Prevalence of type 2 inflammatory diseases in pediatric patients with atopic dermatitis: Real-world evidence

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Background: Patients with atopic dermatitis (AD) are considered at increased risk of developing other type 2 inflammatory diseases. However, real-world evidence based on large commercially insured pediatric populations in the United States is scarce.

Objective: To use a large claims database (IBM MarketScan 2013-2017) in the United States to assess prevalence and incidence of type 2 inflammatory diseases in pediatric patients with AD.

Methods: Pediatric patients with AD were matched 1:1 to patients without AD. Prevalence was assessed for conjunctivitis, rhinitis, urticaria, asthma, eosinophilic esophagitis, and chronic rhinosinusitis/nasal polyps at the 12 months' post-index date (the first AD diagnosis date for patients with AD; a randomly selected outpatient visit for control patients). The incidence of other type 2 inflammatory diseases post-index was assessed among patients 0-2 years of age.

Results: A total of 244,776 AD and matched non-AD patients were selected. The prevalence and incidence of type 2 inflammatory diseases were higher among patients with AD. Overall, the prevalence more than doubled for asthma, eosinophilic esophagitis, urticaria, and rhinitis, and increased with AD severity.

Limitations: AD identification was based on billing diagnoses; the observation period was only 12 months; and the study was limited to commercially insured patients.

Conclusion: The burden of type 2 inflammatory diseases in pediatric patients with AD is substantial, highlighting the need to optimize management of AD and its numerous associated morbidities. (J Am Acad Dermatol 2022;86:758-65.)

Key words: adolescents; atopic dermatitis; children; eczema; infants; morbidity burden; prevalence; real-world evidence; type 2 inflammatory diseases.

INTRODUCTION

Type 2 inflammatory diseases are characterized by the dysregulation of the T helper 2 pathway.[1] Atopic dermatitis (AD) is a chronic, immune-mediated type 2 inflammatory disease characterized by intense pruritus and debilitating effects on patient and caregiver lives.[2-5] In the US, the prevalence of AD in children and adolescents is estimated to range

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between 10% and 20%. Moderate-to-severe forms represent approximately 30% of AD cases.[6-8]

In addition to skin-related symptoms, patients with AD are at increased risk of developing type 2 inflammatory diseases such as asthma and allergic rhinitis.[9-11] AD and other type 2 inflammatory diseases share common inflammatory pathways and genetic risk factors, which could explain their coexistence.[9,11-15] The epidermal barrier dysfunction associated with AD, the severity of AD, as well as parental atopy, early age at onset, and environmental factors (eg, urban upbringing) are also associated with the codevelopment of type 2 inflammatory diseases in patients with AD.[9,16,17]

CAPSULE SUMMARY

- The extracutaneous burden of type 2 inflammatory diseases in pediatric patients with atopic dermatitis is substantial.
- Recognition of concurrent atopic morbidities can inform optimal management and mitigate the overall disease burden.

Prior studies investigated the association between AD and other selected atopic disorders, particularly asthma, allergic rhinitis, and food allergy, but none investigated the spectrum of type 2 inflammatory diseases in a large population of pediatric patients with AD in the US utilizing the third-party payor-supported health care system.[2,11,18] There is also limited real-world evidence on the prevalence of type 2 inflammatory diseases by severity level[2,11,18,19] or with regard to treatment received.

Using a large administrative claims database in the US, the primary objective of this study was to assess the prevalence of type 2 inflammatory diseases in a sample of pediatric patients with AD, both overall and stratified by treatment proxy for AD severity. As a secondary objective, time to development of subsequent type 2 inflammatory diseases was assessed among infants (0-2 years old).

METHODS

Data source

Data from the IBM MarketScan Commercial Database was used (2013-2017), in which patient-level data are deidentified and compliant with the Health Insurance Portability and Accountability Act.

Study design and patient selection

A retrospective matched cohort design was used to match patients with AD 1:1 to non-AD controls based on age, gender, insurance type, region, length of the observation period, and year of index date. To minimize the risk of selection bias, non-AD controls were randomly selected among all patients without AD meeting the selection criteria. The baseline period was defined as the 6 months prior to the index date (defined below) and the study period was defined as the 12 months following the index date.

