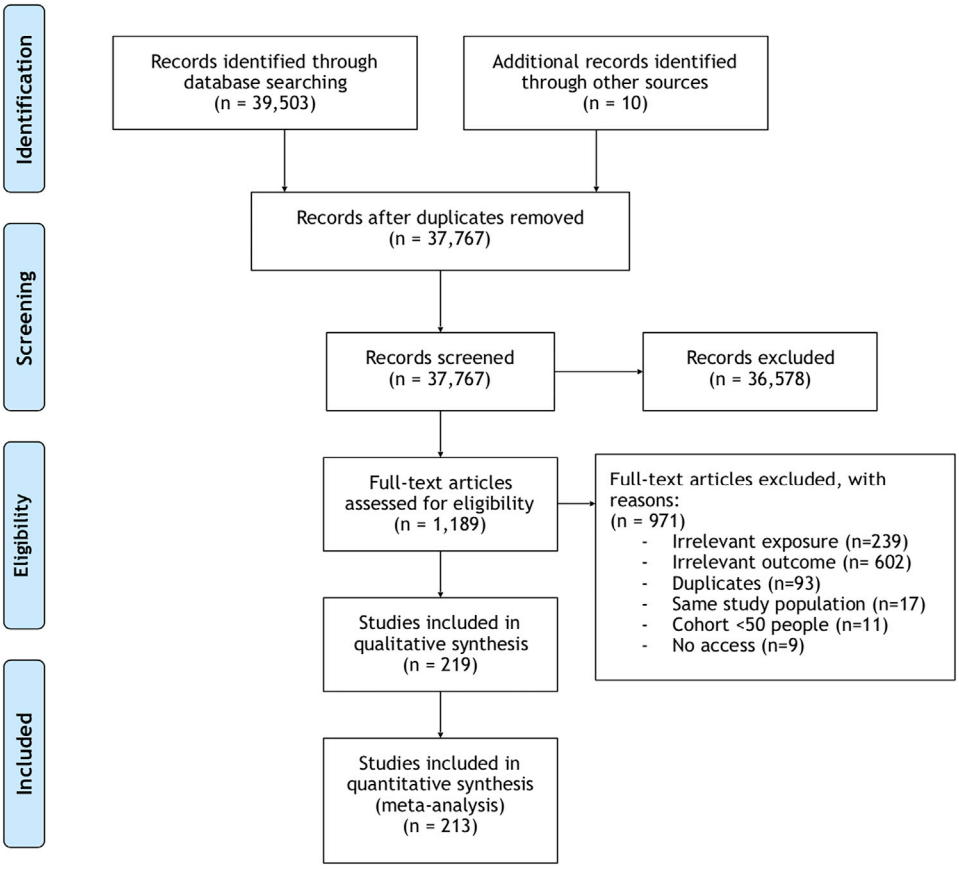


**Fig 1.** Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram of literature review and study selection.

difference in the pooled prevalence of asthma was observed related to study design (Table I). The pooled prevalence of asthma was lower in studies with large study populations (>3000 study participants; 21.2%; 95% CI, 18.5-24.1) compared with smaller study populations (<3000 study participants; 29.2%; 95% CI, 26.3-32.2).

**The association between AD and asthma.** A total of 67 studies, including 237,974 patients with AD and 2,223,921 reference individuals, were used to analyze the association between AD and asthma (pooled OR, 3.03; 95% CI, 2.64-3.47). The association remained significant when the analysis was restricted to studies where AD and asthma were physician diagnosed (pooled OR, 3.01; 95% CI, 2.41-3.77). This was also the case when the analysis comprised only studies in which asthma was defined as wheeze (pooled OR, 2.46; 95% CI, 2.08-2.90). A total of 55 studies in the quantitative analysis had a NOS score of 7 or higher. No variation was seen when studies were stratified by NOS score. Moreover, the association remained essentially similar when studies were divided by age, continent, disease activity, or study design (Table I).

### Qualitative analysis

All 5 studies in the qualitative analysis confirmed the results from the quantitative analysis[14-18] (Supplementary Table IV). Of particular interest, an Australian cohort study found that both active and passive smoking significantly increased the risk of incident asthma over time from ages 8 to 44 years among patients with AD.[19] A Thai cohort study with no control individuals, found more smokers among patients with AD and asthma than among patients with AD without asthma.[20]

## DISCUSSION

Although AD and asthma have traditionally been studied under separate umbrellas, 1 or several endotypes with significant pathogenetic overlap seem to exist.[21] Thus, the underlying shared immune dysfunction of AD and asthma, with type 2 immunity and elevated IgE serum levels,[22] may explain some of their coexistence. The significant disease reduction observed in asthma and AD trials after treatment with the IL-4 receptor $\alpha$-antagonist dupilumab further supports the close connection between AD and asthma[23,24] and gives rise to