Identification of patients with AD. Pediatric patients (<18 years) with ≥1 medical claim, including a diagnosis of AD (International Classification of Diseases 9th Revision code 691.8, International Classification of Diseases 10th Revision code L20.x), were selected. The date of the first observed diagnosis for AD was defined as the index date. Patients were required to have continuous eligibility (medical and pharmacy benefit) for ≥6 months prior to and ≥12 months following the index date. Using the highest potency of AD treatments received during their observation period as proxies for disease severity, patients with AD were classified into 3 mutually exclusive cohorts.

Topical corticosteroids were ranked by potency class (highest 1 to lowest 7).[20,21] Patients who received no treatment, ≥1 dispensing for class 5-7 topical corticosteroids, or topical calcineurin inhibitors alone were classified under the treatment severity level 1 cohort. Those who received ≥1 dispensing for class 1-4 topical corticosteroids, crisaborole, or topical calcineurin inhibitors with other AD therapies were classified under the treatment severity level 2 cohort. Patients who received ≥1 dispensing for systemic corticosteroids, immunosuppressants, intravenous immunoglobulin, or phototherapy were classified under the treatment severity level 3 cohort.

Identification of patients without AD. Pediatric patients without AD (<18 years) were required to be free of any diagnosis of AD over the entire period covered by the database. Their index date was set on the date of a randomly selected outpatient visit (excluding emergency room visits) within a period of continuous eligibility; ie, with ≥6 months of eligibility before and ≥12 months after the visit date.

Definition of outcomes and statistical analysis

Primary objective. The prevalence of type 2 inflammatory diseases during the 12-month study period was compared both between patients with and without AD and among patients with AD with treatment severity level 3 versus levels 1-2.

The type 2 inflammatory diseases investigated included asthma, conjunctivitis (except viral), chronic

Abbreviations used:

AD: atopic dermatitis
CI: confidence intervals
OR: odd ratios
US: United States

rhinosinusitis and nasal polyps, eosinophilic esophagitis, rhinitis, and urticaria. They were identified based on the presence of ≥1 medical claim with corresponding diagnostic codes. For some conditions, the etiology can be atopic or non-atopic. However, given that health care providers might not systematically use the diagnostic code reflecting the appropriate etiology, the list of diagnostic codes to identify type 2 inflammatory diseases was not limited to those specific to atopic conditions. In addition, although food allergy is typically considered a type 2 inflammatory disease, it was excluded from this analysis because this diagnosis is poorly defined and frequently recorded by health care providers without standardized diagnostic criteria.[22,23]

Statistical comparisons were conducted using logistic regression models, which were adjusted for matched pairs to allow comparisons between patients with and without AD. Results were reported as odds ratios (ORs) with their 95% confidence intervals (CIs) and *P* values. For the comparisons between patients with AD with treatment severity level 3 and levels 1-2, models were adjusted to control for gender, region, age, providers type on the index date, and insurance plan types.

Secondary objective. Among infants (0-2 years old as of the index date), time to development of subsequent type 2 inflammatory diseases was assessed. For this analysis, the patient's entire observation period following the index date was considered. To assess incidence cases, for each type 2 inflammatory disease, all AD/non-AD matched pairs for which ≥1 patient had a diagnosis for the study condition during the baseline period or at the index date were excluded. Time to development of subsequent type 2 inflammatory diseases was reported using Kaplan-Meier curves. Risks of developing type 2 inflammatory diseases were compared between patients with AD and without AD using Cox proportional hazard models adjusted for matched pairs. Results were reported as hazard ratios with their 95% CIs and *P* values.

RESULTS

Patient characteristics

A total of 244,776 AD patients met the inclusion criteria and were matched to patients without AD. One-fourth of all AD cases (58,577 patients) met treatment severity level 3 criteria. Patients with AD and without AD were on average 6 years old as of the index date. Both cohorts had an approximate 50:50 ratio for sex and patients were predominantly from the southern region of the US (44.9%) (Table I). A higher proportion of patients with treatment severity level 3 were male compared to those with levels 1-2 (54.4% vs 50.0%; $P < .001$). Patients with treatment severity level 3 were also significantly older than those with levels 1-2, which may reflect greater health care provider comfort prescribing higher potency medications to older patients or sequencing of AD therapies from lower to higher potency options over time.

Among patients with AD, 28.5% were seen by a dermatologist or allergist/immunologist on the index date. Disparities in the provider types seen on the index date were observed between cohorts. When compared to the treatment severity levels 1-2 cohort, a higher proportion of patients in the treatment severity level 3 cohort were seen by a specialist (ie, dermatologists or allergists/immunologists [level 3, 36.6%; levels 1-2, 26.0%]) as opposed to pediatricians (level 3, 41.3%; levels 1-2, 54.0%). The proportion of patients who saw a provider from an acute/emergency room/urgent care setting was also higher in the treatment severity level 3 cohort (2.9% vs 1.9%).

Prevalence of type 2 inflammatory diseases

During the first year after the index date, patients with AD were more than twice as likely than patients without AD to be diagnosed with any type 2 inflammatory disease (OR, 2.17 [2.15; 2.20]; $P < .001$). Notably, prevalences of asthma (OR, 2.29 [2.24; 2.33]), eosinophilic esophagitis (OR, 2.46 [2.09; 2.89]), urticaria (OR, 2.42 [2.35; 2.50]), and rhinitis (OR, 2.80 [2.76; 2.85]) in patients with AD were more than twice those in patients without AD (all $P < .001$). The prevalence of chronic rhinosinusitis and nasal polyps (OR, 1.10 [1.06; 1.13]; $P < .001$) as well as conjunctivitis (OR, 1.47 [1.44; 1.49]; $P < .001$) was also significantly higher among patients with AD (Fig 1).

The prevalence of each type 2 inflammatory disease also increased with AD treatment severity level. In particular, patients with treatment severity level 3 were more than 4 times as likely to be diagnosed with asthma (OR, 4.43 [4.32; 4.54]) and more than twice as likely to be diagnosed with chronic rhinosinusitis and nasal polyps (OR, 2.46 [2.34; 2.58]), eosinophilic esophagitis (OR, 3.22 [2.68; 3.87]), or rhinitis (OR, 2.33 [2.28; 2.38]) when compared to patients with treatment severity levels 1-2. The prevalence of urticaria and conjunctivitis was also 1.70 times and 1.46 times higher in patients with AD with treatment severity level 3 (all $P < .001$) (Fig 1).