**Table I.** The prevalence of asthma among patients with AD and the association between AD and asthma

| | Patients with AD | | | Association between AD and asthma | | |
|---|---|---|---|---|---|---|
| Variable | Studies, n | Study participants with AD, n | Prevalence, % (95% CI) | Studies, n | Study participants with AD, n | OR (95% CI) |
| Sex | | | | | | |
| Female | 14 | 74,283 | 24.1 (18.8-29.9) | * | * | * |
| Male | 13 | 6380 | 27.9 (20.5-36.0) | * | * | * |
| Age | | | | | | |
| Children (<18 y) | 90 | 468,096 | 26.3 (23.5-29.1) | 46 | 185,894 | 2.78 (2.50-3.10) |
| Adults (>18 y) | 31 | 93,574 | 21.8 (18.4-25.4) | 10 | 25,921 | 2.85 (1.67-4.85) |
| Definition of disease | | | | | | |
| Physician-diagnosed AD and physician-diagnosed asthma | 50 | 428,037 | 21.0 (17.9-24.3) | 13 | 157,635 | 3.01 (2.41-3.77) |
| Self-reported and physician-diagnosed AD, asthma defined as wheeze | 33 | 60,582 | 28.8 (20.7-37.6) | 11 | 19,536 | 2.46 (2.08-2.90) |
| Study location | | | | | | |
| Europe | 94 | 302,335 | 24.8 (22.5-27.1) | 25 | 85,926 | 3.33 (2.55-4.35) |
| Asia | 44 | 213,147 | 19.6 (15.8-23.6) | 13 | 120,050 | 2.64 (2.25-3.09) |
| North America | 24 | 49,582 | 30.0 (23.3-37.1) | 11 | 18,075 | 2.47 (2.17-2.81) |
| Middle East | 15 | 13,286 | 32.3 (22.2-43.3) | * | * | * |
| Australia | 10 | 9621 | 34.1 (26.1-42.6) | 5 | 1376 | 2.47 (1.70-3.58) |
| Africa | 10 | 10,797 | 26.6 (20.0-33.8) | 5 | 1601 | 2.99 (2.20-4.06) |
| Central and South America | 8 | 2890 | 29.0 (15.7-44.5) | * | * | * |
| AD severity | | | | | | |
| Mild | 10 | 14,005 | 21.8 (16.1-28.1) | * | * | * |
| Moderate/severe | 15 | 6453 | 28.1 (22.7-33.8) | 5 | 1158 | 4.15 (2.13-8.08) |
| Disease activity | | | | | | |
| Asthma current | 49 | 135,981 | 27.9 (24.0-32.1) | 21 | 32,680 | 2.69 (2.23-3.24) |
| Asthma lifetime | 93 | 429,284 | 24.6 (22.5-26.7) | 35 | 207,398 | 2.97 (2.53-3.49) |
| AD current | 57 | 240,500 | 26.6 (21.3-32.2) | 24 | 29,083 | 3.02 (2.57-3.55) |
| AD lifetime | 70 | 398,452 | 23.7 (21.5-26.0) | 30 | 196,569 | 3.29 (2.59-4.18) |
| Study design, sample size, and study quality | | | | | | |
| Cross sectional | 138 | 418,386 | 25.4 (22.7-28.3) | 43 | 95,155 | 3.36 (2.82-4.01) |
| Cohort | 61 | 220,449 | 25.4 (21.8-29.3) | 16 | 124,010 | 2.39 (2.08-2.75) |
| Case-control | 8 | 1822 | 29.2 (17.4-42.7) | * | * | * |
| Clinical trial | 6 | 3500 | 37.7 (19.5-57.8) | * | * | * |
| n < 3000 | 127 | 35,641 | 29.2 (26.3-32.2) | 35 | 9267 | 3.63 (2.90-4.55) |
| n > 3000 | 85 | 653,286 | 21.2 (18.5-24.1) | 32 | 228,707 | 2.81 (2.33-3.40) |
| NOS score ≥ 7 | 181 | 576,916 | 25.4 (23.7-27.2) | 55 | 223,066 | 3.18 (2.71-3.73) |
| NOS score < 7 | 28 | 21,766 | 30.5 (21.3-40.6) | 10 | 14,908 | 2.80 (2.36-3.31) |

*AD,* Atopic dermatitis; *CI,* confidence interval; *NOS,* Newcastle Ottawa Scale; *OR,* odds ratio.
*Fewer than 5 studies.

continued investigation into potential monotherapy of these 2 disorders in selected patients.