Table I. Demographic and clinical characteristics

			AD patients			
	Patients with AD*	Patients without AD*	Treatment severity *level 3*	Treatment severity *levels 1-2*		
	n = 244,776	n = 244,776	n = 58,577	n = 186,199	StDiff†	*P* value†
Demographics						
Age, mean ± SD [median]	6.0 ± 5.3 [5.0]	6.0 ± 5.3 [5.0]	7.6 ± 5.6 [8.0]	5.5 ± 5.1 [4.0]	-0.385	<.001¶
Age category, n (%)						<.001¶
0-1 y	72,171 (29.5%)	72,171 (29.5%)	12,708 (21.7%)	59,463 (31.9%)	0.233	
2-5 y	56,088 (22.9%)	56,088 (22.9%)	10,984 (18.8%)	45,104 (24.2%)	0.134	
6-11 y	68,596 (28.0%)	68,596 (28.0%)	17,376 (29.7%)	51,220 (27.5%)	-0.048	
12-17 y	47,921 (19.6%)	47,921 (19.6%)	17,509 (29.9%)	30,412 (16.3%)	-0.326	
Male, n (%)	124,863 (51.0%)	124,863 (51.0%)	31,839 (54.4%)	93,024 (50.0%)	-0.088	<.001¶
Geographic location, n (%)						<.001¶
Northeast	47,756 (19.5%)	47,756 (19.5%)	9,899 (16.9%)	37,857 (20.3%)	0.088	
North central	40,916 (16.7%)	40,916 (16.7%)	9,460 (16.1%)	31,456 (16.9%)	0.020	
South	110,003 (44.9%)	110,003 (44.9%)	29,917 (51.1%)	80,086 (43.0%)	-0.162	
West	45,715 (18.7%)	45,715 (18.7%)	9,186 (15.7%)	36,529 (19.6%)	0.103	
Unknown	386 (0.2%)	386 (0.2%)	115 (0.2%)	271 (0.1%)	-0.012	
Commercial insurance plan type, n (%)						<.001¶
Comprehensive	3,899 (1.6%)	3,899 (1.6%)	1,020 (1.7%)	2,879 (1.5%)	-0.015	
EPO/POS	17,777 (7.3%)	17,777 (7.3%)	4,628 (7.9%)	13,149 (7.1%)	-0.032	
HMO/POS with capitation	29,816 (12.2%)	29,816 (12.2%)	6,839 (11.7%)	22,977 (12.3%)	0.020	
PPO	141,290 (57.7%)	141,290 (57.7%)	34,345 (58.6%)	106,945 (57.4%)	-0.024	
CDHP/HDHP	48,992 (20.0%)	48,992 (20.0%)	11,183 (19.1%)	37,809 (20.3%)	0.031	
Unknown	3,002 (1.2%)	3,002 (1.2%)	562 (1.0%)	2,440 (1.3%)	0.033	
Year of the index date, n (%)						<.001¶
2013	52,099 (21.3%)	52,099 (21.3%)	13,947 (23.8%)	38,152 (20.5%)	-0.080	
2014	63,802 (26.1%)	63,802 (26.1%)	17,891 (30.5%)	45,911 (24.7%)	-0.132	
2015	61,581 (25.2%)	61,581 (25.2%)	14,579 (24.9%)	47,002 (25.2%)	0.008	
2016	67,294 (27.5%)	67,294 (27.5%)	12,160 (20.8%)	55,134 (29.6%)	0.205	
Provider type on the index date,‡ n (%)						<.001¶
Dermatology	43,571 (17.8%)	3,255 (1.3%)	11,619 (19.8%)	31,952 (17.2%)	-0.069	
Allergy/Immunology	26,226 (10.7%)	1,985 (0.8%)	9,841 (16.8%)	16,385 (8.8%)	-0.241	
Pediatrics	124,775 (51.0%)	135,616 (55.4%)	24,188 (41.3%)	100,587 (54.0%)	0.257	
Acute/Emergency/Urgent care	5,295 (2.2%)	19,731 (8.1%)	1,692 (2.9%)	3,603 (1.9%)	-0.062	
Family practice/Medical doctor (NEC)	20,377 (8.3%)	29,301 (12.0%)	5,156 (8.8%)	15,221 (8.2%)	-0.023	
Nurse practitioner	3,798 (1.6%)	3,834 (1.6%)	1,048 (1.8%)	2,750 (1.5%)	-0.025	
Other§	18,366 (7.5%)	47,476 (19.4%)	4,512 (7.7%)	13,854 (7.4%)	-0.010	

AD, Atopic dermatitis; *CDHP*, consumer-driven health plan; *EPO*, exclusive provider organization; *HDHP*, high-deductible health plan; *HMO*, health maintenance organization; *NEC*, not elsewhere classified; *POS*, point-of-service; *PPO*, preferred provider organization; *SD*, standard deviation; *StDiff*, standardized difference; *y*, age in years.

*Patients with AD and without AD were matched based on age, gender, health plan type, residential region, length of the observation period, and calendar year, all evaluated at the index date.

†StDiff and *P* values are used to compare AD patients with treatment severity level 3 to those with treatment severity levels 1-2. The *P* values were calculated using t-tests for continuous variables, and Chi-square tests for categorical variables.

‡The provider type was missing for 2368 patients with AD (521 with treatment severity level 3 and 1847 with treatment severity levels 1-2) and 3578 patients without AD.

§Other providers include, for example, laboratory service providers, physicians from other specialties, and pharmacists.

¶Significant at the 5% level.

Development of subsequent type 2 inflammatory diseases

Among infants, the risk of developing subsequent type 2 inflammatory diseases was significantly higher in patients with AD compared to patients without AD (hazard ratio, 1.47 [1.45-1.50]) (Fig 2). Estimates from Kaplan-Meier analyses indicated a greater cumulative probability of developing any type 2 inflammatory disease at 24 months in patients with AD than in patients without AD (51.7% vs 38.9%), including

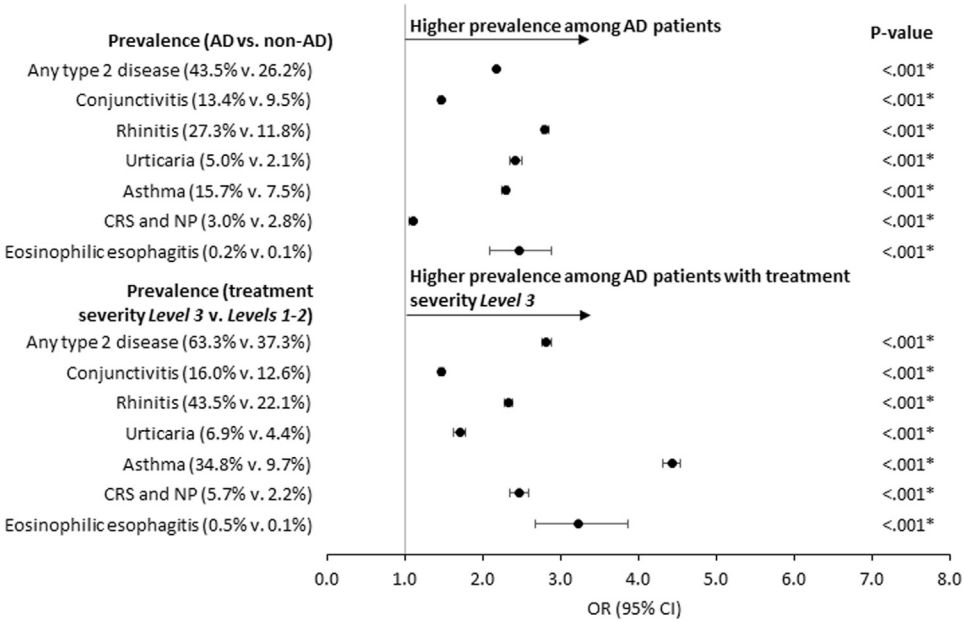

Fig 1. Prevalence of type 2 inflammatory diseases during a 12-month observation period. ORs, CIs, and *P* values were adjusted for matched pairs when comparing patients with AD and patients without AD, and for gender, age, region, provider type on the index date, and insurance plan type when comparing patients with AD with treatment severity level 3 and those with treatment severity levels 1-2. *AD*, Atopic dermatitis; *CI*, confidence intervals; *CRS*, chronic rhinosinusitis; *NP*, nasal polyps; *OR*, odds ratio. *Significant at the 5% level.

conjunctivitis (27.7% vs 22.9%), rhinitis (24.5% vs 13.8%), asthma (12.6% vs 7.0%), urticaria (9.6% vs 5.0%), chronic rhinosinusitis and nasal polyps (4.7% vs 4.0%), and eosinophilic esophagitis (0.2% vs 0.0%) (all $P < .05$).

DISCUSSION

Although prior studies have assessed the association between AD and other selected atopic diseases, particularly asthma, allergic rhinitis, and food allergy,[9,10,18,24] no study has yet investigated the full spectrum of the burden of type 2 inflammatory diseases in a large population of children in the US. This study provides real-world evidence on the prevalence and association between AD and type 2 inflammatory diseases among a large sample of commercially insured children in the US.

Results showed that the burden of extracutaneous type 2 inflammatory diseases in pediatric patients with AD is substantial.[9] The relative prevalence of rhinitis, eosinophilic esophagitis, urticaria, asthma, conjunctivitis, and chronic rhinosinusitis and nasal polyps was greater in children with AD. In addition, the burden of type 2 inflammatory diseases increased in patients with more severe forms of AD, as proxied by the potency of treatments received. Notably, patients with treatment severity level 3 were more than 4 times as likely to be diagnosed with asthma and more than twice as likely to be diagnosed with chronic rhinosinusitis and nasal polyps, rhinitis and eosinophilic esophagitis compared to patients with treatment severity levels 1-2. Among infants, results showed that the risk of developing subsequent type 2 inflammatory diseases was 1.5 times higher in patients with AD than in patients without AD.

Findings are generally consistent with results from prior studies, reporting an approximately 2-fold increase in the risk of asthma in patients with AD compared to non-AD controls. The reported prevalence ranged between 14.2% and 52.5%, depending on the assessment period, study design, and setting (eg, outpatient vs hospital-based cohorts).[9,25] Prior studies also supported the association between AD and allergic rhinitis as well as allergic conjunctivitis.[9,10,15,16,26-28]

The comparisons of the prevalence and incidence estimates are, however, limited due to the different study designs, assessment periods, and data sources used in the prior studies. In a prospective study of 1091 protocol-treated infants with AD, Schneider et al[10] found that 22.4% developed allergic rhinitis; 10.7%, asthma; and 14.1%, allergic conjunctivitis by the study's end (mean of 2.8 years). This is numerically lower than the rates observed in our unselected, less uniformly treated population (Fig 2). However, the difference in the estimates are likely to be driven by the different data sources and designs