We observed a higher rate of asthma when looking at current AD compared with lifetime AD, although the difference was nonsignificant, possibly because of recall bias. We found high prevalence estimates of asthma in patients with AD across all severities, but the asthma prevalence appears to be even higher among patients with AD with moderate to severe disease, despite the nonsignificant finding in this meta-analysis. For example, a large cohort study comprising 6186 adult patients with AD showed that the prevalence of asthma increased with AD severity, because the prevalence was 12.1% among patients with mild AD and 33.7% among patients with severe AD ($P < .001$).[25] Moreover, the prevalence of a history of asthma reached 49.5% among patients with moderate to severe AD in the SOLO 1 and 2 trials on dupilumab,[26,27] and 29.5% of the total population required asthma treatment.[28] Similarly, among adult Danish patients with AD followed in a hospital setting, 35.2% used corticosteroid inhalants.[3] Interestingly, the prevalence of AD among patients with uncontrolled and persistent asthma was recently shown to reach only 10% in a large clinical trial using the IL-13–neutralizing monoclonal antibody tralokinumab.[29] However, based on data from a Canadian

center, 19% of patients with severe asthma reported AD, but on closer examination, it was found that 38% had concomitant AD,[30] indicating that AD may be overlooked in patients with asthma. We found only a few studies that contained data on asthma disease severity in AD, and most[31-34] showed that the forced expiratory volume in 1 second typically indicated mild or moderate asthma. High asthma severity in patients with AD may represent an argument for selecting treatment agents that target both diseases. So far, few studies have examined the consequences of having both AD and asthma, but co-occurrence increased the risk of both cutaneous and systemic infections compared with patients with only AD in a British cohort.[35] Additionally, co-occurrence was seen to have higher impact on the patients' quality of life compared with patients with only AD in a Swedish study,[36] emphasizing the burden of having both diseases.

Both patients with AD and those with asthma often have increased total and specific IgE levels. Indeed, approximately 50% of patients with AD across various races and ages have a personal or family history of asthma or rhinitis[37] as well as elevated serum total IgE levels. Studies from Israel and Germany have shown that elevated IgE levels are associated with AD onset in childhood, whereas patients with adult onset less frequently have elevated IgE.[38,39] Aeroallergen exposure to allergens may lead to worsening of both asthma and AD,[38] emphasizing the pathogenic role of IgE in both diseases. Omalizumab, a monoclonal antibody that specifically binds to the $F_C$ portion of free IgE and to the membrane-bound form of IgE, seems to work in few patients with AD[40,41] but is more effective in asthma, indicating that IgE, to a certain degree, has a secondary role in AD. Mepolizumab, a monoclonal antibody targeting IL-5, has proven to be effective in reducing disease severity in eosinophilic asthma but failed in AD.[42,43] More recently, IL-17–skewed inflammation has been observed in both AD and asthma, but this seems to be much less pronounced and frequent.[44-46]

The atopic march, that is, the observation that pediatric patients first develop AD and then later asthma and rhinitis, was recently challenged by a general population birth cohort study[47] comprising patients with mostly milder AD. However, genetic risk loci associated with AD have also been identified as risk factors for the atopic march, including filaggrin gene mutations and IL-4/KIF3A.[48] The principle of the atopic march seems still to work as a model for some patients with AD, perhaps particularly those with common filaggrin gene mutations and likely those with more severe disease.[49] A recent animal study showed that by keeping the skin acidic, sensitization to allergens could be minimized, putting additional emphasis on the link between a competent skin barrier and resistance against allergic sensitization.[50] A personal history of asthma represents a significant predictor for AD persistence in children,[51] again suggesting a pathogenic link between the conditions.

Certain limitations apply to the interpretation of the study results. The definitions of AD and asthma differed greatly across the included studies and varied from self-report to physician diagnosis, which potentially may lead to misclassification. Few studies examined the severity of AD in connection with asthma status and also used various definitions thereof. A potentially complicating factor is that a proper diagnosis of asthma cannot be made until the age of 6 years,[52,53] so the fact that some studies used infancy wheezing[54-76] to define asthma may affect the results. Also, asthma may be unnoticed by some individuals as they learn to adapt to respiratory problems. Most of the included studies came from the Western part of the world, potentially skewing the results and affecting the generalization of results. We found slightly lower asthma prevalence when restricting the meta-analysis to large studies, but the implication of this is unknown. Smoking has been associated with development and worsening of both AD and asthma, potentially making prevention of parental and patient smoking a disease modifier.[77-79] Along these lines, active and passive smoking, which was not accounted for in our study, could have affected the observed associations.

## CONCLUSIONS

Children and adults with AD often have co-occurring asthma, indicating the general overlap between the 2 conditions. Future studies are needed to understand the relationship with disease severity. It remains unknown to what extent concomitant asthma should influence AD treatment choices.

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