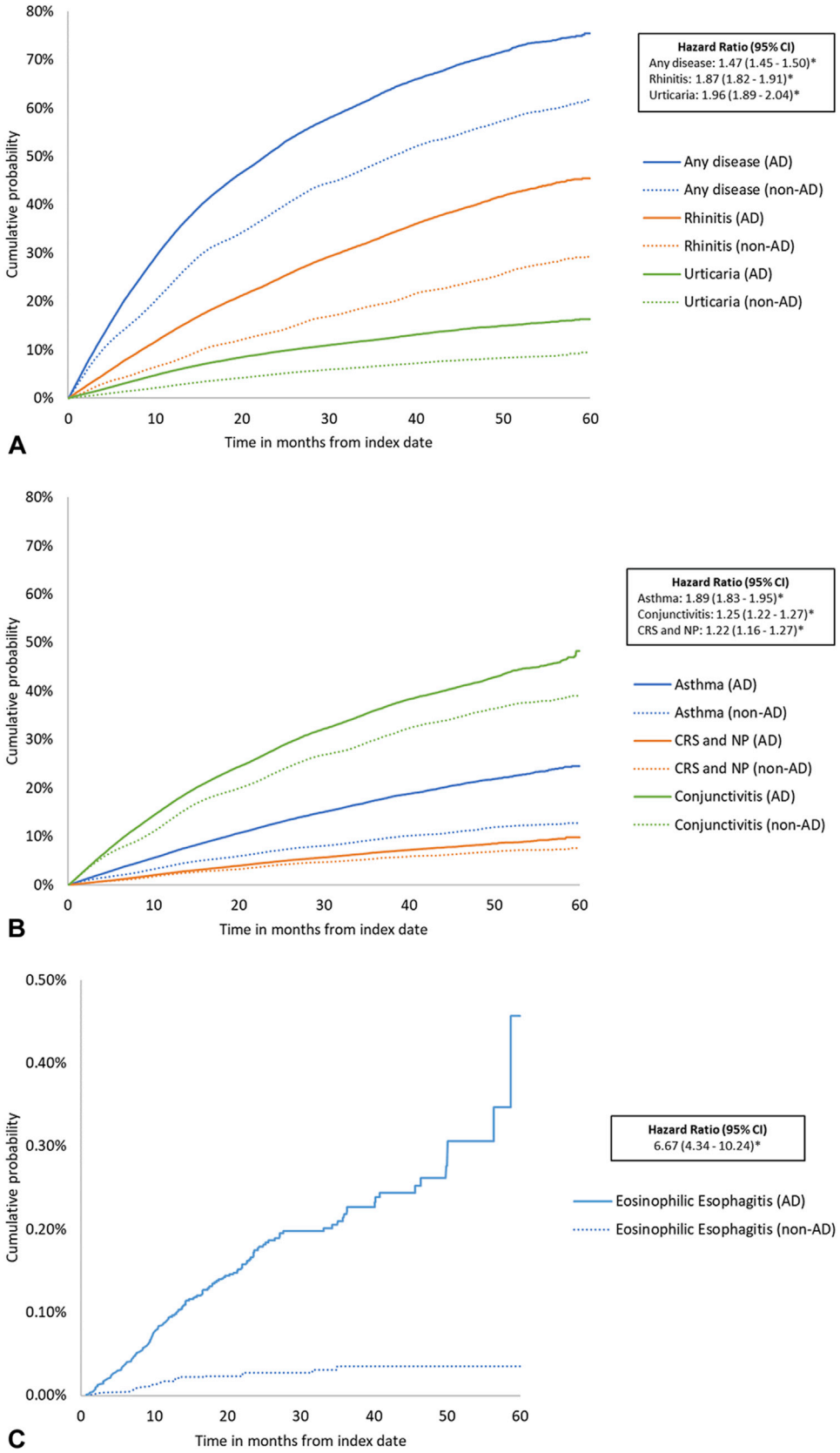

Fig 2. Development of type 2 inflammatory diseases among patients aged 0-2 years old at the index date.* **A**, Any type 2 inflammatory disease, rhinitis, and urticaria. There were 62,909, 77,776, and 84,159 matched pairs of patients with AD and patients without AD at risk of developing any type 2 inflammatory disease, rhinitis, and urticaria at the index date,

(eg, current study includes diagnostic codes that do not distinguish atopic from non-atopic morbidities).

The higher prevalence of type 2 inflammatory diseases among patients with more severe forms of AD is also consistent with findings from recent studies highlighting the role of AD disease severity among risk factors for the development of other atopic diseases.[9,17]

There is no agreement on the mechanisms contributing to the so-called "atopic march" and on predictors for developing extracutaneous atopic morbidities in children with AD.[11,29,30] However, results from this study highlight the high prevalence of type 2 inflammatory diseases in patients with AD and emphasize the need for clinicians treating patients with AD to consider a multidisciplinary approach and recognize these concurrent conditions in order to optimize management.

Results from this study should be interpreted in light of some limitations. First, as there is no information in claims data to identify disease severity, it was proxied based on potency of AD treatment received. Although treatment-based algorithms have been used in prior studies using claims data as a proxy for AD severity,[31,32] misclassification may occur as some of the treatments (eg, systemic corticosteroids) have other indications. It should also be noted that the proportion of patients with severity level 3 may be underestimated given the reluctance of some treating physicians to manage patients with more potent treatments, especially in pediatric patients.

Second, AD and other conditions in this study were identified based on diagnostic codes used for billing purposes, which in some instance could reflect suspected diagnoses. In addition, as AD and other conditions were identified based on the presence of medical claims, only patients who sought care for their conditions were identified. Given inconsistency in coding/recording of AD across physicians (eg, some physicians may use diagnostic codes not specific to AD, such as eczema), it is also possible that some true patients with AD were not included.

Third, health care providers may not systematically use specific diagnostic codes that distinguish atopic from non-atopic morbidities (eg, asthma and rhinitis). Accordingly, diagnostic codes used in this study to identify type 2 inflammatory comorbidities were not limited to the atopic conditions. Although this approach may impact the overall prevalence estimates, it is likely to affect AD and non-AD cohorts to a similar extent and unlikely to alter the conclusions. Moreover, a diagnosis of eosinophilic gastrointestinal disease is difficult to establish and may be under-recognized.

Fourth, the observation period of 12 months may be too short to observe the true prevalence of type 2 inflammatory diseases as not all conditions are expected to be clinically evident within 1 year after an AD diagnosis. Fifth, although all census regions are represented in the MarketScan database, there is a concentration of enrollees in the southern region of the US.[33]

CONCLUSION

Despite many studies suggesting associations between AD and other atopic morbidities, few have investigated the full spectrum of type 2 inflammatory diseases in pediatric patients in a large population of commercially insured pediatric patients. This study finds that the burden of type 2 inflammatory diseases in pediatric patients with AD is substantial and goes beyond skin manifestations and what has been referred to as the atopic march. Findings also highlight the role of AD severity in the risk of developing/having other coexisting type 2 inflammatory diseases. These results emphasize the need for an early recognition and multidisciplinary approach in the management of patients with AD to optimize pharmacologic treatments and mitigate the overall disease burden.

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Conflict of interest

Author Boklage and Dr Mina-Osorio were employees of and stockholders in Regeneron Pharmaceuticals, Inc at the time of study. Dr Kaur is an employee and stockholder of Sanofi. Drs Ganguli and Mallya were employees and stockholders in Sanofi at the time of study. Authors Vekeman and Robitaille are employees of StatLog, Inc, which received research funding for the current study. Dr Paller is an employee of Northwestern University and has

respectively. **B**, Asthma, conjunctivitis, and chronic rhinosinusitis and nasal polyps. There were 82,255, 76,000, and 85,831 matched pairs of patients with AD and patients without AD at risk of developing asthma, conjunctivitis, and CRS and NP at the index date, respectively. **C**, Eosinophilic esophagitis. There were 87,498 matched pairs of patients with AD and patients without AD at risk of developing eosinophilic esophagitis at the index date. *Significant at the 5% level. *AD*, Atopic dermatitis; *CI*, confidence intervals; *CRS*, chronic rhinosinusitis; *NP*, nasal polyps.

been a consultant with honorarium for Regeneron Pharmaceuticals and Sanofi and an investigator for Regeneron Pharmaceuticals. Dr Siegfried is an employee of St Louis University and has been a consultant with honorarium and an investigator for Regeneron Pharmaceuticals and Sanofi.

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